Dextrose Prolotherapy for Musculoskeletal Pain

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PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to conduct timely, rigorous, and independent systematic reviews to support VA clinicians, program leadership, and policymakers improve the health of Veterans. ESP reviews have been used to develop evidence-informed clinical policies, practice guidelines, and performance measures; to guide implementation of programs and services that improve Veterans' health and wellbeing; and to set the direction of research to close important evidence gaps. Four ESP Centers are located across the US. Centers are led by recognized experts in evidence synthesis, often with roles as practicing VA clinicians. The Coordinating Center, located in Portland, Oregon, manages program operations, ensures methodological consistency and quality of products, engages with stakeholders, and addresses urgent evidence synthesis needs.

Nominations of review topics are solicited several times each year and submitted via the ESP website. Topics are selected based on the availability of relevant evidence and the likelihood that a review on the topic would be feasible and have broad utility across the VA system. If selected, topics are refined with input from Operational Partners (below), ESP staff, and additional subject matter experts. Draft ESP reviews undergo external peer review to ensure they are methodologically sound, unbiased, and include all important evidence on the topic. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. In seeking broad expertise and perspectives during review development, conflicting viewpoints are common and often result in productive scientific discourse that improves the relevance and rigor of the review. The ESP works to balance divergent views and to manage or mitigate potential conflicts of interest.

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Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

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Technical Expert Panel

To ensure robust, scientifically relevant work, the technical expert panel (TEP) guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members included:

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Disclosures

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The findings and conclusions in this document are those of the author(s) who are responsible for its contents and do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. The final research questions, methodology, and/or conclusions may not necessarily represent the views of contributing operational and content experts. No investigators have affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

Executive Summary

KEY FINDINGS

- Among 90 eligible studies on dextrose prolotherapy, most had fewer than 100 participants and nearly half were rated as high risk of bias. Studies varied greatly in dextrose concentrations employed, injection technique, cointerventions, and comparators.
- Evidence on adverse effects of dextrose prolotherapy was very uncertain for all included musculoskeletal pain conditions and comparators (very low certainty of evidence [COE]).
- For **knee osteoarthritis**, intra-articular dextrose prolotherapy probably has little to no benefit for pain-related functioning, physical performance, and health-related quality of life, compared with normal saline injection (moderate and high COE). It may also have little to no benefit for pain-related functioning, compared with ozone injection (low COE). Evidence was very uncertain on benefits versus platelet-rich plasma (very low COE).
- For **knee osteoarthritis**, the evidence was very uncertain on the effects of combined intra-articular and extra-articular dextrose prolotherapy on pain-related functioning at short and medium-term follow-up (very low COE) but it may improve long-term outcomes (low COE), compared with either normal saline injection or physical therapy (PT) and home exercise programs.
- For **plantar fasciitis**, dextrose prolotherapy may improve pain-related functioning, compared with normal saline injection (low COE), but may have little to no benefit compared with extracorporeal shockwave therapy (ESWT; low COE). The evidence was very uncertain on benefits for pain-related functioning (very low COE), and it may have little to no benefit for health-related quality of life versus corticosteroid injection (low COE).
- For **shoulder pain** (due to mixed bursitis and rotator cuff pathology), the evidence was very uncertain on the benefit for pain-related functioning (very low COE), and dextrose prolotherapy may have little to no benefit for physical performance (low COE), compared with normal saline injection. The evidence was also very uncertain on the benefit for pain-related functioning (very low COE), and it probably resulted in worse physical performance (moderate COE), compared with corticosteroid injection.
- For **lateral elbow tendinopathy**, dextrose prolotherapy may improve pain-related functioning (low COE), but the evidence was very uncertain or suggested little to no benefit for physical performance over different timeframes (very low or low COE), compared with normal saline injection. The evidence was also very uncertain or suggested little to no benefit for pain-related functioning (very low or low COE), compared with corticosteroid injection.
- For **chronic low back pain**, the evidence was very uncertain on the benefits of dextrose prolotherapy for pain-related functioning, compared with normal saline or corticosteroid injection (very low COE).
- For **temporomandibular joint (TMJ) disorders**, the evidence was very uncertain on the benefits of dextrose prolotherapy compared with normal saline or autologous blood injection (very low COE).

Musculoskeletal disease is the most common reason for chronic pain among adults in the United States (US). Globally, osteoarthritis is the most common musculoskeletal disease, impacting approximately 595 million individuals (7.6% of the worldwide population). Osteoarthritis is a degenerative condition that generally affects older adults and is a leading cause of pain and disability in this population. The knee is the most commonly afflicted joint and an estimated 14 million US adults have symptomatic knee osteoarthritis. Other joint and peri-articular conditions are also common and have substantial associated morbidity. For example, shoulder pain due to various etiologies accounts for 16% of musculoskeletal complaints in US primary care patients, and heel pain from plantar fasciitis has a lifetime incidence of 10% among US adults.

Musculoskeletal pain conditions are often challenging for patients and clinicians, driving demand and health care utilization. The breadth of treatments includes non-pharmacological interventions (*eg,* physical therapy [PT]), topical and systemic pharmacologic therapies, localized injection therapies, and surgical procedures. Most of these treatments address symptoms such as pain and joint instability, without changing disease progression. Additionally, disease severity based on imaging findings often does not correlate with pain and functioning reported by patients (*eg*, for knee osteoarthritis). Because some patients have insufficient improvement in their symptoms from non-pharmacologic and topical/systemic pharmacologic treatments, targeted injection therapies are often offered before more invasive surgical procedures. Surgery is also not the best option for certain patients due to a variety of factors, including patient preferences and individualized expectations for benefits versus risks.

Hypertonic dextrose prolotherapy has been used to treat a variety of musculoskeletal pain conditions, including osteoarthritis and different tendinopathies. Prolotherapy involves injecting an irritant solution into or around an affected structure to improve musculoskeletal pain and function. The true physiologic effects are not well understood but the putative mechanism involves eliciting a low-grade inflammatory response that stimulates natural healing processes in connective tissues and potentially alters pain perception pathways. Hypertonic dextrose is the most commonly utilized prolotherapy solution, but there is variation in dextrose concentration and inclusion of additional chemicals.

In fiscal year 2023, a total of 1,454 dextrose prolotherapy injection procedures were administered in VA health care facilities, and there were 59 VA Care in the Community claims (totaling $20,839). Dextrose prolotherapy is also commonly used in practice outside of VA care, but the total costs and utilization in non-VA settings are difficult to ascertain as these procedures are not covered by major health insurers and there is no corresponding Current Procedural Terminology (CPT) code for it.

CURRENT REVIEW

VA Pain Management, Opioid Safety and Prescription Drug Monitoring Program, and VA Physical Medicine and Rehabilitation are coleading an Integrated Project Team (IPT) to develop VA practice recommendations on injection therapies for musculoskeletal pain conditions. To support these efforts, they requested this evidence report on the effects of dextrose prolotherapy. Evaluation of the current evidence for dextrose prolotherapy is also needed to guide future research in this area.

In this systematic review, we synthesize evidence on the benefits and harms of dextrose prolotherapy for a range of musculoskeletal pain conditions, including knee osteoarthritis, plantar fasciitis, shoulder pain, lateral elbow tendinopathy, chronic low back pain, and pain due to temporomandibular joint (TMJ) dysfunction. Findings within each pain condition are provided separately for different comparators (*eg*, normal saline or corticosteroid injections).

The a priori protocol for this review was registered on the PROSPERO international prospective register of systematic reviews (CRD42024531179). We searched MEDLINE, Embase, and Scopus databases from inception to February 2024, using key words and subject headings for dextrose prolotherapy and musculoskeletal pain conditions (*eg*, prolotherapy, regenerative injection, dextrose or glucose injection for joint or back conditions). Additional citations were identified from consultation with content experts. We also searched clinicaltrials.gov for recently completed and ongoing trials.

Eligible studies evaluated hypertonic dextrose prolotherapy injections for treatment of acute or chronic musculoskeletal pain in outpatient settings. Eligible outcomes of interest were pain-related functioning or interference, physical performance (*eg*, gait speed, strength, range of motion), pain intensity or severity, general health-related quality of life, adverse events, costs, and treatment burden. Studies were required to be randomized controlled trials (RCTs); observational cohorts with ≥ 1 concurrent comparator group; or a single-arm observational cohort (only if including ≥ 100 participants and reporting results on adverse events).

Abstracted data included participant characteristics and eligibility criteria, intervention characteristics (*eg*, content and location of injections, content of exercise programs, frequency, duration), study design and settings, and findings for outcomes of interest, as noted above. For synthesis of findings, we first grouped studies by pain condition (*eg*, knee osteoarthritis, shoulder pain, plantar fasciitis) and then by intervention and comparator characteristics. We conducted meta-analyses when there were ≥3 studies for a given pain condition that evaluated sufficiently similar interventions and comparators, and reported the same outcome (*eg*, comparable measures of pain-related functioning or interference). Otherwise, we provided narrative syntheses of study characteristics and findings. For efficacy outcomes, we focused on between-group comparisons of the mean scores at follow-up time points. When summarizing whether individual studies reported meaningful differences between groups, we compared the study findings against the minimal clinically important difference (MCID), whenever we were able to locate a suitable published reference for MCID. For effect measures without published MCID references, we used statistical significance as reported by the included studies to determine if there were any between-group differences.

With input from IPT members, we prioritized 4 outcomes for certainty of evidence (COE) assessments. The top 3 prioritized efficacy outcomes were pain-related functioning or interference, physical performance, and quality of life. As evidence on adverse events is crucial for weighing the balance of risks and benefits, we also rated COE for adverse events. We assessed COE separately for dextrose prolotherapy compared with different treatments (*eg*, corticosteroid injections or exercise) when there were at least 2 studies evaluating the same comparison. We also separately assessed COE for outcomes at short-term (3-6 weeks), medium-term (3-4 months), and long-term (≥ 6 months) follow-up.

We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology to rate overall COE as high, moderate, low, or very low. We systematically evaluated 5 domains: study limitations (risk of bias [RoB]), imprecision (limitations in precision of effect estimates), inconsistency (in direction and magnitude of effects across studies), indirectness (applicability of the results), and other considerations (including publication bias). For imprecision, we also considered the optimal information size (OIS) for efficacy outcomes and adverse events.

ES Table. GRADE Certainty of Evidence Ratings: Definitions and Recommended Statements

Certainty of Evidence	Rating Definition	Recommended Statements ("What Happens")
High	We are very confident that the true effect lies close to that of the estimate of the effect.	*Intervention reduces/increases/improves outcome.* *Intervention results in little to no difference in outcome.*
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	*Intervention probably reduces/increases/improves outcome.* *Intervention probably results in little to no difference in outcome.*
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.	*Intervention may reduce/increase/improve outcome.* *Intervention may result in little to no difference in outcome.*
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.	*The evidence is very uncertain about the effect of intervention on outcome.*

From 4,742 unique citations, we identified 91 eligible articles reporting 90 unique primary studies (80 RCTs, 10 observational studies). Eligible studies addressed a variety of musculoskeletal pain conditions, with a quarter focused on knee pain from osteoarthritis ($k = 22$). Nearly a fifth of studies evaluated dextrose prolotherapy for TMJ dysfunction ($k = 16$), while remaining studies addressed shoulder pain ($k = 12$), lateral elbow tendinopathy ($k = 11$), low back pain ($k = 9$), plantar fasciitis ($k = 8$), and a variety of other conditions ($k = 12$ single studies of different conditions such as fibromyalgia or patellar tendinopathy). We also found 49 underway or completed studies without publications.

There was wide variation in the dextrose concentration used, as well as the number of injection treatment sessions (range = 1-6) and the overall duration of treatment (up to 5 months). Most studies did not use imaging guidance ($k = 57$), while a third used ultrasound guidance ($k = 30$). There were also a wide variety of comparators examined, with the most common being normal saline or water ($k = 25$) and corticosteroid injection ($k = 14$).

Most studies assessed pain-related functioning or interference ($k = 62$) and pain intensity or severity ($k = 70$); fewer evaluated adverse events ($k = 54$) or physical performance ($k = 42$). Half of all studies were very small ($k = 41$ with total $N \leq 50$), and only 17 studies had total $N > 100$. Nearly all studies were conducted outside of the US ($k = 83$). Most studies included middle-aged adults ($k = 71$) and half were majority women ($k = 45$). Nearly half of studies were rated high RoB ($k = 36$ RCTs) or serious/critical ($k = 7$ observational studies). Only 10 studies were assessed as low RoB, and the remaining studies were rated either some concerns or moderate RoB ($k = 37$).

Key Question (KQ) 1: What Are the Benefits and Harms of Dextrose Prolotherapy for Acute and Chronic Musculoskeletal Pain?

For knee osteoarthritis, we identified 13 RCTs that evaluated intra- or extra-articular dextrose prolotherapy interventions (range = 10-25% dextrose), and 9 studies ($k = 8$ RCTs, $k = 1$ observational

study) that employed combined intra- and extra-articular dextrose injections (range 5-25% dextrose). A third of studies used imaging guidance. Three RCTs compared intra-articular dextrose prolotherapy with normal saline or water injections, and overall, dextrose prolotherapy probably has little to no benefit for pain-related functioning or physical performance at short, medium, and long-term follow-up. Dextrose prolotherapy also had little to no effect on health-related quality of life at long-term follow-up, compared with normal saline injection. Three RCTs evaluated dextrose prolotherapy against platelet-rich plasma (PRP), and the evidence is very uncertain at short and long-term follow-up for pain-related functioning. Dextrose prolotherapy may result in little to no difference in pain-related functioning at medium-term follow-up, compared with PRP. Two RCTs compared dextrose with ozone injection, and overall, dextrose prolotherapy may have little to no benefit for pain-related functioning. The evidence is very uncertain on adverse effects of intra-articular dextrose prolotherapy, compared with other treatments. Two RCTs compared intra- versus extra-articular dextrose prolotherapy, and there is probably little to no difference in pain-related functioning between these injection locations. The remaining RCTs used a variety of other comparators, including hyaluronic acid (HA), PT, autologous conditioned serum, erythropoietin, and pulsed radiofrequency waves.

Among the 9 studies that evaluated combined intra- and extra-articular dextrose injections for knee osteoarthritis, 7 used PT and/or home exercise programs as at least 1 of the comparators. The evidence is very uncertain for the effects of dextrose prolotherapy on pain-related functioning and physical performance at short and medium term, compared with PT/home exercise program, but it may improve these outcomes in the long term. Two of these studies also included normal saline injection as a comparator, and similarly, the evidence is very uncertain for effects on pain-related functioning in the short and medium term, but dextrose prolotherapy may have benefits in the long term. The evidence is very uncertain on adverse effects of combined intra and extra-articular dextrose prolotherapy, compared with either PT/home exercise, or normal saline injection. Remaining comparators examined included HA, corticosteroid, and ozone injections.

For plantar fasciitis, 8 eligible RCTs compared dextrose prolotherapy (range = 3.5-27% dextrose) with normal saline injection ($k = 2$), corticosteroid injection ($k = 2$), extracorporeal shock wave therapy (ESWT, $k = 2$), and a variety of other treatments. Most studies employed imaging guidance for dextrose injections. Dextrose prolotherapy may improve pain-related functioning at short- and medium-term follow-up, compared with normal saline injection, but compared with corticosteroid injection, the evidence is very uncertain for pain-related functioning, and there may be little to no difference in health-related quality of life. The evidence is also very uncertain on benefits of dextrose prolotherapy compared with ESWT. The evidence is very uncertain on adverse effects of dextrose prolotherapy, compared with any of these treatments.

We also identified 12 RCTs that evaluated dextrose prolotherapy (range = 13.5-25% dextrose) for shoulder pain due to either mixed rotator cuff pathology and/or subacromial bursitis ($k = 8$) or specifically supraspinatus tendinopathy ($k = 4$). Each study in the latter group used a different comparator (PRP, corticosteroid, PT, or normal saline injection). Most studies used imaging guidance for dextrose injections. In studies addressing shoulder pain due to mixed pathology, comparators were normal saline ($k = 4$), corticosteroid injection ($k = 3$), or PT/exercise programs ($k = 2$). Compared with normal saline injection, the evidence is very uncertain for pain-related functioning, and dextrose prolotherapy may have little to no benefit for physical performance. The evidence is also very uncertain on the benefits for pain-related functioning, compared with corticosteroid injection or PT/home exercise. For physical performance, dextrose prolotherapy probably results in less improvement in range of motion (*eg*, forward flexion, abduction) compared with corticosteroid

injection. Compared with PT/home exercise, the evidence varied across different timeframes: dextrose prolotherapy may have little to no benefit at short-term follow-up, but it may improve outcomes in the long term. The evidence is very uncertain for physical performance at medium-term follow-up, compared with PT/home exercise. The evidence is also very uncertain on adverse effects of dextrose prolotherapy compared with any of these treatments.

For pain due to lateral elbow tendinopathy, there were 11 RCTs that compared dextrose prolotherapy (range = 5-25% dextrose) to normal saline injection (k = 3), corticosteroid injection (k = 3), ESWT (k = 2), and a variety of other treatments (*e*g, HA and PT). Only a few studies used imaging guidance for dextrose injections. Compared with normal saline, dextrose prolotherapy may improve pain-related functioning at short- and medium-term follow-up, but it may have little to no benefit, or the evidence is very uncertain, for physical performance. Dextrose prolotherapy may also have little to no benefit for physical performance, compared with corticosteroid; the evidence is very uncertain for pain-related functioning for this comparator. The evidence is also very uncertain for pain-related functioning and physical performance, compared with ESWT. The evidence is very uncertain on adverse effects of dextrose prolotherapy, compared with any of these treatments.

For chronic low back pain, 7 studies (k = 4 RCTs, k = 3 observational studies) addressed non-specific low back pain, and 2 RCTs focused on pain due to sacroiliac joint dysfunction. Range of dextrose used was 12.5-25% and a third of studies employed imaging guidance for injections. Of studies examining non-specific low back pain, 5 administered multiple dextrose injections distributed over L4/S1 and sacroiliac areas, and 4 of these used normal saline as the comparator. Two studies on non-specific low back pain administered focal injections (either intradiscal or single-level facet capsule), compared with either corticosteroid or intradiscal electrothermal treatment. Both studies focusing on sacroiliac joint dysfunction used corticosteroid injections as the comparator. The evidence is very uncertain for pain-related functioning, compared with either normal saline or corticosteroid injections. The evidence is also very uncertain for adverse events.

Finally, 16 studies (14 RCTs, 2 observational studies) evaluated dextrose prolotherapy (range = 6.7-50% dextrose) for treatment of symptomatic TMJ dysfunction. No study used imaging guidance for dextrose injections. Half of these studies enrolled participants with normal or reduced TMJ mobility, while the other half included participants with TMJ hypermobility at baseline. For TMJ with normal or reduced mobility, 3 studies used normal saline or water as the comparator, and the remaining studies all employed different comparators (arthrocentesis and lavage, laser, arthrocentesis and HA or PRP, or occlusal splints). Studies addressing TMJ with hypermobility compared dextrose with normal saline injection (k = 3), or autologous blood injection (ABI, k = 4). One of these studies compared dextrose injections at different locations. For TMJ dysfunction with normal/reduced mobility or hypermobility, the evidence is very uncertain for pain-related functioning and physical performance, compared with normal saline or water injection. For TMJ with hypermobility, the evidence is also very uncertain for physical performance, compared with ABI. The evidence is very uncertain on adverse effects of dextrose prolotherapy, compared with any treatment.

KQ2: Do Benefits and Harms of Dextrose Prolotherapy Vary by Patient or Pain Condition Characteristics, Prior Treatment History, or Intervention Characteristics?

No study formally evaluated differences in outcomes by patient or pain condition characteristics, or prior treatment history. We did identify studies that compared different dextrose prolotherapy injection techniques or locations for knee osteoarthritis (k = 3), TMJ (k = 2), and for hip arthritis due to

developmental dysplasia ($k = 1$). There were also 4 studies that compared different dextrose concentrations for knee osteoarthritis ($k = 1$), lateral elbow tendinopathy ($k = 2$), and TMJ ($k = 1$). In general, variations in injection technique, location, or dextrose concentration had little to no impact on prioritized outcomes (pain-related functioning, physical performance, health-related quality of life, and adverse events), but there were some reported differences for reduction of pain severity.

KQ3: What Are the Costs of Dextrose Prolotherapy for Health Care Systems and Patients?

Only 2 studies addressed costs of dextrose prolotherapy treatment; both focused on health care system costs and did not address costs or treatment burden for patients or families. Neither study was conducted in the US. Yelland, 2021 reported a 3-arm RCT comparing dextrose prolotherapy versus supervised exercise program versus combination of both treatments for foot pain due to Achilles tendinosis, and found improvement in all groups in pain-related functioning over 1 year. This study was conducted in Australia and evaluated incremental cost-effectiveness ratio (ICER) in Australian dollars (A$) per additional responder. The ICER was A$1,716 per additional responder for dextrose prolotherapy, and A$1,539 per additional responder for combined dextrose and exercise. The other study examined treatment of osteochondral lesions of the talus and reported the direct cost per injection for the health care system, which was 30 Turkish lira for dextrose prolotherapy and 250 lira for PRP.

Evidence Gaps and Future Research

The evidence on efficacy and safety of dextrose prolotherapy for chronic musculoskeletal disorders is impeded by small sample sizes for most studies and a substantial number of methodological concerns (nearly half were rated high, serious, or critical RoB). There was considerable variation in intervention characteristics, cointerventions, study populations, and choice of outcome measures across studies. To provide clinically relevant interpretations, we assessed between-group differences using published MCID whenever available. The evidence suggests that efficacy of prolotherapy may be condition specific, since there was probably little to no benefit for knee osteoarthritis (for intra-articular injection compared with normal saline), but for conditions like lateral elbow tendinopathy and plantar fasciitis, there may be some benefit (also compared with normal saline). Whether specific populations and conditions benefit from dextrose prolotherapy (particularly compared with other non-surgical treatments) is an important area for future research as some patients do not have sufficient improvement with other treatments for musculoskeletal pain. There are also concerns with side effects of some recommended treatments when used chronically, and some patients may have contraindications to certain pharmacologic options.

Injection therapies for musculoskeletal pain conditions are known to have a large placebo effect that complicates their rigorous evaluation. The natural history of most of these conditions involves waxing and waning of symptoms, where patients seek medical attention during acute exacerbations of pain and pain-related disability, and then improve due to healing or homeostatic processes, lifestyle adjustments, and/or medical treatments. In a large, well-designed RCT, the rates and average timing of improvements are expected to be balanced between groups receiving interventions and comparators (including placebo when appropriate). However, small studies may not adequately achieve balance across arms on these non-intervention effects (and unmeasured confounding). Small trials are also more vulnerable to biases arising from attrition, particularly when the extent of attrition differs between groups. Furthermore, it may be challenging to maintain masking for injection interventions throughout a study, particularly when these involve multiple different injections in and around an

anatomic structure. These factors likely contributed to the low and very low COE for most findings in this report and could be addressed by larger trials with sufficient follow-up.

Inconsistency in study findings was also likely due to the wide variation in dextrose concentrations, treatment duration and number of sessions, and other differences in injection technique, even for interventions addressing the same condition. Some of this variation may be clinically reasonable and expected due to differences in location of maximal pain for the affected joint or area, and factors like patient tolerance. In addition, and as customary in the overall treatment of musculoskeletal pain, there was no standardization of cointerventions or treatment algorithms that specified which options would be tried in sequence or concurrently. It is also possible that some cointerventions (*eg*, home exercise therapy) may be synergistic or antagonistic with the effects of the primary interventions being examined. All of these factors added to the challenges in interpretation of study findings and should be more systematically addressed in future studies.

Only 2 included studies reported on treatment costs for health care systems, and none evaluated cost and burden for patients. These are important considerations for both health care payors, facilities, and patients, particularly given the chronic nature of most musculoskeletal pain conditions. There are likely differences in costs and treatment burden between the wide variety of non-surgical treatment options and dextrose prolotherapy, which all involve somewhat different resource needs for health care facilities and clinician training, as well as demands on patient time and other potential access barriers. In terms of injection therapies, the number and frequency of treatment sessions, as well as any additional clinician education, would be important factors for health care facility resource needs. Future studies of dextrose prolotherapy for musculoskeletal pain conditions should include quantitative and qualitative assessments of the costs and treatment burden for health care systems and patients.

Included studies largely did not use clear and systematic methods to evaluate adverse events for dextrose prolotherapy and comparators. This is an essential gap for future research to address because this information will inform clinician decision-making, promote shared decision-making, and potentially impact prioritization of limited medical resources. Trials should assess adverse events for each treatment arm using open-ended questions and/or checklists administered to all participants on a regular basis. Additionally, studies should clearly define the severity of adverse events (*eg*, serious events can be defined as life threatening, requiring hospitalization, or resulting in persistent disability) and rates of events that led to discontinuation of the treatment. Evaluation of adverse events will also require larger studies for the different musculoskeletal pain conditions, since there is a strong possibility that some effects will be variable across conditions.

In summary, future studies of prolotherapy should be of sufficient size and methodological quality to systematically assess efficacy relative to currently recommended conservative treatments, as well as an appropriate placebo control given the strong placebo effect associated with injection therapies. More work is also needed to evaluate adverse events, cost, and treatment burden.

Implications for Policy and Practice

Regarding efficacy, dextrose prolotherapy appeared to have differential effects across different musculoskeletal pain conditions. Intra-articular dextrose prolotherapy probably had little to no benefit in pain-related functioning or physical performance for knee osteoarthritis, compared with normal saline injections. But evidence suggested benefits for plantar fasciitis and lateral elbow tendinopathy, compared with normal saline. In contrast, our findings indicated that for shoulder pain, dextrose prolotherapy probably led to worse physical performance outcomes, compared with corticosteroid

injections. Therefore, these observations should be explored more thoroughly in well designed and rigorous clinical trials that compare dextrose prolotherapy with other common conservative interventions for these pain conditions. The VA may be uniquely qualified and capable of undertaking these clinical investigations, as pharmaceutical companies are less likely to make the research investments needed to demonstrate the safety and efficacy of an inexpensive, non-proprietary, and easily accessible medication.

Generally, our findings indicate the evidence is very uncertain for adverse effects of dextrose prolotherapy, and more research is needed to establish the safety of these procedures. Most studies were small ($N < 100$) and thus of insufficient size to evaluate infrequent but potentially important adverse effects. Additionally, many did not systematically evaluate or report adverse events.

CONCLUSIONS

Intra-articular dextrose prolotherapy probably had little to no benefit for pain-related functioning or physical performance in knee osteoarthritis, compared with normal saline injections. For shoulder pain due to mixed bursitis and rotator cuff pathology, dextrose prolotherapy probably resulted in worse physical performance outcomes, compared with corticosteroid injections. However, dextrose prolotherapy may improve pain-related functioning for lateral elbow tendinopathy and plantar fasciitis, compared with normal saline injection. Evidence on adverse events was generally lacking and severely limited by methodological concerns. The evidence was also very uncertain on the benefits of prolotherapy compared with other treatments or for other pain conditions. Given the lack of efficacious therapies for musculoskeletal pain conditions, and interest in potential benefits of dextrose prolotherapy, future high-quality RCTs are needed to better understand the benefits and harms for this treatment.

Main Report

Evidence Synthesis Program

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ABBREVIATIONS TABLE

Abbreviation	Definition
ACL	Anterior cruciate ligament
ACR	American College of Radiology
ACR	American College of Rheumatology
ACS	Autologous conditioned serum
ADD	Anterior displacement difference
ADL	Activities of daily living
AE	Adverse effect/event
AOS	Ankle Osteoarthritis Scale
ASES	American Shoulder and Elbow Surgeons Standardized Shoulder Assessment
BMI	Body mass index
cc	Cubic centimeter
COE	Certainty of evidence
DASH	Disabilities of the Arm, Shoulder, and Hand Questionnaire
DDH	Development dysplasia of the hip
DHI	Duruoz Hand Index
dl	Deciliter
DMSO	Dimethyl sulfoxide
DPQ	Dallas Pain Questionnaire
ESWT	Extracorporeal shockwave therapy
EuroQol-5D	European Quality of Life-5 Dimensions
FAAM-ADL	Foot and Ankle Ability Measure-Activities of Daily Living
FAAM-S	Foot and Ankle Ability Measure-Sports
FAOS	Foot and Ankle Outcome Score
FFI	Foot Function Index
FIQR	Revised Fibromyalgia Impaction Questionnaire
G	Gauge
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HA	Hyaluronic acid
HAQ-DI	Health Assessment Questionnaire Disability Index
HD	Hypertonic dextrose
HP	Hot pack
Hz	Hertz
IDET	Intradiscal electrothermal treatment
IU	International units
kg	Kilogram
KL	Kellgren-Lawrence
KOA	Knee osteoarthritis
KOOS	Knee Injury and Osteoarthritis Outcome Score

Abbreviation	Definition
KPS	Knee Pain Scale
LDLPC	Left dorsolateral prefrontal cortex
m	Meters
MCID	Minimal clinically important difference
mg	Milligram
MHz	Megahertz
ml	Milliliter
mm	Millimeters
mo	Month(s)
mOsm	Osmotic concentration
MOXFQ	Manchester-Oxford Foot Questionnaire
MRI	Magnetic resonance imaging
NA	Not applicable
NR	Not reported
NRS	Numeric rating scale
NS	Not significant
NSAIDs	Non-steroid anti-inflammatory drugs
OA	Osteoarthritis
ODI	Oswestry Disability Index
OKS	Oxford Knee Score
OSD	Osgood-Schlatter Disease
PRP	Platelet rich plasma
PrT	Prolotherapy
PRTEE	Patient-Rated Tennis Elbow Evaluation
PT	Physical therapy
PWRE	Patient Rated Wrist Evaluation
QoL	Quality of life
Quick DASH	Shortened version of DASH
RA	Rheumatoid arthritis
RC	Rotator cuff
RCT	Randomized controlled trial
RMDQ	Roland-Morris Disability Questionnaire
RoB	Risk of bias
ROM	Range of motion
rTMS	Repetitive transcranial magnetic stimulation
s	Seconds
SD	Standard deviation
SF-36	Short Form Survey (36 items)
SLE	Systemic lupus erythematosus
SMD	Standardized mean difference

Abbreviation	Definition
SPADI	Shoulder Pain and Disability Index
TENS	Transcutaneous electrical nerve stimulation
THA	Total hip arthroplasty
TUG	Timed Up and Go
U	Units
US	ultrasound
VAS	Visual analog scale
VISA-A	Victorian Institute of Sport Assessment-Achilles
VISA-P	Victorian Institute of Sport Assessment (VISA) Questionnaire, Patellar Tendon
vol	Volume
WDI	Waddell Disability Index
wk	Week(s)
WOMAC	Western Ontario and McMaster Universities Arthritis index
WORC	Western Ontario Rotator Cuff index
yr	Year

BACKGROUND

Musculoskeletal diseases are the most common reason for chronic pain among adults in the US.[1] Osteoarthritis is the most common musculoskeletal disease globally, impacting nearly 8% of the world's population (595 million individuals).[2] Osteoarthritis is a degenerative condition that generally affects older adults and is a leading cause of pain and disability in this population.[3-7] Rates of osteoarthritis are increasing in the US due to an aging population and the increased prevalence of obesity.[8] The knee is the most commonly afflicted joint, affecting an estimated 14 million US adults,[9] and knee osteoarthritis is also responsible for the largest proportion of economic costs and disability related to osteoarthritis.[10,11] Beyond osteoarthritis, other joint and peri-articular conditions are also common and have substantial associated morbidity. For example, shoulder pain due to various etiologies accounts for 16% of musculoskeletal complaints in US primary care patients,[12] and heel pain from plantar fasciitis has a lifetime incidence of 10% among US adults.[13]

Musculoskeletal pain conditions are often challenging for patients and clinicians, which in turn drives demand and utilization of health care services. The breadth of available treatments includes non-pharmacological interventions (*eg,* physical therapy), topical and oral systemic pharmacologic therapies, localized injection therapies, and surgical procedures. Most of these treatments address symptoms such as pain and joint instability, but do not alter disease progression. Furthermore, disease severity based on imaging findings (*eg*, for knee osteoarthritis) often does not correspond with patient-reported symptoms (*eg*, pain and functioning), adding to the complexity of clinical management.[14] For patients who have insufficient symptom improvement from non-pharmacologic, and topical and/or systemic pharmacologic treatments, targeted injection therapies are often offered before more invasive surgical procedures. Additionally, surgery may not be the best option for certain patients due to a variety of factors, such as the expected improvement versus risks from surgery and patient preferences.[15-17]

Prolotherapy involves injecting an irritant solution into an affected joint and/or connective tissues to improve musculoskeletal pain and function.[18] The true physiologic effects are not well understood but the putative mechanism involves eliciting a low-grade inflammatory response that stimulates the natural healing process of connective tissue and potentially alters pain perception pathways. Hypertonic dextrose is the most commonly utilized type of prolotherapy solution, and its use was first reported by Hackett et al. nearly 70 years ago.[19] Current prolotherapy solutions differ both in the concentration of dextrose and the inclusion of other chemicals. Moreover, dextrose prolotherapy interventions vary in the number and duration of injection treatments, the anatomic locations, injection techniques, and use of imaging guidance, even for interventions used to treat the same musculoskeletal pain condition.

In fiscal year 2023, a total of 1,454 dextrose prolotherapy injection procedures were administered in VA health care facilities, and there were 59 VA Care in the Community claims totaling $20,839. Dextrose prolotherapy is also commonly used in practice outside of VA care, but the total costs and utilization in non-VA settings are difficult to ascertain as these procedures are not covered by major health insurers and there is no corresponding Current Procedural Terminology (CPT) code for it.

VA Pain Management, Opioid Safety and Prescription Drug Monitoring Program (PMOP) and Physical Medicine and Rehabilitation Services (PM&RS) are coleading the development of VA practice recommendations on injection therapies for musculoskeletal pain conditions and requested this systematic review to support those effort and help guide future research. This review synthesizes

evidence on the benefits and harms of dextrose prolotherapy for a range of musculoskeletal pain conditions, including knee osteoarthritis, plantar fasciitis, shoulder pain, lateral elbow tendinopathy, chronic low back pain, and pain due to temporomandibular joint dysfunction.

METHODS

TOPIC DEVELOPMENT

The Integrated Project Team (IPT) on joint injectables for musculoskeletal pain was led by representatives from VA PMOP and Physical Medicine and Rehabilitation, and consisted of clinicians with subject matter expertise in pain treatments, including dextrose prolotherapy. This IPT served as the technical expert panel for this review. Collaboratively with the IPT, we defined the scope, formulated key questions, and determined eligibility criteria. We included a wide variety of dextrose prolotherapy interventions (concentrations, locations, and including other additives) that may be used to treat various musculoskeletal pain conditions.

REGISTRATION AND REVIEW

A preregistered protocol for this review can be found on the PROSPERO international prospective register of systematic reviews (CRD42024531179). A draft version of this report was reviewed by the IPT; their comments and author responses are located in **Appendix D**.

KEY QUESTIONS AND ELIGIBILITY CRITERIA

The following key questions (KQs) were the focus of this review:

KQ 1	What are the benefits and harms of dextrose prolotherapy for acute and chronic musculoskeletal pain?
KQ 2	Do benefits and harms of dextrose prolotherapy vary by: - Patient characteristics, - Pain condition characteristics, - Treatment history, - Treatment parameters (*eg,* concentration, number of injections, use of imaging, setting of treatment)
KQ 3	What are the costs of dextrose prolotherapy for health care systems and patients?

Study eligibility criteria are shown in the table below:

	Inclusion Criteria	Exclusion Criteria
Population	Adults (≥18 years) with acute or chronic musculoskeletal pain	<18 years old
Intervention	Dextrose prolotherapy (hypertonic, >5%)	Perineural 5% dextrose or nerve hydrodissection; spinal anesthesia (*eg*, for surgical procedures); nerve blocks
Comparator	Any	—
Outcomes	• Pain-related functioning or interference • Physical performance (*eg*, range of motion, timed up and go) • Health-related quality of life • Adverse events • Pain severity or intensity • Costs, resource use, access to care • Treatment burden (patients and caregivers)	—

	Inclusion Criteria	Exclusion Criteria
Timing	Any	—
Setting	Outpatient	Acute (hospital or emergency room)
Study Design	• RCTs • Observational studies with ≥1 concurrent comparator group(s) • Cohorts with *N* ≥ 100, if reporting adverse events	Systematic reviews, study protocols, case reports, letters, conference abstracts, editorials, non-English studies (of any type), pre-clinical studies (in vitro or animal studies)

Abbreviations. RCT=randomized controlled trial.

SEARCHING AND SCREENING

We searched MEDLINE, Embase, and Scopus databases from inception to February 2024, using key words and subject headings for dextrose prolotherapy for musculoskeletal conditions (*eg*, *prolotherapy, regenerative injection, dextrose or glucose injection for joint or back conditions*; see **Appendix A** for complete search strategies). Additional citations were identified from consultation with content experts. We also searched clinicaltrials.gov for recently completed and ongoing trials. For completed trials, we looked for publications associated with these trials using the protocol title, investigator names, and locations. Ongoing and completed trials without identified publications are noted in **Appendix B**.

Duplicate search results were removed, and abstracts were screened using DistillerSR version 2.35.[20] Exclusion of abstracts required agreement of 2 reviewers. Included abstracts underwent full-text review by 2 individuals, with eligibility decisions requiring consensus of both reviewers.

DATA ABSTRACTION AND RISK OF BIAS ASSESSMENT

Data abstraction was completed by 1 reviewer and verified by a second reviewer. Abstracted data included participant characteristics and inclusion/exclusion criteria, intervention characteristics (*eg*, content and location of injections, content of exercise programs, frequency, duration), study design and settings, and findings for eligible outcomes, as noted above. If findings were only reported in figures, we used PlotDigitizer to extract data from figures, per recommended practices.[21]

Risk of bias (RoB) assessments were conducted independently by 2 researchers, and discrepancies were resolved by consensus or with a third reviewer. RCTs were assessed with Cochrane Risk of Bias 2.0[22] and comparative cohort studies with the Cochrane Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I).[23] The 1 pre-post observational study was evaluated using the Joanna Briggs Institute Critical Appraisal Tool for Cohort Studies.[24] RoB ratings per domain and overall are provided for each eligible study in **Appendix E.**

SYNTHESIS

We first grouped studies by pain condition (*eg*, knee osteoarthritis, shoulder pain, plantar fasciitis) and then by intervention and comparator characteristics. For efficacy outcomes, we focused on between-group comparisons of the mean scores at follow-up time points, which we used to calculate bias-adjusted standardized mean differences (SMDs; Hedges' g). When evaluating whether individual studies reported meaningful differences between groups, we compared the study findings against the minimal clinically important difference (MCID) whenever we were able to locate a suitable published reference for MCID. We required that the MCID reference evaluated a similar participant population

(who were undergoing non-surgical treatments) and conducted rigorous determinations using anchor-based methods (*eg*, assessed specificity and sensitivity of MCID thresholds). For effect measures without published MCID references, we used statistical significance as reported by the included studies to determine if there were any differences. Description of outcome measures used by included studies, as well as MCID (if available) is provided in Table 1.

Table 1. Outcome Measures Reported by Included Studies

Outcome Category	Measure Name	Minimal Clinically Important Difference (MCID)	Scoring Range # of Items and Domains
Knee Osteoarthritis and Other Knee Pain			
Pain-related functioning	WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index)	Total: 12.5 (Salehi, 2023)[25] Stiffness: 4.76 (Angst, 2018)[26] Function: 11.25 (Angst, 2018)[26]	0-96 (lower is better) 24 items (3 domains)
	OKS (Oxford Knee Score)	6.1 (Martín-Fernández, 2017)[27]	0-48 (higher is better) 12 items
	KOOS (Knee injury and Osteoarthritis Outcome Score)	ADL: 2.5 (Mills, 2016)[28] QoL: 6.5 (Mills, 2016)[28]	Scored by domain: ADL 0-100 (higher is better), 17 items QoL 0-100 (higher is better), 4 items
	VISA-P (Victorian Institute of Sport Assessment-Patella)	13 (Hernandez-Sanchez, 2014)[29]	0-100 (higher is better) 8 items
Physical performance	TUG (Timed Up and Go)	No MCID	Normal range varies by age (<10 s for age <80 years old)
	Isometric strength	No MCID	Variable
	ROM (Range of Motion)	No MCID	Variable
Health-related quality of life	EuroQol 5D-3L (European Quality of Life – 5 Dimensions)	No MCID	0-1 (higher is better)
Pain severity or intensity	WOMAC Pain	Pain: 7.09 (Angst, 2018)[26]	Pain 0-20 (lower is better) 5 items
	NRS (Numerical Rating Scale)	1.0 (Salaffi, 2004)[30]	0-10 (lower is better)
	VAS (Visual Analog Scale)	No MCID	0-10 (lower is better)
Plantar Fasciitis and Other Foot Pain			
Pain-related functioning	AOS (Ankle Osteoarthritis Scale)	No MCID	0-100 (lower is better)
	FAAM (Foot and Ankle Ability Measure)	ADL: 8 (Martin, 2005)[31] Sports: 9 (Martin, 2005)[31]	Only scored by domain: ADL 0-84 (higher is better), 29 items Sports 0-32 (higher is better), 8 items
	FAOS (Foot and Ankle Outcome Score)	No MCID	0-100 (higher is better)
	FFI (Foot Function Index)	No MCID	0-100 (lower is better)

Outcome Category	Measure Name	Minimal Clinically Important Difference (MCID)	Scoring Range # of Items and Domains
	MOXFQ (Manchester-Oxford Foot Questionnaire)	No MCID	0-80 (lower is better) 16 items (3 domains)
Health-related quality of life	SF-36 Physical & Mental Component Scores	No MCID	0-100 (higher is better)
Pain severity or intensity	NRS	1.0 (Salaffi, 2004)[30]	0-10 (lower is better)
	VAS	No MCID	0-10 (lower is better)
Shoulder and Elbow Pain			
Pain-related functioning	ASES (American Shoulder and Elbow Surgeons Score)	No MCID	0-100 (higher is better) 13 items (2 domains)
	DASH (Disabilities of the Arm, Shoulder, and Hand Questionnaire)	10.83 (Franchignoni, 2014)[32]	0-100 (lower is better) 30 items
	Quick DASH	15.91 (Franchignoni, 2014)[32]	0-100 (lower is better) 11 items
	SPADI (Shoulder Pain and Disability Index)	8.0 (Paul, 2004)[33]	0-130 (lower is better) 13 items (2 domains)
	WORC (Western Ontario Rotator Cuff Index)	No MCID	0-2100 (lower is better) 21 items (5 domains)
	PRTEE (Patient-rated Tennis Elbow Evaluation)	7 (Poltawski, 2011)[34]	0-100 (lower is better) 15 items (2 domains)
Physical performance	ROM	No MCID	Variable normal range
	Grip strength	No MCID	Variable normal range
Health-related quality of life	EuroQol 5D-3L (European Quality of Life – 5 Dimensions)	No MCID	0-1 (higher is better)
Pain severity or intensity	NRS	1.0 (Salaffi, 2004)[30]	0-10 (lower is better)
	VAS	No MCID	0-10 (lower is better)
Chronic Low Back Pain			
Pain-related functioning	ODI (Oswestry Disability Index)	9.5 (Monticone, 2012)[35]	0-100 (lower is better) 10 items
	RMDQ (Roland-Morris Disability Index)	2.5 (Monticone, 2012)[35]	0-24 (lower is better) 24 items
	DPQ (Dallas Pain Questionnaire)	No MCID	Scored by domain: ADL 0-100 (lower is better) 7 items Work/Leisure 0-100 (lower is better) 3 items
Health-related quality of life	SF-12 Physical & Mental Component Scores	Physical: 3.29 (Díaz-Arribas, 2017)[36] Mental: 3.77 (Díaz-Arribas, 2017)[36]	0-100 (higher is better)
	Isometric strength	No MCID	Variable normal range

Outcome Category	Measure Name	Minimal Clinically Important Difference (MCID)	Scoring Range # of Items and Domains
Physical Performance	ROM	No MCID	Variable normal range
Pain severity or intensity	NRS	2.4 (van der Roer, 2006)[37]	0-10 (lower is better)
	VAS	No MCID	0-10 or 0-100 (lower is better)
Temporomandibular Joint Dysfunction and Pain			
Pain-related functioning	NRS-Dysfunction (Numerical Rating Scale-Dysfunction)	No MCID	0-10 (lower is better)
Physical performance	MMO (maximum mouth opening)	No MCID	35-55 mm
Pain severity or intensity	NRS	No MCID	0-10 (lower is better)
	VAS	No MCID	0-10 (lower is better)
Other Pain Conditions			
Pain-related functioning	PRWE (Patient Rated Wrist Evaluation)	No MCID	0-100 (lower is better)
	HAQDI (Health Assessment Questionnaire Disability Index)	No MCID	0-3 (lower is better)
	DHI (Duruoz Hand Index)	No MCID	0-90 (lower is better) 18 items
	FIQR (Fibromyalgia Impact Questionnaire, Revised)	No MCID	0-100 (lower is better) 21 items (3 domains)
	VISA-A (Victorian Institute of Sport Assessment-Achilles)	No MCID	0-100 (higher is better) 9 items (3 domains)
Physical performance	Grip strength	No MCID	Variable normal range
	ROM	No MCID	Variable normal range
	Lateral pinch strength	No MCID	Variable normal range
Pain severity or intensity	VAS	No MCID	0-10 or 0-100 (lower is better)

Abbreviations. ADL=activities of daily living; MCID=minimal clinically important difference; QoL=quality of life.

We conducted meta-analyses when there were ≥3 studies for a given pain condition that evaluated sufficiently similar interventions and comparators, and reported the same outcome (*eg*, comparable measures of pain-related functioning or interference). Otherwise, we provided narrative syntheses of study characteristics and findings. For meta-analyses, we used random-effects models (with Hartung–Knapp-Sidik–Jonkman estimator) due to the anticipated heterogeneity in effects arising from variation in patient populations, clinical settings, and other study characteristics.

We assessed statistical heterogeneity using visual inspection of forest plots, τ^2, and 95% prediction intervals (PIs). PIs describe the likeliest range of true effects (*eg*, true differences in pain-related functioning between study groups) across studies and provide an estimate of the magnitude and direction of associations that would be found in future studies similar to those included in a synthesis. PIs encompassing values similar to the overall estimate suggest limited heterogeneity, whereas PIs that

include estimates in the same direction as the overall estimate but that vary widely in magnitude (*eg*, small to large positive SMDs) suggest moderate heterogeneity. If the PI encompasses estimates that range widely in both magnitude and direction, then substantial heterogeneity is likely present. We planned to assess publication bias using funnel plots if there were ≥10 sufficiently similar studies (according to considerations described above). We used *meta* and *metafor* packages and R version 4.3.1 to conduct meta-analyses and generate forest plots.[38]

Certainty of Evidence

We prioritized 4 outcomes for certainty of evidence (COE) assessments, with input from IPT members. Before analysis and synthesis of eligible study findings, we met with the IPT to discuss prioritization of outcomes for COE assessments and, after the meeting, conducted an online survey requesting ranking of the outcomes into the top 3 for importance (*ie*, indicate which outcome is first, second, or third, from among the eligible outcomes). The top 3 prioritized outcomes were pain-related functioning or interference, physical performance, and quality of life. As evidence on adverse events is necessary for weighing the balance of risks and benefits, we also rated COE for adverse events. We assessed COE separately for dextrose prolotherapy compared with different treatments (*eg*, corticosteroid injections or exercise), when there were at least 2 studies evaluating the same comparison. Additionally, we separately assessed COE for outcomes at short-term (3-6 weeks), medium-term (3-4 months), and long-term (≥6 months) follow-up. We took into consideration that dextrose prolotherapy is often initially painful over first 1-2 weeks (thought due to activation of inflammatory pathways) and then potentially improves healing thereafter, which would take additional weeks. Furthermore, comparator injections (*eg*, corticosteroids) are often evaluated for clinical efficacy over a period of several months. Thus, we set the short-term interval at a time when we could reasonably expect any improvement with prolotherapy, and then the medium timeframe comparable to other treatments in terms of a reasonable duration of effect. Lastly, we determined that efficacy at 6 months or longer would be an important potential difference from improvements that only lasted 3-4 months.

We used Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology to rate overall COE as high, moderate, low, or very low (**Table 2**).[39,40] Briefly, for each prioritized outcome, we used GRADEpro Guideline Development Tool (GDT)[40] to systematically evaluate 5 domains: study limitations (risk of bias), imprecision (limitations in precision of effect estimates), inconsistency (in direction and magnitude of effects across studies), indirectness (applicability of the results), and other considerations (including publication bias). For imprecision, we also considered the optimal information size (OIS),[41] but used a different approach for efficacy outcomes and adverse events because the former were continuous measures while the latter were usually reported as counts (or participants). For efficacy outcomes, we determined the sample size needed (for 2-tailed $\alpha = 0.05$ and $\beta = 0.2$) to detect either: 1) the MCID (when available) converted to SMD using reported standard deviations (SD), or 2) an SMD of 0.7-0.8 (when there was no established MCID). In these latter cases, we elected to use SMD (for ~large effect size) because our experience with calculating SMD derived from available MCID was that these generally gave SMD in this range or higher. Additionally, in studies where authors described sample size calculations, the targeted SMD was always large (or very large) effect sizes. For adverse events, we applied OIS by considering the minimum detectable event rate using the sample size of the dextrose prolotherapy arm. We downgraded 2 levels if the minimum detectable rate was ≥ 20%, and 1 level if this was ≥ 10%.

Table 2. GRADE Certainty of Evidence Ratings: Definitions and Recommended Statements[39,40]

Certainty of Evidence	Rating Definition	Recommended Statements ("What Happens")
High	We are very confident that the true effect lies close to that of the estimate of the effect.	*Intervention reduces/increases/improves outcome.* *Intervention results in little to no difference in outcome.*
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	*Intervention probably reduces/increases/ improves outcome.* *Intervention probably results in little to no difference in outcome.*
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.	*Intervention may reduce/increase/improve outcome.* *Intervention may result in little to no difference in outcome.*
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.	*The evidence is very uncertain about the effect of intervention on outcome.*

RESULTS

LITERATURE OVERVIEW

We screened 4,742 unique citations and reviewed the full texts for 171 publications (**Figure 1**). Of these, we identified 91 eligible articles reporting 90 unique primary studies (80 RCTs, 10 observational studies). A full list of studies excluded at full-text review is provided in **Appendix C**. Eligible studies addressed a variety of musculoskeletal pain conditions, with about a quarter focused on knee osteoarthritis ($k = 22$). Nearly a fifth of studies evaluated dextrose prolotherapy for temporomandibular joint (TMJ) dysfunction ($k = 16$), while remaining studies addressed shoulder pain ($k = 12$), pain due to lateral elbow tendinopathy ($k = 11$), low back pain ($k = 9$), plantar fasciitis ($k = 8$), and a variety of other conditions ($k = 12$ single studies of different conditions like fibromyalgia or patellar tendinopathy). We also found 49 underway or completed studies without publications (**Appendix B**).

Figure 1. Literature Flow Diagram

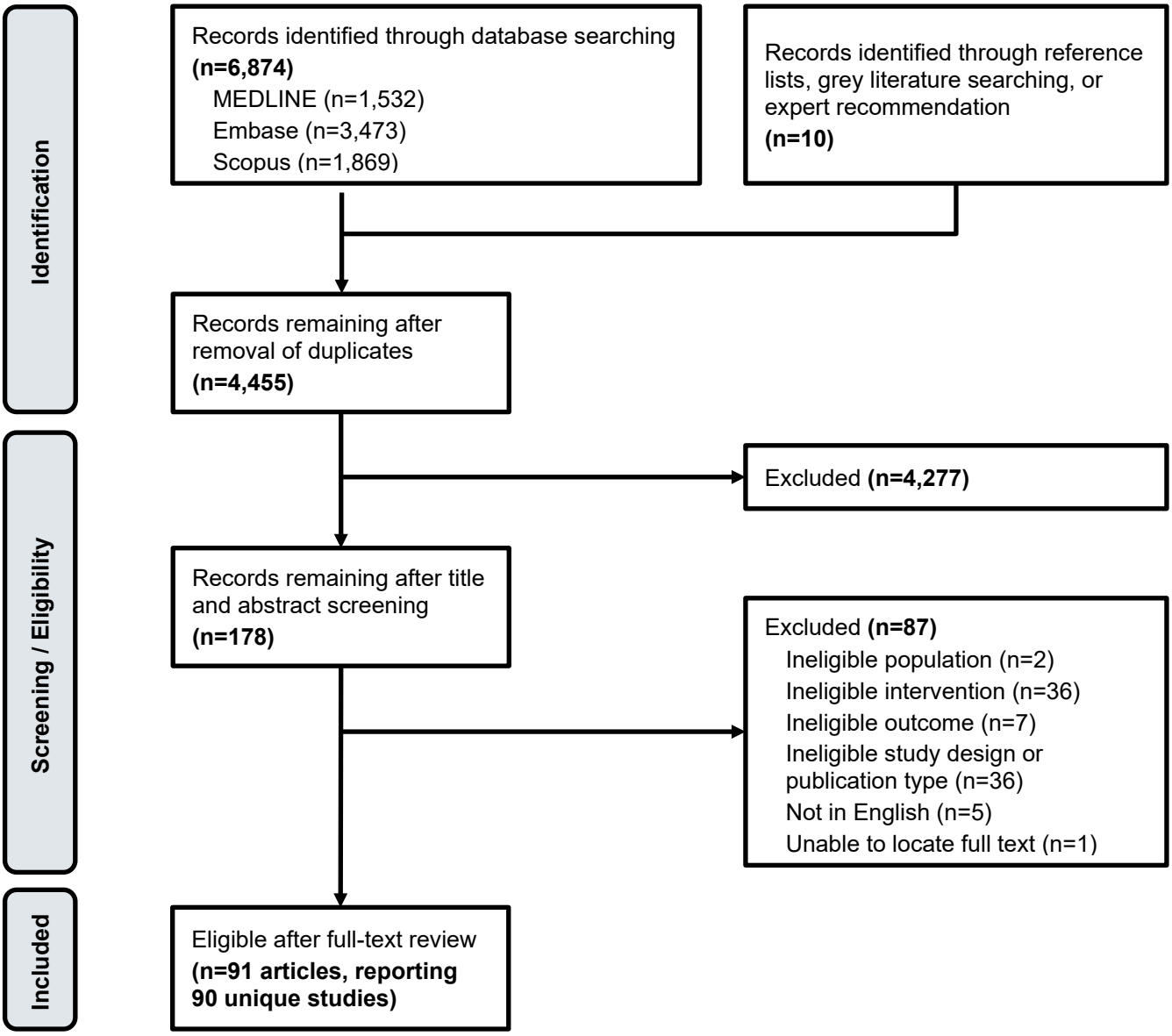


Table 3 provides summary characteristics for all eligible studies, categorized by pain condition. There was wide variation in the dextrose concentration used, as well as the number of injection treatment sessions (range = 1-6) and the overall duration of treatment (up to 5 months). Most studies did not use imaging guidance ($k = 57$), while a third used ultrasound guidance ($k = 30$). There were also a wide variety of comparators examined, with the most common being normal saline or water ($k = 25$) and corticosteroid injection ($k = 14$).

Most studies assessed pain-related functioning or interference ($k = 62$) and pain intensity or severity ($k = 70$); fewer evaluated adverse events ($k = 54$) or physical performance ($k = 42$). Half of all studies were very small ($k = 41$ with total $N \leq 50$), and only 17 studies had total $N > 100$. Nearly all studies were conducted outside of the US ($k = 83$). Most studies included middle-aged adult participants ($k = 71$) and half were majority women ($k = 45$). Nearly half of studies were rated high RoB ($k = 35$ RCTs) or serious/critical ($k = 7$ observational studies). Only 10 studies were assessed as low RoB, and the remaining studies were rated either some concerns/moderate RoB ($k = 38$). Detailed RoB ratings for all articles are provided in **Appendix E**.

Below, we provide more detailed study characteristics and findings organized by the different pain conditions being treated, beginning with knee osteoarthritis. Within each section on the different pain conditions, we describe findings by comparisons (*eg*, normal saline or corticosteroid injection comparators). For certain sections, we have further grouped findings by either the injection technique and site (*eg*, separately for intra-articular only dextrose prolotherapy for knee osteoarthritis), or greater specificity for the pain condition (*eg*, supraspinatus tendinopathy), depending on the characteristics of the studies in that section. Within each of these sections, we provide COE ratings for the 4 prioritized outcomes: pain-related functioning or interference, physical performance, health-related quality of life (QoL), and adverse events. For the section on findings for single studies of a variety of other conditions (for which COE was not assessed), we describe the study characteristics and results. Finally, we summarize the limited study findings that addressed KQs 2 and 3.

Table 3. Overview of Characteristics for Included Studies

Characteristics		Knee OA (*k* = 22)	Plantar Fasciitis (*k* = 8)	Shoulder Pain (*k* = 12)	Lateral Elbow Tendinopathy (*k* = 11)	Low Back Pain (*k* = 9)	TMJ (*k* = 16)	Other Conditions* (*k* = 12)	TOTAL (*k* = 90)
Study design	RCT	21	8	12	11	6	14	8	80
	Observational study	1	-	-	-	3	2	4	10
Risk of bias	Low	4	-	4	1	-	1	-	10
	Some concerns/moderate	4	4	6	8	4	4	8	38
	High/serious/critical	14	4	2	2	5	11	4	42
Prolotherapy duration & doses	Single treatment	2	1	7	4	3	4	4	25
	1 month (2-3 treatments)	11	3	2	1	3	5	1	26
	2 months (2-3 treatments)	5	3	3	5	2	3	5	26
	3-5 months (3-6 treatments)	4	1	-	1	1	4	2	13
Imaging guidance	Ultrasound	7	6	9	3	1	-	4	30
	Fluoroscopy	1	-	-	-	2	-	-	3
	None	14	2	3	8	6	16	8	57
Comparators	Prolotherapy: other dextrose % or location	4	-	-	1	-	3	1	9
	Normal saline or water +/- local anesthetic	5	2	4	2	5	5	2	25
	Corticosteroids injection	1	2	3	3	2	-	3	14
	Hyaluronic acid	2	-	-	1	-	1	-	4
	Autologous blood products†	2	1	2	-	-	4	1	10
	Other injectables‡	5	-	1	1	1	-	-	8
	PT or exercise program	3	1	2	1	-	-	2	9
	Other non-injectable comparator§	-	2	-	2	1	3	3	11
Outcomes reported	Pain-related functioning or interference	20	8	10	8	6	2	8	62
	Physical performance	8	-	8	7	2	16	2	42
	Health-related quality of life	3	1	-	1	2	-	-	7
	Adverse events	14	4	5	9	8	7	7	54
	Pain intensity or severity	20	7	12	2	7	15	7	70
	Costs or resource use	-	-	-	-	-	-	2	2

Characteristics		Knee OA (*k* = 22)	Plantar Fasciitis (*k* = 8)	Shoulder Pain (*k* = 12)	Lateral Elbow Tendinopathy (*k* = 11)	Low Back Pain (*k* = 9)	TMJ (*k* = 16)	Other Conditions* (*k* = 12)	TOTAL (*k* = 90)
	Treatment burden	-	-	-	-	-	-	-	0
Total participants (*N*)	<50	4	4	3	5	2	14	8	41
	50-99	12	3	7	3	3	2	3	33
	100-199	6	1	2	2	4	-	1	16
	200-300	-	-	-	1	-	-	-	1
Follow-up duration	<1 month	1	-	-	-	-	-	1	2
	1-5 months	13	6	9	6	1	6	5	45
	6-11 months	5	1	2	3	5	5	1	23
	≥12 months	3	1	1	2	3	5	5	20
Country	North America	3	-	1	2	3	1	1	11
	Europe	4	5	2	4	3	2	4	24
	Middle East	11	2	2	2	1	8	4	30
	Asia	4	1	6	2	1	4	2	20
	Australia/New Zealand	-	-	1	1	1	-	1	4
	Others	-	-	-	-	-	1	-	1
Mean/median age	<30	-	-	-	-	-	4	1	5
	30-64	19	7	11	10	9	5	10	71
	≥65	1	-	-	-	-	-	-	
	NR	2	1	1	1	-	7	1	13
% Women	<30	-	-	1	-	-	-	1	2
	30-59	7	1	7	5	5	4	1	29
	≥60	13	6	2	5	4	10	8	45
	NR	2	1	2	1	-	2	2	14

Notes. *Includes pes anserine bursitis, Osgood-Schlatter, chronic patellar tendinopathy, osteochondral lesions of the talus, hallux rigidus, Achilles tendinosis, midcarpal or scapholunate ligament laxity, OA of 1st carpometacarpal joint, bilateral hand OA, development dysplasia of the hip, Tietze syndrome, and fibromyalgia.

†Includes platelet-rich plasma, autologous blood, and autologous conditioned serum.

‡Includes botulinum toxin, erythropoietin, and ozone.

§Includes radiofrequency pulses, extracorporeal shock wave therapy, laser, occlusal splint, arthrocentesis, laser, paraffin wax, and NSAIDs.

Abbreviations. OA=osteoarthritis; NR=not reported; PT=physical therapy; RCT=randomized controlled trial; TMJ=temporomandibular joint.

KNEE OSTEOARTHRITIS

Overview

Twenty-two studies (21 RCTs, 1 observational study) evaluated the effect of dextrose prolotherapy for knee osteoarthritis. All studies required that participants met American College of Rheumatology (ACR) criteria for knee osteoarthritis and/or had evidence of arthritis on X-rays (*eg*, Kellgren-Lawrence grade ≥ 2). Most studies included middle-aged adults (k = 19 with mean ages 40-64 years), and more than half of studies included majority women participants (k = 13 with ≥ 60% women). The majority of studies were conducted in the Middle East (k = 11), with others from Asia (k = 4), Europe (k = 4), and North America (k = 3). Most studies had follow-up < 6 months (k = 13), and included small samples (eg, k = 16 for N < 100). Nearly all of the studies reported on pain-related functioning (k = 20) and pain intensity (k = 20); about half reported on adverse events (k = 14) and fewer reported on physical performance (k = 8) or health-related quality of life (k = 2). No study evaluated cost or treatment burden. Most were rated high RoB (k = 15 RCTs) or serious (k = 1 observational study); only 4 studies were rated low RoB and 3 studies were rated some concerns. Detailed RoB ratings (by domain and overall) are presented in **Appendix E**.

Below, we further describe study characteristics and findings, grouping studies according to the dextrose prolotherapy injection technique (*ie*, first studies using intra- or extra-articular injections, then those using combined intra- and extra-articular injections). Then, within each of these 2 groups, we present separately characteristics and findings for studies using different comparators (*eg*, normal saline or corticosteroid injections). We initially considered further separation into groups by dextrose concentration, but this led to most groups having only a single study when comparators were also taken into consideration. Detailed study characteristics and findings for knee osteoarthritis are found in **Appendix F**.

Intra- or Extra-Articular Dextrose Prolotherapy

Ten RCTs evaluated the effects of intra-articular dextrose prolotherapy injections (range = 10-25% dextrose), compared with a variety of other treatments including normal saline or water injection (k = 3), platelet-rich plasma (PRP; k = 3), or ozone injection (k = 2). Additional comparators evaluated in single studies were autologous conditioned serum, botulinum toxin, erythropoietin, hyaluronic acid (HA), hypertonic saline, physical therapy (PT), and pulsed radiofrequency waves (some studies had ≥2 comparators). Additionally, 2 RCTs compared intra- versus extra-articular dextrose prolotherapy injections, and 1 RCT compared extra-articular dextrose prolotherapy with intra-articular HA. Most trials (k = 9) excluded individuals who had any prior knee surgery and/or knee injections within a certain timeframe (prior 3 months to 1 year). Only 1 study required participants to have failed previous conservative treatments.[42] **Table 4** summarizes study characteristics and key findings for studies examining intra-articular dextrose prolotherapy injections.

Below, we further describe findings from studies grouped by comparisons, first for intra-articular dextrose prolotherapy versus normal saline or water injection, then separately PRP and ozone injection comparators. Next, we summarize results from comparisons of intra- versus extra-articular dextrose prolotherapy. Lastly, we briefly describe results for the comparisons with only 1 study each, including the study comparing extra-articular dextrose with intra-articular HA.

Table 4. Summary of Characteristics and Key Findings for Knee Osteoarthritis: Intra-Articular or Extra-Articular Dextrose Injections

Author, Year Study Design; RoB; Country Key Participant Characteristics	Dextrose Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance	Health-Related Quality of Life	Adverse Events
Intra-Articular Dextrose Prolotherapy versus Normal Saline or Water (With Local Anesthetic or Hyaluronic Acid)						
Hsieh 2022[43] RCT; Low; Taiwan Knee OA KL grades 2-3, no history of intra-articular knee injections of HA or prolotherapy in past 6 mo; mean ages 62-63 yrs, 77-79% female, mean BMI 26-27	25% dextrose 7 ml (+ 1% lidocaine) and HA 2 ml (10 mg/dl), ultrasound-guided *N* = 52 (52) Clinic; 3 wk (3 injections)	Normal saline 7 ml (+ 1 % lidocaine) and HA 2 ml (10 mg/dl), ultrasound-guided *N* = 52 (52) Clinic; 3 wk (3 injections)	Modified WOMAC Physical Function (1 mo)*† ↔ Dextrose-Saline Modified WOMAC Physical Function (3, 6 mo)*† ↑ Dextrose-Saline KOOS ADL (1, 6 mo) ↑ Dextrose-Saline KOOS ADL (3 mo) ↔ Dextrose-Saline KOOS Sports & Recreation (1, 3, 6 mo)† ↔ Dextrose- Saline KOOS Knee QoL (1, 3, 6 mo) ↔ Dextrose-Saline	10-m Regular Walking Speed (1 mo)† ↔ Dextrose- Saline 10-m Regular Walking Speed (3, 6 mo)† ↑ Dextrose- Saline Chair Stand Test (1, 3 mo)† ↔ Dextrose- Saline Chair Stand Test (6 mo)† ↑ Dextrose- Saline	—	*"One participant in the control group had local swelling after the third injection… No severe adverse effects occurred for both treatments"* (severe AE not defined)
Reeves, 2000[44] RCT; High; USA Knee pain ≥ 6 mo, with grade ≥ 2 joint narrowing or osteophytic change, and ACL laxity, prior therapies NR; total *N* randomized 77 (68 analyzed) but *N* per arm and demographics NR	10% dextrose 9 ml (+ 0.075% lidocaine) *N* = NR Clinic; 10 mo (6 injections)	0.075% lidocaine 9 ml *N* = NR Clinic; 4 mo (3 injections)	—	ROM (6 mo)‡ ? Dextrose-Lidocaine	—	*"Discomfort after injection did not… vary between groups…One person* [in lidocaine group] *had a flare postinjection… requiring interarticular steroid and then referral to an orthopedic surgeon… No allergic reactions or infections were noted."*

Author, Year Study Design; RoB; Country Key Participant Characteristics	Dextrose Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance	Health-Related Quality of Life	Adverse Events
Sit, 2020[45] RCT; Low; China Knee OA based on ACR criteria with knee pain for at least 3 months with a pain score of ≥3 (0–6 scale), no prior surgery and no knee injections in past 3 mo; mean ages 63-64 yrs, 71% female; mean BMI NR	25% dextrose 5 ml, ultrasound-guided *N* = 38 (38) Clinic; 16 wk (4 injections)	Normal saline 5 ml, ultrasound-guided *N* = 38 (38) Clinic; 16 wk (4 injections)	WOMAC Total (4, 6, 12 mo) ↔ Dextrose-Saline WOMAC Physical Function (4, 6, 12 mo) ↔ Dextrose-Saline	TUG (4, 12 mo)†¶ ↔ Dextrose-Saline TUG (6 mo)†¶ ↑ Dextrose-Saline 30-s Chair Stand (4, 6, 12 mo)†¶ ↔ Dextrose-Saline 40-m Fast Walk (4, 6, 12 mo)†¶ ↔ Dextrose-Saline	EuroQol-5D Index (6,12 mo)†¶ ↔ Dextrose-Saline	*"Serious adverse events"* over 12 mo (serious AE not otherwise defined): Dextrose—5% (n= 2) Saline—16% (n= 6) "*None were related to study interventions."*
Intra-Articular Dextrose Prolotherapy versus Platelet-Rich Plasma						
Mruthyunjaya, 2023[46] RCT; High; India KL grades 2-3 OA, prior treatments NR; mean ages 54-55, 75% female; mean BMI NR	25% dextrose (volume NR) *N* = 40 (40) Clinic; 4 wk (3 injections)	2 comparators: PRP (volume NR) Ozone (volume NR) each group *N*= 40 (40) Clinic; 4 wk (3 injections)	WOMAC Total (KL Grade 2) (1.5, 3, 6 mo) ↔ Dextrose-PRP ↔ Dextrose-Ozone WOMAC Total (KL Grade 3) (1.5, 3, 6 mo) ↔ Dextrose-PRP ↔ Dextrose-Ozone	—	—	—
Pishgahi, 2020[47] RCT; Some concerns; Iran Knee OA grades 2-4, prior treatments NR; mean ages 58-61 yrs, 47-63% female; mean BMI NR	20% dextrose 5 ml (+ 0.4% lidocaine), ultrasound-guided *N* = 30 (30) Clinic; 3 wk (3 injections)	2 comparators: PRP (volume NR), ultrasound-guided Serum 2 ml (autologous conditioned), ultrasound-guided *N* = 30 (30); 32 (32) Clinic; 1 wk (2 injections)	WOMAC Total (1, 6 mo) ↓ Dextrose-PRP ↓ Dextrose-ACS	—	—	—
Rahimzadeh, 2018[48] RCT; Some concerns; Iran	25% dextrose 7 ml, ultrasound-guided *N* = 21 (21)	PRP 7 ml, ultrasound-guided *N* = 21 (21)	WOMAC Total (1, 2, 6 mo) ↔ Dextrose-PRP	—	—	*"No significant side effects were observed."* (significant AE not defined)

Author, Year **Study Design; RoB; Country** **Key Participant Characteristics**	**Dextrose Intervention** ***N* Randomized (*N* Analyzed)** **Setting; Duration**	**Comparators** ***N* Randomized (*N* Analyzed)** **Setting; Duration**	**OUTCOMES**			
			Pain-Related Functioning	**Physical Performance**	**Health-Related Quality of Life**	**Adverse Events**
OA KL grades 1-2; no prior knee surgery; mean ages 64-66 yrs, 48-52% female; mean BMI 28-29	Clinic; 1 mo (2 injections)	Clinic; 1 mo (2 injections)	WOMAC Physical Function (1, 2, 6 mo) ↔ Dextrose-PRP			
Intra- versus Extra-Articular Dextrose Prolotherapy						
Farpour, 2017[49] RCT; Some concerns; Iran Knee OA according to ACR, KL grades 2-3, VAS score ≥3, no knee injections in past 3 mo; mean ages 56 -58 yrs, 68-72% female; mean BMI 26	Intra-articular 25% dextrose 6 ml *N* = 26 (25) Clinic; 2 wk (2 injections)	Extra-articular 25% dextrose 6 ml *N* = 26 (25) Clinic; 2 wk (2 injections)	OKS (1, 2 mo) ↔ intra-articular versus extra-articular WOMAC Total (1, 2 mo) ↔ intra-articular versus extra-articular WOMAC Physical Function (1, 2 mo) ↔ intra-articular versus extra-articular	—	—	*"…there were no significant complications"* (AE not defined)
Rezasoltani, 2017[42] RCT; High; Iran Chronic OA, grade ≥2, failed conservative therapy for ≥3 mo, no knee injections in past 12 mo; mean ages 64 yrs, 74-76% female; mean BMI 29-32	Intra-articular 10% dextrose 8 ml (+ 0.4% lidocaine) *N* = 55 (54) Clinic; 2 wk (3 injections)	Extra-articular 10% dextrose 10 ml (+ 0.5% lidocaine) *N* = 55 (50) Clinic; 2 wk (3 injections)	WOMAC (1,2,3,4,5 mo)** ? intra-articular versus extra-articular	—	—	—
Intra-Articular Dextrose Prolotherapy versus Other Comparators						
Babaeian, 2022[50] RCT; High; Iran KL grades 2-3 OA, met ACR criteria, pain/ stiffness ≥1 mo, no prior surgery and no knee injections in past 3 mo; mean ages 58-60 yrs,	25% dextrose 6 ml (+ 1% lidocaine) *N* = 28 (24) Clinic; 4 wk (3 injections)	Hypertonic 2.5% saline 6 ml (+ 1% lidocaine) *N* = 26 (22) Clinic; 4 wk (3 injections)	OKS (2, 4 wk) ↔ Dextrose-Saline WOMAC Total (2, 4 wk) ↔ Dextrose-Saline WOMAC Function (2, 4 wk) ↔ Dextrose-Saline	—	—	*"The patients reported no adverse effect in the next visit…"* (AE not defined)

Author, Year Study Design; RoB; Country Key Participant Characteristics	Dextrose Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance	Health-Related Quality of Life	Adverse Events
79-86% female; mean BMI 26-27						
Hashemi, 2015[51] RCT; High; Iran Knee OA KL grades 1-2, aged 40 - 75 years, no knee injections in past yr; mean ages 57-59 yrs, 58-65% female; mean BMI 31-32	12.5% dextrose 7 ml, ultrasound-guided *N* = 40 (40) Clinic; 14-20 days (3 injections)	Ozone 5-7 ml, ultrasound-guided *N* = 40 (40) Clinic; 14-20 days (3 injections)	WOMAC Total (3 mo) ↔ Dextrose-Ozone	—	—	—
Rahimzadeh, 2014[52] RCT; Some concerns; Iran OA according ACR criteria, Class I-III and KL grades 1-3, no prior knee surgery; mean ages 57-61 yrs, 54-62% female; mean BMI NR	12.5% dextrose 10 ml (+ 0.25% ropivacaine), fluoroscopy-guided *N* = 26 (26) Clinic; 1 injection	2 comparators: Erythropoietin 4000 IU (+ 0.5% ropivacaine), fluoroscopy-guided Pulsed radiofrequency waves, fluoroscopy-guided *N* = 20 (20); 24 (24) Clinic; 1 injection	—	ROM (2, 4, 12 wk)[§] ? Dextrose-Erythropoietin ? Dextrose-Pulsed radiofrequency waves	—	*"No particular side-effect related to the interventions was observed."* (AE not defined)
Rezasoltani, 2020[53] RCT; High; Iran KL grades 3-4 OA, no prior knee surgery, and no knee injection in past 6 mo; mean ages 65-70 yrs, 53-73% female; mean BMI 32-33	16% dextrose 10 ml (+ 0.4% lidocaine), ultrasound-guided, and home exercise program *N* = 30 (30) Clinic/home; 2 mo (3 injections; daily exercises)	3 comparators (all with home exercise): PT (TENS, therapeutic ultrasound, hotpacks) Botulinum neurotoxin 100 U, ultrasound-guided HA 2 ml, ultrasound-guided each group *N* = 30 (30)	KOOS ADL, Sports & Recreation, & Knee QoL (3 mo)[††] ? Dextrose-PT ? Dextrose-Botulinum ? Dextrose-HA	—	—	*"None of the participants showed or reported serious side effects for the treatments."* (AE not defined)

Author, Year Study Design; RoB; Country Key Participant Characteristics	Dextrose Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance	Health-Related Quality of Life	Adverse Events
		Clinic/home; 2 wk (3 sessions or injections; daily exercises)				
Extra-Articular Dextrose Prolotherapy versus Intra-Articular Hyaluronic Acid Injection						
Hosseini, 2019[54] RCT; High; Iran KL grade ≥2, met ACR criteria, no knee injection in past yr; mean ages 61-64 yrs, 40-48% female; mean BMI 30-31	Extra-articular 12.5% dextrose 10 ml, ultrasound-guided *N* = 52 (52) Clinic; 2 wk (3 injections)	Intra-articular HA 2.5 ml, ultrasound-guided *N* =52 (52) Clinic; 2 wk (3 injections)	Modified WOMAC Total (3 mo)† ↓ Dextrose-HA	—	—	*"Our results have shown no serious adverse events"* (serious AE not defined)

Notes. *Study reported modified WOMAC Physical Function scores that were outside of scoring range (*ie*, scores >100), so unable to interpret against published MCID. Study did not report a between-group comparison at time point(s).

†No established MCID for outcome; direction of effect based on statistical comparison reported by study.

‡No established MCID for outcome and study did not report between-group comparison at time point(s).

¶Study reported estimated differences between groups at each time point from the linear mixed model used to examine group and time effects.

§No established MCID for outcome and study only reported main comparison across all 3 groups (which was significant at all time points) but no pairwise testing.

**Study only reported mean scores for individual WOMAC items at follow-up, and not total or domain scores.

††Study reported mean scores at follow-up only for KOOS total and not individual domains. Statistical testing for differences between groups was also only for KOOS total score; there was a significant overall group effect and pairwise testing showed that HA group had greater improvement than each of the other 3 groups.

Symbols. ↑: At specified follow-up time point, the dextrose arm had a better scale score than the comparator arm (meeting MCID); ↔: At specified follow-up time point, the difference in scale scores between the dextrose and comparator arms did not meet MCID; ↓: At specified follow-up time point, the dextrose arm had a worse scale score than the comparator arm (meeting MCID); ?: Review team was unable to interpret scale scores.

Abbreviations. ACL=anterior cruciate ligament; ACR=American College of Rheumatology; ACS=autologous blood serum; ADL=activities of daily living; AE=adverse event; BMI=body mass index; BPI=brief pain inventory; DPT=dextrose prolotherapy; EuroQoL-5D=European Quality of Life-5 dimensions; HA=hyaluronic acid; KL=Kellgren-Lawrence; KOOS=Knee Injury and Osteoarthritis Outcome Score; mg=milligrams; ml=milliliters; Mo=month; NR=not reported; NS=normal saline; OA=osteoarthritis; OKS=Oxford Knee Score; PRP=platelet-rich plasma; PT=physical therapy; QoL=quality of life; RoB=risk of bias; RCT=randomized controlled trial; ROM=range of motion; SD=standard deviation; SF-36=36-item Short Form health survey; TENS=transcutaneous electrical nerve stimulation; TUG=timed up and go; U=units; VAS=visual analog scale; Wk=week; WOMAC=Western Ontario and McMaster Universities Arthritis Index.

Intra-Articular Dextrose Prolotherapy versus Normal Saline or Water Injection (With or Without Local Anesthetic)

Three RCTs[43-45] compared intra-articular dextrose prolotherapy (10-25% dextrose) with intra-articular normal saline or water injections. Hsieh, 2022[43] also included intra-articular HA in both arms. Intervention duration was 1-10 months (3-6 injection sessions), and 2 studies used ultrasound guidance.[43,45] Hsieh, 2022[43] and Sit, 2020[45] were conducted in Taiwan and China, respectively, with total *N* of 71-104; both were rated low RoB. Reeves, 2000[44] was conducted in the US, had total *N* of 77, and was rated high RoB due to concerns related to high proportion of drop-outs, some "due to lack of efficacy." This introduced substantial bias into the results for participants who completed the intervention and were available for follow-up data.

Dextrose prolotherapy probably results in little to no difference in pain-related functioning (moderate COE for short, medium, and long-term follow-up; **Table 5**). Hsieh, 2022[43] and Sit, 2020[45] both used the Chinese version of the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) to assess pain-related functioning, with Hsieh, 2022[43] additionally evaluating Knee Injury and Osteoarthritis Outcome Scores (KOOS) as well. Both studies showed that functioning improved for both arms over time (maximum follow-up 6-12 months), and the differences between groups were generally less than the MCID. However, there was some inconsistency across the different measures for functioning, for example with the dextrose prolotherapy arm having greater improvement at 1 and 6 months on the KOOS-Activities of Daily Living (ADL) subscale scores but not on the KOOS-Knee Quality of Life (QoL) subscale scores.[43] Differences were also not seen in functioning when assessed by WOMAC in the other study.[45] Reeves, 2000[44] did not evaluate pain-related functioning.

Dextrose prolotherapy probably results in little to no difference in physical performance (moderate COE for short, medium, and long-term follow-up; **Table 5**). Hsieh, 2022[43] assessed a range of measures, including 10 meter (m) regular walking speed and timed chair-stand test. Sit, 2020[45] evaluated timed up and go (TUG), 30 second (s) chair-stand test, and timed 40 m fast walking. Reeves, 2000[44] measured range of motion (ROM) for knee flexion, but did not report mean scores at baseline of follow-up or between-group comparisons. Overall, both Hsieh, 2022[43] and Sit, 2020[45] showed improvements over time for both arms and sometimes there were very small, statistically significant differences between groups. For example, at 3-4 months, Hsieh, 2022[43] reported faster 10 m regular walking speed in the dextrose prolotherapy arm at 3 months (mean 0.95 m/s versus 0.94 m/s in the normal saline arm) but no significant differences in timed chair-stand test (mean 18.1 s for dextrose versus 18.7 s for normal saline arm). Sit, 2020[45] also found no statistically significant differences at 4 months on TUG, 30 s chair-stand test, and 40 m fast walking.

Dextrose prolotherapy results in little to no difference in health-related quality of life at 6-12 months (high COE, **Table 5**). Only Sit, 2020[45] evaluated quality of life and reported no differences between groups in European Quality of Life-5 dimensions (EuroQol-5D) Index scores. Additionally, the evidence is very uncertain for adverse events (very low COE). Although all 3 studies reported on adverse events and 2 of these asserted that severe or serious events did not occur, it was unclear how or when adverse events were assessed. All 3 studies also evaluated pain intensity (using WOMAC pain subscale and/or visual analog scale [VAS]) and found reductions in pain in both arms over time. Neither Hsieh, 2022[43] nor Sit, 2020[45] found differences between groups in improvement of pain scores, and Reeves, 2000[44] did not report mean scores or between-group comparisons for this outcome.

Table 5. Knee Osteoarthritis COE: Intra-Articular Dextrose Prolotherapy versus Normal Saline or Water Injection (With or Without Local Anesthetic and Hyaluronic Acid)

Outcome Measure	Follow-Up Total *N* (# of Studies)	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up Dextrose Prolotherapy	Saline	Difference	Certainty	What Happens
Pain-related functioning WOMAC, KOOS	Short-term (1 mo) *N* = 104 (1 RCT)[43]	48.5*	46.0*	2.5*	Moderate[a] ⊕⊕⊕◯	Dextrose prolotherapy probably results in little to no difference for pain-related functioning at short-term follow-up.
	Medium-term (3-4 mo) *N* = 180 (2 RCTs)[43,45]	30.4†	32.4†	-2.0†	Moderate[b] ⊕⊕⊕◯	Dextrose prolotherapy probably results in little to no difference for pain-related functioning at medium-term follow-up.
	Long-term (6-12 mo) *N* = 180 (2 RCTs)[43,45]	28.8†	33.3†	-4.5†	Moderate[b] ⊕⊕⊕◯	Dextrose prolotherapy probably results in little to no difference for pain-related functioning at long-term follow-up.
Physical performance 10 m Walking Speed, Chair Stand Test, Timed Up & Go; ROM	Short-term (1 mo) *N* = 104 (1 RCT)[43]	0.98‡	1.00‡	-0.02‡	Moderate[b] ⊕⊕⊕◯	Dextrose prolotherapy probably results in little to no difference for physical performance at short-term follow-up.
	Medium-term (3-4 mo) *N* = 180 (2 RCTs)[43,45]	0.99‡	0.98‡	0.01‡	Moderate[b] ⊕⊕⊕◯	Dextrose prolotherapy probably results in little to no difference for physical performance at medium-term follow-up.
	Long-term (6-12 mo) *N* = 180 (2 RCTs)[43,45]	0.95‡	0.94‡	0.01‡	Moderate[b] ⊕⊕⊕◯	Dextrose prolotherapy probably results in little to no difference for physical performance at long-term follow-up.
Health-related Quality of Life EuroQol-5D	Long-term (6-12 mo) *N* = 76 (1 RCT)[45]	0.73	0.62	0.11	High ⊕⊕⊕⊕	Dextrose prolotherapy results in little to no difference for health-related quality of life at long-term follow-up.
Adverse events NR	*N* = 180 (3 RCTs)[43-45]	0¶	0¶	—	Very low[c,d] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on adverse events.

Notes. *Values for mean KOOS-ADL scores at follow-up for intervention and comparator from Hsieh, 2022.[43] Differences calculated by review team.

†Values for mean WOMAC scores at follow-up for intervention and comparator from Sit, 2020.[45] Differences calculated by review team.

‡Values for mean 10 m walking speed (m/s) at follow-up for intervention and comparator from Hsieh, 2022.[43] Differences calculated by review team.

¶No severe adverse events were observed in either group per Hsieh, 2022[43] ("severe" events were not defined in study).

GRADE Working Group grades of evidence:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

a. Downgraded 1 level for inconsistency (effects inconsistent across different measures of pain-related functioning).

b. Downgraded 1 level for inconsistency (effects inconsistent across studies and across different measures of pain-related functioning in the same study).

c. Downgraded 2 levels for study limitations (1 study rated high RoB).

d. Downgraded 1 level for indirectness (no information about how adverse events were assessed).

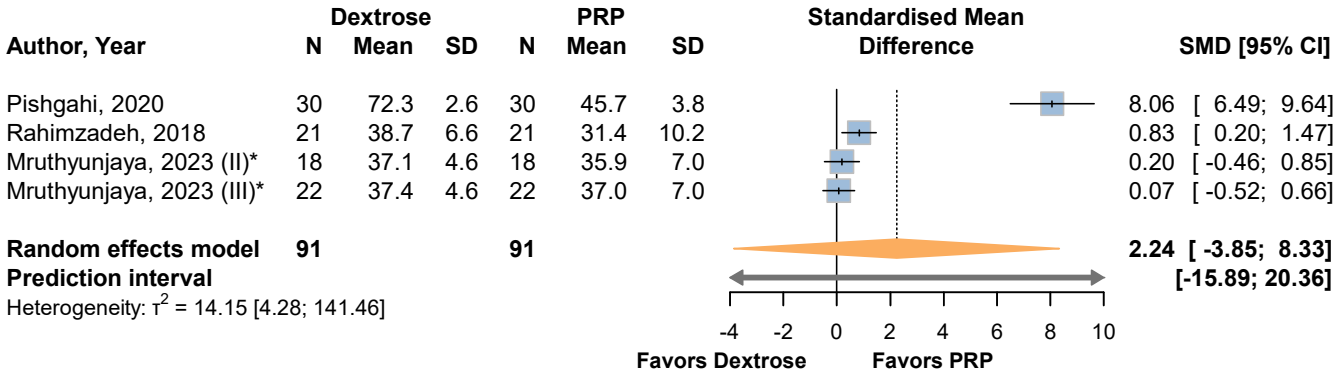
Abbreviations. ADL=activities of daily living; EuroQoL-5D=European Quality of Life-5 dimensions; KOOS=knee injury and osteoarthritis outcome score; mo=month; RCT=randomized controlled trial; RoB=risk of bias; ROM=range of motion.

Intra-Articular Dextrose Prolotherapy versus Platelet-Rich Plasma Injection

Three RCTs compared intra-articular dextrose prolotherapy (20-25% dextrose) with PRP injections.[46-48] For all 3 studies, intervention duration was around 1 month (2-3 injection sessions), and 2 used ultrasound guidance.[47,48] These latter 2 studies were conducted in Iran, and the third study in Turkey.[46] All were small with total $N = 42$-92. Rahimzadeh, 2018[48] and Pishgahi, 202[47] were assessed as some concerns for multiple reasons, including the proportion of participants who received the full course of treatment, lack of allocation concealment, and/or potential bias in assessment of outcomes. Mruthyunjaya, 2023[46] was rated high RoB due to similar concerns with additional problems due to missing data from loss to follow-up. All 3 RCTs evaluated pain-related functioning and pain intensity. Only Rahimzadeh, 2018[48] reported adverse events, and none of the 3 studies evaluated physical performance or health-related quality of life.

The evidence is very uncertain on the effects of dextrose prolotherapy for pain-related functioning at short and long-term follow-up (very low COE), and dextrose prolotherapy may result in little to no difference at medium term (low COE, **Table 6**). All 3 RCTs assessed pain-related functioning using WOMAC, with maximum follow-up of 6 months. The pooled SMD at 6 months was 2.2 (95% CI [-3.9, 8.3]), a very large point estimate favoring PRP, but the 95% CI goes from a very large effect favoring PRP to a very large effect favoring dextrose prolotherapy. All studies reported WOMAC scores at 1-1.5 months of follow-up, but results were inconsistent. For example, Pishgahi, 2020[47] showed PRP arm was better (mean 46.7 versus 71.7 in dextrose arm), while Rahimzadeh, 2018[48] found similar levels of pain-related functioning (mean 42.9 for PRP versus 43.8 in dextrose arm) at 1 month. Only Mruthyunjaya, 2023[46] reported WOMAC scores at 3 months, showing no differences between arms (*eg*, mean 45.5 in PRP arm versus 43.8 in dextrose arm for KL grade 3 participants). In both Rahimzadeh, 2018[48] and Mruthyunjaya, 2023,[46] participants in all arms improved in WOMAC scores over time, but in Pishgahi, 2020[47] the dextrose prolotherapy arm did not improve and instead had slightly higher WOMAC scores at follow-up (though changes did not meet MCID).

Figure 2. Knee Osteoarthritis: Effect of Dextrose Prolotherapy versus Platelet-Rich Plasma on Pain-Related Functioning at 6 Months



Notes. *Study reported data separately for patients with Kellgren-Lawrence grades 2 (II) and 3 (III).

The evidence is very uncertain for adverse events (very low COE, **Table 6**). Rahimzadeh, 2018[48] reported "no significant side effects were observed" but without defining "significant side effects."

Finally, Rahimzadeh, 2018[48] reported WOMAC pain subscale scores, and both Mruthyunjaya, 2023[46] and Pishgahi, 2020[47] used VAS to assess pain intensity or severity. Once again, results were inconsistent across studies. Rahimzadeh, 2018[48] showed that both groups were similar at 1 month but PRP had lower WOMAC pain score at 6 months (mean 6.2 versus 8.0 for dextrose arm, p = 0.003). Pishgahi, 2020[47] also found that PRP groups had lower VAS scores, and this was apparent at 1 month follow-up, though differences were not significant at either time point. Mruthyunjaya, 2023[46] did not report statistical comparisons between groups, but mean VAS scores were similar in both arms at 1.5 and 6 months (*eg*, mean 5.9 in PRP arm versus 5.8 in dextrose arm for KL grade 3 participants at 1.5 months).

Table 6. Knee Osteoarthritis COE: Intra-Articular Dextrose Prolotherapy versus Platelet-Rich Plasma Injection

Outcome Measure	Follow-Up Total *N* (# of Studies)	SMD Pooled Estimate (95% CI)	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up			Certainty	What Happens
			Dextrose Prolotherapy	PRP	Difference		
Pain-related functioning WOMAC	Short-term (1 mo) *N* = 102 (2 RCTs[47,48]	—	43.8*	42.9*	0.9*	Very low[a,b] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on pain-related functioning at short-term follow-up.
	Medium-term (3 mo) *N* = 80 (1 RCT)[46]	—	43.8	45.5	-1.7*	Low[a] ⊕⊕◯◯	Dextrose prolotherapy may result in little to no difference for pain-related functioning at medium-term follow-up.
	Long-term (6 mo) *N* = 182 (3 RCTs)[47,48,55]	SMD: 2.2 (-3.9, 8.3)	50.2 (0, 100)	31.4*	18.8 (-32.3, 69.7)	Very low[a,b] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on pain-related functioning at long-term follow-up.
Adverse events NR	*N* = 42 (1 RCT)[48]	—	0	0	—	Very low[c,d,e] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on adverse events.

Notes. *Values for mean follow-up scores for intervention and/or comparator arms from Rahimzadeh, 2018.[48] Differences calculated by review team.

GRADE Working Group grades of evidence:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

a. Downgraded 2 levels for study limitations (1 study rated high RoB).

b. Downgraded 1 level for inconsistency (direction of effects inconsistent across studies).

c. Downgraded 1 level for study limitations (study rated some concerns for risk of bias).

d. Downgraded 1 level for indirectness (no information about how or when adverse events were assessed).

e. Downgraded 1 level for imprecision (not powered to detect minimum adverse event rate <10%; see Methods for more information).

Abbreviations. mo=month; NR=not reported; PRP=platelet rich plasma; RCT=randomized controlled trial; RoB=risk of bias; SMD=standardized mean difference; WOMAC= Western Ontario and McMaster Universities Arthritis Index.

Intra-Articular Dextrose versus Ozone Injection

Two RCTs[46,51] compared intra-articular dextrose with ozone injection. One of these was Mruthyunjaya, 2023,[46] described above, which evaluated dextrose, PRP, and ozone injections. The second trial, Hashemi, 2015,[51] enrolled 80 participants and administered 3 injections of 12.5% dextrose or ozone over 2-3 weeks, using ultrasound guidance for both arms. This study was rated high RoB due

to deviations from intended interventions and other concerns. Both RCTs evaluated pain-related functioning and pain intensity; neither addressed other eligible outcomes.

Dextrose prolotherapy may result in little to no difference in pain-related functioning at short, medium, and long-term follow-up (low COE, **Table 7**). Both studies stated that WOMAC scores improved in all arms, although Hashemi, 2015[51] reported higher WOMAC scores at follow-up. For pain intensity, both RCTs reported lower VAS scores at follow-up in all arms, with no substantial differences between groups. For example, in Hashemi, 2015,[51] mean VAS at 3 months was 3.0 in the dextrose group and 2.8 in the ozone group (p = 0.512).

Table 7. Knee Osteoarthritis COE: Intra-Articular Dextrose Prolotherapy versus Ozone Injection

Outcome Measure	Follow-Up Total *N* (# of Studies)	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up: Dextrose Prolotherapy	Ozone	Difference	Certainty	What Happens
Pain-related functioning WOMAC	Short-term (1.5 mo) *N* = 80 (1 RCT)[46]	51.6*	48.4*	3.2*	Low[a] ⊕⊕◯◯	Dextrose prolotherapy may result in little to no difference for pain-related functioning at short-term follow-up.
	Medium-term (3 mo) *N* = 160 (2 RCTs)[46,51]	43.8*	36.1*	7.7*	Low[a] ⊕⊕◯◯	Dextrose prolotherapy may result in little to no difference for pain-related functioning at medium-term follow-up.
	Long-term (6 mo) *N* = 80 (1 RCT)[46]	37.3*	34.0*	3.3*	Low[a] ⊕⊕◯◯	Dextrose prolotherapy may result in little to no difference for pain-related functioning at long-term follow-up.

Notes. *Results for Kellgren-Lawrence grade 3 group from Mruthyunjaya, 2023,46 as study separately reported mean scores for grade 2 and grade 3. Difference calculated by review team.

GRADE Working Group grades of evidence:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

a. Downgraded 2 levels for study limitations (1-2 studies rated high RoB).

Abbreviations. mo=month; RCT=randomized controlled trial; RoB=risk of bias; WOMAC= Western Ontario and McMaster Universities Arthritis Index.

Intra- versus Extra-Articular Dextrose Prolotherapy

Two RCTs[42,49] compared dextrose prolotherapy intra- versus extra-articular injections using 10-25% dextrose. These studies include 52-110 participants, administered 2-3 injection sessions over 2 weeks, and used similar extra-articular injection protocols (in 3-4 areas around the knee joint). Neither study used image guidance for injections. Rezasoltani, 2017[42] was rated high RoB mainly due to missing

data from loss to follow-up, and Farpour, 2017[49] was rated some concerns due to deviations from the intended interventions. Both RCTs evaluated pain-related functioning and pain severity, and Farpour, 2017[49] also reported on adverse events; neither addressed the other eligible outcomes.

Intra- versus extra-articular dextrose prolotherapy probably results in little to no difference in pain-related functioning at short-term follow-up (moderate COE, **Table 8**). Although both RCTs evaluated pain-related functioning, Rezasoltani, 2017[42] only reported mean scores on individual WOMAC items. Farpour, 2017[49] assessed both WOMAC and the Oxford Knee Score (OKS), finding no differences between groups at 1 and 2 months with either measure (including WOMAC subdomain scores). In both studies, pain-related functioning improved in all arms (*ie*, WOMAC scores decreased and OKS increased over time).

The evidence is very uncertain on the effect of intra- versus extra-articular dextrose prolotherapy for adverse events (very low COE, **Table 8**). Farpour, 2017[49] reported that "no significant complications" occurred but did not describe criteria or provide definitions.

Table 8. Knee Osteoarthritis COE: Intra- versus Extra-Articular Dextrose Prolotherapy

Outcome	Follow-Up	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up			Certainty	What Happens
Measure	Total *N* (# of studies)	Intra-Articular	Extra-Articular	Difference		
Pain-related functioning WOMAC, OKS	Short-term (4 wk) *N* = 52 (1 RCT)[49]	41.2*	38.6*	2.6*	Moderate[a] ⊕⊕⊕◯	Intra- versus extra-articular dextrose prolotherapy probably results in little to no difference in pain-related functioning at short-term follow-up.
Adverse events	*N* = 52 (1 RCT)[49]	0†	0†	—	Very low[a,b,c] ⊕◯◯◯	The evidence is very uncertain on the effect of intra- versus extra-articular dextrose prolotherapy on adverse events.

Notes. *Mean WOMAC total scores at 1 month.[49] Differences calculated by review team.

†"No significant complications" were reported (terms not defined by study).[49]

GRADE Working Group grades of evidence:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

a. Downgraded 1 level for study limitations (study rated some concerns for RoB).

b. Downgraded 1 level for indirectness (authors do not describe how they measured adverse events).

c. Downgraded 1 level for imprecision (not powered to detect minimum adverse event rate <10%; see Methods for more information).

Abbreviations. mo=month; NR=not reported; OIS=optimal information size; OA=osteoarthritis; OKS=Oxford Knee Score; RCT=randomized controlled trial; RoB=risk of bias; SMD=standardized mean difference; WOMAC= Western Ontario and McMaster Universities Arthritis Index.

Both studies also assessed pain intensity using VAS scores. Rezasoltani, 2017[42] reported that extra-articular arm had lower pain intensity at 2, 3, 4, and 5 months, compared with the intra-articular arm (p = 0.001 for between-group tests at each time point), but the differences were very small (*eg*, mean VAS 2.4 for extra-articular versus 3.3 for intra-articular arm at 2 months). Farpour, 2017[49] also found that the extra-articular group had lower mean VAS at 1 and 2 months (*eg*, 5.5 for extra-articular versus 6.4 for intra-articular arm at 1 month), but reported that there was no statistically significant difference between groups (p = 0.15 using repeated measures analysis of variance [ANOVA]). Overall, these results suggest that extra-articular dextrose may result in slightly lower pain scores, compared with intra-articular injections.

Intra- or Extra-Articular Dextrose Prolotherapy versus Other Comparators

Three additional RCTs evaluated additional comparators, including hypertonic saline[50]; PT, HA, and botulinum toxin[53]; and erythropoietin and pulsed radiofrequency waves.[52] The fourth RCT, Hosseini, 2019,[54] compared extra-articular dextrose with intra-articular HA. Dextrose prolotherapy injections used 12.5-25% dextrose and occurred in 1-3 sessions with maximum duration of 1 month. Three studies employed imaging guidance, 2 with ultrasound,[53,54] and the third used fluoroscopy.[52]

Babaeian, 2022[50] enrolled 54 participants and found that pain-related functioning (assessed with WOMAC and OKS), and pain intensity (measured with VAS) all improved over time for both dextrose prolotherapy and hypertonic saline arms. However, there were no significant differences between groups for any outcome. This study also reported that no patient had an adverse event, but did not describe or further define adverse events.

Rahimzadeh, 2014[52] randomized 70 participants to 3 arms, finding that ROM and pain intensity (assessed with VAS) improved over time for all treatments, but there was greater improvement for all measures in the erythropoietin group, compared with either dextrose prolotherapy or pulsed radiofrequency waves. However, this study did not report pairwise testing statistics, either for repeated measures over time or at individual time points. Rahimzadeh, 2014[52] indicated that no "side effect related to the interventions was observed" but did not describe how it was determined whether adverse events were due to the intervention.

Rezasoltani, 2020[53] enrolled 120 participants, randomized equally into 4 arms comparing dextrose prolotherapy to HA injection, botulinum toxin injection, or PT (with transcutaneous electrical nerve stimulation (TENS) and therapeutic ultrasound). All 4 groups improved in pain-related functioning (assessed with KOOS) and pain intensity (measured with VAS) over 3 months. In mixed ANOVA analyses for both total KOOS and VAS, there were significant group effects and pairwise testing showed that the main difference was the lower improvement in HA arm, compared with each of the other treatments. This study did not report mean scores at follow-up time points or statistical analyses for KOOS domains. Rezasoltani, 2020[53] indicated that no participant had "serious side effects" but did not describe or define what constituted "serious side effects."

Hosseini, 2019[54] randomized 104 participants and found that both arms improved in pain-related functioning (assessed with modified WOMAC) and pain intensity (measured with VAS) over 3 months of follow-up. This study stated that the HA group had significantly better scores than dextrose prolotherapy for both outcomes at 3 months, but the between-group differences were small for both measures (*eg*, mean 83.7 on modified WOMAC for dextrose arm versus 88.5 for HA arm). Authors also reported that no side effects were observed in either group, but did not describe what constituted side effects or how these were assessed.

Finally, Pishgahi, 2020,[47] described above in the section on PRP, also included a third arm treated with autologous conditioned serum injections. As noted previously, the dextrose prolotherapy arm did not improve over time in either pain-related functioning (assessed with WOMAC) or pain intensity (measured with VAS). Thus, autologous serum had substantially better pain-related functioning (*eg*, mean WOMAC of 34.9 versus 72.3 for dextrose arm at 6 months), as well as lower pain intensity (*eg*, mean VAS of 35.0 versus 63.3 for dextrose arm at 6 months).

Combined Intra- and Extra-Articular Dextrose Prolotherapy

Nine studies (8 RCTs and 1 observational study) evaluated the effect of combined intra- and extra-articular dextrose prolotherapy injections (range = 5-25% dextrose). Dextrose was injected both into the knee joint and to a variety of sites surrounding the joint (*ie*, major ligament and tendon attachment points on the femur, tibia, fibula, and patella). Studies compared dextrose prolotherapy to PT and/or home exercise programs ($k = 7$). The remaining comparisons were with normal saline ($k = 2$), corticosteroid ($k = 1$), HA ($k = 1$), and ozone ($k = 1$) injections. Additionally, 2 of the studies that compared dextrose prolotherapy to home exercise programs also evaluated different dextrose concentrations (5%, 10%, and 20%)[56] or different prolotherapy injection techniques (Lyftogt plus Hackett versus Hackett technique alone).[57] All RCTs excluded individuals who had prior surgery and/or recent knee injections, and 3 trials[58-60] also required that participants had failed conservative management. The single observational study did not address history of previous treatments (either in eligibility criteria or participant characteristics).[57] **Table 9** presents the key study characteristics and findings for studies evaluating combined intra- and extra-articular dextrose prolotherapy interventions. Detailed trial characteristics and findings are found in **Appendix F**.

Below, we first describe findings for studies comparing dextrose prolotherapy with PT and/or home exercise programs. Then we present results for dextrose prolotherapy versus normal saline injection, followed by the remaining comparisons (corticosteroid, HA, and ozone injections).

Table 9. Summary of Characteristics and Key Findings for Knee Osteoarthritis: Combined Intra-Articular and Extra-Articular Dextrose Injections

Author, Year Study Design; RoB; Country Key Participant Characteristics	Dextrose Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance*	Health-Related Quality of Life	Adverse Events
Dextrose Prolotherapy versus PT/Exercise Programs						
Baygutalp, 2021[58] RCT; High; Turkey Knee OA according to ACR criteria, KL grades 2-3, failed conservative treatments for ≥3 mo, no history of TKA, no invasive procedure or knee injectionsin in past 6 mo, and no NSAIDs in past wk; mean ages 57 yrs, 84-88% female; mean BMI 32-34	Intra-articular 12.5% dextrose 5 ml and extra-articular 12.5% dextrose 10 ml; and home exercise *N* = 25 (25) Clinic/home; 6 wk (3 injections); exercises 12 wk (2x/day)	2 comparators: • Ozone, intra- and extra-articular; and home exercise • Home exercise program only each group *N* = 25 (25) Clinic/home; 6 wk (3 injections); 12 wk exercises (2x/day)	**WOMAC Total (6, 12 wk)†** **?** Dextrose-Exercise **?** Dextrose-Ozone **WOMAC Physical Function (6, 12 wk)†** **?** Dextrose-Exercise **?** Dextrose-Ozone	**TUG (6, 12 wk)** ↔ Dextrose-Exercise ↔ Dextrose-Ozone **ROM Active (6 wk)** ↔ Dextrose-Exercise ↔ Dextrose-Ozone **(12 wk)** ↑ Dextrose-Exercise ↔ Dextrose-Ozone **ROM Passive (6, 12 wk)** ↔ Dextrose-Exercise ↔ Dextrose-Ozone	—	—
Dumais, 2012[61] RCT; High; Canada Knee OA, knee pain ≥6 mo, no prior knee surgery; mean ages 56-57 yrs, 39-56% female; mean BMI 32-34	Intra-articular 20% dextrose 5 ml (+0.5% lidocaine) and extra-articular 15% dextrose 1 ml (+0.6% lidocaine); and home exercise program *N* = 21 (18) Clinic/home; 4 wk (4 injections); 16 wk exercise	Home exercise program only *N* = 24 (18) Home; 16 wk (exercises daily; PT check-in every 4 wk)	**WOMAC Total (16 wk)†** **?** Dextrose-Exercise **WOMAC Physical Function (16 wk)†** **?** Dextrose-Exercise **BPI Functional Impairment (16 wk)†** **?** Dextrose-Exercise	**TUG (16 wk)** ↔ Dextrose-Exercise	—	"[Prolotherapy] *was ceased as a precautionary measure in one participant …after reports of diffuse edema of both legs...*"
Ozturk, 2023[56] RCT; Some concerns; Turkey	3 concentrations of dextrose (all intra-articular 5 ml and extra-articular 10 ml),	Hot packs + home exercise program only *N* = 32 (30)	**WOMAC Total (6, 12 wk)** ↑ 20%-Exercise ↑ 10%-Exercise	**TUG (6, 12 wk)** ↔ 20%-Exercise ↔ 10%-Exercise ↔ 5%-Exercise	**SF-36 Physical Score (12 wk)‡** **?** 20%-Exercise **?** 10%-Exercise	Post-injection side effects (pain, swelling, and/or color change): 20%: 33% (n= 10)

Author, Year Study Design; RoB; Country Key Participant Characteristics	Dextrose Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance*	Health-Related Quality of Life	Adverse Events
Knee OA according to ACR criteria, KL grades 2-3, no history of TKA, , no knee injections in past 6 mo, no corticosteroids past mo, and no NSAIDs in past wk; mean ages 56-57 yrs, 80-83% female; mean BMI 32-34	and hot packs + home exercise program: • 20% and 20% • 10% and 10% • 5% and 5% *N* = 31 (30); 32 (30); 33 (30) Clinic/home; 6 wk (3 injections, exercise daily)	Clinic/home; 6 wk (hot packs 20 mins wk every 3 wk; home exercise daily)	↑ 5%-Exercise ↔ 20%-5% ↔ 10%-5% **WOMAC Physical Function (6, 12 wk)** ↑ 20%-Exercise ↑ 10%-Exercise ↔ 5%-Exercise ↔ 20%-5% ↔ 10%-5%	↔ 20%-5% ↔ 10%-5% **ROM: active flexion (6 wk)** ↑ 20%-Exercise ↔ 10%-Exercise ↔ 5%-Exercise ↔ 20%-5% ↔ 10%-5% **(12 wk)** ↔ 20%-Exercise ↔ 10%-Exercise ↔ 5%-Exercise ↔ 20%-5% ↔ 10%-5% **ROM: passive flexion (6, 12 wk)** ↑ 20%-Exercise ↔ 10%-Exercise ↔ 5%-Exercise ↔ 20%-5% ↔ 10%-5%	**?** 5%-Exercise **SF-36 Mental Score (12 wk)‡** **?** 20%-Exercise **?** 10%-Exercise **?** 5%-Exercise	10%: 20% (n= 6) 5%: 33% (n= 7) Exercise: NA
Yildiz, 2023[62] RCT; High; Turkey Knee pain ≥3 mo, KL grades 1-4, no prior knee surgery, and no knee injections in past 6 mo; mean ages 60-61 yrs, 100% female; mean BMI 31-32	Intra-articular 25% dextrose 5 ml and extra-articular 15% dextrose 10 ml; and home exercise program *N* = 30 (30) Clinic/home; 2 wk (2 injections)	PT (TENS + therapeutic ultrasound + hot packs) and home exercise program *N* = 30 (30) Clinic/home; 4 wk (PT 5 sessions/wk)	**WOMAC Total (1, 3 mo)** ↔ Dextrose-PT/exercise	**ROM: active flexion (1, 3 mo)** ↔ Dextrose-PT/exercise **50-m Walking Test (1 mo)** ↔ Dextrose-PT/exercise **(3 mo)** ↑ Dextrose-PT/exercise	—	—

Author, Year Study Design; RoB; Country Key Participant Characteristics	Dextrose Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance*	Health-Related Quality of Life	Adverse Events
Soliman, 2016[57] Observational Cohort; Serious; Egypt Knee OA by ACR criteria, pain ≥6 mo, prior treatments NR; mean ages 51-53 yrs, 75% female; mean BMI NR	Intra-articular 25% dextrose 5 ml and extra-articular 15% dextrose 40 ml, using 2 different injection techniques; and home exercise: • Hackett + Lyftogt Hackett only *N* = 52 (52) each arm Clinic/home; 3-5 mo (3-5 injections)	Home exercise only *N* = 24 (24) Home; 20 wk (5 days/wk, 3x/day)	**WOMAC Total (12 mo)** ↔ Dextrose (Hackett + Lyftogt)-Dextrose (Hackett) ↑ Dextrose (Hackett + Lyftogt)-Exercise ↑ Dextrose (Hackett)-Exercise	—	—	*"There were no adverse events"* (AE not defined)
Sert, 2020[59] RCT; High; Turkey Knee OA KL grades 2-3, failed conservative therapies (PT, oral and/or topical medications), and no knee injections in past 3 mo; mean ages 52-56 yrs, 86-91% female; mean BMI 28-32	Intra-articular 25% dextrose 5 ml and extra-articular 15% dextrose 10 ml (+ 0.25% lidocaine); and home exercise program *N* = 22 (21) Clinic/home; 6 wk (3 injections); exercises performed at least 3 days per wk	2 comparators: • Intra- and extra-articular normal saline (+0.5% lidocaine); and home exercise program • Home exercise program only *N* = 22 (22) & 22 (19) Clinic/home; 6 wk (3 injections); exercises ≥ 3 days/wk	**WOMAC Total (6 wk)** ↑ Dextrose-Exercise ↔ Dextrose-Saline **(18 wk)** ↑ Dextrose-Exercise ↑ Dextrose-Saline **WOMAC Physical Function (6 wk)** ↑ Dextrose-Exercise ↔ Dextrose-Saline **(18 wk)** ↑ Dextrose-Exercise ↔ Dextrose-Saline	—	**SF-36 Physical Score (6 wk)*** ↔ Dextrose-Exercise ↔ Dextrose-Saline **SF-36 Physical Score (18 wk)*** ↑ Dextrose-Exercise ↔ Dextrose-Saline **SF-36 Mental Score (6, 18 wk)*** ↔ Dextrose-Exercise ↔ Dextrose-Saline	—
Rabago, 2013a[63] RCT; Some concerns; USA Knee OA by ACR criteria, moderate-severe knee pain ≥3 mo, no history of TKA or prior knee	Intra-articular 25% dextrose (+ 0.5% lidocaine) and extra-articular 15% dextrose 22.5 ml (+ 0.2% lidocaine) *N* = 33 (30)	2 comparators: • Normal saline, intra- (+ 0.5% lidocaine) and extra-articular (+ 0.2% lidocaine) • Home exercise program	**Modified WOMAC Total (5 wk)*** ↔ Dextrose-Exercise ↔ Dextrose-Saline **(9, 24, 52 wk)*** ↑ Dextrose-Exercise ↑ Dextrose-Saline **(12 wk)***	—	—	*"There were no adverse events."* (AE not defined)

Author, Year Study Design; RoB; Country Key Participant Characteristics	Dextrose Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance*	Health-Related Quality of Life	Adverse Events
prolotherapy, and no other knee injections in past 3 mo); mean ages 56-57 yrs, 63-69% female; mean BMI NR	Clinic; 9-17 wk (3-5 injections)	*N* = 31 (29) & 34 (28) Clinic or home; 9-17 wk (3-5 injections) or exercise 20 wk (3-5 x/wk)	↑ Dextrose-Exercise ↔ Dextrose-Saline **Modified WOMAC Physical Function (5 wk)*** ↔ Dextrose-Saline ↔ Dextrose-Exercise **(9, 12, 24, 52 wk)*** ↑ Dextrose-Exercise ↑Dextrose-Saline			
Dextrose Prolotherapy versus Other Comparators						
Bayat, 2023[60] RCT; High; Iran Knee OA KL grades 2-3, "no response to treatment" in past 3 mo, and no knee PT, surgery, or injections in past 3 mo; mean ages 56-57 yrs, 28-40% female; mean BMI 27	Intra-articular 16% dextrose 10 ml and extra-articular 12% dextrose 2.5 ml *N* = 28 (25) Clinic; 1 injection	Triamcinolone 40 mg (+ 0.5% lidocaine) *N* = 28 (25) Clinic; 1 injection	**WOMAC Total (1, 3 mo)†** **?** Dextrose-Triamcinolone **WOMAC Physical Function (1, 3 mo)†** **?** Dextrose-Triamcinolone	—	—	—
Waluyo, 2021[64] RCT; High; Indonesia Knee OA by ACR 2012 criteria, no knee injections in past 3 mo; mean ages 62-63 yrs, 71-77% female; mean BMI NR	Intra-articular 25% dextrose 5 ml and extra-articular 15% dextrose 30-40 ml *N* = 44 (26) Clinic; 9 wk (3 injections)	Intra-articular HA, 10 mg *N* = 32 (21) Clinic; 5 wk (5 injections)	**WOMAC Total (12 wk)** ↔ Dextrose-HA **WOMAC Function (12 wk)** ↔ Dextrose-HA	—	—	*"All participants experienced…mild-to moderate post-injection pain within 2–3 days. Only one participant, from the prolotherapy group, took paracetamol due to a painful knee post-injection. There were no other side-effects or adverse events."*

Notes. *No established MCID for outcome; direction of effect based on statistically significant difference reported by study.

†Means at follow-up time points were not reported (only change scores were provided).

‡Physical and mental health summary scores were not reported (only individual domain scores were provided).

Symbols. ↑: At specified follow-up time point, the dextrose arm had a better scale score than the comparator arm (meeting MCID); ↔: At specified follow-up time point, the difference in scale scores between the dextrose and comparator arms did not meet MCID; ↓: At specified follow-up time point, the dextrose arm had a worse scale score than the comparator arm (meeting MCID); ?: Review team was unable to interpret scale scores.

Abbreviations. ACR=American College of Rheumatology; ADD=anterior displacement difference; ADL=activities of daily living; AE=adverse event; BMI=body mass index; BPI=brief pain inventory; DPT=dextrose prolotherapy; EuroQoL-5D=European Quality of Life-5 dimensions; HA=hyaluronic acid; KL=Kellgren-Lawrence; KOOS=Knee Injury and Osteoarthritis Outcome Score; mg=milligrams; ml=milliliters; mo=month; NR=not reported; NSAIDs=nonsteroidal anti-inflammatory drugs; OA=osteoarthritis; OKS=Oxford Knee Score; PRP=platelet-rich plasma; PT=physical therapy; QoL=quality of life; RoB=risk of bias; RCT=randomized controlled trial; ROM=range of motion; SD=standard deviation; SF-36=36-item Short Form health survey; TENS=Transcutaneous electrical nerve stimulation; TKA=total knee arthroplasty; TUG=timed up and go; VAS=visual analog scale; wk=week; WOMAC=Western Ontario and McMaster Universities Arthritis Index.

Dextrose Prolotherapy versus PT and/or Home Exercise Program

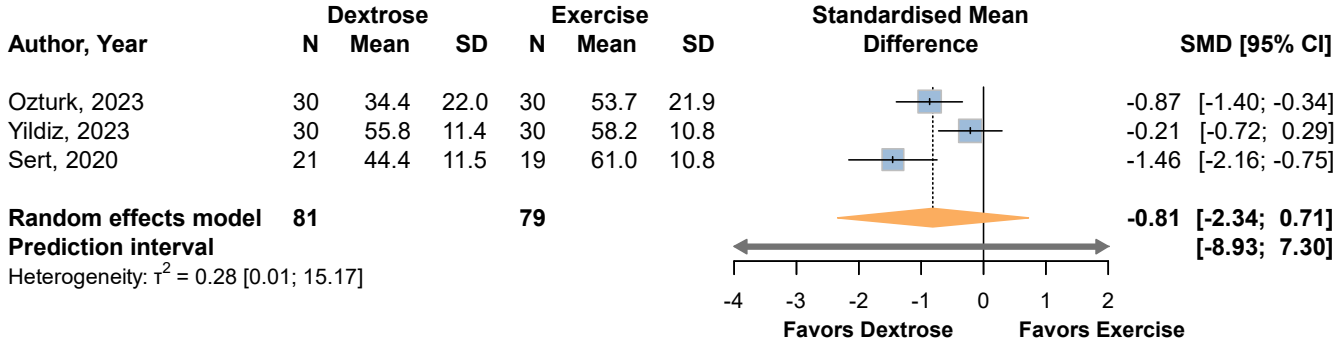
Seven studies (6 RCTs[56,58,59,61-63] and 1 observational study[57]) compared the effects of dextrose prolotherapy with PT and/or home exercise program. Dextrose prolotherapy protocols involved 5-25% intra-articular injections, and 5-20% extra-articular injections, with 1-5 injection sessions over a maximum duration of 5 months. PT and/or home exercise program also lasted 1-5 months. None of the studies used image guidance for the injection interventions. Sample sizes remained small, with 21-52 participants per dextrose prolotherapy arm. As noted above, 2 studies also compared different injection techniques[57] or different dextrose concentrations.[56] Four RCTs[58,59,61,62] were rated high RoB due to a range of concerns, including deviations from the intended intervention and missing data from loss to follow-up. Additionally, Soliman, 2016[57] was rated serious RoB, also for deviations from the intended intervention and missing data. The remaining 2 studies were rated some concerns.[56,63]

The evidence is very uncertain on the effect of dextrose prolotherapy on pain-related functioning at short and medium-term follow-up (very low COE), but it may improve pain-related functioning at long-term follow-up (low COE, **Table 10**). All 7 studies used WOMAC scores to assess pain-related functioning, but 3 studies[58,61,63] did not report mean scores at follow-up and only 2 studies reported findings at 6 months or longer.[59,63] Rabago, 2013a[63] also used a modified version of WOMAC that was scored as 0-100%, with 100% being the best score. The pooled estimates for short and medium-term follow-up favored dextrose prolotherapy (-0.81 and -1.13 SMD, respectively) but there was substantial inconsistency that contributed to the wide 95% CI and even greater PI spanning very large effect sizes in both directions (**Figure 3**). For long-term results, both Soliman, 2016[57] and Rabago, 2013a[63] found that the dextrose prolotherapy group had greater improvements in pain-related functioning at 6 and 12 months, but methodological concerns limit the COE.

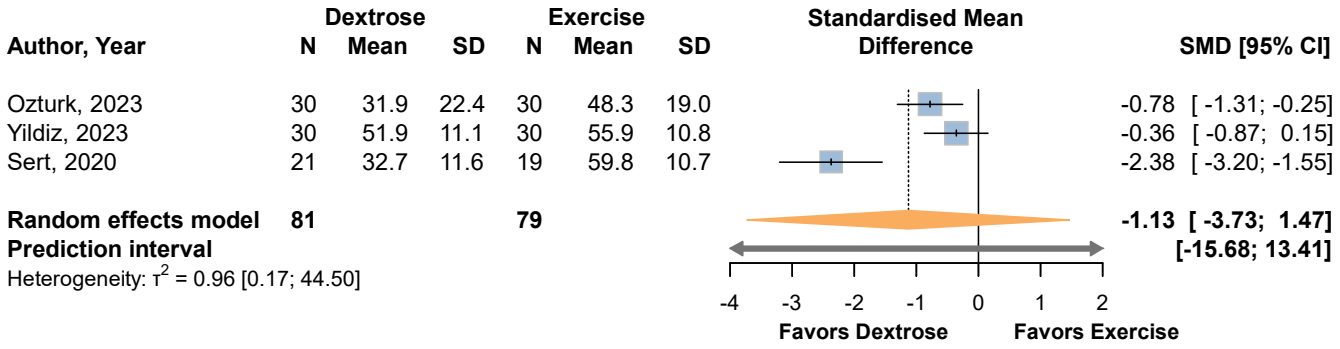
Additionally, Soliman, 2016[57] found that the Hackett plus Lyftogt technique for dextrose prolotherapy injections had lower WOMAC scores (mean 11.3) compared with Hackett technique only (mean 18.5) at 12 months follow-up, but this did not meet MCID (study did not report statistical testing for between-group differences). Both techniques had substantially lower WOMAC scores than the home exercise group (mean 79.5). Ozturk, 2023[56] similarly found no significant between-group differences when comparing outcomes for 5%, 10%, and 20% dextrose injections. At 6 weeks follow-up, 10% and 20% dextrose arms had lower WOMAC scores (mean 33.7 and 34.4, respectively) than the 5% dextrose group (mean 41.1) but this was both not significant and did not meet MCID. At 12 weeks, there were no apparent differences with mean WOMAC 30.4-33.8 across these 3 groups.

Figure 3. Knee Osteoarthritis: Effect of Dextrose Prolotherapy versus Physical Therapy and/or Home Exercise Program on Pain-Related Functioning

A. Short-Term Follow-Up (1-1.5 mo)



B. Medium-Term Follow-Up (3-4 mo)



The evidence is very uncertain on the effect of dextrose prolotherapy on physical performance at short and medium-term follow-up (very low COE, **Table 10**). Four RCTs[56,58,61,62] evaluated physical performance using a variety of measures, including TUG, 50-m walking test, and ROM. Ozturk, 2023[56] and Yildiz, 2023[62] reported mean scores at follow-up (maximum 3 months), while the other 2 studies included changes in measures over 12 or 16 weeks.[58,61] Overall, participants in all arms improved during follow-up (*ie,* faster TUG and 50-m walking times, and higher ROM). No study found significant between-group differences in TUG, while there was inconsistency in results for ROM, with Ozturk, 2023,[56] Yildiz, 2023,[62] and Baygutalp, 2021[58] reporting contrasting results for ROM in active and passive flexion. For example, Ozturk, 2023[56] found small but significantly better ROM in passive flexion at 6 and 12 weeks (*eg*, mean 138.2 degrees for 20% dextrose arm versus mean 136.2 degrees for exercise group), while Baygutalp, 2021[58] indicated there were no significant differences at either 6 or 12 weeks (*eg*, mean change 3.1 degrees for dextrose arm versus mean change 1.2 degrees for exercise group). The inconsistent findings are likely due in part to the different statistical analyses performed by these studies.

The evidence is very uncertain on the effect of dextrose prolotherapy on health-related quality of life at short or medium-term follow-up (very low COE, **Table 10**). Only 2 studies evaluated quality of life and both used SF-36.[56,59] Sert, 2020[59] reported SF-36 Physical and Mental Component Scores (PCS and MCS) and found improvement in all arms with no significant between-group differences in PCS and MCS at 6 weeks. At 18 weeks, PCS was higher in the dextrose prolotherapy group compared with exercise arm at 18 weeks (mean 48.5 for dextrose arm versus 39.6 for exercise group), but there were no significant between-group differences in MCS at time points. These results were inconsistent with

findings from Ozturk, 2023[56] that indicated there were no between-group differences in any of the SF-36 domains (this study did not report PCS and MCS).

The evidence is very uncertain on the effect of dextrose prolotherapy on adverse events (very low COE, **Table 10**). Four studies addressed adverse events, with 2 indicating no events occurred in any arm.[57,63] These 2 studies did not describe how adverse events were assessed. Ozturk, 2023[56] reported the number of patients in each dextrose prolotherapy group (5%, 10%, or 20% dextrose) experiencing post-injection side effects of pain, swelling, and/or color change. The proportion of participants who had at least 1 side effect was 20-33% and there was no apparent dose response.[56] Dumais, 2012[61] reported that dextrose prolotherapy was stopped in 1 participant due to diffuse edema of both legs, but otherwise did not provide more information on adverse events.

Table 10. Knee Osteoarthritis COE: Combined Intra- and Extra-Articular Dextrose Prolotherapy versus Physical Therapy and/or Home Exercise Program

Outcome Measure	Follow-Up Total *N* (# of Studies)	SMD Pooled Estimate (95% CI)	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up Dextrose Prolotherapy	PT/ Exercise	Difference	Certainty	What Happens
Pain-related functioning WOMAC, modified WOMAC	Short-term (1-1.5 mo) *N* = 160 (3 RCTs)[56,59,62]	SMD: -0.8 (-2.3, 0.7)	35.9 (2.2, 69.3)	53.7*	-17.8 (-51.5, 15.6)	Very low[a,b] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on pain-related functioning at short-term follow-up.
	Medium-term (3-4 mo) *N* = 160 (3 RCTs)[56,59,62]	SMD: -1.1 (-3.7, 1.5)	23.0 (0, 81.2)	48.3*	-25.3 (-83.6, 32.9)	Very low[a,c] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on pain-related functioning at medium-term follow-up.
	Long-term (12 mo) *N* = 180 (1 RCT[63], 1 cohort study[57])	—	18.5†	79.5†	-61.0†	Low[a] ⊕⊕◯◯	Dextrose prolotherapy may improve pain-related functioning at long-term follow up.
Physical performance 50-m walking speed, timed up and go; ROM	Short-term (1-1.5 mo) *N* = 238 (4 RCTs)[56,58,62]	—	10.7‡	11.4‡	-0.7‡	Very low[a,c] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on physical performance at short-term follow-up.
	Medium-term (3-4 mo)	—	10.3‡	11.6‡	-1.3‡	Very low[a,c] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on physical performance at medium-term follow-up.

Outcome Measure	Follow-Up Total *N* (# of Studies)	SMD Pooled Estimate (95% CI)	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up Dextrose Prolotherapy	PT/ Exercise	Difference	Certainty	What Happens
	N = 283 (4 RCTs)[56,58,61,62]						
Health-related quality of life SF-36	Short-term (1.5 mo) *N* = 40 (1 RCTs)[59]	—	41.2§	41.2§	0§	Very low[a,d] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on health-related quality of life at short-term follow-up.
	Medium-term (4 mo) *N* = 40 (1 RCT)[59]	—	48.5§	41.1§	7.4§	Very low[a,d] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on health-related quality of life at medium-term follow-up.
Adverse events NR	*N* = 276 (3 RCTs, 1 cohort study)[56,57,61,63]	—	33%¶	—¶	—	Very low[a,e] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on adverse events.

Notes. *Values for mean follow-up scores for intervention and/or comparator arms from Ozturk, 2023.[56] Differences calculated by review team.

†Values for mean follow-up scores for intervention (Hackett injection technique group) and comparator arms from Soliman, 2016.[57] Differences calculated by review team.

‡Mean timed up and go findings at follow-up time points for intervention and/or comparator arms from Ozturk, 2023.[56] Differences calculated by review team.

§Values for SF-36 Physical Component Scores. Differences calculated by review team.

¶Proportion with post-injection effects (pain, swelling, and/or color change) in 20% dextrose group from Ozturk, 2023.[56] No non-injection adverse events reported by study.

GRADE Working Group grades of evidence:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

a. Downgraded 2 levels for study limitations (1-3 studies rated high or serious RoB).

b. Downgraded 1 level for imprecision (CI goes from very large effect favoring dextrose to medium effect favoring exercise).

c. Downgraded 1 level for inconsistency (direction of effects inconsistent across studies).

d. Downgraded 1 level for imprecision (using OIS, studies were not powered to detect minimum SMD of 0.8; see Methods for more information).

e. Downgraded 1 level for indirectness (no information about how or when adverse events were assessed, or only providing adverse events about dextrose prolotherapy groups).

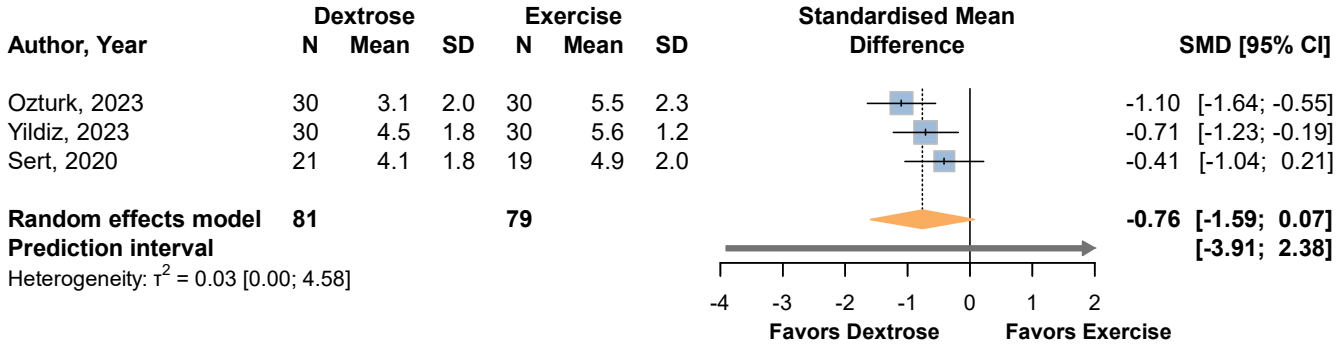
Abbreviations. MD=mean difference; mo=month; PT=physical therapy; RCT=randomized controlled trial; RoB=risk of bias; SF-36=short form health survey; SMD=standardized mean difference; TUG=timed up and go test; VAS=visual analog score; WOMAC= Western Ontario and McMaster Universities Arthritis Index.

All 7 studies also evaluated pain intensity, most using VAS[56-59,61,62] and 1 with the Knee Pain Score (KPS).[63] Two studies[57,63] had 1-year follow-up, while the remaining studies evaluated pain intensity

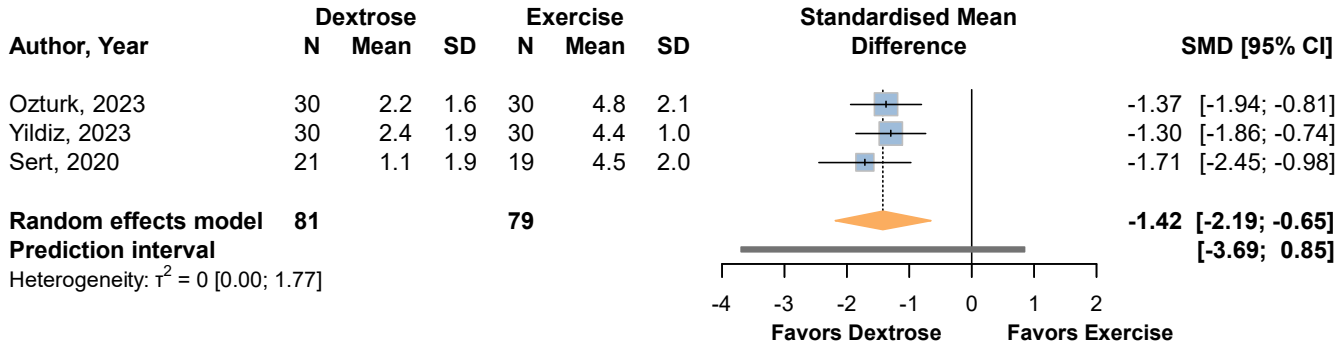
over 3-4 months. Only 3 studies[56,59,62] reported mean scores at short and medium-term follow-up. Pooled estimates were -0.76 (95% CI [-1.59, 0.07]) and -1.42 (95% CI [-2.19, -0.65]) SMD for short and medium-term, respectively (**Figure 4**). While both short and medium-term point estimates favor dextrose prolotherapy, the short-term 95% CI crosses into the other direction (favoring PT/home exercise). The PI, which accounts for between-study variation, extends into both directions for short- and medium-term effects. The 2 studies[57,63] with follow-up at 6-12 months both found that the dextrose prolotherapy group had significantly lower pain intensity at long-term follow-up, but there are serious concerns for confounding in the observational study, Soliman, 2016.[57] This study reported that VAS increased to mean 9.9 in the home exercise group at 12 months (compared with mean 0.32 and 0.44 in the dextrose prolotherapy groups) without any explanation why these participants would have such severe pain.

Figure 4. Knee Osteoarthritis: Effect of Dextrose Prolotherapy versus Physical Therapy and/or Home Exercise Program on Pain Intensity or Severity

A. Short-Term Follow-Up (1-1.5 mo)



B. Medium-Term Follow-Up (3-4 mo)



Dextrose Prolotherapy versus Normal Saline Injection

Two of the studies described in the previous section also included arms treated with intra- and extra-articular normal saline.[59,63] In both studies, normal saline injections followed the same treatment protocol as for the dextrose prolotherapy arm (25% dextrose intra-articular and 15% dextrose extra-articular), and imaging guidance was not used. Certainty of evidence ratings for priority outcomes are listed in **Table 11**.

The evidence is very uncertain on the effect of dextrose prolotherapy on pain-related functioning at short and medium-term follow-up (very low COE), but it may improve pain-related functioning at

long-term follow-up (low COE, **Table 11**). As noted above, both studies evaluated pain-related functioning using WOMAC (modified WOMAC in Rabago, 2013a[63]), finding that participants in all arms improved over time and that the dextrose prolotherapy arm had greater improvement at medium- and long-term follow-up. Sert, 2020[59] showed that at 6 weeks, the dextrose prolotherapy arm had lower total WOMAC scores but these were not significantly different and also did not meet MCID (mean 44.4 for dextrose arm versus 50.5 for normal saline arm). At 18 weeks, there were significant differences between groups, and this exceeded the MCID (mean difference 14.0). Rabago, 2013a[63] also found that there were no significant between-group differences at 5 weeks, but dextrose prolotherapy showed greater improvement over longer follow-up (8-52 weeks). The main concerns leading to lower COE were methodological limitations of both studies, including high RoB for Sert, 2020[59] and small sample sizes with insufficient power to detect MCID and/or medium effect sizes.

The evidence is similarly very uncertain on the effect of dextrose prolotherapy on health-related quality of life at short- and medium-term follow-up (very low COE, **Table 11**). Only Sert, 2020[59] evaluated quality of life, assessed using SF-36 PCS and MCS, and found that participants in all groups improved over time, but there were no significant between-group differences. The evidence is also very uncertain on the effect of dextrose prolotherapy on adverse events (very low COE, **Table 11**). Only Rabago, 2013a[63] assessed adverse events, reporting that none were observed in any group. However, authors did not describe how or when adverse events were evaluated.

Finally, both studies also evaluated pain intensity, with Sert, 2020[59] using VAS and Rabago, 2013a[63] using KPS. Sert, 2020[59] found reduction in pain with activity for participants in all arms, with no significant between-group differences at 6 weeks but greater improvement in dextrose prolotherapy group at 18 weeks, compared with normal saline injection. Similarly, Rabago, 2013a[63] reported that participants on average improved in all arms, and there were no significant between-group differences at short- (5 and 9 weeks) or medium-term follow-up (12 weeks). But there were greater reductions in the dextrose prolotherapy arm at long-term follow-up (24 and 52 weeks).

Table 11. Knee Osteoarthritis COE: Intra-Articular and Extra-Articular Dextrose Prolotherapy versus Normal Saline Injection (With Local Anesthetic)

Outcome / Measure	Follow-Up / Total *N* (# of Studies)	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up: Dextrose Prolotherapy	Normal Saline	Difference	Certainty	What Happens
Pain-related functioning WOMAC, modified WOMAC	Short-term (5-6 wk) *N* = 111 (2 RCTs)[59,63]	44.4*	50.5*	-6.1*	Very low[a,b] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on pain-related functioning at short-term follow up.
	Medium-term (3-4 mo) *N* = 111 (2 RCTs)[59,63]	32.7*	46.7*	-14.0*	Very low[a,b] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on pain-related functioning at medium-term follow up.
	Long-term (6-12 mo) *N* = 51 (1 RCT)[63]	79.1†	71.0†	8.1†	Low[b,c] ⊕⊕◯◯	Dextrose prolotherapy may improve pain-related functioning at long-term follow-up
Health-related quality of life SF-36	Short-term (6 wk) *N* = 40 (1 RCT)[59]	41.2‡	41.2‡	0‡	Very low[a,b] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on health-related quality of life at short-term follow up.
	Medium-term (4 mo) *N* = 44 (1 RCT)[59]	48.5‡	41.1‡	7.4‡	Very low[a,b] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on health-related quality of life at medium-term follow up.
Adverse events NR	*N* = 51 (1 RCT)[63]	0¶	0¶	—	Very low[c,d,e] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on adverse events.

Notes. *Values for mean WOMAC total scores at follow-up for intervention and comparator arms from Sert, 2020.[59] Differences calculated by review team.

†Values for mean modified WOMAC total scores (range 0-100, 100 is best) for intervention and comparator arms at 6 months.

‡Values for SF-36 Physical Component Scores. Differences calculated by review team.

¶No events reported in either group.

GRADE Working Group grades of evidence:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

a. Downgraded 2 levels for study limitations (1 study rated serious RoB).

b. Downgraded 1 level for imprecision (using OIS, studies were not powered to detect minimum SMD of 0.7; see Methods for more information).

c. Downgraded 1 level for study limitations (1 study rated as some concerns RoB).

d. Downgraded 1 level for indirectness (authors do not describe how they measured adverse events).
e. Downgraded 1 level for imprecision (not powered to detect minimum adverse event rate <10%; see Methods for more information).
Abbreviations. KL=Kellgren-Lawrence; mo=month; NR=not reported; RCT=randomized controlled trial; RoB=risk of bias; SF-36=short form survey; SMD=standardized mean difference; WOMAC= Western Ontario and McMaster Universities Arthritis Index.

Dextrose Prolotherapy versus Other Comparators

Two additional RCTs compared dextrose prolotherapy to intra-articular injection of corticosteroid[60] or HA.[64] Bayat, 2023[60] enrolled 56 participants and compared 1 injection each of dextrose prolotherapy versus corticosteroid. This study showed that both pain-related functioning (assessed with WOMAC) and pain intensity (measured with VAS) improved in both arms at follow-up at 1 and 3 months. In the short-term, there were no between-group differences in pain-related functioning, but corticosteroid injection was significantly better at reducing pain intensity (both outcomes evaluated as change scores). At 3 months, dextrose prolotherapy was significantly better at improving both pain-related functioning and pain intensity.

The second trial, Waluyo, 2021,[64] randomized 76 participants to 3 injection sessions of dextrose prolotherapy versus 5 injections of HA. This study also found that both pain-related functioning (assessed with WOMAC) and pain intensity (measured with numeric rating scale [NRS]) improved in both arms at 12 weeks follow-up. Dextrose prolotherapy had significantly greater reductions in pain intensity but there were no significant between-group differences in pain-related functioning. For adverse effects, 1 participant in the dextrose group was reported to need acetaminophen for pain, and all participants had some pain 2-3 days post-injection.

Babaeian, 2022[50] enrolled 54 participants and found that pain-related functioning (assessed with WOMAC and OKS), and pain intensity (measured VAS) all improved over time for both dextrose prolotherapy and hypertonic saline arms. However, there were no significant differences between groups for any outcome. This study also reported that no patient had an adverse event, but did not describe or further define adverse events.

Finally, Baygutalp, 2021,[58] described previously in the section on PT/home exercise comparators, also included an arm treated with intra- and extra-articular injections of ozone. There were no significant between-group differences in pain-related functioning (assessed with WOMAC) at 6 and 12 weeks. Pain intensity was evaluated with VAS at rest and VAS with activity; although there were significant between-group differences in both measures at 6 and 12 weeks, showing greater reductions in the ozone group, the ozone group also had significantly higher VAS at baseline (*eg*, mean 9.7 VAS at rest versus mean 5.1 in dextrose prolotherapy group). For physical performance, there were no significant between-group differences in TUG and ROM at 6 and 12 weeks.

PLANTAR FASCIITIS

Overview

We identified 8 RCTs that compared dextrose prolotherapy with normal saline ($k = 2$), corticosteroid injections ($k = 2$), extracorporeal shock wave therapy (ESWT; $k = 2$), PT ($k = 1$), PRP ($k = 1$), or phonophoresis ($k = 1$). **Table 12** summarizes key study characteristics and main findings for prioritized outcomes. All participants had heel or foot pain for ≥ 8 weeks, and the majority of studies ($k = 5$) required ultrasound findings consistent with plantar fasciitis. More than half of studies ($k = 5$) also

required that participants had failed prior conservative treatments. Participants were mostly young and middle-aged women (mean ages 37-57 years, 66-86% female). The majority of trials ($k = 5$) were conducted in Turkey[65-69] and the remaining occurred in Iran ($k = 2$)[70,71] and Korea ($k = 1$).[72] Only 1 trial enrolled > 100 participants (total $N = 146$),[65] and the remaining had 21-65 participants. Only 2 trials reported long-term follow-up at 6 months[72] and 1 year.[66] All 8 studies evaluated pain-related functioning and most addressed pain severity ($k = 7$); half reported on adverse events ($k = 4$). Only 1 trial provided findings on health-related quality of life,[65] and none evaluated physical performance measures, cost, or treatment burden. Half of the studies were rated high RoB[65-67,72] for a variety of reasons, including concerns regarding the randomization and allocation process, proportion of participants receiving the intended interventions, missing data from loss to follow-up, and bias in outcome assessments. The remaining 4 RCTs were rated some concerns.[68-71] Detailed RoB ratings (by domain and overall) are presented in **Appendix E**.

Below, we further describe study characteristics and findings, grouping studies according to comparators: first normal saline injection, then corticosteroid injection, and ESWT. Lastly, we summarize results for comparisons with single studies. Detailed trial characteristics and findings are found in **Appendix G**.

Table 12. Summary of Characteristics and Key Findings for Plantar Fasciitis

Author, Year Study Design; RoB; Country Key Participant Characteristics	Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Health-Related Quality of Life	Adverse Events
Dextrose Prolotherapy versus Normal Saline Injection (With or Without Local Anesthetic)					
Mansiz-Kaplan, 2020[68] RCT; Some concerns; Turkey Unilateral heel pain >6 mo, plantar fascia thickness >4 mm on ultrasound, failed prior treatment with NSAIDs >1 mo, exercise therapy, and arch support; mean age 46 yrs, 73-77% female, mean BMI 29-31	15% dextrose 10 ml (+ 0.2% lidocaine) *N* = 32 Clinic; 6 wk (2 sessions)	Normal saline 10 ml (+ 0.2% lidocaine) *N* = 33 Clinic; 6 wk (2 sessions)	**Modified FFI-Total (7, 15 wk)*†** ↑ Dextrose-Saline **FFI-Disability (7, 15 wk)†** ↑ Dextrose-Saline **FFI-Activity (7, 15 wk)†** ↑ Dextrose-Saline	--	*"No adverse events were observed in either group."* (AE not defined)
Umay Altas, 2018[69] RCT; Some concerns; Turkey Unilateral heal pain >2 mo, no prior injections or surgery, no PT in prior 3 mo and no NSAIDs in prior 2 wk; mean age 47-51 yrs, 80-93% female, mean BMI 29-30	15% dextrose 3 ml, and home exercises *N* = 15 Clinic, home; 9 wk (3 sessions); home exercises daily for 3 mo	Normal saline 3 ml, and home exercises *N* = 15 Clinic, home; 9 wk (3 sessions), home exercises daily for 3 mo	**FFI-Total (3 mo)‡** **?** Dextrose-Saline **FFI-Disability (3 mo)‡** **?** Dextrose-Saline **FFI-Activity (3 mo)‡** **?** Dextrose-Saline	--	*"No adverse effects were seen in any of our patients during the study."* (AE not defined)
Dextrose Prolotherapy versus Corticosteroid Injection					
Karakılıc, 2023[65] RCT; High; Turkey Heel pain >3 mo, plantar fascia thickness >4 mm and areas of hypoechogenicity on ultrasound, failed prior conservative treatments; total participants 146 but demographics and *N* per arm NR	27% dextrose 4 ml (+ lidocaine %NR), ultrasound-guided NR* Clinic; 1 mo (3 sessions, 2 wk apart)	2 comparators: • Methylprednisolone 40 mg (+ 2% prilocaine), ultrasound-guided • Phonophoresis, 1.5W/cm2 1 MHz NR* for both groups Clinic (both arms); 1 corticosteroid injection, 10 sessions of phonophoresis (frequency NR)	**FFI-Total (1, 3 mo)†** ↔ Dextrose-Steroid ↔ Dextrose-Phonophoresis **FFI-Disability (1, 3 mo)†** ↔ Dextrose-Steroidf ↔ Dextrose-Phonophoresis **FFI-Activity (1, 3 mo)†** ↔ Dextrose-Steroid ↔ Dextrose-Phonophoresis	**SF-36 Physical Score (1, 3 mo)¶** **?** Dextrose-Steroid **?** Dextrose-Phonophoresis **SF-36 Mental Score (1, 3 mo)¶** **?** Dextrose-Steroid **?** Dextrose-Phonophoresis	--

Author, Year Study Design; RoB; Country Key Participant Characteristics	Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Health-Related Quality of Life	Adverse Events
Raissi, 2023[70] RCT; Some concerns; Iran Heel pain (NRS >4) for >8 wk, plantar fascia thickness >4 mm and areas of hypoechogenicity on ultrasound; prior treatments NR; mean ages 42-50 yrs, 75-90% female, mean BMI 27-29	20% dextrose 3 ml (+ 1% lidocaine), ultrasound-guided *N* = 22 Clinic; 1 injection	Methylprednisolone 40 mg, ultrasound-guided *N* = 22 Clinic; 1 injection	**FAAM-ADL (2 wk)** ↔ Dextrose-Steroid **FAAM-Sport (2 wk)** ↔ Dextrose-Steroid **FAAM-ADL (12 wk)** ↑ Dextrose-Steroid **FAAM-Sport (12 wk)** ↔ Dextrose-Steroid	--	--
Dextrose Prolotherapy versus Extracorporeal Shock Wave Therapy					
Asheghan, 2021[71] RCT; Some concerns; Iran Heel pain >8 wk, failed prior conservative management; mean age 45 yrs, 63-69% female, mean BMI 25-26	20% dextrose 2 ml, ultrasound-guided *N* = 31 Clinic; 2 wk (2 sessions)	ESWT, 2000 shocks (2 bars pressure, 10 Hz) to heel *N* = 31 Clinic; 3 wk (3 sessions)	**FAAM-ADL (6, 12 wk)** ↔ Dextrose-ESWT **FAAM-Sport (6, 12 wk)** ↔ Dextrose-ESWT	--	*"All patients tolerated the interventions well and no serious adverse events (hematomas, infections, or soft tissue atrophy) were observed in any of the cases."*
Kesikburun, 2022[67] RCT; High; Turkey Heel pain >3 mo, plantar fascia thickness >4 mm and areas of hypoechogenicity on ultrasound, failed prior conservative treatments; mean ages 51-57 yrs, 69-79% female, mean BMI 31-32	15% dextrose 3 ml (+ 1% lidocaine), ultrasound-guided *N* = 14 Clinic; 6 wk (3 sessions)	ESWT, 1800-2000 shocks (0.20-0.30 mJ/mm^2, 4-6 Hz) to heel and 3000-3500 shocks (1.8-3.0 bars pressure, 15-21 Hz) to foot muscles *N* = 15 Clinic; 6 wk (3 sessions)	**FFI (6, 12 wk)**† ↔ Dextrose-ESWT	--	*"It was not detected any adverse effects during the study."* (AE not defined)
Dextrose Prolotherapy versus Other Comparators					
Ersen, 2018[66] RCT; High; Turkey Symptoms and exam findings consistent with plantar fasciitis (details NR); prior treatments	13.5% dextrose 4 ml (+ lidocaine %NR), ultrasound-guided *N* = 29 Clinic; 6 wk (3 sessions)	PT and home exercises *N* = 31 Clinic/home; 3 mo (PT 3 days/wk + home exercises 3 days/wk)	**FFI-Total (3 wk, 12 mo)**† ↔ Dextrose-PT/exercises **FFI-Total (6 wk, 3 mo)**† ↑ Dextrose-PT/exercises	--	--

Author, Year **Study Design; RoB; Country** **Key Participant Characteristics**	**Intervention** ***N* Randomized (*N* Analyzed)** **Setting; Duration**	**Comparators** ***N* Randomized (*N* Analyzed)** **Setting; Duration**	**OUTCOMES**		
			Pain-Related Functioning	**Health-Related Quality of Life**	**Adverse Events**
NR; mean ages 45-46 yrs, 79-81% female, BMI or weight NR			**FAOS (3 wk)**† ↔ Dextrose-PT/exercises **FAOS (6 wk, 3 & 12 mo)**† ↑ Dextrose-PT/exercises		
Kim, 2014[72] RCT; High; Korea Heel pain >6 mo, plantar fascia thickness >4 mm on ultrasound, failed prior conservative therapy; mean ages 36-38 yrs, 36-60% female, mean weight 30-65 kg	15% dextrose 2 ml, ultrasound-guided *N* = 11 Clinic; 4 wk (2 sessions)	PRP ~2ml, ultrasound-guided *N* = 10 Clinic; 4 wk (2 sessions)	**FFI-Total (3, 7 mo)**† ↔ Dextrose-PRP **FFI-Disability (3, 7 mo)**† ↔ Dextrose-PRP **FFI-Activity (3, 7 mo)**† ↔ Dextrose-PRP	--	--

Notes. *Study reported FFI-Total scores that were outside of standard scoring range (*ie*, scores >100).

†No established MCID for outcome; direction of effect based on statistically significant difference reported by study.

‡Study only reported median (range), no mean scores at follow-up.

¶Study only reported SF-36 domain scores, not physical or mental component scores.

Symbols. ↑: At specified follow-up time point, the dextrose arm had a better scale score than the comparator arm (meeting MCID or statistical significance, if no MCID available); ↔: At specified follow-up time point, the difference in scale scores between the dextrose and comparator arms did not meet MCID or statistical significance; ↓: At specified follow-up time point, the dextrose arm had a worse scale score than the comparator arm (meeting MCID or statistical significance); ?: Review team was unable to interpret scale scores.

Abbreviations. ADL=activity of daily living; AE=adverse effect/event; BMI=body mass index; cm=centimeter; ESWT=extracorporeal shock wave therapy; FAAM=Foot and Ankle Ability Measure; FAOS=Foot and Ankle Outcome Score; FFI=Foot Function Index; h/o=history of; kg=kilogram; MCID=minimal clinically important difference; MHz=megahertz; ml=milliliter; mm=millimeter; mo=month; NR=not reported; NSAIDs=nonsteroidal anti-inflammatory drugs; PF=plantar fasciitis; PFT=plantar fascia thickness; PRP=platelet rich plasma; RCT=randomized controlled trial; RoB=risk of bias; SF-36=36-item SHORT Form health survey; wk=week; yr=year.

Dextrose Prolotherapy versus Normal Saline Injection (With or Without Local Anesthetic)

Two RCTs[68,69] compared dextrose prolotherapy to normal saline injection. Both used 15% dextrose in 2-3 injection sessions over 6-9 weeks. Similar injection techniques were employed and did not include imaging guidance. One trial, Umay Atlas, 2018,[69] instructed participants in both arms to also complete home exercises, which included stretching, rolling solid objects, resistance, and inversion and eversion. Both RCTs evaluated pain-related functioning, adverse events, and pain intensity. Neither addressed the other eligible outcomes.

Dextrose prolotherapy may improve pain-related functioning at short- and medium-term follow-up, compared with normal saline injection (low COE, **Table 13**). Both RCTs assessed Foot Function Index (FFI) total and domain scores, but Mansiz-Kaplan, 2020[68] seemed to have used a modified FFI (scores were out of range for established scale) and Umay Atlas, 2018[69] only reported median and range at baseline and follow-up. Overall, both studies reported participants in all arms improved over time and the dextrose prolotherapy arms had greater improvement.

The evidence is very uncertain on the effect of dextrose prolotherapy on adverse events (very low COE, **Table 13**). Both trials reported that no adverse events were observed in any arm, but neither study described how or when adverse events were assessed. Additionally, the small study size limited the ability to detect less common side effects.

Table 13. Plantar Fasciitis COE: Dextrose Prolotherapy versus Normal Saline Injection (With or Without Local Anesthetic)

Outcome Measure	Follow-Up Total *N* (# of Studies)	Anticipated Absolute Effects on Mean Score at Follow-Up			Certainty	What Happens
		Dextrose Prolotherapy	Normal Saline	Mean Difference		
Pain-related functioning FFI	Short-term (7 wk) *N* = 65 (1 RCTs)[68]	20.1*	113.4*	-93.3*	Low[a,b] ⊕⊕◯◯	Dextrose prolotherapy may improve pain-related functioning at short-term follow-up.
	Medium-term (3 mo) *N* = 90 (2 RCTs)[68,69]	14.4*	118.9*	-104.5*	Low[a,b] ⊕⊕◯◯	Dextrose prolotherapy may improve pain-related functioning at medium-term follow-up.
Adverse events NR	Medium-term (3-4 mo) *N* = 90 (2 RCTs)[68,69]	0†	0†	—	Very low[a,c,d] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on adverse events.

Notes. *Values for FFI-total mean scores at follow-up for dextrose prolotherapy and normal saline groups from Mansiz-Kaplan, 2020.[68] Differences calculated by review team.

†No adverse events were reported in either trial (adverse events not defined).

GRADE Working Group grades of evidence:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

a. Downgraded 1 level for study limitations (1-2 studies rated as some concerns for RoB).
b. Downgraded 1 level for indirectness (likely modified FFI as total scores extend past maximal possible range of FFI).
c. Downgraded 1 level for indirectness (no information about how or when adverse events were assessed).
d. Downgraded 1 level for imprecision (not powered to minimum adverse event rate <10%; see Methods for more information).
Abbreviations. FFI=Foot Function Index; mo=month; OIS=optimal information size; RCT=randomized controlled trial; RoB=risk of bias; wk=weeks.

Both trials also evaluated pain intensity using VAS, only reporting median scores and interquartile range (IQR) or total range. Similar to pain-related functioning, while all groups improved over time, the dextrose prolotherapy arm had greater reductions in pain at 2-3 months. For example, Mansiz-Kaplan, 2020[68] reported that median VAS with activity at 7 weeks was 1 (IQR 0-3) for dextrose prolotherapy, compared with 5 (4-7) for normal saline injection.

Dextrose Prolotherapy versus Corticosteroid Injection

Two trials[65,70] compared dextrose prolotherapy (20-27%) to 1 injection of methylprednisolone acetate (40 mg). Dextrose injections occurred in 1-3 sessions over a maximum of 1 month. Both studies used ultrasound guidance for injections. Both RCTs evaluated pain-related functioning and pain intensity, 1 addressed health-related quality of life. Neither addressed adverse events or other eligible outcomes.

The evidence is very uncertain about the effect of dextrose prolotherapy on pain-related functioning at short and medium-term follow-up (very low COE, **Table 14**). RCTs assessed FFI[65] or the Foot and Ankle Ability Measure (FAAM) Activities of Daily Living (ADL) and Sports subscales.[70] Both studies showed that participants in all arms improved over time, but differences between groups were inconsistent across studies and also between measures in the same study. For example, at 3 months, Raissi, 2023[70] reported better FAAM-ADL scores in the dextrose prolotherapy group (mean 78.5 versus 70.0 in the corticosteroid arm), but slightly worse FAAM-Sport scores (mean 66.2 versus 70.0), though this did not meet MCID. Karakilic, 2023[65] also found no significant differences between groups in FFI scores at 3 months, but mean scores favored the dextrose prolotherapy arm (*eg*, FFI total 27.9 versus 35.7 in the corticosteroid group).

Prolotherapy may result in little to no difference in health-related quality of life at short- and medium-term follow-up (low COE, **Table 14**). Karakilic, 2023[65] assessed the 36 item Short-Form Health Survey (SF-36) and only reported individual domain scores, instead of the physical or mental health component scores. Participants in all arms improved on all domain scores over time, and there were no significant differences between groups for any domain.

Both RCTs reported reductions in pain intensity for participants in all arms, as assessed with VAS[65] or NRS.[70] Raissi, 2023[70] reported that the corticosteroid group had lower NRS at 2 weeks, but there were no differences between groups at 3 months. Karakilic, 2023[65] also found no significant differences between groups at 1 and 3 months.

Table 14. Plantar Fasciitis COE: Dextrose Prolotherapy versus Corticosteroid Injection

Outcome Measure	Follow-Up Total *N* (# of Studies)	Anticipated Absolute Effects on Mean Score at Follow-Up			Certainty	What Happens
		Dextrose Prolotherapy	Cortico-steroid	Mean Difference		
Pain-related functioning FFI, FAAM-ADL, FAAM-Sport	Short-term (2-4 wk) *N* = 191 (2 RCTs)[65,70]	70.3*	76.7*	-6.4*	⊕◯◯◯ Very low[a,b]	The evidence is very uncertain about the effect of dextrose prolotherapy on pain-related functioning at short-term follow-up.
	Medium-term (3 mo) *N* = 191 (2 RCTs)[65,70]	78.5*	70.0*	8.5*	⊕◯◯◯ Very low[a,b]	The evidence is very uncertain about the effect of dextrose prolotherapy on pain-related functioning at medium-term follow-up.
Health-related quality of life SF-36	Short-term (1 mo) *N* = 147 (1 RCT)[65]	—†	—†	—†	⊕⊕◯◯ Low[a]	Prolotherapy may result in little to no difference in health-related quality of life at short-term follow-up.
	Medium-term (3 mo) *N* = 147 (1 RCT)[65]	—†	—†	—†	⊕⊕◯◯ Low[a]	Prolotherapy may result in little to no difference in health-related quality of life at medium-term follow-up.

Notes. *Values for mean FAAM-ADL scores at follow-up for dextrose prolotherapy and corticosteroid groups from Raissi, 2023.[70] Differences calculated by review team.

†Study only reported SF-36 domains, and there were no statistically significant differences between groups in any domain.

GRADE Working Group grades of evidence:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

a. Downgraded 2 levels for study limitations (1 study rated high for RoB).

b. Downgraded 1 level for inconsistency (direction of effects is different between the 2 studies).

Abbreviations. ADL=activities of daily living; FAAM=Foot and Ankle Ability Measure; FFI=Foot Function Index; mo=month; QoL=quality of life; RCT=randomized controlled trial; RoB=risk of bias; wk=weeks.

Dextrose Prolotherapy versus Extracorporeal Shock Wave Therapy

We identified 2 trials that compared dextrose prolotherapy (15-20%) to ESWT, 1 of which applied shocks only to the heel,[71] and the other used shocks to both the heel and foot muscles.[67] Dextrose prolotherapy involved 2-3 injection sessions over 2-6 weeks. Both RCTs evaluated pain-related functioning, pain intensity, and adverse events. Neither addressed the other eligible outcomes.

Prolotherapy may result in little to no difference in pain-related functioning at short and medium-term follow-up (low COE, **Table 15**). Both trials reported improvements in participants for all arms over time. Kesikburn, 2022[67] found no differences between groups in FFI total scores at 6 and 12 weeks. Asheghan, 2021[71] assessed FAAM-ADL and FAAM-Sport at 6 and 12 weeks, and showed no

significant between-group differences in FAAM-ADL but reported that the ESWT arm had significantly greater improvement in FAAM-Sport. However, mean differences in FAAM-Sport did not meet established MCID at either time point (*eg*, mean 83.3 in dextrose arm versus 88.7 in ESWT arm at 6 weeks).

The evidence is very uncertain about the effect of dextrose prolotherapy on adverse events (very low COE, **Table 15**). Both trials addressed adverse events and reported that no adverse events (or no serious events) were detected in any group. Once again, assessments for adverse events were not clearly described and defined.

Both trials reported no significant differences in pain severity between groups at 6 or 12 weeks as measured by the VAS. However, both groups showed significant improvement in pain severity when compared to baseline.

Table 15. Plantar Fasciitis COE: Dextrose Prolotherapy versus Extracorporeal Shock Wave Therapy

Outcome Measure	Follow-Up Total *N* (# of Studies)	Anticipated Absolute Effects on Mean Score at Follow-Up			Certainty	What Happens
		Dextrose Prolotherapy	ESWT	Mean Difference		
Pain-related functioning FFI, FAAM-ADL, FAAM-Sport	Short-term (6 wk) *N* = 91 (2 RCTs)[67,71]	87.5*	88.3*	-0.8*	⊕⊕◯◯ Low[a]	Prolotherapy may result in little to no difference in pain-related functioning at short-term follow-up.
	Medium-term (12 wk) *N* = 91 (2 RCTs)[67,71]	90.0*	91.3*	-1.3*	⊕⊕◯◯ Low[a]	Prolotherapy may result in little to no difference in pain-related functioning at medium-term follow-up.
Adverse events NR	Medium-term (12 wk) *N* = 91 (2 RCTs)[67,71]	0†	0†	—	⊕◯◯◯ Very low[a,b]	The evidence is very uncertain about the effect of dextrose prolotherapy on adverse events.

Notes. *Values for mean FAAM-ADL scores at follow-up for dextrose prolotherapy and extracorporeal shock wave therapy groups from Asheghan, 2021.[71] Differences calculated by review team.

†No adverse events were reported in either trial (adverse events not defined).

GRADE Working Group grades of evidence:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

a. Downgraded 2 levels for study limitations (1 study rated high for RoB).

b. Downgraded 1 level for indirectness (no information about how or when adverse events were assessed).

Abbreviations. ADL=activities of daily living; ESWT=extracorporeal shock wave therapy; FAAM=Foot and Ankle Ability Measure; FFI=Foot Function Index; mo=month; NR=not reported; RCT=randomized controlled trial; RoB=risk of bias; wk=weeks.

Dextrose Prolotherapy versus Other Comparators

Two RCTs, both rated high RoB, compared dextrose prolotherapy with PT and home exercises[66] and PRP.[72] Ersen, 2018[66] evaluated 3 sessions of dextrose prolotherapy injections (over 6 weeks), compared with therapeutic exercises during PT sessions and a home exercise program for 3 months. This study enrolled 60 participants and found that pain-related functioning (assessed with FFI and the Foot and Ankle Outcome Score [FAOS]) improved for both groups, with the dextrose prolotherapy group having significantly greater improvement at 6 weeks and 3 months on both measures. At 3 weeks, there were no significant between-group differences on both measures, and at 12 months, there were no differences on the FFI, but on the FAOS the dextrose prolotherapy arm still showed greater improvements. Similarly, for pain intensity (measured with VAS), both groups improved over time and the dextrose prolotherapy arm had greater improvements at 6 weeks, and 3 and 12 months. At 3 weeks, there were no significant between-group differences. This study did not report other eligible outcomes.

The second study, Kim, 2014,[72] compared dextrose prolotherapy with hypertonic saline injections, both administered in 2 sessions over 4 weeks and using ultrasound guidance. This study reported that participants in both groups improved in FFI during follow-up over 7 months, but there were no significant between-group differences in pain-related functioning. No other eligible outcomes were reported.

Finally, Karakilic, 2023,[65] described above in the corticosteroid section, also included a third arm that received 10 sessions of phonophoresis. As noted previously, participants in all groups improved over time, and there were no significant between-group differences in FFI, SF-36 domains, or VAS. Although there were no statistically significant differences, mean scores for FFI were lower for the dextrose prolotherapy group, particularly at 3 months (mean 27.9 versus 35.5 for the phonophoresis group).

SHOULDER PAIN

Overview

Twelve RCTs (reported in 13 articles) evaluated dextrose prolotherapy for the treatment of shoulder pain. **Table 16** summarizes key study characteristics and main findings for prioritized outcomes. The majority of studies ($k = 8$) included participants with a variety of rotator cuff conditions and/or bursitis, while 4 focused exclusively on supraspinatus tendinopathy. Included participants had to have symptoms (*eg*, pain and activity limitations) that were at least 3-6 months in duration and all but 1 required imaging evidence (either ultrasound or magnetic resonance imaging [MRI]) to confirm shoulder pathology. All studies required participants to not be responsive to conventional treatment or to not have received shoulder injections or surgery in at least the past 8 weeks. Participants were young and middle-aged adults (mean ages 46-60 years) and included variable proportions of women (32-77% female). None of the RCTs were conducted in the US; 6 were conducted in Asia,[73-79] 4 in the Middle East,[80-83] and 1 each in Australia[84] and Canada.[85] Most studies were small with total N range 12-77 ($k = 10$), and only 2 RCTs had $N > 100$.[82,83] Three RCTs[78,82,83] had follow-up over 6-12 months, but most studies evaluated outcomes over 3-4 months ($k = 7$). Most trials evaluated pain-related functioning ($k = 10$), 8 assessed physical performance, and all reported on pain intensity or severity. No studies assessed health-related quality of life, cost, or treatment burden. Most RCTs were also rated high RoB ($k = 9$) for a variety of reasons, including concerns about randomization and allocation, deviations from the intended interventions, missing data from loss to follow-up, and bias in outcome assessments.

One study were assessed as low RoB[74,76] and 2 rated as some concerns.[73,75] Detailed RoB ratings (by domain and overall) are presented in **Appendix E**.

Below, we first describe study characteristics and findings for shoulder pain due to a variety of rotator cuff conditions and/or bursitis, grouping studies by comparators within this subsection. Then, we summarize results for the 4 studies that specifically addressed supraspinatus tendinopathy. Detailed trial characteristics and findings are found in **Appendix H**.

Table 16. Summary of Characteristics and Key Findings for Shoulder Pain

Author, Year Study Design; RoB; Country Key Participant Characteristics	Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance*	Adverse Events
Subacromial Bursitis/Mixed Rotator Cuff Pathology					
Bertrand, 2016[85] RCT; High; Canada Shoulder pain > 3 mo, exam positive for shoulder impingement, and ultrasound findings (supraspinatus tendinosis, partial or full-thickness tear), no corticosteroid injection in past 8 wk; mean ages 51-54, 32-41% female	25% dextrose volume variable (+0.1% lidocaine), 0.5-1 ml at each of multiple points in shoulder; and PT (exercises, ice massage), home exercise program *N* = 27 (27) Clinic/home; 2 mo (3 injections, 1 mo apart), 3 mo (7 PT sessions, daily home exercise)	2 comparators, both with PT/home exercise: • Normal saline volume variable (+0.1% lidocaine) using same injection procedure as dextrose • Normal saline volume variable (+0.1% lidocaine) superficial injections only *N* = 24 (19); 26 (26) Clinic/home; 2 mo (3 injections, 1 mo apart), 3 mo (7 PT sessions, daily home exercise)	—	—	"One subject in the [normal saline] group developed adhesive capsulitis…[and] was removed from the study. No other side effects or adverse events were noted other than discomfort with injection and minor postinjection soreness."
Chang, 2021[75] RCT; Some concerns; Taiwan Shoulder pain ≥ 3 mo, exam positive for shoulder impingement, and ultrasound findings (subacromial bursa thickness >2 mm, no full-thickness rotator cuff tear), no adhesive capsulitis, no prior shoulder surgery or corticosteroid injection, no “regular” oral corticosteroids or NSAIDs; mean ages 46-48 yrs, 36-44% female	13.5% dextrose 5 ml (+ 0.1% xylocaine) in subacromial bursa, ultrasound-guided *N* = 25 (25) Clinic; 4 wk (3 injections, 2 wk apart)	Normal saline 5 ml (+ 0.1% xylocaine) in subacromial bursa, ultrasound-guided *N* = 25 (25) Clinic; 4 wk (3 injections, 2 wk apart)	**SPADI (5 wk, 2 & 4 mo)‡** ↑ Dextrose-Saline	**ROM: Forward Flexion, Abduction (5 wk, 2 & 4 mo)‡** ↔ Dextrose-Saline	1 participant in dextrose group dropped out due to side effects

Author, Year Study Design; RoB; Country Key Participant Characteristics	Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance*	Adverse Events
Sam, 2023[79] RCT; High; Indonesia Frozen shoulder (chronic symptoms >3 mo, shoulder pain with activities, increasing stiffness, pain and restricted ROM on exam), no shoulder injection in past 3 mo; mean ages 58 yrs, 55-68% female	Dextrose (%NR volume NR), injections along rotator cuff, in the glenohumeral joint, subacromial bursa, and other points *N* = 26 (19) Clinic; 6 wk (4 injections, 2 wk apart)	Normal saline (volume NR), injections along rotator cuff, in the glenohumeral joint, subacromial bursa, and other points *N* = 25 (20) Clinic; 6 wk (4 injections, 2 wk apart)	**DASH (6, 12 wk)** ↔ Dextrose-Saline	**ROM: Forward Flexion, Abduction, Adduction, External Rotation, Internal Rotation (6, 12 wk)** ↔ Dextrose-Saline	—
Sari, 2020[82] RCT; High; Turkey Shoulder pain ≥ 3 mo, rotator cuff pathology on MRI (bursitis tendinosis or partial tears grade I), and failed non-invasive treatments (NSAIDs, PT or exercises) for ≥ 2 mo, no prior shoulder injection, and no shoulder surgery in past12 wk ; mean age 52 yrs, 77% female	16% dextrose 5 ml (+ 0.2% lidocaine) in subacromial bursa ultrasound-guided; and home exercise program *N* = 32 (30) Clinic/home; Single injection, 6 wk exercises	3 comparators, all with same injection procedure and home exercise program: • Normal saline 6 ml (+0.6% lidocaine) • Triamcinolone 80 mg (+0.6% lidocaine) • PRP 5 ml *N* = 31 (30); 33 (30); 33 (30) Clinic/home; Single injection, 6 wk exercises	**ASES (3 wk)*§** ? Dextrose-Saline ↓ Dextrose-Steroid ? Dextrose-PRP **ASES (12, 24 wk)*** ↔ Dextrose-Saline ↔ Dextrose-Steroid ↔ Dextrose-PRP **WORC (3 wk)*§** ? Dextrose-Saline ↓ Dextrose-Steroid ? Dextrose-PRP **WORC (12 wk)*** ↔ Dextrose-Saline ↔ Dextrose-Steroid ↔ Dextrose-PRP **WORC (24 wk)*§** ? Dextrose-Saline ? Dextrose-Steroid ? Dextrose-PRP	—	—

Author, Year Study Design; RoB; Country Key Participant Characteristics	Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance*	Adverse Events
Lin, 2023[73] RCT; Some concerns; Taiwan Shoulder pain ≥ 6 mo and ultrasound findings of chronic subacromial bursitis, no adhesive capsulitis or limitation in ROM, no prior shoulder surgery, and no shoulder injection in past 3 mo; mean ages 53-57 yrs, 36-58% female	20% dextrose 3 ml in subacromial bursa, ultrasound-guided *N* = 28 (28) Clinic; Single injection	Triamcinolone 40 mg (+ lidocaine %NR) in subacromial bursa, ultrasound-guided *N* = 26 (26) Clinic; Single injection	**SPADI (2, 6, 12 wk)** ↓ Dextrose-Steroid	**ROM: Forward Flexion, Abduction, External Rotation, Internal Rotation (2, 6, 12 wk)** ↓ Dextrose-Steroid	—
Nasiri, 2021[80] RCT; High; Iran Shoulder pain and/or loss of ROM minimum of 6 mo or failed conservative treatment for ≥ 3 mo, rotator cuff lesion confirmed by exam and ultrasound, not frozen shoulder, no prior shoulder surgery, and no shoulder injection in past 12 wk; mean ages 47-51 yrs, 63-65% female	25% dextrose 2 ml (+ 1% lidocaine) in hypoechoic areas of supraspinatus tendon, ultrasound-guided; and home exercise program *N* = 20 (14) Clinic/home; Single injection	Triamcinolone 40 mg (+ 1% lidocaine) in subacromial bursa, ultrasound-guided; and home exercise program *N* = 20 (15) Clinic/home; Single injection	**SPADI (3, 12 wk)** ↔ Dextrose-Steroid	—	"*developed exacerbation of pain after injections and therefore…excluded from study*": Prolotherapy—18% (n= 3) Steroid—6% (n= 1)
Mofrad, 2021[81] RCT; High; Iran Shoulder pain ≥ 3 mo and small rotator cuff tear or tenopathy on MRI, no subdeltoid bursitis or adhesive capsulitis, no shoulder surgery, and no shoulder injection in past yr; mean ages 53-57 yrs, 48-59% female	12.5% dextrose 8 ml (+ lidocaine %NR) in multiple areas of shoulder, ultrasound-guided *N* = 33 (32) Clinic/home; 1 wk (2 injections), 3 wk (10 PT sesion, daily exercises)	PT (hot packs, TENS, therapeutic ultrasound) with home exercise program *N* = 33 (33) Home; 3 wk (10 PT sessions, daily exercises)	**Modified SPADI (2 wk, 3 mo)†** ↔ Dextrose-PT	—	*"…we did not find adverse reactions to dextrose prolotherapy except for post-injection soreness in 6 patients."*

Author, Year Study Design; RoB; Country Key Participant Characteristics	Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance*	Adverse Events
Seven, 2017[83] RCT; High; Turkey Symptoms ≥ 6 mo and failed conservative treatment for ≥ 3 mo, rotator cuff lesions on MRI (tendinosis, partial tear), no prior shoulder surgery, and no corticosteroid injection in past 12 wk; mean ages 46-50 yrs, 45-46% female	22.5% dextrose 4 ml (+ lidocaine %NR) in subacromial bursa and 13.5% dextrose 20 ml (+ lidocaine %NR) in various other areas of shoulder, ultrasound-guided; and home exercise program *N* = 60 (57) Clinic/home; 6 wk (3 injections, 3 wk apart), unclear duration exercises (3 times daily)	PT (stretching and exercises in clinic) *N* = 60 (44) Clinic/home; 12 wk (3 sessions/wk), unclear duration exercises (3 times daily)	**SPADI (3 wk)** ↔Dextrose–PT **SPADI (6, 12 wk, 1 yr)** ↑ Dextrose–PT **Modified WORC (3 wk)*** ↔Dextrose–PT **Modified WORC (6, 12 wk, 1 yr)*** ↑ Dextrose–PT	**ROM: Forward Flexion, Abduction (3, 6 wk)** ↔Dextrose–PT **ROM: Forward Flexion, Abduction (12 wk, 1 yr)** ↑ Dextrose–PT **ROM: Internal rotation (3, 6, 12 wk)** ↔Dextrose–PT **ROM: Internal rotation (1 yr)** ↑ Dextrose–PT **ROM: External rotation (3, 6 & 12 wk, 1 yr)** ↔ Dextrose - PT	*"None…experienced any serious complications (eg, bleeding, infection, cellulitis, septic joint)… 3 patients had extreme pain one or two days after injections in the prolotherapy group that was reduced after 2 days of rest and local application of heat therapy, 2 patients had grade 2 skin burns after first injection because of improper use of hot water bags and local anesthetic effect of the injections, and 1 patient had hypotension."*
Supraspinatus Tendinopathy Only					
Abd Karim, 2023[78] RCT; High; Malaysia Shoulder pain ≥ 3 mo, supraspinatus tendinosis or partial tendon tear on ultrasound or MRI, failed conventional treatment for ≥ 3 mo; mean ages 51-58 yrs, 46-54% female	16.7% dextrose 3 ml (+ lignocaine %NR) in the lesion, ultrasound-guided; and home exercise program *N* = 32 (28) Clinic/home; Single injection, 3 wk for exercise	PRP 2 ml in the lesion, ultrasound-guided; and home exercise program *N* = 32 (31) Clinic/home; Single injection, 3 wk for exercise	**SPADI (3 & 6 wk, 3 & 6 mo)** ↔ Dextrose-PRP	**ROM: Forward Flexion, Abduction, External Rotation, Internal Rotation (3 & 6 wk, 3 & 6 mo)** ↔ Dextrose-PRP	"*There were no reports of serious adverse effects, such as cellulitis, septic arthritis, or damage extension caused by ultrasound…*" Pain (>2 days after injection): Prolotherapy—38% (n= 12) PRP—62% (n= 20)
Cole, 2017[84] RCT; High; Australia Symptomatic supraspinatus tendinopathy ≥ 3 mo based on history, exam, and ultrasound, no shoulder surgery in past 12 mo; mean	25% dextrose 2 ml (+ 0.5% lignocaine) in subacromial bursa and supraspinatus tendon (hypoechoic or anechoic areas), ultrasound-guided *N* = 19 (16)	Methylprednisolone 40 mg (+ 0.5% lignocaine) in subacromial bursa and supraspinatus tendon (hypoechoic or anechoic areas), ultrasound-guided	—	**ROM: Forward Flexion, Abduction, External Rotation (6 mo)** ↔ Dextrose-Corticosteroid	—

Author, Year Study Design; RoB; Country Key Participant Characteristics	Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance*	Adverse Events
ages 46-51 yrs, 24-26% female	*N* = 17 (15) Clinic; Single injection	Clinic; Single injection			
George, 2018[77] RCT; High; Malaysia Symptoms ≥ 6 mo, supraspinatus tendinosis on ultrasound, functional score did not improve > 30% after 1 mo of conventional treatment; mean ages 58-60 yrs, % female NR	12.5% dextrose 0.5-1.0 ml (+0.5% lignocaine) in "area of painful tendinosis," ultrasound-guided; and PT *N* = 7 (7) Clinic; Single injection	PT *N* = 5 (4) NR; NR	**DASH (12 wk)** ↔ Dextrose-PT	—	—
Lin, 2022[74,76] RCT; Low; Taiwan Shoulder pain ≥ 6 mo and ultrasound consistent with chronic degenerative supraspinatus tendinosis, no adhesive capsulitis or limited ROM, no prior shoulder surgery, and no shoulder injection in past 3 mo; mean ages 49-52 yrs, 45-50% female	20% dextrose 5 ml in supraspinatus tendon insertion site, ultrasound-guided *N* = 29 (29) Clinic; Single injection	Normal saline (volume NR) in supraspinatus tendon insertion site, ultrasound-guided *N* = 28 (28) Clinic; Single injection	**SPADI (2 wk)** ↑ Dextrose-Saline **SPADI (6, 12 wk)** ↔ Dextrose-Saline	**ROM: Forward Flexion (2 wk)** ↑ Dextrose-Saline **ROM: Forward Flexion (6, 12 wk)** ↔ Dextrose-Saline **ROM: Abduction, External Rotation, Internal Rotation (2, 6, 12 wk)** ↔ Dextrose-Saline	—

Notes. *No MCID available, direction of effect based on statistical significance.

†Study used modified scoring of SPADI and also did not report mean scores at follow-up points (only change of modified scores).

‡Study reported statistically non-significant group x time effect in repeat measures analysis of variance.

§Study reported statistically significant difference comparing all 4 arms but not pairwise comparisons.

Symbols. ↑: At specified follow-up time point, the dextrose arm had a better scale score than the comparator arm (meeting MCID); ↔: At specified follow-up time point, the difference in scale scores between the dextrose and comparator arms did not meet MCID; ↓: At specified follow-up time point, the dextrose arm had a worse scale score than the comparator arm (meeting MCID); ?: Review team was unable to interpret scale scores.

Abbreviations. AE=adverse effect/event; ASES= American Shoulder and Elbow Surgeons Standardized Shoulder Assessment; DASH=disability of the arm, shoulder, and hand; MCID=minimal clinically important difference; mg=milligram; mo=month; MRI= Magnetic resonance imaging; NR=not reported; NSAIDs= Non-steroidal anti-inflammatory drugs; PRP=platelet rich plasma; PT=physical therapy; SPADI=Shoulder Pain and Disability Index; RC=rotator cuff; RCT=randomized controlled trial; RoB=risk of bias; ROM=range of motion; TENS=transcutaneous electrical nerve stimulations; wk=week; WORC=Western Ontario Rotator Cuff Index; yr=year.

Mixed Rotator Cuff Pathology and/or Subacromial Bursitis

Eight RCTs evaluated dextrose prolotherapy for shoulder pain due to varied rotator cuff pathology and/or subacromial bursitis. All RCTs excluded individuals with prior shoulder surgery and/or injections. Three trials[80,82,83] also required that participants had failed previous conservative management. Comparators included normal saline injection ($k = 4$),[74-76,79,82,85] corticosteroid injection ($k = 3$),[73,80,82] PT and/or home exercise program ($k = 2$),[81,83] and PRP ($k = 1$).[82] Sari, 2020[82] compared dextrose prolotherapy with 3 other treatments (normal saline, corticosteroid, and PRP injections). Prolotherapy injections used 12-25% dextrose in 1-4 injection sessions over a maximum duration of 2 months. Injection sites included the subacromial bursa, the supraspinatus tendon, and other areas in and around the rotator cuff. The majority of studies used ultrasound guidance for all injections ($k = 6$).

Dextrose Prolotherapy versus Normal Saline Injection (With or Without Local Anesthetic)

Four trials[75,79,82,85] evaluated dextrose prolotherapy (13.5-25% dextrose) versus normal saline injection. Dextrose prolotherapy involved 1-4 injection sessions over a maximum duration of 2 months, and 2 studies used imaging guidance.[75,82] Two RCTs also included PT and/or home exercise program in all arms.[82,85]

The evidence is very uncertain about the effect of dextrose prolotherapy on pain-related functioning at short- and medium-term follow-up (very low COE) but may result in little to no difference in the long term (low COE, **Table 17**). Three RCTs[75,79,82] evaluated pain-related functioning using the questionnaire on Disability of the Arm, Shoulder, and Hand (DASH), Shoulder Pain and Disability Index (SPADI), American Shoulder and Elbow Surgeons Standardized Shoulder Assessment (ASES), and Western Ontario Rotator Cuff Index (WORC). Chang, 2021[75] and Bertrand, 2016[85] found that participants in both arms improved over the 3-4 months of follow-up. Sari, 2020[82] also found that all groups improved in ASES scores over 6 months, but WORC scores for all groups improved only through 3 months and then worsened at 6 months. The pooled estimates for short- and medium-term pain-related functioning did not indicate a clear direction of effect (*eg*, -0.29 SMD, 95% CI [-1.15, 0.57] for short-term effect) and the PI included very large effect sizes in both directions (**Figure 5**). For long-term pain-related functioning, Sari, 2020[82] found no significant between-group differences in ASES scores at 6 months, and did not report statistical comparisons for WORC scores between dextrose prolotherapy versus normal saline arms.

Prolotherapy may result in little to no difference in physical performance at short- and medium-term follow-up (low COE, **Table 17**). Two RCTs [75,79] evaluated ROM for a range of movements (*eg*, forward flexion and abduction) through a maximum of 4 months follow-up. Both studies found that participants in both arms generally improved on all measures over time, and neither showed significant between-group differences at either short- or medium-term follow-up.

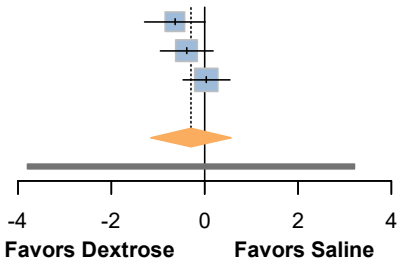
The evidence is very uncertain on the effect of dextrose prolotherapy on adverse events (very low COE, **Table 17**). Two studies addressed adverse events, with Chang, 2021[75] reporting that 1 participant (4%) dropped out of the dextrose prolotherapy group due to “side effect” but providing no further description of what occurred. Bertrand, 2016[85] indicated that 1 participant in the normal saline group was excluded after developing adhesive capsulitis and there was post-injection discomfort but without indicating the proportion of participants who experienced this outcome.

Figure 5. Mixed Rotator Cuff Pathology and/or Subacromial Bursitis: Effect of Dextrose Prolotherapy versus Normal Saline on Pain-Related Functioning

A. Short-Term Follow-Up (3-6 wk)

Author, Year	Dextrose N	Dextrose Mean	Dextrose SD	Saline N	Saline Mean	Saline SD	Standardised Mean Difference	SMD [95% CI]
Sam, 2023	19	13.5	9.7	20	20.3	10.9	-0.64	[-1.28; 0.01]
Chang, 2021	25	25.2	18.8	25	34.7	28.5	-0.39	[-0.95; 0.17]
Sari, 2020	30	52.0	7.8	30	51.7	9.7	0.04	[-0.47; 0.54]
Random effects model	**74**			**75**			**-0.29**	**[-1.15; 0.57]**
Prediction interval								**[-3.79; 3.21]**

Heterogeneity: τ^2 = 0.04 [0.00; 4.51]



B. Medium-Term Follow-Up (3 mo)

Author, Year	Dextrose N	Dextrose Mean	Dextrose SD	Saline N	Saline Mean	Saline SD	Standardised Mean Difference	SMD [95% CI]
Sam, 2023	19	10.0	10.1	20	13.3	10.8	-0.31	[-0.94; 0.32]
Chang, 2021	25	19.2	20.5	25	28.6	28.0	-0.38	[-0.94; 0.18]
Sari, 2020	30	46.4	9.0	30	48.3	7.4	-0.23	[-0.73; 0.28]
Random effects model	**74**			**75**			**-0.30**	**[-1.01; 0.41]**
Prediction interval								**[-2.40; 1.80]**

Heterogeneity: τ^2 = 0 [0.00; 0.16]

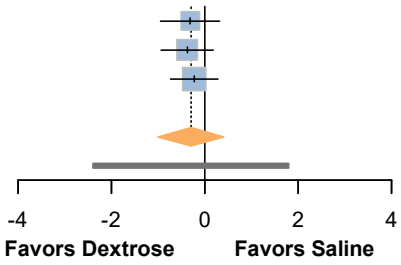


Table 17. Mixed Rotator Cuff Pathology/Subacromial Bursitis COE: Dextrose Prolotherapy versus Normal Saline Injection (With or Without Local Anesthetic)

Outcome Measure	Follow-Up Total *N* (# of Studies)	SMD Pooled Estimate (95% CI)	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up			Certainty	What Happens
			Dextrose Prolotherapy	Saline	Difference		
Pain-related functioning ASES, DASH, SPADI, WORC	Short-term (3-6 wk) *N* = 164 (3 RCTs)[75,79,82]	-0.3 (-1.2, 0.6)	26.4* (1.9, 50.9)	34.7*	-8.3* (-32.8, 16.3)	Very low[a,b] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on pain-related functioning at short-term follow-up.
	Medium-term (3 mo) *N* = 164 (3 RCTs)[75,79,82]	-0.3 (-1.0, 0.4)	20.2* (0.6, 39.8)	28.6*	-8.4* (-28.0, 11.2)	Very low[a,b] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on pain-related functioning at medium-term follow-up.
	Long-term (6 mo) *N* = 63 (1 RCT)[82]	—	91.3†	96.6†	-5.3†	Low[a] ⊕⊕◯◯	Dextrose prolotherapy may have little to no effect on pain-related functioning at long-term follow-up.
Physical performance ROM	Short-term (5-6 wk) *N* = 101 (2 RCTs)[75,79]	—	163.6‡	157.0‡	6.6‡	Low[a] ⊕⊕◯◯	Dextrose prolotherapy may have little to no effect on physical performance at short-term follow-up.
	Medium-term (3-4 mo) *N* = 101 (2 RCTs)[75,79]	—	168.8‡	160.2‡	8.6‡	Low[a] ⊕⊕◯◯	Dextrose prolotherapy may have little to no effect on physical performance at medium-term follow-up.
Adverse events NR	*N* = 96 (2 RCTs)[75,86]	—	4%§	0§	4%§	Very low[a,c,d] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on adverse events.

Notes. *Anticipated mean SPADI score at follow-up for intervention arm and MD calculated by review team, based on pooled SMD and mean SPADI score at follow-up for comparator arm from Chang, 2021.[75]

†Values for mean follow-up scores on WORC for intervention and comparators from Sari, 2020.[82] Difference calculated by review team.

‡Values for mean ROM (degrees) forward flexion at follow-up for intervention and comparator arms from Chang, 2021.[75] Differences calculated by review team.

§Chang, 2021[75] reported 1 participant dropped out in dextrose group from side effects.

GRADE Working Group grades of evidence:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

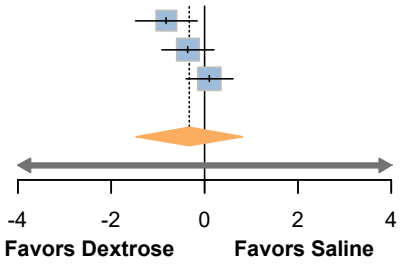
Explanations:

a. Downgraded 2 levels for study limitations (1-2 studies rated high RoB).
b. Downgraded 1 level for imprecision (CI goes from large effect favoring dextrose prolotherapy to medium effect favoring normal saline).
c. Downgraded 1 level for indirectness (no information about how or when adverse events were assessed).
d. Downgraded 1 level for imprecision (not powered to detect minimum adverse event rate <10%; see Methods).
Abbreviations. ASES=American Shoulder and Elbow Surgeons; DASH=Disabilities of the Arm, Shoulder, and Hand; mo=month; RCT=randomized controlled trial; RoB=risk of bias; ROM=range of motion; SPADI=Shoulder Pain and Disability Index; wk=week; WORC=Western Ontario Rotator Cuff Index.

All 4 RCTs evaluated pain intensity or severity, using VAS[75,82,85] or NRS[79] over a maximum follow-up of 3-9 months. As with pain-related functioning and physical performance, participants generally improved in all groups. Three studies[75,82,85] found no significant differences between dextrose prolotherapy and normal saline arms in pain reduction (over follow-up up to 3-9 months), but Sam, 2023[79] indicated that there was significantly greater improvement in the dextrose arm at 6 and 12 weeks. Pooled estimates for short- and medium-term effects did not indicate a clear effect in either direction, with inconsistency between studies contributing to very wide PI at both time points (**Figure 6**).

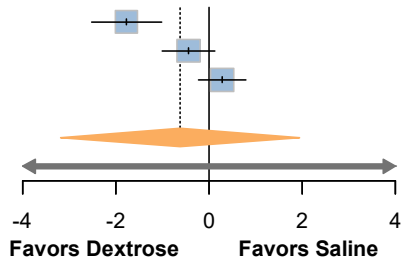
Figure 6. Mixed Rotator Cuff Pathology and/or Subacromial Bursitis: Effect of Dextrose Prolotherapy versus Normal Saline on Pain Intensity or Severity

A. Short-Term Follow-Up (3-6 wk)



Author, Year	Dextrose N	Dextrose Mean	Dextrose SD	Saline N	Saline Mean	Saline SD	Standardised Mean Difference	SMD [95% CI]
Sam, 2023	19	1.1	0.8	20	2.0	1.3		-0.82 [-1.48; -0.17]
Chang, 2021	25	3.8	2.4	25	4.8	2.8		-0.36 [-0.92; 0.20]
Sari, 2020	30	4.4	1.2	30	4.2	1.5		0.10 [-0.40; 0.61]
Random effects model	**74**			**75**				**-0.33 [-1.47; 0.81]**
Prediction interval								**[-5.91; 5.26]**
Heterogeneity: τ^2 = 0.12 [0.00; 8.38]								

B. Medium-Term Follow-Up (3-4 mo)



Author, Year	Dextrose N	Dextrose Mean	Dextrose SD	Saline N	Saline Mean	Saline SD	Standardised Mean Difference	SMD [95% CI]
Sam, 2023	19	0.6	0.8	20	2.4	1.2		-1.77 [-2.52; -1.02]
Chang, 2021	25	3.0	2.4	25	4.2	3.0		-0.44 [-1.01; 0.12]
Sari, 2020	30	4.3	1.4	30	3.9	1.5		0.28 [-0.23; 0.79]
Random effects model	**74**			**75**				**-0.62 [-3.18; 1.94]**
Prediction interval								**[-15.10; 13.87]**
Heterogeneity: τ^2 = 0.95 [0.18; 42.54]								

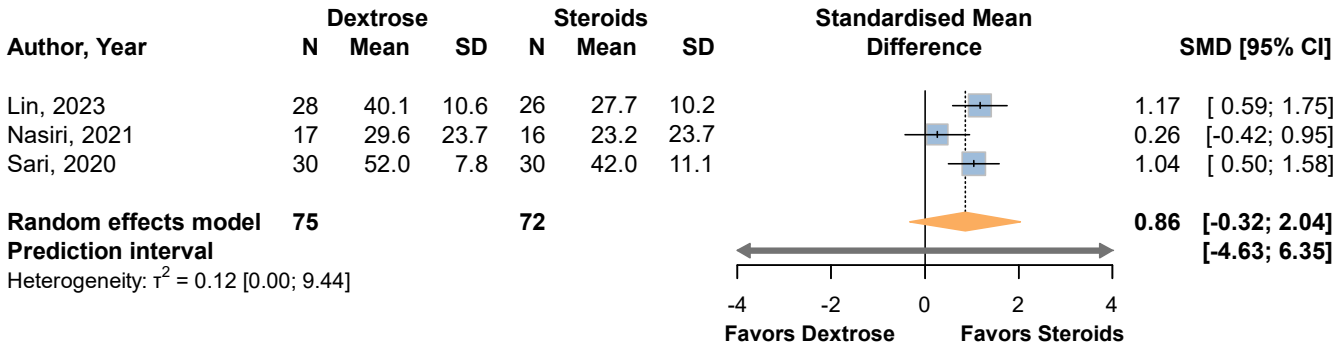
Dextrose Prolotherapy versus Corticosteroid Injection

Three RCTs[73,80,82] compared single injections of dextrose prolotherapy (16-25% dextrose) versus corticosteroid, all using ultrasound guidance. Two studies[80,82] included PT or home exercise program as part of treatments in all arms.

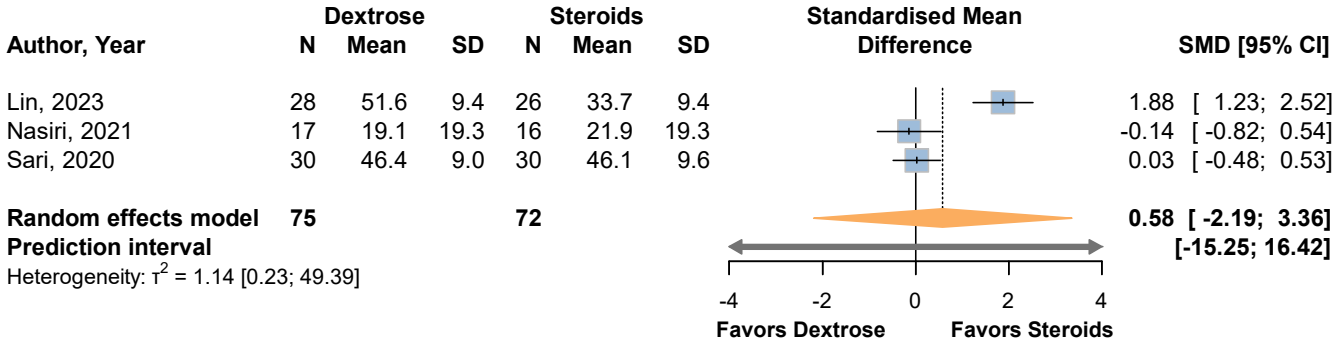
The evidence is very uncertain about the effect of dextrose prolotherapy on pain-related functioning at short- and medium-term follow-up (very low COE) but may result in little to no difference in the long term (low COE, **Table 18**). All 3 trials assessed pain-related functioning, using SPADI,[73,80] or ASES and WORC,[82] over a maximum follow-up of 6 months. All groups in all studies improved at follow-up compared to baseline, except for the dextrose prolotherapy group in Lin, 2023,[73] which improved at 2 and 6 weeks but then returned to baseline functioning by 3 months. Pooled estimates for short- and medium-term effects did not show a clear direction of effect, with inconsistency contributing to the very wide PI (**Figure 7**). For long-term pain-related functioning, Sari, 2020[82] once again showed no significant between-group differences in ASES scores at 6 months, and also did not report between-group comparisons for WORC scores between dextrose prolotherapy versus corticosteroid.

Figure 7. Mixed Rotator Cuff Pathology and/or Subacromial Bursitis: Effect of Dextrose Prolotherapy versus Corticosteroid Injection on Pain-Related Functioning

A. Short-Term Follow-Up (3-6 wk)



B. Medium-Term Follow-Up (12 wk)



Dextrose prolotherapy probably results in worse physical performance compared with steroids, at short- and medium-term follow-up (moderate COE, **Table 18**). Only Lin, 2023[73] assessed physical performance, finding that the corticosteroid group had greater improvements in all ROM (forward flexion, abduction, external rotation, and internal rotation) throughout follow-up over 3 months. In the corticosteroid group, the mean ROM increased for all movements at all time points. In the dextrose prolotherapy arm, while ROM for forward flexion and abduction increased at 2 and 6 weeks, these measures then decreased at 3 months to below baseline levels. There was also no improvement in ROM for external and internal rotation.

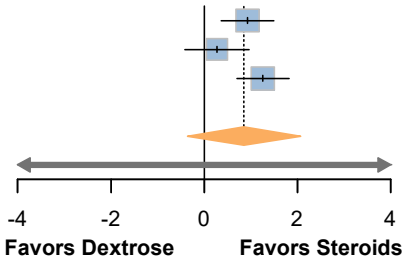
The evidence is very uncertain on the effect of dextrose prolotherapy on adverse events (very low COE, **Table 18**). Only 1 RCT[80] addressed adverse events, reporting that 3 participants (18%) in the

prolotherapy group had exacerbation of pain and were excluded from the study, compared with 1 participant (6%) in the corticosteroid group who had the same outcome.

All 3 RCTs assessed pain intensity and used VAS, over a maximum follow-up of 6 months. All studies showed reductions in pain intensity in all groups at follow-up compared to baseline. Pooled estimates for short- and medium-term effects did not show clear direction of effect (**Figure 8**). Sari, 2020[82] also found no statistically significant between-group differences at 6 months.

Figure 8. Mixed Rotator Cuff Pathology and/or Subacromial Bursitis: Effect of Dextrose Prolotherapy versus Corticosteroid Injection on Pain Intensity or Severity

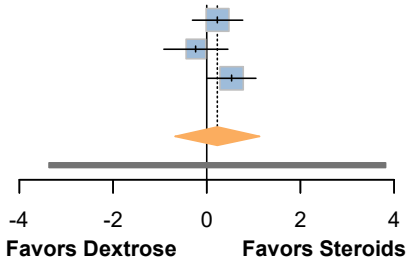
A. Short-Term Follow-Up (3-6 wk)



Author, Year	Dextrose N	Dextrose Mean	Dextrose SD	Steroids N	Steroids Mean	Steroids SD	Standardised Mean Difference	SMD [95% CI]
Lin, 2023	28	4.3	1.0	26	3.0	1.7		0.93 [0.36; 1.49]
Nasiri, 2021	17	4.5	3.5	16	3.5	3.5		0.28 [-0.41; 0.96]
Sari, 2020	30	4.4	1.2	30	2.4	1.8		1.26 [0.70; 1.82]
Random effects model	**75**			**72**				**0.85 [-0.36; 2.06]**
Prediction interval								**[-4.97; 6.67]**

Heterogeneity: τ^2 = 0.13 [0.00; 9.76]

B. Medium-Term Follow-Up (3 mo)



Author, Year	Dextrose N	Dextrose Mean	Dextrose SD	Steroids N	Steroids Mean	Steroids SD	Standardised Mean Difference	SMD [95% CI]
Lin, 2023	28	4.0	1.3	26	3.7	1.3		0.23 [-0.31; 0.76]
Nasiri, 2021	17	2.6	5.4	16	3.9	5.4		-0.23 [-0.92; 0.45]
Sari, 2020	30	4.3	1.4	30	3.5	1.4		0.53 [0.01; 1.04]
Random effects model	**75**			**72**				**0.22 [-0.68; 1.13]**
Prediction interval								**[-3.37; 3.82]**

Heterogeneity: τ^2 = 0.04 [0.00; 5.70]

Table 18. Mixed Rotator Cuff Pathology/Subacromial Bursitis COE: Dextrose Prolotherapy versus Corticosteroid Injection

Outcome Measure	Follow-Up Total *N* (# of Studies)	SMD Pooled Estimate (95% CI)	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up Dextrose Prolotherapy	Steroid	Difference	Certainty	What Happens
Pain-related functioning ASES, SPADI, WORC	Short-term (3-6 wk) *N* = 159 (3 RCTs)[73,80,82]	SMD: 0.9 (-0.3, 2.0)	36.9* (24.6, 48.1)	27.7*	9.2* (-3.1, 20.4)	Very low[a,b] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on pain-related functioning at short-term follow-up.
	Medium-term (12 wk) *N* = 147 (3 RCTs)[73,80,82]	SMD: 0.6 (-2.2, 3.4)	39.2* (13.0, 65.7)	33.7*	5.5* (-20.7, 32.0)	Very low[a,b,c] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on pain-related functioning at medium-term follow-up.
	Long-term (6 mo) *N* = 63 (1 RCT)[82]	—	91.3†	93.9†	-2.6†	Low[a] ⊕⊕◯◯	Dextrose prolotherapy may have little to no effect on pain-related functioning at long-term follow-up.
Physical performance ROM	Short-term (3-6 wk) *N* = 54 (1 RCT)[73]	—	158.8‡	162.5‡	-3.7‡	Moderate[d] ⊕⊕⊕◯	Dextrose prolotherapy probably results in worse physical performance at short-term follow-up.
	Medium-term (12 wk) *N* = 54 (1 RCT)[73]	—	140.5‡	157.2‡	-16.7‡	Moderate[d] ⊕⊕⊕◯	Dextrose prolotherapy probably results in worse physical performance at medium-term follow-up.
Adverse events NR	Medium-term (12 wk) *N* = 40 (1 RCT)[80]	—	18%¶	6%¶	12%¶	Very low[a,e,f] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on adverse events.

Notes. *Anticipated mean SPADI score at follow-up for intervention arm and MD calculated by review team, based on pooled SMD and mean SPADI score at follow-up for comparator arm from Lin, 2023.[73]

†Values for mean follow-up scores on WORC for intervention and comparators from Sari, 2020.[82] Difference calculated by review team.

‡Values for mean flexion (degrees) at follow-up for intervention and comparator arms from Lin, 2023.[73] Differences calculated by review team.

¶Proportion with pain exacerbated after injections in each group. Difference calculated by review team.

GRADE Working Group grades of evidence:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

a. Downgraded 2 levels for study limitations (studies rated high RoB).

b. Downgraded 1 level for imprecision (CI goes from large effect favoring prolotherapy to large effect favoring steroids).

c. Downgraded 1 level for inconsistency (effect varied across studies).

d. Downgraded 1 level for study limitations (studies rated some concerns RoB).

e. Downgraded 1 level for indirectness (no information about how or when adverse events were assessed).

f. Downgraded 1 level for imprecision (not powered to minimum adverse event rate <10%; see Methods for more information).

Abbreviations. ASES=American Shoulder and Elbow Surgeons; mo=month; NR=not reported; NRS=numerical rating scale; RCT=randomized controlled trial; RoB=risk of bias; ROM: SMD=standardized mean difference; SPADI=Shoulder Pain and Disability Index; wk=week.

Dextrose Prolotherapy versus Physical Therapy With or Without Home Exercise Program

Two RCTs[81,83] compared dextrose prolotherapy (12.5-22.5%) to PT with or without home exercise program. Dextrose prolotherapy injections used ultrasound guidance and occurred in 2-3 sessions lasting 1-6 weeks, while duration of PT/home exercise program was 3-12 weeks. Both studies excluded participants with prior corticosteroid injections. Both assessed pain-related functioning, adverse events, and pain intensity, while Seven, 2017[83] also reported physical performance outcomes.

The evidence is very uncertain on the effect of dextrose prolotherapy on pain-related functioning at short- and medium-term follow-up (very low COE) but it may improve outcomes in the long term (low COE, **Table 19**). Pain-related functioning was assessed over 3-12 months, using SPADI and modified WORC (reported as inverted percentage score),[83] or a modified SPADI (reported as percentage of the maximum score).[81] Both studies found that participants in both groups improved in pain-related functioning over time. Mofrad, 2021[81] did not find between-group differences at 2 weeks and 3 months, but Seven, 2017[83] showed that the dextrose prolotherapy had better SPADI and modified WORC scores at 6 weeks, 3 months, and 1 year (there were no significant differences at 3 weeks).

Dextrose prolotherapy may have little to no effect on physical performance at short-term follow-up (low COE) but evidence is very uncertain at medium- and long-term follow-up (very low COE, **Table 19**). Seven, 2017[83] assessed ROM for forward flexion, internal rotation, external rotation, and abduction, finding that measures improved for both groups over time. At 3 and 6 weeks, there were no significant between-group differences for any ROM assessment, but at 3 months and 1 year, there were mixed results for different movements. For example, at 3 months, there was higher ROM for abduction in the dextrose prolotherapy arm (mean 170.8 degrees), compared with the PT group (mean 162.4 degrees); no significant differences were found in the other assessments.

The evidence is very uncertain on the effect of dextrose prolotherapy on adverse events (very low COE, **Table 19).** Both RCTs[81,83] addressed adverse events. Seven, 2017[83] indicated that several participants experienced side effects in the dextrose prolotherapy group (extreme post-injection pain, burns, and hypotension), but did not describe any assessments of the PT group. Mofrad, 2021[81] reported that several participants in the prolotherapy group had post-injection pain and did not provide any information about the PT/exercise group.

Table 19. Mixed Rotator Cuff Pathology/Subacromial Bursitis COE: Dextrose Prolotherapy versus Physical Therapy/Home Exercise

Outcome Measure	Follow-Up Total *N* (# of Studies)	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up Dextrose Prolotherapy	Physical Therapy	Difference	Certainty	What Happens
Pain-related functioning SPADI, modified SPADI, modified WORC	Short-term (2-6 wk) *N* = 186 (2 RCTs)[81,83]	31.3*	42.0*	-10.7*	Very low[a,b] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy pain-related functioning at short-term follow-up.
	Medium-term (3 mo) *N* = 186 (2 RCTs)[81,83]	16.1*	37.3*	-21.2*	Very low[a,b] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy pain-related functioning at medium-term follow-up.
	Long-term (1 yr) *N* = 120 (1 RCT)[83]	7.7*	34.9*	-27.2*	Low[a] ⊕⊕◯◯	Dextrose prolotherapy may improve pain-related functioning at long-term follow-up.
Physical performance ROM	Short-term (3-6 wk) *N* = 120 (1 RCT)[83]	167.2†	161.6†	5.6†	Low[a] ⊕⊕◯◯	Dextrose prolotherapy may have little to no effect on physical performance at short-term follow-up.
	Medium-term (12 wk) *N* = 120 (1 RCT)[83]	173.5†	165.0†	8.5†	Very low[a,c] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on physical performance at medium-term follow-up.
	Long-term (1 yr) *N* = 120 (1 RCT)[83]	176.6†	166.4†	10.2†	Very low[a,c] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on physical performance at long-term follow-up.
Adverse events NR	*N* = 186 (2 RCTs)[81,83]	0*	0*	—	Very low[a,d] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on adverse events.

Notes. *Values for mean SPADI scores at follow-up for intervention and comparator from Seven, 2017.[83] Differences calculated by review team.

†Values for mean forward flexion (degrees) at follow-up for intervention and comparator from Seven, 2017.[83] Differences calculated by review team.

GRADE Working Group grades of evidence:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:
a. Downgraded 2 level for study limitations (studies rated high RoB).
b. Downgraded 1 level for inconsistency (effect varied across studies).
c. Downgraded 1 level for inconsistency (effect varied across ROM assessments).
d. Downgraded 1 level for indirectness (no information about how or when adverse events were assessed).
Abbreviations. mo=month; NR=not reported; RCT=randomized controlled trial; RoB=risk of bias; ROM=range of motion; SPADI=Shoulder Pain and Disability Index; WORC=Western Ontario Rotator Cuff Index; wk=week; yr=year.

Both trials evaluated the effect of dextrose prolotherapy against PT. Using the pain domain of SPADI, Mofrad, 2021 found statistically significant less pain in the prolotherapy group at 2 weeks but not 3 months. On a 10-point VAS, Seven, 2017 found statistically significant less pain in the prolotherapy group at 3 weeks, 6 weeks, 12 weeks, and 1 year.

Dextrose Prolotherapy versus PRP

Finally, Sari, 2020,[82] described above (in the sections on normal saline and corticosteroid comparators), also compared dextrose prolotherapy with 1 injection of PRP. Both pain-related functioning (assessed with ASES and WORC) and pain intensity (measured with VAS) improved for all groups during follow-up through 24 weeks. There were no significant between-group differences in ASES and WORC at 12 weeks, and in ASES at 24 weeks. Although authors reported significant between-group differences between all groups overall for ASES and WORC at the other time points (3 and 24 weeks), they did not provide pairwise comparisons that clearly indicate whether there were significant differences between dextrose prolotherapy and PRP. For pain intensity, there were no significant differences between dextrose prolotherapy and PRP.

Supraspinatus Tendinopathy Only

Four RCTs evaluated dextrose prolotherapy for shoulder pain due to supraspinatus tendinopathy, compared with PRP ($k = 1$),[78] corticosteroid injection ($k = 1$),[84] PT ($k = 1$),[77] and normal saline injection($k = 1$).[74,76] All studies used a single injection of dextrose (12.5-25%) with ultrasound guidance, and required ultrasound or MRI imaging consistent with supraspinatus tendinopathy. Two RCTs excluded individuals with prior shoulder surgery and/or shoulder injections,[84,87] and 2 trials[77,78] required participants to have failed prior conservative treatment.

Abd Karim, 2023[78] randomized 64 participants to 16.7% dextrose prolotherapy versus PRP injection, with both arms also including a home exercise program. Pain-related functioning (SPADI), physical performance (ROM), pain severity (NRS), and adverse events were assessed at 3 weeks to 6 months. Participants in both groups improved for all outcomes over time. There were no statistically significant between-group differences in SPADI at any time point, and differences also did not meet MCID. For physical performance and pain intensity, there were also no significant differences between dextrose prolotherapy and PRP at any time point. In the dextrose prolotherapy group, 12 participants (38%) experienced pain more than 2 days after injection, compared to 20 (62%) in the PRP group.

Cole, 2018[84] enrolled 36 participants and compared 25% dextrose prolotherapy to corticosteroid injection. ROM and pain severity (5-point Likert scale) were assessed at 6 weeks-6 months, and generally, there were minimal improvements in both groups for any outcome over time and no significant between-group differences.

George, 2018[77] randomized only 12 participants to 12.5% dextrose versus PT, and evaluated pain-related functioning with the DASH. Both groups improved in pain-related functioning at 12 weeks, but

there was a small between-group difference (mean difference -2.8) that was not statistically significant and also did not meet MCID.

Finally, Lin, 2022[74,76] enrolled 54 participants to compare 20% dextrose prolotherapy with normal saline injection. Pain-related functioning (SPADI), physical performance (ROM), and pain severity (VAS) were assessed. For the normal saline group, there was generally no to minimal improvement in all of these outcomes. The dextrose prolotherapy group had brief improvement on SPADI, ROM for forward flexion, and VAS at 2 weeks, but all outcomes trended back towards baseline by 6 and 12 weeks. Thus, at the early time point of 2 weeks, dextrose prolotherapy had significantly better outcomes (and for SPADI, the difference exceeded MCID).

LATERAL ELBOW TENDINOPATHY

Overview

We identified 11 RCTs that evaluated dextrose prolotherapy for treatment of elbow pain due to lateral elbow tendinopathy. Comparators included normal saline injection ($k = 3$), corticosteroid injection ($k = 3$), ESWT ($k = 2$), and a variety of other treatments (*e*g, HA and PT). **Table 20** describes the key study characteristics and main findings for prioritized outcomes. Most RCTs ($k = 8$) required that participants had elbow pain for a minimum of 3-6 months, and most ($k = 8$) required positive exam findings (*eg*, pain on palpation and resisted wrist extension). All trials excluded individuals with prior elbow surgery and/or certain types of elbow injections (*eg*, recent corticosteroids). Half of the trials ($k = 5$)[88-92] also included only participants who had failed prior conservative treatment (*eg*, PT or corticosteroid injection). Participants were middle-aged adults (mean ages 43-52 years) and included variable proportions of women (14-78% female). Two RCTs were conducted in the US,[90,91] while the majority occurred in the Middle East ($k = 6$).[88,89,93-96] The remaining studies were conducted in India ($k = 2$)[92,97] and Australia ($k = 1$).[98] Most RCTs were small and only 3 had total $N > 100$,[95,97,98] Most studies evaluated pain-related functioning ($k = 8$), physical performance with grip strength ($k = 8$), and adverse events ($k = 9$). Only 1 study assessed health-related quality of life[98] and 2 reported pain intensity. No studies assessed cost or treatment burden. Nearly all studies ($k = 9$) were rated high RoB for a variety of reasons, including concerns about randomization and allocation, deviations from the intended interventions, missing data from loss to follow-up, and bias in outcome assessments. Only 2 RCTs[93,98] were rated some concerns. Detailed RoB assessments can be found in **Appendix E**.

Below, we further describe study characteristics and findings, grouping studies according to comparators: first normal saline injection, then corticosteroid injection, and ESWT. Lastly, we summarize results for comparisons with single studies. Detailed trial characteristics and findings are found in **Appendix I**.

Table 20. Summary of Characteristics and Key Findings for Lateral Elbow Tendinopathy

Author, Year Study Design; RoB; Country Key Participant characteristics	Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance*	Health-Related Quality of Life	Adverse Events
Dextrose Prolotherapy versus Normal Saline Injection						
Akcay, 2020[88] RCT; High; Turkey Elbow pain ≥3 mo, positive exam findings, failed conservative treatments (NSAIDs, splint, PT or steroid injection), no corticosteroid injection in past 6 mo and no prior prolotherapy; mean ages 47-48 yr, 70-78% female	15% dextrose, 4.5 ml at lateral epicondyle, annular ligament, and supracondylar ridge (needle touching bone); and home exercise program *N* = 30 (23) Clinic/home; 8 wk (3 injections, 4 wk apart)	Normal saline 4.5 ml, with same injection method; and home exercise program *N* = 30 (27) Clinic/home; 8 wk (3 sessions)	**DASH (4, 8, 12 wk)†** ? Dextrose-Saline **PRTEE (4, 8, 12 wk)†** ? Dextrose-Saline	**Grip strength (4, 8, 12 wk)** ↔ Dextrose-Saline	—	*"no adverse effects… except pain while having injections in any of the interventions."* (AE not further defined)
Ciftci, 2023[93] RCT; Some concerns; Turkey Elbow pain and function limitations ≥3 mo, no elbow surgery or injection in past 3 mo; mean ages 43-47 yr, 65% female	2 concentrations of dextrose with same injection method (in enthesis area of extensor muscle origins, and annular ligament, ultrasound-guided): • 15% dextrose 1 ml • 5% dextrose 1 ml *N* = 20 (20); 21 (20) Clinic; 6 wk (3 injections, 3 wk apart)	Normal saline 1 ml with same injection method *N* = 22 (20) Clinic; 6 wk (3 injections, 3 wk apart)	**Quick DASH (3, 12 wk)** ↑15% Dextrose-Saline ↑5% Dextrose-Saline ↔15% Dextrose-5% Dextrose	**Grip strength (3 wk)** ↔15% Dextrose-Saline ↔5% Dextrose-Saline ↔15% Dextrose-5% Dextrose Grip strength (**12 wk)** ↑15% Dextrose-Saline ↔5% Dextrose-Saline ↔15% Dextrose-5% Dextrose	—	"*no difference regarding side effects and complications. Two patients in* [15% dextrose group] *had pain and 1 patient in* [normal saline group] *had a rash at the injection site…No severe side effects or complications were encountered."* (severe AE not defined)
Scarpone, 2008[91] RCT; High; US Elbow pain ≥ 6 mo, failed conservative treatments	10.7% dextrose 1.5 ml (+ 0.7% sodium morrhuate, 0.3% ldicoaine) into tendon insertions (needle touching bone) at	Normal saline 1.5 ml with same injection method *N* = 12 (10)	—	**Grip strength (2, 4 mo)** ↔Dextrose-Saline	—	"All subjects… experienced expected, self-limited postinjection pain; 2 [prolotherapy] group subjects experienced 1

Author, Year Study Design; RoB; Country Key Participant characteristics	Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance*	Health-Related Quality of Life	Adverse Events
(PT, NSAIDs, and 2 corticosteroid injections), and no corticosteroid injection in past 6 wk; mean ages 48 yr, 40-60% female	supracondylar ridge, lateral epicondyl, and annular ligament *N* = 12 (10) Clinic; 8 wk (3 injections, 4 wk apart)	Clinic; 8 wk (3 injections, 4 wk apart)				episode each of local erythema, irritation, and discomfort approximately 1 day after injection."
Dextrose Prolotherapy versus Corticosteroid Injection						
Bayat, 2019[94] RCT; High; Iran Elbow pain ≥ 3 mo, positive exam findings, no elbow injection in past 3 mo, and no history of surgery; mean ages 46-51 yr, 43-79% female	16% dextrose 3 ml (+ 0.7% lidocaine) at the point of maximal tenderness using a peppering technique; and splint, home exercise program *N* = 16 (14) Clinic/home; Single injection, 7 wk exercises (2-3x/wk)	Methylprednisolone 40 mg (+ 0.7% lidocaine) with same injection method; and splint, home exercise program *N* = 14 (14) Clinic/home; Single injection, 7 wk exercises (2-3x/wk)	**Quick DASH (1 mo)** ↔ Dextrose–Steroid **Quick DASH (3 mo)** ↑ Dextrose-Steroid	—	—	Post-injection pain: Prolotherapy—0% Steroid—14% (n= 2) Decreased range of motion, redness at site: Prolotherapy—0% Steroid—7% (n= 1)
Gupta, 2022[97‡] RCT; High; India Diagnosed tennis elbow (based on history, exam, and ultrasound findings), no prior elbow injections; mean age 44 yr, 61% female	25% dextrose 1 ml (+ 2% lignocaine) injected 5 mm distal to lateral epicondyle, in the extensor tendons *N* = 130 (130) Clinic; Single injection	Triamcinolone mg NR (+2% lignocaine) with same injection method *N* = 130 (130) Clinic; Single injection	—	—	—	—
Kaya, 2022[95] RCT; High; Turkey Elbow pain ≥ 1 mo, positive exam findings, VAS ≥ 40, no prior elbow injection; mean ages 45-48 yr, 60-75% female	24% dextrose 2.5 ml (+ 0.4% prilocaine) in most tender area using peppering technique *N* = 30 (25) Clinic; 1 mo (2 injections, 1 mo apart)	3 comparators: • Methylprednisolone 20 mg (+ 1.6% prilocaine) with same injection method • Autologous blood 2 ml (+ 0.4%	**PRTEE (1, 6 mo)†** ? Dextrose-Steroid ? Dextrose-ABI ? Dextrose-Splint	**Grip strength (1, 6 mo)** ↔ Dextrose-Steroid ↔ Dextrose-ABI ↔ Dextrose-Splint	—	"*One patient* [in autologous blood group] *developed hand drop…improved in 24 h without any sequelae. Another complication didn't occur…*"

Author, Year Study Design; RoB; Country Key Participant characteristics	Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance*	Health-Related Quality of Life	Adverse Events
		prilocaine) with same method • Wrist splint (wear 6-8 hr during the day) *N* = 30 (24); 30 (30); 30 (25) Clinic/home; Single injection (steroid, blood); duration NR (splint)				
Dextrose Prolotherapy versus Extracorporeal Shockwave Therapy						
Ahadi, 2019[89] RCT; High; Iran Elbow pain ≥3 mo, positive exam and ultrasound findings, VAS > 4, failed ≥ 1 conservative treatments (NSAIDs, PT or corticosteroid injection), no corticosteroid injection in past 3 mo and no prior surgery or prolotherapy; mean ages 47 yr, 65-75% female	20% dextrose 3 ml (+ 2% lidocaine), at point of maximal tenderness (needle touching bone), ultrasound-guided *N* = 17 (17) Clinic; Single injection	ESWT (2000 J with 1.5 bars intensity, 10 Hz) *N* = 16 (16) Clinic; 2 wk (3 sessions, 1 wk apart)	**Quick DASH (1, 2 mo)** ↓ Dextrose–ESWT	**Grip strength (1, 2 mo)** ↔ Dextrose-ESWT	—	"*No noticeable adverse effects of the treatment were reported in either group.*" ("noticeable" AE not defined)
Deb, 2020[92] RCT; High; India Symptoms ≥ 6 mo, failed conservative treatment, no prior elbow surgery; mean ages nr (range 30-50 yr), 52-67% female	20% dextrose 2.5 ml (+ 0.4% lignocaine) in the lateral epicondyle and using peppering technique along the tendon in tender area *N* = 42 (NR) Clinic; Single injection	ESWT (2000 J with 1.9 bar intensity, 10 Hz) *N* = 42 (NR) Clinic; 2 wk (3 sessions, 1 wk apart)	—	**Grip strength (1, 3, 6 mo)** ↑ Dextrose-ESWT	—	—

Author, Year Study Design; RoB; Country Key Participant characteristics	Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance*	Health-Related Quality of Life	Adverse Events
Dextrose Prolotherapy versus Other Comparators						
Apaydin, 2020[96] RCT; High; Turkey Elbow pain ≥ 6 mo, positive exam findings, VAS ≥ 30/100, no prior elbow surgery; mean ages 43-46 yr, 81% female	15% dextrose 5 ml (+ 0.2% lidocaine) to lateral epicondyle tender point, annular ligament, lateral collateral ligament, and extensor tendon tender points *N* = 16 (16) Clinic; 6 wk (3 injections, 3 wk apart)	HA 2 ml to most sensitive point of lateral epicondyle *N* = 16 (16) Clinic; Single injection	**Quick DASH (6,12 wk)** ↔ Dextrose-HA	**Grip strength (6, 12 wk)** ↔ Dextrose-HA	—	Post-injection pain (lasting 1-2 days): Prolotherapy—25% (n= 4) HA—19% (n= 3) "[Pain] *completely resolved with rest and application of cold therapy.*"
Rabago, 2013b[90] RCT; High; US Elbow pain ≥ 3 mo, NRS ≥ 4 (average pain in past week), positive exam findings, failed ≥ 1 conservative treatment (NSAIDs, PT, and/or steroid injection), no elbow injection in past 3 mo, no prior prolotherapy or elbow surgery; mean ages 43-52 yr, 14-44% female	2 types of prolotherapy with same injection method (in lateral epicondyle, then in tender areas along tendon and annular ligaments with peppering technique, ultrasound-guided): • 20% dextrose 0.5-2.5 ml (+ 0.2% lidocaine) • 11% dextrose 0.5-2.5 ml (+ 0.7% sodium morrhuate, 0.3% lidocaine) *N* = 8 (8); 9 (9) Clinic; 7 wk (3 injections, 3-4 wk apart)	Waitlist *N* = 10 (10) NA; NA	**PRTEE (1, 2, 4 mo)** ↑ Dextrose-Waitlist ↑ Dextrose (+sodium morrhuate)-Waitlist	**Grip strength (1 mo)** ↔ Dextrose-Waitlist ↔ Dextrose (+sodium morrhuate)-Waitlist **Grip strength (2, 4 mo)** ↑ Dextrose-Waitlist ↔ Dextrose (+sodium morrhuate)-Waitlist	—	"*all participants reported mild-to-moderate self-limited injection-related pain. This pain tended to resolve within 1 week in* [dextrose prolotherapy] *group. However,* [dextrose+ sodium morrhuate] *participants reported more severe and persistent injection-related pain taking up to 3 weeks to resolve… There were no unexpected or serious adverse events.*" (serious AE not defined)
Yelland, 2019[98] RCT; Some concerns; Australia Elbow pain ≥ 6 wk, positive exam findings, PRTEE ≥ 20, no prior elbow surgery, no	20% dextrose 0.5-5 ml (+ 0.4% lignocaine), in each tender point using peppering technique; with or without PT/home exercise program	PT (manual therapy and therapeutic exercises), home exercise program *N* = 40 (34)	**PRTEE (6 wk, 3 & 6 mo, 1 yr)** ↔ Dextrose (+PT) - PT ↔ Dextrose-PT	—	EuroQoL-5D **(6 wk, 3 & 6 mo, 1 yr)** ↔ Dextrose (+PT) - PT ↔ Dextrose-PT	Prolotherapy—6% (n= 2: 1 with neuropraxia of posterior interosseous nerve after 4th injection, resolved over 3 mo; 1 with painful bruising of forearm

Author, Year Study Design; RoB; Country Key Participant characteristics	Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance*	Health-Related Quality of Life	Adverse Events
treatment for elbow pain in past 3 mo; mean ages 48-51 yr, 40-45% female	*N* = 40 (33) with PT/exercise; 40 (35) without PT/exercise Clinic/home; 12 wk (maximum 4 injections, 4 wk apart), 4 wk (4 PT sessions, 1-2 wk apart)	Clinic/home; 3 wk (4 PT sessions, 1 wk apart)				after 2nd injection, resolved over 2 wk) PT —0%

Notes. *No MCID available, direction of effect based on statistical significance.

†Study did not report mean scores at follow-up time points.

‡Only eligible outcome reported by this study was pain intensity (measured with VAS).

Symbols. ↑: At specified follow-up time point, the dextrose arm had a better scale score than the comparator arm (meeting MCID); ↔: At specified follow-up time point, the difference in scale scores between the dextrose and comparator arms did not meet MCID; ↓: At specified follow-up time point, the dextrose arm had a worse scale score than the comparator arm (meeting MCID); ?: Review team was unable to interpret scale scores.

Abbreviations. ABI=autologous blood injection; AE=adverse effect/event; DASH=Disabilities of the Arm, Shoulder, and Hand questionnaire; ESWT=extracorporeal shockwave therapy; EuroQol-5D= European Quality of Life-5 dimensions; HA=hyaluronic acid; MCID=minimal clinically important difference; ml=milliliter; mo=month; NA=not applicable; NSAIDs=nonsteroidal anti-inflammatory drugs; NR=not reported; PRP=platelet rich plasma; PRTEE=Patient-rated Tennis Elbow Evaluation; PT=physical therapy; Quick DASH=shortened version of DASH (11 items); RCT=randomized controlled trial; RoB=risk of bias; VAS=Visual Analog Scale; wk=week; yr=year.

Dextrose Prolotherapy versus Normal Saline Injection

Three RCTs[88,91,93] compared dextrose prolotherapy with normal saline injection. Studies used 5-15% dextrose, all in 3 injection sessions over 6-8 weeks, and employed the same frequency and technique with normal saline injections. Akcay, 2020[88] also included home exercise program in both arms. Ciftci, 2023[93] included 2 arms for dextrose prolotherapy, comparing 5% with 15% dextrose; this study was also the only one to use ultrasound guidance. Two of these studies only included participants who failed prior conservative treatments.[88,91]

Dextrose prolotherapy may improve pain-related functioning at short- and medium-term follow-up (low COE, **Table 21).** Two studies evaluated pain-related functioning using DASH and the Patient-rated Tennis Elbow Evaluation (PRTEE),[88] or Quick DASH[93] over 3 months. In both studies, participants in all groups improved over time, with the dextrose prolotherapy arm generally having greater improvements at both 3-4 weeks and 3 months. Akcay, 2020[88] only reported median scores (and IQR) at each time point, but indicated that there were significant between-group differences favoring dextrose prolotherapy in PRTEE score changes at 4 weeks and 3 months but no significant differences in DASH. Cifci, 2023[93] showed significantly greater reductions in Quick DASH in both of the dextrose prolotherapy group at both 3 weeks and 3 months (*eg*, mean 9.5 for 15% dextrose, 11.6 for 5% dextrose, and 40.0 for normal saline at 3 months). These differences all exceeded MCID.

Dextrose prolotherapy may result in little to no difference on physical performance at short-term follow-up and the evidence is very uncertain at medium-term follow-up (very low COE, **Table 21**). All 3 studies evaluated grip strength, which improved for all groups during maximum follow-up of 3-4 months. Two studies[88,91] found no significant between-group differences at any time point, but Ciftci, 2023[93] showed a significant difference favoring 15% dextrose at 3 months. This study also found no significant between-group differences for 15% dextrose versus normal saline at 3 weeks, and no difference between 5% dextrose versus normal saline at any time point.

The evidence is very uncertain on the effect of dextrose prolotherapy on adverse events (very low COE, **Table 21**). All 3 studies reported on adverse events, indicating that local pain and irritation was observed in a variable number of participants. No study described how adverse events were assessed or what constituted severe events.

All 3 studies assessed pain intensity or severity using VAS over 3-4 months. As with the other outcomes, participants in all groups improved over time. The timing of effects was inconsistent across studies, with Akcay, 2020[88] showing significant differences (favoring dextrose prolotherapy) only at 1 month but not at 2 or 3 months, and the other 2 studies[91,93] finding significant differences (also favoring dextrose prolotherapy) only at later follow-up at 3-4 months, but not at 1-2 months. Ciftci, 2023[93] also compared 5% versus 15% dextrose, reporting that the latter group had significantly greater reductions in pain intensity at all time points.

Table 21. Lateral Elbow Tendinopathy COE: Dextrose Prolotherapy versus Normal Saline Injection

Outcome Measure	Follow-Up Total *N* (# of Studies)	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up Dextrose Prolotherapy	Saline	Difference	Certainty	What Happens
Pain-related functioning DASH, Quick DASH, PRTEE	Short-term (3-4 wk) *N* = 122 (2 RCTs)[88,93]	29.0*	53.4*	-24.4*	Low[a] ⊕⊕◯◯	Dextrose prolotherapy may improve pain-related functioning at short-term follow-up.
	Medium-term (12 wk) *N* = 122 (2 RCTs)[88,93]	9.5*	40.0*	-30.5*	Low[a] ⊕⊕◯◯	Dextrose prolotherapy may improve pain-related functioning at medium-term follow-up.
Physical performance Grip strength	Short-term (3-4 wk) *N* = 122 (2 RCTs)[88,93]	62.3†	43.2†	19.1†	Low[a] ⊕⊕◯◯	Dextrose prolotherapy may result in little to no difference in physical performance at short-term follow-up.
	Medium-term (3-4 mo) *N* = 147 (3 RCTs)[88,91,93]	71.5†	42.5†	29.0†	Very low[a,b] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on physical performance at medium-term follow-up.
Adverse events NR	*N* = 147 (3 RCTs)[88,91,93]	0‡	0‡	—	Very low[a,c] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on adverse events.

Notes. *Values for mean Quick DASH scores at follow-up for intervention (15% dextrose prolotherapy) and comparator arms from Ciftci, 2023.[93] Differences calculated by review team.

†Values for mean strength (kg) at follow-up for intervention (15% dextrose prolotherapy) and comparator arms from Ciftci, 2023.[93] Differences calculated by review team.

‡No adverse events in either group as reported in Ciftci, 2023.[93]

GRADE Working Group grades of evidence:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

a. Downgraded 2 levels for study limitations (1-2 studies rated high RoB).

b. Downgraded 1 level for inconsistency (effect varies across studies).

c. Downgraded 1 level for indirectness (no information about how or when adverse events were assessed).

Abbreviations. DASH=Disabilities of the Arm, Shoulder, and Hand; mo=month; NR=not reported; PRTEE=Patient-Rated Tennis Elbow Evaluation; RCT=randomized controlled trial; RoB=risk of bias; wk=week.

Dextrose Prolotherapy versus Corticosteroid Injection

Three RCTs[94,95,97] compared dextrose prolotherapy with corticosteroid injection. Studies employed 16-25% dextrose in 1-2 injection sessions over 1 month maximum duration, and used the same injection frequency and technique with corticosteroid injections. Bayat, 2019[94] also included use of splint and home exercise program in both arms.

The evidence is very uncertain on the effect of dextrose prolotherapy on pain-related functioning at short-, medium-, and long-term follow-up (very low COE, **Table 22**). Two studies[94,95] evaluated pain-related functioning using Quick DASH[94] and PRTEE,[95] finding that outcomes improved for participants in all groups over maximum follow-up of 3-6 months. However, there was inconsistency in results of between-group comparisons, with Bayat, 2019[94] showing that dextrose prolotherapy arm had greater reductions in Quick DASH at both 1 and 3 months, although this was only statistically significant (and also met MCID) at 3 months. Kaya, 2022[95] only provided changes in PRTEE scores at 1 and 6 months, and did not report between-group comparisons for dextrose prolotherapy versus corticosteroids. However, the corticosteroid injection arm at greater reductions in PRTEE at both time points (*eg*, mean change of 36.2 versus 19.1 in dextrose prolotherapy group).

Dextrose prolotherapy may result in little to no difference on physical performance at short- and medium-term follow-up (low COE, **Table 22**). Only Kaya, 2022[95] evaluated physical performance, finding that grip strength improved in all arms during follow-up and that there were no significant between-group differences at either 1 or 6 months.

The evidence is very uncertain on the effect of dextrose prolotherapy on adverse effects (very low COE, **Table 22**). Two studies[94,95] assessed adverse events. Bayat, 2019[94] reported that 3 participants (21%) in the corticosteroid group experienced side effects, compared with none in the dextrose prolotherapy arm. Kaya, 2022[95] indicated that no participants in either group had an adverse effect, but did not further define how or when assessments occurred.

All 3 studies[94,95,97] evaluated the pain intensity or severity using VAS over maximum follow-up of 3 months to 1 year. As with other outcomes, pain severity decreased over time for participants in all groups, but between-group differences were inconsistent overall. Gupta, 2022[97] found that the corticosteroid group had significantly lower pain severity at 6 weeks, 3 and 6 months, although there were no significant differences at 1 year. In contrast, Bayat, 2019[94] showed that dextrose prolotherapy group had significantly lower VAS at 3 months, and there were no significant between-group differences at 1 month. Finally, Kaya, 2022[95] found no significant between-group differences at either 1 or 6 months.

Table 22. Lateral Elbow Tendinopathy COE: Dextrose Prolotherapy versus Corticosteroid Injection

Outcome Measure	Follow-Up Total *N* (# of Studies)	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up Dextrose Prolotherapy	Steroid	Difference	Certainty	What Happens
Pain-related functioning PRTEE, Quick DASH	Short-term (1 mo) *N* = 90 (2 RCTs)[94,95]	24.3*	34.8*	-10.5*	Very low[a,b] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy pain-related functioning at short-term follow-up.
	Medium-term (3 mo) *N* = 30 (1 RCT)[94]	14.7*	34.6*	-19.9*	Very low[a,c] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on pain-related functioning at medium-term follow-up.
	Long-term (6 mo) *N* = 60 (1 RCT)[95]	—†	—†	—†	Very low[a,d] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on pain-related functioning at long-term follow-up.
Physical performance Grip strength	Short-term (1 mo) *N* = 60 (1 RCT)[95]	—‡	—‡	—‡	Low[a] ⊕⊕◯◯	Dextrose prolotherapy may result in little to no difference in physical performance at short-term follow-up.
	Long-term (6 mo) *N* = 60 (1 RCT)[95]	—‡	—‡	—‡	Low[a] ⊕⊕◯◯	Dextrose prolotherapy may result in little to no difference in physical performance at long-term follow-up.
Adverse events NR	*N* = 90 (2 RCTs)[94,95]	0¶	0¶	—	Very low[a,d,e] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on adverse events.

Notes. *Values for mean Quick DASH scores at follow-up for intervention and comparator from Bayat, 2019.[94] Differences calculated by review team.

†Only median scores and change in scores provided at follow-up (means were not reported), and no pairwise comparison was reported for dextrose prolotherapy versus corticosteroids.

‡Only median scores and change in scores provided at follow-up (means were not reported) and there were no statistically significant differences between groups.

¶No events in either dextrose prolotherapy or steroid group, per Kaya, 2022.[95]

GRADE Working Group grades of evidence:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

a. Downgraded 2 levels for study limitations (1-2 studies rated high RoB).

b. Downgraded 1 level for inconsistency (effects vary across studies).

c. Downgraded 1 level for imprecision (using OIS, study not powered to detect MCID for Quick DASH; see Methods for more information).

d. Downgraded 1 level for indirectness (no information about how or when adverse events were assessed).

e. Downgraded 1 level for imprecision (not powered to minimum adverse event rate <10%; see Methods for more information).

Abbreviations. ASES=American Shoulder and Elbow Surgeons; DASH=Disabilities of the Arm, Shoulder, and Hand; mo=month; NR=not reported; OIS=optimal information size; RCT=randomized controlled trial; RoB=risk of bias; ROM=range of motion; SPADI=Shoulder Pain and Disability Index; wk=week.

Dextrose Prolotherapy versus Extracorporeal Shockwave Therapy

Two studies [89,92] compared a single injection of 20-25% dextrose prolotherapy with 3 sessions of ESWT (treatment duration 2 weeks), and one of these used imaging guidance for dextrose injection.[89]

The evidence is very uncertain on the effect of dextrose prolotherapy on pain-related functioning at short- and medium-term follow-up (very low COE, **Table 23**). Only Ahadi, 2019[89] evaluated pain-related functioning. It showed significantly greater reductions in Quick DASH in the ESWT group at 4 and 8 weeks, and these differences met MCID. Both groups improved at follow-up compared to baseline.

The evidence is very uncertain for pain-related functioning and physical performance at short- and medium-term follow-up, compared with ESWT (very low COE), but dextrose prolotherapy may improve physical performance in the long-term (low COE, **Table 23**). Both studies evaluated grip strength with maximum follow-up of 2-6 months, and showed increases in participants for all groups over time. While Deb, 2020[92] reported statistically significant differences that favored dextrose prolotherapy at 1, 3, and 6 months, Ahadi, 2019[89] found no significant between-group differences at either 1 or 2 months. In the latter study, mean scores were very similar for dextrose prolotherapy and ESWT groups, but slightly favored the ESWT arm at both time points (*eg*, mean 8.0 pounds for dextrose prolotherapy versus mean 8.3 for ESWT at 1 month).

The evidence is very uncertain on the effect of dextrose prolotherapy on adverse events (very low COE, **Table 23**). Only Ahadi, 2019[89] evaluated adverse events, finding no events occurred in either group. This study did not describe or define what constituted adverse events.

Both studies[89,92] evaluated pain severity and used VAS. Both showed reductions in VAS in both groups during follow-up, but there were conflicting results for between-group comparisons. Deb, 2020[92] found that the dextrose prolotherapy arm had significantly lower VAS scores at 1 and 3 months, while Ahadi, 2019[89] reported that the ESWT group had significantly lower scores at 1 and 2 months.

Table 23. Lateral Elbow Tendinopathy COE: Dextrose Prolotherapy versus Extracorporeal Shock Wave Therapy

Outcome Measure	Follow-Up Total *N* (# of Studies)	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up Dextrose Prolotherapy	ESWT	Difference	Certainty	What Happens
Pain-related functioning Quick DASH	Short-term (1 mo) *N* = 33 (1 RCT)[89]	39.7*	22.3*	17.4*	Very low[a,b] ⊕◯◯◯	The evidence is very uncertain of the effect of dextrose prolotherapy on pain-related functioning at short-term follow-up.
	Medium-term (2 mo) *N* = 33 (1 RCT)[89]	37.4*	22.1*	14.3*	Very low[a,b] ⊕◯◯◯	The evidence is very uncertain of the effect of dextrose prolotherapy on pain-related functioning at medium-term follow-up.
Physical performance Grip strength	Short-term (1 mo) *N* = 117 (2 RCTs)[89,92]	12.0†	10.7†	1.3†	Very low[a,c] ⊕◯◯◯	The evidence is very uncertain of the effect of dextrose prolotherapy on physical performance at short-term follow-up.
	Medium-term (2–3 mo) *N* = 117 (2 RCTs)[89,92]	13.8†	11.8†	2.0†	Very low[a,c] ⊕◯◯◯	The evidence is very uncertain of the effect of dextrose prolotherapy on physical performance at medium-term follow-up.
	Long-term (6 mo) *N* = 120 (1 RCT)[92]	15.4†	13.1†	2.3†	Low[a] ⊕⊕◯◯	Dextrose prolotherapy may improve physical performance at long-term follow-up.
Adverse events NR	Medium-term (1 yr) *N* = 33 (1 RCT)[89]	0*	0*	0*	Very low[a,d,e] ⊕◯◯◯	The evidence is very uncertain of the effect of dextrose prolotherapy on adverse events at medium-term follow-up.

Notes. *Values for mean follow-up scores for intervention and comparator from Ahadi, 2019.[89] Differences calculated by review team.

†Values for mean grip strengths scores at follow-up for intervention and comparator from Deb, 2020.[92] Differences calculated by review team.

GRADE Working Group grades of evidence:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

a. Downgraded 2 levels for study limitations (1-2 studies rated high RoB).

b. Downgraded 1 level for imprecision (using OIS, studies were not powered to detect minimum SMD of 0.8; see Methods for more information).
c. Downgraded 1 level for inconsistency (effect varied across studies).
d. Downgraded 1 level for indirectness (no information about how or when adverse events were assessed).
e. Downgraded 2 levels for imprecision (not powered to minimum adverse event rate <20%; see Methods for more information).
Abbreviations. ESWT=extracorporeal shock wave therapy; mo=month; NR=not reported; Quick DASH=shortened version of DASH (11 items); RCT=randomized controlled trial; RoB=risk of bias; wk=week.

Dextrose Prolotherapy versus Other Comparators

Three additional studies compared dextrose prolotherapy to HA,[96] waitlist control,[90] or PT.[98] Apaydin, 2020[96] randomized 32 participants to 3 sessions of 15% dextrose injection versus a single injection of HA. This study evaluated pain-related functioning (Quick DASH), physical performance (grip strength), pain severity (VAS), and adverse events. Both groups improved in all efficacy outcomes at 6 and 12 weeks follow-up, and there were no statistically significant between-group differences for any of the outcomes. For adverse events, 4 participants (25%) in the dextrose prolotherapy group and 3 (19%) in the HA arm experienced post-injection pain.

Rabago, 2013[90] enrolled 27 participants into a 3-arm trial, comparing 3 sessions of either 11% dextrose (with sodium morrhuate) or 20% dextrose (no sodium morrhuate) with a waitlist control. For pain-related functioning, participants in all groups had improvements in PRTEE over a maximum follow-up of 4 months, with both dextrose and dextrose with sodium morrhuate groups showing greater reductions at all time points, compared with waitlist. For grip strength, participants in both the dextrose-only and the waitlist groups improved over time, but those in the dextrose with sodium morrhuate group did not. This study reported that all participants in the dextrose-only arm had mild to moderate pain (that lasted < 1 week) but those in the dextrose with sodium morrhuate group had more severe and lengthy symptoms (sometimes lasting 3 weeks).

Yelland, 2019[98] randomized 120 participants to 3 arms comparing 1 month of PT/home exercise program versus 20% dextrose injections (maximum of 4 sessions, lasting up to 3 months) versus both treatments. Outcomes assessed included pain-related functioning (PRTEE), health-related quality of life (EuroQol-5D), pain severity (VAS), and adverse events. For all efficacy outcomes, participants in all groups improved over maximum follow-up of 1 year. There were no significant between-group differences at any time point, except at 3 months when PRTEE was significantly lower in the PT/home exercise group, compared with the dextrose-only group (mean 12.2 versus 18.2). However, this difference did not meet MCID. For adverse events, 1 participant (3%) in the dextrose prolotherapy group experienced neuropraxia of the posterior interosseous nerve and another person (3%) had painful bruising after the second injection.

Finally, Kaya, 2022,[95] described in the section above on corticosteroid comparator, also included 2 other comparator arms for autologous blood injection (ABI) and wrist splint. Pain-related functioning (PRTEE), physical performance (grip strength), pain intensity (VAS), and adverse events were evaluated. All outcomes improved for all arms over follow-up for 1-6 months. There were no significant between-group differences for grip strength or VAS. Authors only reported change in PRTEE and found that there were no significant between-group differences for dextrose prolotherapy versus wrist splint; comparison with ABI was not reported. For adverse events, 1 participant in the ABI group developed hand drop that improved in 24 hours.

CHRONIC LOW BACK PAIN

Overview

Nine studies (k = 6 RCTs, k = 3 observational) evaluated dextrose prolotherapy for treatment of chronic low back pain (LBP). Seven of the studies[99-105] addressed non-specific chronic low-back pain, while the remaining 2 studies[106,107] included only pain due to sacroiliac joint dysfunction. **Table 24** summarizes key study characteristics and main findings from all RCTs and observational studies with concurrent comparators. Included participants for all but 2 studies failed prior conservative treatment[99,101,104,107] and did not respond to non-surgical treatment[102] or prior pharmacological treatments.[106] Participants were middle-aged adults with variable proportion of women (mean ages 42-62 years, and 40-77% female). Three studies were conducted in the US,[101,102,104] 2 in the Middle East,[105,106] and 1 each in Australia,[99] South Korea,[107] and the United Kingdom.[103] Four studies had $N > 100$, including all 3 observational studies (N = 109-197) and 1 RCT (N = 110).[99] Remaining RCTs were small with total N = 40-81. Most studies reported on pain-related functioning, adverse events, and pain intensity or severity (k = 7 for each outcome). Only 2 studies addressed physical performance and 1 evaluated health-related quality of life. No study reported on cost or treatment burden. The vast majority of studies were rated high RoB (k = 3 RCTs)[99-101] or some concerns (k = 3 RCTs)[102,106,107] for a variety of reasons, including issues with randomization and allocation process, deviations from the intended interventions, missing data from loss to follow-up, and bias in outcome assessment. Only 1 observational study[104] was assessed as serious and another observational study[105] rated moderate. Detailed RoB ratings (by domain and overall) are presented in **Appendix E**.

Below, we first summarize results for studies that employed dextrose prolotherapy to treat non-specific low back pain. Then, we provide findings for the 2 trials that specifically targeted pain from sacroiliac joint dysfunction. Detailed study characteristics and findings for all studies are presented in **Appendix J**.

Table 24. Summary of Characteristics and Key Findings from Comparative Studies of Chronic Low Back Pain

Author, Year Study Design; RoB; Country Key Participant Characteristics	Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance*	Health-Related Quality of Life	Adverse Events
Non-Specific Low Back Pain: Injections in L4-S1 and Sacroiliac Areas						
Dechow, 1999[100] RCT; High; United Kingdom Mechanical low back pain > 6 mo, prior treatments NR; mean ages 44-46 yrs, 47-56% female	12.5% dextrose 10 ml (+ 12.5% glycerine, 1.2% phenol, 0.5% lignocaine) *N* = 36 (36) Clinic; 2 wk (3 injections, 1 wk apart)	normal saline 10 ml (+ 0.5% lignocaine) *N* = 38 (38) Clinic; 2 wk (3 injections, 1 wk apart)	**ODI (1, 3, 6 mo)** ↔Dextrose-Saline	**ROM: Lumbar Flexion (1, 3, 6 mo)** ↔ Dextrose-Saline	—	"*A few subjects reported a transient increase in back pain following the injections, but…no differences between the treatment and control groups and no other significant adverse reactions.*" (AE not defined)
Klein, 1993[101] RCT; High; United States Low back pain > 6 mo, no acute radiculopathy or exacerbation of pain, no hip arthritis, failed prior conservative treatment; mean ages 43-45 yrs; 35-46% female	12.5% dextrose 30 ml (+ 12.5% glycerine, 1.2% phenol, 0.3% lignocaine); day preceding first dextrose injection, 8 patients received triamcinolone (maximum 20 mg) at "hyperirritable foci"; home exercise program *N* = 39 (31) Clinic/home; 5 wk (6 injections, 1 wk apart), 6 mo (4x/day daily exercises)	normal saline 30 ml (+ 0.3% lignocaine); day preceding first saline injection, 5 patients received triamcinolone (maximum 20 mg) at "hyperirritable foci"; home exercise program *N* = 40 (35) Clinic/home; 5 wk (6 injections, 1 wk apart), 6 mo (4x/day daily exercises)	**RMDQ (6 mo)** ↔Dextrose-Saline	**ROM: Rotation, Flexion-Extension, Side Flexion (6 mo)** ↔Dextrose-Saline **Isometric Strength: Rotation, Flexion, Extension, Side Flexion (6 mo)** ↔Dextrose-Saline **Velocity: Rotation, Flexion-Extension, Side Flexion (6 mo)** ↔Dextrose-Saline	—	"*one in each group…* [developed] *lumbar puncture headaches…during the course of treatment, lasting approximately 3 days each before spontaneously abating without sequelae… All patients complained of varying degrees of stiffness and soreness for 1-3 days following injection, but in no case was this severe enough…to discontinue treatment".*
Ongley, 1987 [102] RCT; Some concerns; United States Back pain >1 year, no acute radiculopathy, not on disability or have	12.5% dextrose 20 ml (+ 12.5% glycerine, 1.2% phenol, 0.3% lignocaine); day before dextrose, 60 ml 0.5% lignocaine injected in	0.9% normal saline 20 ml; day before full volume saline injections, 10 ml 0.5% lignocaine injected in same areas, non-forceful manipulation of	**Modified RMDQ (1, 3, 6 mo)*†** ↑ Dextrose-Saline	—	—	"*Patients in both groups complained of pain and stiffness for 12-24 h after each injection…*[not] *severe enough to*

Author, Year Study Design; RoB; Country Key Participant Characteristics	Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance*	Health-Related Quality of Life	Adverse Events
pending worker's compensation claim, failed non-surgical treatments; mean ages 43-45 yrs; 51-55% female	same areas, forceful manipulation of lower back, and triamcinolone injected in gluteus medius origin; home exercise program *N* = 40 (40) Clinic/home; 5 wk (maximum 6 injections, 1 wk apart), 6 mo (daily exercises)	lower back, lignocaine injected in gluteus medius origin, home exercise program *N* = 41 (41) Clinic/home; 5 wk (maximum 6 injections, 1 wk apart), 6 mo (daily exercises)				*necessitate bed rest or absence from work*." **Dextrose group:** 2 with increased menstrual bleeding, 2 with post-menopausal bleeding (at 4 wk) **Normal saline group:** 1 with increased menstrual bleeding, 1 withdrew after second day of injections due to severe headache and cough
Yelland, 2004[99] RCT; High; Australia Low back pain for >half of days in past 6 mo, modified RMDQ >3, no acute exacerbation or radiculopathy, failed prior conservative treatment, no prior spine surgery or prolotherapy; mean ages 49-52 yrs, 41-45% female	20% dextrose 10 ml (+ 0.2% lignocaine); 50% randomized to home exercise program (factorial design) *N* = 54 (50) Clinic/home: 6 mo (6 injections, 2 wk apart; then injections at 4 and 6 mo, if partial response; daily exercise for 6 mo)	normal saline 10 ml; 50% randomized to home exercise program (factorial design) *N* = 56 (56) Clinic/home: 6 mo (6 injections, 2 wk apart; then injections at 4 and 6 mo, if partial response; daily exercise for 6 mo)	**Modified RMDQ (12, 24 mo)*‡** ↔Dextrose-Saline	—	**SF-12 Physical (12, 24 mo)*¶** **?** Dextrose-Saline **SF-12 Mental (12, 24 mo)*¶** **?** Dextrose-Saline	*"Incidence of potential adverse effects did not differ between groups."* (AE were described for total participants but proportion by arm NR, included increased pain in back or legs, nausea or diarrhea, headaches, etc.)
Non-Specific Low Back Pain: Intradiscal or Facet Joint Injections						
Derby, 2004[104] Observational Cohort; Serious; United States Chronic low back pain, being considered for additional surgery, failed range of prior therapies;	16.7% dextrose volume NR (+ 0.2% chondroitin sulfate, 6.7% glucosamine, 4% DMSO, 0.7% bupivacaine), fluoroscopy-guided intradiscal injection; 5 participants also	intradiscal electrothermal treatment (+0.5% bupivacaine, cefazolin), fluoroscopy-guided *N* = 74 (74) Clinic; 1 treatment	—	—	—	"*Post-procedure flare-up*" of pain: Dextrose—81% (duration 8.6 days) Electrothermal —69% (duration 33.1 days)

Author, Year Study Design; RoB; Country Key Participant Characteristics	Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance*	Health-Related Quality of Life	Adverse Events
mean ages 41-42 yrs; 51-57% female	received corticosteroid injections 1-3 wk after dextrose *N* = 35 (35) Clinic; 1 injection					
Yildirim, 2021[105] Observational Cohort; Moderate; Turkey Chronic low back pain, prior treatments NR; mean ages 57-60 yrs; 64-77% female	25% dextrose 5 ml, injection at single-level facet joint *N* = 87 (87) Clinic; 1 injection	20 mg methylprednisolone (+ 0.25% bupivacaine), injection at single-level facet joint *N* = 91 (91) Clinic; 1 injection	**ODI (3 mo)** ↔Dextrose-Steroid	—	—	—
Sacroiliac Joint Dysfunction (Focal)						
Kim, 2010 [107] RCT; Some concerns; South Korea Pain >2 mo in buttock, groin or thigh, diagnosis confirmed by intra-articular injection of local anesthetic at sacroiliac joint, failed prior medical treatment for >1 mo; mean ages 59-62 yrs, 70-72% female	Intra-articular 25% dextrose 2.5 ml (+ 0.1% levobupivacaine), fluoroscopy-guided at sacroiliac joint *N* = 24 (23) Clinic; 4 wk (up to 3 injections, 2 wk apart)	Intra-articular triamcinolone 40 mg (+ 0.1% levobupivacaine), fluoroscopy-guided at sacroiliac joint *N* = 26 (25) Clinic; 4 wk (up to 3 injections, 2 wk apart)	**ODI (2 wk)** ↔Dextrose-Steroid	—	—	"*None of the participants reported serious adverse events such as long-lasing exacerbation of pain, numbness or weakness, or signs of skin infection.*"
Raissi, 2022[106] RCT; Some concerns; Iran Sacroiliac joint dysfunction with	20% dextrose 2.5 ml, ultrasound-guided at sacroiliac joint *N* = 20 (18)	2.5 ml triamcinolone (100 mg) ultrasound-guided at sacroiliac joint *N* = 20 (18)	**DPQ (2, 8 wk)[§]** ↔ Dextrose-Steroid	—		*"mild flare"* post-injection: Dextrose—17% (3) Corticosteroid—17% (3)

Author, Year Study Design; RoB; Country Key Participant Characteristics	Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance*	Health-Related Quality of Life	Adverse Events
unilateral hip, thigh and groin pain ≥ 2 mo, diagnosis confirmed by intra-articular injection of local anesthetic at sacroiliac joint, failed prior pharmacological treatments for >1 mo, no surgery or invasive procedure in the lumbosacral region in past 6 mo; mean ages 50-53 yrs; 66-72% female	Clinic; 1 injection	Clinic; 1 injection				

Notes. *No established MCID for outcome; direction of effect based on statistically significant difference reported by study.

†Authors assessed disability using a combined measure of 24 items from Roland-Morris Disability Questionnaire (RMDQ) and 9 questions from Waddell Disability Index.

‡23 items from RMDQ.

¶Study only reported change in SF-12 scores, no mean scores at follow-up time points.

§Study did not report DPQ domains, but indicated no significant between-group differences in total DPQ.

Symbols. ↑: At specified follow-up time point, the dextrose arm had a better scale score than the comparator arm (meeting MCID); ↔: At specified follow-up time point, the difference in scale scores between the dextrose and comparator arms did not meet MCID; ↓: At specified follow-up time point, the dextrose arm had a worse scale score than the comparator arm (meeting MCID); ?: Review team was unable to interpret scale score.

Abbreviations. AE=adverse events; DPQ=Dallas Pain Questionnaire; mo=month; ODI=Oswestry Disability Index; RMDQ=Roland Morris Disability Questionnaire; ; RoB=risk of bias; ROM=range of motion; rTMS=repetitive transcranial magnetic stimulation; wk=week.

Chronic Non-Specific Low Back Pain

Seven studies (k = 4 RCTs[99-102], k = 3 observational[103-105]) evaluated dextrose prolotherapy for non-specific low back pain, with 5 using multiple injections distributed over L4/S1 and sacroiliac areas. The remaining 2 studies employed more focused dextrose injections either intra-disc or at a single-level facet joint capsule. All 4 RCTs required low back pain ≥ 6 months and 3 of these only included participants who had failed prior conservative treatments.[99,101,102] None of the observational studies required a minimum duration of low back pain. Only 1 study excluded individuals with prior spine surgery or prolotherapy injections.[99] Three RCTs[99-101] were assessed as high RoB due to concerns about randomization and allocation, deviations from the assigned intervention, and/or missing data from loss to follow-up. One observational study was rated serious RoB because of deviations from the assigned intervention and missing data due to loss to follow-up.[104] Remaining RCT[102] and the second observational study[105] were rated some concerns or moderate RoB, respectively. The third observational study lacked a concurrent comparator and thus was not assessed for RoB; we include it only for adverse event findings. Detailed RoB ratings (by domain and overall) are presented in **Appendix E**.

Below, we first present findings for studies using multiple injections over a variety of areas, and then we summarize results for the 2 studies on more focused dextrose prolotherapy injections.

Multiple Injections in L4-S1 and Sacroiliac Area

Four RCTs[99-102] compared 12.5-20% dextrose prolotherapy with normal saline injections in multiple areas at L4-S1, and iliolumbar and sacroiliac ligaments. Dextrose injections occurred in 3-6 sessions, over a maximum duration of 6 months, and none used imaging guidance. Three trials[100-102] included 1.2% phenol mixed with dextrose for injections, and 2 studies[101,102] used corticosteroid injections for some or all participants in the dextrose prolotherapy arm. Two trials[101,102] also included home exercise programs in both arms, while Yelland, 2004[99] used a 4-arm 2x2 factorial design to compare both dextrose versus normal saline, and presence versus absence of home exercise. [99,101,102] RCTs were small, with total N = 74-110 and included middle-aged adults (mean age 45-46 years, 45-49% female). Additionally, we include in this section findings on adverse events from an observational cohort study (N = 197) that lacked comparator[103]; we do not present efficacy outcomes from this study due to the lack of concurrent comparators.

The evidence is very uncertain on the effects of dextrose prolotherapy for pain-related functioning at short-, medium-, and long-term follow-up, compared with normal saline (very low COE, **Table 25**). All 4 RCTs evaluated pain-related functioning, but due to the substantial variation in dextrose prolotherapy intervention characteristics, we did not conduct quantitative meta-analyses for this outcome. Ongley, 1987[102] employed a modified Roland-Morris Disability Questionnaire (RMDQ) with 9 additional questions from the Waddell Disability Index (WDI). The remaining studies used the Oswestry Disability Index (ODI)[100] or RMDQ.[99,101] All 4 trials showed improvements in pain-related functioning over time for all arms, but there was inconsistency in between-group comparisons. While Ongley, 1987[102] reported that the dextrose prolotherapy group had significantly better functioning at 1, 3, and 6 months, all of the 3 other studies[99-101] found no significant between-group differences collectively from 1-24 months. For example, Klein, 1993[101] reported that mean RMDQ was 4.0 in the dextrose group versus 4.4 in the normal saline arm at 6 months.

Dextrose prolotherapy may have little to no benefit for physical performance at long-term follow-up, compared to normal saline (low COE, **Table 25**). Two RCTs[100,101] evaluated physical performance

with a variety of measures, including ROM for a range of movements, isometric strength, and velocity of movements. Generally, participants in both arms improved on all measures over time, but neither study found statistically significant differences between the groups.

The evidence is very uncertain on the effect of dextrose prolotherapy for adverse events, compared to normal saline (very low COE, **Table 25**). All 4 RCTs addressed adverse events and noted a range of potential side effects, including stiffness, increased back pain, new radiculopathy, lumbar puncture headaches, and menstrual bleeding. Ongley, 1987[102] reported higher proportion of participants with side effects (*N* = 4, 10%) in the dextrose prolotherapy group, as compared with the normal saline group (*N* = 2, 5%), but the other RCTs indicated there were no differences between groups (with 2 studies[99,100] not providing any rates per arm). Jacks, 2012,[103] the observational study, reported that 2 patients (1%) had "marked itching" at the injection area and also "some patients had marked localized tenderness or numbness for several weeks" post-injection.

All 4 studies[99-102] evaluated pain intensity or severity, and assessed VAS over maximum follow-up of 6 months to 2 years. One trial[101] reported a statistically significant improvement in pain severity and intensity at 6-month follow-up, and another trial[102] reported a statistically significant improvement in pain severity and intensity at 1-, 3-, and 6-months follow-up to those in the prolotherapy arm when compared to the saline control arm. The remaining 2 trials[99,100] reported no statistically significant difference across multiple time points.

Table 25. Chronic Non-Specific Low Back Pain COE: Dextrose Prolotherapy versus Normal Saline Injection (With Local Anesthetic)

Outcome Measure	Follow-Up Total *N* (# of Studies)	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up Dextrose Prolotherapy	Saline	Difference	Certainty	What Happens
Pain-related functioning ODI, RMDQ, modified RMDQ	Short-term (1 mo) *N* = 81 (2 RCTs)[100,102]	4.0*	8.4*	-4.4*	Very low[a,b] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on pain-related functioning at short-term follow-up.
	Medium-term (3-4 mo) *N* = 191 (3 RCTs)[99,100,102]	4.7*	8.5*	-3.8*	Very low[a,b] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on pain-related functioning at medium-term follow-up.
	Long-term (6-12 mo) *N* = 270 (4 RCTs)[99-102]	3.4*	8.3*	-4.9*	Very low[a,b] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on pain-related functioning at long-term follow-up.
Physical performance ROM, Isometric Strength, Velocity	Long-term (6 mo) *N* = 79 (2 RCTs[100,101]	100.5†	102.3†	-1.8†	Low[a] ⊕⊕◯◯	Dextrose prolotherapy may result in little to no difference in physical performance at long-term follow-up.
Health-related quality of life SF-12	Long-term (12 mo) *N* = 110 (1 RCT)[99]	5.5‡	6.0‡	-0.5‡	Very low[a,c] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on health-related quality of life at long-term follow-up.
Adverse events	*N* = 81 (4 RCTs)[99-102]	10%§	5%§	5%§	Very low[a,b,d,e] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on adverse events.

Notes. *Values for mean scores on modified RMDQ at follow-up for intervention and comparator from Ongley, 1987.[102] Differences calculated by review team.

†Values for mean ROM on flexion-extension at follow-up for intervention and comparator from Klein, 1993.[101] Difference calculated by review team.

‡Values for mean SF-12 Physical Component Scores at follow-up for intervention and comparator from Yelland, 2004.[99] Difference calculated by review team.

§Adverse event data for intervention and comparator arms from Ongley, 1987.[102]

GRADE Working Group grades of evidence:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:
a. Downgraded 2 levels for study limitations (1-3 studies assessed as high RoB).
b. Downgraded 1 level for inconsistency (effect varied across trials).
c. Downgraded 1 level for imprecision (using OIS, study was not powered to detect MCID for SF-12; see Methods for more information).
d. Downgraded 1 level for indirectness (no information about how or when adverse events were assessed).
e. Downgraded for imprecision (not powered to minimum adverse event rate <10%; see Methods for more information).
Abbreviations. mo=month; NR=not reported; NRS=numerical rating scale; ODI=Oswestry Disability Index; OIS=optimal information size; RCT=randomized controlled trial; RoB=risk of bias; ROM=range of motion.

Focused Injections (Intradiscal and Single-Level Facet Capsule Injection)

A single observational study[104] compared dextrose prolotherapy ($N = 35$) with intradiscal electrothermal treatment (IDET; $N = 74$). In the prolotherapy arm, 16.7% dextrose was injected "at each involved disc level" under fluoroscopy guidance during a single session, and 5 participants (14%) in this group also received corticosteroid injections 1-3 weeks later. This study only evaluated pain intensity or severity (using VAS), finding that both groups improved and no significant between-group differences. For adverse events, the majority of participants in both groups had "post-procedure flare-up" of pain (81% of dextrose arm versus 69% of IDET group). Pain-related functioning, physical performance, health-related quality of life, and cost/treatment burden were not addressed.

Another observational study[105] evaluated a single injection of 25% dextrose prolotherapy ($N = 87$) versus corticosteroids ($N = 91$) at a single-level facet capsule. No imaging guidance was reported. Both groups improved in pain-related functioning and pain intensity at 2 weeks and 3 months. While the corticosteroid group had significantly lower ODI at 3 months, the difference did not meet MCID; there were no significant differences at 2 weeks. For pain intensity, dextrose prolotherapy group had significantly lower VAS at 3 months, with similarly no significant differences at 2 weeks. Health-related quality of life, physical performance, costs/treatment burden, and adverse events were not addressed.

Sacroiliac Joint Dysfunction

Two RCTs[106,107] examined dextrose prolotherapy specifically for back pain due to sacroiliac joint dysfunction, and both compared prolotherapy to corticosteroid injection. Kim, 2010 [107] compared a maximum of 3 sessions of 25% dextrose (with phenol) versus corticosteroid injections (over a maximum of 4 weeks). Raissi, 2022[106] evaluated a single injection of 20% dextrose versus corticosteroids. Both studies used imaging guidance (ultrasound[106] or fluoroscopy[107]) for injections. Both RCTs were very small (total $N = 40$-50) and participants were predominantly middle-aged women (mean age range 50-62 years, 67-72% women). Both trials also required ≥ 2 months of pain and confirmation of sacroiliac joint involvement with injection of local anesthetic. Participants were also required to have failed prior medical or pharmacologic treatment for ≥ 1 month. One trial excluded individuals with surgery or other invasive procedures within the past 6 months.[106] Both trials were rated some concerns for RoB, mainly due to concerns about deviations from the assigned intervention. Detailed RoB ratings (by domain and overall) are presented in **Appendix E**. Both studies evaluated pain-related functioning, adverse events, and pain intensity. Physical performance, health-related quality of life, or cost/treatment burden were not addressed by either study.

The evidence is very uncertain on the effects of dextrose prolotherapy for pain-related functioning at short-term follow-up, (very low COE, **Table 26**). Both studies showed improvement for participants in both groups over time. Kim, 2010[107] evaluated pain-related functioning using ODI at 2 weeks, and

found that the dextrose prolotherapy group had slightly lower scores (mean 11.1 versus 15.5 for corticosteroid group), but this was not statistically significant and also did not meet MCID. Raissi, 2022[106] assessed functioning at 2 and 8 weeks using the Dallas Pain Questionnaire (DPQ), also finding no significant between-group differences at these time points. Although there were no significant differences, DPQ scores were lower in the corticosteroid group at both time points.

The evidence is very uncertain on the effect of dextrose prolotherapy for adverse events, compared to steroid injection (very low COE, **Table 26**). Raissi, 2022[106] found that an equal proportion of participants (*N* = 3, 17%) in each arm experienced a "mild flare reaction" post-injection. Kim, 2010[107] reported that no participants had serious adverse events "such as long-lasting exacerbation of pain, numbness or weakness, or signs of skin infection."

Finally, both studies evaluated pain intensity or severity using NRS[107] or VAS.[106] As with pain-related functioning, participants in both groups improved over time. Kim, 2010[107] found no significant between-group differences at 2 weeks, and similarly Raissi, 2022[106] also showed no significant differences at 2 weeks, 2 or 9 months.

Table 26. Sacroiliac Joint Dysfunction COE: Dextrose Prolotherapy versus Corticosteroid Injection

Outcome	Follow-Up	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up			Certainty	What Happens
Measure	Total *N* (# of Studies)	Dextrose Prolotherapy	Steroids	Difference		
Pain-related functioning ODI, DPQ	Short-term (2 wk) *N* = 84 (2 RCTs)[106,107]	11.1*	15.5*	-4.4*	Very low[a,b] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on pain-related functioning at short-term follow-up.
Adverse events	*N* = 84 (2 RCTs)[106,107]	0†	0†	—	Very low[a,c,d] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on adverse events.

Notes. *Values for mean ODI scores at follow-up for intervention and comparator from Kim, 2010.[107] Differences calculated by review team.

†Study reported no serious adverse events.[107]

GRADE Working Group grades of evidence:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

a. Downgraded 2 levels for study limitations (1-2 studies assessed as some concerns RoB).

b. Downgraded 1 level for imprecision (using OIS, studies were not powered to detect MCID for ODI or SMD of 0.7; see Methods for more information).

c. Downgraded 1 level for indirectness (no information about how or when adverse events were assessed).

d. Downgraded 1 level for imprecision (not powered to minimum adverse event rate <10%; see Methods for more information).

Abbreviations. DPQ=Dallas Pain Questionnaire; NRS=Numeric Rating Scale; ODI=Oswestry Disability Index; OIS=optimal information size; RCT=randomized controlled trial; RoB=risk of bias; wk=weeks.

TEMPOROMANDIBULAR JOINT DISORDERS

Overview

We identified 16 studies (14 RCTs, 2 observational studies) that evaluated dextrose prolotherapy for treatment of symptomatic temporomandibular joint (TMJ) dysfunction. Eight studies enrolled participants with normal or reduced TMJ mobility,[108-115] while the other studies included participants with TMJ hypermobility.[116-123] All studies enrolled mainly young and middle-aged women (mean ages 23-50 years, $k = 10$ studies with >60% female participants). All studies had small sample sizes with total $N = 12$-72. None of the studies were conducted in the US. The majority occurred in the Middle East ($k = 10$),[108-111,113,116,119,120,122,123] 4 were completed in India,[114,117,118,121] and 1 each was conducted in Canada[112] and Argentina.[115] All studies evaluated the maximal mouth opening (MMO) for physical performance and all but one also assessed pain intensity. Seven studies reported on adverse events, and only 2 assessed pain-related functioning. No studies reported on health-related quality of life, cost, or treatment burden. The vast majority of studies were rated high RoB ($k = 12$ RCTs)[109-111,113,114,116-120,122,123] or serious ($k = 2$ observational studies)[108,121] for a variety of reasons, including issues with the randomization and allocation process, proportion of participants receiving the intended interventions, missing data from loss to follow-up, and bias in outcome assessments. Only 1 RCT[115] was assessed as low RoB and another RCT[112] rated some concerns. Detailed RoB ratings (by domain and overall) are presented in **Appendix E**.

Below, we first present findings for studies evaluating dextrose prolotherapy for TMJ dysfunction with normal or restricted mobility. Then, we describe results for studies addressing symptomatic TMJ hypermobility. Detailed characteristics and findings are presented in **Appendix K**.

TMJ Dysfunction with Normal or Restricted Mobility

Eight studies examined dextrose prolotherapy for painful TMJ dysfunction with normal ($k = 1$)[109] or restricted mobility ($k = 7$).[108,110-115] **Table 27** presents key study characteristics and findings for these studies. Three RCTs compared dextrose prolotherapy to normal saline or water injection,[108,110,112,115] and the remaining studies all examined a range of other comparators (*eg*, occlusal splints, arthrocentesis, or PRP). A single RCT also evaluated different injection locations for dextrose prolotherapy.[109] Most studies required clinical signs and/or symptoms of TMJ dysfunction including pain and sounds during mandibular movements. Six studies excluded participants with previous TMJ surgical intervention,[108-110,114] injections,[108,110,115] or prior treatment of TMJ pain.[111] Three studies only included participants who had failed prior conservative treatment (*eg*, NSAIDs, corticosteroid injections, soft diet, occlusal splint).[108,110,111]

Here, we first describe characteristics and findings from the 3 studies comparing dextrose prolotherapy with normal saline or water injection. Then, we present results from the study examining different injection locations for dextrose prolotherapy. Lastly, we summarize findings from the remaining 4 studies that each evaluated different comparators.

Table 27. Summary of Characteristics and Key Findings for Temporomandibular Joint Disorders With Normal or Restricted Mobility

Author, Year Study Design; RoB; Country Key Participant Characteristics	Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparator(s) *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance*	Adverse Events
Dextrose Prolotherapy versus Water or Normal Saline (With Local Anesthetic)					
Haggag, 2022[110] RCT; High; Egypt TMJ with pain and bilateral disc displacement with reduction, limited unassisted MMO, failed conservative treatment, no prior TMJ injection or surgery; mean ages 23-24 yr, 100% female	25% dextrose 2 ml (+4% articaine) intra-articular in superior joint space and retrodiscal tissue *N* = 15 (NR) Clinic; up to 3 wk (up to 4 injections, 1 wk apart)	Normal saline 2 ml (+4% articaine) with same injection method *N* = 15 (NR) Clinic; up to 3 wk (up to 4 injections, 1 wk apart)	—	**MMO (1, 3, 6 mo)** ↑ Dextrose-Saline	—
Louw, 2019[112] RCT; Some concerns; Canada Symptoms >3 mo, baseline NRS pain and dysfunction ≥6, no long-term use of NSAIDs or steroids; mean ages 44-50 yrs, 73-96% female	20% dextrose 1 ml (+ 0.2% lidocaine) intra-articular in superior joint space *N* = 22 (20) Clinic; 2 mo (3 injections, 1 mo apart)	Water 1ml (+ 0.2% lidocaine) with same injection method *N* = 20 (20) Clinic; 2 mo (3 injections, 1 mo apart)	**NRS-Dysfunction (1, 2, 3 mo)*†** ↑ Dextrose-Water	**MMO (3 mo)** ↑ Dextrose-Water	—
Zarate, 2020[115] RCT; Low; Argentina Symptoms ≥3 mo, baseline NRS pain and dysfunction ≥6, no prior TMJ injections, no ongoing NSAIDs or steroids; mean ages 45-50 yr, 86-87% female	20% dextrose 1 ml (+ 0.2% lidocaine) intra-articular in the superior joint space (25 mm depth) *N* = 15 (14) Clinic; 2 mo (3 injections, 1 mo apart)	Water 1ml (+ 0.2% lidocaine) with same injection method *N* = 14 (13) Clinic; 2 mo (3 injections, 1 mo apart)	**NRS-Dysfunction (1 mo)*†** ↑ Dextrose-Water **NRS-Dysfunction (2, 3 mo)*†** ↔ Dextrose-Water	**MMO (3 mo)** ↔ Dextrose-Water	*"There were no adverse events."* (AE not defined)
Dextrose Prolotherapy—Different Injection Locations					
Fouda, 2018[109] RCT; High; Egypt Unilateral pain, clicking sounds, normal MMO, MRI showed disc displacement with	4 different intra-articular injection locations for 22% dextrose 1.7 ml (+ 0.2% mepivacaine): • Outer capsule	—	—	**MMO (2 wk, 3 mo)‡** **?** Dextrose different locations	*"…painful injections and burning sensations…in 18 of the 72 patients. Two patients in group [with retrodiscal injection] developed paralysis of*

reduction, no PT in past 3 mo, no prior TMJ surgery; demographics NR	• Superior joint space • Inferior joint space • Retrodiscal tissues *N* = 18 (NR) per group Clinic; 3 wk (4 injections, 1 wk apart)				*the temporal branch of the facial nerve…* [and] *a temporary inability to blink."*
Dextrose Prolotherapy versus Other Comparators					
Elwerfelli, 2019[108] Observational Cohort; Serious; Egypt Symptoms, exam and MRI findings consistent with TMJ, failed conservative treatment (NSAIDs, soft diet, and occlusal splint ≥4 wk), MMO < 35 mm, no prior TMJ surgery or injections; mean age 29 yr, 86% female	50% dextrose 2 ml intra-articular in superior joint space, after arthrocentesis and lavage with 50 ml normal saline *N* = 7 (7) Clinic; single injection	Arthrocentesis and lavage with 50 ml normal saline *N* = 7 (7) Clinic; single session	—	**MMO (1, 2 wk)** ↔ Dextrose-Arthrocentesis **MMO (3, 4, 5, 6 wk)** ↑ Dextrose-Arthrocentesis	*"Three female patients in* [arthrocentesis group had] *mild preauricular swelling in immediate post-operative phase. One female patient in* [normal saline group] *reported difficult closure of the eyelid."*
Hassanien, 2020[111] RCT; High; Egypt TMJ pain, sounds during mandibular movements (clicking, popping), "functional disability," no prior treatment for TMJ and no current corticosteroids; mean age 26 yrs, 50% female	12.5% dextrose 3 ml (+ 0.5% lidocaine) intra-articular in posterior joint space and anetrior disc attachment, and extra-articular at masseter muscle attachment *N* = 10 (NR) Clinic; 4 wk (3 injections, 2 week part)	Low level laser therapy (980 nm wavelength, 0.2 Watt, 12 J for 60 s) *N* = 10 (NR) Clinic; 4 wk (3 sessions/week)	—	**MMO (2, 4 wk)** ↑ Dextrose-Laser	—
Mahmoud, 2018[113] RCT; High; Egypt "suffered from internal [TMJ] derangement", all had MRI, prior treatments NR; mean age NR, 60-67% female	12.5% dextrose 3ml (+ 1% lidocaine) intra-articular at posterior joint space and anterior disc attachment, and extra-articular at masseter muscle attachment *N* = 15 (NR) Clinic; 4 wk (3 injections, 2 wk apart)	2 comparators: • Arthrocentesis, then HA intra-articular (volume and location NR) • PRP 1 ml intra-articular (location NR) *N* = 15 (NR); 15 (NR) Clinic; 1 injection	—	**MMO (1 mo)** ↔ Dextrose-HA ↔ Dextrose-PRP **MMO (3, 6, 12 mo)** ↔ Dextrose-HA ↑ Dextrose-PRP	—

Priyadarshini, 2021[114] RCT; High; India TMJ internal derangement confirmed by MRI (Wilkes stage II and III), no prior TMJ surgery; mean ages 28-32 yr, 59-71% female	12.5% dextrose 3ml (+ 1% lignocaine) intra-articular at posterior joint space and anterior disc attachment, and extra-articular at masseter muscle attachment *N* = 17 (17) Clinic; 3 mo (4 injections, 2-6 wk apart)	Occlusal splints *N* = 17 (17) Home; 3 mo (wear for 12 hrs daily)	—	**MMO (1, 3, 6, 12 mo)** — ↑ Dextrose-Splint

Notes. *No established MCID for outcome; direction of effect based on statistically significant difference reported by study.

†NRS dysfunction on 0-10 scale, where 0 is no dysfunction and 10 is worst dysfunction (*eg*, difficulty chewing, jaw tension, or grinding).

‡Study reported significant differences in overall comparison across all 4 groups (p= 0.014 at 2 wk, p= 0.003 at 3 mo) but not pairwise between-group comparisons to indicate which locations were superior.

Symbols. ↑: At specified follow-up time point, the dextrose arm had a better scale score than the comparator arm (meeting MCID); ↔: At specified follow-up time point, the difference in scale scores between the dextrose and comparator arms did not meet MCID; ↓: At specified follow-up time point, the dextrose arm had a worse scale score than the comparator arm (meeting MCID); ?: Review team was unable to interpret scale scores (*eg*, no MCID, study did not report statistically significant difference between arms).

Abbreviations. AE=adverse event; HA=hyaluronic acid; MCID=minimal clinically important difference; MMO=maximum mouth opening; mo=month; MRI=magnetic resonance imaging; NR=not reported; NRS=numeric rating scale; NSAIDs=nonsteroidal anti-inflammatory drugs; RCT=randomized controlled trial; RoB=risk of bias; TMJ=temporomandibular joint; wk=week; yr=year.

Dextrose Prolotherapy versus Normal Saline or Water Injection (With Local Anesthetic)

Three RCTs[110,112,115] compared dextrose prolotherapy with normal saline or water injections. Two trials[112,115] implemented a treatment protocol of 3 sessions of 20% dextrose injections over 2 months. The third study[110] used 25% dextrose every week for up to 4 weeks. Normal saline or water injections followed the same protocol. None of the studies used imaging guidance for injections. All 3 studies advised participants to use acetaminophen for post-injection pain management. One study[115] instructed participants to avoid NSAIDs, and 2 studies[110,115] discouraged other types of TMJ care (*eg*, oral devices). All trials were small, with total $N = 29$-42. Maximal length of follow-up was 3-6 months. All 3 studies assessed physical performance and pain severity or intensity, 2 studies evaluated pain-related functioning, and 1 study reported on adverse events.

The evidence is very uncertain about the effect of dextrose prolotherapy on pain-related functioning at short- and medium-term follow-up (very low COE, **Table 28**). Two studies[112,115] assessed pain-related functioning, both with a single-item NRS for jaw dysfunction at 1-3 months. In both studies, participants in both groups improved over time and the dextrose prolotherapy group had significantly greater improvement at 1 month. However, at later time points, Zarate, 2020[115] found no significant difference between arms, while Louw, 2019[112] reported that improvements remained significantly greater for the dextrose arm.

The evidence is very uncertain about the effect of dextrose prolotherapy on physical performance at short-, medium-, and long-term follow-up (very low COE, **Table 28)**. All 3 RCTs evaluated physical performance by measuring MMO with maximum follow-up of 3-6 months. As participants had restricted TMJ mobility at baseline, higher MMO indicated improvement. Haggag, 2022[110] found significantly higher MMO in the dextrose prolotherapy arm at all time points (1-6 months), and Louw, 2019[112] similarly reported greater improvement in MMO for the dextrose group at 3 months. In contrast, Zarate, 2020[115] found no statistically significant difference between arms at 3 months.

The evidence is very uncertain about the effect of dextrose prolotherapy on adverse events (very low COE, **Table 28**). Only Zarate, 2020[115] evaluated adverse events, finding that none were observed in either group. However, authors did not describe the assessment for adverse events.

All 3 studies also evaluated pain severity using the VAS or NRS, with inconsistent results. Haggag, 2022[110] reported significantly lower NRS in the dextrose prolotherapy arm at 1-6 months. Louw, 2019[112] also reported significantly greater improvements in the dextrose prolotherapy group at 3 months, but Zarate, 2020[115] found no significant differences between arms at 3 months.

Table 28. Temporomandibular Joint Disorder with Restricted or Normal Mobility COE: Dextrose Prolotherapy versus Normal Saline or Water Injection (With Local Anesthetic)

Outcome Measure	Follow-Up Total *N* (# of Studies)	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up Dextrose Prolotherapy	 Saline or Water	 Difference	Certainty	What Happens
Pain-related functioning NRS-Dysfunction	Short-term (1 mo) *N* = 71 (2 RCTs)[112,115]	4.0*	5.9*	-1.9*	Very low[a,b,c] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on pain-related functioning at short-term follow-up.
	Medium-term (3 mo) *N* = 71 (2 RCTs)[112,115]	3.4*	4.0*	-0.6*	Very low[a,b,c,d] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on pain-related functioning at medium-term follow-up.
Physical performance MMO (mm)	Short-term (1 mo) *N* = 30 (1 RCT)[110]	40.8	35.3	5.5	Very low[b,e] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on physical performance at short-term follow-up.
	Medium-term (3 mo) *N* = 101 (3 RCTs)[110,112,115]	43.4*	47.8*	-4.4*	Very low[b,d,e] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on physical performance at medium-term follow-up.
	Long-term (6 mo) *N* = 30 (1 RCT)[110]	41.7	29.1	12.6	Very low[b,e] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on physical performance at long-term follow-up.
Adverse events NR	*N* = 29 (1 RCT)[115]	0†	0†	—	Very low[f,g] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on adverse events.

Notes. *Values for mean NRS scores at follow-up for intervention and comparator from Zarate, 2020.[115] Differences calculated by review team.

†One study reported "there were no adverse events" (AE not defined).[115]

GRADE Working Group grades of evidence:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

a. Downgraded 1 level for study limitations (1 study assessed as some concerns RoB).

b. Downgraded 1 level for imprecision (using OIS, studies were not powered to detect minimum SMD of 0.8; see Methods for more information).

c. Downgraded 1 level for indirectness (NRS-dysfunction is single-item measure without validation or MCID).

d. Downgraded 1 level for inconsistency (effect varied across trials).
e. Downgraded 2 levels for study limitations (1 study assessed as high RoB).
f. Downgraded 1 level for indirectness (no information about how or when adverse events were assessed).
g. Downgraded 2 levels for imprecision (not powered to minimum adverse event rate <20%; see Methods for more information).
Abbreviations. MMO=maximum mouth opening; mo=month; NR=not reported; NRS=numerical rating scale; OIS=optimal information size; RCT=randomized controlled trial; RoB=risk of bias; SMD=standardized mean difference.

Dextrose Prolotherapy—Different Injection Locations

Fouda, 2018[109] enrolled 72 participants and compared 22% dextrose prolotherapy injections at 4 different locations: outer capsule, superior joint space, inferior joint space, and retrodiscal tissues. All groups received 4 injection sessions, each 1 week apart, for a total treatment duration of 3 weeks. This study evaluated MMO, pain intensity (assessed with VAS), and adverse events. At 2 weeks and 3 months, there were significant between-group differences overall for both MMO and pain intensity (*eg*, p< 0.0005 for comparison across all 4 groups of MMO at 2 weeks). Authors did not report pairwise comparisons between 2 specific locations, but the retrodiscal tissues group had the highest MMO (*eg*, mean 40.1 mm at 3 months) and lowest VAS scores (*eg*, mean 1.0 at 3 months), while the outer capsule had the lowest MMO (*eg*, mean 29.6 mm at 3 months) and highest VAS scores (*eg*, mean 4.1 at 3 months). Authors reported that 18 participants experienced pain and burning with injections, but did not provide breakdown by arms. Additionally, 2 participants in the retrodiscal tissue group developed paralysis of the temporal branch of the facial nerve.

Dextrose Prolotherapy versus Other Comparators

The remaining 4 studies[108,111,113,114] used a variety of comparators: arthrocentesis and lavage ($k = 1$),[108] laser ($k = 1$),[111] arthrocentesis and HA or PRP ($k = 1$),[113] or occlusal splints ($k = 1$).[114] Elwerfelli, 2019[108] reported a very small observational study of 14 patients who underwent a single session of either arthrocentesis and lavage, or combined arthrocentesis/lavage and 50% dextrose injection. Participants in both groups improved in MMO and pain intensity (assessed with VAS) during follow-up over 6 weeks, and there were no significant between-group differences in VAS at any time point. For MMO, there were no significant differences at 1 and 2 weeks, but the dextrose arm had better scores at 2-6 weeks. Four patients, all in the arthrocentesis/lavage only group, experienced side effects (preauricular swelling or difficulty with closing eyelid).

Hassanien, 2020[111] conducted a very small RCT that randomized 20 participants to either 12.5% dextrose injections (3 sessions over 4 weeks) or low-level laser therapy (3 sessions per week for 4 weeks). This study only evaluated MMO and pain intensity (assessed with VAS) at 2 and 4 weeks, finding improvements in both groups over time. The dextrose prolotherapy group had significantly higher MMO at 2 and 4 weeks, but there were no significant between-group differences in VAS at any time point.

Mahmoud, 2018[113] reported a small 3-arm RCT ($N = 45$) comparing 12.5% dextrose injections (3 sessions over 4 weeks) versus arthrocentesis with intra-articular HA versus PRP injections. There were no statistically significant differences between the 3 arms of dextrose prolotherapy, hyaluronic acid, and PRP at 1 month. Over maximum follow-up of 1 year, only the arthrocentesis/HA and dextrose arms demonstrated improvements in MMO and had significantly higher MMO than the PRP group. For VAS, all 3 groups had substantial decreases over follow-up, with the PRP group having significantly lower scores at 6 and 12 months.

Finally, Priyadarshini, 2021[114] also conducted a small RCT (*N* = 34) that evaluated 12.5% dextrose injections (4 sessions over 3 months) versus occlusal splints. The dextrose prolotherapy group had significantly higher MMO and lower pain intensity (VAS) at all follow-up time points (1 month-1 year).

TMJ Dysfunction with Hypermobility

Eight studies[116-123] evaluated dextrose prolotherapy for symptomatic TMJ hypermobility. **Table 29** summarizes key study characteristics and findings for these studies. Three RCTs[119,120,122] compared dextrose with normal saline injections, and 4 studies[116-118,121] with autologous blood injection (ABI). One RCT examined different locations for dextrose injections.[123] All studies required evidence of TMJ hypermobility on clinical exam (*eg*, subluxation or dislocation) and half also used X-rays or computed tomography imaging as confirmation. Half the studies excluded participants with prior TMJ treatment;[117,119,121,124] 3 studies[117,119,124] excluded both invasive and conservative prior treatment, while 1 study[121] only excluded prior surgery. No study required failed conservative treatment prior to enrollment. Every study reported MMO for physical performance and none evaluated health-related quality of life, costs, or treatment burden.

Below, we first describe characteristics and findings from the 3 studies comparing dextrose prolotherapy with normal saline injections. Then, we present results from studies evaluating using ABI comparators. Lastly, we summarize findings from the study examining different injection locations for dextrose prolotherapy.

Dextrose Prolotherapy versus Normal Saline Injection

Three RCTs[119,120,122] compared 6.7-15% dextrose prolotherapy with normal saline injections. Mustafa, 2018[120] also compared 3 dextrose concentrations (5%, 10%, and 15%). All studies administered 3-4 sessions of injection over 2-4 months, and none used imaging guidance. One study[122] asked participants to reduce or stop pain medication and follow a soft diet, while the other 2 studies[119,120] instructed participants to take acetaminophen and avoid wide mouth opening. All studies were very small with total *N* =12-40. All 3 studies assessed physical performance, while 2 studies reported on adverse events. Two studies also evaluated pain intensity or severity.

The evidence is very uncertain on the effect of dextrose prolotherapy on physical performance at short-, medium-, and long-term follow-up (very low COE, **Table 30**). Because participants all had TMJ hypermobility at baseline, lower MMO at follow-up indicated improvement. Refai, 2011[122] found no statistically significant differences between arms at 6 weeks and 3 months, but the dextrose prolotherapy group had significantly lower MMO at 4.5 and 5 months. In contrast, Mustafa, 2018[120] demonstrated no significant between-group differences in MMO at 1-4 months, although all groups improved over time. Comert Kilic, 2016[119] also found no significant between-group differences in MMO improvement at 12 months.

Table 29. Summary of Characteristics and Key Findings for Temporomandibular Joint Disorders with Hypermobility

Author, Year Study Design; RoB; Country Key Participant Characteristics	Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparator(s) *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Physical Performance*	OUTCOMES Adverse Events
Dextrose Prolotherapy versus Normal Saline (With Local Anesthetic)				
Comert Kilic, 2016[119] RCT; High; Turkey Joint sounds, open-locking, and facial pain, TMJ hypermobility on exam and CT, no prior TMJ treatment or surgery; mean ages 29-32 yrs, 71-75% female	12% dextrose 5 ml (+0.4% articaine or mepivacaine) Intra-articular at superior joint space, posterior disc attachment, superior and inferior capsular attachments, and extra-articular at stylomandibular attachment *N* =15 (14) Clinic; 2 mo (3 injections, 1 mo apart)	Normal saline 5 ml (+ 0.4% articaine or mepivacaine) with same injection method *N* =15 (12) Clinic; 2 mo (3 injections, 1 mo apart)	**MMO (12 mo)** ↔ Dextrose-Saline	Paresthesias (in the zygomatic arch and pre-auricular regions): Dextrose—21% (n=3) Saline—0% Transient blepharospasm (recovered after a few wk): Dextrose—7% (n=1) Saline—0%
Mustafa, 2018[120] RCT; High; Turkey Joint sounds, open-locking, and facial pain, TMJ hypermobility on exam, prior treatments NR; mean ages 24-27 yrs, 56-89% female	3 concentrations of dextrose intra-articular at superior joint space, posterior disc attachment, superior and inferior capsular attachments: • 15% dextrose 3 ml • 10% dextrose 3 ml • 5% dextrose 3 ml *N* = 10 (9); 10 (9); 10 (10) Clinic; 3 mo (4 injections, 1 mo apart)	Normal saline 3 ml (+ 1% lidocaine) with same injection method *N* = 10 (9) Clinic; 3 mo (4 injections, 1 mo apart)	**MMO (1, 2, 3, 4 mo)** ↔ Dextrose 15%-Saline ↔ Dextrose 10%-Saline ↔ Dextrose 5%-Saline	—
Refai, 2011[122] RCT; High; Egypt Positive history, TMJ hypermobility on exam and CT, prior treatments NR; mean ages 23-30 yrs, 67-100% female	6.7% dextrose 3 ml (+ 0.7% mepivacaine) intra-articular at superior joint space, superior and inferior capsular attachments *N* = 6 (NR) Clinic; 18 wk (4 injections, 6 wk apart)	Normal saline 3ml (+ 0.7% mepivacaine) with same injection method *N* = 6 (NR) Clinic; 18 wk (4 injections, 6 wk apart)	**MMO (6, 12 wk)** ↔ Dextrose-Saline **MMO (18, 20 wk)** ↑ Dextrose-Saline	Post-injection pain, mild: Dextrose—50% (n= 3) Saline—50% (n= 3) Post-injection itching: Dextrose—67% (n= 4) Saline—33% (n= 2) *"Some patients had transient facial palsy due to the anesthetic…[this] effect diminished within 60 to 90 minutes postoperatively."*

Dextrose Prolotherapy versus Autologous Blood Injection				
Arafat, 2019[116] RCT; High; Egypt Positive history, TMJ hypermobility on exam and CT, no prior TMJ treatment; mean age NR, 37% female	6.7% dextrose 3 ml (+ 0.7% mepivacaine) intra-articular at superior joint space, inferior capsular attachment, and superficial to capsule *N* = 15 (NR) Clinic; up to 4 wk (up to 3 injections, 2 wk apart)	Autologous blood 3 ml intra-articular to superior joint space, and outer surface of capsule *N* = 15 (NR) Clinic; up to 2 wk (up to 2 injections, 2 wk apart)	**MMO (3, 6 mo)** ↓ Dextrose-ABI	*"All patients …tolerated the technique well and complained of no or minimal pain on injection."* Transient facial nerve palsy: Dextrose—33% (n= 5) ABI—0% *"[Facial palsy] resolved 2 hours post-operatively as the effect of local anesthesia subsided."*
Bhargava, 2023[117] RCT; High; India Positive history, TMJ hypermobility on exam and CT, no prior TMJ treatment, no long-term NSAIDs or steroids; mean age 29 yrs, 40-53% female	8% dextrose 3 ml (+ 0.5% heavy bupivacaine) intra-articular at superior joint space and retro-discal regions, and peri-capsular; and lavage with 50-100 ml LR afterwards *N* = 30 (NR) Clinic; up to 18 wk (up to 4 injections every 6 wk)	Autologous blood 3 ml with same injection method (no lavage) *N* = 30 (NR) Clinic; up to 18 wk (up to 4 injections every 6 wk)	**MMO (6, 12 mo)†** ? Dextrose-ABI	*"No complications/adverse reactions were recorded in any of the patient among both the groups."* (AE not defined)
Chhapane, 2023[118] RCT; High; India History of multiple episodes of TMJ dislocation, and positive Xray findings, prior treatments NR; mean age 37 yr, 56% female	50% dextrose 3 ml (+ lignocaine %NR) intra-articular in superior joint space (after lavage with LR), and peri-capsular; and home exercise program *N* = 23 (16) Clinic/home; single injection, home exercises duration NR	Autologous blood 3 ml with same injection method (including lavage); and home exercise program *N* = 23 (16) Clinic/home; single injection, home exercises duration NR	**MMO (1, 3 mo)** ↔ Dextrose-ABI **MMO (6, 12 mo)** ↑ Dextrose-ABI	—
Pandey, 2022[121] Observational Cohort; Serious; India TMJ dislocations >2x/wk, pain and sounds in joint, dislocation on exam and Xrays, MMO >40 mm, no prior invasive TMJ treatment; mean age 34 yrs, female %NR	25% dextrose 3 ml intra-articular in superior joint space, and peri-capsular *N* = 10 (10) Clinic; single injection	Autologous blood 3 ml with same injection method *N* = 10 (10) Clinic; single injection	**MMO (1, 3, 6 mo)** ↓ Dextrose-ABI	—

Dextrose Prolotherapy: Different Locations				
Saadat, 2018[123] RCT; High; Egypt Recurrent dislocation of TMJ >2x in past mo, prior treatments NR; mean ages 29-30 yrs, 63-75% female	2 different intra-articular injection locations for 25% dextrose 2 ml: • Superior joint space • Retrodiscal tissues *N* = 8 (NR) per group Clinic; single injection	—	**MMO (1, 3, 6 mo)** ↔ Superior joint space versus retro-discal tissues	—

Notes. *No established MCID for outcome; direction of effect based on statistically significant difference reported by study.

†No established MCID for outcome and study did not report between-group comparison at time point(s).

Symbols. ↑: At specified follow-up time point, the dextrose arm had a better scale score than the comparator arm (meeting MCID); ↔: At specified follow-up time point, the difference in scale scores between the dextrose and comparator arms did not meet MCID; ↓: At specified follow-up time point, the dextrose arm had a worse scale score than the comparator arm (meeting MCID); ?: Review team was unable to interpret scale scores (*eg*, no MCID, study did not report statistically significant difference between arms).

Abbreviations. ABI=autologous blood injection; AE=adverse events; CT=computed tomography; LR=lactated ringers; MCID=minimal clinically important difference; MMO=maximum mouth opening; mo=month; MRI=magnetic resonance imaging; NR=not reported; NRS=numeric rating scale; NSAIDs=nonsteroidal anti-inflammatory drugs; RCT=randomized controlled trial; RoB=risk of bias; TMJ=temporomandibular joint; wk=week; yr=year.

The evidence is very uncertain about the effect of dextrose prolotherapy on adverse events (very low COE, **Table 30**). Two studies[119,122] reported on adverse events, with Refai, 2011[122] stating that there were no "serious complications," but the majority of participants had some post-injection symptoms, including mild pain and/or itching. There were also some participants who had facial palsy, but exact numbers were not reported. Comert Kilic, 2016[119] reported that side effects were observed in 4 participants (28%) of the prolotherapy group, including paresthesia ($N = 3$) and a transient blepharospasm ($N = 1$).

Table 30. Temporomandibular Joint Disorder with Hypermobility COE: Dextrose Prolotherapy versus Normal Saline Injection (With Local Anesthetic)

Outcome	Follow-Up	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up			Certainty	What Happens
Measure	Total *N* (# of Studies)	Dextrose Prolotherapy	Normal Saline	Difference		
Physical performance MMO (mm)	Short-term (4-6 wk) *N* = 52 (2 RCTs)[120,122]	43.8*	44.7*	-0.9*	Very low[a,b] ⊕◯◯◯	The evidence is very uncertain on the effect of dextrose prolotherapy on physical performance at short-term follow-up.
	Medium-term (3 mo) *N* = 52 (2 RCTs)[120,122]	39.7*	43.4*	-3.7*	Very low[a,b] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on physical performance physical at medium-term follow-up.
	Long-term (5-12 mo) *N* = 42 (2 RCTs)[119,122]	43.3†	43.7†	-0.4†	Very low[a,b,c] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on physical performance at long-term follow-up.
Adverse events NR	*N* = 42 (2 RCTs)[119,122]	28.6%	0%	28.6%	Very low[a,d, e] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on adverse events.

Notes. *Values for mean follow-up scores for intervention (10% dextrose group) and comparators from Mustafa, 2018.[120] Differences calculated by review team.

†Values for mean follow-up scores or adverse event rate for intervention and comparators from Comert Kilic, 2016.[119] Differences calculated by review team.

GRADE Working Group grades of evidence:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

a. Downgraded 2 levels for study limitations (1-2 studies assessed as high RoB).

b. Downgraded 1 level for imprecision (using OIS, studies were not powered to detect minimum SMD of 0.8; see Methods for more information).

c. Downgraded 1 level for inconsistency (effect varied across trials).

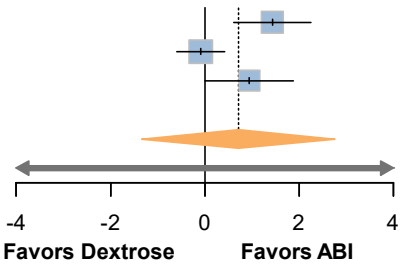
d. Downgraded 1 level for indirectness (no information about how or when adverse event were assessed).
e. Downgraded 2 levels for imprecision (not powered to detect minimum adverse event rate <20%; see Methods for more information).
Abbreviations. MMO=maximum mouth opening; mo=months; NR=not reported; OIS=optimal information size; RCT=randomized controlled trial; RoB=risk of bias; wk=week.

Dextrose Prolotherapy versus Autologous Blood Injection

Four studies[116-118,121] compared 6.7-50% dextrose prolotherapy with autologous blood injection (ABI). Studies administered 1-4 injection sessions over maximum duration of 4.5 months. Three studies[116,121,123] instructed participants to follow a soft diet and use analgesics post-injection. Studies were small with total *N* = 20-60. All 4 studies assessed MMO and VAS, and 2 also reported on adverse events.[116,117]

The evidence is very uncertain about the effect of dextrose prolotherapy on physical performance at short-, medium-, and long-term follow-up (very low COE, **Table 31**). There were inconsistent results across studies. All studies showed that participants in both groups improved over time. Two studies[116,121] found that the ABI group had significantly higher reductions in MMO at 1-6 months, while Bhargava, 2023[117] observed a larger decrease in MMO in the dextrose prolotherapy arm at 6 and 12 months but did not provide a statistical comparison between groups. Meta-analysis for MMO at 6 months demonstrated unclear direction of effect for the pooled estimate (**Figure 9**). We did not include Chhapane, 2023[118] in the meta-analysis because this study showed increasing MMO at 6-12 months (in both arms), despite describing the participants as having TMJ with hypermobility at baseline.

Figure 9. Temporomandibular Joint Disorder With Hypermobility: Effect of Dextrose Prolotherapy versus Autologous Blood Injection on Maximal Mouth Opening at 6 Months



The evidence is very uncertain about the effect of dextrose prolotherapy on adverse events. Two studies[116,117] addressed adverse events, with Arafat, 2019[116] reporting that 5 participants (33%) in the dextrose prolotherapy arm experienced transient facial palsy that resolved within 2 hours post-injection. No participants in the ABI group experienced this side effect. Bhargava, 2023[117] found no adverse events in either group.

All 4 studies assessed VAS, and there were also inconsistent results across studies. Chhapane, 2023[118] and Bhargava, 2023[117] found no significant between-group differences over follow-up 1-12 months, while Arafat, 2019[116] reported significantly better VAS score in ABI group at 2 weeks and 1 month. In contrast to both of these studies, Pandey, 2022[121] showed that the dextrose prolotherapy group had significantly lower VAS at all time points (1 week to 6 months).

Dextrose Prolotherapy—Different Injection Locations

Saadat, 2018[123] conducted a very small RCT ($N = 16$) to compare single injection of 25% dextrose prolotherapy into the retrodiscal tissues versus the superior joint space. Both groups improved during follow-up and there were no significant between-group differences in MMO at 1-6 months. Authors also report that there was only pain observed at baseline and 2 weeks follow-up, and the retrodiscal tissues group had significantly lower mean VAS (5.9 versus 7.4 for superior joint space group).

Table 31. Temporomandibular Joint Disorder With Hypermobility COE: Dextrose Prolotherapy versus Autologous Blood Injection

Outcome Measure	Follow-Up Total *N* (# of Studies)	SMD Pooled Estimate (95% CI)	Anticipated Absolute Effects on Mean Score or Event Rate at Follow-Up Dextrose Prolotherapy	ABI	Difference	Certainty	What Happens
Physical performance MMO (mm)	Short-term (1 mo) *N* = 20 (1 cohort)[121]	—	36.6*	33.8*	2.8*	Very low[a,b] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on physical performance at short-term follow-up.
	Medium-term (3 mo) *N* = 50 (1 RCT, 1 cohort)[116,121]	—	34.4*	32.2*	2.2*	Very low[a,b] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on physical performance at medium-term follow-up.
	Long-term (6 mo) *N* = 110 (2 RCTs, 1 cohort)[116,117,121]	SMD: 0.7 (-1.3, 2.8)	33.2† (30.7, 35.7)	32.3*	0.9† (-1.6, 3.4)	Very low[a,c,d] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on physical performance at long-term follow-up.
Adverse events NR	*N* = 90 (2 RCTs)[116,117]	—	0‡	0‡	—	Very low[a,e,f] ⊕◯◯◯	The evidence is very uncertain about the effect of dextrose prolotherapy on adverse events.

Notes. *Values for mean follow-up scores for intervention and/or comparator arms from Arafat, 2022.[116] Differences calculated by review team.

†Anticipated follow-up mean for intervention arm and MD calculated by review team based on SMD and mean follow-up score for comparator arm from Arafat, 2022.[116]

‡Adverse event data from for intervention and comparator arms from Bhargava, 2023.[117]

GRADE Working Group grades of evidence:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

a. Downgraded 2 levels for study limitations (2-3 studies assessed as high or serious RoB).

b. Downgraded 1 level for imprecision (using OIS, studies were not powered to detect minimum SMD of 0.8; see Methods for more information).

c. Downgraded 1 level for inconsistency (effect varied across studies).

d. Downgraded 1 level for imprecision (CI extends from very large effect favoring dextrose to very large effect favoring ABI).

e. Downgraded 1 level for indirectness (no information about how or when adverse events were assessed).

f. Downgraded 1 level for imprecision (not powered to detect minimum adverse event rate <10%; see Methods for more information).

Abbreviations. ABI=autologous blood injection; AE=adverse event; MD=mean difference, MMO=maximum mouth opening; mo=month; OIS=optimal information size; RCT=randomized controlled trial; RoB=risk of bias; SMD=standardized mean difference.

OTHER PAIN CONDITIONS

Overview

Twelve studies (8 RCTs, 4 observational) evaluated the effect of dextrose prolotherapy for a range of other pain conditions. **Table 32** summarizes key study characteristics and findings. Studies addressed non-arthritis knee pain (pes anserine bursitis, Osgood-Schlatter disease, chronic patellar tendinopathy), other types of foot pain (due to osteochondral lesions of the talus, hallux rigidus, Achilles tendinosis), and various hand pain conditions (midcarpal or scapholunate ligament laxity and hand osteoarthritis). There were also 3 studies that examined fibromyalgia, hip osteoarthritis (due to developmental dysplasia), and Tietze syndrome. A variety of comparators were used, including corticosteroid injection ($k = 3$),[125-127] normal saline or water with local anesthetic injection ($k = 2$),[128,129] and PT/home exercise program ($k = 3$).[128-130] Remaining comparators were PRP,[131] oxygen/ozone injection,[125] paraffin wax,[132] repetitive transcranial magnetic stimulation (rTMS),[133] and naproxen.[134] Participants were predominantly young and middle-aged women (mean ages 32-64 years, 30-100% female), except for the study on Osgood-Schlatter disease, which included only young men.[135] None of the studies were conducted in the US; the highest number were from the Middle East ($k = 8$),[125-127,131-134] and fewer from the East Asia ($k = 2$),[128,135] Australia,[129] and Canada.[136] Only 1 trial enrolled > 100 participants (total $N = 120$),[133] and the remaining had 30-75 participants. The most commonly addressed outcomes were pain-related functioning ($k = 10$), pain intensity or severity ($k = 8$), and adverse events ($k = 7$). Only 2 studies evaluated physical performance reported and 1 reported on cost. No studies assessed health-related quality of life or treatment burden. A third of the studies were rated high RoB ($k = 1$ RCT)[135] or serious/critical ($k = 3$ observational studies),[128,131,134] due to multiple concerns related to deviations from intended interventions, missing data from loss to follow-up, and bias in outcome assessments. The remaining studies were rated some concerns ($k = 7$ RCTs)[125-127,129,130,132,136] or moderate RoB ($k = 1$ observational study).[133] Detailed RoB ratings (by domain and overall) are presented in **Appendix E**.

Below, we first describe study characteristics and findings for non-arthritis knee pain, followed by results for other foot pain (not due to plantar fasciitis). Then we present studies addressing hand pain conditions, and finally individual studies of the remaining pain conditions. Detailed study characteristics and outcomes for these studies are presented in **Appendix L.**

Table 32. Summary of Characteristics and Key Findings for Other Conditions (With Single Studies)

Author, Year Study Design; RoB; Country Key Participant Characteristics	Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance*	Adverse Events
Babaei-Ghazani, 2023[125] RCT; Some concerns; Iran **Pes anserine bursitis:** pain, and occasional swelling of inferomedial knee (below medial joint line), no PT in past 3 mo, no injections in past 6 mo, and no prior history of surgery; mean ages 59-64 yrs, 79.2-92% female; mean BMI 30-33	20% dextrose 2 ml (+2% lidocaine), ultrasound-guided *N* = 25 (23) Clinic; 1 injection	2 comparators: • Triamcinolone 40 mg, ultrasound-guided • Oxygen/Ozone 5 ml, ultrasound-guided *N* = 25 (25) & 25 (24) Clinic; 1 injection	**WOMAC (1 wk)** ↓ Dextrose-Steroid ↓ Dextrose-Oxygen/Ozone **(8 wk)** ↔ Dextrose-Corticosteroid ↔ Dextrose-Oxygen/Ozone **WOMAC Physical Function (1 wk)** ↔ Dextrose-Corticosteroid ↓ Dextrose-Oxygen/Ozone **(8 wk)** ↔ Dextrose-Corticosteroid ↔ Dextrose-Oxygen/Ozone	—	—
Cho, 2017[128] Observational; Serious; Korea **Chronic patellar tendinopathy:** "diagnosed with chronic patellar tendinopathy"; mean ages 32-35 yrs, 30-60% female; mean BMI 22-23	12.5% dextrose10 ml (+0.5% lidocaine), ultrasound-guided. Two groups: • Dextrose • Dextrose and supervised exercise program *N* = 10 (10) & 10 (10) Clinic/NR; 4 wk (3 sessions); exercise 12 wk (3 dats/wk)	Supervised exercise program only *N* = 10 (10) Setting NR: 12 wk (3 days/wk)	**VISA-P (6, 12 wk)** ↓ Dextrose-Exercise ↔ Dextrose/ Exercise-Exercise	**Isometric knee strength, 60% Extensor/flexor (6, 12 wk)†** **?** Dextrose-Exercise **?** Dextrose/ Exercise-Exercise	—

Author, Year **Study Design; RoB; Country** **Key Participant Characteristics**	**Intervention** ***N* Randomized (*N* Analyzed)** **Setting; Duration**	**Comparators** ***N* Randomized (*N* Analyzed)** **Setting; Duration**	**OUTCOMES** **Pain-Related Functioning**	**Physical Performance***	**Adverse Events**
Wu, 2022[135] RCT; High; China **Osgood-Schlatter Disease:** Positive signs on Xrays or MRI, continued symptoms with ≥ 1 mo of conservative treatment; mean age 22 yrs, 0% female; mean BMI 22	12.5% dextrose 4 ml (+0.5% lidocaine), ultrasound-guided *N* = 35 (35) Clinic; 2 months (3 injections)	Normal saline 4 ml (+0.5% lidocaine), ultrasound-guided *N* = 35 (35) Clinic; 2 months (3 injections)	**VISA-P (3 wk)** ↑ Dextrose-Saline **(6, 12 mo)** ↔ Dextrose-Saline	—	*"No adverse events were reported in either group"* (AE not defined)
Akpancar, 2019[131] Observational; Critical; Turkey **Osteochondral lesions of the talus**: ≥ 6 mo of pain, stiffness, disability, and dissatisfaction after other treatments and grade I-III lesions on X-rays, no prior history of surgery; mean ages 54-58 yrs, 70-73% female	25% dextrose 2 ml intra-articular, and 13.5% dextrose (+ lidocaine %NR) at tibial edge and talar dome adjacent to the joint surface *N* = 27 (27) Clinic; 3 injections	2 ml PRP intra-articular and 2 ml PRP at tibial edge and talar dome adjacent to the joint surface *N* = 22 (22) Clinic; 3 injections	**AOS (21 days, 3, 6, 12 mo)*** ↔ Dextrose-PRP	—	*"Patients did not suffer from any side effects such as infection, fever, hematoma, or rupture. Only 3 patients reported extreme pain 1 or 2 days after injection in the prolotherapy group, which was alleviated after 2 days of non-weight bearing."* (study excluded participants who could not complete all 3 injections)
Hadianfard, 2023[126] RCT; Some concerns; Iran **Hallux rigidus**: pain or decreased ROM ≥ 3 mo without response to other treatments, no signs of arthritis on Xrays, no prior history of surgery or trauma; mean ages 47-50 yrs, 81-88% female	25% dextrose 2 ml (+1% lidocaine) *N* = 16 (16) Clinic; 1 injection	Methylprednisolone acetate 40 mg (+ 1% lidocaine) *N* = 16 (16)	**MOXFQ (1, 4, 8 wk)*** ↔ Dextrose-Steroid	—	—
Yelland, 2011[129] RCT; Some concerns; Australia **Achilles tendinosis**: activity related pain ≥ 6 wk, pain near calcaneal attachment of Achilles tendon, VISA-A < 80 (involved in	20% dextrose 5 ml (+0.1% lignocaine, +0.1% ropivacine), using Lyftogt technique: • Dextrose	Eccentric loading exercises only *N* = 15 (15) Home; 12 wk (twice daily)	**VISA-A (6 wk, 12 mo)*** ? Dextrose-Exercise‡ ↑ Dextrose/ Exercise-Exercise	—	*"One adverse event was reported in the trial. A participant in the* [exercise only] *group had a partial calf tear while playing tennis. An independent sports physician did not*

Author, Year Study Design; RoB; Country Key Participant Characteristics	Intervention *N* Randomized (*N* Analyzed) Setting; Duration	Comparators *N* Randomized (*N* Analyzed) Setting; Duration	OUTCOMES Pain-Related Functioning	Physical Performance*	Adverse Events
sports) or <70 (not in sports), no previous injections or prior history of surgery; median ages 46-48 yrs, % female NR	• Dextrose and home exercise program *N* = 14 (14) & *N* = 14 (14) Clinic/Home; 4-12 weekly injections, 12 wk exercises				*attribute this to the* [intervention]*."*
Hooper, 2011[136] RCT; Some concerns; Canada **Midcarpal or scapholunate ligament laxity:** dorsal–radial wrist pain ≥ 6 mo, PRWE score ≥ 20, normal wrist X-ray; mean ages 33-35 yrs, 68-75% female	20% dextrose 5 ml (+0.6% lidocaine) injected with peppering technique in ≥ 3 sites of maximal tenderness and other areas of secondary tenderness *N* = 20 (16) Clinic; 5 mo (max of 6 injections, 1 mo apart)	1% lidocaine 5 ml using same injection technique *N* = 19 (18) Clinic; 5 mo (max of 6 injections, 1 mo apart)	**PRWE (3 mo)*** ↔ Dextrose-Saline **(12 mo)*** ↑ Dextrose-Saline	**Grip strength, flexion, extension, supination, pronation (12 mo)** ↔ Dextrose-Saline	—
Jahangiri, 2014[127] RCT; Some concerns; Iran **Osteoarthritis of 1st carpometacarpal (CMC) joint:** joint pain ≥ 3 mo, >30 on VAS, and signs of osteoarthritis on Xrays; mean ages 63-64 yrs, 70-77% female	10% dextrose (+2% lidocaine) in the snuffbox and intra- and peri-articular locations *N* = 30 (28) Clinic; 2 mo (3 injections, 1 mo apart)	40 mg methylprednisolone acetate (+ 2% lidocaine) in the snuffbox and intra- and peri-articular locations *N* = 30 (27) Clinic; 2 mo (3 injections, 1 mo apart)	**HAQDI (1 mo)*** ↔ Dextrose-Steroid **HAQDI (2, 6 mo)*** ↑ Dextrose-Steroid	**Lateral Pinch Strength (1 mo)** ↓ Dextrose-Steroid **Lateral Pinch Strength (2, 6 mo)** ↔ Dextrose-Steroid	*"The participants did not report any significant side effects…three patients* [had] *transient increases in pain at the site of injection which subsided within several days. There was no sign of infection or any other complication ..."*
Ustun, 2023[132] RCT; Some concerns; Turkey **Bilateral hand osteoarthritis:** per ACR criteria, no prior surgery, no PT or joint injections in past 6 mo; mean ages 60 yrs, 100% female	15% dextrose ml NR, in periarticular ligaments of symptomatic hand joints *N* = 23 (21) Clinic; 1 injection	Paraffin wax *N* = 23 (21) Clinic; 10 sessions, 20 minutes a day, 5 days a wk, for 2 wk	**DHI (2 wk)*** ↑ Dextrose-Paraffin wax **DHI (1, 3 mo)*** ↔ Dextrose-Paraffin wax	—	"*1* [participant in dextrose group] *discontinued due to…. increasing pain, and subsequently, a Heberden's nodule was detected in the pain site*."

Author, Year **Study Design; RoB; Country** **Key Participant Characteristics**	**Intervention** ***N* Randomized (*N* Analyzed)** **Setting; Duration**	**Comparators** ***N* Randomized (*N* Analyzed)** **Setting; Duration**	**OUTCOMES**		
			Pain-Related Functioning	**Physical Performance***	**Adverse Events**
Abd, 2019[133] Observational; Moderate; Egypt **Fibromyalgia:** met ACR criteria, prior treatments not described; mean ages NR (age-matched), 100% female	12.5% dextrose 10 ml (+ 0.3% xylocaine) into trigger points *N* = 60 Clinic; 1 month (3 injections bi-weekly)	repetitive transcranial magnetic stimulation (rTMS) 10 Hz *N* = 60 Clinic; 1 month (15 sessions total, 1 every other day)	**FIQR (1 mo)*** ↔ Dextrose-rTMS **(2 mo)*** ↑ Dextrose-rTMS	—	—
Gul, 2020[130] RCT; Some concerns; Turkey **Hip osteoarthritis due to developmental dysplasia**: Hip pain > 6 mo, failed prior conservative treatment for > 3 mo, positive hip Xrays, and awaiting total hip arthroplasty surgery; mean ages 46-48 yrs, 60-67% female	Intra-articular 22.5% dextrose 8 ml (+ lidocaine %NR) and extra-articular 13.5% dextrose maximum volume 20 ml (+ lidocaine %NR), ultrasound-guided *N* = 20 Clinic; 15 wk (6 injections maximum, 3 wk apart)	PT/home exercise program *N* = 21 Clinic & home; 12 wk (30 training sessions, 45-60 minutes per session)	—	—	Severe post-injection pain (needing to take acetaminophen 4 times/day for 5-7 days): Dextrose—15% (n= 3) Exercise—NA *"Serious complications such as cellulitis, septic joint arthritis, osteomyelitis or bleeding were not observed in any patient."*
Senturk, 2017[134] Observational; Serious; Turkey **Tietze syndrome:** No history of thoracic trauma, prior treatments no described; mean ages 45-48 yrs; 66-77% female	16% dextrose 10 ml (+0.4% lidocaine) into symptomatic costochondral joint *N* = 21 (21) Clinic; 1 injection	5 mg/kg naproxen sodium twice daily *N* = 13 (13) Home; daily	—	—	*"Complications during the course of treatment included superficial skin pigmentation (n= 1) for the prolotherapy group."*

Notes. *No established MCID for outcome; direction of effect based on statistically significant difference reported by study.

†Study reported significant group x time effects for knee extensor strength (p= 0.002) but not for knee flexor strength (p= 0.185). No pairwise comparisons were conducted. Study also reported results for 1 leg hop and 25° decline board squat tests.

‡Pairwise comparisons between dextrose-only and exercise-only arms were not reported.

Symbols. ↑: At specified follow-up time point, the dextrose arm had a better scale score than the comparator arm (meeting MCID); ↔: At specified follow-up time point, the difference in scale scores between the dextrose and comparator arms did not meet MCID; ↓: At specified follow-up time point, the dextrose arm had a worse scale score than the comparator arm (meeting MCID); ?: Review team was unable to interpret scale scores.

Abbreviations. ACR=American College of Rheumatology; AE=adverse event; AOS=Ankle Osteoarthritis Scale; BMI=body mass index; DHI=Duruoz Hand Index; EuroQoL-5D=European Quality of Life-5 dimensions; FIQR=Revised Fibromyalgia Impaction Questionnaire; KL=Kellgren-Lawrence; HAQDI=Health Assessment

Questionnaire Disability Index; KOOS=Knee Injury and Osteoarthritis Outcome Score; ml=milliliters; Mo=month; MOXFQ=Manchester-Oxford foot questionnaire; MRI=magnetic resonance imaging; NC=not calculable; NR=not reported; NRS=Numeric Rating Scale; OKS=Oxford Knee Score; OSD=Osgood-Schlatter Disease; PRP=platelet-rich plasma; PRWE=Patient Rated Wrist Evaluation; PT=physical therapy; QoL=quality of life; RCT=randomized controlled trial; RoB=risk of bias; ROM=range of motion; rTMS=repetitive transcranial magnetic stimulation; VISA-A=Victorian Institute of Sport Assessment-Achilles; VISA-P=Victorian Institute of Sport Assessment-Patella; Wk=week; WOMAC=Western Ontario and McMaster Universities Arthritis Index.

Non-Arthritic Knee Pain

Babaei-Ghazani, 2023[125] reported a 3-arm RCT ($N = 75$) to compare single injections of 20% dextrose prolotherapy versus corticosteroid and oxygen/ozone for pes anserine bursitis. Pain-related functioning was assessed using WOMAC and pain intensity with VA, both at 1 week and 2 months. Outcomes for participants in all groups improved during follow-up, but improvements in the dextrose prolotherapy arm lagged behind those seen in the corticosteroid and ozone/oxygen groups. For both WOMAC and VAS, dextrose prolotherapy group had higher scores than either of the other groups at 1 week, and for WOMAC, the differences met MCID. By 8 weeks, scores in the dextrose prolotherapy arm were similar to those in the other groups, and for WOMAC, no differences met MCID. Authors reported that there were significant group effects for both outcomes, but did not report group x time interactions or statistical testing for pairwise comparisons.

Cho, 2017[128]conducted an observational study ($N = 30$) comparing 12.5% dextrose prolotherapy with dextrose prolotherapy plus rehabilitation exercise program, or exercise program alone for chronic patellar tendinopathy. This study assessed pain-related functioning (using the Victorian Institute of Sport Assessment-Patella [VISA-P] questionnaire), physical performance (isometric knee strength), and pain intensity (with VAS) at 6 and 12 weeks. Pain-related interference and pain intensity generally improved in all groups during follow-up, but the dextrose-only group had less improvement compared with the exercise-only group. For pain-related functioning, the dextrose-only group had significantly worse VISA-P scores, compared with the exercise-only group, and these differences met MCID. There were no significant differences between the dextrose and exercise group, compared with the exercise-only group (differences also did not meet MCID). Similarly, for pain intensity, the dextrose-only group had significantly higher mean VAS then the exercise-only group, but there were no significant differences between the combined dextrose and exercise group, and the exercise-only arm. For isometric knee strength, the dextrose-only group had some increases at 6 weeks but returned to baseline (or was slightly worse) by 12 weeks, whereas both of the other groups had improvements at both 6 and 12 weeks. Authors stated that there was significant group x time interaction ($p= 0.002$) for knee extensor strength but not for flexor strength ($p= 0.185$); no pairwise comparisons were reported.

Wu, 2022[135] described an RCT ($N = 70$) that compared 12.5% dextrose prolotherapy with normal saline for Osgood-Schlatter disease. This study showed that both groups improved in VISA-P scores over follow-up of 1 year, and the dextrose group had significantly higher VISA-P at all the time points. The between-group differences only met MCID at 3 weeks. There were no adverse events observed in either group.

Other Foot Pain (Not Plantar Fasciitis)

Akpancar, 2019[131] reported an observational study ($N = 49$) comparing dextrose prolotherapy with PRP injections for pain due to osteochondral lesions of the talus. There were improvements in all groups over 12 months for both pain-related functioning (measured with the Ankle Osteoarthritis Scale) and pain intensity (assessed with VAS), and no significant between-group differences at any time point. Three participants (11%) in the dextrose group had “extreme pain” post-injection. This study also reported on cost per injection to the hospital, indicating this was 30 Turkish lira ($6.80) for dextrose, compared to 250 lira ($56.80) for PRP.

Hadianfard, 2023[126]conducted a very small RCT ($N = 32$) to compare 25% dextrose prolotherapy with corticosteroid injection for pain due to hallux rigidus. Both groups improved on pain-related

functioning (measured by the Manchester-Oxford Foot Questionnaire) and pain intensity (assessed with VAS) over 8 weeks, and there were no significant between-group differences at any time point.

Yelland, 2011[129] reported another very small, 3-arm RCT ($N = 43$) that compared 20% dextrose prolotherapy with eccentric loading exercises and a third group with both treatments, for Achilles tendinosis. Pain-related functioning was measured with the Victorian Institute of Sport Assessment-Achilles (VISA-A) at 6 weeks and 12 months. All groups improved during follow-up, with the combined arm having significantly better VISA-A scores at 6 weeks and 12 months, compared with exercise only. Pairwise comparisons between dextrose-only and exercise-only arms were not reported. One participant had a partial calf tear, but this was determined to be unrelated to study activities. This study also examined the cost effectiveness of dextrose prolotherapy and combined treatments, compared with exercises only; the incremental cost-effectiveness ratio (ICER) per responder (≥ 20 improvement on VISA-A) was $1,716 (Australian dollars) for dextrose alone and $1,539 for the combined treatment.

Hand Pain Conditions

Hooper, 2011[136] conducted a very small RCT ($N = 39$) comparing 20% dextrose prolotherapy with 1% lidocaine for dorsal wrist pain due to midcarpal or scapholunate ligament laxity. Pain-related functioning was assessed with the Patient Rated Wrist Evaluation (PRWE) score at 3 and 12 months. Participants in both arms improved in functioning over time, and the dextrose arm had significantly greater improvements at 12 month (no significant differences at 3 months). This study also evaluated grip strength, flexion, extension, supination, and pronation, finding improvements over time only for grip strength, which was similar in both groups.

Jahangiri, 2014[127] reported an RCT ($N = 60$) evaluating dextrose prolotherapy versus corticosteroid injection for thumb pain due to osteoarthritis of the first carpometacarpal joint. This study assessed pain-related functioning using the Health Assessment Questionnaire Disability Index (HAQDI), lateral pinch strength, and pain intensity (with VAS), all at 1, 2, and 6 months. Participants in both groups improved on all measures during follow-up, with no significant between-group differences in pain-related functioning and pain intensity at 1 month, but significantly greater improvements in the dextrose prolotherapy group at 2 and 6 months. The corticosteroid group had significantly better lateral pinch strength at 1 month, but there were no significant between-group differences at 2 and 6 months. Three participants (arm NR) had increases in pain for several days after injection. The study also reported no "significant side effects," without further defining what constituted "significant" effects.

Ustun, 2023[132] conducted an RCT ($N = 46$) comparing dextrose prolotherapy versus paraffin for bilateral hand osteoarthritis. This study found significantly better pain-related functioning (assessed with Duruoz Hand Index) in the dextrose prolotherapy group at 2 weeks, but there were no significant differences between groups at 1 and 3 months. Both groups improved in both pain-related functioning and pain intensity (measured with VAS) over time, but there were also no significant between-group differences in VAS at any time point. One participant in the prolotherapy group discontinued the intervention due to pain and was found to have a Heberden's nodule at the pain site.

Other Conditions

Abd Elghany, 2019[133] reported an observational study ($N = 120$) comparing 12.5% dextrose with rTMS for fibromyalgia. Participants in both groups improved in pain-related functioning (assessed with Revised Fibromyalgia Impact Questionnaire) and pain intensity (measured with VAS) over 2

months, and the dextrose prolotherapy group had significantly lower scores for both at 2 months (differences were non-significant at 1 month).

Gul, 2020[130] conducted a small RCT ($N = 41$) comparing prolotherapy with PT/home exercise program for hip osteoarthritis due to developmental dysplasia. This study only evaluated pain intensity or severity, using VAS, at 3 weeks and 3-12 months. Both groups improved during follow-up and the dextrose prolotherapy arm had significantly lower mean VAS scores at all time points. This study also reported that 3 participants (15%) had severe post-injection pain that required acetaminophen 4 times per day for 5-7 days, but serious adverse events (*eg*, cellulitis or septic arthritis) were not observed in the dextrose prolotherapy group.

Finally, Senturk, 2017[134] reported an observational study ($N = 34$) comparing single injection of 16% dextrose into the chest wall with naproxen (5 mg/kg twice daily) for Tietze syndrome. This study also only assessed pain intensity, using VAS, at 1 day, and 1 and 4 weeks. Participants in both groups improved immediately, with substantial decreases in VAS on day 1 (*eg*, mean 2.6 versus 7.2 at baseline for naproxen group), and maintained these benefits throughout follow-up. There were no significant between-group differences until 4 weeks, when the dextrose prolotherapy group had lower VAS (mean 1.5) compared with the naproxen arm (mean 2.6). For adverse events, authors only reported that 1 participant in the dextrose group had increased skin pigmentation post-injection.

SUMMARY OF FINDINGS FOR KQ 2: DO BENEFITS AND HARMS OF DEXTROSE PROLOTHERAPY VARY BY PATIENT OR PAIN CONDITION CHARACTERISTICS, PRIOR TREATMENT HISTORY, OR INTERVENTION CHARACTERISTICS?

No study formally evaluated differences in outcomes by patient or pain condition characteristics, or prior treatment history. We summarized these characteristics in descriptions of KQ 1 findings to assist with understanding of the applicability of these results. We did identify studies comparing different dextrose prolotherapy injection techniques or locations for knee osteoarthritis ($k = 3$),[42,49,57] TMJ ($k = 2$),[109,123] and for hip arthritis due to developmental dysplasia ($k = 1$).[130] There were also 4 studies that compared different dextrose concentrations for knee osteoarthritis ($k = 1$),[56] lateral elbow tendinopathy ($k = 2$),[90,93] and TMJ ($k = 1$).[120] In general, variations in injection technique, location, or dextrose concentration had no to little impact on treatment outcomes. Detailed characteristics and findings for these studies and comparisons are presented in the individual Results sections above for each pain condition.

SUMMARY OF FINDINGS FOR KQ 3: WHAT ARE THE COSTS OF DEXTROSE PROLOTHERAPY FOR HEALTH CARE SYSTEMS AND PATIENTS?

Only 2 studies addressed costs of dextrose prolotherapy treatment; both focused on health care system costs and did not address costs or treatment burden for patients or families.[129,131] Neither study was conducted in the US. Yelland, 2021[129] reported a 3-arm RCT comparing dextrose prolotherapy versus supervised exercise program versus combination of both treatments for foot pain due to Achilles tendinosis, and found improvement in all groups in pain-related functioning over 1 year. This study was conducted in Australia and evaluated incremental cost-effectiveness ratio (ICER) in Australian dollars per additional responder, defined as individuals with ≥ 20 points improvement on the VISA-A. The ICER was $1,716 per additional responder for dextrose prolotherapy, and $1,539 per additional

responder for combined dextrose and exercise. The other study only reported the direct costs per session for the health care system of injections for osteochondral lesions of the talus, which were 30 Turkish lira for dextrose prolotherapy and 250 Turkish lira for PRP.[131] Detailed characteristics and findings for both studies were presented in the Other Conditions Results section above.

DISCUSSION

There are substantial limitations to the evidence on efficacy and harms of dextrose prolotherapy for musculoskeletal pain conditions. Most available studies (83%) were very small with fewer than 100 participants, and nearly half (48%) were rated high risk of bias. Studies varied greatly in dextrose concentrations employed, injection technique, cointerventions, and comparators. The most commonly assessed outcomes were pain-related functioning and intensity, while fewer studies reported on physical performance, health-related quality of life, and adverse events. Only 2 studies (neither in the US) examined costs for health care systems, and none reported costs or treatment burden for patients.

In most studies, efficacy outcomes improved for all arms (intervention and comparators) over time. Intra-articular dextrose prolotherapy for knee osteoarthritis probably has little to no additional benefit for pain-related functioning and physical performance compared with normal saline injection (moderate COE). Combined intra- and extra-articular dextrose prolotherapy for knee osteoarthritis may improve pain-related functioning compared with either PT/home exercise or normal saline injection, but only at long-term follow-up (low COE). For plantar fasciitis and lateral elbow tendinopathy, dextrose prolotherapy may improve pain-related functioning, compared with normal saline injection (low COE). For shoulder pain due to mixed bursitis and rotator cuff pathology, dextrose prolotherapy probably results in worse physical performance outcomes, compared with corticosteroid injections. The evidence was uncertain for other efficacy outcomes and other comparators across these pain conditions, as well as for adverse events for all conditions (very low COE). Summary findings are presented below by individual musculoskeletal pain conditions (for comparisons with at least 2 available studies).

SUMMARY OF KEY FINDINGS

Knee Osteoarthritis

- Intra-articular dextrose prolotherapy probably had little to no benefit for pain-related functioning and physical performance at short-, medium-, and long-term follow-up, compared with normal saline injection (moderate COE). It also had little to no benefit for health-related quality of life, compared with normal saline injection (high COE).
- Intra-articular dextrose prolotherapy may have little to no benefit for pain-related functioning at short-, medium-, and long-term follow-up, compared with ozone injection (low COE).
- The evidence was very uncertain on the benefits of intra-articular dextrose prolotherapy for pain-related functioning at short- and long-term follow-up, compared with PRP (very low COE). It also may have little to no effect at medium term (low COE).
- Combined intra-articular and extra-articular dextrose prolotherapy may improve pain-related functioning and physical performance at long-term follow-up, compared with PT/home exercise programs (low COE). But at short- and medium-term follow-up, the evidence is very uncertain for these outcomes (very low COE).
- Combined intra-articular and extra-articular dextrose prolotherapy may improve pain-related functioning at long-term follow-up, compared with normal saline (low COE), but the evidence is very uncertain at short and medium term (very low COE).

- The evidence was also very uncertain on adverse effects of dextrose prolotherapy versus any comparator (very low COE).

Plantar Fasciitis

- Dextrose prolotherapy may improve pain-related functioning at short- and medium-term follow-up, compared with normal saline, but may have little to no benefit compared with ESWT (low COE).
- The evidence was very uncertain on the effects of dextrose prolotherapy on pain-related functioning (very low COE), but it may have no to little benefit for health-related quality of life (low COE), compared with corticosteroid injection.
- The evidence was very uncertain on adverse effects of dextrose prolotherapy (very low COE).

Shoulder Pain (Due to Mixed Bursitis and Rotator Cuff Pathology)

- The evidence was very uncertain on the effect of dextrose prolotherapy on pain-related functioning at short- and medium-term follow-up (very low COE), and it may have little to no benefit for physical performance (low COE), compared with normal saline injection.
- The evidence was also very uncertain on the effect of dextrose prolotherapy on pain-related functioning at short- and medium-term follow-up (very low COE), and it probably resulted in worse physical performance (moderate COE), compared with corticosteroid injection.
- The evidence was very uncertain on the benefits of dextrose prolotherapy for pain-related functioning at short- and medium-term (very low COE) follow-up, compared with PT/home exercise. For physical performance, findings differed at short, medium, and long-term (low and very low COE).
- The evidence was very uncertain on adverse effects of dextrose prolotherapy (very low COE).

Lateral Elbow Tendinopathy

- Dextrose prolotherapy may improve pain-related functioning at short- and medium-term follow-up, compared with normal saline injection (low COE), but the evidence was uncertain or suggested little to no benefit for physical performance (very low or low COE).
- The evidence was also very uncertain for pain-related functioning, compared with corticosteroid injection (very low COE), and dextrose prolotherapy may have little to no benefit for physical performance at short- and long-term follow-up (low COE).
- The evidence was very uncertain for pain-related functioning and physical performance at short- and medium-term follow-up, compared with ESWT (very low COE), but dextrose prolotherapy may improve physical performance in the long term (low COE).
- The evidence was very uncertain on adverse effects of dextrose prolotherapy (very low COE).

Chronic Low Back Pain

- For non-specific low back pain, the evidence was very uncertain on the benefits of dextrose prolotherapy for pain-related functioning (very low COE), and it may have little to no benefit for physical performance (low COE), compared with normal saline injection.
- For back pain related to sacroiliac joint dysfunction, the evidence was very uncertain on the benefits of dextrose prolotherapy for pain-related functioning (very low COE), compared with corticosteroid injection.
- The evidence was very uncertain on adverse effects of dextrose prolotherapy (very low COE).

Temporomandibular Joint Dysfunction and Pain

- For TMJ disorders with restricted or normal mobility at baseline, the evidence was very uncertain on the benefits and adverse effects of dextrose prolotherapy, compared with normal saline (very low COE).
- For TMJ disorders with hypermobility at baseline, the evidence was very uncertain on the benefits and adverse effects of dextrose prolotherapy, compared with normal saline or autologous blood injection (very low COE).

LIMITATIONS

When synthesizing the evidence for each musculoskeletal pain condition, we grouped together studies based primarily on comparator characteristics and thus included a variety of dextrose concentrations and injection locations in the dextrose prolotherapy arms. We also grouped a variety of PT-provided treatments and home exercise programs together as a similar comparator. To better assess the clinical importance of findings, we sought and used published MCID to determine whether there were meaningful differences in effects, but for a substantial number of outcomes measures, we were unable to locate published MCID values. In those situations, we used statistical significance, which is subject to the appropriateness of analyses reported by authors. We also limited eligibility to English-language studies, and thus did not include or review non-English studies. However, a large proportion of identified studies were conducted in countries where English is not the primary language, so it appears this did not substantially limit our ability to locate relevant evidence.

EVIDENCE GAPS AND FUTURE RESEARCH

The evidence on efficacy and safety of dextrose prolotherapy for musculoskeletal disorders is limited by small sample sizes for most studies and substantial methodological concerns (nearly half were rated high, serious, or critical RoB). There was considerable variation in intervention characteristics, cointerventions, study populations, and choice of outcome measures across studies. To provide clinically relevant interpretations, we assessed between-group differences using published MCID whenever available. The evidence suggests that efficacy of prolotherapy may be condition specific since there is probably little to no benefit for knee osteoarthritis (for intra-articular injection compared with normal saline), but for conditions like lateral elbow tendinopathy and plantar fasciitis, there may be some benefit (also compared with normal saline). Whether specific populations and conditions benefit from dextrose prolotherapy (particularly compared with other non-surgical treatments) is an important area for future research, as some patients do not have sufficient improvement with other treatments for musculoskeletal pain. There are also concerns about side effects of some recommended

treatments when used chronically (*eg*, corticosteroids) and some patients may have contraindications to certain pharmacologic options.

Injection therapies for musculoskeletal pain conditions are known to have large placebo effects that complicate rigorous evaluation of treatments.[137] The natural history of most musculoskeletal pain conditions involves waxing and waning of symptoms, where patients seek medical attention during acute exacerbations of pain and pain-related disability, and then improve due to healing or homeostatic processes, lifestyle adjustments, and/or medical treatments.[138] In a large well-designed RCT, the rates and average timing of improvements resulting from factors other than the treatment under study are expected to be balanced between intervention and comparator groups (including placebo when appropriate). However, small randomized trials may not adequately achieve balance across arms on these non-intervention effects and on other sources of confounding. Small trials are also more vulnerable to biases arising from attrition, particularly when the extent of attrition differs between groups. Furthermore, it may be challenging to maintain masking for injection interventions throughout a study, particularly when the these involve multiple different injections in and around an anatomic structure.[139] These factors likely contributed to the low and very low COE for many findings in this report, and could be addressed by larger trials with sufficient follow-up.

Inconsistency in study findings was also likely due to the wide variation in dextrose concentrations, treatment duration and number of sessions, and other differences in injection technique, even for interventions addressing the same condition. Some of this variation may be clinically reasonable and expected due to differences in location of maximal pain for the affected joint or area and patient tolerance of procedures involving the specific anatomic structures implicated. In addition, and as customary in the overall treatment of musculoskeletal pain, there was no standardization of cointerventions or treatment algorithms that specified which options would be tried in sequence or concurrently. It is also possible that some cointerventions (*eg*, home exercise therapy) may be synergistic or antagonistic with the effects of the primary interventions being examined. All of these factors added to the challenges in interpretation of study findings and should be more systematically addressed in future studies.

Only 2 included studies reported on treatment costs for health care systems, and none evaluated cost and burden for patients. These are important considerations for health care payors, facilities, and patients, particularly given the chronic nature of most musculoskeletal pain conditions. There are likely differences in costs and treatment burden between the wide variety of non-surgical treatment options and dextrose prolotherapy, which all involve somewhat different resource needs for health care facilities and clinician training, as well as demands on patient time and other potential access barriers. In terms of injection therapies, the number and frequency of treatment sessions, as well as any additional clinician education would be important factors for health care facility resource needs. Future studies of dextrose prolotherapy for musculoskeletal pain conditions should include quantitative and qualitative assessments of the costs and treatment burden for health care systems and patients.

Most included studies did not use clear and systematic methods to evaluate adverse events for dextrose prolotherapy and various comparators. This is an essential gap for future research to address because this information will inform clinician decision-making, promote shared decision-making with well-informed patients, and potentially impact prioritization of limited medical resources. Trials should assess adverse events for each treatment arm using open-ended questions and/or checklists administered to all participants on a regular basis. Additionally, studies should clearly define the severity of adverse events (*eg*, serious events can be defined as life threatening, requiring

hospitalization, or resulting in persistent disability) and rates of events that led to discontinuation of the treatment. Evaluation of adverse events will also require larger studies that are adequately powered to detect differences in adverse event rates across groups, and these studies will be necessary for each musculoskeletal pain condition because there is a strong possibility that harms could differ across conditions (and different injection locations).

In summary, future studies of prolotherapy should be of sufficient size and methodological quality to systematically assess efficacy and safety relative to currently recommended conservative treatments, as well as appropriate placebo controls given the likelihood of placebo effects associated with injection therapies. More work is also needed to evaluate treatment costs and burden.

IMPLICATIONS FOR POLICY AND PRACTICE

Regarding efficacy, dextrose prolotherapy appeared to have differential effects across musculoskeletal pain conditions. Intra-articular dextrose prolotherapy probably had little to no benefit in pain-related functioning or physical performance for knee osteoarthritis, compared with normal saline injections. But evidence suggested benefits for plantar fasciitis and lateral elbow tendinopathy, compared with normal saline. In contrast, dextrose prolotherapy probably led to worse physical performance outcomes for shoulder pain, compared with corticosteroid injections. Therefore, these observations should be explored more thoroughly in well-designed and rigorous clinical trials that compare dextrose prolotherapy with other common conservative interventions for these pain conditions. The VA may be uniquely qualified and capable of undertaking these clinical investigations, as pharmaceutical companies are less likely to make the research investments needed to demonstrate the safety and efficacy of an inexpensive, non-proprietary, and easily accessible medication.

Generally, our report findings indicate that the evidence is very uncertain for adverse effects of dextrose prolotherapy, and more research is needed to establish the safety for clinical use of these procedures. Most studies on dextrose prolotherapy were small ($N < 100$) and many did not systematically evaluate or report adverse events. Even for treatments that were tested in larger clinical trials (with hundreds to thousands of participants), it is fairly common to find additional rare but serious side effects during more widespread use. An example of this is the reports of aseptic arthritis found in certain patients after repeat injections of hyaluronic acid.[140]

CONCLUSIONS

Intra-articular dextrose prolotherapy probably had little to no benefit for pain-related functioning or physical performance in knee osteoarthritis, compared with normal saline injections. For shoulder pain due to mixed bursitis and rotator cuff pathology, dextrose prolotherapy probably resulted in worse physical performance outcomes, compared with corticosteroid injections. However, dextrose prolotherapy may improve pain-related functioning for lateral elbow tendinopathy and plantar fasciitis, compared with normal saline injection. Evidence on adverse events was generally lacking and severely limited by methodological concerns. The evidence was also very uncertain on the benefits of prolotherapy compared with other treatments or for other pain conditions. Given the lack of efficacious therapies for musculoskeletal pain conditions and interest in potential benefits of dextrose prolotherapy, future high-quality RCTs are needed to better understand the benefits and harms for this treatment.

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Appendix

APPENDIX A. SEARCH STRATEGIES

Search Date: 02/02/24		Search Statement	Results
MEDLINE	1	Prolotherapy/ or (prolotherap* or proliferation therap* or regenerative injection*).ti,ab,kf.	474
	2	(dextrose adj1 inject*).ti,ab,kf.	460
	3	Injections, Intra-Articular/ or ((intra-articular or intraarticular or intra-coxal or intracoxal or intra-synovial or intrasynovial or joint* or orthobiologic*) adj1 (administration or deliver* or infusion* or inject*)).ti,ab,kf.	14323
	4	exp Spine/ or (columna dorsis or dorsal column or interspinous or intervertebral or spinal or spine or spinous or vertebra*).ti,ab,kf.	651336
	5	3 or 4	664824
	6	Glucose/ or dextrose.ti,ab,kf.	190062
	7	5 and 6	1390
	8	1 or 2 or 7	2192
	9	8 not (Animals/ not (Animals/ and Humans/)	1532

Search Date: 02/06/24		Search Statement	Results
EMBASE	1	Prolotherapy/ or (prolotherap* or proliferation therap* or regenerative injection*).ti,ab,kf.	824
	2	(dextrose adj1 inject*).ti,ab,kf.	500
	3	exp Intraarticular Drug Administration/ or ((intra-articular or intraarticular or intra-coxal or intracoxal or intra-synovial or intrasynovial or joint* or orthobiologic*) adj1 (administration or deliver* or infusion* or inject*)).ti,ab,kf.	18263
	4	exp Spine/ or (columna dorsis or dorsal column or interspinous or intervertebral or spinal or spine or spinous or vertebra*).ti,ab,kf.	871789
	5	3 or 4	888905
	6	Glucose/ or dextrose.ti,ab,kf.	564031
	7	5 and 6	5672
	8	1 or 2 or 7	6827
	9	8 not ((exp Animal/ or Nonhuman) not exp Human/)	5203
	10	Limit 9 to (article or article in press or “review”)	3473

Search Date: 02/02/24		Search Statement	Results
SCOPUS	1	TITLE-ABS-KEY(prolotherap* or (proliferation W/1 therap*) or (regenerative W/1 inject*))	1238
	2	TITLE-ABS-KEY(dextrose W/1 inject*)	625
	3	TITLE-ABS-KEY((intra-articular or intraarticular or intra-coxal or intracoxal or intra-synovial or intrasynovial or joint* or orthobiologic*) W/1 (administration or deliver* or infusion* or inject*)).ti,ab,kf.	19222

	4	TITLE-ABS-KEY(“columna dorsis” or “dorsal column” or interspinous or intervertebral or spinal or spine or spinous or vertebra*)	1010307
	5	#3 or #4	1028104
	6	TITLE-ABS-KEY(dextrose)	21834
	7	#5 and #6	438
	8	1 or 2 or 7	2109
	9	TITLE-ABS-KEY(mouse or mice or rat or rats or rodent*)	4406856
	10	#8 and not #9	1869
		Total	6,874
		Total after deduplication	**4,742**

APPENDIX B. ONGOING AND COMPLETED TRIALS (WITHOUT PUBLICATIONS)

Trial #	Study Title	Status	Total *N**	Location
NCT00674622	Prolotherapy for the Treatment of Chronic Lateral Epicondylitis	Completed (no publication)	67	Pittsburgh, Pennsylvania, USA
NCT05429827	The Therapeutic Effects of Dextrose Injection for Myofascial Pain Syndrome	Recruiting (no publication)	30	Tainan, Taiwan
NCT05239091	Comparison of the Efficacy of Prolotherapy Injection Therapy & Local Anesthetic Injection Therapy	Completed (no publication)	28	Istanbul, Turkey
NCT05326763	Functional and Electromyographical Changes After PRP or Dextrose Injection in Chronic Lateral Epicondylitis	Unknown (no publication)	90	Tainan, Taiwan
NCT00835939	Treatment for Achilles Tendinopathy	Unknown (no publication)	17	Calgary, Alberta, Canada
NCT05966948	HDP vs NS Intra-articular Injection Among KOA With Obese Patient	Completed (no publication)	40	Surabaya, East Java, Indonesia
NCT05220527	Effects of Knee Injections on Patients With Knee Osteoarthritis	Unknown (no publication)	60	Taipei, Taiwan
NCT06345222	Examining the Effect of Prolotherapy on Quality of Life and Painkiller Use in Patients With Knee Pain	Completed (no publication)	65	Bursa, Turkey
NCT06301958	Dextrose Prolotherapy on Articular Cartilage	Recruiting (no publication)	60	Chiayi City, Taiwan
NCT04178304	Effect of Prolotherapy in Knee Osteoarthritis	Completed (no publication)	63	Alexandria, Egypt
NCT03942640	Perineural Injection and Supraspinatus Tendinopathy	Unknown (no publication)	60	Mansoura, Egypt
NCT04478344	Ultrasound Localization and Guided Injection for Superior Cluneal Nerve Entrapment	Recruiting (no publication)	30	Taipei, Taiwan
NCT03174080	PET MRI for Evaluation of Knee Osteoarthritis in Patients With Bilateral Knee OA	Unknown (no publication)	150	Tel Aviv, Israel
NCT02052089	Comparative Study for the Optimal Treatment Method of Lateral Epicondylosis	Completed (no publication)	231	Seoul, Republic of Korea
NCT00685880	Prolotherapy Versus Steroids for Thumb Carpometacarpal Joint Arthritis	Terminated (no publication)	2	Rochester, Minnesota, USA
NCT04941118	Myofascial Pain Syndrome and Dextrose Prolotherapy	Unknown (no publication)	60	Hatay, Turkey

Trial #	Study Title	Status	Total *N**	Location
NCT05160532	Intraarticular Dextrose Prolotherapy for Symptomatic Knee Osteoarthritis	Recruiting (no publication)	160	Scottsdale, Arizona, USA
NCT04319406	Comparative Efficacy of Prolotherapy and Dry Needling in Management of ADD	Unknown (no publication)	50	Rohtak, Haryana, India
NCT03675659	Intra-articular Magnesium Sulfate for TMJ Dysfunction	Unknown (no publication)	100	Giza, Egypt
NCT04805242	Effects of Dextrose Prolotherapy in Rotator Cuff Disease	Unknown (no publication)	60	Istanbul, Turkey
NCT05984121	Comparison of the Effectiveness of Local Ozone Injection and Dextrose Prolotherapy Injection in Chronic Plantar Fasciitis	Completed (no publication)	60	Kirsehir, Turkey
NCT04165902	Additional Effects of Steroid and Dextrose to Hyaluronic Acid on Knee Osteoarthritis	Unknown (no publication)	60	Taipei, Taiwan
NCT06161038	Precision Medicine for Nociception, Sngception and Proprioception.	Recruiting (no publication)	160	Taipei, Taiwan
NCT01761838	The Underlying Mechanism of Spinal Manipulative Therapy and the Effect of Pain on Physical Outcome Measures	Completed (no publication)	103	Edmonton, Alberta, Canada
NCT05548738	Caudal Epidural Prolotherapy Versus Steroids in Failed Back Surgery Syndrome	Active, Not Recruiting (no publication)	80	Alexandria, Egypt
NCT03161210	Evaluation of Pain Regression in Patients With Myofascial Facial Pain Using Dextrose, Local Anaesthesia and Saline.	Unknown (ineligible publication)	80	Cairo, Egypt
NCT05154695	Precision Medicine for Sng/Pain Control	Recruiting (no publication)	88	Taipei, Taiwan
NCT05416255	Measuring Synovial Fluid Components	Active, Not Recruiting (no publication)	80	Rosario, Santa Fe, Argentina
NCT04006314	Platelet Rich Plasma and Neural Prolotherapy Injections in Treating Knee Osteoarthritis	Unknown (no publication)	24	Taoyuan, Taiwan
NCT01934868	Prolotherapy Versus Epidural Steroid Injections (ESI) for Lumbar Pain Radiating to the Leg	Completed (no publication)	110	Jerusalem, Israel
NCT04062838	Prolotherapy for the Treatment of Partial Rotator Cuff Tears	Withdrawn (no publication)	0	Jerusalem, Israel
NCT04796103	The Effectiveness of Prolotherapy (%5 Dextrose) in the Treatment of Patients With Chondromalacia Patella	Completed (no publication)	52	Ankara, Turkey
NCT05688787	Efficacy of Perineural Injection Therapy in Primary Fibromyalgia	Not Yet Recruiting (no publication)	60	Cairo, Egypt
NCT06308887	Comparison of Ultrasound-Guided Perimeniscal Steroid and 5% Dextrose Injections in Knee Osteoarthritis	Completed (protocol only)	31	Kastamonu, Turkey

Trial #	Study Title	Status	Total *N**	Location
NCT04088045	High Frequency Intensive Autologous PRP Injection and Genicular Nerve Blocks in Treating Knee Osteoarthritis	Unknown (no publication)	36	Taoyuan, Taiwan
NCT06063356	Effects of Dextrose Prolotherapy in Patients With Knee Osteoarthritis	Active, Not Recruiting (no publication)	66	Istanbul, Turkey
NCT03000205	Effects of Hypertonic Dextrose Water Injection for Supraspinatus Tendinosis Patients	Completed (no publication)	60	New Taipei City, Taiwan
NCT04557878	Role of Liquid Phase Concentrated Growth Factors vs. Hypertonic Dextrose Prolotherapy for Management of Patients With Disc Displacement Without Reduction	Unknown (ineligible publication)	24	Alexandria, Egypt
NCT02116075	Caudal Corticosteroid vs. Dextrose Injection for Lumbosacral Radicular Pain.	Unknown (no publication)	50	Long Beach, California, USA
NCT04212975	Arthrocentesis Followed by Prolotherapy	Unknown (no publication)	60	Cairo, Egypt
NCT03411811	Ulnar Wrist Pain Treatment With Dextrose Prolotherapy	Unknown (no publication)	60	Rosario, Santa Fe, Argentina
NCT03690232	Intra-articular Glucose Versus Hyaluronic Acid Injection for Knee Osteoarthrosis	Unknown (no publication)	100	Taipei, Taiwan
NCT05279937	The Ultrasound-Guided Dextrose Prolotherapy in Ehlers-Danlos Syndrome Patients	Not Yet Recruiting	40	New Orleans, Louisiana, USA
NCT05821985	Evaluation of the Effect of Dextrose Prolotherapy Versus Dry Needling Therapy	Completed (no publication)	40	Bani Suwayf, Egypt
NCT01897259	Comparison of Conservative Methods for the Treatment of Lateral Epicondylitis: A Randomized, Prospective Study	Unknown (no publication)	200	Louisville, Kentucky, USA
NCT05066451	5% and 15% Dextrose Prolotherapy Efficacy in Lateral Epicondylitis	Completed (no publication)	26	Istanbul, Turkey
NCT02492945	Bundang Rehabilitative Impact Study of the Elbow Epicondylitis	Completed (no publication)	40	SeongNam-Si, Gyeonggi-Do, Republic of Korea
NCT04916353	Effects of Ultrasound-guide Hypertonic Dextrose Injection for Chronic Subacromial Bursitis	Unknown (no publication)	60	New Taipei City, Taiwan
NCT01326351	Prolotherapy for the Treatment of Plantar Fasciitis	Unknown (no publication)	60	Moncton, New Brunswick, Canada

APPENDIX C. EXCLUDED STUDIES

Citation	Exclude Reason
1. Corrigendum to: Prolotherapy vs Radial Extracorporeal Shock Wave Therapy in the Short-term Treatment of Lateral Epicondylosis: A Randomized Clinical Trial. *Pain medicine (Malden, Mass)*. 2019;20(12):2612. Erratum for: Pain Med. 2019 Sep 1;20(9):1745-1749 PMID: 30698771 [https://www.ncbi.nlm.nih.gov/pubmed/30698771]	*Ineligible study design or publication type*
2. Allen Hooper R, Yelland M, Fonstad P, Southern D. Prospective case series of litigants and non-litigants with chronic spinal pain treated with dextrose prolotherapy. Article. *Int Musculoskelet Med*. 2011;33(1):15-20	*Ineligible study design or publication type*
3. Amanollahi A, Asheghan M, Hashemi SE. Subacromial corticosteroid injection versus subcutaneous 5% dextrose in patients with chronic rotator cuff tendinopathy: A short-term randomized clinical trial. *Interventional medicine & applied science*. 2020;11(3):154-160	*Ineligible intervention*
4. Babaei-Ghazani A, Moradnia S, Azar M, et al. Ultrasound-guided 5% dextrose prolotherapy versus corticosteroid injection in carpal tunnel syndrome: a randomized, controlled clinical trial. Pain management. 2022;12(6):687-697	*Ineligible intervention*
5. Berberet B, Burda A, Breier C, Lodolce AE. Discontinuation of 5% alcohol in 5% dextrose injection: implications for antidote stocking. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists*. 2008;65(23):2200-2203	*Ineligible study design or publication type*
6. Carayannopoulos A, Borg-Stein J, Sokolof J, Meleger A, Rosenberg D. Prolotherapy versus corticosteroid injections for the treatment of lateral epicondylosis: a randomized controlled trial. *PM & R : the journal of injury, function, and rehabilitation*. 2011;3(8):706-15. Comment in: PM R. 2012 Apr;4(4):322-3; author reply 323 PMID: 22541380 [https://www.ncbi.nlm.nih.gov/pubmed/22541380]	*Ineligible intervention*
7. Chen CPC, Suputtitada A. Prolotherapy at Multifidus Muscle versus Mechanical Needling and Sterile Water Injection in Lumbar Spinal Stenosis. *Journal of pain research*. 2023;16:2477-2486	*Ineligible intervention*
8. Chen JL, Chen CH, Cheng CH, Chen CC, Lin KY, Chen CPC. Can the addition of ultrasound-guided genicular nerve block using 5% dextrose water augment the effect of autologous platelet rich plasma in treating elderly patients with knee osteoarthritis? Article. *Biomed J*. 2021;44(6):S144-S153	*Ineligible intervention*
9. Comert Kilic S, Kilic N, Gungormus M. Botulinum Toxin Versus Dextrose Prolotherapy: Which is More Effective for Temporomandibular Joint Subluxation? A Randomized Clinical Trial. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons*. 2023;81(4):389-395	*Ineligible outcome*
10. Covey CJ, Sineath MH, Jr P, Joseph F L. Prolotherapy: Can it help your patient? *The Journal of family practice*. 2015;64(12):763-8	*Ineligible study design or publication type*
11. Dean Reeves K, Fullerton BD, Topol G. Evidence-Based Regenerative Injection Therapy (Prolotherapy) in Sports Medicine. *The Sports Medicine Resour Man*. 2008:611-619	*Ineligible study design or publication type*
12. Ferouz F, Norris MC, Arkoosh VA, Leighton BL, Boxer LM, Corba RJ. Baricity, needle direction, and intrathecal sufentanil labor analgesia. *Anesthesiology*. 1997;86(3):592-8	*Ineligible population*

Citation	Exclude Reason
13. Furman MB, Reeves RS, Ante WA. Intradiscal Steroids and Prolotherapy: Clinical Relevance, Outcomes and Efficacy. *Interventional Spine E-Book: An Algorithmic Approach*. 2007:1049-1055	*Ineligible study design or publication type*
14. Hackett GS. Prolotherapy in whiplash and low back pain. *Postgraduate medicine*. 1960;27:214-9	*Ineligible study design or publication type*
15. Hackett GS, Huang TC, Raftery A. Prolotherapy for headache. Pain in the head and neck, and neuritis. *Headache*. 1962;2:20-8	*Ineligible study design or publication type*
16. Hackett GS, Huang TC, Raftery A, Dodd TJ. Back pain following trauma and disease--prolotherapy. *Military medicine*. 1961;126:517-25	*Ineligible study design or publication type*
17. Hashemi SM, Madadi F, Razavi S, Nikooseresht M, Kiyabi FH, Nasiripour S. Intra-articular hyaluronic acid injections Vs. dextrose prolotherapy in the treatment of osteoarthritic knee pain. *Tehran University Medical Journal*. 2012;70(2):119-125	*Not published in English*
18. Hauser R, Woldin B. Treating osteoarthritic joints using dextrose prolotherapy and direct bone marrow aspirate injection therapy. *Open Arthritis Journal*. 2014;7(1):1-9	*Ineligible intervention*
19. Hauser RA. Punishing the pain. Treating chronic pain with prolotherapy. *Rehab management*. 1999;12(2):26-30	*Ineligible study design or publication type*
20. Hauser RA, Blakemore PJ, Wang J, Steilen D. Structural basis of joint instability as cause for chronic musculoskeletal pain and its successful treatment with regenerative injection therapy (Prolotherapy). *Open Pain Journal*. 2014;7(1):9-22	*Ineligible study design or publication type*
21. Hoffman MD, Agnish V. Functional outcome from sacroiliac joint prolotherapy in patients with sacroiliac joint instability. *Complementary therapies in medicine*. 2018;37:64-68	*Ineligible study design or publication type*
22. Hu LP, Huang AB, Xu YL. Effective assessment of hip joint soft tissue release in lightening the ache symptom of ankylosing spondylitis. *Chinese Journal of Clinical Rehabilitation*. 2005;9(34):80-81	*Not published in English*
23. Hung C-Y, Chang K-V, Ozcakar L. Snapping Hip due to Gluteus Medius Tendinopathy: Ultrasound Imaging in the Diagnosis and Guidance for Prolotherapy. *Pain medicine (Malden, Mass)*. 2015;16(10):2040-1	*Ineligible study design or publication type*
24. Imani F, Hejazian K, Kazemi M-R, Narimani-Zamanabadi M, Malik KM. Adding Ozone to Dextrose and Somatropin for Intra-articular Knee Prolotherapy: A Randomized Single-Blinded Controlled Trial. *Anesthesiology and pain medicine*. 2020;10(5):e110277	*Ineligible intervention*
25. Isik R, Karapolat H, Bayram KB, Usan H, Tanigor G, Atamaz Calis F. Effects of Short Wave Diathermy Added on Dextrose Prolotherapy Injections in Osteoarthritis of the Knee. *Journal of alternative and complementary medicine (New York, NY)*. 2020;26(4):316-322	*Ineligible intervention*
26. Jacks A, Barling T. Lumbosacral prolotherapy. Letter. *Int Musculoskelet Med*. 2013;35(1):44	*Ineligible study design or publication type*
27. Kajbaf J. Prolotherapy. *Regenerative MedicineL: A Complete Guide for Musculoskeletal and Spine Disorders*. 2022:15-27	*Ineligible study design or publication type*
28. Katsinelos P, Kountouras J, Chatzimavroudis G, et al. A novel technique of injection treatment for endoscopic sphincterotomy-induced hemorrhage. Article. *Endoscopy*. 2007;39(7):631-636	*Ineligible population*
29. Kayfetz DO, Blumenthal LS, Hackett GS, Hemwall GA, Neff FE. Whiplash injury and other ligamentous headache--its management with prolotherapy. *Headache*. 1963;3:21-8	*Ineligible study design or publication type*

Citation	Exclude Reason
30. Kersschot J. Low-Dose Dextrose Prolotherapy as Effective as High-Dose Dextrose Prolotherapy in the Treatment of Lateral Epicondylitis? A Double-Blind, Ultrasound Guided, Randomized Controlled Study. *Archives of physical medicine and rehabilitation*. 2023;104(7):1154-1155. Comment on: Arch Phys Med Rehabil. 2023 Feb;104(2):179-187 PMID: 36243123 [https://www.ncbi.nlm.nih.gov/pubmed/36243123] Comment in: Arch Phys Med Rehabil. 2023 Jul;104(7):1155-1156 PMID: 36990377 [https://www.ncbi.nlm.nih.gov/pubmed/36990377]	*Ineligible study design or publication type*
31. Khalil SI. Effect of Perineural Dextrose Injection on Myofascial Pain Syndrome. Article. *Al-Anbar Med J*. 2022;18(2):61-65	*Ineligible intervention*
32. Khan SA, Kumar A, Varshney MK, Trikha V, Yadav CS. Dextrose prolotherapy for recalcitrant coccygodynia. *Journal of orthopaedic surgery (Hong Kong)*. 2008;16(1):27-9. Comment in: J Orthop Surg (Hong Kong). 2008 Aug;16(2):270; author reply 270 PMID: 18725689 [https://www.ncbi.nlm.nih.gov/pubmed/18725689]	*Ineligible study design or publication type*
33. Kidd R. Re: Yelland MJ, Glasziou PP, Bogduk N, et al. Prolotherapy injections, saline injections, and exercises for chronic low-back pain: a randomized study. Spine. 2003;29:9-16. *Spine*. 2004;29(16):1841-3. Comment on: Spine (Phila Pa 1976). 2004 Jan 1;29(1):9-16; discussion 16 PMID: 14699269 [https://www.ncbi.nlm.nih.gov/pubmed/14699269]	*Ineligible study design or publication type*
34. Kiliç SC, Güngörmüş M. Is dextrose prolotherapy superior to placebo for treatment of TMJ hypermobility: Comparison of pain changes at masseter, lateral pterygoid, sternocleidomastoid and trapezius muscles. Article. *Curr Res Dent Sci*. 2022;32(3):226-230	*Not published in English*
35. Kim JE, Yi YH, Lee SY, Kim YJ, Lee JG, Cho BM. The efficacy of ten weeks prolotherapy as add-on therapy in the treatment of chronic low back pain. *Kuwait Medical Journal*. 2016;48(3):215-218	*Unable to locate PDF*
36. Kishore S, Ravi P, Dominic D, Gnanapragasam R. COMPARISON OF EFFECTIVENESS OF PROLOTHERAPY AND CORRECTIVE EXERCISE PROGRAM VS PROLOTHERAPY AND ISOMETRICS STRENGTHENING ON PAIN AND FUNCTIONAL IMPROVEMENT IN SUPRASPINATUS TENDINOPATHY IN A TERTIARY CARE CENTRE. Article. *Cent Eur J Sport Sci Med*. 2023;42(2):65-73	*Ineligible intervention*
37. Koehn G, Jackson L, Ablah E, Okut H, Porter A. Use of Ultrasound-Guided Tendon Fenestration and Injection Procedures for Treatment of Tendinosis. *Kansas journal of medicine*. 2023;16:258-260	*Ineligible outcome*
38. Köroğlu Ö, Örsçelik A, Karasimav Ö, Demir Y, Solmaz I. Is 5% dextrose prolotherapy effective for radicular low back pain? Article. *Gulhane Med J*. 2019;61(3):123-127	*Ineligible intervention*
39. Lee HS, Jo DH, Kim MG, Kim MH, Park SH, Chung SH. Comparision of remifentanil and remifentanil/midazolam for outpatient anesthesia in prolotherapy. *Korean journal of anesthesiology*. 2009;56(2):175-180	*Not published in English*
40. Lin C-L, Yang M-T, Lee Y-H, Chen Y-W, Vitoonpong T, Huang S-W. Comparison of Clinical and Ultrasound Imaging Outcomes Between Corticosteroid and Hypertonic Dextrose Injections for Chronic Supraspinatus Tendinopathy. *Orthopaedic journal of sports medicine*. 2022;10(11):23259671221129603	*Ineligible study design or publication type*
41. Lin M-T, Liao C-L, Hsiao M-Y, Hsueh H-W, Chao C-C, Wu C-H. Volume Matters in Ultrasound-Guided Perineural Dextrose Injection for Carpal Tunnel Syndrome: A Randomized, Double-Blinded, Three-Arm Trial. *Frontiers in pharmacology*. 2020;11:625830	*Ineligible intervention*

Citation	Exclude Reason
42. Lin M-T, Liu IC, Syu W-T, Kuo P-L, Wu C-H. Effect of Perineural Injection with Different Dextrose Volumes on Median Nerve Size, Elasticity and Mobility in Hands with Carpal Tunnel Syndrome. *Diagnostics (Basel, Switzerland)*. 2021;11(5)	*Ineligible intervention*
43. Liu S, Pollock JE, Mulroy MF, Allen HW, Neal JM, Carpenter RL. Comparison of 5% with dextrose, 1.5% with dextrose, and 1.5% dextrose-free lidocaine solutions for spinal anesthesia in human volunteers. *Anesthesia and analgesia*. 1995;81(4):697-702	*Ineligible intervention*
44. Loeser JD. Prolotherapy Injections, Saline Injections, and Exercises for Chronic Low-Back Pain: A Randomized Trial - Point of View. Note. *Spine*. 2004;29(1):16	*Ineligible study design or publication type*
45. Louw F. The occasional prolotherapy for lateral epicondylosis (tennis elbow). *Canadian journal of rural medicine : the official journal of the Society of Rural Physicians of Canada = Journal canadien de la medecine rurale : le journal officiel de la Societe de medecine rurale du Canada*. 2014;19(1):31-3	*Ineligible study design or publication type*
46. Maniquis-Smigel L, Dean Reeves K, Jeffrey Rosen H, et al. Short Term Analgesic Effects of 5% Dextrose Epidural Injections for Chronic Low Back Pain: A Randomized Controlled Trial. *Anesthesiology and pain medicine*. 2017;7(1):e42550	*Ineligible intervention*
47. Mansiz-Kaplan B, Nacir B, Pervane-Vural S, Tosun-Meric O, Duyur-Cakit B, Genc H. Effect of Perineural Dextrose Injection on Ulnar Neuropathy at the Elbow: A Randomized, Controlled, Double-Blind Study. *Archives of physical medicine and rehabilitation*. 2022;103(11):2085-2091	*Ineligible intervention*
48. Martinez-Barro D, Rivera-Bello JD, Cruz-Lopez JM, Hernandez-Amaro H, Rojano-Mejia D. [Functionality/isokinetic work of quadriceps in patients with gonarthrosis managed with prolotherapy]. *Funcionalidad/trabajo isocinetico de cuadriceps de pacientes con gonartrosis manejados con proloterapia*. 2023;61(6):788-795	*Not published in English*
49. Martinez-Pizarro S. Prolotherapy With Dextrose To Reduce Pain In Osteoarthritis Of The Knee. *Proloterapia con dextrosa para reducir el dolor en la osteoartritis de rodilla*. 2020;	*Ineligible study design or publication type*
50. McNair PJ, Marshall RN, Maguire K, Brown C. Knee joint effusion and proprioception. Article. *Archives of Physical Medicine and Rehabilitation*. 1995;76(6):566-568	*Ineligible intervention*
51. Medin Ceylan C, Sahbaz T, Cigdem Karacay B. Demonstrating the effectiveness of Platelet Rich Plasma and Prolotherapy treatments in knee osteoarthritis. *Irish journal of medical science*. 2023;192(1):193-198	*Ineligible intervention*
52. Memis S. Evaluation of the effects of prolotherapy on condyles in temporomandibular joint hypermobility using fractal dimension analysis. *Journal of the Korean Association of Oral and Maxillofacial Surgeons*. 2022;48(1):33-40	*Ineligible outcome*
53. Merriman JR. PROLOTHERAPY VERSUS OPERATIVE FUSION IN THE TREATMENT OF JOINT INSTABILITY OF THE SPINE AND PELVIS. *The Journal of the International College of Surgeons*. 1964;42:150-9	*Ineligible study design or publication type*
54. Miller MR, Mathews RS, Reeves KD. Treatment of painful advanced internal lumbar disc derangement with intradiscal injection of hypertonic dextrose. *Pain physician*. 2006;9(2):115-21	*Ineligible study design or publication type*

Citation	Exclude Reason
55. Mistraletti G, De La Cuadra-Fontaine JC, Asenjo FJ, et al. Comparison of Analgesic Methods for Total Knee Arthroplasty: Metabolic Effect of Exogenous Glucose. Article. *Reg Anesth Pain Med*. 2006;31(3):260-269	*Ineligible intervention*
56. Murphy GS, Avram MJ, Greenberg SB, et al. Perioperative Methadone and Ketamine for Postoperative Pain Control in Spinal Surgical Patients: A Randomized, Double-blind, Placebo-controlled Trial. *Anesthesiology*. 2021;134(5):697-708. Comment in: Anesthesiology. 2021 May 1;134(5):676-679 PMID: 33740051 [https://www.ncbi.nlm.nih.gov/pubmed/33740051]	*Ineligible intervention*
57. Myers A. Prolotherapy treatment of low back pain and sciatica. *Bulletin of the Hospital for Joint Diseases*. 1961;22:48-55	*Ineligible study design or publication type*
58. Nair A. Prolotherapy as an intervention for chronic, refractory musculoskeletal pain. *Saudi journal of anaesthesia*. 2021;15(4):463-465	*Ineligible study design or publication type*
59. Nasiri A, Rezaei Motlagh F, Vafaei MA. Efficacy comparison between ultrasound-guided injections of 5% dextrose with corticosteroids in carpal tunnel syndrome patients. Article. *Neurol Res*. 2023;45(6):554-563	*Ineligible intervention*
60. Nourani BB. Osteopathic considerations in sports medicine: Prolotherapy for knee pain with enthesopathy. *Found of Osteopat Med: Philos, Sci, Clin Appl, and Res: Fourth Ed*. 2018;	*Ineligible study design or publication type*
61. Pereira Pires JA, Rey Moura EC, Oliveira CMBd, Vieira Dibai-Filho A, Soares Brandao Nascimento MdD, Cunha Leal P. Hypertonic glucose in the treatment of low back pain: A randomized clinical trial. *Medicine*. 2023;102(38):e35163	*Ineligible intervention*
62. Rabago D, Kijowski R, Woods M, et al. Association between disease-specific quality of life and magnetic resonance imaging outcomes in a clinical trial of prolotherapy for knee osteoarthritis. *Archives of physical medicine and rehabilitation*. 2013;94(11):2075-82	*Ineligible outcome*
63. Rabago D, Mundt M, Zgierska A, Grettie J. Hypertonic dextrose injection (prolotherapy) for knee osteoarthritis: Long term outcomes. *Complementary therapies in medicine*. 2015;23(3):388-95	*Ineligible outcome*
64. Rabago D, Patterson JJ. Prolotherapy: an effective adjunctive therapy for knee osteoarthritis. *The Journal of the American Osteopathic Association*. 2013;113(2):122-3. Comment on: J Am Osteopath Assoc. 2012 Nov;112(11):709-15 PMID: 23139341 [https://www.ncbi.nlm.nih.gov/pubmed/23139341]	*Ineligible study design or publication type*
65. Rabago D, Patterson JJ, Mundt M, et al. Dextrose and morrhuate sodium injections (prolotherapy) for knee osteoarthritis: a prospective open-label trial. *Journal of alternative and complementary medicine (New York, NY)*. 2014;20(5):383-91	*Ineligible study design or publication type*
66. Reeves KD, Hassanein K. Randomized, prospective, placebo-controlled double-blind study of dextrose prolotherapy for osteoarthritic thumb and finger (DIP, PIP, and trapeziometacarpal) joints: evidence of clinical efficacy. *Journal of alternative and complementary medicine (New York, NY)*. 2000;6(4):311-20	*Ineligible intervention*
67. Remvig L, Jensen KE. MRI outcomes in prolotherapy for lateral epicondylosis. Letter. *Int Musculoskelet Med*. 2011;33(1):37-38	*Ineligible study design or publication type*
68. Ryan M, Wong A, Taunton J. Favorable outcomes after sonographically guided intratendinous injection of hyperosmolar dextrose for chronic insertional and midportion achilles tendinosis. *AJR American journal of roentgenology*. 2010;194(4):1047-53	*Ineligible outcome*

Citation	Exclude Reason
69. Schwartz RG, Sagedy N. Prolotherapy: A literature review and retrospective study. *Journal of Neurological and Orthopaedic Medicine and Surgery*. 1991;12(3):220-223	*Ineligible intervention*
70. Sert AT, Ozcan E, Esmaeilzadeh S. Poster 383 Effects of Dextrose Prolotherapy in the Treatment of Patients with Knee Osteoarthritis: A Randomized Controlled Trial. *PM & R : the journal of injury, function, and rehabilitation*. 2016;8(9S):S286	*Ineligible study design or publication type*
71. Shen Y-P, Li T-Y, Chou Y-C, et al. Comparison of perineural platelet-rich plasma and dextrose injections for moderate carpal tunnel syndrome: A prospective randomized, single-blind, head-to-head comparative trial. *Journal of tissue engineering and regenerative medicine*. 2019;13(11):2009-2017	*Ineligible intervention*
72. Solmaz I, Orscelik A, Koroglu O. Modified prolotherapy by 5% dextrose: Two years experiences of a traditional and complementary medicine practice center in Turkey. *Journal of back and musculoskeletal rehabilitation*. 2022;35(4):763-770	*Ineligible intervention*
73. Soneral S. Effective use of dextrose-prolotherapy within the scope of osteopathic family medicine. *Osteopathic Family Physician*. 2015;7(4):8-12.	*Ineligible study design or publication type*
74. Suputtitada A, Chen J-L, Wu C-K, Peng Y-N, Yen T-Y, Chen CPC. Determining the Most Suitable Ultrasound-Guided Injection Technique in Treating Lumbar Facet Joint Syndrome. *Biomedicines*. 2023;11(12)	*Ineligible intervention*
75. Taskesen F, Cezairli B. Efficacy of prolotherapy and arthrocentesis in management of temporomandibular joint hypermobility. *Cranio : the journal of craniomandibular practice*. 2023;41(5):423-431	*Ineligible intervention*
76. Trescot A, Brown M. Peripheral nerve entrapment, hydrodissection, and neural regenerative strategies. *Techniques in Regional Anesthesia and Pain Management*. 2015;19(1-2):85-93	*Ineligible intervention*
77. Tsatsos G, Mandal R. Prolotherapy in the treatment of foot problems. *Journal of the American Podiatric Medical Association*. 2002;92(6):366-8	*Ineligible study design or publication type*
78. Ugurlar M, Sonmez MM, Ugurlar OY, Adiyeke L, Yildirim H, Eren OT. Effectiveness of Four Different Treatment Modalities in the Treatment of Chronic Plantar Fasciitis During a 36-Month Follow-Up Period: A Randomized Controlled Trial. *The Journal of foot and ankle surgery : official publication of the American College of Foot and Ankle Surgeons*. 2018;57(5):913-918	*Ineligible intervention*
79. Uzun Ş, Karagöz AH, Köse EA, Canbay Ö, Özgen S. The effect of dexmedetomidine diluted in 5 % dextrose to prevent propofol injection pain. Article. *Anestezi Derg*. 2009;17(4):201-204	*Ineligible intervention*
80. Watson JD, Shay BL. Treatment of chronic low-back pain: a 1-year or greater follow-up. *Journal of alternative and complementary medicine (New York, NY)*. 2010;16(9):951-8	*Ineligible intervention*
81. Wilkinson HA. Injection therapy for enthesopathies causing axial spine pain and the "failed back syndrome": a single blinded, randomized and cross-over study. *Pain physician*. 2005;8(2):167-73	*Ineligible intervention*
82. Won SJ, Kim D-Y, Kim JM. Effect of platelet-rich plasma injections for chronic nonspecific low back pain: A randomized controlled study. *Medicine*. 2022;101(8):e28935	*Ineligible intervention*

Citation	Exclude Reason
83. Yelland M, Hooper A, Faris P. Minimum clinically important changes in disability in a prospective case series with chronic thoracic and lumbar spinal pain. Article. *Int Musculoskelet Med*. 2011;33(2):49-53	*Ineligible study design or publication type*
84. Yelland MJ, Del Mar C, Pirozzo S, Schoene ML, Vercoe P. Prolotherapy injections for chronic lowback pain. Short survey. *Praxis*. 2004;93(39):1597	*Ineligible study design or publication type*
85. Yelland MJ, Schluter PJ. Defining worthwhile and desired responses to treatment of chronic low back pain. *Pain medicine (Malden, Mass)*. 2006;7(1):38-45	*Ineligible outcome*

APPENDIX D. PEER REVIEW COMMENTS AND RESPONSES

Comment #	Reviewer #	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
1	1	Yes	Thank you for your comment.
2	3	Yes	Thank you for your comment.
3	5	Yes	Thank you for your comment.
4	6	Yes	Thank you for your comment.
Is there any indication of bias in our synthesis of the evidence?			
5	1	No	Thank you for your comment.
6	3	No	Thank you for your comment.
7	5	No	Thank you for your comment.
8	6	Yes - Overall I feel the information presented skews prolotherapy in a negative light. Even when some semblances of positive outcomes are noted in a study, the next line if followed by a negative comment. There are many phrases that include 'probably" which seems to imply that the data was looked at and although there was benefit, it probably wasn't meaningful to the author.	Our goal is to provide a balanced and accurate synthesis of the existing evidence on benefits and harms of dextrose prolotherapy. We sought to report completely the findings from relevant published evidence on this treatment. In the conduct of this review, we followed recommended protocols for identifying, assessing, and synthesizing the evidence on dextrose prolotherapy. We involved an expert advisory panel and stakeholders in developing the review protocol, which was established a priori before we finalized selection of eligible studies and analysis of study findings. We also engaged the advisory panel in deciding how to categorize and synthesize the evidence, before any analysis of findings. As noted below in response to comment #21, we have provided more information about GRADE ratings for certainty of evidence, and the recommended language to reflect a specific rating (*eg*, "probably" is used for moderate certainty)
Are there any published or unpublished studies that we may have overlooked?			
9	1	No	Thank you for your comment.
10	3	No	Thank you for your comment.
11	5	No	Thank you for your comment.
12	6	No	Thank you for your comment.

Comment #	Reviewer #	Comment	Author Response
Additional suggestions or comments can be provided below.			
13	1	None.	Thank you for your comment.
14	3	I found the report to be well written and balanced. The conclusions are supported by the Evidence that was found.	Thank you for your comment.
15	5	PDF p. 12, line 4 – "eligibles" should be "eligible" PDF p. 12, line 31 – is "KQ" defined prior to this in the executive summary (it is defined in the main report)?	We have corrected this and spelled out "Key Question" for KQ.
16	5	PDF p. 13, line 27 – comparators were normal saline, corticosteroid or PT/exercise programs, or were there 2 arms in the same study (e.g., normal saline in 1 arm and corticosteroid injection in another arm)? I wasn't clear from this sentence.	We have clarified this sentence to indicate that these were mostly separate studies with these different comparators. There was one study that had 4 arms, comparing dextrose prolotherapy with normal saline, corticosteroid injection, and PRP (Table 15).
17	5	PDF p. 14, lines 25-35 (KQ2) – the question asks about benefits and harms, but the text below mostly discusses (lack of) benefit, not harms (or even a statement here saying there was not enough evidence to comment on this, etc.).	We have clarified that lack of an impact on the 4 prioritized outcomes include both efficacy outcomes (pain-related functioning, physical performance, and health-related quality of life), and adverse events.
18	5	PDF p. 15, line 5 – "benefits" should probably be "benefit" PDF p. 15, line 14 – just FYI, an additional reason is that some patients are not surgical candidates (e.g., high risk because of comorbidities, do not wish to undergo surgery, don't have sufficient support during rehabilitation from surgery, etc.).	We have corrected this. We agree with reviewer's point and had noted these same points in the Introduction (pg. viii): "*…surgery may not be the best option for certain patients due to a variety of factors, such as the expected improvement vs. risks from surgery and patient preferences.*"
19	5	PDF p. 17, line 12 – RCTS should be RCTs? This occurs multiple times in the manuscript – find & replace.	We have corrected this.
20	5	PDF p. 32, Figure 1 – it wasn't clear to me how many studies were excluded because of low N – would this be under "ineligible study design or publication" or some other heading (e.g., ineligible population)?	The exclusion criteria related to study sample size (≥ 100) was only applied to non-comparative cohort studies, RCTs and comparative cohorts of any size were included (if they met the other eligibility criteria). We included non-comparative cohort studies in order to supplement the evidence on harms from RCTs and comparative cohort studies, which we anticipated

Comment #	Reviewer #	Comment	Author Response
			may be limited. The number of non-comparative cohort studies with N <100 was not specifically tracked but included within the category “ineligible study design or publication type” (as the reviewer noted).
21	5	General comments • pain-related is sometimes hyphenated, sometimes not hyphenated throughout the text. Consider standardizing. • GRADE Working Group grades of evidence – might be helpful to have this definition (e.g., PDF p. 61, lines 44-50) earlier in the manuscript, as this may be more unfamiliar to readers than “letter grades” or other grading systems?I	We have corrected this to be “pain-related functioning” throughout the report. Regarding GRADE ratings, we have now added the definition of these ratings to the Methods (in both the Executive Summary and the main report), along with the recommended language for describing these ratings.
22	6	Page 12 Lines 37-38 "Probably" seems like a vague descriptor.	As noted above in response to comment #21, we have provided more information about the GRADE ratings and the recommended language for describing these ratings (*eg*, “probably” is used for moderate certainty).
23	6	Serious side effects is mentioned but not described from my reading. This feels biased.	Please see our response below to comment #28.
24	6	Page 12 Line 7 For shoulder what is the “Worse physical outcome when compared to steroid.”?	We are uncertain if reviewer is still referencing lines 37-38 on pg. xiii (in the original draft report), which states “*In contrast, our findings indicated that for shoulder pain, dextrose prolotherapy probably led to worse physical performance outcomes, compared with corticosteroid injections*.” If so, then the physical performance outcomes referred to in this sentence included range of motion for a variety of movements, such as forward flexion, abduction, etc. For studies addressing other pain conditions, other physical performance measures were used (*eg*, gait speed in studies of knee osteoarthritis). As this is a summary sentence in the Discussion, we did not list all the measures again. The exact physical performance measures are described in the main report (Tables 15 and 17, and text sections), We have also added clarifications to these outcomes in the Executive Summary results portion (pg. xii).
25	6	Page 12 Lines 37-38 “probably has…” I don’t feel this is an appropriate word. It either did or did not.	As indicated in response to comment #21, we added more information about the GRADE ratings and the recommended language for describing these ratings (*eg*, “probably” is used for moderate certainty).

Comment #	Reviewer #	Comment	Author Response
26	6	In discussion of Prolotherapy costs, it is NOT pointed out that dextrose is cheap. And burden of care for patients is talked about as it if were implied to be high but no evidence suggests that. Also where is safety data?	Our Discussion focuses on the evidence gaps regarding treatment costs and burden because we only identified 2 studies that addressed costs and neither examined treatment burden from the perspective of patients and caregivers. We highlight the factors that generally contribute to costs and resource needs for in-clinic treatments, including staff training as needed to establish and maintain competence. Similarly, for treatment burden, we are also alluding generally to factors that would impact this for patients, such as various access barriers. The findings on harms or safety are presented in the sections on KQ 1 and 2 in both the Executive Summary and the Main text. In general, the evidence on harms or safety was lacking, due to a variety of factors. The included studies generally did not systematically evaluate adverse events and varied greatly in what was reported. Additionally, most studies were very small, which meant they had limited power to detect side effects that were uncommon.
27	6	Page 16 lines 33-34. Again, the line reads 'Probably' had little to no benefit. It either did or did not. This phrasing makes it sound like the study showed it had some effect but you don't want to acknowledge it or you don't feel like it was significant enough. Same in lines 38-39	As noted above in response to comment #21, we added more information about the GRADE ratings and the recommended language for describing these ratings (*eg*, "probably" is used for moderate certainty).
28	6	Page 16 Line 49. State more research it needed to establish the 'safety" yet nothing has been described as being unsafe or harmful with the treatments. Lines 53-54. What is the common, rare, serious side effect you are trying to make readers believe if present?	Clinical decision-making (and guidelines) must weigh efficacy (improvement in outcomes) vs. harms (risks and side effects) for any given treatment; thus, evidence is needed to address both sides of this equation. The included studies generally did not systematically evaluate adverse events and varied greatly in what was reported. For example, some rates reported the rates (and extent) of post-injection pain and others made only general statements that no severe side effects were observed (but did not define what was considered to be severe). Therefore, even for something that appeared to be fairly common (*eg*, higher pain post-injection), there was insufficient evidence for pooled estimates of the risk. In the main report, we also provide a specific example of a serious but rare side effect that was observed only after more widespread use of viscosupplementation. Although not included in our report, there

Comment #	Reviewer #	Comment	Author Response
			are also many other examples of infrequent, serious side effects that emerged (or were better understood) only with larger studies or greater population exposure. These include rates of deep venous thromboembolism with oral contraceptives (<1%/year) and liver failure with terbinafine (<<0.1%). Some of these infrequent side effects may be anticipated based on the mechanism of the treatment, but others were surprising and more idiosyncratic. Therefore, our main point here is to highlight the uncertainty regarding the evidence for safety of dextrose prolotherapy.
29	6	Page 25, line 46-47. What about the safety record of PROLO? Something should mentioned here.	An important part of the goal of this systematic review was to identify and synthesize evidence on the harms of dextrose prolotherapy. As noted above in response to comments #26 and 28, studies had a variety of methodological limitations that led to very low certainty of evidence for harms across different pain conditions.

APPENDIX E. RISK OF BIAS ASSESSMENTS

Appendix Table 1. Risk of Bias Ratings for All Eligible Randomized Controlled Trials (ROB-2)

Trial Name or Author Year	Bias from Randomization Process	Bias from Deviation from Intended Interventions (Assignment)	Bias from Deviation from Intended Interventions (Adherence)	Bias from Missing Outcome Data	Bias in Measurement Of Outcome	Bias in Selection Of Reported Result	Overall Risk Of Bias (Low, Some Concerns, High)
Abd Karim, 2023[78]	Low	Low	Low	High	Low	Low	**High**
Ahadi, 2019[89]	Some concerns	Low	High	Low	Some concerns	Some concerns	**High**
Akcay, 2020[88]	Low	High	Low	Some concerns	Low	Some concerns	**High**
Apaydin, 2020[96]	Some concerns	Low	Some concerns	Low	Some concerns	Low	**High**
Arafat, 2019[116]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns	**High**
Asheghan, 2021[71]	Some concerns	Low	Low	Low	Some concerns	Low	**Some concerns**
Babaeian, 2022[50]	Low	High	Low	Some concerns	Low	Low	**High**
Babaei-Ghazani, 2023[125]	Low	Some concerns	Low	Low	Low	Low	**Some concerns**
Bayat, 2019[94]	Some concerns	High	High	Low	Low	Low	**High**
Bayat, 2023[60]	High	High	High	High	Low	Low	**High**
Baygutalp, 2021[58]	Some concerns	Some concerns	High	Low	High	Some concerns	**High**
Bertrand, 2016[85]	Some concerns	High	Low	Some concerns	Low	Low	**High**
Bhargava, 2023[117]	Some concerns	High	High	High	Some concerns	Some concerns	**High**

Trial Name or Author Year	Bias from Randomization Process	Bias from Deviation from Intended Interventions (Assignment)	Bias from Deviation from Intended Interventions (Adherence)	Bias from Missing Outcome Data	Bias in Measurement Of Outcome	Bias in Selection Of Reported Result	Overall Risk Of Bias (Low, Some Concerns, High)
Chang, 2021[75]	Some concerns	Low	Low	Low	Low	Low	**Some concerns**
Chhapane, 2023[118]	Some concerns	Low	Some concerns	Some concerns	Some concerns	Low	**High**
Ciftci, 2023[93]	Low	Some concerns	Low	Low	Low	Low	**Some concerns**
Cole, 2018[84]	Some concerns	Low	Some concerns	Some concerns	Low	Some concerns	**High**
Comert, 2016[119]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns	**High**
Deb, 2020[92]	Some concerns	High	High	High	Some concerns	Some concerns	**High**
Dechow, 1999[100]	Some concerns	Some concerns	High	Low	Low	Some concerns	**High**
Dumais, 2012[61]	Low	High	High	High	Low	Low	**High**
Ersen, 2018[66]	Low	Low	High	Some concerns	High	Some concerns	**High**
Eua, 2018[69]	Low	Some concerns	Low	Low	Some concerns	Some concerns	**Some concerns**
Farpour, 2017[49]	Low	Low	Some concerns	Low	Low	Low	**Some concerns**
Fouda, 2018[109]	Some concerns	Low	High	High	Low	Some concerns	**High**
George, 2018[77]	Some concerns	Low	High	Low	Some concerns	Some concerns	**High**
Gul, 2020[130]	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns	**Some concerns**
Gupta, 2022[97]	High	Low	Low	Low	Some concerns	Some concerns	**High**

Trial Name or Author Year	Bias from Randomization Process	Bias from Deviation from Intended Interventions (Assignment)	Bias from Deviation from Intended Interventions (Adherence)	Bias from Missing Outcome Data	Bias in Measurement Of Outcome	Bias in Selection Of Reported Result	Overall Risk Of Bias (Low, Some Concerns, High)
Hadianfard, 2023[126]	Low	Low	Low	Low	Low	Some concerns	**Some concerns**
Haggag, 2022[110]	Some concerns	High	Low	High	Low	Some concerns	**High**
Hashemi, 2015[51]	Some concerns	High	Some concerns	Low	Some concerns	Some concerns	**High**
Hassanien, 2020[111]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns	**High**
Hooper, 2011[136]	Low	High	Low	Some concerns	Low	Some concerns	**High**
Hosseini, 2019[54]	Low	High	High	Low	Some concerns	Low	**High**
Hsieh, 2022[43]	Low	Low	Low	Low	Low	Low	**Low**
Jahangiri, 2016[127]	Low	Low	Low	Some concerns	Low	Low	**Some concerns**
Karakilic, 2023[65]	Some concerns	Low	High	High	Some concerns	Some concerns	**High**
Kaya, 2022[95]	Low	High	High	High	Some concerns	Some concerns	**High**
Kazempour Mofrad, 2021[81]	High	Low	Low	Low	Some concerns	Low	**High**
Kesikburun, 2022[67]	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns	**High**
Kim, 2010[107]	Low	Some concerns	Low	Low	Low	Some concerns	**Some concerns**
Kim, 2014[72]	High	Some concerns	Low	Low	Low	Some concerns	**High**
Klein, 1993[101]	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns	**High**

Trial Name or Author Year	Bias from Randomization Process	Bias from Deviation from Intended Interventions (Assignment)	Bias from Deviation from Intended Interventions (Adherence)	Bias from Missing Outcome Data	Bias in Measurement Of Outcome	Bias in Selection Of Reported Result	Overall Risk Of Bias (Low, Some Concerns, High)
Lin, 2022[74]; Lin, 2019[76]	Low	Low	Low	Low	Low	Low	**Low**
Lin, 2023[73]	Low	Low	Some concerns	Low	Low	Low	**Some concerns**
Louw, 2019[112]	Low	Low	Low	Some concerns	Low	Low	**Some concerns**
Mahmoud, 2018[113]	Some concerns	Some concerns	High	Some concerns	Some concerns	Some concerns	**High**
Mansiz-Kaplan, 2020[68]	Low	Some concerns	Low	Some concerns	Low	Low	**Some concerns**
Mruthyunjaya, 2023[46]	Low	High	Low	High	Some concerns	Low	**High**
Mustafa, 2018[120]	Some concerns	High	Low	Low	Some concerns	Some concerns	**High**
Nasiri, 2021[80]	Some concerns	Some concerns	High	Some concerns	Low	Low	**High**
Ongley, 1987[102]	Some concerns	Some concerns	Low	Low	Low	Some concerns	**Some concerns**
Ozturk, 2023[56]	Some concerns	Low	Low	Low	Some concerns	Low	**Some concerns**
Pishgahi, 2020[47]	Some concerns	Low	Low	Low	Some concerns	Low	**Some concerns**
Priyadarshini, 2021[114]	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns	**High**
Rabago, 2013a[63]	Low	Low	Low	Some concerns	Low	Low	**Some concerns**
Rabago, 2013b[90]	Some concerns	Low	Some concerns	Some concerns	High	Some concerns	**High**
Rahimzadeh, 2014[52]	Low	Low	Some concerns	Low	Low	Low	**Some concerns**

Trial Name or Author Year	Bias from Randomization Process	Bias from Deviation from Intended Interventions (Assignment)	Bias from Deviation from Intended Interventions (Adherence)	Bias from Missing Outcome Data	Bias in Measurement Of Outcome	Bias in Selection Of Reported Result	Overall Risk Of Bias (Low, Some Concerns, High)
Rahimzadeh, 2018[48]	Low	Some concerns	Low	Low	Low	Low	**Some concerns**
Raissi, 2022[106]	Low	Some concerns	Low	Low	Low	Low	**Some concerns**
Raissi, 2023[70]	Some concerns	Low	Some concerns	Some concerns	Low	Low	**Some concerns**
Reeves, 2000[44]	Low	High	Low	High	Low	Some concerns	**High**
Refai, 2011[122]	High	High	Low	Some concerns	Low	Some concerns	**High**
Rezasoltani, 2017[42]	Low	Low	Some concerns	High	Low	Low	**High**
Rezasoltani, 2020[53]	Some concerns	Some concerns	High	Low	High	High	**High**
Saadat, 2018[123]	Some concerns	Low	Low	Some concerns	Some concerns	Some concerns	**High**
Sam, 2023[79]	Low	High	Low	Some concerns	Low	High	**High**
Sari, 2020[82]	Some concerns	Some concerns	Low	Low	Low	Some concerns	**High**
Scarpone, 2008[91]	Some concerns	Low	Low	Some concerns	Low	Some concerns	**High**
Sert, 2020[59]	Low	High	High	Low	High	Low	**High**
Seven, 2017[83]	Some concerns	High	High	High	Some concerns	Some concerns	**High**
Sit, 2020[45]	Low	Low	Low	Low	Low	Low	**Low**
Ustun, 2023[132]	High	Some concerns	High	Low	Some concerns	Low	**High**

Trial Name or Author Year	Bias from Randomization Process	Bias from Deviation from Intended Interventions (Assignment)	Bias from Deviation from Intended Interventions (Adherence)	Bias from Missing Outcome Data	Bias in Measurement Of Outcome	Bias in Selection Of Reported Result	Overall Risk Of Bias (Low, Some Concerns, High)
Waluyo, 2021[64]	Some concerns	High	High	High	Low	Low	**High**
Wu, 2022[135]	Low	Low	Low	High	Low	Some concerns	**High**
Yelland, 2004[99]	Low	Low	Some concerns	High	Low	Low	**High**
Yelland, 2011[129]	Low	Low	Low	Low	Some concerns	Low	**Some concerns**
Yelland, 2019[98]	Low	Low	High	Some concerns	Some concerns	High	**High**
Yildiz, 2023[62]	Some concerns	Low	Low	Low	High	Low	**High**
Zarate, 2020[115]	Low	Low	Low	Low	Low	Low	**Low**

Appendix Table 2. Risk of Bias Ratings for All Eligible Nonrandomized Comparison Studies (ROBINS-I)

Study Name or Author Year	Bias Due To Confounding	Selection Bias	Bias in Classification of Interventions	Bias Due to Departures from Intended Interventions	Bias Due to Measurement of Outcomes	Bias Due to Missing Data	Bias in the Selection of Reported Results	Overall Risk of Bias (Low, Moderate, Serious, Critical, No Information)
Abd Elghany, 2019[133]	Low (except for concerns about uncontrolled confounding)	Low	Low	Moderate	Low	Moderate	Low	**Moderate**
Akpancar, 2019[131]	Low (except for concerns about uncontrolled confounding)	Low	Moderate	Critical	Serious	Moderate	Low	**Critical**

Study Name or Author Year	Bias Due To Confounding	Selection Bias	Bias in Classification of Interventions	Bias Due to Departures from Intended Interventions	Bias Due to Measurement of Outcomes	Bias Due to Missing Data	Bias in the Selection of Reported Results	Overall Risk of Bias (Low, Moderate, Serious, Critical, No Information)
Cho, 2017[128]	Low (except for concerns about uncontrolled confounding)	Low	Low	Moderate	Serious	Moderate	Low	**Serious**
Derby, 2004[104]	Low (except for concerns about uncontrolled confounding)	Low	Low	Moderate	Serious	Serious	Moderate	**Serious**
Elwerfelli, 2019[108]	Serious	Low	Low	Low	Serious	Moderate	Low	**Serious**
Jacks, 2012[103]	Low (except for concerns about uncontrolled confounding)	Low	Low	Low	Low	Low	Low	**Low**
Pandey, 2022[121]	Low (except for concerns about uncontrolled confounding)	Low	Low	Moderate	Serious	Moderate	Moderate	**Serious**
Senturk, 2017[134]	Low (except for concerns about uncontrolled confounding)	Low	Low	Moderate	Serious	Serious	Low	**Serious**
Soliman, 2016[57]	Low (except for concerns about uncontrolled confounding)	Low	Low	Moderate	Serious	Serious	Low	**Serious**

Study Name or Author Year	Bias Due To Confounding	Selection Bias	Bias in Classification of Interventions	Bias Due to Departures from Intended Interventions	Bias Due to Measurement of Outcomes	Bias Due to Missing Data	Bias in the Selection of Reported Results	Overall Risk of Bias (Low, Moderate, Serious, Critical, No Information)
Yildirim, 2021[105]	Low (except for concerns about uncontrolled confounding)	Low	Low	Low	Low	Moderate	Low	**Moderate**

APPENDIX F. KNEE OSTEOARTHRITIS

Appendix Table 3. Detailed Study Characteristics for All Eligible Knee OA Studies

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
Intra-articular or Extra-articular Dextrose Injections				
Babaeian, 2022[50] IRCT2016122931458N1 High 4 Weeks Iran (1) NR	**Inclusion**: "Patients aged 40-70 years who met clinical criteria of knee osteoarthritis defined by American college rheumatology and grade 2 or 3 Kellgren and Lawrence, and complained of pain and stiffness for at least one month." **Exclusion**: "Diabetes mellitus, pregnancy, rheumatologic or inflammatory diseases involving the knee joint, previous arthroplasty, intra-articular or peri-articular injection in the past three months, and body mass index (BMI) more than 42."	**Dextrose prolotherapy**: *N*=28 Age, mean (SD): 60.2 (9.1) 79% Female Clinic or health care facility 4 wk (3 injections) Dextrose: "3 ml of dextrose with 50% concentration was diluted with 3 ml of lidocaine 2%" Other treatments: "[Patients] were recommended not to use non-steroid anti-inflammatory and other KOA therapies in the trial…no drug was consumed other than acetaminophen which was taken occasionally."	**Hypertonic saline**: *N*=26 Age, mean (SD): 57.5 (10.0) 86% Female Clinic or health care facility 4 wk (3 injections) Hypertonic Saline: "3 ml of saline with 5% concentration was diluted with 3 ml of lidocaine 2%" Other treatments: Patients were recommended against therapies other than acetaminophen the same as the prolotherapy arm.	**Primary outcome NR** **Pain-related functioning (2, 4 wk)** • OKS • WOMAC (total, pain, stiffness, function) **Adverse events** **Other outcomes:** • Pain severity or intensity (2, 4 wk)
Farpour, 2017[49]	**Inclusion**: "Age 38-70 years; being diagnosed with knee	**Dextrose prolotherapy**: *N*=26	**Dextrose prolotherapy**: *N*=26	**Primary outcome NR**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
IRCT2016091229795N1 Some concerns 8 Weeks Iran (2) NR	osteoarthritis according to clinical criteria of the American College of Rheumatology; having grade 2 and 3 based on the Kellgern-Lawrence grading scale; complaining of pain, crepitation, and knee joint stiffness continuing for at least three months before the study. The VAS score should be 3 or more." **Exclusion**: "The exclusion criteria were any infection involving the knee skin such as cellulitis, any intra- or peri-articular injection during the three last months, history of diabetes mellitus, rheumatological or inflammatory disease involving the knee joints, prior total knee arthroplasty, BMI more than 42, history of knee trauma or fracture during the three last months, history of acute lumbosacral radiculopathy or peripheral neuropathy, history of cancer, bleeding disorders, and pregnancy."	Age, mean (SD): 58.4 (9.5) 68% Female Clinic or health care facility 2 wk (2 injections) Peri-articular prolotherapy: "Patients were placed in a supine position with the 10°-15° knee flexion…An expert physiatrist examined the knee and marked tender points around the knee up to three points. [Six] milliliters of the dextrose 25% were injected totally. We used a 25 G needle to the subcutaneous tissue; then we brought the needle to just below the skin and redirected it in a new direction (fan shape) and repeated this protocol two to three times; 2 milliliters of the solution were injected in each tender point." Other treatments: "We prescribed an acetaminophen tablet if the patient had post-injection pain…They were advised to avoid anti-inflammatory drugs or other therapies for knee osteoarthritis."	Age, mean (SD): 56.4 (11.2) 72% Female Clinic or health care facility 2 wk (2 injections) Intra-articular prolotherapy: "Injections were performed for both groups on the first day and repeated two weeks later. In both groups, the patients were placed in a supine position with the 10°-15° knee flexion. In the intra-articular group, 6 milliliters of dextrose 25% were injected with inferolateral approach under sterile conditions." Other treatments: Acetaminophen was prescribed as in the prolotherapy arm and other treatments were discouraged.	**Pain-related functioning (4, 8 wk)** • OKS • WOMAC (total, pain, stiffness, function) **Adverse events** **Other outcomes:** • Pain severity or intensity (4, 8 wk)
Hashemi, 2015[51]	**Inclusion**: "Patients with mild to moderate OA of the medial knee	**Dextrose prolotherapy**: *N*=40	**Ozone**: *N*=40	**Primary outcome NR**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
NR High 3 Months Iran (NR) NR	compartment (Kellgren-Lawrence grade I and II), aged 40-75 years" **Exclusion**: "Pregnancy, severe underlying diseases such as diabetes, anticoagulant use, being a candidate for knee joint replacement (Kellgren- Lawrence grade III and IV), OA of the lateral knee compartment, previous prolotherapy or any intraarticular injection during the last year, with suspicion for infectious or inflammatory arthritis, and daily use of opioid or nonopioid analgesic drugs."	Age, mean (SD): 57.3 (15.1) 65% Female Clinic or health care facility 14-20 days (3 injections) Hypertonic Dextrose: "Through the inferomedial approach [...] 7 cm3 of 12.5% hypertonic dextrose was injected intraarticularly in the HDP group, by using a 25-G needle under ultrasound guidance. Before the prolotherapy, 1% lidocaine was injected as a local anesthetic to the skin and underlying tissues." Other treatments: None reported	Age, mean (SD): 59.1 (12.3) 57.5% Female Clinic or health care facility 14-20 days (3 injections) Ozone: "Through the inferomedial approach, 15 g/mL of ozone-oxygen mixture (5 - 7 cm3) was injected intraarticularly [...] by using a 25-G needle under ultrasound guidance." Lidocaine was administered the same as in the prolotherapy arm. Other treatments: None reported	**Pain-related functioning (3 mo)** • WOMAC (total) **Other outcomes:** • Pain severity or intensity (3 mo)
Hosseini, 2019[54] IRCT20130518013364N6 High 3 Months Iran (1)	**Inclusion**: mild-to-moderate KOA, grade II or more, were enrolled. [KOA] was diagnosed according to American College of Rheumatology Criteria, and grade was determined according to Kellgren-Lawrence. All patients were aged between 50–75 years and had experienced less than 30 minutes of morning stiffness.	**Dextrose prolotherapy**: *N*=52 Age, mean (SD): 61.2 (11.5) 48% Female Clinic or health care facility 2 wk (3 injections)	**Hyaluronic acid**: *N*=52 Age, mean (SD): 63.7 (12.2) 40% Female Clinic or health care facility 2 wk (3 injections)	**Primary outcome NR** **Pain-related functioning (3 mo)** • Modified WOMAC (0-100 scale) **Adverse events** **Other outcomes:** • Pain severity or intensity (3 mo)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
NR	**Exclusion**: "Exclusion criteria [were] severe underlying diseases like diabetes and/or hypothyroidism, immune suppression or deficiency, serious local infectious or inflammatory knee disease, anticoagulant drug history during the last 3 months, lateral knee compartment involvement, being a candidate for knee joint replacement, any intraarticular injection based treatment as prolotherapy during the last year, and opioid drugs addiction."	Extra-articular hypertonic dextrose: "Before the main injections, lidocaine 2% was used as local anesthetic. The HD group received 10 mL of 12.5% hypertonic dextrose through four point injections, two points at superolateral of patella, one point at the medial knee joint line and another point was at the anterior of fibula head, via a fan wise technique, 2.5 cc for each point. All injections were done by a 23-G needle subcutaneously under ultrasound guidance." Other treatments: None reported	Intra-articular HA: "Before the main injections, lidocaine 2% was used as local anesthetic. For the HA group, 2.5 mL of hyaluronic acid was injected intraarticularly via the inferomedial of patella. All injections were done by a 23-G needle subcutaneously under ultrasound guidance." Other treatments: None reported	
Hsieh, 2022[43] NCT03238183 Low 6 Months Taiwan (1) Partially supported by research grants from Shin Kong Wu Ho-Su Memorial Hospital (2019SKHADR038, 2020SKHADR035,	**Inclusion**: "Age of 40-85 years, knee OA diagnosis satisfying the American College of Rheumatology clinical and radiographic criteria, Kellgren-Lawrence scores of 2 or 3 determined by radiographs (standing anteroposterior views of both knees), the ability to undergo 3 weeks of treatment and 6 months of follow-up, and agreement to avoid nonsteroidal anti-inflammatory drugs during the research." **Exclusion**: "A self-reported history of knee surgery, fracture, or infection;	**Dextrose prolotherapy**: *N*=52 Age, mean (SD): 62.4 (10.4) 79% Female Clinic or health care facility 3 wk (3 injections) HA+Prolotherapy: "The participants were placed in the supine position and had their skin carefully sterilized. After the aseptic preparation, an ultrasound-guided	**Saline**: *N*=52 Age, mean (SD): 62.8 (9.7) 77% Female Clinic or health care facility 3 wk (3 injections) Saline+HA: "The participants were placed in the supine position and had their skin carefully sterilized. After the aseptic preparation, an ultrasound-guided	**Performance-based physical function measures (regular and fastest walking speed, stair climbing time, and chair rising time)** **Pain-related functioning (1 wk [KOOS]; 1, 3, 6 mo)** • KOOS (pain, other symptoms, ADL, sports, QoL) • WOMAC (pain, stiffness, function) **Physical performance (1 wk, 1, 3, 6 mo)** • Chair stand test (s)

Author, Year Registry # Risk of Bias Follow-up Duration Location (# Sites) Funding source	Inclusion/Exclusion Criteria	Intervention: *N* Randomized Demographics/clinical information (pain duration, etc.) Setting Frequency; Duration Detailed Intervention Characteristics Other treatments/co-interventions	Comparator(s): *N* Randomized Demographics/clinical information (pain duration, etc.) Setting Frequency; Duration Detailed Comparator Characteristics Other treatments/co-interventions	Primary Outcome Prioritized Outcomes • Measurement tool(s) (Time points) Other Outcomes Reported
2021SKHADR032, 2022SKHADR033) and the Ministry of Science and Technology, Taiwan	pregnancy or plans for pregnancy; malignant neoplasms; neurologic deficits, including a history of vertigo or stroke; autoimmune disease; a history of intra-articular knee injections of HA or prolotherapy within 6 months; or other therapies for knee OA."	injection was administered with a 21-gauge needle to the lateral suprapatellar pouch through the in-plane approach. The treatment group received a 7-mL 25% dextrose injection (3.5mL of 50% dextrose mixed with 3.5mL of 2% lidocaine) followed by a 2-mL 10 mg/dL HA injection with the same needle" Other treatments: "Acetaminophen was prescribed for intractable pain"	injection was administered with a 21-gauge needle to the lateral suprapatellar pouch through the in-plane approach. The control group received a 7-mL injection of 3.5 mL of normal saline with 3.5 mL of 2 % lidocaine followed by a 2-mL 10 mg/dL HA injection using the same needle" Other treatments: Same as Arm 1	• Regular walking speed (m/s) **Adverse events**
Mruthyunjaya, 2023[46] NR High 6 Months India (1) NR	**Inclusion**: "Patients aged between 35 and 70 years with KL grade 2, 3 stage of OA." **Exclusion**: "OA occurring secondary to rheumatoid arthritis or septic arthritis, patients with G6PD deficiency, hypothyroidism, pregnancy, type 2 diabetes mellitus, patients on anticoagulants therapy, [or] patients who had undergone total knee replacement..."	**Dextrose prolotherapy**: *N*=40 Age, mean (SD): NR % Female NR Clinic or health care facility 4 wk (3 injections) Dextrose: 25% dextrose (no further info on solution): "IA injections were given...in supine position with knee flexed at 90°. In all patients 5 mL (22G) sterile needles were used. The point of entrance of the needle was the femorotibial articular interline, 1.5 cm	**Ozone**: *N*=40 Age, mean (SD): NR % Female NR Clinic or health care facility 4 wk (3 injections) Ozone: The injection protocol was the same as in the prolotherapy arm (no further information given on solution). Other treatments: Patients were asked to avoid analgesics the same as the prolotherapy arm.	**Primary outcome NR** **Pain-related functioning (6 mo)** • WOMAC (total) **Other outcomes:** • Pain severity or intensity (6 mo)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
		lateral to the patellar tendon, 1.5 cm below the apex of the patella..." Other treatments: "Patients were advised…to avoid any analgesics."	**PRP**: *N*=40 Age, mean (SD): NR % Female NR Clinic or health care facility 4 wk (3 injections) PRP: The injection protocol was the same as in the prolotherapy arm (no further information given on solution). Other treatments: Patients were asked to avoid analgesics the same as the prolotherapy arm.	
Pishgahi, 2020[47] IRCT20100720004422N6 Some concerns 6 Months Iran (1)	**Inclusion**: "The following inclusion criteria for patient selection were used: inflammation, pain, or any other symptom related to knee OA lasting at least three months; radiologic signs of grade II, III and IV knee OA and no use of NSAIDs." **Exclusion**: "The exclusion criteria were as follows: rheumatic disease, any	**Dextrose prolotherapy**: *N*=30 Age, mean (SD): 57.9 (1.6) 50% Female Clinic or health care facility 3 wk (3 injections)	**Platelet rich plasma**: *N*=30 Age, mean (SD): 58.9 (1.7) 46.7% Female Clinic or health care facility 1 wk (2 injections)	**Primary outcome NR** **Pain-related functioning (1, 6 mo)** • WOMAC (total) **Other outcomes:** • Pain severity or intensity (1, 6 mo)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
Physical Medicine and Rehabilitation Research center, Tabriz University of Medical Sciences, Tabriz, Iran (Grant No. 63138)	surgical intervention of the knee, infection, liver disease, diabetes, severe cardiovascular disease, coagulopathy, anticoagulant therapy, pregnancy."	Dextrose: "[Authors] used a combination of 50% dextrose (2 mL), bacteriostatic water (2 mL), and 2% lidocaine (1 mL). Dextrose prolotherapy solutions were injected into the knee joint once a week for three weeks under ultrasound guidance through the supra-lateral approach." Other treatments: None reported	PRP: "About 20 mL of venous blood was drained under aseptic precautions each time; platelet concentrate was injected into the knee joint by a skilled specialist under aseptic conditions two times every seven days through the supra-lateral approach. The knees were immobilized for 10 minutes after injection." Other treatments: None reported **ACS**: *N*=32 Age, mean (SD): 61.3 (1.7) 62.5% Female Clinic or health care facility 1 wk (2 injections) Autologous Conditioned Serum: "20 mL of whole blood was taken from each patient under aseptic condition by sterile syringes containing glass beads. The remaining injection procedure was the same as in the prolotherapy arm. Other treatments: None reported	

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
Rahimzadeh, 2014[52] IRCT2013092210336N4 Some concerns 12 Weeks Iran (1) NR	**Inclusion**: "Osteoarthritis according to the American College of Rheumatology's criteria, age 40-70, clinical Class I-III and radiologic Stage 1-3 based on Kellgren–Lawrence criteria." **Exclusion**: "Drugs or alcohol addiction, hemophilia, knee surgery, rheumatoid arthritis, or other rheumatologic diseases."	**Dextrose prolotherapy**: *N*=26 Age, mean (SD): 60.6 (7.5) 62% Female Clinic or health care facility Single injection Dextrose: "[The] patients were transferred to pain operating room lying supine. [T]he needle 22G and 10 cm length through anteroposterior method from the superolateral part of the patella with an angle of about 45°, was entered into the knee articular area; The dextrose group (Group 2) received fluoroscopically guided intra-articular injection of 5 cc 0.5% ropivacaine together with 5 cc dextrose 25%." Other treatments: None reported	**Erythropoietin**: *N*=20 Age, mean (SD): 61.2 (7.5) 55% Female Clinic or health care facility Single injection Erythropoietin: The injection protocol was the same in in the prolotherapy group. "The erythropoietin group received intra-articular injection of 5 cc of ropivacaine 0.5% together with 4000 international units of erythropoietin." Other treatments: None reported **Pulsed radiofrequency**: *N*=24 Age, mean (SD): 57 (8.3) 54.2% Female Clinic or health care facility	**Primary outcome NR** **Physical performance (2, 4, 12 wk)** • ROM **Adverse events** **Other outcomes:** • Pain severity or intensity (2, 4, 12 wk)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
			Pulsed radiofrequency: "[Under] aseptic conditions and local anesthesia with fluoroscopic guidance, through anteroposterior method from the superolateral part of the patella with an angle of about 45°, RF needle G 22, 100 mm long and 10 mm active tip entered the articular area. From the anteroposterior fluoroscopic view the needle tip was embedded at the center of patella. Then, the probe was entered and the patients underwent pulsed radiofrequency (20 ms, 2 Hz, 45 V, 15 min, 42°C, 2 cycles). Other treatments: None reported	
Rahimzadeh, 2018[48] IRCT2014101810599N2 Some concerns 6 Months Iran (1) NR	**Inclusion**: "[Ages] 40–70 and stage 1 or 2 OA (based on the Kellgren Lawrence [KL] scale of the Radiological Society of America)" **Exclusion**: "Rheumatoid arthritis or hemophilia, previous history of knee surgery, drug or alcohol addiction, and use of anticoagulant or nonsteroidal anti-inflammatory drugs (NSAIDs) in the previous 7 days"	**Dextrose prolotherapy**: *N*=21 Age, mean (SD): 64.3 (5.31) 48% Female Clinic or health care facility 1 mo (2 injections) Prolotherapy: Patients in the PRL group received 7 mL 25% dextrose. After administration of local anesthesia and placement of a multi-frequency linear probe of (6–13	**Platelet rich plasma**: *N*=21 Age, mean (SD): 65.5 (6.64) 52% Female Clinic or health care facility 1 mo (2 injections) PRP: "A 20-mL blood sample was drawn under sterile conditions… the blood was centrifuged for 20 minutes at a speed of 3,200 rpm. The plasma was separated	**Primary outcome NR** **Pain-related functioning (1, 2, 6 mo)** • WOMAC (total, pain, stiffness, function) **Adverse events**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
		MHz with a depth of 6 cm) an ultrasound machine at the top of the patella, the intra-articular injection was administered under sterile conditions. Then, a 50 mm long 22-gauge needle was inserted into the knee joint at the upper outer quadrant of the patella under ultrasonographic guidance via the Inplane technique. Then, the prepared solution was injected into the knee joint" Other treatments: "In case of postprocedural pain, paracetamol was prescribed."	and recentrifuged for 5 minutes at a speed of 1,500 rpm. Then, 7 mL of the separated plasma was prepared for intra-articular injection." The remaining injection protocol was the same as in the prolotherapy arm. Other treatments: Paracetamol was prescribed as in the prolotherapy arm.	
Reeves, 2000[44] NR High 6 Months USA (1) NR	**Inclusion**: "6 months or more of pain in the knee, accompanied by either grade 2 or more joint narrowing or grade 2 or more osteophytic change...A standard radiographic atlas was used to determine joint narrowing and osteophytic grades...ACL laxity by... KT1000...an ADD of 2 is estimated to be 85% sensitive and 85% specific for ACL laxity..." **Exclusion**: "Blood was obtained for sedimentation rate, rheumatoid factor, uric acid, and antinuclear antibody. Significant laboratory	**Dextrose prolotherapy**: *N*=NR Age, mean (SD): NR % Female NR Clinic or health care facility 10 mo (6 injections) Prolotherapy: "Using a 27 gauge needle via an inferomedial approach, tibiofemoral injection was conducted with 9 cc of 611.4 mOsm (10% dextrose and .075% lidocaine in bacteriostatic water)	**Saline/Local anesthetic**: *N*=NR Age, mean (SD): NR % Female NR Clinic or health care facility 4 mo (3 injections) Saline + Lidocaine: "105.4 mOsm (.075% lidocaine in bacteriostatic water) solution. Bacteriostatic water consisted of .9% benzyl alcohol [was injected]." The	**WOMAC Total** **Physical performance (6 mo)** • Flexion range **Adverse events** **Other outcomes:** • Pain severity or intensity (6 mo)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
	abnormalities led to referral to primary physician or rheumatologist for determination of the presence or absence of inflammatory arthritis. No patients required exclusion due to the laboratory battery."	solution. Bacteriostatic water consisted of .9% benzyl alcohol." Other treatments: "Patients who were taking any medication or oral supplement for osteoarthritis other than calcium, multivitamins, NSAIDS, acetaminophen, or occasional narcotic, were asked to discontinue them."	injection protocol was the same as in the prolotherapy group. Other treatments: Patients were asked to discontinue medications and supplements the same as the prolotherapy arm.	
Rezasoltani, 2017[42] IRCT2015102713364N3 High 5 Months Iran (1) NR	**Inclusion**: "Inclusion criteria were patients with chronic OA over 50 years of age, grade 2 or higher OA documented by radiology studies, morning stiffness of <30 minutes, and 3 months of no response to conservative therapy." **Exclusion**: "Severe underlying disease, coagulopathy, history of rheumatologic disorders, diabetes or history of corticosteroid therapy, prolotherapy or intra-articular injection in the past year, and indication for surgical arthroplasty."	**Dextrose prolotherapy**: *N*=55 Age, mean (SD): 63.9 (11.0) 76% Female Clinic or health care facility 2 wk (3 injections) Periarticular prolotherapy: "In the periarticular group, 5 mL of 1% lidocaine and 5 mL of 20% dextrose were mixed in a syringe and 2.5 cc of the solution was injected subcutaneously at 4 points around the knee where the periarticular nerves exit the joint capsule. Two points were located at upper lateral and medial parts of knee joint, one point at a line medial to knee and one point located at the head of fibula. The injection was	**Dextrose prolotherapy**: *N*=55 Age, mean (SD): 63.5 (8.9) 74% Female Clinic or health care facility 2 wk (3 injections) Intra-articular prolotherapy: "In intraarticular group, 8 mL of 10% dextrose and 2 mL of 2% lidocaine were injected through an infra-patellar approach by a 23G needle." Other treatments: Same as Arm 1	**Primary outcome NR** **Pain-related functioning (5 mo)** • WOMAC (pain) **Other outcomes:** • Pain severity or intensity (5 mo)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
		performed fan-wise by 2.5 mL of drug solution (5 mL of 1% lidocaine and 5 mL of 20% dextrose) at each point with a 23G needle." Other treatments: “All analgesics were discontinued 48 hours before the procedure and for up to 2 weeks after the procedure.”		
Rezasoltani, 2020[53] IRCT20181217042028N2 High 3 Months Iran (1) NR	**Inclusion**: "Patients with knee osteoarthritis were eligible for the study if their age was greater than or equal to 50 years if they had established chronic knee osteoarthritis and if they were at the third or fourth grade of Kellgren– Lawrence based on radiological data." **Exclusion**: "Exclusion criteria were a history of intra-articular injection within the last 6 months, history of surgery on the knee joint or major trauma to the lower limb causing fracture, and BMI more than 40 kg/m2. [Patients with] severe osteoporosis, rheumatoid arthritis, collagen vascular diseases, and gout. Patients were also excluded if they were addicted to narcotics, had diabetes or any contraindication to intra-articular injections for	**Dextrose prolotherapy**: *N*=30 Age, mean (SD): 64.8 (5.8) 63% Female Clinic or health care facility; Home 2 mo (3 injections; daily exercises) Prolotherapy: "For prolotherapy, we prepared a solution containing 8 ml of 20% dextrose plus 2 ml of 2% lidocaine. Each patient received three intraarticular injections, 1 month apart; Patients were instructed to keep the supine position throughout the procedure. Under ultrasonic guidance, the joint cavity was recognized and a 22-gauge needle was inserted into the joint space, and the solution injected.”	**Exercise/PT**: *N*=30 Age, mean (SD): 70 (6.3) 60% Female Clinic or health care facility; Home 2 wk (3 sessions or injections; daily exercises) Physical therapy: "An exercise program was prescribed daily for all participants throughout the study. Each session lasted approximately 30 minutes including isometric exercise for the quadriceps and stretch exercises for the gastrocnemius and soleus muscles. Knee isometric exercises were prescribed in three angles: 0°, 45°, and 90° of knee flexion. Each contraction	**VAS** **Pain-related functioning (3 mo)** • KOOS (pain, other symptoms, stiffness, ADL, sports, QoL) **Adverse events** • Serious side effects **Other outcomes:** • Pain severity or intensity (1 wk, 1, 3 mo)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
	instance immunodeficiency, coagulation defect or anticoagulation therapy, skin infection at the site of injection, or hypersensitivity to botulinum neurotoxin."	The exercise program was the same as noted in the PT arm. Other treatments: “[Patients] were also instructed to take acetaminophen for 24 hours if needed.”	lasted 10 seconds and repeated 10 times, in every angle with 2-second rest intervals. Participants received 20 minutes of superficial heat using a hot pack. Then, we prescribed transcutaneous electrical nerve stimulation, 80−100 Hz for 100−200 ms with maximum tolerable intensity. [P]atients received pulsed ultrasound 1 MHz, 0.8−1.0 W/cm2, 50% duty cycle, 5 minutes per session." Other treatments: Same as Arm 1 **Botulinum neurotoxin**: *N*=30 Age, mean (SD): 67.7 (7.3) 73% Female Clinic or health care facility; Home 2 wk (3 sessions or injections; daily exercises) "We used 250 units of Dysport, equivalent to 100 units of botulinum neurotoxin type A , diluted with 5 ml of normal saline. Each participant in group botulinum received a single intra-articular injection of the solution; The	

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
			remaining procedure was the same as in the prolotherapy arm. The exercise program was the same as noted in the PT arm. Other treatments: Same as Arm 1 **Hyaluronic acid**: *N*=30 Age, mean (SD): 66.1 (9.1) 53% Female Clinic or health care facility; Home 2 wk (3 sessions or injections; daily exercises) Hyaluronic acid: "2 ml of hyaluronic acid [was injected] into the joint space three times [one week apart each]. The remaining procedure was the same as in the prolotherapy arm. The exercise program was the same as noted in the exercise arm. Other treatments: Same as Arm 1	
Sit, 2020[45]	**Inclusion**:	**Dextrose prolotherapy**: *N*=38	**Saline/Local anesthetic**: *N*=38	**WOMAC Pain score**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
ChiCTR-IPC-15006617 Low 52 Weeks China (1) The study was funded by the Chinese University of Hong Kong Direct Grant for Research 2013-14 (HKD 40,000).	"The inclusion criteria were: age 45–75 years; diagnosis of KOA based on clinical and radiographic criteria as defined by the American Rheumatology College; moderate to severe knee pain for at least 3 months, defined as a score of ≥3 (on a 0–6-point ordinal scale) and failure to achieve a reduction to less than 3 points, using the same pain scale, after 6 months of conservative care." **Exclusion**: "The exclusion criteria included: corn allergy; previous knee replacement surgery; pregnancy; body mass index ≥35; current anti-coagulant therapy; knee injections within the previous 3 months; a diagnosis of inflammatory or post-infectious knee arthritis, gouty arthritis, psoriatic arthritis, or septic arthritis; significant effusion as defined by a ballotable patella; and comorbidity or lifestyle factors precluding participation in the study."	Age, mean (SD): 62.8 (5.8) 71.1% Female Clinic or health care facility 16 wk (4 injections) Dextrose: "Participants were placed in the supine position. Following aseptic preparation and injection of 1 ml of 1% lidocaine […] the study injection was administered under ultrasound guidance (using a linear probe and in-plane approach) with a 25-gauge needle directed to the suprapatellar pouch…" "The DPT solution comprised 5 ml of 25% dextrose…The solution was prepared by mixing 2.5 ml of 50% dextrose with 2.5 ml of sterile water." Other treatments: "Conventional medications, physical therapy, acupuncture, herbal medicines, over-the-counter drugs, and other active treatments were discouraged but allowed and tracked during the study period. All participants were asked to avoid other injection therapies during this time.	Age, mean (SD): 63.7 (5.2) 71.1% Female Clinic or health care facility 16 wk (4 injections) Saline: "Participants in the control group received 5-ml injections of normal saline." The remaining injection procedure was the same as in the prolotherapy arm. Other treatments: Same as Arm 1	**Pain-related functioning (16, 26, 52 wk)** • WOMAC (total, pain, stiffness, function) **Health-related QoL (26, 52 wk)** • EuroQol-5D index **Physical performance (16, 26, 52 wk)** • TUG **Adverse events** • Serious adverse events **Other outcomes:** • Pain severity or intensity (16, 26, 52 wk)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
Combined Intra-articular and Extra-articular Dextrose Injections				
Bayat, 2023[60] IRCT20170311033000N4 High 3 Months Iran (1) NR	**Inclusion**: Knee OA patients age between 45-75 years with radiologic grading of 2 and 3 according to Kellgren Lawrence (KL) criteria who had no response to treatments over the past three months. **Exclusion**: History of any intra-articular injection, knee physiotherapy or knee surgery over the past three months, systemic diseases (rheumatoid arthritis), BMI over 35 and allergy or hypersensitivity to the studied drugs.	**Dextrose prolotherapy**: *N*=28 Age, mean (SD): 56.2 (6.1) 28% Female Clinic or health care facility Single injection Prolotherapy: "One session of dextrose prolotherapy as one intra-articular injection in the form of a combination of 8 cc dextrose 20% + 2 cc lidocaine 1% and periarticular intradermal injections of dextrose 12% at four points around the knee (two points above the patella in the medial and lateral parts, one point in the knee medial joint line and one point in the lateral part of the knee anterior to the head of fibula) with injection of 2.5 cc at each point (a combination of 3 cc dextrose 20% and 2 cc lidocaine 1% in a 5 cc syringe, where only 2.5 cc of it would be injected); [The] the injections were accomplished in a circular pattern around the needle entrance site with about 5 points of infiltration of 0.5 cc of solution."	**Corticosteroid**: *N*=28 Age, mean (SD): 57.1 (6.8) 40% Female Clinic or health care facility Single injection Corticosteroid: "[Patients] received one session of intraarticular injection of triamcinolone (40 mg) with 1 cc of lidocaine 1%. Injections were performed using G22 needle under sterilized conditions. For joint injection lateral mid-patellar approach with knee in the extension was chosen." Exercise therapy was the same in both groups as descirbed in the prolotherapy arm. Other interventions: None reported	**Primary outcome NR** **Pain-related functioning (1, 3 mo)** • WOMAC (total, pain, stiffness, function) **Other outcomes:** • Pain severity or intensity (1, 3 mo)

Author, Year Registry # Risk of Bias Follow-up Duration Location (# Sites) Funding source	Inclusion/Exclusion Criteria	Intervention: *N* Randomized Demographics/clinical information (pain duration, etc.) Setting Frequency; Duration Detailed Intervention Characteristics Other treatments/co-interventions	Comparator(s): *N* Randomized Demographics/clinical information (pain duration, etc.) Setting Frequency; Duration Detailed Comparator Characteristics Other treatments/co-interventions	Primary Outcome Prioritized Outcomes • Measurement tool(s) (Time points) Other Outcomes Reported
		"Exercise therapy including isometric strengthening of quadriceps femoris, thigh adductors and abductors plus stretching of hamstring muscles was prescribed for both groups." Other interventions: None reported		
Baygutalp, 2021[58] NR High 12 Weeks Turkey (1) NR	**Inclusion**: "Being diagnosed with primary KOA according to ACR clinical/radiological diagnostic criteria, not responding to conservative treatments for at least 3 months, having a score of 2 or 3 from the Kellgren–Lawrence radiologic scoring system (scores ranging from 0 to 4 grades), and age of between 40–70 years." **Exclusion**: "History of trauma, surgery, or any invasive procedure on the affected joint in the past 6 months; secondary osteoarthritis due to systemic diseases; uncontrolled diabetes mellitus; rheumatological diseases; systemic infection; tuberculosis; malignancy; hyperthyroidism; severe cardiovascular disease; glucose-6-phosphate dehydrogenase deficiency; abnormalities in hemogram and	**Dextrose prolotherapy**: *N*=25 Age, mean (SD): 56.6 (7.1) 84% Female Disease duration, months (SD): 35.1 (29.6) Clinic or health care facility; Home 6 wk (3 injections); exercises 12 wk (2x/day) Dextrose Prolotherapy: "Intraarticular 5 mL 12.5% dextrose was applied with a lateral approach. Periarticular 1 mL 12.5% dextrose was applied to 10 points with a total volume of 10 mL. The points were medial and lateral coronary ligaments, proximal and distal medial and lateral collateral ligaments, the quadriceps tendon region of patella upper edge, the distal and	**Ozone**: *N*=25 Age, mean (SD): 57 (7.6) 88% Female Disease duration, months (SD): 34.3 (27.6) Clinic or health care facility; Home 6 wk (3 injections); home exercises 12 wk (2x/day) Ozone Therapy: "The patient was in a sitting position, and the knee was flexed. Lidocaine was injected (2%, 2 mL) Intraarticular 15 mL ozone solution (15 g/mL) was applied with a lateral approach…Periarticular 1 mL ozone solution was applied to 10 points with a total volume of 10 mL.The remaining injection protocol was the same as in the prolotherapy arm. The	**Primary outcome NR** **Pain-related functioning (6, 12 wk)** • WOMAC (total, stiffness, function) **Physical performance (6, 12 wk)** • TUG • ROM (active/passive) **Other outcomes:** • Pain severity or intensity (6, 12 wk)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
	coagulation tests; total knee replacement, undergoing anti-inflammatory, anticoagulant, or immunosuppressive therapy; taking a nonsteroidal anti-inflammatory drug (NSAID) in the last week; taking steroid drugs in the last month; using angiotensin converting enzyme inhibitors; knee injection in the last 6 months; and pregnancy and breastfeeding."	proximal region of the patellar tendon, and the tendon region of pes anserine..." The exercise program was the same as noted in the exercise arm. Other interventions: None reported	exercise program was the same as noted in the exercise arm. Other interventions: None reported **Exercise/PT**: *N*=25 Age, mean (SD): 56.5 (7.4) 84% Female Disease duration, months (SD): 30.8 (31.9) Home Exercise: "This program consisted of isometric and isotonic exercises to strengthen quadriceps muscles and improve range of motion...The protocol consisted of 7 movements: -Sitting on a chair, stretch your legs and place a rolled towel under your right knee. Straighten your leg by stretching your knee, pressing your knee down. -Sitting on a chair, stretch your legs and place a rolled towel between your knees, count to 10, then relax for a few seconds. -In the supine position, with the knee	

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
			straight, raise your right leg 15–30 cm, count to 10, then relax for a few seconds. -In the supine position, straighten your legs, and pull your right leg towards you for a count of 10, then relax. -Lie face down and bend your right knee (pull it towards you), count to 10, then relax for a few seconds -Lie on your side, bend your right leg and hip towards you, and count to 10. Then straighten your leg and extend your back as far as you can, then relax for a few seconds." Other interventions: None reported	
Dumais, 2012[61] NCT01206634 High 16 Weeks Canada (1) NR	**Inclusion**: "Diagnosis of knee OA, experience pain in the knee for a minimum of 6 months, be capable to understand and execute physiotherapy exercises, and be 18 years or older." **Exclusion**: "Previous operation of the referring knee, infection of the skin surrounding the knee or of the articulation, abnormal coagulation, allergy to lidocaine, pregnancy, or breast-feeding."	**Dextrose prolotherapy**: *N*=21 Age, mean (SD): 57.3 (12.6) 39% Female Clinic or health care facility; Home 4 wk (4 injections); 16 wk exercise Prolotherapy: "The osteotendinous junction of both insertion sites of the collateral ligaments was identified. The patients then received injections of 1 cc of a 15%	**Physical Therapy**: *N*=24 Age, mean (SD): 56.2 (10.9) 56% Female Home 16 wk (exercises daily; PT check-in every 4 wk) PT: "[The] exercise program was composed of four strengthening exercises (isometric	**WOMAC Index** **Pain-related functioning (16 wk)** • BPI Functional Impairment • WOMAC (total, pain, stiffness, function) **Physical performance (16 wk)** • TUG **Adverse events** • One patient with diffuse edema **Other outcomes:** • Pain severity or intensity (16 wk)

Author, Year Registry # Risk of Bias Follow-up Duration Location (# Sites) Funding source	Inclusion/Exclusion Criteria	Intervention: *N* Randomized Demographics/clinical information (pain duration, etc.) Setting Frequency; Duration Detailed Intervention Characteristics Other treatments/co-interventions	Comparator(s): *N* Randomized Demographics/clinical information (pain duration, etc.) Setting Frequency; Duration Detailed Comparator Characteristics Other treatments/co-interventions	Primary Outcome Prioritized Outcomes • Measurement tool(s) (Time points) Other Outcomes Reported
		dextrose and 0.6% lidocaine solution free of adrenaline in each of eight administration sites in the collateral ligaments... A 5 cc injection of 20% dextrose and 0.5% lidocaine without adrenaline solution was also administered inside the knee joint. The intra-articular injection was performed using the anterior approach." The exercise program was the same as noted in the PT arm. Other interventions: None reported	quadriceps exercises, leg extension exercises with quadriceps roll, strait leg raise, and sitting end-range knee extension) for which the participants were asked to perform three sets of 10 repetitions daily. The participants were instructed on how to do the exercises by a senior physiotherapist, who also reviewed the exercises every 4 weeks..." Other interventions: None reported	
Ozturk, 2023[56] NCT05537077 Some concerns 12 Weeks Turkey (1) NR	**Inclusion**: Patients aged 40–70 years with knee pain for more than 3 months; Diagnosis of primary KOA according to ACR clinical/ radiologic diagnostic criteria and classified as stages II–III of Kellgren–Lawrence **Exclusion**: Patients with total knee arthroplasty; Presence of rheumatic disease, active systemic infection, and malignancy; Those receiving anticoagulant therapy; Patients who had intra-articular injections in the knee within the previous 6 months; Use of steroids in the last month and NSAIDs (nonsteroidal anti-inflammatory	**Dextrose prolotherapy (20%)**: *N*=31 Age, mean (SD): 55.8 (6.8) 80% Female Clinic or health care facility; Home 6 wk (3 injections, exercise daily) 20% DPT: "DPT at a concentration of 20% performed in three sessions at weeks 0, 3, and 6. Five milliliters of intra-articular and 10 ml of periarticular dextrose were injected into the knee during each session. The periarticular injection was given in ten areas, 1 ml in each. A 22-	**Dextrose prolotherapy (5%)**: *N*=33 Age, mean (SD): 55.9 (7.2) 83.3% Female Clinic or health care facility; Home 6 wk (3 injections, exercise daily) 5% DPT: DPT at a concentration of 5% performed in three sessions… The remaining injection technique is the same as in the 20% prolotherapy arm. The exercise program was the same as noted in the Exercise arm.	**Primary outcome NR** **Pain-related functioning (6, 12 wk)** • WOMAC (total, pain, stiffness, function) **Health-related QoL (12 wk)** • SF-36 (PCS, MCS) **Physical performance (6, 12 wk)** • TUG • Flexion (active, passive) **Adverse events** • Patients with side effects **Other outcomes:**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
	drugs) in the last week; Pregnant and breastfeeding women.	gauge needle tip was used for intra-articular injection, while a 27-gauge needle tip was used for periarticular injection. No local anesthetic was used. Hotpack therapy was applied for 20 min each session at weeks 0, 3, and 6. The exercise program was the same as noted in the Exercise arm. Other interventions: None reported	**Dextrose prolotherapy (10%)**: *N*=32 Age, mean (SD): 55.5 (7) 83.3% Female Clinic or health care facility; Home 6 wk (3 injections, exercise daily) 10% DPT: DPT at a concentration of 10% performed in three sessions… The remaining injection technique is the same as in the 20% prolotherapy arm. The exercise program was the same as noted in the Exercise arm. Other interventions: None reported **Exercise**: *N*=32 Age, mean (SD): 56.6 (7.4) 83.3% Female Clinic or health care facility; Home	• Pain severity or intensity (6, 12 wk)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
			6 wk (home exercise daily) Exercise: "The home exercise program of 2 sets of 10 repetitions per day of [the following] home exercise program: (1) Sit with your legs extended. Roll up a towel and place it under your knee. Press the towel down by straightening your knee. Count to 10 in this position. (2) While lying in the prone position, bend both knees alternately. Repeat the movement rhythmically. (3) Lie down on your side. Bend the raised knee as far as you can, pulling it toward your stomach. Then straighten your leg and extend it as far back as possible. (4) Sit on a chair. Tie a 1 kg weight to your ankle. Lift your foot off the floor and extend your leg straight. Count to 10 in this position. Then slowly lower your foot to the floor." Other interventions: None reported	
Rabago, 2013[63] NCT00085722 Some concerns 52 Weeks	**Inclusion**: "A diagnosis of knee osteoarthritis based on clinical criteria (American College of Rheumatology), identification of knee osteoarthritis by a radiologist on an existing knee radiograph obtained within 5 years of enrollment, tenderness of 1 or more anterior knee	**Dextrose prolotherapy**: *N*=33 Age, mean (SD): 56.8 (7.9) 63% Female Clinic or health care facility	**Saline**: *N*=31 Age, mean (SD): 56.8 (6.7) 69% Female Clinic or health care facility	**WOMAC Composite score** **Pain-related functioning (5, 9, 12, 24, 52 wk)** • WOMAC (total, pain, stiffness, function **Adverse events**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
USA (1) National Institutes of Health: National Center for Complementary and Alternative Medicine: 5K23AT001879-02.	structures on physical examination, and self-reported moderate-to-severe knee pain for at least 3 months, defined as a score of 3 or more (0 to 6 ordinal response scale)" **Exclusion**: "Exclusion criteria included pregnancy, diabetes, anticoagulation therapy, history of total knee replacement, prior knee prolotherapy, any knee injection within 3 months, inflammatory or postinfectious knee arthritis, daily use of opioid medication, allergy or intolerance to study medication, body mass index (BMI) greater than 40 kg/m2, and comorbidity severe enough to prevent participation in the study protocol, including at-home exercise or attendance at scheduled injection appointments."	9-17 wk (3-5 injections) Dextrose: Intra-articular [25%] injection: "[Solution] in a 10-mL syringe: 5 mL 50% dextrose, 5 mL lidocaine, 1% saline… 6.0 mL was injected using an inferomedial approach." Extra-articular [15%] injection: "[Solution] 22.5 mL distributed in 3, 10-mL syringes (7.5 mL each) using the following recipe: 6.75 mL 50% dextrose, 4.5 mL 1% lidocaine, 11.25 mL 0.9% saline…Extra-articular injections were done on bone by palpation at major tender tendon and ligament insertions through up to 15 skin punctures using a peppering technique, placing a possible total 22.5 mL of solution; ultrasound guidance was not used." Other treatments: "Participants were offered acetaminophen and 8.5 mg oxycodone tablets to use as needed for up to 1 week [and] were discouraged from using [NSAIDs] and from starting new therapies for their osteoarthritis during the study period.	9-17 wk (3-5 injections) Saline: "Intra-articular [solution]: 5 mL 0.9% sodium chloride, 5 mL 1% lidocaine…Injection technique identical to intra-articular [prolotherapy]…" "Extra-articular [solution]: 22.5 mL distributed in 3, 10-mL syringes (7.5 mL each) using the following recipe: 18 mL 0.9% sodium chloride, 4.5 mL 1% lidocaine…Injection technique identical to [prolotherapy]…" Other treatments: Same as Arm 1 **Exercise/PT**: *N*=34 Age, mean (SD): 56.4 (7.0) 68% Female Home 20 wk (3-5 x/wk) Exercise: "Exercise group participants received an informational pamphlet about knee osteoarthritis (Visual Health	• Post-injection pain, other side effects **Other outcomes:** • Pain severity or intensity (6, 9, 12, 24, 52 wk)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
			Information, at http://www.vhikits.com/Default.aspx) depicting 10 at-home knee exercises demonstrated by the study coordinator at baseline." Other treatments: Same as Arm 1	
Sert, 2020[59] NR High 18 Weeks Turkey (1) This work was supported, in part, by funding from the Scientific Research Projects Unit of the Istanbul University (ID:41877).	**Inclusion**: "Patients with chronic (>3 months) symptomatic KOA aged between 40 and 70 years had grade II or III KOA according to the Kellgren–Lawrence classification and had not responded to conservative therapies, such as physiotherapy, oral analgesic medications, and/or topical nonsteroidal anti-inflammatory drugs." **Exclusion**: "Exclusion criteria were the following: a previous diagnosis of a neuromuscular, infectious, or inflammatory disease; the presence of diabetes mellitus and neuropathic pain; a body mass index above 40 kg/m2; a history of knee trauma or severe meniscus or ligament injuries that could lead to knee pain or surgery; or a history of	**Dextrose prolotherapy**: *N*=22 Age, mean (SD): 55.7 (6.6) 85.7% Female Clinic or health care facility; Home 6 wk (3 injections); exercises performed at least 3 days per wk Prolotherapy: "Each patient received three intra- and extra-articular dextrose prolotherapy injections…A 5mL injection of 25% dextrose solution (4mL 30% dextrose +1mL 0.9% sodium chloride) was applied to the patellofemoral joint space with a superolateral approach using a 20-gauge needle with the patient placed in the supine position. A 25-gauge needle was then used to perform extra-articular injections, using the peppering technique, and applying a total of 10mL	**Saline:** *N*=22 Age, mean (SD): 54.4 (7.3) 90.9% Female Clinic or health care facility; Home 6 wk (3 injections) Saline: "Patients were administered, as per the prolotherapy protocol, intra-articular (2.5mL 0.9% sodium chloride +2.5mL 1% lidocaine) and extra-articular (5mL 0.9% sodium chloride +5mL 1% lidocaine) saline injections" The exercise program was the same as noted in the exercise arm. “All participants were discouraged from using nonsteroidal anti-inflammatory medications and from starting new therapies...during the study period. The	**WOMAC pain subscale** **Pain-related functioning (6, 18 wk)** • WOMAC (total, pain, stiffness, function) **Health-related QoL (6, 18 wk)** • SF-36 (PCS, MCS) **Other outcomes:** • Pain severity or intensity (6, 18 wk)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
	prolotherapy or knee injections in the past 3 months."	15% dextrose solution (5mL 30% dextrose +2.5mL 0.9% sodium chloride +2.5mL 1% lidocaine) into the medial collateral ligament (femur and tibia attachment points), lateral collateral ligament (femur and fibula attachment points), superior patellar pole, patellar tendon (tuberosity of the tibia attachment point), coronary ligaments, and pes anserinus ligament bone attachment points." The exercise program was the same as noted in the exercise arm. Other treatments: "All participants were discouraged from using nonsteroidal anti-inflammatory medications and from starting new therapies...during the study period. The participants were recommended to take acetaminophen as needed…"	participants were recommended to take acetaminophen as needed…" **Exercise/PT**: *N*=22 Age, mean (SD): 52 (6.1) 89.5% Female Home ≥3 days/wk Exercise: "[The] exercise program, which was the same for all three groups, was performed for at least 3 days a week and included hamstring and quadriceps stretching, isometric quadriceps strengthening exercises, and terminal knee extension exercises, each comprising 3 sets with 10 repetitions." Other treatments: Same as Arm 1	
Soliman, 2016[57] NR Serious	**Inclusion**: "Diagnosis of knee OA based on clinical criteria (American College of Rheumatology) with at least 6 months of pain."	**Dextrose prolotherapy**: *N*=52 Age, mean (SD): 51.1 (12.1) 75% Female	**Dextrose prolotherapy**: *N*=52 Age, mean (SD): 51 (10.5) 75% Female	**Primary outcome NR** **Pain-related functioning (12 mo)** • WOMAC (total) **Adverse events**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
12 Months Egypt (1) NR	**Exclusion**: "Cancers and undernutrition in order not to interfere with the healing process of the body. Secondary knee OA cases were excluded as well, such as osteoarthritis associated with any autoimmune diseases, gouty arthritis, hormonal imbalance, infection or hematological disorders."	Disease duration, years (SD): 6.9 (9.0) Clinic or health care facility; Home 3-5 mo (3-5 injections) Prolotherapy using Hackett+Lyftogt injection techniques: [The] knee was examined, tender anterior–medial–lateral knee locations were marked, anesthetic skin wheals of 1% lidocaine were placed…Extra-articular injections were administered on bone by palpation at major tender tendon and ligament insertions through up to 15 skin punctures using a peppering technique…placing a possible total 40 ml of [15% dextrose] solution (24 ml 25% dextrose + 8 ml 1% lidocaine, 8 ml normal saline)" The 5-ml intra-articular injection was then delivered using an inferomedial approach..." 25% intra-articular (5 ml of 25% dextrose) using inferomedial or inferolateral approach…ultrasound guidance was not used." "All patients enrolled in this study underwent a quadriceps strengthening program before the start of the study." Other treatments: "[Participants] were offered acetaminophen tablets to use as	Disease duration, years (SD): 6.6 (9.0) Clinic or health care facility; Home 3-5 mo (3-5 injections) Prolotherpay using Hackett injection technique: " Subgroup Ib was treated with the Hackett... technique alone." The remaining injection protocol was the same as in the other prolotherapy arm. "All patients enrolled in this study underwent a quadriceps strengthening program before the start of the study." Participants were discouraged from therapies other than NSAIDs the same as the other prolotherapy arm. **Exercise/PT**: *N*=24 Age, mean (SD): 52.8 (11.1) 75% Female Disease duration, years (SD): 6.0 (8.7)	• Adverse events not defined **Other outcomes:** • Pain severity or intensity (12 mo)

Author, Year Registry # Risk of Bias Follow-up Duration Location (# Sites) Funding source	Inclusion/Exclusion Criteria	Intervention: *N* Randomized Demographics/clinical information (pain duration, etc.) Setting Frequency; Duration Detailed Intervention Characteristics Other treatments/co-interventions	Comparator(s): *N* Randomized Demographics/clinical information (pain duration, etc.) Setting Frequency; Duration Detailed Comparator Characteristics Other treatments/co-interventions	Primary Outcome Prioritized Outcomes • Measurement tool(s) (Time points) Other Outcomes Reported
		needed for up to 1 week…They were discouraged from using NSAIDs and from starting new therapies for their OA during the study period."	Home 20 wk (5 days/wk, 3x/day) Exercise: "At-home exercise intervention was demonstrated to all patients at baseline. Patients were advised to begin exercises (three sessions per week, one session daily, 10 repetitions per exercise), and then gradually increase therapy as tolerated over 20 weeks (five sessions per week, three times daily, 15 repetitions per exercise), and to continue them thereafter if desired." Other treatments: Same as Arm 1	
Waluyo, 2021[64] NCT04557943 High 12 Weeks Indonesia (1) NR	**Inclusion**: "Inclusion criteria were: patients aged >40 years; and diagnosis of knee OA based on the American College of Rheumatology (ACR) 2012 criteria and radiological examination." **Exclusion**: "Exclusion criteria were: previous intra-articular injection within 3 months; previous use of non-steroidal anti-inflammatory drugs (NSAIDs) one week before intervention; or contraindications to prolotherapy, such as	**Dextrose prolotherapy**: *N*=44 Age, mean (SD): 62.6 (6.9) 76.9% Female Clinic or health care facility 9 wk (3 injections) Dextrose Prolotherapy: "The DPT group was given a 5 ml 25% intra-articular dextrose injection and 30–	**Hyaluronic acid**: *N*=32 Age, mean (SD): 62 (10.8) 71.4% Female Clinic or health care facility 5 wk (5 injections) Hyaluronic Acid:	**Changes in sCOMP and uCTX-II as specific biomarkers of cartilage degradation.** **Pain-related functioning (12 wk)** • WOMAC (total, pain, stiffness, function) **Adverse events** • Post-injection pain/other side effects **Other outcomes:** • Pain severity or intensity (12 wk)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
	abscess, cellulitis, or septic arthritis."	40 ml 15% peri-articular dextrose injection in several sites, such as the medial collateral ligament, pes anserine, tibial tubercle, coronary ligament, patellar edge, lateral collateral ligament, and tibiofibular ligament." Other treatments: "Participants were advised to take only acetaminophen (500 mg every 8 h, as needed) if the pain flared up and to avoid NSAIDs in the first 72 h after injection."	"The HA group was given a 2 ml Adant® intra-articular injection (~10 mg) on weeks 1, 2, 3, 4 and 5." Other treatments: Same as Arm 1	
Yildiz, 2023[62] NCT04958213 High 3 Months Turkey (1) NR	**Inclusion**: "The main inclusion criterion was the radio graphically confirmed presence of mechanical knee pain, around the knee joint, which had been ongoing for at least 3 months." **Exclusion**: "The study exclusion criteria were defined as an age <50 years, the presence of an inflammatory rheumatological disease, grade 1 or 4 OA based on the Kellgren-Lawrence radiological criteria, a history of knee surgery or joint replacement, trauma, any intra-articular injection (hyaluronic acid, steroids or platelet-rich plasma) over the past 6 months, malignancy, or	**Dextrose prolotherapy**: *N*=30 Age, mean (SD): 60.1 (6.8) 100% Female Clinic or health care facility; Home 2 wk (2 injections) Hypertonic dextrose prolotherapy: "With the patient placed in the supine position, and the knee placed at 20-30˚ flexion, The injection points were designated as the medial and lateral coronary ligaments, proximal and distal medial and lateral collateral ligaments, the quadriceps tendon region of the patella upper edge, the distal and	**Exercise/PT**: *N*=30 Age, mean (SD): 60.6 (6.1) 100% Female Clinic or health care facility; Home 4 wk (PT 5 sessions/wk) Conventional physiotherapy: "All patients received combined hot pack (HP), US and TENS treatments. Using a two-channel portable TENS unit (BTL-4620, BTL Corporate), TENS therapy was applied around the knee region for 30 min with two electrodes in conventional mode, at a frequency of	**Primary outcome NR** **Pain-related functioning (1, 3 mo)** • WOMAC (total) **Physical performance (1, 3 mo)** • Knee ROM • 50-m walking test (sec) • Extensor, Flexor PT (60,180 degrees/sec) **Other outcomes:** • Pain severity or intensity (1, 3 mo)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics/clinical information (pain duration, etc.)** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
	any other neurological disorder that could contribute to the symptoms."	proximal region of the patellar tendon, and the tendon region of pes anserine. Using a 27-G needle [...] the injection was then performed. The patients received an intra-articular injection of 5 ml 25% dextrose (2.5 ml 20% dextrose + 2.5 ml 30% dextrose), and a peri-articular injection of 10 ml 15% dextrose (5 ml 0.9% NaCl + 5 ml 30% dextrose) to each ligament-bone insertion. The exercise program was the same as noted in the Exercise arm. Other treatments: "Throughout the study period, the patients were requested not to take any painkillers, but were permitted to take paracetamol if deemed necessary."	100 Hz and a pulse width of 60 msec and intensity adjusted according to the threshold for each patient without causing pain or muscular contraction. US sessions of 5 min continuously were performed 5 days a week for 4 weeks for a total of 20 sessions, using a power of 1 W/cm2, and frequency of 1 MHz. HP therapy was applied for 30 min per session for a total." "A home-based exercise program was performed by all patients in both groups. The program included active isotonic and isometric strengthening exercises for 15 min, and stretching and relaxation exercises for 15 min." Other treatments: Same as Arm 1	

Abbreviations. ACL= anterior cruciate ligament; ACR=American College of Radiology; ACS=autologous conditioned serum; ADD=anterior displacement difference; ADL=Activities of Daily Living; BMI=body mass index; cc=cubic centimeter; DPT=dextrose prolotherapy; EuroQol-5D=European Quality of Life-5 Dimensions; G=gauge; HA=hyaluronic acid; HD=hypertonic dextrose; HP=Hot pack; kg=kilograms; KL=Kellgren-Lawrence; KOA=knee osteoarthritis; KOOS=Knee Injury and Osteoarthritis Outcome Score; m=meters; MCS=Mental component score; MHz=megahertz; ml=milliliters; mm=millimeters; mo=months; mOsm=osmotic concentration; NR=not reported; NSAID=Non-steroidal anti-inflammatory drug; OA=osteoarthritis; OKS=Oxford Knee Score; PCS=Physical component score; PRP=platelet rich plasma; PT=physical therapy; QoL=quality of life; ROM=range of motion; SD=standard deviation; SF-36=Short Form Survey (36 items); TENS=Transcutaneous electrical nerve stimulation; TUG=Timed Up and Go; US=ultrasound; USA=United States of America; VAS=Visual Analog Scale; Wk=week; WOMAC=Western Ontario and McMaster Universities Arthritis index.

Appendix Table 4. Detailed Results for Eligible Knee Osteoarthritis Studies: Intra-Articular and Extra-Articular Dextrose Injections

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up P-value* Other results reported
Dextrose Prolotherapy vs. PT/Exercise Programs				
Baygutalp, 2021[58] High	Pain-related functioning WOMAC Total† 6, 12 wk	**Dextrose prolotherapy** Baseline: 55.9 (17.0) 6, 12 wk: NR	**Ozone** Baseline: 58.0 (9.5) 6, 12 wk: NR	**Dextrose prolotherapy vs. Ozone** 6 wk: NR 12 wk: NR
				Difference in difference 6 wk: NR, p= 0.562 12 wk: NR, p=0.096
			Home exercise Baseline: 57.6 (21.5) 6, 12 wk: NR	**Dextrose prolotherapy vs. Home exercise** 6 wk: NR 12 wk: NR
				Difference in difference 6 wk: NR, p=0.053 12 wk: NR, p=0.023
	Pain-related functioning WOMAC Physical Function† 6, 12 wk	**Dextrose prolotherapy** Baseline: 38.6 (11.8) 6, 12 wk: NR	**Ozone** Baseline: 39.5 (6.7) 6, 12 wk: NR	**Dextrose prolotherapy vs. Ozone** 6 wk: NR 12 wk: NR
				Difference in difference 6 wk: NR, p=0.158 12 wk: NR, p=0.919
			Home exercise Baseline: 40.0 (15.3) 6, 12 wk: NR	**Dextrose prolotherapy vs. Home exercise** 6 wk: NR 12 wk: NR
				Difference in difference 6 wk: NR, p=0.058 12 wk: NR, p=0.007
	Pain-related functioning WOMAC Stiffness† 6, 12 wk	**Dextrose prolotherapy** Baseline: 4.2 (1.8) 6, 12 wk: NR	**Ozone** Baseline: 5.2 (1.8) 6, 12 wk: NR	**Dextrose prolotherapy vs. Ozone** 6 wk: NR 12 wk: NR

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up P-value* Other results reported
				Difference in difference 6 wk: NR, p=0.004 12 wk: NR, p=0.035
			Home exercise Baseline: 4.7 (2.0) 6, 12 wk: NR	**Dextrose prolotherapy vs. Home exercise** 6 wk: NR 12 wk: NR
				Difference in difference 6 wk: NR, p=0.029 12 wk: NR, p=0.302
	Physical performance TUG† 6, 12 wk	**Dextrose prolotherapy** Baseline: 11.8 (2.3) 6, 12 wk: NR	**Ozone** Baseline: 13.8 (2.6) 6, 12 wk: NR	**Dextrose prolotherapy vs. Ozone** 6 wk: NR 12 wk: NR
				Difference in difference 6 wk: NR, p=0.588 12 wk: NR, p=0.102
			Home exercise Baseline: 12.6 (2.9) 6, 12 wk: NR	**Dextrose prolotherapy vs. Home exercise** 6 wk: NR 12 wk: NR
				Difference in difference 6 wk: NR, p=0.588 12 wk: NR, p=0.102
	Physical performance ROM Active† 6, 12 wk	**Dextrose prolotherapy** Baseline: 126.0 (13.8) 6, 12 wk: NR	**Ozone** Baseline: 125.8 (10.0) 6, 12 wk: NR	**Dextrose prolotherapy vs. Ozone** 6 wk: NR 12 wk: NR
				Difference in difference 6 wk: NR, p=0.109 12 wk: NR, p=0.891
			Home exercise Baseline: 129.8 (10.6) 6, 12 wk:	**Dextrose prolotherapy vs. Home exercise** 6 wk: NR 12 wk: NR

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up P-value* Other results reported
				Difference in difference 6 wk: NR, p=0.109 12 wk: NR, p=0.006
	Physical performance ROM Passive† 6, 12 wk	**Dextrose prolotherapy** Baseline: 133.7 (10.8) 6, 12 wk: NR	**Ozone** Baseline: 132.9 (9.9) 6, 12 wk: NR	**Dextrose prolotherapy vs. Ozone** 6 wk: NR 12 wk: NR
				Difference in difference 6 wk: NR, p=0.291 12 wk: NR, p=0.172
			Home exercise Baseline: 136.3 (6.0) 6, 12 wk: NR	**Dextrose prolotherapy vs. Home exercise** 6 wk: NR 12 wk: NR
				Difference in difference 6 wk: NR, p=0.291 12 wk: NR, p=0.172
	Pain severity or intensity VAS Movement† 6, 12 wk	**Dextrose prolotherapy** Baseline: 7.9 (1.8) 6 wk: NR 12 wk: NR	**Ozone** Baseline: 9.8 (0.5) 6, 12 wk: NR	**Dextrose prolotherapy vs. Ozone** 6 wk NR 12 wk: NR
				Difference in difference 6 wk: NR, p<0.01 12 wk: NR, 0.003
			Home exercise Baseline: 8.2 (1.3) 6, 12 wk: NR	**Dextrose prolotherapy vs. Home exercise** 6 wk: NR 12 wk: NR
				Difference in difference 6 wk: NR, p=0.233 12 wk: NR, p=0.003
	Pain severity or intensity VAS Rest† 6, 12 wk	**Dextrose prolotherapy** Baseline: 5.1 (2.1) 6, 12 wk: NR	**Ozone** Baseline: 9.7 (0.6) 6, 12 wk: NR	**Dextrose prolotherapy vs. Ozone** 6 wk: NR 12 wk: NR

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up** **P-value*** **Other results reported**
				Difference in difference 6 wk: NR, p<0.01 12 wk: NR, p<0.01
			Home exercise Baseline: 5.8 (2.7) 6, 12 wk: NR	**Dextrose prolotherapy vs. Home exercise** 6 wk: NR 12 wk: NR
				Difference in difference 6 wk: NR, p=0.376 12 wk: NR, p=0.744
Ozturk, 2023[56] Some concerns	Pain-related functioning WOMAC Total 6, 12 wk	**20% DPT** Baseline: 58.9 (20.7) 6 wk: 34.4 (22) 12 wk: 31.9 (22.4)	**5% DPT** Baseline: 64.6 (17.4) 6 wk: 41.1 (20.3) 12 wk: 33.8 (19.7)	**5% DPT vs. 10% DPT** 6 wk: 7.4, p=NS 12 wk: 3.4, p=NS
				5% DPT vs. 20% DPT 6 wk: 6.7, p=NS 12 wk: 1.9, p=NS
			10% DPT Baseline: 49.6 (18.1) 6 wk: 33.7 (19.7) 12 wk: 30.4 (20.6)	**10% DPT vs. 20% DPT** 6 wk: -0.7, p=NS 12 wk: -1.5, p=NS
			Exercise Baseline: 60.8 (21.7) 6 wk: 53.7 (21.9) 12 wk: 48.3 (19.0)	**5% DPT vs. Exercise** 6 wk: -12.6, p=NS 12 wk: -14.5, p=0.003
				10% DPT vs. Exercise 6 wk: -20.0, p=0.001 12 wk: -17.9, p=0.003
				20% DPT vs. Exercise 6 wk: -19.3, p=0.001 12 wk: -16.4, p=0.003
	Pain severity WOMAC Pain 6, 12 wk	**20% DPT** Baseline: 11.8 (3.8) 6 wk: 6.0 (3.9) 12 wk: 5.8 (3.9)	**5% DPT** Baseline: 12.9 (3.8) 6 wk: 8.1 (4.3) 12 wk: 6.6 (4.6)	**5% DPT vs. 10% DPT** 6 wk: 1.6, p=NS 12 wk: 0.0, p=NS
				5% DPT vs. 20% DPT 6 wk: 2.1, p=NS 12 wk: 0.8, p=NS

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up P-value* Other results reported
			10% DPT Baseline: 11.4 (4.3) 6 wk: 6.5 (4.0) 12 wk: 6.6 (4.5)	**10% DPT vs. 20% DPT** 6 wk: 0.5, p=NS 12 wk: 0.8, p=NS
			Exercise Baseline: 11.6 (3.6) 6 wk: 10.0 (4.0) 12 wk: 8.9 (3.3)	**5% DPT vs. Exercise** 6 wk: -1.9, p=NS 12 wk: -2.3, p=NS
				10% DPT vs. Exercise 6 wk: -3.5, p=0.001 12 wk: -2.3, p=NS
				20% DPT vs. Exercise 6 wk: -4.0, p=0.001 12 wk: -3.1, p=0.028
	Pain-related functioning WOMAC Stiffness 6, 12 wk	**20% DPT** Baseline: 4.1 (2.3) 6 wk: 2.9 (2.2) 12 wk: 2.6 (2.1)	**5% DPT** Baseline: 4.7 (1.6) 6 wk: 2.7 (2.2) 12 wk: 3.0 (2.1)	**5% DPT vs. 10% DPT** 6 wk: 0.3, p=NS 12 wk: 0.5, p=NS
				5% DPT vs. 20% DPT 6 wk: -0.2, p=NS 12 wk: 0.4, p=NS
			10% DPT Baseline: 3.6 (1.9) 6 wk: 2.4 (1.6) 12 wk: 2.5 (2.0)	**10% DPT vs. 20% DPT** 6 wk: -0.5, p=NS 12 wk: -0.1, p=NS
			Exercise Baseline: 4.5 (1.9) 6 wk: 4.2 (2.1) 12 wk: 3.6 (1.7)	**5% DPT vs. Exercise** 6 wk: -1.5, p=0.007 12 wk: -0.6, p=NS
				10% DPT vs. Exercise 6 wk: -1.8, p=0.007 12 wk: -1.1, p=NS
				20% DPT vs. Exercise 3 mo: -1.3, p=NS 3 mo: -1.0, p=NS
	Pain-related functioning WOMAC Physical Function 6, 12 wk	**20% DPT** Baseline: 40.7 (14.7) 6 wk: 24.3 (15.6) 12 wk: 22.3 (15.9)	**5% DPT** Baseline: 44.4 (12.0) 6 wk: 28.7 (13.8) 12 wk: 22.8 (13.7)	**5% DPT vs. 10% DPT** 6 wk: 5.4, p=NS 12 wk: 2.5, p=NS
				5% DPT vs. 20% DPT

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up P-value* Other results reported
				6 wk: 4.4, p=NS 12 wk: 0.5, p=NS
			10% DPT Baseline: 33.3 (13.0) 6 wk: 23.3 (13.0) 12 wk: 20.3 (13.9)	**10% DPT vs. 20% DPT** 6 wk: -1.0, p=NS 12 wk: -2.0, p=NS
			Exercise Baseline: 42.3 (16.3) 6 wk: 37.3 (16.0) 12 wk: 34.0 (14.3)	**5% DPT vs. Exercise** 6 wk: -8.6, p=NS 12 wk: -11.2, p=0.001
				10% DPT vs. Exercise 6 wk: -14.0, p=0.001 12 wk: -13.7, p=0.001
				20% DPT vs. Exercise 6 wk: -13.0, p=0.001 12 wk: -11.7, p=0.001
	Physical performance TUG 6, 12 wk	**20% DPT** Baseline: 11.8 (2.4) 6 wk: 10.7 (2.1) 12 wk: 10.3 (2.2)	**5% DPT** Baseline: 12.4 (2.7) 6 wk: 11.5 (2.2) 12 wk: 11.2 (1.9)	**5% DPT vs. 10% DPT‡** 6 wk: 0.7, p=NS 12 wk: 0.4, p=NS
				5% DPT vs. 20% DPT‡ 6 wk: 0.8, p=NS 12 wk: 0.9, p=NS
			10% DPT Baseline: 11.7 (3.0) 6 wk: 10.8 (2.1) 12 wk: 10.8 (2.2)	**10% DPT vs. 20% DPT‡** 6 wk: 0.1, p=NS 12 wk: 0.5, p=NS
			Exercise Baseline: 12.1 (3.1) 6 wk: 11.4 (2.5) 12 wk: 11.6 (2.4)	**5% DPT vs. Exercise‡** 6 wk: 0.1, p=NS 12 wk: -0.4, p=NS
				10% DPT vs. Exercise‡ 6 wk: -0.6, p=NS 12 wk: -0.8, p=NS
				20% DPT vs. Exercise 6 wk: -0.7, p=NS 12 wk: -1.3, p=NS
	Physical performance Active flexion	**20% DPT** Baseline: 123.5 (16.7)	**5% DPT** Baseline: 118.7 (16.2)	**5% DPT vs. 10% DPT** 6 wk: -0.9, p=NS

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up P-value* Other results reported
	6, 12 wk	6 wk: 134.2 (10.1) 12 wk: 134.3 (9.8)	6 wk: 129.2 (11.2) 12 wk: 131.6 (10.9)	12 wk: -0.1, p=NS§
				5% DPT vs. 20% DPT 6 wk: -5.0, p=NS 12 wk: -2.7, p=NS§
			10% DPT Baseline: 118.3 (16.7) 6 wk: 130.1 (10.5) 12 wk: 131.7 (10.4)	**10% DPT vs. 20% DPT** 6 wk: -4.1, p=NS 12 wk: -2.6, p=NS§
			Exercise Baseline: 127.5 (10.7) 6 wk: 129.5 (8.4) 12 wk: 130.8 (7.9)	**5% DPT vs. Exercise** 6 wk: -0.3, p=NS 12 wk: 0.8, p=NS§
				10% DPT vs. Exercise 6 wk: 0.6*, p=NS 12 wk: 0.9, p=NS§
				20% DPT vs. Exercise 6 wk: 4.7, p=0.027 12 wk: 3.5, p=NS§
	Physical performance Passive flexion 6, 12 wk	**20% DPT** Baseline: 131.8 (13.1) 6 wk: 137.8 (8.4) 12 wk: 138.2 (6.8)	**5% DPT** Baseline: 132.1 (10.6) 6 wk: 135.8 (9.3) 12 wk: 136.5 (8.8)	**5% DPT vs. 10% DPT** 6 wk: 0.6, p=NS 12 wk: 0.8, p=NS
				5% DPT vs. 20% DPT 6 wk: -2.0, p=NS 12 wk: -1.7, p=NS
			10% DPT Baseline: 129.3 (11.7) 6 wk: 135.2 (8.3) 12 wk: 135.7 (8.7)	**10% DPT vs. 20% DPT** 6 wk: -2.6, p=NS 12 wk: -2.5, p=NS
			Exercise Baseline: 133.8 (7.0) 6 wk: 135.2 (5.1) 12 wk: 136.2 (4.7)	**5% DPT vs. Exercise** 6 wk: 0.6, p=NS 12 wk: 0.3, p=NS
				10% DPT vs. Exercise 6 wk: 0.0, p=NS 12 wk: -0.5, p=NS
				20% DPT vs. Exercise 6 wk: 2.6, p=0.022 12 wk: 2.0, p=0.039

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up P-value* Other results reported
	Health-related quality of life SF-36 Physical Score¶ 12 wk	**20% DPT** Baseline: NR 12 wk: NR	**5% DPT** Baseline: NR 12 wk: NR	**5% DPT vs. 10% DPT** 12 wk: NR, p=NR
				5% DPT vs. 20% DPT 12 wk: NR, p=NR
			10% DPT Baseline: NR 12 wk: NR	**10% DPT vs. 20% DPT** 12 wk: NR, p=NR
			Exercise Baseline: NR 12 wk: NR	**5% DPT vs. Exercise** 12 wk: NR, p=NR
				10% DPT vs. Exercise 12 wk: NR, p=NR
				20% DPT vs. Exercise 12 wk: NR, p=NR
	Health-related quality of life SF-36 Mental Score¶ 6, 12 wk	**20% DPT** Baseline: NR 12 wk: NR	**5% DPT** Baseline: NR 12 wk: NR	**5% DPT vs. 10% DPT** 12 wk: NR, p=NR
				5% DPT vs. 20% DPT 12 wk: NR, p=NR
			10% DPT Baseline: NR 12 wk: NR	**10% DPT vs. 20% DPT** 12 wk: NR, p=NR
			Exercise Baseline: NR 12 wk: NR	**5% DPT vs. Exercise** 12 wk: NR, p=NR
				10% DPT vs. Exercise 12 wk: NR, p=NR
				20% DPT vs. Exercise 12 wk: NR, p=NR
	Pain severity or intensity VAS Rest 6, 12 wk	**20% DPT** Baseline: 5.5 (2.7) 6 wk: 3.1 (2.0) 12 wk: 2.2 (1.6)	**5% DPT** Baseline: 6.8 (2.5) 6 wk: 4.4 (2.8) 12 wk: 3.6 (2.6)	**5% DPT vs. 10% DPT** 6 wk: 0.7, p=NS 12 wk: 0.6, p=NS
				5% DPT vs. 20% DPT 6 wk: 1.3, p=NS 12 wk: 1.4, p=NS
			10% DPT Baseline: 5.2 (1.8) 6 wk: 3.7 (2.5)	**10% DPT vs. 20% DPT** 6 wk: 0.6, p=NS 12 wk: 0.8, p=NS

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up** **P-value*** **Other results reported**
			12 wk: 3.0 (2.2)	
			Exercise Baseline: 6.2 (2.6) 6 wk: 5.5 (2.3) 12 wk: 4.8 (2.1)	**5% DPT vs. Exercise** 6 wk: -1.1, p=NS 12 wk: -1.2, p=NS
				10% DPT vs. Exercise 6 wk: -1.8, p=0.002 12 wk: -1.8, p<0.001
				20% DPT vs. Exercise 6 wk: -2.4, p=0.002 12 wk: -2.6, p<0.001
	Pain severity or intensity VAS Activity 6 wk	**20% DPT** Baseline: 7.8 (2.1) 6 wk: 4.2 (2.2) 12 wk: 3.6 (2.6)	**5% DPT** Baseline: 8.6 (1.6) 6 wk: 5.4 (2.7) 12 wk: 5.1 (2.9)	**5% DPT vs. 10% DPT** 6 wk: 0.4, p=NS 12 wk: 1.4, p=NS
				5% DPT vs. 20% DPT 6 wk: 1.2, p=NS 12 wk: 1.5, p=NS
			10% DPT Baseline: 7.0 (2.6) 6 wk: 5.0 (2.6) 12 wk: 3.7 (2.5)	**10% DPT vs. 20% DPT** 6 wk: 0.8, p=NS 12 wk: 0.1, p=NS
			Exercise Baseline: 8.2 (1.6) 6 wk: 6.8 (2.0) 12 wk: 6.4 (1.7)	**5% DPT vs. Exercise** 6 wk: -1.4, p=NS 12 wk: -1.3, p=NS
				10% DPT vs. Exercise 6 wk: -1.8, p<0.001 12 wk: -2.7, p=0.007
				20% DPT vs. **Exercise** 6 wk: -2.6, p<0.001 12 wk: -2.8, p=0.007
	Adverse Events Post-injection side effects (pain, swelling, and/or color change) 12 wk	**20% DPT** 33% (n=10)	**5% DPT** 33% (n=7)	**5% DPT vs. 10% DPT:** 13% **5% DPT vs. 20% DPT:** 0 **10% DPT vs. 20% DPT:** -13%
			10% DPT 20% (n=6)	
			Exercise NA	

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up** **P-value*** **Other results reported**
Yildiz, 2023[62] High	Pain-related functioning WOMAC Total 1, 3 mo	**Dextrose prolotherapy** Baseline: 59.8 (11.2) 1 mo: 55.8 (11.4) 3 mo: 51.9 (11.1)	**Conventional physiotherapy** Baseline: 60.7 (10.5) 1 mo: 58.2 (10.8) 3 mo: 55.9 (10.8)	**Dextrose prolotherapy vs. Conventional physiotherapy** 1 mo: -2.4, p=0.398 3 mo: -4.0, p=0.164
	Physical performance Knee ROM 1, 3 mo	**Dextrose prolotherapy** Baseline: 123.3 (3.8) 1 mo: 124.4 (3.7) 3 mo: 126.2 (3.5)	**Conventional physiotherapy** Baseline: 123.5 (3.4) 1 mo: 124.5 (3.4) 3 mo: 125.6 (3.5)	**Dextrose prolotherapy vs. Conventional physiotherapy** 1 mo: -0.1, p=0.942 3 mo: 0.6, p=0.508
	Physical performance 50-m walking test (sec) 1, 3 mo	**Dextrose prolotherapy** Baseline: 52.3 (6.3) 1 mo: 49.6 (6.1) 3 mo: 47 (6.2)	**Conventional physiotherapy** Baseline: 54.1 (6.8) 1 mo: 52.1 (6.8) 3 mo: 50.4 (6.8)	**Dextrose prolotherapy vs. Conventional physiotherapy** 1 mo: -2.5, p=0.137 3 mo: -3.4, p=0.046
	Physical performance Extensor PT 60 degrees/sec 1, 3 mo	**Dextrose prolotherapy** Baseline: 43.4 (16.6) 1 mo: 53.1 (17.1) 3 mo: 63.2 (16.8)	**Conventional physiotherapy** Baseline: 39.6 (17.5) 1 mo: 46.7 (18.4) 3 mo: 54.7 (16.9)	**Dextrose prolotherapy vs. Conventional physiotherapy** 1 mo: 6.4, p=0.167 3 mo: 8.5, p=0.056
	Physical performance Extensor PT 180 degrees/sec 1, 3 mo	**Dextrose prolotherapy** Baseline: 29.3 (9.3) 1 mo: 37.3 (9.2) 3 mo: 47.7 (10.6)	**Conventional physiotherapy** Baseline: 30.3 (10.7) 1 mo: 39.57 (12.3) 3 mo: 46.0 (11.9)	**Dextrose prolotherapy vs. Conventional physiotherapy** 1 mo: -2.3, p=0.424 3 mo: 1.7, p=0.561
	Physical performance Flexor PT 60 degrees/sec 1, 3 mo	**Dextrose prolotherapy** Baseline: 17.6 (10.3) 1 mo: 23.7 (11.8) 3 mo: 32.3 (15.4)	**Conventional physiotherapy** Baseline: 21.9 (13.0) 1 mo: 28.5 (15.99) 3 mo: 37.0 (21.0)	**Dextrose prolotherapy vs. Conventional physiotherapy** 1 mo: -4.8, p=0.195 3 mo: -4.7, p=0.324
	Physical performance Flexor PT 180 degrees/sec 1, 3 mo	**Dextrose prolotherapy** Baseline: 11.7 (6.8) 1 mo: 17.7 (7.4) 3 mo: 25.8 (10.1)	**Conventional physiotherapy** Baseline: 19.9 (9.6) 1 mo: 28.8 (12.6) 3 mo: 35.3 (15.2)	**Dextrose prolotherapy vs. Conventional physiotherapy** 1 mo: -11.1, p=0.001 3 mo: -9.5, p=0.006
	Pain severity or intensity VAS 1, 3 mo	**Dextrose prolotherapy** Baseline: 7.3 (1.3) 1 mo: 4.5 (1.8) 3 mo: 2.4 (1.9)	**Conventional physiotherapy** Baseline: 7.2 (1.4) 1 mo: 5.6 (1.2) 3 mo: 4.4 (1)	**Dextrose prolotherapy vs. Conventional physiotherapy** 1 mo: -1.1, p=0.006 3 mo: -2.0, p=0.001
Dumais, 2012[61] High	Pain-related functioning WOMAC Total‡ 16 wk	**Dextrose prolotherapy** Baseline: 44.4 (13.7) 16 wk: NR	**Physical therapy** Baseline: 36.2 (16.8) 16 wk: NR	**Dextrose prolotherapy vs. Physical therapy** 16 wk: NR

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up P-value* Other results reported
				Difference in difference 16 wk: NR, p=0.002
	Pain-related functioning WOMAC Physical Function‡ 16 wk	**Dextrose prolotherapy** Baseline: 33.6 (10.7) 16 wk: NR	**Physical therapy** Baseline: 26.8 (12.8) 16 wk: NR	**Dextrose prolotherapy vs. Physical therapy** 16 wk: NR **Difference in difference** 16 wk: NR, p=0.004
	Pain-related functioning WOMAC Stiffness‡ 16 wk	**Dextrose prolotherapy** Baseline: 4.1 (1.7) 16 wk: NR	**Physical therapy** Baseline: 3.5 (1.5) 16 wk: NR	**Dextrose prolotherapy vs. Physical therapy** 16 wk: NR **Difference in difference** 16 wk: NR, p=0.02
	Pain-related functioning WOMAC Pain‡ 16 wk	**Dextrose prolotherapy** Baseline: 9.5 (2.9) 16 wk: NR	**Physical therapy** Baseline: 8.7 (4.0) 16 wk: NR	**Dextrose prolotherapy vs. Physical therapy** 16 wk: NR **Difference in difference** 16 wk: NR, p=0.01
	Physical performance TUG† 16 wk	**Dextrose prolotherapy** Baseline: NR 16 wk: NR	**Physical therapy** Baseline: NR 16 wk: NR	**Dextrose prolotherapy vs. Physical therapy** 16 wk: NR **Difference in difference** 16 wk: NR, p=0.89
	Pain severity or intensity VAS 16 wk	**Dextrose prolotherapy** Baseline: 48.6 (21.8) 16 wk: NR	**Physical therapy** Baseline: 38.3 (24.8) 16 wk: NR	**Dextrose prolotherapy vs. Physical therapy** 16 wk: NR **Difference in difference** 16 wk: NR, p=0.03
	Pain severity or intensity BPI Pain Intensity 16 wk	**Dextrose prolotherapy** Baseline: 4.1 (2.2) 16 wk: NR	**Physical therapy** Baseline: 4.1 (1.9) 16 wk: NR	**Dextrose prolotherapy vs. Physical therapy** 16 wk: NR **Difference in difference** 16 wk: NR, p=0.32

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up** **P-value*** **Other results reported**
	BPI Functional Impairment 16 wk	**Dextrose prolotherapy** Baseline: 4.0 (2.5) 16 wk: NR	**Physical therapy** Baseline: 3.2 (1.8) 16 wk: NR	**Dextrose prolotherapy vs. Physical therapy** 16 wk: NR **Difference in difference** 16 wk: NR, p=0.12
	Adverse Events 32 wk	*"[Prolotherapy] was ceased as a precautionary measure in one participant …after reports of diffuse edema of both legs"*		
Rabago, 2013[63] Some concerns	Pain-related functioning Modified WOMAC Total 5, 9, 12, 24, 52 wk	**Dextrose prolotherapy**[#] Baseline: 63.1 (15.0) 5 wk: 71.2 9 wk: 77.1 12 wk: 76.5 24 wk: 79.1 52 wk: 78.6	**Saline**[#] Baseline: 62.7 (14.3) 5 wk: 68.2 9 wk: 70.0 12 wk: 70.9 24 wk: 71.0 52 wk: 70.5	**Dextrose prolotherapy vs. Saline** 5 wk: 3.0 9 wk: 7.1 12 wk: 5.6 24 wk: 8.1 52 wk: 8. **Difference in difference:** 5 wk: NR, p=NS 12 wk: NR, p=NS 9, 24, 52 wk: NR, p<0.05
			Exercise[#] Baseline: 60.5 (11.3) 5 wk: 65.0 9 wk: 63.2 12 wk: 64.8 24 wk: 69.1 52 wk: 68.9	**Dextrose prolotherapy vs. Exercise** 5 wk: 6.2 9 wk: 13.9 12 wk: 11.7 24 wk: 10.0 52 wk: 9.7 **Difference in difference:** 5 wk: NR, p=NS 9, 12, 24, 52 wk: NR, p<0.05
	Pain severity or intensity Modified WOMAC Pain 5, 9, 12, 24, 52 wk	**Dextrose prolotherapy** Baseline: 66.8 (14.9) 5, 9, 12, 24, 52 wk: NR	**Saline** Baseline: 66.7 (16.1) 5, 9, 12, 24, 52 wk: NR	**Dextrose prolotherapy vs. Saline** 5, 9, 12, 24, 52 wk: NR **Difference in difference:** 5, 12, 52 wk: NR, p=NR 9 wk, 24 wk: NR, p<.05
			Exercise Baseline: 63.2 (13.1) 5, 9, 12, 24, 52 wk: NR	**Dextrose prolotherapy vs. Exercise** 5, 9, 12, 24, 52 wk: NR

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up P-value* Other results reported
				Difference in difference: 5, 52 wk: NR, p=NS 9, 12, 24 wk: NR, p<0.05
	Pain-related functioning Modified WOMAC Stiffness 5, 9, 12, 24, 52 wk	**Dextrose prolotherapy** Baseline: 57.1 (15.0) 5, 9, 12, 24, 52 wk: NR	**Saline** Baseline: 53.9 (14.3) 5, 9, 12, 24, 52 wk: NR	**Dextrose prolotherapy vs. Saline** 5, 9, 12, 24, 52 wk: NR
				Difference in difference: 5, 12, 24, 52 wk: NR, p=NS 9 wk: NR, p=<.05
			Exercise Baseline: 55.3 (11.3) 5, 9, 12, 24, 52 wk: NR	**Dextrose prolotherapy vs. Exercise** 5, 9, 12, 24, 52 wk: NR
				Difference in difference: 5, 9, 24, 52 wk: NR, p=NS 12 wk: NR, p<0.05
	Pain-related functioning Modified WOMAC Physical Function 5, 9, 12, 24, 52 wk	**Dextrose prolotherapy** Baseline: 65.2 (15.8) 5, 9, 12, 24, 52 wk: NR	**Saline** Baseline: 67.6 (17.5) 5, 9, 12, 24, 52 wk: NR	**Dextrose prolotherapy vs. Saline** 5, 9, 12, 24, 52 wk: NR
				Difference in difference: 5 wk NR, p=NS 9, 12, 24, 52 wk: NR, p<0.05
			Exercise Baseline: 61.9 (12.7) 5, 9, 12, 24, 52 wk: NR	**Dextrose prolotherapy vs. Exercise** 5, 9, 12, 24, 52 wk: NR
				Difference in difference: 5 wk: NR, p=NS 9, 12, 24, 52 wk: NR, p<0.05
	Pain severity or intensity Knee Pain Scale Severity 5, 9, 12, 24, 52 wk	**Dextrose prolotherapy** Baseline: 1.8 (0.8) 5, 9, 12, 24, 52 wk: NR	**Saline** Baseline: 1.7 (0.7) 5, 9, 12, 24, 52 wk: NR	**Dextrose prolotherapy vs. Saline** 5, 9, 12, 24, 52 wk: NR
				Difference in difference: 5, 9, 12 wk: NR, p=NS 24, 52 wk: NR, p<0.05
			Exercise Baseline: 1.7 (0.8) 5, 9, 12, 24, 52 wk: NR	**Dextrose prolotherapy vs. Exercise** 5, 9, 12, 24, 52 wk: NR
				Difference in difference:

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up** **P-value*** **Other results reported**
				5, 9, 12 wk: NR, p=NS 24, 52 wk: NR, p<0.05
	Adverse Events 52 wk	*"There were no adverse even"s."* (AE not defined)		
Soliman, 2016[57] Serious	Pain-related functioning WOMAC 12 mo	**Hackett + Lyftogt prolotherapy** Baseline: NR 12 mo: 11.3 (10.3)	**Hackett prolotherapy** Baseline: NR 12 mo: 18.5 (10.3)	**Hackett + Lyftogt prolotherapy vs. Hackett prolotherapy** 12 mo: -7.2, p=NR
			Exercise Baseline: NR 12 mo: 79.5 (22.6)	**Hackett + Lyftogt prolotherapy vs. Exercise** 12 mo: -68.2, p=NR
				Hackett vs. Exercise 12 mo: -61.0, p=NR
	Pain severity or intensity VAS 12 mo	**Hackett + Lyftogt prolotherapy** Baseline: NR 12 mo: 0.3 (0.3)	**Hackett prolotherapy** Baseline: NR 12 mo: 0.4 (0.5)	**Hackett + Lyftogt prolotherapy** vs. **Hackett prolotherapy** 12 mo: -0.1, p=NR
			Exercise Baseline: NR 12 mo: 9.9 (1.7)	**Hackett + Lyftogt prolotherapy vs. Exercise** 12 mo: -9.6, p=NR
				Hackett vs. Exercise 12 mo: -9.5, p=NR
	Adverse Events 12 mo	*"There were no adverse events"* (AE not defined).		
Sert, 2020[59] High	Pain-related functioning WOMAC Total 6, 18 wk	**Dextrose prolotherapy** Baseline: 68.7 (11.4) 6 wk: 44.4 (11.5) 18 wk: 32.7 (11.6)	**Saline** Baseline: 69.2 (17.6) 6 wk: 50.5 (16.7) 18 wk: 46.7 (13.5)	**Dextrose prolotherapy vs. Saline** 6 wk: -6.1, p=0.118 18 wk: -14.0, p=0.002
			Home Exercise Baseline: 68.9 (11.9) 6 wk: 61.0 (10.8) 18 wk: 59.8 (10.7)	**Dextrose prolotherapy vs. Home Exercise** 6 wk: -16.6, p=<0.001 18 wk: -27.1, p=<0.001
	Pain-related functioning WOMAC Pain 6, 18 wk	**Dextrose prolotherapy** Baseline: 13.7 (3.0) 6 wk: 9.0 (2.6) 18 wk: 6.4 (2.6)	**Saline** Baseline: 12.9 (3.2) 6 wk: 9.7 (3.8) 18 wk: 9.4 (3.4)	**Dextrose prolotherapy vs. Saline** 6 wk: -0.7, p=0.046 18 wk: -3.0, p=0.002
			Home Exercise Baseline: 14.4 (3.4)	**Dextrose prolotherapy vs. Home Exercise**

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up P-value* Other results reported
			6 wk: 11.7 (2.9) 18 wk: 11.4 (2.6)	6 wk: -2.7, p=0.006 18 wk: -5.0, p=<0.001
	Pain-related functioning WOMAC Stiffness 6, 18 wk	**Dextrose prolotherapy** Baseline: 5.4 (1.1) 6 wk: 3.7 (1.5) 18 wk: 2.7 (1.2)	**Saline** Baseline: 5.9 (1.5) 6 wk: 4.0 (1.8) 18 wk: 3.9 (1.6)	**Dextrose prolotherapy vs. Saline** 6 wk: -0.3, p=NS** 18 wk: -1.2, p=0.204
			Home Exercise Baseline: 5.4 (1.6) 6 wk: 4.4 (1.4) 18 wk: 4.2 (1.1)	**Dextrose prolotherapy vs. Home Exercise** 6 wk: -0.7, p=NS** 18 wk: -1.5, p=0.001
	Pain-related functioning WOMAC Physical Function 6, 18 wk	**Dextrose prolotherapy** Baseline: 49.0 (7.9) 6 wk: 31.5 (8.6) 18 wk: 23.5 (8.1)	**Saline** Baseline: 50.1 (13.4) 6 wk: 36.5 (11.6) 18 wk: 34.0 (10.8)	**Dextrose prolotherapy vs. Saline** 6 wk: -5.0, p=0.142 18 wk: -10.5, p=<0.001
			Home Exercise Baseline: 49.0 (8.2) 6 wk: 44.8 (8.8) 18 wk: 44.0 (8.5)	**Dextrose prolotherapy vs. Home Exercise** 6 wk: -13.3, p=<0.001 18 wk: -20.5, p=<0.001
	Health-related quality of life SF-36 Physical Score 6, 18 wk	**Dextrose prolotherapy** Baseline: 34.1 (8.9) 6 wk: 41.2 (8.9) 18 wk: 48.5 (7.5)	**Saline** Baseline: 30.0 (7.4) 6 wk: 37.0 (10.1) 18 wk: 39.6 (8.5)	**Dextrose prolotherapy vs. Saline** 6 wk: 4.2, p=NS†† 18 wk: 8.9, p=0.124
			Home Exercise Baseline: 35.0 (9.3) 6 wk: 41.2 (10.4) 18 wk: 41.1 (11.7)	**Dextrose prolotherapy vs. HomeExercise** 6 wk: 0.0, p=NS†† 18 wk: 7.4, p=0.016
	Health-related quality of life SF-36 Mental Score 6, 18 wk	**Dextrose prolotherapy** Baseline: 45.4 (10.9) 6 wk: 52.7 (9.1) 18 wk: 53.5 (6.8)	**Saline** Baseline: 46.6 (13.0) 6 wk: 48.7 (11.9) 18 wk: 52.0 (7.7)	**Dextrose prolotherapy vs. Saline‡‡** 6 wk: 4.0, p=NS 18 wk: 1.5, p=NS
			Home Exercise Baseline: 44.1 (8.7) 6 wk: 45.9 (10.0) 18 wk: 49.6 (10.9)	**Dextrose prolotherapy vs. Home Exercise‡‡** 6 wk: 6.8, p=NS 18 wk: 3.9, p=NS
	Pain severity or intensity VAS Pain Activity	**Dextrose prolotherapy** Baseline: 7.2 (1.0)	**Saline** Baseline: 7.4 (2.0)	**Dextrose prolotherapy vs. Saline** 6 wk: -0.8, p=NR§§

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up P-value* Other results reported
	6, 18 wk	6 wk: 4.1 (1.8) 18 wk: 1.1 (1.9)	6 wk: 4.9 (2.2) 18 wk: 4.6 (1.8)	18 wk: -3.5, p=<0.001
			Home Exercise Baseline: 7.0 (0.9) 6 wk: 4.9 (2.0) 18 wk: 4.5 (2.0)	**Dextrose prolotherapy vs. Home Exercise**[§§] 6 wk: -0.8, p=NR 18 wk: -3.4, p=<0.001
Dextrose prolotherapy vs. Other Comparators				
Bayat, 2023[60] High	Pain-related functioning WOMAC Total[‡] 1, 3 mo	**Dextrose prolotherapy** Baseline: 43.0 (6.3) 1 mo: NR 3 mo: NR	**Triamcinolone corticosteroid** Baseline: 41.8 (7.9) 1 mo: NR 3 mo: NR	**Dextrose prolotherapy vs. Triamcinolone corticosteroid** 1 mo: NR 3 mo: NR
				Difference in difference 1 mo: 2.02, 95% CI (-1.5, 5.6), p=0.262 3 mo: -9.64, 95% CI (-12.0, -6.2), p<0.001
	Pain-related functioning WOMAC Pain 1, 3 mo	**Dextrose prolotherapy** Baseline: 9.8 (1.4) 1 mo: NR 3 mo: NR	**Triamcinolone corticosteroid** Baseline: 9.2 (1.6) 1 mo: NR 3 mo: NR	**Dextrose prolotherapy vs. Triamcinolone corticosteroid** 1 mo: NR 3 mo: NR
				Difference in difference 1 mo: 0.9, 95% CI (0.06, 1.7), p= 0.048 3 mo: -2.95, 95% CI (-3.6, -2.0), p<0.001
	Pain-related functioning WOMAC Stiffness 1, 3 mo	**Dextrose prolotherapy** Baseline: 2.96 (0.8) 1 mo: NR 3 mo: NR	**Triamcinolone corticosteroid** Baseline: 2.6 (1.2) 1 mo: NR 3 mo: NR	**Dextrose prolotherapy vs. Triamcinolone corticosteroid** 1 mo: NR 3 mo: NR
				Difference in difference 1 mo: -0.1, 95% CI (-0.06, 0.3), p=0.560 3 mo: -0.8, 95% CI (-1.2, -0.3), p=0.001
	Pain-related functioning WOMAC Physical Function 1, 3 mo	**Dextrose prolotherapy** Baseline: 30.3 (5.3) 1 mo: NR 3 mo: NR	**Triamcinolone corticosteroid** Baseline: 30.2 (5.2) 1 mo: NR 3 mo: NR	**Dextrose prolotherapy vs. Triamcinolone corticosteroid** 1 mo: NR 3 mo: NR
				Difference in difference 1 mo: 1.75, 95% CI (1.04, 4.56), p=0.219

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up P-value* Other results reported
				3 mo: -6.9, 95% CI (-6.5, -2.2), p<0.001
	Pain severity or intensity VAS 1, 3 mo	**Dextrose prolotherapy** Baseline: 7.7 (1.1) 1 mo: NR 3 mo: NR	**Triamcinolone corticosteroid** Baseline: 7.9 (1.1) 1 mo: NR 3 mo: NR	**Dextrose prolotherapy vs. Triamcinolone corticosteroid** 1 mo: NR 3 mo: NR **Difference in difference** 1 mo: 0.9 95% CI (0.06, 1.7), p=0.048 3 mo: -2.95, 95% CI (-3.6, -2.0), p<0.001
Waluyo, 2021[64] High	Pain-related functioning WOMAC Total 12 wk	**Dextrose prolotherapy** Baseline: 36.08 (10.06) 12 wk: 19.15 (12.04)	**Hyaluronic acid** Baseline: 24.81 (17.25) 12 wk: 15.86 (14.78)	**Dextrose prolotherapy vs. Hyaluronic acid** 12 wk: 3.3, p=0.801
	Pain-related functioning WOMAC Pain 12 wk	**Dextrose prolotherapy** Baseline: 7.15 (3.09) 12 wk: 3.04 (2.76)	**Hyaluronic acid** Baseline: 4.90 (2.93) 12 wk: 3.19 (3.04)	**Dextrose prolotherapy vs. Hyaluronic acid** 12 wk: -0.1, p=0.076
	Pain-related functioning WOMAC Stiffness 12 wk	**Dextrose prolotherapy** Baseline: 3.08 (2.24) 12 wk: 1.50 (1.44)	**Hyaluronic acid** Baseline: 2.52 (1.83) 12 wk: 1.10 (1.22)	**Dextrose prolotherapy vs. Hyaluronic acid** 12 wk: 0.4, p=0.761
	Pain-related functioning WOMAC Physical Function 12 wk	**Dextrose prolotherapy** Baseline: 25.85 (7.88) 12 wk: 14.62 (9.65)	**Hyaluronic acid** Baseline: 17.38 (15.99) 12 wk: 11.57 (11.64)	**Dextrose prolotherapy vs. Hyaluronic acid** 12 wk: 3.0, p=0.850
	Pain severity or intensity NRS Pain 12 wk	**Dextrose prolotherapy** Baseline: 4.85 (1.71) 12 wk: 1.46 (1.3)	**Hyaluronic acid** Baseline: 3.48 (1.53) 12 wk: 1.86 (1.52)	**Dextrose prolotherapy vs. Hyaluronic acid** 12 wk: -0.4, p=0.042
	Adverse Events 12 wk	"*All participants experienced expected mild-to moderate post-injection pain within 2–3 days. Only one participant, from the prolotherapy group, took paracetamol due to a painful knee post-injection. There were no other side-effects or adverse events.*" (AE not defined)		

Notes. *Mean differences calculated by review team; p-values reported by study (otherwise NR).
†Means at follow-up time points were not reported (only change scores were provided).
‡Authors report p-value=0.399 at 6-week and p-value=0.154 at 12-week follow-up comparison across all arms.
§Authors report p-value=0.154 at 12-week follow-up comparison across all arms.
¶Physical and mental health summary scores were not reported (only individual domain scores were provided).
#Mean scores at follow-up time points abstracted by review team using plot digitizer from Figure 2.
**Authors report p-value=0.238 at 6-week follow-up for comparison across all arms.
†† Authors report p-value=0.594 at 6-week follow-up across all arms.
‡‡ Authors report p-value=0.238 at 6-week follow-up and p-value=0.599 at 12-week follow-up across all arms.

§§ Authors report p-value=0.178 at 6-week follow-up across all arms.

Symbols. ↑: At specified follow-up time point, the dextrose arm had a better scale score than the comparator arm (meeting MCID); ↔: At specified follow-up time point, the difference in scale scores between the dextrose and comparator arms did not meet MCID; ↓: At specified follow-up time point, the dextrose arm had a worse scale score than the comparator arm (meeting MCID); ?: Review team was unable to interpret scale scores.

Abbreviations. ACR=American College of Rheumatology; ADD=anterior displacement difference; ADL=activities of daily living; AE=adverse event; BMI=body mass index; BPI=brief pain inventory; DPT=dextrose prolotherapy; EuroQoL-5D=European Quality of Life-5 dimensions; HA=hyaluronic acid; KL= Kellgren-Lawrence; KOOS=Knee Injury and Osteoarthritis Outcome Score; mg=milligrams; mL=milliliters; mo=month; NR=not reported; NS=not significant; OA=osteoarthritis; OKS=Oxford Knee Score; PRP=platelet-rich plasma; PT=physical therapy; QoL=quality of life; RoB=risk of bias; RCT=randomized controlled trial; ROM=range of motion; SD=standard deviation; SF-36=36-item Short Form health survey; TENS=Transcutaneous electrical nerve stimulation; TUG=timed up and go; VAS=Visual Analog Scale; wk=week; WOMAC=Western Ontario and McMaster Universities Arthritis Index.

Appendix Table 5. Detailed Results for Eligible Knee Osteoarthritis Studies: Intra-Articular or Extra-Articular Dextrose Injections

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, p-value*** **Other results reported**
Intra-articular Dextrose prolotherapy vs. Normal Saline or Water (with Local Anesthetic or Hyaluronic acid)				
Hsieh, 2022[43] Low	Pain-related functioning WOMAC Function 1 wk 1, 3, 6 mo	**Dextrose prolotherapy + HA** Baseline: 523.5 (318.1) 1 wk: 512.8 (303.9) 1 mo: 491.9 (287.2) 3 mo: 415.6 (299.6) 6 mo: 529.8 (292.7)	**Saline + HA** Baseline: 513.5 (326.8) 1 wk: 500.8 (330.0) 1 mo: 495.8 (295.5) 3 mo: 434.3 (301.2) 6 mo: 540.9 (298.2)	**Dextrose prolotherapy + HA** vs. **Saline + HA** 1 wk: 12.0 1 mo: -3.9 3 mo: -18.7 6 mo: -11.1 Group x Time p=0.003†
	Pain severity or intensity WOMAC Pain 1 wk 1, 3, 6 mo	**Dextrose prolotherapy + HA** Baseline: 230.8 (97.9) 1 wk: 214.7 (85.1) 1 mo: 194.7 (94.4) 3 mo: 186.6 (92.1) 6 mo: 180.3 (77.9)	**Saline + HA** Baseline: 216.9 (89.4) 1 wk: 205.8 (95.9) 1 mo: 192.4 (76.9) 3 mo: 200.6 (93.4) 6 mo: 199.6 (91.9)	**Dextrose prolotherapy + HA** vs. **Saline + HA** 1 wk: 8.9 1 mo: 2.3 3 mo: -14.0 6 mo: -19.3 Group x Time p=0.287†
	Pain-related functioning WOMAC Stiffness 1 wk 1, 3, 6 mo	**Dextrose prolotherapy + HA** Baseline: 100.4 (40.6) 1 wk: 90.1 (44.6) 1 mo: 91.0 (45.3) 3 mo: 82.2 (41.5) 6 mo: 90.6 (40.6)	**Saline + HA** Baseline: 105.2 (39.6) 1 wk: 91.6 (40.6) 1 mo: 90.3 (40.8) 3 mo: 85.8 (39.8) 6 mo: 97.8 (42.8)	**Dextrose prolotherapy + HA** vs. **Saline + HA** 1 wk: -1.5 1 mo: 0.7 3 mo: -3.6 6 mo: -7.2 Group x Time p<0.001†
	Pain-related functioning KOOS ADL 1 wk 1, 3, 6 mo	**Dextrose prolotherapy + HA** Baseline: 45.5 (19.2) 1 wk: 50.0 (15.8) 1 mo: 48.5 (18.6) 3 mo: 46.5 (18.0) 6 mo: 44.6 (19.7)	**Saline + HA** Baseline: 39.2 (18.4) 1 wk: 40.5 (15.5) 1 mo: 46.0 (15.4) 3 mo: 44.6 (19.5) 6 mo: 40.3 (15.1)	**Dextrose prolotherapy + HA** vs. **Saline + HA** 1 wk: 9.5 1 mo: 2.5 3 mo: 1.9 6 mo: 4.3 Group x Time p=0.242†
	Pain-related functioning KOOS Sports and recreation	**Dextrose prolotherapy + HA** Baseline: 19.5 (15.5)	**Saline + HA** Baseline: 18.8 (13.9)	**Dextrose prolotherapy + HA** vs. **Saline + HA**

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, p-value*** **Other results reported**
	1 wk 1, 3, 6 mo	1 wk: 21.6 (14.0) 1 mo: 25.5 (15.4) 3 mo: 30.1 (13.5) 6 mo: 25.4 (15.0)	1 wk: 19.5 (15.1) 1 mo: 21.0 (14.2) 3 mo: 24.2 (15.6) 6 mo: 25.5 (13.4)	1 wk: 2.1 1 mo: 4.5 3 mo: 5.9 6 mo: -0.1 Group x Time p=0.059†
	Pain-related functioning KOOS QoL 1 wk 1, 3, 6 mo	**Dextrose prolotherapy + HA** Baseline: 20.7 (17.2) 1 wk: 22.5 (17.5) 1 mo: 23.0 (16.9) 3 mo: 26.5 (15.4) 6 mo: 24.5 (16.0)	**Saline + HA** Baseline: 19.0 (18.2) 1 wk: 19.5 (17.9) 1 mo: 21.6 (16.8) 3 mo: 23.0 (15.9) 6 mo: 22.5 (19.1)	**Dextrose prolotherapy + HA** vs. **Saline + HA** 1 wk: 3.0 1 mo: 1.4 3 mo: 3.5 6 mo: 2.0 Group x Time p=0.012†
	Pain-related functioning KOOS Pain 1 wk 1, 3, 6 mo	**Dextrose prolotherapy + HA** Baseline: 40.9 (16.5) 1 wk: 45.9 (17.4) 1 mo: 50.8 (18.2) 3 mo: 48.3 (17.5) 6 mo: 47.4 (19.5)	**Saline + HA** Baseline: 42.5 (19.5) 1 wk: 45.6 (19.0) 1 mo: 49.5 (17.4) 3 mo: 46.2 (18.5) 6 mo: 43.8 (20.5)	**Dextrose prolotherapy + HA** vs. **Saline + HA** 1 wk: 0.3 1 mo: 1.3 3 mo: 2.1 6 mo: 3.6 Group x Time p=0.035†
	Pain-related functioning KOOS Other symptoms 1 wk 1, 3, 6 mo	**Dextrose prolotherapy + HA** Baseline: 38.5 (16.2) 1 wk: 40.9 (17.5) 1 mo: 43.6 (17.0) 3 mo: 44.3 (18.5) 6 mo: 40.5 (18.0)	**Saline + HA** Baseline: 37.5 (20.0) 1 wk: 38.4 (19.5) 1 mo: 40.1 (18.6) 3 mo: 42.3 (18.5) 6 mo: 39.5 (19.5)	**Dextrose prolotherapy + HA** vs. **Saline + HA** 1 wk: 2.5 1 mo: 3.5 3 mo: 2.0 6 mo: 1.0 Group x Time p=0.022†
	Physical perfromance Regular walking speed (m/s) 1 wk 1, 3, 6 mo	**Dextrose prolotherapy + HA** Baseline: 0.89 (0.32) 1 wk: 0.94 (0.27) 1 mo: 0.98 (0.37) 3 mo: 0.99 (0.46) 6 mo: 0.95 (0.42)	**Saline + HA** Baseline: 0.92 (0.37) 1 wk: 0.95 (0.38) 1 mo: 1.0 (0.40) 3 mo: 0.98 (0.39) 6 mo: 0.94 (0.38)	**Dextrose prolotherapy + HA** vs. **Saline + HA** 1 wk: 0.0*, p=.005 1 mo: 0.0*, p=.340 3 mo: 0.0*, p=.001 6 mo: 0.0*, p<.001 Group x Time p=0.001†

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, p-value*** **Other results reported**
	Physical perfromance Chair stand test (s) 1 wk 1, 3, 6 mo	**Dextrose prolotherapy + HA** Baseline: 20.5 (12.6) 1 wk: 19.0 (10.5) 1 mo: 18.0 (11.1) 3 mo: 18.1 (10.6) 6 mo: 19.2 (12.5)	**Saline + HA** Baseline: 21.4 (12.4) 1 wk: 21.0 (11.5) 1 mo: 19.4 (10.3) 3 mo: 18.7 (11.3) 6 mo: 19.5 (11.0)	**Dextrose prolotherapy + HA** vs. **Saline + HA** 1 wk: -2.0, p<0.001 1 mo: -1.4 3 mo: -0.6 6 mo: -0.3 Group x Time p=0.038[†]
	Adverse events 6 mo	*"One participant in the control group had local swelling after the third injection…No severe adverse effects occurred for both treatments"* (severe AE not defined)		
Reeves, 2000[44] High	Physical perfromance Flexion range 6 mo	**Dextrose prolotherapy** Baseline: 112.4 (19.5) 6 mo: 125.6 (8.6)	**Lidocaine** Baseline: 117.8 (11.3) 6 mo: 125.4 (7.5)	**Dextrose prolotherapy** vs. **Lidocaine** 6 mo: 0.2
	Pain severity or intensity VAS Pain at rest 6 mo	**Dextrose prolotherapy** Baseline: 2.15 (2.2) 6 mo: 1.6 (1.7)	**Lidocaine** Baseline: 2.7 (2.0) 6 mo: 1.7 (1.7)	**Dextrose prolotherapy** vs. **Lidocaine** 6 mo: -0.1
	Pain severity or intensity VAS Pain with walking 6 mo	**Dextrose prolotherapy** Baseline: 3.9 (2.8) 6 mo: 2.6 (2.0)	**Lidocaine** Baseline: 3.8 (2.2) 6 mo: 2.9 (2.2)	**Dextrose prolotherapy** vs. **Lidocaine** 6 mo: -0.3
	Pain severity or intensity VAS Pain with stair use 6 mo	**Dextrose prolotherapy** Baseline: 5.3 (2.8) 6 mo: 4.0 (2.7)	**Lidocaine** Baseline: 5.8 (2.6) 6 mo: 4.6 (2.9)	**Dextrose prolotherapy** vs. **Lidocaine** 6 mo: -0.6
	Adverse events NR	*"Discomfort after injection did not… vary between groups…One person [in control group] had a flare postinjection [requiring] steroid [treatment] and then referral to an orthopedic surgeon… No allergic reactions or infections were noted."*		
Sit, 2020[45‡] Low	Pain-related functioning WOMAC Total 16, 26, 52 wk	**Dextrose prolotherapy** Baseline: 49.1 (21.8) 16 wk: 30.4[¶] 26 wk: 28.8[¶] 52 wk: 28.3[¶]	**Saline** Baseline: 45.6 (21.2) 16 wk: 32.4[¶] 26 wk: 33.3[¶] 52 wk: 36.0[¶]	**Dextrose prolotherapy** vs. **Saline** 16 wk: -2.0 26 wk: -4.5 52 wk: -7.7 **Difference in difference** 16 wk: -4.33, 95% CI (-12.27, 3.62), p=0.285 26 wk: -7.34, 95% CI (-15.28, 0.61), p=0.285 52 wk: -9.65, 95% CI (-17.77, -1.53), p<.05 (0.020)
	Pain-related functioning WOMAC Function	**Dextrose prolotherapy** Baseline: 49.0 (21.8)	**Saline** Baseline: 45.9 (22.1)	**Dextrose prolotherapy** vs. **Saline** 16 wk: 0.0

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
	16, 26, 52 wk	16 wk: 29.8¶ 26 wk: 28.6¶ 52 wk: 28.0¶	16 wk: 29.8¶ 26 wk: 32.5¶ 52 wk: 35.7¶	26 wk: -0.9 52 wk: -3.1 **Difference in difference** 16 wk: -4.50, 95% CI (-12.49, 3.49), p=0.269 26 wk: -6.71, 95% CI (-14.70, 1.28), p=0.100 52 wk: -9.55, 95% CI (-17.72, -1.39), p<.05 (0.022)
	Pain-related functioning WOMAC Pain 16, 26, 52 wk	**Dextrose prolotherapy** Baseline: 49.9 (23.1) 16 wk: 30.2¶ 26 wk: 27.5¶ 52 wk: 26.8¶	**Saline** Baseline: 44.0 (20.4) 16 wk: 32.0¶ 26 wk: 33.9¶ 52 wk: 34.9¶	**Dextrose prolotherapy** vs. **Saline** 16 wk: -1.8 26 wk: -6.4 52 wk: -8.1 **Difference in difference** 16 wk: -4.81, 95% CI (-13.47, 3.85), p=0.275 26 wk: -9.73, 95% CI (-18.39, -1.07), p<.05 (0.028) 52 wk: -10.34, 95% CI (-19.20, -1.49), p<.05 (0.022)
	Pain-related functioning WOMAC Stiffness 16, 26, 52 wk	**Dextrose prolotherapy** Baseline: 48.0 (26.3) 16 wk: 35.3¶ 26 wk: 30.1¶ 52 wk: 32.8¶	**Saline** Baseline: 46.8 (27.0) 16 wk: 35.3¶ 26 wk: 35.7¶ 52 wk: 40.7¶	**Dextrose prolotherapy** vs. **Saline** 16 wk: 0.0 26 wk: -5.6 52 wk: -7.9 **Difference in difference** 16 wk: -0.74, 95% CI (-11.06, 9.58), p=0.887 26 wk: -5.79, 95% CI (-16.11, 4.53), p=0.270 52 wk: -8.01, 95% CI (-18.56, 2.54), p=0.136
	Physical performance TUG 16, 26, 52 wk	**Dextrose prolotherapy** Baseline: 12.6 (7.1) 16 wk: 10.9¶ 26 wk: 10.1¶ 52 wk: 9.9¶	**Saline** Baseline: 12.5 (4.3) 16 wk: 11.9¶ 26 wk: 11.7¶ 52 wk: 10.2¶	**Dextrose prolotherapy** vs. **Saline** 16 wk: -1.0 26 wk: -0.9 52 wk: -3.1

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
				Difference in difference 16 wk: -1.13, 95% CI (-2.74, 0.49), p=0.170 26 wk: -1.73, 95% CI (-3.34, -0.12), p<.05 52 wk: -0.3, 95% CI (-2.38, 0.92), p=0.385
	Physical performance 30-s chair stand 16, 26, 52 wk	**Dextrose prolotherapy** Baseline: 8.6 (2.6) 16 wk: 8.8¶ 26 wk: 9.8¶ 52 wk: 9.7¶	**Saline** Baseline: 8.5 (3.0) 16 wk: 8.7¶ 26 wk: 8.9¶ 52 wk: 9.7¶	**Dextrose prolotherapy** vs. **Saline** 16 wk: 0.1 26 wk: 0.9 52 wk: 0.0 **Difference in difference** 16 wk: 0.02 (-0.96, 0.99), p=0.974 26 wk: 0.81 (-0.17, 1.78), p=0.105 52 wk: 0.03 (-0.96, 1.03), p=0.952
	Physical performance 40-m fast-paced walk 16, 26, 52 wk	**Dextrose prolotherapy** Baseline: 42.1 (12.9) 16 wk: 29.2¶ 26 wk: 26.2¶ 52 wk: 25.8¶	**Saline** Baseline: 42.7 (14.6) 16 wk: 31.3¶ 26 wk: 30.9¶ 52 wk: 27.8¶	**Dextrose prolotherapy** vs. **Saline** 16 wk: -2.1 26 wk: -0.9 52 wk: -3.1 **Difference in difference** 16 wk: -1.07 (-4.29, 2.16), p=0.515 26 wk: -2.62 (-5.84, 0.61), p=0.111 52 wk: -1.78 (-5.07, 1.51), p=0.287
	Health-related quality of life EuroQol-5D index score 26, 52 wk	**Dextrose prolotherapy** Baseline: 0.569 (0.295) 26 wk: 0.73¶ 52 wk: 0.72¶	**Saline** Baseline: 0.558 (0.318) 26 wk: 0.62¶ 52 wk: 0.63¶	**Dextrose prolotherapy** vs. **Saline** 26 wk: 0.11 52 wk: 0.09 **Difference in difference** 16 wk: 0.10, 95% CI (-0.004, 0.21) p=0.058 52 wk: 0.08, 95% CI (-0.02, 0.19) p=0.126
	Pain severity or intensity VAS 16, 26, 52 wk	**Dextrose prolotherapy** Baseline: 63.1 (21.2) 16 wk: 41.63¶ 26 wk: 33.65¶	**Saline** Baseline: 60.1 (19.2) 16 wk: 44.48¶ 26 wk: 38.92¶	**Dextrose prolotherapy** vs. **Saline** 16 wk: -2.85 26 wk: -5.27 52 wk: -10.27

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
		52 wk: 35.78¶	52 wk: 46.05¶	**Difference in difference** 16 wk: -3.70, 95% CI (-13.83, 6.43), p=0.473 26 wk: -6.73, 95% CI (-16.86, 3.40), p=0.192 52 wk: -10.98, 95% CI (-21.36, -0.61), p<.05 (0.038)
	Adverse events (*"Serious adverse events,"* not otherwise defined): 52 wk	**Dextrose prolotherapy** 5% (n=2)	**Saline** 16% (n=6)	52 wk: -11%
Intra-articular Dextrose prolotherapy vs. Platelet-rich Plasma (PRP)				
Mruthyunjaya, 2023[46] High	Pain-related functioning WOMAC Total (KL Grade 2) 6 mo	**Dextrose prolotherapy** Baseline: 57.2 6 mo: 37.1	**Ozone** Baseline: 64.6 6 mo: 33.4	**Dextrose prolotherapy** vs. **Ozone** 6 mo: 3.7, p=NR
			PRP Baseline: 59.2 6 mo: 35.9	**Dextrose prolotherapy** vs. **PRP** 6 mo: 1.2, p=NR
	Pain-related functioning WOMAC Total (KL Grade 3) 6 mo	**Dextrose prolotherapy** Baseline: 69.9 6 mo: 37.4	**Ozone** Baseline: 63.6 6 mo: 34.0	**Dextrose prolotherapy** vs. **Ozone** 6 mo: 3.4, p=NR
			PRP Baseline: 69.2 6 mo: 37.0	**Dextrose prolotherapy** vs. **PRP** 6 mo: 0.4, p= NR
	Pain severity or intensity VAS (KL Grade 2) 6 mo	**Dextrose prolotherapy** Baseline: 7.6 6 mo: 4.0	**Ozone** Baseline: 8.2 6 mo: 2.7	**Dextrose prolotherapy** vs. **Ozone** 6 mo: 1.3, p=NR
			PRP Baseline: 7.2 6 mo: 3.2	**Dextrose prolotherapy** vs. **PRP** 6 mo: 0.8, p= NR
	Pain severity or intensity VAS (KL Grade 3) 6 mo	**Dextrose prolotherapy** Baseline: 8.7 6 mo: 3.7	**Ozone** Baseline: 8.6 6 mo: 2.9	**Dextrose prolotherapy** vs. **Ozone** 6 mo: 0.8, p=NR
			PRP Baseline: 8.7 6 mo: 3.3	**Dextrose prolotherapy** vs. **PRP** 6 mo: 0.4, p=NR

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, p-value*** **Other results reported**
Pishgahi, 2020[47] Some concerns	Pain-related functioning WOMAC Total 1, 6 mo	**Dextrose prolotherapy** Baseline: 65.9 (1.7) 1 mo: 71.7 (3.0) 6 mo: 72.3 (2.6)	**PRP** Baseline: 60.3 (3.7) 1 mo: 46.7 (4.3) 6 mo: 45.7 (3.8)	**Dextrose prolotherapy** vs. **PRP** 1 mo: 25.0, p<0.001 6 mo: 26.6, p<0.001
			ACS Baseline: 56.3 (3.1) 1 mo: 49.5(3.7) 6 mo: 34.9(3.4)	**Dextrose prolotherapy** vs. **ACS** 1 mo: 22.2, p<0.001 6 mo: 37.4, p<0.001
	Pain severity or intensity VAS 1, 6 mo	**Dextrose prolotherapy** Baseline: 67.0 (2.5) 1 mo: 63.3 (2.5) 6 mo: 63.3 (2.9)	**PRP** Baseline: 61.1 (1.2) 1 mo: 56.3 (1.0) 6 mo: 55.0 (2.3)	**Dextrose prolotherapy** vs. **PRP** 1 mo: 7.0, p=0.319 6 mo: 8.3, p=0.891
			ACS Baseline: 61.3 (3.4) 1 mo: 46.9 (4.5) 6 mo: 35.0(3.5)	**Dextrose prolotherapy** vs. **ACS** 1 mo: 16.4, p=0.044 6 mo: 28.3, p<0.001
Rahimzadeh, 2018[48] Some concerns	Pain-related functioning WOMAC Total 1, 2, 6 mo	**Dextrose prolotherapy** Baseline: 67.1 (7.9) 1 mo: 43.8 (8.2) 2 mo: 34.8 (6.9) 6 mo: 38.7 (6.6)	**PRP** Baseline: 67.9 (7.3) 1 mo: 42.9 (10.85) 2 mo: 27.1 (9.1) 6 mo: 31.4 (10.2)	**Dextrose prolotherapy** vs. **PRP** 1 mo: 0.9, p=0.77 2 mo: 7.7, p=0.004 6 mo: 7.3, p=0.009
	Pain-related functioning WOMAC Function 1, 2, 6 mo	**Dextrose prolotherapy** Baseline: 47.3 (6.7) 1 mo: 31 (6.3) 2 mo: 25 (5.5) 6 mo: 27.8 (5.2)	**PRP** Baseline: 47.8 (4.7) 1 mo: 30.3 (7.6) 2 mo: 19.6 (7.2) 6 mo: 22.8 (7.9)	**Dextrose prolotherapy** vs. **PRP** 1 mo: 0.7, p=0.74 2 mo: 5.4, p=0.009 6 mo: 5.0, p=0.021
	Pain severity or intensity WOMAC Pain 1, 2, 6 mo	**Dextrose prolotherapy** Baseline: 14.6 (1.4) 1 mo: 9.5 (2.3) 2 mo: 7.1 (1.7) 6 mo: 8.0 (1.6)	**PRP** Baseline: 14.8 (1.5) 1 mo: 9.2 (2.7) 2 mo: 5.4 (1.8) 6 mo: 6.2 (2.1)	**Dextrose prolotherapy** vs. **PRP** 1 mo: 0.3, p=0.71 2 mo: 1.7, p=0.002 6 mo: 1.8, p=0.003
	Pain-related functioning WOMAC Stiffness 1, 2, 6 mo	**Dextrose prolotherapy** Baseline: 5.2 (1.3) 1 mo: 3.2 (1.1) 2 mo: 2.6 (0.7) 6 mo: 3.0 (0.7)	**PRP** Baseline: 5.4 (1.2) 1 mo: 3.3 (1.1) 2 mo: 2.1 (0.7) 6 mo: 2.5 (0.8)	**Dextrose prolotherapy** vs. **PRP** 1 mo: -0.1, p=0.65 2 mo: 0.5, p=0.055 6 mo: 0.5, p=0.091

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
	Adverse Events 6 mo	*"No significant side effects were observed."* (significant AE not defined)		
Intra- vs. Extra-articular Dextrose prolotherapy				
Farpour, 2017[49] Some concerns	Pain-related functioning WOMAC Total 4, 8 wk	**Intra-articular Dextrose prolotherapy** Baseline: 45.7 (11.2) 4 wk: 41.2 (13.7) 8 wk: 39.4 (14.9)	**Extra-articular Dextrose prolotherapy** Baseline: 46.5 (14.2) 4 wk: 38.6 (16.2) 8 wk: 36.4 (16.2)	***Intra- vs. Extra-articular Dextrose prolotherapy*** 4 wk: 2.6, p=0.68 8 wk: 3.0, p=0.68
	Pain-related functioning WOMAC Function 4, 8 wk	**Intra-articular Dextrose prolotherapy** Baseline: 32.6 (8.1) 4 wk: 29.7 (9.7) 8 wk: 26.96 (11.5)	**Extra-articular Dextrose prolotherapy** Baseline: 33.9 (10.1) 4 wk: 28.4 (11.1) 8 wk: 26.7 (11.2)	***Intra- vs. Extra-articular Dextrose prolotherapy*** 4 wk: 1.3, p=0.96 8 wk: 0.3, p=0.96
	Pain severity or intensity WOMAC Pain 4, 8 wk	**Intra-articular Dextrose prolotherapy** Baseline: 9.96 (2.5) 4 wk: 8.8 (3.0) 8 wk: 9.4 (6.4)	**Extra-articular Dextrose prolotherapy** Baseline: 10.4 (3.9) 4 wk: 8.4 (4.2) 8 wk: 7.9 (5.3)	***Intra- vs. Extra-articular Dextrose prolotherapy*** 4 wk: 0.4, p=0.65 8 wk: 1.5, p=0.65
	Pain-related functioning WOMAC Stiffness 4, 8 wk	**Intra-articular Dextrose prolotherapy** Baseline: 3.2 (1.8) 4 wk: 2.8 (1.8) 8 wk: 3.2 (2.7)	**Extra-articular Dextrose prolotherapy** Baseline: 2.6 (2.0) 4 wk: 1.9 (1.6) 8 wk: 1.8 (1.5)	***Intra- vs. Extra-articular Dextrose prolotherapy*** 4 wk: 0.9, p=0.75 8 wk: 1.4, p=0.75
	Pain-related functioning OKS 4, 8 wk	**Intra-articular Dextrose prolotherapy** Baseline: 24.7 (7.1) 4 wk: 25.5 (8.5) 8 wk: 27.8 (8.7)	**Extra-articular Dextrose prolotherapy** Baseline: 23.5 (7.8) 4 wk: 27.4 (9.0) 8 wk: 28.4 (9.6)	***Intra- vs. Extra-articular Dextrose prolotherapy*** 4 wk: -1.9, p=0.84 8 wk: -0.6, p=0.84
	Pain severity or intensity VAS 4, 8 wk	**Intra-articular Dextrose prolotherapy** Baseline: 7.8 (1.7) 4 wk: 6.4 (2.2) 8 wk: 5.9 (2.7)	**Extra-articular Dextrose prolotherapy** Baseline: 7.3 (1.5) 4 wk: 5.5 (1.9) 8 wk: 5.0 (2.3)	***Intra- vs. Extra-articular Dextrose prolotherapy*** 4 wk: 0.9, p=0.15 8 wk: 0.9, p=0.15
	Adverse events 8 wk	*"In our trial there were no significant complications"* (AE not defined)		
Rezasoltani, 2017[42] High	Pain-related functioning WOMAC[§]	**Intra-articular Dextrose prolotherapy** 1,2,3,4,5 mo: NR	**Exra-articular Dextrose prolotherapy** 1,2,3,4,5 mo: NR	***Intra- vs. Extra-articular Dextrose prolotherapy*** 1,2,3,4,5 mo: NC

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, p-value*** **Other results reported**
	1,2,3,4,5 mo			
	Pain severity or intensity VAS 5 mo	**Intra-articular Dextrose prolotherapy** Baseline: NR 1 mo: 6.9¶ 2 mo: 3.4¶ 3 mo: 2.7¶ 4 mo: 3.0¶ 5 mo: 2.5¶	**Extra-articular Dextrose prolotherapy** Baseline: NR 1 mo: 6.7¶ 2 mo: 2.5¶ 3 mo: 2.1¶ 4 mo: 1.9¶ 5 mo: 1.7¶	***Intra- vs. Extra-articular Dextrose prolotherapy*** 1 mo: 0.2, p=0.22 2 mo: 0.9, p=0.001 3 mo: 0.6, p=0.001 4 mo: 1.1, p=0.001 5 mo: 0.8, p=0.001
Intra- or Extra-articular Dextrose prolotherapy vs. Other Comparators				
Babaeian, 2022[50] High	Pain-related functioning WOMAC Total 2, 4 wk	**Dextrose prolotherapy** Baseline: 0.52 (0.1) 2 wk: 0.5 (0.11) 4 wk: 0.5 (0.12)	**Hypertonic saline** Baseline: 0.6 (0.14) 2 wk: 0.47 (0.14) 4 wk: 0.47 (0.16)	**Dextrose prolotherapy** vs. **Hypertonic saline**** 2 wk: 0.0 4 wk: 0.0
	Pain-related functioning WOMAC Function 2, 4 wk	**Dextrose prolotherapy** Baseline: 0.53 (0.09) 2, 4 wk: 0.5 (0.11)	**Hypertonic saline** Baseline: 0.58 (0.13) 2 wk: 0.51 (0.13) 4 wk: 0.5 (0.2)	**Dextrose prolotherapy** vs. **Hypertonic saline**** 2 wk: 0.0 4 wk: 0.0,
	Pain-related functioning WOMAC Pain 2, 4 wk	**Dextrose prolotherapy** Baseline: 0.5 (0.12) 2 wk: 0.5 (0.12) 4 wk: 0.48 (0.1)	**Hypertonic saline** Baseline: 0.5 (0.2) 2 wk: 0.48 (0.18) 4 wk: 0.44 (0.18)	**Dextrose prolotherapy** vs. **Hypertonic saline**** 2 wk: 0.0 4 wk: 0.0
	Pain-related functioning WOMAC Stiffness 2, 4 wk	**Dextrose prolotherapy** Baseline: 0.45 (0.22) 2 wk: 0.45 (0.22) 4 wk: 0.44 (0.22)	**Hypertonic saline** Baseline: 0.5 (0.26) 2 wk: 0.5 (0.2) 4 wk: 0.47 (0.23)	**Dextrose prolotherapy** vs. **Hypertonic saline**** 2 wk: -0.1 4 wk: 0.0
	Pain-related functioning OKS 2, 4 wk	**Dextrose prolotherapy** Baseline: 20.3 (7.6) 2 wk: 21.1 (7.8) 4 wk: 21.5 (7.8)	**Hypertonic saline** Baseline: 19.2 (6.5) 2 wk: 21.6 (6.6) 4 wk: 24.5 (7.2)	**Dextrose prolotherapy** vs. **Hypertonic saline**** 2 wk: -0.5 4 wk: -3.0
	Pain severity or intensity VAS 2, 4 wk	**Dextrose prolotherapy** Baseline: 77.5 (19.8) 2 wk: 71.0 (20.4) 4 wk: 68.2 (19.9)	**Hypertonic saline** Baseline: 83.2 (14.6) 2 wk: 75.5 (18.9) 4 wk: 70.0 (18.5)	**Dextrose prolotherapy** vs. **Hypertonic saline**** 2 wk: -4.5 4 wk: -1.8
	Adverse events 4 wk	*"The patients reported no adverse effect in the next visit…"* (AE not defined)		

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, p-value*** **Other results reported**
Hashemi, 2015[51] High	Pain-related functioning WOMAC Total 3 mo	**Dextrose prolotherapy** Baseline: 58.5 (13.3) 3 mo: 83.7 (15.3)	**Ozone** Baseline: 56.3 (11.5) 3 mo: 81.6 (13.7)	**Dextrose prolotherapy** vs. **Ozone** 3 mo: 2.1, p=0.173
	Pain severity or intensity VAS 3 mo	**Dextrose prolotherapy** Baseline: 8.1 (1.1) 3 mo: 3.0 (1.2)	**Ozone** Baseline: 7.6 (1.3) 3 mo: 2.8 (1.1)	**Dextrose prolotherapy** vs. **Ozone** 3 mo: 0.2, p=0.512
Hosseini, 2019[54] High	Pain-related functioning Modified WOMAC 3 mo	**Dextrose prolotherapy** Baseline: 52.7 (9.8) 3 mo: 83.7 (12.7)	**Hyaluronic acid** Baseline: 55.9 (10.4) 3 mo: 88.5 (15.6)	**Dextrose prolotherapy vs. Hyaluronic acid** 3 mo: -4.8, p=<0.001
	Pain severity or intensity VAS 3 mo	**Dextrose prolotherapy** Baseline: 7.8 (1.4) 3 mo: 2.5 (1.1)	**Hyaluronic acid** Baseline: 8.2 (1.7) 3 mo: 2.1 (0.6)	**Dextrose prolotherapy vs. Hyaluronic acid** 3 mo: 0.4, p=0.02
	Adverse Events 3 mo	*"Our results have shown no serious adverse events"*		
Rahimzadeh, 2014[52] Some concerns	Physical performance ROM 2, 4, 12 wk	**Dextrose prolotherapy** Baseline: 101.0 (1.4) 2 wk: 106.0 (1.4) 4 wk: 110.0 (1.3) 12 wk: 113.0 (2.2)	**Erythropoietin** Baseline: 98.1 (1.6) 2 wk: 124.0 (1.5) 4 wk: 124.0 (1.4) 12 wk: 123.0 (1.5)	**Dextrose prolotherapy** vs. **Erythropoietin** 2 wk: -18.0 4 wk: -14.0 12 wk: -10.0
			Pulsed radio frequency Baseline: 95.0 (2.0) 2 wk: 105.0 (2.1) 4 wk: 110.0 (2.1) 12 wk: 113.0 (2.2)	**Dextrose prolotherapy** vs. **Pulsed radio frequency** 2 wk: 1.0 4 wk: 0.0 12 wk: 0.0
				p-value comparing across all 3 groups: 2 wk: p=0.005 4 wk: p=0.004 12 wk: p=0.04
	Pain severity or intensity VAS 2, 4, 12 wk	**Dextrose prolotherapy** Baseline: 7.1 (1.0) 2 wk: 4.5 (1.4) 4 wk: 4.7 (1.4) 12 wk: 5.5 (1.6)	**Erythropoietin** Baseline: 6.7 (1.0) 2 wk: 3.2 (1.1) 4 wk: 3.2 (0.9) 12 wk: 3.5 (1.2)	**Dextrose prolotherapy** vs. **Erythropoietin** 2 wk: 1.3 4 wk: 1.5 12 wk: 2.0

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, p-value*** **Other results reported**
			Pulsed radio frequency Baseline: 7.1 (1.4) 2 wk: 3.3 (2.0) 4 wk: 3.9 (1.7) 12 wk: 5.5 (1.9)	**Dextrose prolotherapy** vs. **Pulsed radio frequency** 2 wk: 1.2 4 wk: 0.8 12 wk: 0.0
				p-value comparing across all 3 groups: 2 wk: p=0.005 4 wk: p=0.002 12 wk: p=0.002
	Adverse events 12 wk	*"No particular side-effect related to the interventions was observed."* (AE not defined)		
Rezasoltani, 2020[53] High	Pain-related functioning KOOS Other symptoms 3 mo	**Dextrose prolotherapy** Baseline: 10.3 (4.7) 3 mo: NR	**Physical therapy** Baseline: 11.4 (3.4) 3 mo: NR	**Dextrose prolotherapy** vs. **Physical therapy** 3 mo: NC
			Botulinum neurotoxin Baseline: 12.6 (4.9) 3 mo: NR	**Dextrose prolotherapy** vs. **Botulinum neurotoxin** 3 mo: NC
			Hyaluronic acid Baseline: 11.5 (3.0) 3 mo: NR	**Dextrose prolotherapy** vs. **Hyaluronic acid** 3 mo: NC
	Pain-related functioning KOOS Stiffness 3 mo	**Dextrose prolotherapy** Baseline: 3.3 (1.8) 3 mo: NR	**Physical therapy** Baseline: 3.4 (1.4) 3 mo: NR	**Dextrose prolotherapy** vs. **Physical therapy** 3 mo: NC
			Botulinum neurotoxin Baseline: 3.7 (2.3) 3 mo: NR	**Dextrose prolotherapy** vs. **Botulinum neurotoxin** 3 mo: NC
			Hyaluronic acid Baseline: 4.0 (1.8) 3 mo: NR	**Dextrose prolotherapy** vs. **Hyaluronic acid** 3 mo: NC
	Pain severity or intensity KOOS Pain 3 mo	**Dextrose prolotherapy** Baseline: 21.5 (5.9) 3 mo: NR	**Physical therapy** Baseline: 21.3 (5.0) 3 mo: NR	**Dextrose prolotherapy** vs. **Physical therapy** 3 mo: NC
			Botulinum neurotoxin Baseline: 19.0 (6.5)	**Dextrose prolotherapy** vs. **Botulinum neurotoxin** 3 mo: NC

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, p-value*** **Other results reported**
			3 mo: NR	
			Hyaluronic acid Baseline: 20.2 (6.6) 3 mo: NR	**Dextrose prolotherapy** vs. **Hyaluronic acid** 3 mo: NC
	Pain-related functioning KOOS ADL 3 mo	**Dextrose prolotherapy** Baseline: 39.6 (14.1) 3 mo: NR	**Physical therapy** Baseline: 34.7 (12.9) 3 mo: NR	**Dextrose prolotherapy** vs. **Physical therapy** 3 mo: NC
			Botulinum neurotoxin Baseline: 36.8 (10.0) 3 mo: NR	**Dextrose prolotherapy** vs. **Botulinum neurotoxin** 3 mo: NC
			Hyaluronic acid Baseline: 33.7 (13.6) 3 mo: NR	**Dextrose prolotherapy** vs. **Hyaluronic acid** 3 mo: NC
	Pain-related functioning KOOS Sports function 3 mo	**Dextrose prolotherapy** Baseline: 12.4 (2.0) 3 mo: NR	**Physical therapy** Baseline: 13.0 (1.8) 3 mo: NR	**Dextrose prolotherapy** vs. **Physical therapy** 3 mo: NC
			Botulinum neurotoxin Baseline: 13.1 (1.9) 3 mo: NR	**Dextrose prolotherapy** vs. **Botulinum neurotoxin** 3 mo: NC
			Hyaluronic acid Baseline: 10.8 (1.9) 3 mo: NR	**Dextrose prolotherapy** vs. **Hyaluronic acid** 3 mo: NC
	Pain-related functioning KOOS Quality of life 3 mo	**Dextrose prolotherapy** Baseline: 12.2 (1.5) 3 mo: NR	**Physical therapy** Baseline: 10.2 (2.1) 3 mo: NR	**Dextrose prolotherapy** vs. **Physical therapy** 3 mo: NC
			Botulinum neurotoxin Baseline: 8.2 (2.4) 3 mo: NR	**Dextrose prolotherapy** vs. **Botulinum neurotoxin** 3 mo: NC
			Hyaluronic acid Baseline: 9.5 (1.1) 3 mo: NR	**Dextrose prolotherapy** vs. **Hyaluronic acid** 3 mo: NC
	Pain severity or intensity VAS 1 wk 1, 3 mo	**Dextrose prolotherapy** Baseline: 6.5 (1.3) 1 wk: 2.8¶ 1 mo: 2.8¶ 3 mo: 2.5¶	**Physical therapy** Baseline: 7.2 (1.1) 1 wk: 4.6¶ 1 mo: 3.7¶ 3 mo: 3.8¶	**Dextrose prolotherapy** vs. **Physical therapy** 1 wk: -1.8, p<0.001 1 mo: -0.9, p<0.001 3 mo: -3.1, p<0.001

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, p-value*** **Other results reported**
			Botulinum neurotoxin Baseline: 6.6 (1.6) 1 wk: 3.4¶ 1 mo: 3.1¶ 3 mo: 2.3¶	**Dextrose prolotherapy** vs. **Botulinum neurotoxin** 1 wk: -0.6, p<0.001 1 mo: -0.3, p<0.001 3 mo: 0.2, p<0.001
			Hyaluronic acid Baseline: 6.7 (0.7) 1 wk: 4.9¶ 1 mo: 4.8¶ 3 mo: 5.7¶	**Dextrose prolotherapy** vs. **Hyaluronic acid** 1 wk: -2.1, p<0.001 1 mo: -2.0, p<0.001 3 mo: -3.2, p<0.001
	Adverse events 3 mo	*"None of the participants showed or reported serious side effects for the treatments."* (AE not defined)		

Notes. *Mean differences calculated by review team; p-values reported by study (otherwise NR)

†Study used repeated measured ANOVA to test the group x time interaction effects at each follow-up time point.

‡Study used linear mixed models analysis to test the overall group effect and reported estimated mean difference-in-difference (95% CI) between groups at each follow-up time point.

¶Mean time point scores estimated by review team using plot digitizer (data only reported graphically).

§Study only reported mean scores for individual WOMAC items, and not total or domain scores.

**Study reported that there were no significant differences between groups for these outcomes, but did not provide p-values.

Abbreviations. ACS=autologous blood serum; ADL=activities of daily living; AE=adverse event; EuroQoL-5D=European Quality of Life-5 dimensions; HA=hyaluronic acid; KOOS=Knee Injury and Osteoarthritis Outcome Score; mo=month; NC=not calculable; NR=not reported; OA=osteoarthritis; OKS=Oxford Knee Score; PRP=platelet-rich plasma; QoL=quality of life; RoB=risk of bias; ROM=range of motion; SD=standard deviation; TUG=timed up and go; VAS=Visual Analog Scale; wk=week; WOMAC=Western Ontario and McMaster Universities Arthritis Index.

APPENDIX G. PLANTAR FASCIITIS

Appendix Table 6. Detailed Study Characteristics for All Eligible Plantar Fasciitis Studies

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Participant Characteristics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Participant Characteristics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes (Time points)** • **Measure(s)** **Other Outcomes Reported**
Asheghan, 2021[71] IRCT20140306016865N2 Some concerns 12 Weeks Iran (1) None	**Inclusion**: "(i) age between 18 and 75 years; (ii) heel pain at the antero-medial side of the heel consistent with a diagnosis of plantar fasciitis; (iii) exacerbation of the pain by manual compression of the plantar fascia attachment to the medial border of the calcaneus; and (iv) chronic recalcitrant heel pain for more than 8 weeks with failed conservative management." **Exclusion**: "history of any injection into the plantar fascia, ESWT or surgery to the heel, history of bleeding disorders or systemic inflammatory diseases like rheumatoid arthritis, history of trauma to the heel and calcaneus, a history of uncontrolled diabetes mellitus, Achilles tendinopathy, S1 radiculopathy, crystal arthropathy or neuropathy related heel pain."	**Dextrose prolotherapy**: *N*=31 Age, mean (SD): 46.5 (6.5) 63% Female Pain duration, mean (SD): 4.5 (1.3) mo Clinic or health care facility 2 weeks (2 sessions) "Patients were placed in the prone position with their feet hanging over edge of the table in the neutral ankle position. The transducer was placed longitudinally over the medial aspect of the heel and the plantar fascia was visualized in a long-axis view. The plantar fascia was followed to its origin on the medial tuberosity of the calcaneus...the transducer was positioned transversely along the antero-medial side of the heel, and a short-axis view of the plantar fascia	**ESWT**: *N*=31 Age, mean (SD): 43.7 (7.6) 69% Female Pain duration, mean (SD): 4.8 (1.2) mo Clinic or health care facility 3 weeks (3 sessions) "The shockwave probe was placed perpendicularly on the plantar surface of the patient's heel, over the point of maximal tenderness after application of the coupling gel. The procedure was performed without using local anesthesia. Shockwaves were administrated using a radial shockwave device (MP 100, Storz Medical, Switzerland) for all patients. In each session, patients received 2000 shocks at a pressure of 2 Bars and a frequency of 10 Hz. Due to pain	**Primary outcome NR** **Pain-related functioning (6, 12 wk)** • FAAM (ADL, Sport) **Adverse events** **Other outcomes:** • Pain severity or intensity

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Participant Characteristics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Participant Characteristics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes (Time points)** • **Measure(s)** **Other Outcomes Reported**
		and the underlying calcaneus bone was obtained. Under ultrasound guidance and using in-plane injection technique, the needle was inserted on the medial side of the heel and it was visualized as it was approaching from the medial to lateral aspect of the field, targeting the hypoechogenic and mixed echogenic region of the plantar fascia... In each session, an intrafascial injection of 2 cc dextrose 20% was performed using a Luer-lock syringe with a 25 gauge 1.5-inch needle." Other treatments: "All patients were asked to avoid using braces, non-steroidal anti-inflammatory drugs, local steroid injections, or physiotherapy for 12 weeks after the first treatment session... All patients in both groups were instructed to perform calf muscle and plantar fascia stretching exercises and intrinsic foot muscle strengthening."	and intolerance of a high energy protocol in 3 patients, we used a painless lowest intensity protocol as a pilot, and then increased the intensity level gradually to the study protocol. All ESWT sessions were performed by a single expert physiatrist." Other treatments: Same as arm 1	
Ersen, 2018[66] NR High 1 Years	**Inclusion**: "patients diagnosed with plantar fasciitis...Diagnosis was based on the identification of symptoms and physical examination findings." **Exclusion**:	**Dextrose prolotherapy**: *N*=29 Age, mean (SD): 45.1 (6.7) 81% Female Pain duration, mean: 32.8 mo	**Exercise/PT**: *N*=31 Age, mean (SD): 46.3 (7.6) 79% Female Pain duration, mean: 34.3 mo	**Primary outcome NR** **Pain-related functioning (90, 360 days)** • FFI (total) • FAOS **Other outcomes:**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Participant Characteristics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Participant Characteristics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes (Time points)** • **Measure(s)** **Other Outcomes Reported**
Turkey (1) None	"Patients with tarsal tunnel syndrome and epin calcanei were excluded..."	Clinic or health care facility 42 days (3 injections) "prolotherapy injections with a 27-gauge needle (3.6 mL dextrose [15% solution] and 0.4 mL lidocaine) were administered in up to five different points in the plantar fascia under aseptic conditions...The medial-oblique approach was used...ultrasound probe was placed on the medial calcaneal tubercle. The needle was inserted from the medial side of the heel, perpendicular to the long axis of the ultrasound transducer, and advanced under continuous ultrasound guidance into the proximal plantar fascia." Other treatments: "[Patients] were given heel lifts…"	Clinic or health care facility; Home 3 months (PT 3x/wk + home exercises 3x/other days) "plantar fascia and Achilles tendon stretching exercise...physical therapist with a 3-year experience provided instructions...patients also advised to perform a home-based exercise program with same exercise protocol on their own three times a day for the other days…" Other treatments: Same as arm 1	• Pain severity or intensity
Karakılıc, 2023[65] NR High 3 Months	**Inclusion**: 18-65 years old, heel pain >3mo, "worsening of plantar fascia tenderness by manual compression of medial border of the calcaneus, proximal PFT >4mm and areas of hypoechogenicity, history of unsuccessful conservative treatments including nonsteroidal	**Dextrose prolotherapy**: *N*=NR Total *N*=147 Age, mean (SD): NR % Female NR Clinic or health care facility	**Steroid injectable**: *N*=NR Age, mean (SD): NR % Female NR Clinic or health care facility	**Primary outcome NR** **Pain-related functioning (1, 3 mo)** • FFI (total, disability, activity) **Health-related QoL (1, 3 mo)** • SF-36

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Participant Characteristics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Participant Characteristics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes (Time points)** • **Measure(s)** **Other Outcomes Reported**
Turkey (1) NR	anti-inflammatory therapy, stretching exercises, heel cups, shoe modifications, arch support, orthotics, and ESWT" **Exclusion**: "diabetes mellitus, systemic inflammatory and rheumatologic diseases, infection, bleeding disorders, vasculitis, malignancy, pregnancy or lactation, peripheral neuropathy, skin disorders, previous surgery for PF, and recent trauma to the foot and ankle...[P]atients who underwent local steroid injection therapy within 3 months or took nonsteroidal anti-inflammatory drugs within 2 weeks before treatment and those who refused to come for follow-up visits were excluded..."	1 month (1x/2 wks) "Patients were placed in the prone position with their feet hanging over the edge of the table in the neutral ankle position... Ultrasound guided dextrose prolotherapy injections were administered with a 27-gauge needle (3.6 mL dextrose [30% solution]) and 0.4 mL lidocaine...application was made with palpation guidance by the drilling center and around the damaged area 5 times using the peppering technique." Other treatments: "Acetaminophen and cold pack were permitted in case of necessity, but the use of anti-inflammatory agents was not allowed."	Single dose "injection of methylprednisolone acetate 40 mg/1 ML after injection of 2% prilocaine at the site of maximum tenderness on the medial side of heel by ultrasound-guided...27-gauge needle..." Other treatments: Same as arm 1 **Other non-injectable**: *N*=NR Age, mean (SD): NR % Female NR Clinic or health care facility 10 total sessions (frequency NR) "phonophoresis using prednisolone gel topically at the site of the plantar fascia within 20 minutes at the 1.5W/cm2 1 MHz dose" Other treatments: Same as arm 1	**Other outcomes:** • Pain severity or intensity
Kesikburun, 2022[67] NR	**Inclusion**: "(1) heel pain with more than 3 months of symptoms, (2) localized	**Dextrose prolotherapy**: *N*=14 Age, mean (SD): 57.4 (8.3)	**Other non-injectable**: *N*=15 Age, mean (SD): 51.2 (7.4)	**Overall VAS score at 12 weeks** **Pain-related functioning (6, 12 wk)**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Participant Characteristics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Participant Characteristics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes (Time points)** • **Measure(s)** **Other Outcomes Reported**
High 12 Weeks Turkey (1) None ("This research did not receive any specific grant...")	pain and tenderness on palpation of medial aspect of the calcaneal tuberosity with an ankle in full dorsiflexion, (3) VAS score of ≥50 mm during the first steps of walking, (4) lesion imaged by ultrasound (thickening in proximal plantar fascia greater than 4 mm with hypoechogenic areas and modifications in normal fibrillary pattern), (5) history of unsuccessful conservative treatments including any NSAIDs and at least 2 of the followings (stretching, heel cushion, shoe modifications, heel cups, orthotics, cold, heat, ultrasound, corticosteroid injection, taping, massage), and (6) greater than 18 years old. In cases where symptoms were present on both sides, the side with more pronounced symptoms was included." **Exclusion**: "(1) generalized inflammatory arthritis, (2) any skin lesion on the heel, (3) pregnancy, (4) infection, (5) malignancy, (6) coagulopathy, (7) cardiac pacemaker, (8) previous ESWT, dextrose prolotherapy or surgical procedure according to the area of heel, and	69.2% Female Pain duration, mean (SD): 12.6 (9.3) mo Clinic or health care facility 6 weeks (3 injections) "injections were performed to the lesion throughout the medial part of the heel... solution utilized for dextrose prolotherapy was a mix of 1.5 ml of 30% dextrose and 1.5 ml of 2% lidocaine, with a sum of 3 ml 15% dextrose arrangement. Real-time ultrasound guidance...was used during the injection... Abnormal hypoechoic and/or disturbed fibrillary pattern regions in the thickened proximal plantar fascia were focused on. A 25-gauge [sic] needle was inserted through the medial heel with an in-plane technique (parallel to long-axis view). The dextrose mixture was infused into center and 4 locations around the damaged area through a skin portal using a peppering technique. The patients had been suggested to lie down in supine position without moving the foot for 15 minutes after the procedure."	78.6% Female Pain duration, mean (SD): 12.7 (10.5) mo Clinic or health care facility 6 weeks (3 sessions) Extracorporeal shock wave therapy was given by a single investigator using a standardized protocol with Duolith SD1 shock wave machine... The patients were placed prone with the study foot placed in a supported position. Before the procedure, the target area determined as the thickest part of the plantar fascia contiguous to the calcaneus in ultrasound scanning, which was mostly area of maximum tenderness, was marked on the skin for focused shock waves. The participants received 1800 to 2000 focused shock waves (session of 0.20-0.30 mJ/mm2 with a 4-6 Hz frequency). In each session, focused shock waves were followed by soft tissue radial shock waves to muscles connected with the heel. About 3000 to 3500 radial pulses (session of 1.8-3.0 bar with a frequency of 15-21 Hz) were applied to the gastrosoleus	• FFI (total) **Adverse events** **Other outcomes:** • Pain severity or intensity

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Participant Characteristics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Participant Characteristics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes (Time points)** • **Measure(s)** **Other Outcomes Reported**
	(9) anamnesis of local corticosteroid injection or oral corticosteroid within the previous 6 weeks and/or topical or oral NSAID use during last 2 weeks."	Other treatments: "Acetaminophen and cold was permitted if necessary for post-injection control of pain;... the utilization of NSAIDs was restricted…the patients were not allowed to get any other therapies for the duration of the study."	muscle and the foot intrinsic muscles. The frequency of the pulses for both focused and radial ESWT was progressively raised through to the maximum tolerable degree of pain for each patient. A dose of 1000 mJ/mm2 at least was delivered." Other treatments: Same as arm 1	
Kim, 2014[72] NR High 6 Months Korea (1) NR	**Inclusion**: "unilateral foot symptoms for a minimum of 6 months, and to have previously failed therapy using conservative measures such as nonsteroidal anti-inflammatory drugs, stretching and physical therapy, a night splint, arch supports, corticosteroid injections, and extracorporeal shock wave therapy... To confirm the diagnosis, the thickness of the proximal plantar fascia was measured by ultrasound at the inferior calcaneal border, and patients with a plantar fascia thickness >=4 mm were included." **Exclusion**: "received local steroid injections within 6 months or nonsteroidal anti-inflammatory drugs within 1 week before randomization...also	**Dextrose prolotherapy**: *N*=11 Age, mean (SD): 37.8 (NR) 36% Female Pain duration, mean (range): 2.9 (1-6) yrs Clinic or health care facility 4 weeks (2 injections) "combination of 1.5 mL of 20% dextrose and 0.5 mL of 0.5% lidocaine, resulting in a 15% dextrose solution, within a 2.5-mL syringe. ...blood also was collected from the patients in the DP group. The injection procedure was performed...using a 22-gauge needle. Abnormal hypoechoic areas in the thickened	**PRP**: *N*=10 Age, mean (SD): 36.2 (NR) 60% Female Pain duration, mean (range): 2.8 (1-6) yrs Clinic or health care facility 4 weeks (2 injections) The injection procedure was performed...using a 22-gauge needle. Abnormal hypoechoic areas in the thickened proximal plantar fascia were targeted under the longitudinal plane of ultrasound guidance, and the needle was inserted through the medial heel along the long-axis view (in-plane technique) toward the target	**FFI** (only outcome) **Pain-related functioning (10, 28 wk)** • FFI (total, disability, activity)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Participant Characteristics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Participant Characteristics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes (Time points)** • **Measure(s)** **Other Outcomes Reported**
	excluded if they had cardiovascular, renal, or hepatic disease, diabetes, anemia, vascular insufficiency, peripheral neuropathy, active bilateral PF, or previous surgery for PF."	proximal plantar fascia were targeted under the longitudinal plane of ultrasound guidance, and the needle was inserted through the medial heel along the long-axis view (in-plane technique) toward the target area. Then, ~2mL of... dextrose solution was injected using a peppering technique, which involved a single skin portal followed by 5 penetrations of the fascia." Other treatments: "[Patients] were sent home with instructions to…use acetaminophen for pain. The use of nonsteroidal anti-inflammatory drugs and any type of foot orthoses was not allowed."	area. Then, ~2mL of PRP... was injected using a peppering technique, which involved a single skin portal followed by 5 penetrations of the fascia." Other treatments: Same as arm 1	
Mansiz-Kaplan, 2020[68] NCT03731897 Some concerns 15 Weeks Turkey (1) NR	**Inclusion**: "(a) being 18 yrs or older, (b) having unilateral resistant heel [sic] pain for at least 6 mos, (c) having undergone nonsteroidal anti-inflammatory therapy at least 1 mo, exercise therapy, and arch support among conservative treatments but with no desired outcome, (d) morning pain measured by the VAS being higher than 5, (e) the plantar fascia thickness measured by ultrasound being greater than 4mm"	**Dextrose prolotherapy**: *N*=32 Age, mean (SD): 46.7 (9.3) 73% Female Clinic or health care facility 6 weeks (2 injections) "A 10 ml of solution (15% dextrose solution) consisting of 5 ml of 30% dextrose, 4 ml of saline (0.9% NaCl), and 1 ml of 2% lidocaine was	**Saline/Local anesthetic**: *N*=33 Age, mean (SD): 46.2 (9.6) 77% Female Clinic or health care facility 6 weeks (2 injections) "a 10 ml of solution containing the combination of 9 ml of saline (0.9% NaCl) and 1 ml of 2% lidocaine was prepared... The application was	**FFI** (used to estimate sample size but not directly stated as primary outcome) **Pain-related functioning (7, 15 wk)** • FFI (total, disability, activity) **Adverse events** **Other outcomes:** • Pain severity or intensity

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Participant Characteristics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Participant Characteristics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes (Time points)** • **Measure(s)** **Other Outcomes Reported**
	Exclusion: "(a) bilateral PF, (b) the presence of other diseases of the foot or ankle (arthritis, old or new fractures, tarsal tunnel syndrome, etc.), (c) history of surgical treatment for PF, (d) having received steroid injections for PF within the last 6 mos, (e) having undergone oral nonsteroidal anti-inflammatory therapy in the last week, (f) the presence of chronic pain syndromes, (g) being diagnosed with diabetes mellitus, rheumatologic disease, central neurologic diseases (epilepsy, cerebrovascular disease, etc.), or mental disorders causing lack of insight and judgment (schizophrenia spectrum and other psychotic disorders, bipolar and related disorders, etc.), (h) the presence of peripheral vascular disease or peripheral neuropathy related to the lower limbs, (i) having a disorder or using medication that impairs the bleeding profile, and (j) the presence of infection at the injection site."	prepared... The application was carried out with palpation guidance by drilling the fascia five times using the peppering technique...with a 22-gauge needle. The injection sites were where the plantar fascia was attached to the metatarsal bones (top of the first and fifth bones) and where it was attached to the heel (medial and lateral) and the midpoint of the plantar fascia. One milliliter of solution was injected into each injection site (total injected solution: 5 ml)." Other treatments: "The patients were asked not to…use painkillers other than paracetamol for 72 hrs after the injection."	carried out with palpation guidance by drilling the fascia five times using the peppering technique... with a 22-gauge needle. The injection sites were where the plantar fascia was attached to the metatarsal bones (top of the first and fifth bones) and where it was attached to the heel (medial and lateral) and the midpoint of the plantar fascia. One milliliter of solution was injected into each injection site (total injected solution: 5 ml)." Other treatments: Same as arm 1	
Raissi, 2023[70]	**Inclusion**: "a diagnosis of chronic PF based on clinical symptoms NRS score	**Dextrose prolotherapy**: *N*=22	**Steroid injectable**: *N*=22	**Primary outcome NR**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Participant Characteristics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Participant Characteristics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes (Time points)** • **Measure(s)** **Other Outcomes Reported**
IRCT2015041321744N1 Some concerns 12 Weeks Iran (1) Iran University of Medical Sciences	>4 for more than 8 weeks), signs, and ultrasound findings (proximal plantar fascia thickness greater than 4 mm and areas of hypo-echogenicity) and aged between 18 and 75 years old...clinical criteria for diagnosing chronic PF were based on localized tenderness at the plantar fascia insertion site (proximal of the plantar fascia or medial of the heel) for more than 2 months, start-up pain after rest, and negative radiographic findings to exclude other causes of heel pain (such as trauma, mass, and cysts)." **Exclusion**: "history of direct trauma; positive Tinel's sign at the medial ankle; systemic inflammation and connective tissue disease; history of disc herniation; uncontrolled diabetes; history of gout; surgery or injections in the past 6 mo; presence of cyst, mass, or skin infection at the site of pain; presence of paresthesia or numbness; coagulation disorders; pregnancy; sensitivity to corticosteroids; presence of posterior heel pain; and any special treatment in the past 4 wk,	Age, mean (SD): 50.3 (11.64) 75% Female Clinic or health care facility Single dose "participants in both groups received ultrasound-guided local anesthesia with 1 mL of 1% lidocaine hydrochloride. Injections in both groups were carried out with a 22-gauge needle in a long-axis view of plantar fascia at the point of maximal thickness...prolotherapy group received an intrafascial injection of 2 mL of 20% dextrose..." Other treatments: "For the first 48 hours after injection, all patients were advised to…use a cold pack for 20 minutes 3 to 5 times daily, and acetaminophen tablet 325 mg twice daily if needed."	Age, mean (SD): 42.15 (9.42) 90% Female Clinic or health care facility Single dose "participants in both groups received ultrasound-guided local anesthesia with 1 mL of 1% lidocaine hydrochloride. Injections in both groups were carried out with a 22-gauge needle in a long-axis view of plantar fascia at the point of maximal thickness... corticosteroid group received an intrafascial injection with 1 mL of 40 mg methylprednisolone plus 1 mL normal saline (0.9% sodium chloride)." Other treatments: Same as arm 1	**Pain-related functioning (2, 12 wk)** • FAAM (ADL, Sport) **Other outcomes:** • Pain severity or intensity

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Participant Characteristics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Participant Characteristics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes (Time points)** • **Measure(s)** **Other Outcomes Reported**
	including PT, using splints, iontophoresis, phonophoresis, and shockwave."			
Umay Altas, 2018[69] NR Some concerns 3 Months Turkey (1) None ("No financial support was received for this project.")	**Inclusion**: "clinical diagnosis of PFs (pain during first few minutes in the morning with walking and with pain by pressure on calcaneal tubercle when the foot was on passive dorsiflexion) and with unilateral symptoms ongoing for at least 2 months and had minimal pain levels of 4 on VAS..." **Exclusion**: "used NSAIDs in the last 2 weeks, received PT for PFs in last 3 months, received previous injections, had history of foot, ankle or heel surgical interventions or had detected anatomical anomalies such as pes planus or pes cavus on x-rays...also excluded if they had infections on injection site, coagulation disorders/anticoagulant treatments, pregnancy or nursing, peripheral neuropathies or lower extremity paresis or paraplegia."	**Dextrose prolotherapy**: *N*=15 Age, mean (SD): 47.06 (8.67) 80% Female Pain duration, mean (range): 10 (2-18) mo Clinic or health care facility; Home 9 weeks (3 injections); home exercises daily for 3 mos "3 ml 15% dextrose into the plantar fascia-bone insertion point... using a 22-gauge needle with a single skin entry on the fascia ligament-bone insertion point with peppering technique which contained 5 penetrations." PLUS home exercises: "exercise program...included plantar fascial stretching, towel carrying using toes, rolling solid objects with the sole, dorsiflexion against resistance, resistant plantar flexion, inversion and eversion. Exercises were initiated 72	**Saline/Local anesthetic**: *N*=15 Age, mean (SD): 50.60 (8.93) 93% Female Pain duration, mean (range): 11 (6-14) mo Clinic or health care facility; Home 9 weeks (3 injections); home exercises daily for 3 mos "3 ml saline injected... with the same peppering technique" as described above for prolotherapy group, PLUS same exercise program Other treatments: Same as arm 1	**Primary outcome NR** **Pain-related functioning (3 mo)** • FFI (total, disability, activity) **Adverse events** **Other outcomes:** • Pain severity or intensity

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Participant Characteristics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Participant Characteristics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes (Time points)** • **Measure(s)** **Other Outcomes Reported**
		hours following the initial injections and were demonstrated to the patients on their first sessions." Other treatments: "Following injections [patients were] instructed to apply heat to the injection surface 3 times for 10 minutes for 3 days…and were told not to take any NSAIDs during the treatment, but can take acetaminophen for pain if necessary [and] begin exercises 72 hours after the injections. None of the patients were given foot orthoses."		

Abbreviations. cm=centimeter; DP=dextrose prolotherapy; ESWT= extracorporeal shock wave therapy; FAAM-ADL=Foot and Ankle Ability Measure-Activities of Daily Living; FAAM-S= Foot and Ankle Ability Measure-Sport; FAOS=Foot and Ankle Outcomes Score; FFI=Foot Function Index; Hz=hertz; mg=milligram; MHz=megahertz; mJ=millijoules; mL=milliliter; mm=millimeter; mo=month; NaCl=sodium chloride; NSAIDS=nonsteroidal anti-inflammatory drugs; NR=not reported NRS=Numeric Rating Scale; PF=plantar fasciitis; PFT=plantar fascia thickness; PRP=platelet-rich plasma; PT=physical therapy; SD=standard deviation; SF-36=Short Form Survey (36-item); VAS=Visual Analog Scale; wk=week.

Appendix Table 7. Detailed Results for All Eligible Plantar Fasciitis Studies

Author, Year Risk of Bias	Outcome Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
Asheghan, 2021[71] Some concerns	Pain-related functioning FAAM-ADL 6, 12 wk	**Dextrose prolotherapy 20%** Baseline: 72.4 (12.8) 6 wk: 87.5 (8.7) 12 wk: 90.0 (8.9)	**EWST** Baseline: 74.2 (10.2) 6 wk: 88.3 (7.2) 12 wk: 91.3 (6.8)	**Arm 1 vs. Arm 2** 6 wk: -0.8, NR 12 wk: -1.3, NR
	Pain-related functioning FAAM-S 6, 12 wk	**Dextrose prolotherapy 20%** Baseline: 70.1 (11.8) 6 wk: 83.3 (10.8) 12 wk: 85.8 (9.3)	**EWST** Baseline: 72.6 (12.3) 6 wk: 88.7 (11.1) 12 wk: 92.3 (10.2)	**Arm 1 vs. Arm 2** 6 wk: -5.4 NR 12 wk: -6.5, NR
	Pain severity or intensity VAS 6, 12 wk	**Dextrose prolotherapy 20%** Baseline: 74.7 (11.2) 6 wk: 53.3 (10.1) 12 wk: 44.2 (9.5)	**EWST** Baseline: 72.3 (13.2) 6 wk: 56.6 (12.5) 12 wk: 40.8 (10.3)	**Arm 1 vs. Arm 2** 6 wk: -3.3, NR 12 wk: 3.4, NR
	Adverse Events NA 12 wk	*"All patients tolerated the interventions well and no serious adverse events (hematomas, infections, or soft tissue atrophy) were observed in any of the cases."*		
Ersen, 2018[66] High	Pain-related functioning FFI-Total 21, 42, 90, 360 days	**Dextrose prolotherapy 13.5%** Baseline: 57.7 (13.6) 21 days: 52.7 (15.3) 42 days: 38.6 (15.8) 90 days: 31.1 (17.0) 360 days: 26.0 (20.3)	**Physical Therpay** Baseline: 56.9 (12.8) 21 days: 53.9 (14.0) 42 days: 51.3 (16.9) 90 days: 47.8 (20.7) 360 days: 34.3 (25.2)	**Arm 1 vs. Arm 2** 21 days: -1.2 42 days: -12.7 90 days: -16.7 360 days: -8.3 **Difference in difference** 21 days: p=0.235 42 days: p<0.001 90 days: p<0.001 360 days: p=0.113
	Pain-related functioning FAOS 21, 42, 90, 360 days	**Dextrose prolotherapy 13.5%** Baseline: 55.1 (15.5) 21 days: 61.8 (13.9) 42 days: 71.9 (16.4) 90 days: 78.2 (16.4) 360 days: 82.6 (16.0)	**Physical Therpay** Baseline: 57.4 (14.4) 21 days: 61.3 (15.6) 42 days: 61.9 (19.0) 90 days: 65.0 (24.5) 360 days: 73.4 (22.0)	**Arm 1 vs. Arm 2** 21 days: 0.5 42 days: 10 90 days: 13.2 360 days: 9.2 **Difference in difference** 21 days: p=0.270 42 days: p=0.001 90 days: p=0.002

Author, Year Risk of Bias	Outcome Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
				360 days: p=0.023
	Pain severity or intensity VAS 21, 42, 90, 360 days	**Dextrose prolotherapy 13.5%** Baseline: 6.9 (1.5) 21 days: 5.9 (1.9) 42 days: 4.3 (2.2) 90 days: 3.1 (2.4) 360 days: 2.4 (2.6)	**Physical Therpay** Baseline: 6.7 (1.4) 21 days: 6.0 (1.5) 42 days: 5.7 (2.1) 90 days: 5.0 (2.8) 360 days: 3.7 (3.0)	**Arm 1 vs. Arm 2** 21 days: -0.1 42 days: -1.4 90 days: -1.9 360 days: -1.3 **Difference in difference** 21 days: p=0.319 42 days: p=0.001 90 days: p=0.002 360 days: p=0.042
Karakılıc, 2023[65] High	Pain-related functioning FFI-Total 1, 3 mo	**Dextrose prolotherapy 27%** Baseline: 61.8 (9.1) 1 mo: 27.0 (20.7) 3 mo: 27.9 (21.8)	**Corticosteroid** Baseline: 61.7 (10.2) 1 mo: 25.9 (23.6) 3 mo: 35.7 (24.8) **Phonophoresis** Baseline: 63.0 (9.0) 1 mo: 27.9 (20.6) 3 mo: 35.5 (25.2)	**Arm 1 vs. Arm 2** 1 mo: 1.1 3 mo: -7.8 **Arm 1 vs. Arm 3** 1 mo: -0.9 3 mo: -7.6 Comparison between all 3 groups: 1 mo: p=0.82 3 mo: p=0.29
	Pain-related functioning FFI-Disability 1, 3 mo	**Dextrose prolotherapy 27%** Baseline: 72.8 (11.4) 1 mo: 29.8 (23.3) 3 mo: 32.3 (25.0)	**Corticosteroid** Baseline: 71.2 (12.7) 1 mo: 27.8 (24.1) 3 mo: 39.4 (28.9) **Phonophoresis** Baseline: 71.3 (14.9) 1 mo: 30.7 (21.9) 3 mo: 40.5 (28.9)	**Arm 1 vs. Arm 2** 1 mo: 2.0 3 mo: -7.1 **Arm 1 vs. Arm 3** 1 mo: -0.9 3 mo: -8.2 Comparison between all 3 groups: 1 mo: p=0.76 3 mo: p=0.35
	Pain-related functioning FFI-Activity 1, 3 mo	**Dextrose prolotherapy 27%** Baseline: 25.5 (15.3) 1 mo: 9.2 (12.4) 3 mo: 10.0 (12.5)	**Corticosteroid** Baseline: 25.5 (15.8) 1 mo: 9.2 (12.4) 3 mo: 12.1 (14.3)	**Arm 1 vs. Arm 2** 1 mo: 0.0 3 mo: -2.1

Author, Year Risk of Bias	Outcome Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
			Phonophoresis Baseline: 26.1 (14.6) 1 mo: 10.6 (12.2) 3 mo: 13.0 (14.9)	**Arm 1 vs. Arm 3** 1 mo: -1.4 3 mo: -3.0 Comparison between all 3 groups: 1 mo: p=0.84 3 mo: p=0.74
	Pain severity or intensity VAS 1, 3 mo	**Dextrose prolotherapy 27%** Baseline: 70.6 (11.9) 1 mo: 27.2 (23.8) 3 mo: 30.5 (27.9)	**Corticosteroid** Baseline: 71.4 (11.1) 1 mo: 27.2 (26.6) 3 mo: 41.2 (31.6) **Phonophoresis** Baseline: 71.3 (10.0) 1 mo: 30.7 (27.4) 3 mo: 42.3 (31.5)	**Arm 1 vs. Arm 2** 1 mo: 0.0 3 mo: -10.7 **Arm 1 vs. Arm 3** 1 mo: -3.5 3 mo: -11.8 Comparison between all 3 groups: 1 mo: p=0.90 3 mo: p=0.16
	QoL SF-36 Physical Functioning 1, 3 mo	**Dextrose prolotherapy 27%** Baseline: 36.8 (14.9) 1 mo: 78.1 (24.3) 3 mo: 75.3 (26.1)	**Corticosteroid** Baseline: 35.9 (15.5) 1 mo: 78.3 (24.6) 3 mo: 65.2 (29.7) **Phonophoresis** Baseline: 38.2 (15.4) 1 mo: 77.6 (23.4) 3 mo: 66.3 (30.2)	**Arm 1 vs. Arm 2** 1 mo: -0.2 3 mo: 9.9 **Arm 1 vs. Arm 3** 1 mo: 0.5 3 mo: 9.0 Comparison between all 3 groups: 1 mo: p=0.95 3 mo: p=0.30
	QoL SF-36 Physical Role 1, 3 mo	**Dextrose prolotherapy 27%** Baseline: 25.5 (35.5) 1 mo: 75.9 (32.8) 3 mo: 73.3 (32.5)	**Corticosteroid** Baseline: 30.3 (35.2) 1 mo: 77.8 (33.3) 3 mo: 56.9 (40.8) **Phonophoresis** Baseline: 31.0 (35.0) 1 mo: 79.0 (32.6) 3 mo: 56.0 (41.0)	**Arm 1 vs. Arm 2** 1 mo: -1.9 3 mo: 16.4 **Arm 1 vs. Arm 3** 1 mo: -3.1 3 mo: 17.3 Comparison between all 3 groups: 1 mo: p=0.83

Author, Year Risk of Bias	Outcome Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
				3 mo: p=0.09
	QoL SF-36 Body Pain 1, 3 mo	**Dextrose prolotherapy 27%** Baseline: 42.4 (12.0) 1 mo: 73.5 (22.4) 3 mo: 71.6 (23.6)	**Corticosteroid** Baseline: 44.6 (10.0) 1 mo: 75.7 (22.8) 3 mo: 64.0 (26.1) **Phonophoresis** Baseline: 45.8 (10.3) 1 mo: 74.2 (23.9) 3 mo: 63.0 (26.3)	**Arm 1 vs. Arm 2** 1 mo: -2.2 3 mo: 7.6 **Arm 1 vs. Arm 3** 1 mo: -0.7 3 mo: 8.7 Comparison between all 3 groups: 1 mo: p=0.83 3 mo: p=0.19
	QoL SF-36 General Health 1, 3 mo	**Dextrose prolotherapy 27%** Baseline: 41.0 (16.3) 1 mo: 56.7 (15.9) 3 mo: 56.9 (17.2)	**Corticosteroid** Baseline: 39.4 (15.6) 1 mo: 54.0 (17.6) 3 mo: 50.3 (19.9) **Phonophoresis** Baseline: 36.0 (15.1) 1 mo: 48.0 (15.2) 3 mo: 44.9 (15.5)	**Arm 1 vs. Arm 2** 1 mo: 2.7 3 mo: 6.6 **Arm 1 vs. Arm 3** 1 mo: 8.7 3 mo: 12.0 Comparison between all 3 groups: 1 mo: p=0.03 3 mo: p=0.005
	QoL SF-36 Vitality 1, 3 mo	**Dextrose prolotherapy 27%** Baseline: 29.4 (13.8) 1 mo: 48.6 (21.3) 3 mo: 49.8 (22.7)	**Corticosteroid** Baseline: 29.0 (12.7) 1 mo: 47.7 (18.3) 3 mo: 41.2 (22.2) **Phonophoresis** Baseline: 28.5 (12.2) 1 mo: 46.3 (17.7) 3 mo: 39.9 (18.5)	**Arm 1 vs. Arm 2** 1 mo: 0.9 3 mo: 8.6 **Arm 1 vs. Arm 3** 1 mo: 2.3 3 mo: 9.9 Comparison between all 3 groups: 1 mo: p=0.90 3 mo: p=0.08
	QoL SF-36 Social Functioning 1, 3 mo	**Dextrose prolotherapy 27%** Baseline: 48.0 (8.1) 1 mo: 73.1 (19.8) 3 mo: 74.8 (20.2)	**Corticosteroid** Baseline: 47.5 (9.4) 1 mo: 75.4 (19.8) 3 mo: 65.3 (22.4)	**Arm 1 vs. Arm 2** 1 mo: -2.3 3 mo: 9.5

Author, Year Risk of Bias	Outcome Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
			Phonophoresis Baseline: 48.2 (12.1) 1 mo: 75.2 (18.7) 3 mo: 65.7 (22.2)	**Arm 1 vs. Arm 3** 1 mo: -2.1 3 mo: 9.1 Comparison between all 3 groups: 1 mo: p=0.78 3 mo: p=0.07
	QoL SF-36 Emotional Role 1, 3 mo	**Dextrose prolotherapy 27%** Baseline: 33.6 (17.1) 1 mo: 52.1 (22.2) 3 mo: 51.2 (22.0)	**Corticosteroid** Baseline: 32.5 (16.6) 1 mo: 53.5 (21.4) 3 mo: 44.5 (22.9) **Phonophoresis** Baseline: 31.6 (15.4) 1 mo: 47.3 (18.1) 3 mo: 42.6 (19.5)	**Arm 1 vs. Arm 2** 1 mo: -1.4 3 mo: 6.7 **Arm 1 vs. Arm 3** 1 mo: 4.8 3 mo: 8.6 Comparison between all 3 groups: 1 mo: p=0.33 3 mo: p=0.12
	QoL SF-36 Mental Health 1, 3 mo	**Dextrose prolotherapy 27%** Baseline: 28.7 (38.1) 1 mo: 79.5 (34.3) 3 mo: 76.1 (35.4)	**Corticosteroid** Baseline: 34.7 (36.5) 1 mo: 79.3 (34.1) 3 mo: 58.5 (41.3) **Phonophoresis** Baseline: 34.2 (36.1) 1 mo: 83.0 (30.3) 3 mo: 59.2 (40.5)	**Arm 1 vs. Arm 2** 1 mo: 0.2 3 mo: 17.6 **Arm 1 vs. Arm 3** 1 mo: -3.5 3 mo: 16.9 Comparison between all 3 groups: 1 mo: p=0.88 3 mo: p=0.07
Kesikburun, 2022[67] High	Pain-related functioning FFI-Total 6, 12 wk	**Dextrose prolotherapy 15%** Baseline: 70.5 (15.4) 6 wk: 43.6 (32.9) 12 wk: 29.3 (27.7)	**ESWT** Baseline: 62.7 (12.2) 6 wk: 42.1 (21.5) 12 wk: 27.4 (25.8)	**Arm 1 vs. Arm 2** 6 wk: 1.5, NR 12 wk: 1.9, NR
	Pain severity or intensity VAS 6, 12 wk	**Dextrose prolotherapy 15%** Baseline: 80.9 (18.1) 6 wk: 48.1 (37.9) 12 wk: 34.0 (34.1)	**ESWT** Baseline: 74.6 (14.8) 6 wk: 48.9 (23.4) 12 wk: 33.9 (32.2)	**Arm 1 vs. Arm 2** 6 wk: -0.8, NR 12 wk: 0.1, NR
	Adverse Events	*"It was not detected any adverse effects during the study."*		

Author, Year **Risk of Bias**	**Outcome** **Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, p-value*** **Other results reported**
	NA 12 wk			
Kim, 2014[72] High	Pain-related functioning FFI-Total 10, 28 wk	**Dextrose prolotherapy 15%** Baseline: 132.5 (31.1) 10 wk: 123.7 (47.4) 28 wk: 97.7 (52.5)	**PRP** Baseline: 151.5 (37.9) 10 wk: 123.8 (45.4) 28 wk: 81.6 (55.3)	**Arm 1 vs. Arm 2** 10 wk: -0.1, p=0.88 28 wk: 16.1, p=0.60
	Pain-related functioning FFI-Disability 10, 28 wk	**Dextrose prolotherapy 15%** Baseline: 53.4 (15.7) 10 wk: 50.9 (22.4) 28 wk: 40.3 (21.8)	**PRP** Baseline: 55.8 (19.5) 10 wk: 49.2 (19.4) 28 wk: 31.9 (22.4)	**Arm 1 vs. Arm 2** 10 wk: 1.7, p=0.88 28 wk: 8.4, p=0.55
	Pain-related functioning FFI-Activity 10, 28 wk	**Dextrose prolotherapy 15%** Baseline: 22.6 (9.8) 10 wk: 20.4 (10.4) 28 wk: 16.4 (12.9)	**PRP** Baseline: 31.3 (10.2) 10 wk: 22.7 (11.2) 28 wk: 17.3 (11.6)	**Arm 1 vs. Arm 2** 10 wk: -2.3, p=0.77 28 wk: -0.9, p=0.94
Mansiz-Kaplan, 2020[68] Some concerns	Pain-related functioning FFI-Total 7, 15 wk	**Dextrose prolotherapy 15%** Baseline: 202 (32.4) 7 wk: 20.1 (28.9) 15 wk: 14.4 (23.1)	**Saline** Baseline: 190 (38.6) 7 wk: 113.4 (50.8) 15 wk: 118.9 (47.6)	**Arm 1 vs. Arm 2** 7 wk: -93.3, p<0.001 15 wk: -104.5, p<0.001
	Pain-related functioning FFI-Disability 7, 15 wk	**Dextrose prolotherapy 15%** Baseline: 88.2 (11.1) 7 wk: 7.4 (12.9) 15 wk: 5.6 (10.2)	**Saline** Baseline: 81.7 (16.3) 7 wk: 52.1 (23.8) 15 wk: 53.1 (22.8)	**Arm 1 vs. Arm 2** 7 wk: -44.7, p≤0.001 15 wk: -47.5, p≤0.001
	Pain-related functioning FFI-Activity 7, 15 wk	**Dextrose prolotherapy 15%** Baseline: 28 (14.5) 7 wk: 1.2 (2.8) 15 wk: 0.5 (2)	**Saline** Baseline: 23.3 (11.3) 7 wk: 9.7 (8.2) 15 wk: 10.5 (7.7)	**Arm 1 vs. Arm 2** 7 wk: -8.5, p≤0.001 15 wk: -10.0, p≤0.001
	Pain severity or intensity VAS (during activity) 7, 15 wk	**Dextrose prolotherapy 15%** Baseline: NR 7 wk: NR 15 wk: NR	**Saline** Baseline: NR 7 wk: NR 15 wk: NR	**Arm 1 vs. Arm 2** Mean time point scores and difference between arms NR
	Pain severity or intensity VAS (during rest) 7, 15 wk	**Dextrose prolotherapy 15%** Baseline: NR 7 wk: NR 15 wk: NR	**Saline** Baseline: NR 7 wk: NR 15 wk: NR	**Arm 1 vs. Arm 2** Mean time point scores and difference between arms NR
	Adverse Events NA 15 wk	*"No adverse events were observed in either group."*		

Author, Year **Risk of Bias**	**Outcome** **Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, p-value*** **Other results reported**
Raissi, 2023[70] Some concerns	Pain-related functioning FAAM-ADL 2, 12 wk	**Dextrose prolotherapy 20%** Baseline: 56.6 (10.5) 2 wk: 70.3 (10.4) 12 wk: 78.5 (10.9)	**Corticosteroid** Baseline: 57.6 (16.3) 2 wk: 76.7 (20.3) 12 wk: 70.0 (18.3)	**Arm 1 vs. Arm 2** 2 wk: -6.4, p=0.22 12 wk: -8.5, p=0.82
	Pain-related functioning FAAM-Sport 2, 12 wk	**Dextrose prolotherapy 20%** Baseline: 43.6 (14.7) 2 wk: 54.2 (15.2) 12 wk: 66.2 (14.9)	**Corticosteroid** Baseline: 47.2 (21.2) 2 wk: 66.8 (23.0) 12 wk: 70.0 (24.0)	**Arm 1 vs. Arm 2** 2 wk: -12.7, p=0.05 12 wk: -3.8, p=0.56
	Pain severity or intensity NRS (in the morning) 2, 12 wk	**Dextrose prolotherapy 20%** Baseline: 7.2 (1.6) 2 wk: 4.7 (1.8) 12 wk: 2.7 (1.7)	**Corticosteroid** Baseline: 7.0 (2.1) 2 wk: 2.8 (2.7) 12 wk: 2.7 (3.0)	**Arm 1 vs. Arm 2** 2 wk: 1.9, p=0.01 12 wk: 0.0, p=0.95
	Pain severity or intensity NRS (during the day) 2, 12 wk	**Dextrose prolotherapy 20%** Baseline: 5.6 (1.1) 2 wk: 4.1 (1.4) 12 wk: 2.5 (1.6)	**Corticosteroid** Baseline: 5.2 (1.1) 2 wk: 2.6 (1.8) 12 wk: 2.9 (2.1)	**Arm 1 vs. Arm 2** 2 wk: 1.6, p=0 12 wk: -0.4, p=0.56
Umay Altas, 2018[69] Some concerns	Pain-related functioning FFI-Total 3 mo	**Dextrose prolotherapy 15%** Basline: NR 3 mo: NR Median change (range) 34.7 (23.2-45.3), p=0.001	**Saline** Basline: NR 3 mo: NR	**Arm 1 vs. Arm 2** Mean time point scores and difference between arms NR
	Pain-related functioning FFI-Disability 3 mo	**Dextrose prolotherapy 15%** Basline: NR 3 mo: NR Median change (range) 41 (21-62), p=0.001	**Saline** Basline: NR 3 mo: NR	**Arm 1 vs. Arm 2** Mean time point scores and difference between arms NR
	Pain-related functioning FFI-Activity 3 mo	**Dextrose prolotherapy 15%** Basline: NR 3 mo: NR Median change (range) 41 (21-62), p=0.001	**Saline** Basline: NR 3 mo: NR	**Arm 1 vs. Arm 2** Mean time point scores and difference between arms NR
	Pain severity or intensity VAS 3 mo	**Dextrose prolotherapy 15%** Basline median (range): 8.0 (5.0-10.0) 3 mo: NR	**Saline** Basline median (range): 6.0 (4.0-9.0) 3 mo: NR	**Arm 1 vs. Arm 2** Mean time point scores and difference between arms NR
	Adverse Events NA 3 mo	*"No adverse effects were seen in any of our patients during the study."*		

Notes: *Mean differences calculated by review team; p-values reported by study (otherwise NR).

Abbreviations. EWST=extracorporeal shock wave therapy; FAAM-ADL=Foot and Ankle Ability Measure-Activities of Daily Living; FAAMS=Foot and Ankle Ability Measure-Sports; FAOS=Foot and Ankle Outcome Score; FFI=Foot Function Index; mo=month; NA=not applicable; NR=not reported; NRS=Numeric Rating Scale; PRP=platelet-rich plasma; QoL=quality of life; SD=standard deviation; SF36=Short-Form Survey (36-item); VAS=Visual Analog Scale; wk=week.

APPENDIX H. SHOULDER PAIN

Appendix Table 8. Detailed Study Characteristics for All Eligible Shoulder Pain Studies

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
Subacromial Bursitis/Mixed Rotator Cuff Pathology				
Bertrand, 2016[85] NCT01402011 Some concerns 9 Months Canada (1) " Supported by WorkSafeBC (Workers' Compensation Board of British Columbia; grant no. RS2010-OG07)."	**Inclusion**: 19-75 years with shoulder pain lasting >3 months, with "positive Neer sign, a positive Hawkins-Kennedy test, or positive painful arc testing. Supraspinatus pathology was required in the form of either noncalcific or calcific tendinosis, partial tear, or full-thickness tear as noted on high-resolution ultrasound scanning." **Exclusion**: "allergy to local anesthetic, unwillingness to avoid anti-inflammatories for 3 days before and 2 weeks after treatments, corticosteroid injection within the last 8 weeks, passive shoulder abduction <100 or external rotation <25 , a rotator cuff calcification diameter >0.8cm on plain film or ultrasound, grade II to IV (KellgrenLawrence classification) osteoarthritis, type III acromion, supraspinatus tear width >1.2cm, or comorbidity	**Dextrose prolotherapy**: *N*=27 Age, mean (SD): 53.8 (13.5) 41% Female Clinic or health care facility Three injections, each 1 month apart 25% dextrose volume variable (+0.1% lidocaine) injected into the "supraspinatus, infraspinatus, and teres minor insertions, as well as insertions on the coracoid process, were injected with the shoulder in neutral rotation. The biceps long head, subscapularis insertion, and inferior glenohumeral ligament were injected with the shoulder in various degrees of external rotation and abduction/adduction. Origins of the teres minor, teres major, and the posterior inferior glenohumeral ligament were injected posteriorly. Participants received injections of 1mL	**Saline/Local anesthetic**: *N*=24 Age, mean (SD): 51.1 (9.2) 32% Female Clinic or health care facility Three injections, each 1 month apart Normal aline (+0.1% lidocaine), as per intervention protocol Other treatments: Same as Arm 1 **Saline/Local anesthetic**: *N*=26 Age, mean (SD): 49.0 (11.9) 38% Female Clinic or health care facility Three injections, each 1 month apart	**Pain severity or intensity** **Adverse events** **Other outcomes:** • Pain severity or intensity: 10-point VAS

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
	severe enough to affect full participation."	of solution at each primary injection site. Other tender areas along the enthesis and adjacent to the primary site were injected at 1-cm intervals, each with 0.5mL of solution" Other treatments: Physical therapy after each injection (included ice massage), particpants "encouraged to maintain the exercise program 3 times a week through the point of 3 month follow-up."	Normal saline (+0.1% lidocaine), injected superficially (0.5-1.0 cm) to painful entheses Other treatments: Same as Arm 1	
Chang, 2021[75] NCT03447158 Some concerns 3 Months Taiwan (1) NR	**Inclusion**: 20-65 years, shoulder pain lasting >3 months, "painful arc between 40 and 120 during abduction, tested positive on impingement tests, experienced pain during daily life activities, and had a subacromial bursa thickness of more than 2 mm on musculoskeletal ultrasound examination" **Exclusion**: "shoulder pain associated with trauma, adhesive capsulitis, a fullthickness rotator cuff tear, or a bicep tendon rupture; contraindications to local dextrose injection…; steroid injection or surgical treatment for shoulder pain; or regular oral nonsteroidal	**Dextrose prolotherapy**: *N*=25 Age, mean (SD): 46.40 (9.59) 36% Female Clinic or health care facility 3 sessions, each 2 weeks apart 13.5% dextrose 5 ml (+ 0.1% xylocaine), injected into the subacromial bursa, ultrasound guided Other treatments: None reported	**Saline/Local anesthetic**: *N*=25 Age, mean (SD): 47.72 (11.79) 44% Female Clinic or health care facility 3 sessions, each 2 weeks apart Normal saline 5 ml (+ 0.1% xylocaine), injected into the subacromial bursa, ultrasound guided Other treatments: None reported	**Pain severity or intensity** **Pain-related functioning (1, 3 wk, 3 mo)** • SPADI **Physical performance (5 wk, 2, 4 mo)** • Flexion • Abduction **Adverse events** **Other outcomes:** • Pain severity or intensity: 10-point VAS max and 10-point VAS at rest

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
	anti-inflammatory drug or steroid treatment"			
Sam, 2023[79] NCT05131269 High 12 Weeks Indonesia (1) "no funding"	**Inclusion**: "35 to 70 years; and diagnosis of FS by criteria (with chronic symptoms (>3 months):The pain in the shoulder during activities. Pain occurring insidiously in the deltoid region with increasing shoulder stiffness. Pain and restriction of ROM by testing. No apparent crepitus in movement." **Exclusion**: "Previous intra-articular injection within 3 months; Previous use of non-steroidal anti-inflammatory drugs (NSAIDs) 1 week before intervention; or contraindications to prolotherapy include inflammatory disease (abscess, cellulitis, or septic arthritis)."	**Dextrose prolotherapy**: *N*=26 Age, mean (SD): 58.16 (6344 (sic)) 68.4% Female Clinic or health care facility 4 sessions, each two weeks apart Dextrose (% NR, volume NR), injected into “points on the rotator cuff include the supraspinatus, infraspinatus, teres minor, and subscapularis. Intraarticular injection of the glenohumeral joint, subacromial bursa, long head biceps tendon, and acromioclavicular joint…” Other treatments: None reported	**Normal Saline/Local anesthetic**: *N*=25 Age, mean (SD): 57.60 (10.704) 55% Female Clinic or health care facility 4 sessions, each two weeks apart Normal saline (volume NR), as per intervention protocol Other treatments: None reported	**Ratio of MMP-1/TIMP-1** **Pain-related functioning (6, 12 wk)** • DASH **Physical performance (6, 12 wk)** • Flexion • Extension • Abduction • Adduction • External rotation • Internal rotation **Other outcomes:** • Pain severity or intensity: 10-point NRS
Sari, 2020[82] NR Some concerns 24 Weeks	**Inclusion**: 18–75 years, shoulder pain lasting >3 months, “had RC pathology (bursitis, RC tendinosis, or partial tears grade I) treated with non-invasive treatments, including NSAIDs and/or at least 2 months of regular exercise and/or physical therapy agents…; and their condition had been evaluated via	**Dextrose prolotherapy**: *N*=32 Age, mean (SD): NR (NR) % Female NR Clinic or health care facility	**PRP**: *N*=33 Age, mean (SD): NR (NR) % Female NR Clinic or health care facility	**Primary outcome NR** **Pain-related functioning (3, 12, 24 wk)** • ASES • WORC **Other outcomes:**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
Turkey (NR) NR	clinical and physical examination and confirmed with recent MRI" **Exclusion**: "RC total or > grade 1 partial rupture, treatment with NSAID within the last week, allergic reactions to disinfectants, local anesthetics, sodium citrate and calcium chloride, thrombocytopenia, acute and chronic infections, anticoagulation or anti-aggregation therapy, any previous shoulder injection, glaucoma, hypertension, systemic allergy or hypersensitivity, severe renal or hepatic insufficiency, within 6–12 weeks of surgery at the treatment site, malignancy, pregnancy, uncontrolled diabetes, prosthetic joint,… significant skin breakdown at the proposed injection site, the presence of a joint prosthesis, joint instability, adjacent superficial skin lesions or abrasions, severe osteoporosis of bones adjacent to the joint…"	Single injection 16% dextrose 5 ml (+ 0.2% lidocaine), participants positioned "in an upright position with the arms behind the back, internal rotation, shoulder in hyperextension, and elbow 90 degrees parallel to the ground" injected "on the sagittal axis with the long axis in plane technique" into the subacromial bursae, ultrasound-guided Other treatments: Participants "told not to take any pain medication other than paracetamol" and received "standard shoulder strengthening and stretching exercise programs"	Single injection PRP 5 ml, as per intervention protocol Other treatments: Same as Arm 1 **Steroid injectable**: *N*=33 Age, mean (SD): NR (NR) % Female NR Clinic or health care facility Single injection Triamcinolone 80 mg (+0.6% lidocaine), as the intervention protocol Other treatments: Same as Arm 1 **Saline/Local anesthetic**: *N*=31 Age, mean (SD): NR (NR) % Female NR Clinic or health care facility Single injection	• Pain severity or intensity: 10-point VAS

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
			Normal saline 6 ml (+0.6% lidocaine), as per intervention protocol Other treatments: Same as Arm 1	
Lin, 2023[73] NCT04916353 Some concerns 12 Weeks Taiwan (1) NR	**Inclusion**: >20 years with chronic shoulder pain lasting >6 months, and chronic subacromial bursitis on ultrasound **Exclusion**: "shoulder pain comorbid with adhesive capsulitis and limited range of motion…; history of joint replacement or arthroscopy surgery in the affected shoulder;… history of steroid, hyaluronic acid, or platelet-rich plasma injection or any type of injection in the shoulder joint within the previous 3 mos;… neurological disease that caused weakness on the affected side and impaired cognitive function…; or simultaneously participating in another clinical trial…"	**Dextrose prolotherapy**: *N*=28 Age, mean (SD): 53.21 (9.15) 35.7% Female Clinic or health care facility Single injection 20% dextrose 3 ml, participants in modified Crass position, injected into the subacromial bursitis using an in-plane approach, ultrasounded-guided Other treatments: None reported	**Steroid injectable**: *N*=26 Age, mean (SD): 57.46 (11.49) 57.7% Female Clinic or health care facility Single injection Triamcinolone 40 mg (+ lidocaine %NR), as per intervention protocol Other treatments: None reported	**Pain severity or intensity and pain-related functioning** **Pain-related functioning (2, 6, 12 wk)** • SPADI **Physical performance (2, 6, 12 wk)** • Flexion • Abduction • Internal rotation • External rotation **Other outcomes:** • Pain severity or intensity: 10-point VAS
Nasiri, 2021[80] IRCT20191129045542N1 Some concerns	**Inclusion**: 30-65 years, symptoms “including shoulder pain and loss of range of motion” ≥6 months or refractory to ≥3 months of “conservative methods with definitive clinical	**Dextrose prolotherapy**: *N*=20 Age, mean (SD): 50.52 (9.08) 64.7% Female	**Steroid injectable**: *N*=20 Age, mean (SD): 47.06 (8.90) 62.5% Female	**Primary outcome NR** **Pain-related functioning (3, 12 wk)** • SPADI

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
12 Weeks Iran (1) Shirza University of Medical Sciences	diagnosis of RC lesions which were confirmed by history, physical examination…, and ultrasonography… referring to physical medicine and rehabilitation units..." **Exclusion**: "rheumatic disease, diabetes mellitus, osteomyelitis, active infectious disease, history of chronic infections in the treatment area,… previous operation of the involved shoulder,… local injection at treatment area in previous 12 weeks, bleeding tendency, pregnancy, and frozen shoulder..."	Clinic or health care facility; Home Single injection 25% dextrose 2 ml (+ 1% lidocaine), participants positioned "in lateral decubitus and the involved arms were behind their backs," injected into "multiple points of the hypoechoic supraspinatus tendon," ultrasound-guided Other treatments: Participants were told to apply cold packs for up to three days after injection, not use anti-inflammatory drugs other than acetaminophen. Participants also enrolled in an exercise program which included" pendulum and wall walking exercises… 3 times a day for 5-10 minutes… as well as wall push-up exercise…"	Clinic or health care facility; Home Single injection Triamcinolone 40 mg (+ 1% lidocaine), positioned as per intervention group, injected into the "subacromial bursa using an injection site that is in posterolateral aspect of the acromion" Other treatments: Same as Arm 1	**Adverse events** **Other outcomes:** • Pain severity or intensity: 10-point VAS
Mofrad, 2021[81] IRCT20181217042028N1 High 3 Months Iran (1)	**Inclusion**: "chronic rotator cuff tendinopathy… if they had small rotator cuff tear or tendinopathy on a magnetic resonance imaging scan, and if their symptoms lasted for more than 3 months." **Exclusion**:	**Dextrose prolotherapy**: *N*=33 Age, mean (SD): 56.9 (13.6) 48% Female Clinic or health care facility 2 doses, each 1 week apart	**Exercise/PT**: *N*=33 Age, mean (SD): 52.5 (13.9) 59% Female Home 3 wk (10 sessions, 30 minutes each)	**Pain severity or intensity** **Pain-related functioning (2 wk, 3 mo)** • SPADI **Other outcomes:** • Pain severity or intensity: SPADI Pain subscore

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
"This research did not receive any specific grant from funding agencies in public, commercial, or not-for-profit sectors."	"large or full-thickness rotator cuff tear, a history of major trauma at the shoulder, allergy to local anesthetic, and discopathies or any other spinal pathology causing shoulder pain… subdeltoid bursitis and adhesive capsulitis... previous surgery on the shoulder of the affected side… any intra-articular injection within the last year, rheumatoid arthritis or other inflammatory joint diseases, immunodeficiency, diabetes mellitus, active joint infections, and coagulation disorders."	12.5% dextrose 8 ml (+ lidocaine %NR), participants were "positioned supine with the arm placed in supination," and injected superficially into "the anterior, posterior, and lateral sides of the shoulder and also to tender points" Other treatments: Participants instructed to not "use analgesics except for as-needed acetaminophen"	"Participants received 20 minutes of superficial heat using hot pack. Then, we prescribed transcutaneous electrical nerve stimulation…,80 to 100 Hz for 100 to 200 milliseconds with a maximum tolerable intensity. In addition, patients received pulsed ultrasound… 1 MHz, 0.8 to 1.0 W/cm2, 50% duty cycle, 5 minutes per session." The PT "consisted of stretching and flexibility, range of motion, and strengtehning exercises of the shoulder and rotator cuff." Other treatments: Same as arm 1	
Seven, 2017[83] NR Some concerns 1 Years Turkey (NR) NR	**Inclusion**: 30-60 years, symptoms lasting > 6 months and refractory to ≥3 months of "conservative methods, and rotator cuff lesions in the form oftendinosis, partial tear as determined on MRI" **Exclusion**: "Patients with rheumatic disease or other systemic inflammatory disease, diabetes mellitus, osteomyelitis, active infection or history of chronic infection in the treatment area, previous operation on the shoulder, local corticosteroid injection within previous 12 weeks, bleeding	**Dextrose prolotherapy**: *N*=60 Age, mean (SD): 50.19 (12.13) 45.2% Female Clinic or health care facility 6 sessions 22.5% dextrose 4 ml (+ lidocaine %NR) in subacromial bursa and 13.5% dextrose 20 ml (+ lidocaine %NR), participants position "in an upright position and the arms were position behind their backs with internal rotation and hyperextension of	**Exercise/PT**: *N*=60 Age, mean (SD): 46.31 (10.6) 45.7% Female Clinic or health care facility; Home 3 30-minute sessions + 3 sessions a day "Limited glenohumeral internal rotation and tightness of muscles originating from the coracoid process were rehabilitated with open stretching in the supine position, while patients one arm extended out into a keep their palm	**Pain severity or intensity** **Pain-related functioning (3, 6, 12 wk, 1 yr)** • SPADI • WORC **Physical performance (3, 6, 12 wk, 1 yr)** • Forward flexion • Internal rotation • Abduction • External rotation **Adverse events**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
	tendency (hereditary or acquired), evidence of infection (systemic or local to shoulder), and pregnancy"	the shoulder and the elbow bent for longitudinal supraspinatus view," injections were as follows:" 4 mL of prolotherapy solution (a mixture containing 3.6 mL of 25% dextrose and 0.4 mL lidocaine) was injected to the subacromial bursa using an injection site that is in posterolateral aspect of the acromion, and a maximum of 20 mL dextrose solution (a mixture containing 18 mL of 15% dextrose and 2 mL lidocaine) to supraspinatus, infraspinatus, teres minor insertions (tuberculum majus), pectoralis minor, coracobrachialis and biceps brachii insertions (coracoid process) with the shoulder in neutral rotation. The biceps long head, subscapularis, and inferior glenohumeral ligament insertions (supraglenoid tubercle, tuberculum minus) were injected with the shoulder in external rotation and abduction/adduction. Origins of the teres minor, teres major, and the posterior inferior glenohumeral ligament were injected posteriorly," ultrasound-guided Other treatments: Participants were told to apply hot water bags and not use anti-inflammatory drugs other than acetaminophen. Participants also received a home exercise program 3 times a day after injections	facing down and arm at 90° to their body. Other arm is by their other shoulder. They slowly roll the other side of their body off the floor, and rotation–stretching exercises; while the patients lay on their back with their shoulder abducted to 90° and elbow flexed to 90°, the physiotherapist externally rotates the shoulder. Scapula control was provided by exercises of the trapezius and serratus anterior muscles with the arm below 90° of abduction. RC activation exercises were then given, including horizontal and vertical closed-chain, horizontal open-chain, and diagonal closed-chain exercises. In closed-chain exercises, patient's hands remain in a fixed position while their body moves. They keep their hand stationary stabilizes the supporting muscles of their shoulder without putting unwanted stress on the joint and its supporting connective tissue. In open-chain exercises, patient's body remains in place and the limb performing the action moves and overcome the resistance. The final stage open-chain plyometric exercises were given. Patients were instructed to refrain from any heavy lifting activity. The patients were also advised to perform a home exercise program with same exercises on their own three times a day for the other days."	**Other outcomes:** • Pain severity or intensity: 10-point VAS

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
			Other treatment: Same as Arm 1, sans hot water bags	
Supraspinatus Tendinoapthy Only				
Abd Karim, 2023[78] NCT04640662 High 6 Months Malaysia (1) "This research was funded by a grant from UMSC care fund (pV062-2018), faculty of Medicine, university of Malaya."	**Inclusion**: ">18 years old with shoulder pain lasting > 3 months, supraspinatus tendinosis or partial tendon tear seeon on imaging, unresponsive to ≥3 months of conventional treatment (physiotherapy or steroid injection)" **Exclusion**: "shoulder pain caused by referred pain from the cervical spine, shoulder surgery within the previous year, shoulder instability, complete rotator cuff tear, and adhesive capsulitis; medical conditions such as autoimmune rheumatology conditions, blood disorders, and malignancies; and medication such as anticoagulants, recent injections of corticosteroids, or other substances into the involved shoulder within the previous 6 months"	**Dextrose prolotherapy**: *N*=32 Age, mean (SD): 51.1 (12.6) 46.4% Female Clinic or health care facility Single injection 16.7% dextrose 3 ml (+ lignocaine % NR), patients positioned prone at the edge of a bed with the affected hand at the ipsilateral lower back at the iliac bone, injection site cleaned with 10% povidone-iodine and spirit solutions, ultrasound-guided Other treatments: Cryotherapy used on the shoulder for ten minutes after injection, participants "instructed to avoid NSAIDS."	**PRP**: *N*=32 Age, mean (SD): 57.8 (11.5) 53.6% Female Clinic or health care facility Single injection 3 ml PRP 2 ml PRP injected into supraspinatus tendons, as per intervention protocol Other treatments: Same as Arm 1	**Pain-related functioning, pain severity or intensity** **Pain-related functioning (3 & 6 wk, 3 & 6 mo)** • SPADI **Physical performance (3 & 6 wk, 3 & 6 mo)** • Abduction • Forward flexion • Internal rotation • External rotation **Adverse events** **Other outcomes:** • Pain severity or intensity
Cole, 2017[84] NR High	**Inclusion**: > 18 years old, symptomatic supraspinatus tendinopathy lasting ≥ 3 months, "diagnosed on the basis of a history of shoulder	**Dextrose prolotherapy**: *N*=17 Age, mean (SD): 51 (16) 23.5% Female	**Corticosteroid injection**: *N*=19 Age, mean (SD): 46 (15) 26.3% Female	**Pain severity or intensity with overhead activities** **Physical performance (6 wk, 3 & 6 mo)** • Forward flexion

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
3 Months Australia (1) None	pain with overhead activities, positive impingement signs, pain with supraspinatus testing and ultrasound evidence of abnormal hypoechoic areas or anechoic clefts or foci in the supraspinatus tendon suggesting tendinopathy" **Exclusion**: "previous shoulder surgery in the past 12 months, rotator cuff tears greater than 50% of the tendon thickness, calcific tendinitis, adhesive capsulitis, inflammatory arthritis, acromioclavicular joint pain, os acromiale, glenohumeral osteoarthritis, previous fracture in the past 6 months, bone tumours or osteonecrosis as seen on X-ray"	Clinic or health care facility Single injection 25% dextrose 2 ml (+ 0.5% lignocaine), "injected into the area of supraspinatus tendinopathy," ultrasound-guided Other treatments: None reported	Clinic or health care facility Single injection Methylprednisolone 40 mg (+ 0.5% lignocaine), injected "into the subacromial bursa adjacent to the area of supraspinatus tendinopathy," ultrasound-guided Other treatments: None reported	• Abduction • External rotation **Other outcomes:** • Pain severity or intensity: 5-point Likert (activities above the head) and 5-point Likert (during sleep)
George, 2018[77] 43520960 High 12 Weeks Malaysia (1) Post Graduate Research Grant (no. P0155/2010B)	**Inclusion**: "duration of symptoms up to 6 months, supraspinatus tendinosis confirmed on ultrasound, and failure of functional score to improve more than 30% after 1 month of conventional treatment, which was physiotherapy and analgesics" **Exclusion**: "mechanical impingement as cause of shoulder pain based on ultrasound dynamic testing for	**Dextrose prolotherapy**: *N*=7 Age, mean (SD): 60 (NR) % Female NR Clinic or health care facility Single injection 12.5% dextrose 0.5-1.0 ml (+0.5% lignocaine), injected "into area of painful tendinosis." Prior to	**Exercise/PT**: *N*=5 Age, mean (SD): 58 (NR) % Female NR NR NR Other treatments: "standard physiotherapy"	**Primary outcome NR** **Pain-related functioning (12 wk)** • DASH **Other outcomes:** • Pain severity or intensity: DASH Pain subscore

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
of the University of Malaya	impingement…, autoimmune diseases, patients on anticoagulants, congenital or acquired platelet dysfunction abnormality/disorder, haemoglobin level less than 10g/L and/or platelet count less than 100,000/μL, corticosteroid or any shoulder injection within the past 6 weeks, and self-reported immunocompromised status."	prolotherapy injection, the area of tendinosis was needled and lignocaine was injected "along the intended tract prior to prolotherapy injection." Ultrasound-guided. Other treatments: Physiotherapy provided 2 weeks after injection		
Lin, 2022[74] NCT03000205 Low 12 Weeks Taiwan (1) NR	**Inclusion**: >20 years, experiencing chronic shoulder pain >6 months, with "ultrasound findings of chronic degenerative supraspinatus tendinosis" **Exclusion**: "pain comorbid with adhesive capsulitis and limited shoulder ROM;… history of … joint replacement or arthroscopy surgery on the affected shoulder;… steroid, hyaluronic acid, platelet rich plasma injection, or any other type of injection in the shoulder joint within the 3 months preceding the study;… neurologic disease causing weakness of the affected side and impairing cognitive function ;… simultaneously participating in another clinical trial…"	**Dextrose prolotherapy**: *N*=29 Age, mean (SD): 49.10 (8.44) 50% Female Clinic or health care facility Single injection 20% dextrose 5 ml, "injected into the insertion site of the supraspinatus tendon" Other treatments: None reported	**Saline/Local anesthetic**: *N*=28 Age, mean (SD): 52.18 (9.83) 44.8% Female Clinic or health care facility Single injection Normal saline, as per intervention protocol Other treatments: None reported	**Pain severity or intensity, pain-related functioning** **Pain-related functioning (2, 6, 12 wk)** • SPADI **Physical performance (2, 6, 12 wk)** • Flexion • Abduction • Internal rotation • External rotation **Other outcomes:** • Pain severity or intensity: 10-point VAS

Abbreviations. AE=adverse effect/event; ASES= American Shoulder and Elbow Surgeons Standardized Shoulder Assessment; DASH=disability of the arm, shoulder, and hand; MCID=minimal clinically important difference; mg=milligram; MRI= Magnetic resonance imaging; NR=not reported; NSAIDs= Non-steroidal anti-inflammatory drugs; PRP=platelet rich plasma; PT=physical therapy; SPADI=Shoulder Pain and Disability Index; RC=rotator cuff; RCT=randomized controlled trial; WORC=Western Ontario Rotator Cuff Index.

Appendix Table 9. Detailed Results for All Eligible Shoulder Pain Studies

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, P-value* Other results reported
Subacromial Bursitis/Mixed Rotator Cuff Pathology				
Bertrand, 2016[85] Some concerns	Pain severity or intensity 10-point VAS 3, 9 mo	**Prolotherapy** Baseline: 7.3 (0.4) 3 mo: NR 9 mo: NR	**Normal Saline (same injection technique)** Baseline: 6.9 (0.5) 3 mo: NR 9 mo: NR	**Arm 1 vs. Arm 2** 3 mo:NR 9 mo: NR
			Normal Saline (superficial injection only) Baseline: 6.9 (0.4) 3 mo: NR 9 mo: NR	**Arm 1 vs. Arm 3** 3 mo: NR 9 mo: NR
	Adverse events Narrative description 9 mo	*"One subject in the* [Normal] *Saline group developed adhesive capsulitis, with resolution after therapy provision, but was removed from the study. No other side effects or adverse events were noted other than discomfort with injection and minor postinjection soreness."*		
Chang, 2021[75] Low	Pain-related functioning or interference SPADI-total 1 wk, 1, 3 mo	**Prolotherapy** Baseline: 50.16 (27.31) 1 wk: 27.6 (18.63) 1 mo: 25.2 (18.78) 3 mo: 19.16 (20.51)	**Saline** Baseline: 57.80 (26.96) 1 wk: 43.12 (26.31) 1 mo: 34.68 (28.51) 3 mo: 28.64 (28.02)	**Arm 1 vs. Arm 2** 1 wk: -15.52, NR 1 mo: -9.48, NR 3 mo: -9.48, NR
	Pain-related functioning or interference SPADI disability 1 wk, 1, 3 mo	**Prolotherapy** Baseline: 25.08 (27.31) 1 wk: 13.4 (11.39) 1 mo: 13.28 (11.45) 3 mo: 8.8 (12.0)	**Saline** Baseline: 29.12 (19.79) 1 wk: 21.96 (16.36) 1mo: 17.64 (16.94) 3 mo: 14.40 (16.45)	**Arm 1 vs. Arm 2** 1 wk: -8.56, NR 1 mo: -4.36, NR 3 mo: -5.60, NR
	Physical performance Flexion 3 mo	**Prolotherapy** Baseline: 146.8 (23.04) 1 wk: 160.8 (17.0) 1 mo: 163.6 (14.2) 3 mo: 168.8 (11.8)	**Saline** Baseline: 144.60 (25.66) 1 wk: 150.2 (24.0) 1 mo: 157.0 (20.2) 3 mo: 160.2 (22.80)	**Arm 1 vs. Arm 2** 1 wk: 10.6, NR 1 mo: 6.6, NR 3 mo: 8.6, NR
	Physical performance Abduction 3 mo	**Prolotherapy** Baseline: 117.4 (23.04) 1 wk:138.4 (32.2) 1 mo: 138.6 (31.5) 3 mo: 153.0 (29.5)	**Saline** Baseline: 115.60 (27.20) 1 wk: 127.8 (31.3) 1 mo: 137.6 (30.7) 3 mo: 144.0 (31.3)	**Arm 1 vs. Arm 2** 1 wk: 10.6, NR 1 mo: 1.0, NR 3 mo: 9, NR
	Pain severity or intensity	**Prolotherapy**	**Saline**	**Arm 1 vs. Arm 2**

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, P-value*** **Other results reported**
	10-point VAS max 1 wk, 1, 3 mo	Baseline: 7.36 (2.06) 1 wk: 4.52 (2.34) 1 mo: 3.84 (2.43) 3 mo: 3.0 (2.45)	Baseline: 7.68 (1.70) 1 wk: 5.68 (2.27) 1 mo: 4.8 (2.83) 3 mo: 4.24 (3.02)	1 wk: -1.16, NR 1 mo: -0.96, NR 3 mo: -1.24, NR
	Pain severity or intensity 10-point VAS at rest 1 wk, 1, 3 mo	**Prolotherapy** Baseline: 7.36 (2.06) 1 wk: 4.52 (2.34) 1 mo: 3.84 (2.43) 3 mo: 3.0 (2.45)	**Saline** Baseline: 7.68 (1.7) 1 wk: 5.68 (2.27) 1 mo: 4.8 (2.83) 3 mo: 4.24 (3.02)	**Arm 1 vs. Arm 2** 1 wk: -1.16, NR 1 mo: -0.96, NR 3 mo: -1.24, NR
	Pain severity or intensity SPADI pain 1 wk, 1, 3 mo	**Prolotherapy** Baseline: 7.36 (2.06) 1 wk: 4.52 (2.34) 1 mo: 3.84 (2.43) 3 mo: 3.0 (2.45)	**Saline** Baseline: 7.68 (1.7) 1 wk: 5.68 (2.27) 1 mo: 4.80 (2.83) 3 mo: 4.24 (3.02)	**Arm 1 vs. Arm 2** 1 wk: -1.16, NR 1 mo: -0.96, NR 3 mo: -1.24, NR
	Adverse events Narrative description 3 mo	One member of the dextrose prolotherapy group dropped out due to “side effect.”		
Lin, 2023[73] Some concerns	Pain-related functioning or interference SPADI 2, 6, 12 wk	**Prolotherapy** Baseline: 53.1 (9.6) 2 wk: 39.3 (10.8) 6 wk: 40.1 (10.6) 12 wk: 51.6 (9.4)	**Corticosteriod** Baseline: 55.0 (10.0) 2 wk: 30.0 (10.1) 6 wk: 27.7 (10.2) 12 wk: 33.7 (9.4)	**Arm 1 vs. Arm 2** 2 wk: 9.3, p=0.002 6 wk: 12.4, p<0.001 12 wk: 17.9, p<0.001
	Physical performance Flexion 12 wk	**Prolotherapy** Baseline: 144.6 (9.5) 12 wk: 140.5 (12.8)	**Corticosteroid** Baseline: 142.8 (10.6) 12 wk: 157.2 (7.1)	**Arm 1 vs. Arm 2** 12 wk: -16.7, p<0.001
	Physical performance Abduction 12 wk	**Prolotherapy** Baseline: 137.3 (9.5) 12 wk: 133.9 (15.2)	**Corticosteroid** Baseline: 136.3 (14.1) 12 wk: 157.5 (12.4)	**Arm 1 vs. Arm 2** 12 wk: -23.6, p<0.001
	Physical performance Internal rotation 12 wk	**Prolotherapy** Baseline: 44.6 (9.5) 12 wk: 45.4 (6.7)	**Corticosteroid** Baseline: 43.8 (9.8) 12 wk: 54.2 (4.4)	**Arm 1 vs. Arm 2** 12 wk: -8.8, p<0.001
	Physical performance External rotation 12 wk	**Prolotherapy** Baseline: 57.9 (9.5) 12 wk: 53.6 (4.9)	**Corticosteroid** Baseline: 55.4 (11.0) 12 wk: 61.5 (5.1)	**Arm 1 vs. Arm 2** 12 wk: -7.9, p<0.001
	Pain severity or intensity	**Prolotherapy**	**Corticosteriod**	**Arm 1 vs. Arm 2**

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, P-value*** **Other results reported**
	10-point VAS 2, 6, 12 wk	Baseline: 6.0 (1.4) 2 wk: 4.9 (1.4) 6 wk: 4.3 (1.0) 12 wk: 4.0 (1.3)	Baseline: 6.3 (0.8) 2 wk: 2.9 (1.2) 6 wk: 3.0 (1.7) 12 wk: 3.7 (1.3)	2 wk: 2, p<0.001 6 wk: 1.3, p=0.001 12 wk: 0.3, p=0.39
Mofrad, 2021[81] High	Pain-related functioning or interference Modified SPADI Disability 2 wk, 3 mo	**Prolotherapy** Baseline: 75.3 (12.20) 2 wk: 30.2 (95% CI 24.5, 38.0) 3 mo: 35.6 (95% CI 30.4, 41.4)	**Physiotherapy** Baseline: 62.0 (5.50) 2 wk: 35.8 (95% CI 33.5, 37.8) 3 mo: 32.0 (95% CI 30.4, 33.6)	**Arm 1 vs. Arm 2** 2 wk: -5.6, NR 3 mo: 3.6, p=0.219
	Pain-related functioning or interference Modified SPADI Total 2 wk, 3 mo	**Prolotherapy** Baseline: 78.1 (9.0) 2 wk: 30.9 (95% CI 24.5, 36.2) 3 mo: 35.7 (95% CI 30.0, 41.0)	**Physiotherapy** Baseline: 62.6 (5.8) 2 wk: 34.3 (95% CI 32.0, 37.2) 3 mo: 31.3 (95% CI 30.1, 32.6)	**Arm 1 vs. Arm 2** 2 wk: -3.4, NR 3 mo: 4.4, NR
	Pain severity or intensity Modified SPADI Pain domain 2 wk, 3 mo	**Prolotherapy** Baseline: 82.7 (6.5) 2 wk: 31.5 (95% CI 23.9, 39.4) 3 mo: 35.7 (95% CI 29.7, 41.2)	**Physiotherapy** Baseline: 63.4 (9.6) 2 wk: 31.5 (95% CI 28.4, 34.8) 3 mo: 29.9 (95% CI 27.7, 32.0)	**Arm 1 vs. Arm 2** 2 wk: 0.0, NR 3 mo: 5.8, p=0.064
	Adverse events Narrative description 3 mo	*"None of the participants reported important adverse effects for the treatments. Particularly, we did not find adverse reactions to dextrose prolotherapy except for postinjection soreness in 6 patients."*		
Nasiri, 2021[80] Some concerns	Pain-related functioning or interference SPADI 3, 12 wk	**Prolotherapy** Baseline: 44.54 (NR) 3 wk: 29.62 (NR) 12 wk: 19.14 (NR)	**Corticosteriod** Baseline: 65.75 (NR) 3 wk: 23.24 (NR) 12 wk: 21.90 (NR)	**Arm 1 vs. Arm 2** 3 wk: 6.38, p=0.29 12 wk: -2.76, p=0.83
	Pain severity or intensity 10-point VAS 3, 12 wk	**Prolotherapy** Baseline: 6.83 (NR) 3 wk: 4.46 (NR) 12 wk: 2.60 (NR)	**Corticosteriod** Baseline: 8.28 (NR) 3 wk: 3.46 (NR) 12 wk: 3.90 (NR)	**Arm 1 vs. Arm 2** 3 wk: 1, p=0.24 12 wk: -1.30, p=0.41
	Adverse events Narrative description 12 wk	*"developed exacerbation of pain after injections and therefore… excluded from study"* 12 wk: 3 (18%)	*"developed exacerbation of pain after injections and therefore… excluded from study"* 12 wk: 1 (6%)	**Arm 1 vs. Arm 2** 12 wk: 2, NR
Sam, 2023[79] Low	Pain-related functioning or interference DASH 6, 12 wk	**Prolotherapy** Baseline: 52.50 (13.69) 6 wk: 13.51 (9.73) 12 wk: 10.01 (10.06)	**Saline** Baseline: 49.90 (9.67) 6 wk: 20.28 (10.95) 12 wk: 13.34 (10.77)	**Arm 1 vs. Arm 2** 6 wk: -6.77, p=0.05 12 wk: -3.33, p=0.17

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, P-value*** **Other results reported**
	Physical performance Flexion 12 wk	**Prolotherapy** Baseline: 129.60 (16.10) 12 wk: 151.05 (29.70)	**Saline** Baseline: 123.87 (19.64) 12 wk: 140.75 (31.47)	**Arm 1 vs. Arm 2** 12 wk: 10.3, p=0.31
	Physical performance Extension 12 wk	**Prolotherapy** Baseline: 45.92 (16.10) 12 wk: 53.16 (11.81)	**Saline** Baseline: 44.75 (18.99) 12 wk: 47.75 (10.57)	**Arm 1 vs. Arm 2** 12 wk: 5.41, p=0.13
	Physical performance Abduction 12 wk	**Prolotherapy** Baseline: 125.00 (16.10) 12 wk: 153.68 (26.71)	**Saline** Baseline: 117.13 (24.00) 12 wk: 140.50 (32.96)	**Arm 1 vs. Arm 2** 12 wk: 13.18, p=0.25
	Physical performance Adduction 12 wk	**Prolotherapy** Baseline: 47.63 (16.10) 12 wk: 57.37 (10.46)	**Saline** Baseline: 49.50 (22.09) 12 wk: 56.00 (7.71)	**Arm 1 vs. Arm 2** 12 wk: 1.37, p=0.87
	Physical performance External rotation 12 wk	**Prolotherapy** Baseline: 43.68 (16.10) 12 wk: 66.58 (21.67)	**Saline** Baseline: 46.75 (26.03) 12 wk: 55.00 (22.77)	**Arm 1 vs. Arm 2** 12 wk: 11.58, p=0.11
	Physical performance Internal rotation 12 wk	**Prolotherapy** Baseline: 61.05 (16.10) 12 wk: 75.00 (12.91)	**Saline** Baseline: 53.13 (25.34) 12 wk: 71.25 (14.13)	**Arm 1 vs. Arm 2** 12 wk: 3.75, p=0.42
	Pain severity or intensity 10-point NRS 6, 12 wk	**Prolotherapy** Baseline: 5.32 (1.00) 6 wk: 1.10 (0.83) 12 wk: 0.62 (0.80)	**Saline** Baseline: 5.60 (0.68) 6 wk: 2.00 (1.26) 12 wk: 2.43 (1.16)	**Arm 1 vs. Arm 2** 6 wk: -0.9, p=0.02 12 wk: -1.81, p=0.00
Sari, 2020[82] Some concerns	Pain-related functioning or interference ASES 3, 12, 24 wk	**Prolotherapy** Baseline: 45 (9.42) 3 wk: 52.6 (11.25) 12 wk: 56.1 (9.62) 24 wk: 60.37 (11.4)	**PRP** Baseline: 46.28 (8.61) 3 wk: 46.17 (7.9) 12 wk: 55.78 (7.9) 24 wk: 63.87 (11.96)	**Arm 1 vs. Arm 2** 3 wk: 6.43, NR 12 wk: 0.32, NR 24 wk: -3.5, NR
			Corticosteriod Baseline: 40.13 (8.18)	**Arm 1 vs. Arm 3** 3 wk: -8.1 p=0.019

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, P-value* Other results reported
			3 wk: 60.7 (11.49) 12 wk: 58.1 (9.03) 24 wk: 55.63 (11)	12 wk: -2, NR 24 wk: 4.74, NR
			Lidocaine Baseline: 47.27 (7.44) 3 wk: 55.67 (10.5) 12 wk: 58.85 (8.88) 24 wk: 60.27 (11.92)	**Arm 1 vs. Arm 4** 3 wk: -3.07, NR 12 wk: -2.75, NR 24 wk: 0.1, NR
	Pain-related functioning or interference WORC 3, 12, 24 wk	**Prolotherapy** Baseline: 53.67 (8.43) 3 wk: 52.03 (7.79) 12 wk: 46.38 (9.01) 24 wk: 91.27 (21.79)	**PRP** Baseline: 50.79 (6.48) 3 wk: 51.65 (5.79) 12 wk: 42.83 (9.63) 24 wk: 79.46 (24.09)	**Arm 1 vs. Arm 2** 3 wk: 0.38, NR 12 wk: 3.55, NR 24 wk: 11.81, NR
			Corticosteriod Baseline: 51.4 (7.73) 3 wk: 41.97 (11.05) 12 wk: 46.14 (9.64) 24 wk: 93.90 (17.94)	**Arm 1 vs. Arm 3** 3 wk: 10.06, p=0.002 12 wk: 0.24, NR 24 wk: -2.63, NR
			Lidocaine Baseline: 52.13 (7.92) 3 wk: 51.71 (9.71) 12 wk: 48.27 (7.38) 24 wk: 96.55 (20.43)	**Arm 1 vs. Arm 4** 3 wk: 0.32, NR 12 wk: -1.89, NR 24 wk: -5.28, NR
	Pain severity or intensity 10-point VAS 3, 12, 24 wk	**Prolotherapy** Baseline: 5.90 (0.88) 3 wk: 4.37 (1.16) 12 wk: 4.27 (1.36) 24 wk: 3.1 (1.52)	**PRP** Baseline: 5.63 (1.00) 3 wk: 4.83 (0.95) 12 wk: 3.9 (0.99) 24 wk: 2.57 (1.19)	**Arm 1 vs. Arm 2** 3 wk: -0.46, NR 12 wk: 0.37, NR 24 wk: 0.53, NR
			Corticosteriod Baseline: 5.63 (0.93) 3 wk: 2.43 (1.81) 12 wk: 3.53 (1.41) 24 wk: 3.77 (1.41)	**Arm 1 vs. Arm 3** 3 wk: 1.94, p=0.001 12 wk: 0.74, NR 24 wk: -0.67, NR
			Lidocaine Baseline: 5.47 (0.86) 3 wk: 4.23 (1.48)	**Arm 1 vs. Arm 4** 3 wk: 0.14, NR 12 wk: 0.4, NR

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, P-value*** **Other results reported**
			12 wk: 3.87 (0.97) 24 wk: 3.2 (1.19)	24 wk: -0.1, NR
Seven, 2017[83] Some concerns	Pain-related functioning or interference SPADI 3, 6, 12 wk, 1 yr	**Prolotherapy** Baseline: 74.76 (18.54) 3 wk: 53.17 (16.44) 6 wk: 31.30 (14.19) 12 wk: 16.12 (12.82) 1 yr: 7.66 (10.64)	**PT** Baseline: 68.62 (20.40) 3 wk: 58.70 (18.49) 6 wk: 41.97 (16.42) 12 wk: 37.25 (20.32) 1 yr: 34.94 (10.64)	**Arm 1 vs. Arm 2** 3 wk: -5.53, p=0.12 6 wk: -10.67, p=0.01 12 wk: -21.13, p<0.001 1 yr: -27.28, p<0.0001
	Physical performance Flexion 1 yr	**Prolotherapy** Baseline: 126.89 (40.89) 1 yr: 176.57 (9.50)	**PT** Baseline: 133.75 (34.84) 1 yr: 166.36 (16.95)	**Arm 1 vs. Arm 2** 1 yr: 10.21, p<0.001
	Physical performance Abduction 1 yr	**Prolotherapy** Baseline: 125.96 (40.89) 1 yr: 175.26 (12.15)	**PT** Baseline: 128.52 (34.54) 1 yr: 164.65 (17.92)	**Arm 1 vs. Arm 2** 1 yr: 10.61, p=0.001
	Physical performance Internal Rotation 1 yr	**Prolotherapy** Baseline: 59.73 (40.89) 1 yr: 68.77 (4.25)	**PT** Baseline: 56.47 (15.64) 1 yr: 66.02 (7.11)	**Arm 1 vs. Arm 2** 1 yr: 2.75, p=0.02
	Physical performance External Rotation 1 yr	**Prolotherapy** Baseline: 77.19 (40.89) 1 yr: 88.94 (4.09)	**PT** Baseline: 79.31 (17.30) 1 yr: 86.59 (9.69)	**Arm 1 vs. Arm 2** 1 yr: 2.35, p=0.10
	Health-related quality or life WORC 3, 6, 12 wk, 1 yr	**Prolotherapy** Baseline: 32.21 (17.49) 3 wk: 52.25 (16.43) 6 wk: 72.07 (14.48) 12 wk: 84.98 (12.13) 1 yr: 90.37 (10.12)	**PT** Baseline: 37.77 (16.03) 3 wk: 46.59 (15.28) 6 wk: 59.98 (16.03) 12 wk: 66.14 (17.11) 1 yr: 69.08 (10.12)	**Arm 1 vs. Arm 2** 3 wk: 5.66, p=0.08 6 wk: 12.09, p<0.001 12 wk: 18.84, p<0.001 1 yr: 21.29, p<0.001
	Pain severity or intensity 10-point VAS 3, 6, 12 wk, 1 yr	**Prolotherapy** Baseline: 7.85 (1.29) 3 wk: 5.47 (1.58) 6 wk: 3.35 (1.67) 12 wk: 2.35 (1.98) 1 yr: 0.89 (1.64)	**PT** Baseline: 7.36 (1.38) 3 wk: 6.63 (1.30) 6 wk: 4.39 (1.92) 12 wk: 4.00 (2.11) 1 yr: 3.77 (2.15)	**Arm 1 vs. Arm 2** 3 wk: -1.16, p<0.001 6 wk: -1.04, p=0.04 12 wk: -1.65, p<0.001 1 yr: -2.88, p<0.001

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	Adverse events Narrative description 1 yr	*"None of the patients in the groups experienced any serious complications (e.g., bleeding, infection, cellulitis, septic joint). Only 3 patients had extreme pain one or two days after injections in the prolotherapy group that was reduced after 2 days of rest and local application of heat therapy, 2 patients had grade 2 skin burns after first injection because of improper use of hot water bags and local anesthetic effect of the injections, and 1 patient had hypotension."*		
Supraspinatus Tendinopathy Only				
Abd Karim, 2023[78] Low	Pain-related functioning or interference SPADI Total 3, 6 wk, 3, 6 mo	**Prolotherapy** Baseline: 43.02 (23.12) 3 wk: 37.20 (22.32) 6 wk: 28.76 (20.93) 3 mo: 24.40 (21.85) 6 mo: 22.08 (20.88)	**PRP** Baseline: 47.79 (20.78) 3 wk: 39.67 (23.93) 6 wk: 36.54 (22.78) 3 mo: 30.49 (23.81) 6 mo: 28.49 (22.72)	**Arm 1 vs. Arm 2** 3 wk: -2.47, p=0.76 6 wk: -7.78, p=0.90 3 mo: -6.09, p=0.90 6 mo: -6.41, p=0.51
	Physical performance Abduction 6 mo	**Prolotherapy** Baseline: 146.29 (32.56) 6 mo: 161.00 (25.84)	**PRP** Baseline: 138.00 (34.50) 6 mo: 156.07 (26.84)	**Arm 1 vs. Arm 2** 6 mo: 4.93, p=0.58
	Physical performance Forward flexion 6 mo	**Prolotherapy** Baseline: 133.39 (32.56) 6 mo: 155.18 (30.93)	**PRP** Baseline: 126.70 (37.33) 6 mo: 144.40 (36.29)	**Arm 1 vs. Arm 2** 6 mo:10.78, p=0.27
	Physical performance Internal rotation 6 mo	**Prolotherapy** Baseline: 57.50 (32.56) 6 mo: 82.00 (20.92)	**PRP** Baseline: 67.03 (27.55) 6 mo: 86.00 (15.56)	**Arm 1 vs. Arm 2** 6 mo: -4, p=0.37
	Physical performance External rotation 6 mo	**Prolotherapy** Baseline: 54.82 (32.56) 6 mo: 78.75 (20.53)	**PRP** Baseline: 55.67 (29.99) 6 mo: 73.00 (22.65)	**Arm 1 vs. Arm 2** 6 mo: 5.75, p=0.43
	Pain severity or intensity 10-point NRS 3, 6 wk, 3, 6 mo	**Prolotherapy** Baseline: 5.86 (2.41) 3 wk: 4.04 (2.40) 6 wk: 3.39 (2.48) 3 mo: 2.82 (2.42) 6 mo: 2.71 (2.66)	**PRP** Baseline: 6.40 (2.70) 3 wk: 4.60 (2.54) 6 wk: 4.23 (2.45) 3 mo: 3.47 (2.57) 6 mo: 3.50 (2.78)	**Arm 1 vs. Arm 2** 3 wk: -0.56, p=0.55 6 wk: -0.84, p=0.73 3 mo: -0.65, p=0.73 6 mo: -0.79, p=0.41
	Adverse events 6 mo	Pain (>2 days): 12 (37.5%) Spasm/stifness: 5 (15.6%) Swelling: 2 (6.3%) Disturbed sleep: 3 (9.4%) Burisitis (ultrasound): 3 (9.4%)	Pain (>2 days): 20 (62.5%) Spasm/stifness: 7 (21.9%) Swelling: 2 (6.3%) Disturbed sleep: 6 (18.8%) Burisitis (ultrasound): 1 (3.1%)	Pain (>2 days): p=0.003 Spasm/stiffness: p=0.614 Swelling: p=0.583 Disturbed sleep: p=0.393 Bursitis (ultrasound): 1 p=0.613
Cole, 2017[84] Some concerns	Physical performance Forward flexion (degrees) 6 wk, 3, 6 mo	**Prolotherapy** Baseline: 167 (3) 6 wk: 169 (3)	**Corticosteriod** Baseline: 161 (7) 6 wk: 165 (4)	**Arm 1 vs. Arm 2** 6 wk: 4, p=0.38 3 mo: 1, p=0.70

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, P-value* Other results reported
		3 mo: 173 (2) 6 mo: 172 (2)	3 mo: 172 (3) 6 mo: 165 (7)	6 mo: 7, p=0.31
	Physical performance Abduction (degrees) 6 wk, 3, 6 mo	**Prolotherapy** Baseline: 166 (3) 6 wk: 168 (6) 3 mo: 175 (0) 6 mo: 175 (2)	**Corticosteriod** Baseline: 153 (8) 6 wk: 158 (8) 3 mo: 163 (7) 6 mo: 163 (8)	**Arm 1 vs. Arm 2** 6 wk: 10, p=0.3 3 mo: 12, p=0.1 6 mo: 12, p=0.15
	Physical performance External rotation (degrees) 6 wk, 3, 6 mo	**Prolotherapy** Baseline: 67 (3) 6 wk: 55 (3) 3 mo: 65 (3) 6 mo: 61 (3)	**Corticosteriod** Baseline: 60 (4) 6 wk: 58 (4) 3 mo: 57 (5) 6 mo: 63 (5)	**Arm 1 vs. Arm 2** 6 wk: -3, p=0.45 3 mo: 8, p=0.18 6 mo: -2, p=0.79
	Pain severity or intensity 5-point Likert (activities above the head) 6 wk, 3, 6 mo	**Prolotherapy** Baseline: 2.3 (0.2) 6 wk: 2.1 (0.2) 3 mo: 1.9 (0.2) 6 mo: 1.7 (0.2)	**Corticosteriod** Baseline: 2.6 (0.2) 6 wk: 2.4 (0.2) 3 mo: 2.2 (0.3) 6 mo: 1.7 (0.3)	**Arm 1 vs. Arm 2** 6 wk: -0.3, p=0.5 3 mo: -0.3, p=0.42 6 mo: 0.0, p=0.99
	Pain severity or intensity 5-point Likert (during sleep) 6 wk, 3, 6 mo	**Prolotherapy** Baseline: 1.5 (0.3) 6 wk: 1.7 (0.3) 3 mo: 1.4 (0.3) 6 mo: 1.4 (0.2)	**Corticosteriod** Baseline: 2.0 (0.2) 6 wk: 2.0 (0.3) 3 mo: 1.6 (0.2) 6 mo: 1.2 (0.3)	**Arm 1 vs. Arm 2** 6 wk: -0.3, p=0.69 3 mo: -0.2, p=0.37 6 mo: 0.2, p=0.53
George, 2018[77] High	Pain-related functioning or interference DASH 12 wk	**Prolotherapy** Baseline: 60.14 (NR) 12 wk: 43.89 (NR)	**Control** Baseline: 56.86 (NR) 12 wk: 46.68 (NR)	**Arm 1 vs. Arm 2** 12 wk: -2.79, p=0.36
	Pain severity or intensity Pain score (1-5, subset of DASH) 12 wk	**Prolotherapy** Baseline: 3.29 (NR) 12 wk: 1.86 (NR)	**Control** Baseline: 3.20 (NR) 12 wk: 2.40 (NR)	**Arm 1 vs. Arm 2** 12 wk: -0.54, p=0.25
Lin, 2022[74] Low	Pain-related functioning or interference SPADI 2, 6, 12 wk	**Prolotherapy** Baseline: 54.8 (10.7) 2 wk: 43.2 (12.0) 6 wk: 50.5 (14.3) 12 wk: 48.5 (16.0)	**Saline** Baseline: 57.5 (12.9) 2 wk: 52.9 (16.1) 6 wk: 51.3 (16.1) 12 wk: 49.3 (14.5)	**Arm 1 vs. Arm 2** 2 wk: -9.7, p=0.01 6 wk: -0.80, p=0.83 12 wk: -0.80, p=0.85
	Physical performance Flexion 12 wk	**Prolotherapy** Baseline: 150.5 (14.0) 12 wk: 156.5 (13.7)	**Saline** Baseline: 152.2 (9.0) 12 wk: 155.3 (9.1)	**Arm 1 vs. Arm 2** 12 wk: 1.2, p=0.71

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, P-value*** **Other results reported**
	Physical performance Abduction 12 wk	**Prolotherapy** Baseline: 141.1 (14.0) 12 wk: 146.6 (14.8)	**Saline** Baseline: 140.96 (11.24) 12 wk: 144.75 (11.03)	**Arm 1 vs. Arm 2** 12 wk: 1.85, p=0.59
	Physical performance Internal rotation 12 wk	**Prolotherapy** Baseline: 44.8 (14.0) 12 wk: 45.8 (6.2)	**Saline** Baseline: 44.6 (6.4) 12 wk: 47.0 (10.3)	**Arm 1 vs. Arm 2** 12 wk: -1.2, p=0.64
	Physical performance External rotation 12 wk	**Prolotherapy** Baseline: 57.6 (14.0) 12 wk: 56.7 (6.5)	**Saline** Baseline: 59.6 (8.8) 12 wk: 54.5 (9.8)	**Arm 1 vs. Arm 2** 12 wk: 2.2, p=0.31
	Pain severity or intensity 10-point VAS 2, 6, 12 wk	**Prolotherapy** Baseline: 5.8 (1.2) 2 wk: 3.7 (1.0) 6 wk: 5.7 (1.0) 12 wk: 5.6 (1.1)	**Saline** Baseline: 5.7 (1.2) 2 wk: 5.3 (1.00) 6 wk: 5.3 (1.3) 12 wk: 5.0 (1.5)	**Arm 1 vs. Arm 2** 2 wk: -1.6, p=0.00 6 wk: 0.4, p=0.20 12 wk: 0.6, p=0.0

Notes. *Mean differences calculated by review team (unless otherwise noted) ; p-values reported by studies.

Abbreviations. AE=adverse effect/event; ASES= American Shoulder and Elbow Surgeons Standardized Shoulder Assessment; DASH=disability of the arm, shoulder, and hand; MCID=minimal clinically important difference; mg=milligram; mo=month; MRI= Magnetic resonance imaging; NR=not reported; NSAIDs= Non-steroidal anti-inflammatory drugs; PRP=platelet rich plasma; PT=physical therapy; SPADI=Shoulder Pain and Disability Index; RC=rotator cuff; RCT=randomized controlled trial; RoB=risk of bias; ROM=range of motion; TENS=transcutaneous electrical nerve stimulations; wk=week; WORC=Western Ontario Rotator Cuff Index; yr=year.

APPENDIX I. LATERAL ELBOW TENDINOPATHY

Appendix Table 10. Detailed Study Characteristics for All Eligible Elbow Pain Studies

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
Dextrose Prolotherapy vs. Normal Saline (with Local Anesthetic)				
Akcay, 2020[88] NR High 12 Weeks Turkey (1) "No funding was received for this article."	**Inclusion**: 18-65 years, pain at the lateral side of the elbow lasting ≥3 months **Exclusion**: corticosteroid injection ≤6 months, radial nerve compression, pregnancy/breastfeeding, and trauma history ≤3 months; thrombocytopenia, coagulopathy, bleeding diathesis; diffuse pain syndrome, history of DPT, and inflammatory arthritis; and fear of needles	**Dextrose prolotherapy**: *N*=30 Age, mean (SD): 48.1 (8.9) 78.3% Female Clinic/home 3 sessions 15% dextrose 4.5 ml, patients' arms positioned with elbow flexion and forearm pronation, injected into the lateral epicondyle, annular ligament, and supracondylar ridge Other treatments: Home exercise program, anti-inflammatories discontinued during study	**Saline/Local anesthetic**: *N*=30 Age, mean (SD): 46.7 (8.3) 70.4% Female Clinic/home 3 sessions Normal saline 4.5 ml, as per intervention protocol Other treatments: Same as Arm 1	**Pain severity or intensity; pain-related functioning** **Pain-related functioning (4, 8, 12 wk)** • DASH • PRTEE **Physical performance (4, 8, 12 wk)** • Grip strength **Adverse events** **Other outcomes:** • Pain severity or intensity: 10-point VAS
Ciftci, 2023[93] NCT04680936 Some concerns	**Inclusion**: 18-65 years, Diagnosed chronic lateral epicondyylitis, pain and function limitations ≥3 months	**15% dextrose prolotherapy; 5% dextrose prolotherapy**: *N*=20; *N*=21 Age, mean (SD): 43.2 (9.46); 43.0 (10.9)	**Saline/Local anesthetic**: *N*=22 Age, mean (SD): 46.70 (10.57) 65% Female	**Handgrip strength, visual analog scale-rest (VAS-R), visual analog scale-activity (VAS-A), pressure-pain threshold, and Quick Disability of the Arm, Shoulder and Hand (Q-DASH)**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
12 Weeks Turkey (1) "The financial supporter of the study is the principal investigator."	**Exclusion**: "previous injection, surgery or trauma ≤3 months, an infection and allergy in the treatment area, non-aspirin anticoagulant usage, unregulated hypertension, immune dysfunction, active endocrine and neurologic disorder, malignancy, pregnancy, and lactation"	65% Female; 65% Female Clinic/home Three injections, each 3 weeks apart Two concentrations of dextrose "into the enthesis area of the extensor muscle origins in the lateral epicondyle and the annular ligament, with in-plane technique," ultrasound guided Concentrations: 15% dextrose 1 ml 5% dextrose 1 ml Other treatments: And "wrist and finger extensors in the dorsal forearm stretching, elbow joint range of motion, eccentric and concentric strengthening exercises, and myofascial mobilization twice a day"	Clinic/home Three injections, each 3 weeks apart Normal saline, as per intervention protocol Other treatments: Same as Arm 1	**Pain-related functioning (3, 12 wk)** • Quick Dash **Physical performance (3, 12 wk)** • Grip strength **Adverse events** **Other outcomes:** • Pain severity or intensity: 10-point VAS
Scarpone[91] NR High 4 Months	**Inclusion**: "diagnosis of LE and elbow pain for ≥6 months and failure of each of the following conservative care modalities: relative rest, physical therapy, nonsteroidal antiinflammatory drugs, and 2 corticosteroid injections"	**Dextrose prolotherapy**: *N*=12 Age, mean (SD): 48.2 (9.5) 60% Female Clinic	**Saline/Local anesthetic**: *N*=12 Age, mean (SD): 47.7 (8.6) 40% Female Clinic	**Pain severity or intensity** **Physical performance (8, 16 wk)** • Grip strength **Adverse events** **Other outcomes:**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
America (1) NR	**Exclusion**: "diabetes, corticosteroid elbow injection ≤6 weeks, and self-reported immunocompromised status"	3 injections, each 4 weeks apart 10.7% dextrose 1.5 ml (+ 0.7% sodium morrhuate, 0.3% lidocaine) injected into "tendon insertions, with needle touching bone, at the supracondylar ridge, lateral epicondyl, and the annular ligament) Other treatments: None reported	3 injections, each 4 weeks apart Normal saline, as per invervention protocol Other treatments: None reported	• Pain severity or intensity: 10-point Likert
Dextrose Prolotherapy vs. Steroids				
Bayat, 2019[94] IRCT201703110330 00N3 High 3 Months Iran (1) "This study had no funding source and the authors report no conflicts of interest in this work."	**Inclusion**: "confirmed diagnosis...made clinically based on symptoms, point tenderness, and pain elicited by Cozen's test. Subjects aged 18–55 years who had had symptoms for longer than 3 months were included." **Exclusion**: "(a) any history of local trauma, surgery, or prior injection about the lateral epicondyle during the last 3 months; (b) the presence of any concomitant cervical radiculopathy in the same limb; and (c) systemic comorbidities such as diabetes, rheumatologic disorders, etc."	**Dextrose prolotherapy**: *N*=16 Age, mean (SD): 46.2 (6.4) 42.9% Female Clinic/home Single injection, 7 wk exercises (2-3x/week) 16% dextrose 3 ml (+ 0.7% lidocaine), patients in lateral-decubitus position, injected into point of maximal tenderness with peppering technique Other treatments: Advised to use acetaminophen for first 48 hours after injection, non-steroidal anti-	**Steroid injectable**: *N*=14 Age, mean (SD): 50.7 (7.5) 78.6% Female Clinic/home Single injection, 7 wk exercises (2-3x/week) Methylprednisolone 40 mg (+ 0.7% lidocaine), as per intervetion protocol Other treatments: Same as Arm 1	**Pain-related disability** **Pain-related functioning (1, 3 mo)** Quick Dash **Adverse events** **Other outcomes:** • Pain severity or intensity: 10-point VAS

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
		inflammatory drugs not allowed, split and home exercise program		
Gupta, 2022[97] NR High 1 Year India (1) "Nil"	**Inclusion**: 18-60 years, clinically diagnosed tennis elbow **Exclusion**: "previous treatment in the form of local injections, symptoms of pain around the elbow because of other reasons, and uncrontrolled diabetes mellitus"	**Dextrose prolotherapy**: *N*=130 Age, mean (SD): 43.88 (NR) % Female NR Clinic Single injection 25% dextrose 1 ml (+ 2% lignocaine), injected into the site "5 mm distal to the lateral epicondyle in the extensor tendons, particularly the extensor carpi radialis brevis tendon… lignocaine with adrenaline was injected." Other treatments: None reported	**Steroid injectable**: *N*=130 Age, mean (SD): 44.14 (NR) % Female NR Clinic Single injection Triamcinolone mg NR (+ 2% lignocaine), as per intervention protocol Other treatments: None reported	**Primary outcome NR** **Other outcomes:** • Pain severity or intensity: 100-point VAS
Kaya, 2022[95] NR High 6 Months Turkey (1)	**Inclusion**: 18 - 65 years, diagnosed lateral epicondylitis **Exclusion**: "history of injection treatment for LE, pain for < one month, a Visual Analog Scale (VAS) score below 40, ipsilateral shoulder	**Dextrose prolotherapy**: *N*=30 Age, mean (SD): 45.4 (7.9) 60% Female Clinic 2 injections, each 1 month apart	**Steroid injectable**: *N*=30 Age, mean (SD): 47.8 (7.1) 75% Female Clinic Single injection	**Primary outcome NR** **Pain-related functioning (1, 6 mo)** • PRTEE **Adverse events** **Other outcomes:**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
"The authors received no financial support for the research and/or authorship of this article."	or cervical disease, a diagnosis of fibromyalgia, carpal tunnel syndrome, or inflammatory disease, a history of trauma in the elbow, bilateral elbow pain, a coagulation disorder, and a history of allergic reaction for local anesthetic drugs"	24% dextrose 2.5 ml (+ 0.4% prilocaine), patients in lateral decubitus position, injected into most tender area with peppering technique Other treatments: None reported Ice massage after injection, acetaminophen during first 48 hours after injection, no NSAIDs	Methylprednisolone 20 mg (+ 1.6% prilocaine) with same injection method, as per intervention protocol Other treatments: Same as Arm 1 **ABI/ACS**: *N*=30 Age, mean (SD): 46.7 (8.7) 60% Female Clinic Single injection Autologous blood 2 ml (+ 0.4% prilocaine), as per intervention protocol Other treatments as per intervention protocol **Splint**: *N*=30 Age, mean (SD): 43.0 (7.1) 60% Female Home	• Pain severity or intensity: 100-point VAS

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
			NR "The fourth group was recommended to use only a wrist splint for 6 to 8 h during the daytime. The wrist splint allowed wrist and hand movements, fixed at 5-10° dorsiflexion to improve loading stress on the common extensors of the wrist."	
Dextrose Prolotherapy vs. Extracorporal Shockwave Therapy (ESWT)				
Ahadi, 2019[89] NR High 8 Weeks Iran (1) "This study had no financial support"	**Inclusion**: " aged 18–70years, diagnosed with CLE by having a history of at least three months of pain, having tenderness over the lateral epicondyle on palpation, having resisted wrist extension during physical examination, and having confirmatory hypoechoic lesions on ultrasonography. All the patients had pain with visual analog scale (VAS) score >4 and failure of at least one of the conservative treatments for CLE (nonsteroidal anti-inflammatory drugs [NSAIDs], physiotherapy, or steroid injection)." **Exclusion**: "history of steroid injection in the past three months, history of prolotherapy, radicular neck pain,	**Dextrose prolotherapy**: *N*=17 Age, mean (SD): 46.65 (NR) 64.7% Female Not Reported 1 session "after subcutaneous anesthesia with 2cc of lidocaine 2%, under aseptic conditions and using a 25-gauge 1.5-inch needle, 3cc of dextrose 20% was injected deeply, with the needle touching bone, into the maximal tenderness point and ultrasound-documented p Other treatments: None reported	**Shockwave**: *N*=16 Age, mean (SD): 47.25 (NR) 75% Female Not Reported 3 sessions " patients received three sessions of shock wave therapy at a weekly interval. The shock wave machine BTL6000 (2010, Baltimore, UK) was used for all patients, and in each session, 2000J shocks with an intensity of 1.5bars and a frequency of 10Hz were exe Other treatments: None reported	**Primary outcome NR** **Pain-related functioning (4, 8 wk)** • Quick Dash **Physical performance (4, 8 wk)** • Grip strength **Adverse events** **Other outcomes:** • Pain severity or intensity: 10-point VAS

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
	coagulation disorder or on anticoagulant treatment, pregnancy, coexisting pathology or history of any surgery on the upper limb, taking opioids, allergy to local anesthetics, diabetes, any history or active rheumatologic disorder, or fibromyalgia"			
Deb, 2020[92] NR High 6 Months India (1) "No funding sources"	**Inclusion**: "Patients diagnosed with lateral epicondylitis fulfilling following criteria was included in this study Age between 30-50 years, Duration of symptoms for at least 6 months, Failed conservative treatment, Willingness to comply with treatment and follow-up assessment." **Exclusion**: "Duration of symptoms less than 6 months, History of previous surgery in the same tendon, Implanted hardware adjacent to the target treatment region, Abnormal radiographic findings like Osteophtyes, Calcification, or Exostosis, Pregnancy, Diabetes, Cancer. "	**Dextrose prolotherapy**: *N*=42 Age, mean (SD): NR (NR) 52.4% Female Not Reported 1 session " Prolotherapy injections using dextrose 25% solution was prepared by the injector at the time of procedure. Tenderness at the lateral epicondyle was confirmed by palpation. Patient was positioned in supine lying with elbow flexed around 10 degree. Other treatments: None reported	**Shock**: *N*=42 Age, mean (SD): NR (NR) 66.7% Female Not Reported 3 sessions over 3 weeks "Control group: In this group patients received a total 3 sessions of shock wave therapy at weekly interval for 3 weeks. Patient was positioned in supine lying with elbow flexed around 10 to 20 degree. During every session by using Swiss Dolorclast Smart Other treatments: None reported	**Primary outcome NR** **Physical performance (1, 3, 6 mo)** • Grip strength **Other outcomes:** • Pain severity or intensity: 10-point VAS
Dextrose Prolotherapy vs. Other Comparators				

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
Apaydin, 2020[96] NCT04395417 High 12 Weeks Turkey (1) "No funding was received for this article."	**Inclusion**: " (1) aged 20–60 years; (2) clinical diagnosis of LE, defined as pain over the lateral humeral epicondyle of at least 6 months' duration; (3) pain provoked by palpation and resisted wrist/middle finger extension or gripping; (4) a score of at least 30/100 on the Visual Analog Scale (VAS)…" **Exclusion**: Treatment for elbow pain ≤6 months, "concomitant neck or other arm pain causing disability or requiring treatment within the last 6 months, clinical evidence of other primary sources of lateral elbow pain, upper limb fractures within the preceding 10 years, elbow surgery, systemic inflammatory disorder or malignancy, any contraindications to the study treatments, and pregnancy or breastfeeding"	**Dextrose prolotherapy**: *N*=16 Age, mean (SD): 43.3 (7.4) 81.25% Female Clinic 3 injections, each 3 weeks apart 15% dextrose 5 ml (+ 0.2% lidocaine), injected into "the tenderest point of the lateral epicondyle… annular ligament, lateral collateral ligament, and tender areas of the extensor tendon," using a peppering technique Other treatments: None reported	**Hyaluronic Acid**: *N*=16 Age, mean (SD): 45.6 (4.7) 81.25% Female Not Reported Clinic Hyaluronic acid 2 ml, injected into "the most sensitive point in the lateral epicondyle" Other treatments: None reported	**Pain severity or intensity; pain-related functioning** **Pain-related functioning (6, 12 wk)** • Quick Dash **Physical performance (6, 12 wk)** • Grip strength **Adverse events** **Other outcomes:** • Pain severity or intensity: 10-point VAS
Rabago, 2013[90] NCT01476605 High 32 Weeks	**Inclusion**: 18-65 years, "self-reported lateral elbow pain [for ≥ 3 months] and rated as "4" or more on a 0-10 ordinal response scale… presence of pain over the lateral epicondyle on palpation and with resisted wrist extension during	**Dextrose prolotherapy; Dextrose prolotherapy = morrhuate**: *N*=8; *N*=9 Age, mean (SD): 50.4 (6.8); 42.6 (9.8) 14% Female; 44% female	**Waitlist**: *N*=10 Age, mean (SD): 51.7 (6.8) 40% Female NA	**Pain-related function** **Pain-related functioning (8, 16 wk)** • PRTEE **Physical performance (8, 16 wk)**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
America (NR) NR	physical exam… and having failed at least one of the three most common treatments for CLE (NSAIDs, physician initiated physical therapy or a corticosteroid injection)" **Exclusion**: "prior elbow PrT, other elbow injection-based therapies [≤3 months] other concurrent upper extremity pathology, prior upper extremity surgery, self-reported pregnancy, significant co-morbidity precluding participation, bleeding disorders, allergy or intolerance to study medication, use of chronic opioid, anticoagulant or immunosuppressive medication, and standard MRI-related exclusions at our institution..."	Clinic 3 sessions, each 3-4 weeks apart 2 types of prolotherapy with the same injection method: 0.5 ml injected into the lateral epicondyle, ≤2.5 ml injected “on bone along a short sement of the tendon and annular ligament at the areas of palpated tenderness” using a peppering technique, ultrasound guided: 20% dextrose 0.5-2.5 ml (+ 0.2% lidocaine) 11% dextrose 0.5-2.5 ml (+ 0.7% sodium morrhuate, 0.3% lidocaine) Other treatments: None reported	NA "Wait-and-see participants were counseled about CLE risk modification in daily living and work activities." Other treatments: None reported	• Grip strength **Adverse events** **Other outcomes:** • Pain severity or intensity: PRTEE Pain subscore
Yelland, 2019[98] ACTRN12612000993897 Some concerns 52 Weeks Australia (1)	**Inclusion**: 18–70 years, “clinical diagnosis of LE, defined as pain over the lateral humeral epicondyle [≥6 weeks] provoked by palpation and resisted wrist/middle finger extension or gripping. In addition, participants needed to score at least 20/100 on the Patient Rated Tennis Elbow Evaluation (PRTEE) ..."	**Dextrose prolotherapy; dextrose prolotherapy + physical therapy**: *N*=40; *N*=40 Age, mean (SD): 49.2 (7.2); 47.8 (7.0) 45% Female; 45% Female Clinic/home	**Exercise/PT**: *N*=40 Age, mean (SD): 51.0 (9.0) 40% Female Clinic/home 4 physical therapy sessions, lasting 30 minutes, each 1-2 weeks apart	**Pain-related functioning** **Pain-related functioning (6, 12, 26, 52 wk)** • PRTEE **Health-related QoL (6, 12, 26, 52 wk)** • EuroQoL-5D

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
"Griffith Health Institute, Griffith University; Australasian Faculty of Musculoskeletal Medicine Grant; Australian Association of Musculoskeletal Medicine Grant; Hackett-Hemwall Foundation."	**Exclusion**: "any treatment for their elbow pain by a health care practitioner [≤3 months], concomitant neck or other arm pain causing disability or requiring treatment within the last 6 months, clinical evidence of other primary sources of lateral elbow pain, upper limb fractures [≤10 years], elbow surgery, systemic inflammatory disorder or malignancy, any contraindications to the study treatments, unresolved litigation or workers compensation claims, and pregnancy or breastfeeding."	4 sessions, each 4 weeks apart; 4 physical therapy sessions, lasting 30 minutes, each 1-2 weeks apart 20% dextrose 0.5-5 ml (+ 0.4% lignocaine), 0.5 – 1.0 ml injected into each tender point in the "lateral epicondyle, supracondylar ridge, radial head, lateral collateral, and annular ligaments," using a peppering technique Other treatments: "[w]ritten educational material on their condition." Physical therapy included "Mobilisation-With Movement…[and] (a) Sensorimotor retraining of gripping and posture correction were commenced early in the physiotherapy intervention; (b) progressive resistance exercise for the wrist extensors were prescribed based on identified strength deficits; and (c) exercises geared towards general arm strengthening were also prescribed."	Other treatments: Same as Arm 1	**Adverse events** **Other outcomes:** • Pain severity or intensity: 10-point VAS

Abbreviations. AE=adverse effect/event; DASH= Disabilities of the Arm, Shoulder, and Hand questionnaire; ESWT= Extracorporeal shockwave therapy; EuroQol-5D= European Quality of Life-5 dimensions; ml=milliliter; NA=not applicable; NSAIDs=nonsteroidal anti-inflammatory drugs; NR=not reported; PRP=platelet rich plasma; PRTEE=Patient-rated Tennis Elbow Evaluation; PT=physical therapy; Quick DASH=shortened version of DASH (11 items); RCT=randomized controlled trial; RoB=risk of bias; VAS=Visual Analog Scale.

Appendix Table 11. Detailed Results for All Eligible Elbow Pain Studies

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, P-value* Other results reported
Ahadi, 2019[89] Some concerns	Pain-related functioning or interference Q-DASH 4, 8 wk	**Dextrose prolotherapy 20%** Baseline: 47.82 (4.78) 4 wk: 39.67 (4.30) 8 wk: 37.39 (4.40)	**ESWT** Baseline: 41.84 (3.04) 4 wk: 22.25 (3.57) 8 wk: 23.13 (3.20)	**Arm 1 vs. Arm 2** 4 wk: 17.42, p=0.003 8 wk: 14.26, p=0.009
	Physical performance Grip strength	**Dextrose prolotherapy 20%** Baseline: 7.02 (0.64) 4 wk: 8.02 (0.64) 8 wk: 8.00 (0.64)	**ESWT** Baseline: 7.28 (0.52) 4 wk: 8.31 (0.49) 8 wk: 8.36 (0.50)	**Arm 1 vs. Arm 2** 4 wk: -0.29, p=0.94 8 wk: -0.36, p=0.77
	Pain severity or intensity 10-point VAS 4, 8 wk	**Dextrose prolotherapy 20%** Baseline: 7.35 (0.47) 4 wk: 5.71 (0.50) 8 wk: 5.47 (0.53)	**ESWT** Baseline: 6.13 (0.32) 4 wk: 3.19 (0.50) 8 wk: 2.60 (0.40)	**Arm 1 vs. Arm 2** 4 wk: 2.5, p=0.01 8 wk: 2.9, p=0.008
	Adverse events 8 wk	*"No noticeable adverse effects of the treatment were reported in either group"*		
Akcay, 2020[88] High	Pain-related functioning or interference DASH 4, 8, 12 wk	**Dextrose prolotherapy 15%** Baseline median (range): 65.8 (48.2-74.0) 4 wk median (range): 48.3 (37.5-56.6) 8 wk Median: 35.0 (14.1- 46.6) 12 wk Median: 29.1 (5.0- 55.0)	**Normal saline** Baseline median (range): 60.0 (46.6-74.1) 4 wk median (range): 55.8 (40.0-68.3) 8 wk median (range): 44.0 (25.8-49.1) 12 wk median (range): 41.6 (13.0-52.5)	**Arm 1 vs. Arm 2** 4 wk: -7.5, NR 8 wk: -9, NR 12 wk: -12.5, NR **Difference in difference** 4 wk: NR, p= 0.27 8 wk: NR, p=0.32 12 wk: NR, p=0.31
	Pain-related functioning or interference PRTEE Total 4, 8, 12 wk	**Dextrose prolotherapy 15%** Baseline median (range): 75.0 (65.5-79.5) 4 wk median (range): 51.5 (42.0-71.5) 8 wk median (range): 34.5 (20.0-66.5) 12 wk median (range): 22.5 (13.5-67.0)	**Normal saline** Baseline median (range): 67.0 (57.0-80.5) 4 wk median (range): 57 (42.5-76.0) 8 wk median (range): 45.0 (34.0-61.0) 12 wk median (range): 39.5 (27.0-63.0)	**Arm 1 vs. Arm 2** 4 wk: -5.5, NR 8 wk: -10.5, NR 12 wk: -17, NR **Difference in difference** 4 wk: NR, p=0.04 8 wk: NR, p=0.12 12 wk: NR, p=0.04
	Physical performance Grip strength 4, 8, 12 wk	**Dextrose prolotherapy 15%** Baseline median (range): 0.25 (0.15-0.36) 4 wk median (range): 0.30 (0.25-0.40) 8 wk median (range): 0.40 (0.25-0.40) 12 wk median (range): 0.40 (0.30-0.42)	**Normal saline** Baseline median (range): 0.33 (0.20-0.40) 4 wk median (range): 0.35 (0.25-0.45) 8 wk median (range): 0.38 (0.30-0.50) 12 wk median (range): 0.40 (0.30-0.51)	**Arm 1 vs. Arm 2** 4 wk: -0.05, NR 8 wk: 0.02, NR 12 wk: 0.0, NR **Difference in difference** 4 wk: NR, p=0.40 8 wk: NR, p=0.98 12 wk: NR, p=0.75
	Pain severity or intensity VAS rest 4, 8, 12 wk	**Dextrose prolotherapy 15%** Baseline median (range): 6.0 (5.0-8.0) 4 wk median (range): 4.0 (3.0-5.0) 8 wk median (range): 3.0 (1.0-5.0) 12 wk median (range): 2.0 (1.0-4.0)	**Normal saline** Baseline median (range): 5.5 (5.0-7.0) 4 wk median (range): 4.0 (3.0-6.0) 8 wk median (range): 3.0 (2.0-4.0) 12 wk median (range): 3.0 (1.0-4.0)	**Arm 1 vs. Arm 2** 4 wk: 0.0, NR 8 wk: 0.0, NR 12 wk: -1.0, NR

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, P-value* Other results reported
				Difference in difference 4 wk: NR, p=0.01 8 wk: NR, p=0.33 12 wk: NR, p=0.34
	Pain severity or intensity VAS motion 4, 8, 12 wk	**Dextrose prolotherapy 15%** Baseline median (range): 9.0 (8.0-10.0) 4 wk median (range): 6.0 (4.0-9.0) 8 wk median (range): 4.0 (2.0-7.0) 12 wk median (range): 3.0 (1.0-6.0)	**Normal saline** Baseline median (range): 9.0 (8.0-10.0) 4 wk median (range): 7.0 (5.0-8.0) 8 wk median (range): 5.0 (4.0-7.0) 12 wk median (range): 4.0 (3.0-6.0)	**Arm 1 vs. Arm 2** 4 wk: -1.0, NR 8 wk: -1.0, NR 12 wk: -1.0, NR
				Difference in difference 4 wk: NR, p=0.16 8 wk: NR, p=0.20 12 wk: NR, p=0.12
	Adverse events Narrative description 12 wk	*"We observed no adverse effects in this study except pain while having injections in any of the interventions. None of the participants reported a need for analgesics beyond paracetamol in both study groups. Although the drop-out rate is higher in the DPT group than the saline group, neither pain nor other possible adverse events were the reason."*		
Apaydin, 2020[96] Some concerns	Pain-related functioning or interference Q-DASH 6, 12 wk	**Dextrose prolotherapy 15%** Baseline: 53.2 (18.7) 6 wk: 20.6 (11.7) 12 wk: 9.7 (6.4)	**Hyaluronic acid** Baseline: 53.1 (12.5) 6 wk: 27.9 (11.1) 12 wk: 24.7 (10.1)	**Arm 1 vs. Arm 2**† 6 wk: -7.2, 95% CI -15.0, 0.98 12 wk: -15, 95% CI -21.1, -8.9
	Physical performance Grip strength 6, 12 wk	**Dextrose prolotherapy 15%** Baseline: 19.87 (9.0) 6 wk: 24.25 (9.1) 12 wk: 27.19 (9.6)	**Hyaluronic acid** Baseline: 18.13 (8.6) 6 wk: 22.06 (8.9) 12 wk: 22.94 (8.5)	**Arm 1 vs. Arm 2**† 6 wk: 2.18, 95% CI 0.06, 4.53 12 wk: 4.25, 95% CI 2.02, 7.00
	Pain severity or intensity VAS rest 6, 12 wk	**Dextrose prolotherapy 15%** Baseline: 4.94 (2.0) 6 wk: 2.12 (1.3) 12 wk: 1.06 (0.8)	**Hyaluronic acid** Baseline: 5.19 (1.1) 6 wk: 3.25 (1.9) 12 wk: 2.44 (1.7)	**Arm 1 vs. Arm 2**† 6 wk: -1.1, 95% CI -2.3, 0.7 12 wk: -1.4, 95% CI -2.4, -0.4
	Pain severity or intensity VAS activity 6, 12 wk	**Dextrose prolotherapy 15%** Baseline: 7.00 (1.5) 6 wk: 3.75 (1.4) 12 wk: 2.19 (0.8)	**Hyaluronic acid** Baseline: 7.25 (0.8) 6 wk: 4.94 (2.4) 12 wk: 4.06 (2.3)	**Arm 1 vs. Arm 2**† 6 wk: -1.2, 95% CI -1.8, -0.7 12 wk: -1.9, 95% CI -2.4, -1.4
	Pain severity or intensity VAS at night 6, 12 wk	**Dextrose prolotherapy 15%** Baseline: 6.31 (2.3) 6 wk: 2.25 (1.4) 12 wk: 1.19 (0.7)	**Hyaluronic acid** Baseline: 6.8 (1.4) 6 wk: 3.56 (2.3) 12 wk: 2.75 (2.0)	**Arm 1 vs. Arm 2**† 6 wk: -1.3, 95% CI -1.8, -0.8 12 wk: -1.6, 95% CI -1.8, -1.3
Bayat, 2019[94] Some concerns	Pain-related functioning or interference Q-DASH 1, 3 mo	**Dextrose prolotherapy 16%** Baseline: 43.2 (20.8) 1 mo: 24.3 (18.6) 3 mo: 14.7 (21.1)	**Steroid injectable** Baseline: 52.2 (16.4) 1 mo: 34.8 (18.1) 3 mo: 34.6 (16.4)	**Arm 1 vs. Arm 2** 1 mo: -10.5, p=0.14 3 mo: -19.9, p=0.01
	Pain severity or intensity	**Dextrose prolotherapy 16%**	**Steroid injectable**	**Arm 1 vs. Arm 2**

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, P-value* Other results reported
	VAS 1, 3 mo	Baseline: 7.3 (1.5) 1 mo: 5.3 (3.1) 3 mo: 2.8 (3.2)	Baseline: 7.2 (1.8) 1 mo: 5.7 (2.6) 3 mo: 5.2 (2.4)	1 mo: -0.4, p=0.74 3 mo: -2.4, p=0.03
	Adverse events Narrative description 3 mo	*"In the prolotherapy group, none of the patients mentioned any adverse events. However, one subject in the steroid group reported a transient redness and decreased range of movement, and two patients mentioned post-injection pain"*		
Ciftci, 2023[93] Low	Pain-related functioning or interference Q-DASH 3, 12 wk	**Dextrose prolotherapy 15%** Baseline: 55.45 (15.64) 3 wk: 28.97 (18.58) 12 wk: 9.45 (7.35)	**Normal saline** Baseline: 59.99 (14.05) 3 wk: 53.74 (13.81) 12 wk: 39.99 (11.04) **Dextrose prolotherapy 5%** Baseline: 64.08 (5.29) 3 wk: 36.98 (13.51) 12 wk: 11.59 (9.22)	**Arm 1 vs. Arm 2** 3 wk: -24.77, p=0.003 12 wk: -30.54, p<0.001 **Arm 1 vs. Arm 3** 3 wk: -8.0, p=0.238 12 wk: -2.1, p=751
	Physical performance Grip strength 3, 12 wk	**Dextrose prolotherapy 15%** Baseline: 58.50 (40.20) 3 wk: 62.25 (39.48) 12 wk: 71.50 (38.04)	**Normal saline** Baseline: 44.75 (26.38) 3 wk: 43.21 (23.53) 12 wk: 42.50 (20.22) **Dextrose prolotherapy 5%** Baseline: 40.50 (17.61) 3 wk: 51.25 (17.23) 12 wk: 59.50 (18.70)	**Arm 1 vs. Arm 2** 3 wk: 19.04, p=0.664 12 wk: 29.0, p=0.126 **Arm 1 vs. Arm 3** 3 wk: 11.0, p=0.442 12 wk: 12.0,=0.348
	Pain severity or intensity 10-point VAS rest 3, 12 wk	**Dextrose prolotherapy 15%** Baseline: 2.18 (1.66) 3 wk: 0.27 (0.58) 12 wk: 0.02 (0.08)	**Normal saline** Baseline: 2.51 (1.91) 3 wk: 2.20 (1.64) 12 wk: 1.59 (1.44) **Dextrose prolotherapy 5%** Baseline: 2.79 (1.05) 3 wk: 2.64 (1.58) 12 wk: 0.50 (0.94)	**Arm 1 vs. Arm 2** 3 wk: -1.9, p=0.565 12 wk: -1.6, p=0.003 **Arm 1 vs. Arm 3** 3 wk: 0.27, p<0.001 12 wk: 0.02, p=0.289
	Pain severity or intensity 10-point VAS activity 3, 12 wk	**Dextrose prolotherapy 15%** Baseline: 6.69 (1.24) 3 wk: 3.74 (1.65) 12 wk: 1.39 (1.10)	**Normal saline** Baseline: 6.18 (0.88) 3 wk: 6.92 (1.57) 12 wk: 6.05 (1.16) **Dextrose prolotherapy 5%** Baseline: 6.40 (0.69) 3 wk: 5.59 (1.78) 12 wk: 2.50 (1.08)	**Arm 1 vs. Arm 2** 3 wk: -3.2, p=0.38 12 wk: -4.7, p<0.001 **Arm 1 vs. Arm 3** 3 wk: 3.74, p=0.033 12 wk: 1.39, p=0.007
	Adverse events Narrative description 12 wk	*"There was no difference regarding side effects and complications (P>.05). Two patients in Group [Dextrose prolotherapy 15%] had pain and 1 patient in Group [Saline] had a rash at the injection site after the injection. No severe side effects or complications were encountered."*		
Deb, 2020[92] Some concerns	Pain severity or intensity VAS 1, 3, 6 mo	**Dextrose prolotherapy 20%** Baseline: 7.57 (0.67) 1 mo: 5.36 (0.82)	**ESWT** Baseline: 7.57 (0.50) 1 mo: 6.26 (0.77)	**Arm 1 vs. Arm 2** 1 mo: -0.9, p≤0.001 3 mo: -1.3, p≤0.001

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, P-value*** **Other results reported**
		3 mo: 3.17 (1.03) 6 mo: 1.45 (0.59)	3 mo: 4.45 (1.27) 6 mo: 3.07 (0.92)	6 mo: -1.6, p≤0.001
	Physical performance Grip strength	**Dextrose prolotherapy 20%** Baseline: 10.00 (0.99) 1 mo: 11.99 (0.93) 3 mo: 13.84 (0.87) 6 mo: 15.44 (0.65)	**ESWT** Baseline: 9.69 (0.84) 1 mo: 10.74 (0.88) 3 mo: 11.83 (0.96) 6 mo: 13.1 (0.84)	**Arm 1 vs. Arm 2** 1 mo: 1.25, p≤0.001 3 mo: 2.01, p≤0.001 6 mo: 2.34, p≤0.001
Gupta, 2022[97] High	Pain severity or intensity VAS 6, 12, 24, 52 wk	**Dextrose prolotherapy 25%** Baseline: 68.79 (1.19) 6 wk: 52.34 (1.15) 12 wk: 43.46 (3.18) 24 wk: 32.70 (2.40) 52 wk: 21.84 (2.23)	**Steroid injectable** Baseline: 67.16 (2.89) 6 wk: 49.13 (1.63) 12 wk: 40.68 (2.77) 24 wk: 32.06 (2.45) 52 wk: 27.02 (2.23)	**Arm 1 vs. Arm 2** 6 wk: 3.2, NR 12 wk: 2.8, NR 24 wk: 0.6, NR 52 wk: -5.18, NR
Kaya, 2022[95] Some concerns	Pain-related functioning or interference PRTEE Total 1, 6 mo	**Dextrose prolotherapy 24%** Baseline: 73.9 (15.9) 1 mo: NR 6 mo: NR Change from baseline: 1 mo: 19.1 (18.6) 6 mo: 41.6 (26.1)	**Steroid injectable** Baseline: 59.2 (19.6) 1 mo: NR 6 mo: NR Change from baseline: 1 mo: 36.2 (21.4) 6 mo: 34.1 (35.6)	**Arm 1 vs. Arm 2** 1 mo: NR 6 mo: NR
			ABI Baseline: 67.4 (16.4) 1 mo: NR 6 mo: NR Change from baseline: 1 mo: 26.9 (22.9) 6 mo: 48.1 (25.1)	**Arm 1 vs. Arm 3** 1 mo: NR 6 mo: NR
			Wrist splint Baseline: 53.5 (16.2) 1 mo: NR 6 mo: NR Change from baseline: 1 mo: 12.4 (15.6) 6 mo: 20.1 (19.7)	**Arm 1 vs. Arm 4** 1 mo: NR 6 mo: NR **Difference in difference for all groups** 1 mo: NR, p=0.01 6 mo: NR, p=0.04
	Physical performance Grip strength 1, 6 mo	**Dextrose prolotherapy 24%** Baseline: 22.3 (9.3) 1 mo: NR 6 mo: NR Change from baseline: 1 mo: -2.0 (4.9) 6 mo: -5.95 (5.5)	**Steroid injectable** Baseline: 21.9 (10.8) 1 mo: NR 6 mo: NR Change from baseline: 1 mo: -4.17 (4.4) 6 mo: -3.96 (5.4)	**Arm 1 vs. Arm 2** 1 mo: NR 6 mo: NR

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, P-value* Other results reported
			ABI Baseline: 22.98 (7.98) 1 mo: NR 6 mo: NR Change from baseline: 1 mo: -3.87 (7.6) 6 mo: -7.97 (8.0)	**Arm 1 vs. Arm 3** 1 mo: NR 6 mo: NR
			Wrist splint Baseline: 28.3 (13.0) 1 mo: NR 6 mo: NR Change from baseline: 1 mo: -2.1 (1.9) 6 mo: -2.64 (2.7)	**Arm 1 vs. Arm 4** 1 mo: NR 6 mo: NR **Difference in difference for all groups** 1 mo: NR, p=0.51 6 mo: NR, p=0.05
	Pain severity or intensity 100-point VAS 1, 6 mo	**Dextrose prolotherapy 24%** Baseline: 73.9 (15.9) 1 mo: NR 6 mo: NR Change from baseline: 1 mo: 22.4 (23.1) 6 mo: 56.0 (34.6)	**Steroid injectable** Baseline: 70.0 (15.6) 1 mo: NR 6 mo: NR Change from baseline: 1 mo: 41.2 (31.7) 6 mo: 37.9 (39.5)	**Arm 1 vs. Arm 2** 1 mo: NR 6 mo: NR
			ABI Baseline: 76.3 (16.1) 1 mo: NR 6 mo: NR Change from baseline: 1 mo: 30.0 (32.3) 6 mo: 47.6 (32.1)	**Arm 1 vs. Arm 3** 1 mo: NR 6 mo: NR
			Wrist splint Baseline: 66.3 (19.1) 1 mo: NR 6 mo: NR Change from baseline: 1 mo: 20.0 (20.9) 6 mo: 28.1 (28.6)	**Arm 1 vs. Arm 4** 1 mo: NR 6 mo: NR **Difference in difference for all groups** 1 mo: NR, p=0.51 6 mo: NR, p=0.05
	Adverse events	1 ABI patient developed hand drop; no other group reported an AE		

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, P-value*** **Other results reported**
	Narrative description 6 mo			
Rabago, 2013[90] Some concerns	Pain-related functioning or interference PRTEE Total 4, 8, 16, 32 wk	**Dextrose prolotherapy 20%** Baseline: 41.5 (6.4) 4 wk: 27.4 (5.3) 8 wk: 27.2 (5.9) 16 wk: 22.8 (7.2) 32 wk: 17.8 (5.55)	**Waitlist control** Baseline: 50.9 (6.1) 4 wk: 44.8 (5.1) 8 wk: 46.7 (5.6) 16 wk: 41.6 (6.9) 32 wk: NR	**Arm 1 vs. Arm 2** 4 wk: -17.4, p≥0.05 8 wk: -19.5, p≥0.05 16 wk: -14.4, p≥0.05 32 wk: NR
			Dextrose prolotherapy 11% + Morrhuate Baseline: 32.7 (7.1) 4 wk: 31.0 (6.0) 8 wk: 24.9 (6.6) 16 wk: 15.2 (8.1) 32 wk: 8.2 (6.7)	**Arm 1 vs. Arm 3** 4 wk: -3.6, p<0.05 8 wk: 2.3, p<0.05 16 wk: 7.6, p>0.05 32 wk: 9.6, NR
	Pain-related functioning or interference PRTEE Function 4, 8, 16, 32 wk	**Dextrose prolotherapy 20%** Baseline: 16.4 (3.9) 4 wk: 11.1 (3.0) 8 wk: 11.6 (3.1) 16 wk: 9.1 (3.7) 32 wk: 8.5 (3.0)	**Waitlist control** Baseline: 26.0 (3.5) 4 wk: 22.2 (2.8) 8 wk: 23.2 (3.0) 16 wk: 20.6 (3.6) 32 wk: NR (3.0)	**Arm 1 vs. Arm 2** 4 wk: -11.1, p≤0.05 8 wk: -11.6, p≥0.05 16 wk: -9.0, p≥0.05 32 wk: NR
			Dextrose prolotherapy 11% + Morrhuate Baseline: 18.1 (4.2) 4 wk: 16.6 (3.3) 8 wk: 13.3 (3.5) 16 wk: 7.3 (4.2) 32 wk: 5.0 (3.0)	**Arm 1 vs. Arm 3** 4 wk: -5.5, p>0.05 8 wk: -1.7, p<0.05 16 wk: 1.8 p<0.05 32 wk: 3.5, NR
	Physical performance Grip strength 4, 8, 16, 32 wk	**Dextrose prolotherapy 20%** Baseline: 299.4 (61.7) 4 wk: NR 8 wk: 348.6 (56.8) 16 wk: 364.4 (50.3) 32 wk: 368.9 (49.9)	**Waitlist control** Baseline: 181.7 (42.6) 4 wk: NR 8 wk: 210.1 (40.2) 16 wk: 200.4 (53.0) 32 wk: NR	**Arm 1 vs. Arm 2** 4 wk: NR 8 wk: 138.5, p<0.05 16 wk: 164.0, p<0.05 32 wk: NR
			Dextrose prolotherapy 11% + Morrhuate Baseline: 201.3 (29.9) 4 wk: NR 8 wk: 208.4 (23.9) 16 wk: 202.2 (21.5) 32 wk: 239.9 (28.8)	**Arm 1 vs. Arm 3** 4 wk: NR 8 wk: 140.2, p≥0.05 16 wk: 162.2, p≥0.05 32 wk: 129
	Pain severity or intensity PRTEE pain domain 4, 8, 16, 32 wk	**Dextrose prolotherapy 20%** Baseline: 24.2 (2.7) 4 wk: 16.2 (2.6) 8 wk: 15.5 (3.0) 16 wk: 13.6 (3.6)	**Waitlist control** Baseline: 24.8 (2.6) 4 wk: 22.4 (2.5) 8 wk: 23.2 (2.9) 16 wk: 20.9 (3.5)	**Arm 1 vs. Arm 2** 4 wk: -6.2, p≥0.05 8 wk: -7.7, p≥0.05 16 wk: -7.3, p≥0.05 32 wk: NR

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, P-value* Other results reported
		32 wk: 11.1 (3.3)	32 wk: NR (3.3)	
			Dextrose prolotherapy 11% + Morrhuate Baseline: 20.8 (3.0) 4 wk: 20.4 (2.9) 8 wk: 16.7 (3.4) 16 wk: 7.9 (4.0) 32 wk: 4.9 (3.3)	**Arm 1 vs. Arm 3** 4 wk: -4.2, p>0.05 8 wk: -1.2, p>0.05 16 wk: 5.7, p>0.05 32 wk: 6.2, NR
	Adverse events Narrative description 32 wk	*"Inspection of qualitative comments showed all participants reported mild-to-moderate self-limited injection-related pain. This pain tended to resolve within 1 week in the PrT-D group. However, PrT-DM participants reported more severe and persistent injection-related pain taking up to 3 weeks to resolve. One PrT-DM participant's 4-week PrT session was postponed by two weeks due to post-procedural pain. There were no unexpected or serious adverse events"*		
Scarpone[91] Some concerns	Pain severity or intensity 10-point Likert at rest 8, 16 wk	**Dextrose prolotherapy 10.7%** Baseline: 5.1 (0.8) 8 wk: 3.3 (0.9) 16 wk: 0.5 (0.4)	**Normal saline** Baseline: 4.5 (1.7) 8 wk: 3.6 (1.2) 16 wk: 3.5 (1.5)	**Arm 1 vs. Arm 2** 8 wk: -0.3, NR 16 wk: -3.0, p≤0.001
	Physical performance Grip strength 8, 16 wk	**Dextrose prolotherapy 10.7%** Baseline: 29.8 (18.0) 8 wk: 46.4 (23.9) 16 wk: 54.2 (23.4)	**Normal saline** Baseline: 32.8 (20.6) 8 wk: 59.6 (30.2) 16 wk: 63.1 (29.9)	**Arm 1 vs. Arm 2** 8 wk: -13.2, NR 16 wk: -8.9, NR
	Adverse events Narrative description 18 wk	*"Side effects of injection therapy were minimal. All subjects (n = 20) experienced expected, self-limited postinjection pain; two PrT group subjects experienced 1 episode each of local erythema, irritation, and discomfort approximately 1 day after injection. These symptoms resolved with acetaminophen with codeine. This is consistent with an anecdotally reported occurrence rate (approximately 10%) of self-limited post-injection pain flares. There were no allergic reactions to sodium morrhuate."*		
Yelland, 2019[98] Some concerns	Pain-related functioning or interference PRTEE Total 6, 12, 26, 52 wk	**Dextrose prolotherapy 20%** Baseline: 31.6 (10.3) 6 wk: 24.5 (14.6) 12 wk: 18.2 (13.5) 26 wk: 8.9 (8.2) 52 wk: 4.9 (7.4)	**PT** Baseline: 33.5 (10.0) 6 wk: 19.7 (14.3) 12 wk: 12.2 (12.4) 26 wk: 9.3 (10.4) 52 wk: 4.4 (7.4)	**Arm 1 vs. Arm 2** 6 wk: 4.8, p≥0.05 12 wk: 6, p≥0.05 26 wk: 8.9, p≥0.05 52 wk: 0.5, p≥0.05
			Dextrose prolotherapy 20% + PT Baseline: 31.3 (10.8) 6 wk: 18.3 (12.2) 12 wk: 12.4 (10.1) 26 wk: 8.2 (10.5) 52 wk: 3.9 (5.5)	**Arm 1 vs. Arm 3** 6 wk: 6.2, p>0.05 12 wk: 5.8, p<0.05 26 wk: 0.7, p>0.05 52 wk: 1.0, p>0.05
	Health-related QoL EuroQol 6, 12, 26, 52 wk	**Dextrose prolotherapy 20%** Baseline: 82.7 (12.9) 6 wk: 80.6 (11.8) 12 wk: 83.1 (9.9) 26 wk: 86.3 (12.1) 52 wk: 88.5 (9.3)	**PT** Baseline: 80.4 (16.9) 6 wk: 83.9 (13.4) 12 wk: 83.9 (13.6) 26 wk: 87.2 (12.7) 52 wk: 85.3 (9.3)	**Arm 1 vs. Arm 2** 6 wk: -3.3, p≥0.05 12 wk: -0.8, NR 26 wk: -0.9, p≥0.05 52 wk: 3.2, p≥0.05

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, P-value* Other results reported
			Dextrose prolotherapy 20% + PT Baseline: 83.1 (11.2) 6 wk: 83.0 (11.6) 12 wk: 86.2 (8.9) 26 wk: 87.8 (8.9) 52 wk: 86.9 (11.3)	**Arm 1 vs. Arm 3** 6 wk: -2.4, p>0.05 12 wk: -3.1, NR 26 wk: -1.5, p>0.05 52 wk: 1.6, p>0.05
	Pain severity or intensity VAS rest 6, 12, 26, 52 wk	**Dextrose prolotherapy 20%** Baseline: 2.0 (1.6) 6 wk: 1.9 (2.0) 12 wk: 0.8 (1.3) 26 wk: 0.3 (0.7) 52 wk: 0.2 (0.5)	**PT** Baseline: 2.1 (2.0) 6 wk: 1.5 (1.5) 12 wk: 1.0 (1.5) 26 wk: 0.8 (1.3) 52 wk: 0.2 (0.5)	**Arm 1 vs. Arm 2** 6 wk: 0.4, p≥0.05 12 wk: -0.2, p≥0.05 26 wk: -0.5, p≥0.05 52 wk: 0.0, p≥0.05
			Dextrose prolotherapy 20% + PT Baseline: 1.8 (1.5) 6 wk: 1.3 (1.9) 12 wk: 0.8 (1.2) 26 wk: 0.5 (1.7) 52 wk: 0.2 (0.5)	**Arm 1 vs. Arm 3** 6 wk: 0.6, p>0.05 12 wk: 0, p>0.05 26 wk: -0.2, p>0.05 52 wk: 0, p>0.05
	Pain severity or intensity 10-point VAS worst pain in the last week 6, 12, 26, 52 wk	**Dextrose prolotherapy 20%** Baseline: 7.4 (1.6) 6 wk: 5.4 (2.2) 12 wk: 4.0 (2.5) 26 wk: 2.0 (2.0) 52 wk: 1.1 (2.0)	**PT** Baseline: 7.3 (2.0) 6 wk: 3.7 (2.6) 12 wk: 2.5 (2.6) 26 wk: 1.6 (2.1) 52 wk: 0.9 (2.0)	**Arm 1 vs. Arm 2** 6 wk: 1.7, p≥0.05 12 wk: 1.5, p≥0.05 26 wk: 0.4, p=<0.05 52 wk: 0.2, p≥0.05
			Dextrose prolotherapy 20% + PT Baseline: 6.1 (2.4) 6 wk: 3.7 (2.3) 12 wk: 3.0 (2.1) 26 wk: 2.1 (2.1) 52 wk: 0.9 (1.6)	**Arm 1 vs. Arm 3** 6 wk: 1.7, p<0.05 12 wk: 1.0, p<0.05 26 wk: -0.1, p>0.05 52 wk: 0.2, p>0.05
	Adverse events Narrative description 52 wk	*"There were no significant adverse events in the Physiotherapy group. In the Prolotherapy group, one participant developed neuropraxia of the posterior interosseous nerve after the 4th treatment. This resolved over 3 months. Another participant developed painful bruising throughout the forearm after the 2nd treatment, which settled over 2 weeks."*		

Notes. *Mean differences calculated by review team (unless otherwise noted); p-values reported by studies.

†Mean differences reported by study.

Abbreviations. ABI=autologous blood injection; AE=adverse effect/event; DASH= Disabilities of the Arm, Shoulder, and Hand questionnaire; ESWT= Extracorporeal shockwave therapy; EuroQol-5D= European Quality of Life-5 dimensions; HA=hyaluronic acid; MCID=minimal clinically important difference; ml=milliliter; mo=month; NA=not applicable; NSAIDs=nonsteroidal anti-inflammatory drugs; NR=not reported; PRP=platelet rich plasma; PRTEE=Patient-rated Tennis Elbow Evaluation; PT=physical therapy; Quick DASH=shortened version of DASH (11 items); RCT=randomized controlled trial; RoB=risk of bias; VAS=Visual Analog Scale; wk=week; yr=year.

APPENDIX J. CHRONIC LOW BACK PAIN (LBP)

Appendix Table 12. Detailed Study Characteristics for All Eligible Chronic Low Back Pain (LBP) Studies

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and Clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported** **Measurement tools(s) (Time points)**
Injections in L4-S1 and Sacroiliac Areas				
Dechow, 1999[100] NR High 6 mo United Kingdom (1) “South and West Region Research and Development Programme (Project Grant R/21/9.95/Thompson)”	**Inclusion**: "The inclusion criteria included males and females aged 18-71 yr with mechanical low back pain of more than 6 months' duration." **Exclusion**: "Patients were excluded if they were pregnant or contemplating pregnancy, had evidence of nerve root entrapment, unresolved litigation, severe co-existing disease or body weight greater than 20 kg over their ideal."	**Dextrose Prolotherapy**: *N*=36 Age, mean (SD): 44 (11) 55.56% Female Clinic or health care facility 3 injections per week 12.5% DPT + triamcinolone + home exercise program: "A solution of 5 ml of dextrose 25%, glycerine 25% and phenol 2.4% made up to 100 ml with sterile water combine with 5 ml of 1% lignocaine. A rigid 3" x 20G, 3" x 22G or occasionally 3.5" x 20G needle was used. All injections were made from a single insertion into the following sites: tip of the spinous process of L4 and L5 and associated supraspinous and interspinous ligaments; apophyseal joint capsules at L4-5 and L5-S1;	**Normal Saline:** *N*=38 Age, mean (SD): 46 (11) 47.4% Female Clinic or health care facility 3 injections per week Saline: "5 ml of the normal saline solution combine with 5 ml of 1% lignocaine. A rigid 3" x 20G, 3" x 22G or occasionally 3.5" x 20G needle was used. All injections were made from a single insertion into the following sites: tip of the spinous process of L4 and L5 and associated supraspinous and interspinous ligaments; apophyseal joint capsules at L4-5 and L5-S1; attachment of the iliolumbar ligaments at the transverse processes of L5; attachment of the iliolumbar and	**Primary outcome NR** **Pain-related functioning (1, 3, 6 mo)** • ODI **Physical performance (1, 3, 6 mo)** • Modified Schober Test ROM*: Lumbar Flexion **Adverse events** **Other outcomes:** • Pain severity or intensity: VAS*‖ (1, 3, 6 mo) • Cost

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and Clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes Measurement tool(s) (Time points)** **Other Outcomes Reported Measurement tools(s) (Time points)**
		attachment of the iliolumbar ligaments at the transverse processes of L5; attachment of the iliolumbar and dorsolumbar fascia to the iliac crest; and attachments of the long and short fibres of the posterior sacroiliac ligaments and the sacral and iliac attachments of the interosseous sacroiliac ligaments. The majority of patients received light intravenous sedation with midazolam." Other treatments: None reported	dorsolumbar fascia to the iliac crest; and attachments of the long and short fibres of the posterior sacroiliac ligaments and the sacral and iliac attachments of the interosseous sacroiliac ligaments. The majority of patients received light intravenous sedation with midazolam." Other treatments: None reported	
Klein, 1993[101] NR High 6 mo United States of America (1) "This work was supported by grants and contributions from Santa Barbara Cottage Hospital, Sansum Medical Research Foundation, Sansum Medical Clinic, Max and Amy Klein, Dr. and Mrs. Farouk Akhdar, Mr. and Mrs. Bernard	**Inclusion**: "Eligibility…required low back pain of at least 6 months' duration that had failed to respond to prior conservative treatments. Men or nonpregnant women between the ages of 21-60 were eligible...Straight leg raising was possible to at least 70 degrees without pain in patients accepted for the study. All patients accepted for the study screened for inflammatory conditions with complete blood cell counts and Westergren sedimentation rate test." **Exclusion**:	**Dextrose Prolotherapy**: *N*=39 Age, mean (SD): 44.6 (8.6) 46.2% Female Clinic or health care facility 1 injection per week, up to 6 weeks 12.5% DPT + triamcinolone + home exercise program: "The experimental solution consisted of dextrose 25% (694 mosmol/l), glycerine 25% (2720 mosmol/l), phenol 2.5% (266 mosmol/l), and pyrogen-free water to 100%. Because	**Normal Saline:** *N*=40 Age, mean (SD): 43.5 (9.2) 35% Female Clinic or health care facility 1 injection per week, up to 6 weeks Saline + triamcinolone + home exercise program: "The control group was also injected with a maximum of 30 ml of solution at each treatment session, made up by mixing 15 ml of 1/2% lidocaine with 15 ml of sterile normal saline	**Primary outcome NR** **Pain-related functioning (6 mo)** • RMDQ **Physical performance (6 mo)** • B-200 Triaxial Dynamometer ROM*: Rotation, Flexion-Extension, Side Flexion • Isometric Strength*: Rotation, Flexion, Extension, Side Flexion • Velocity*: Rotation, Flexion-Extension, Side Flexion **Adverse events** **Other outcomes:**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and Clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes Measurement tool(s) (Time points)** **Other Outcomes Reported Measurement tools(s) (Time points)**
Fauber, and K-Mart Corporation, and additional donations from patients and friends."	"Criteria for exclusion: unresolved litigation or workers' compensation claims, prior lumbar laminectomy, body weight>40lbs over the ideal (making injections technically difficult), known serious medical conditions such as cancer, heart disease, or uncontrolled diabetes,…contemplating pregnancy during the study period,...clinical evidence of central or peripheral nervous system disease including acute radiculopathy, or acute exacerbation of their chronic pain. Patients with significant hip joint arthritis were excluded."	this solution may cause a temporary irritation it was diluted with an equal volume of 0.5% plain lignocaine hydrochloride ('Xylocaine') to make it comparable with the placebo injection in terms of initial provocation of post-injection pain. All patients were given 10 mg diazepam intravenously for relaxation and amnesia before the start of treatment. Patients in the experimental group were injected with 0.5% lignocaine in the following manner. The spinous process of L5 was identified and the skin overlying this area was sterilised and anaesthetised. A rigid 7.6 cm or 8.9cm (19-gauge) needle was used for all injections. All injections were made from this single insertion into (1) tip of the spinous pattern of L4 and L5 and associated supraspinous and interspinous ligaments; (2) attachment of the ligamentum flavum along the borders of L4 and L5 laminae; (3) apophyseal joint capsules at L4-5, L5-SI; (4) attachment of the iliolumbar ligaments at the transverse processes of L4 and L5; (5) attachment of the iliolumbar ligament and dorsolumbar fascia to the iliac crest; and (6) attachments of the short and long fibres of the posterior sacroiliac ligaments, and the sacral and iliac attachments of the interosseous sacroiliac ligaments...additional	solution....On the initial and all subsequent days of treatment patients were sedated with a combination of i.v. midazolam and/or meperidine. Dosage was individually titrated to achieve satisfactory relaxation and analgesia. The initial day of treatment prior to instituting the double-blind phase consisted of identifying the L4-5 and L5-S1 midline interspinous spaces by palpation. Lidocaine wheals were raised lateral to the midline at each of these levels, approximately over the apophyseal joint capsules bilaterally. Lidocaine wheals were also raised just medial to the posterior superior iliac spines, allowing access to the posterior sacroiliac and interosseous ligaments. Wheals were also placed bilaterally over the iliac crests at the point of insertion of the iliolumbar ligaments and dorsolumbar fascia. Using 1/2-1 ml at each injection site, 50-60 ml of 1/2% lidocaine were infiltrated into these sites on the initial day of treatment...Body landmarks were lightly touched with the needle tip and aspiration was performed before each injection to be certain the fibro-osseous junctions were being contacted and that intrathecal injections were avoided. The interspinous and supraspinous ligaments were injected obliquely to minimized the risk of intrathecal	• Pain severity or intensity: VAS[*Φ] (6 mo)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and Clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes Measurement tool(s) (Time points)** **Other Outcomes Reported Measurement tools(s) (Time points)**
		injections were made from a separate entry point into the sacrospinous and sacrotuberous ligament origins along the lateral sacral border. A maximum of 60 ml 0.5% lignocaine was used in the experimental group patients. Gluteal muscle irritation, which we have found to be a nearly universal phenomenon in chronic back pain patients, was treated in the experimental group by infiltration of 50 mg triamcinolone in 10 ml 0.5% lignocaine into the fascial origin primarily of the gluteus medius muscle. A forceful manipulation was then performed in the experimental group patients...The manipulation required an assistant to immobilise the thorax, the thigh being used as a lever to achieve a rotary and flexion strain across the sacroiliac and low lumbar area. About 85% of patients in both groups requested and were given premedication with intravenous diazepam, with or without pethidine, to lessen the discomfort of the weekly injections." Other treatments: "All patients in the study were instructed to perform 30 standing forward flexion followed by 20 standing extension exercises four times each day during the treatment and follow-up period of 6 months. Patients were encouraged to walk	injections potentially associated with a vertical midline approach. If any foci of tissue hypersensitivity were located on the initial day of treatment these areas were infiltrated with a maximum of 20 mg of triamcinolone for each patient. Only those patients with hyperirritable foci, defined as an exaggerated withdrawal response to light palpation, were injected with corticosteroid. Corticosteroid administration was limited to the 1st day of treatment prior to beginning the double-blind phase of the study." Other treatments: Same as Arm 1	

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and Clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported** **Measurement tools(s) (Time points)**
		briskly for at least 1 mile 5 days each week and to continue to pursue their normal daily activities during the study...The back exercise program was reviewed with all patients at each visit, and the importance of these exercises was repeatedly stressed. Patients were instructed to use extra-strength acetaminophen and heat or ice as needed for pain control during the course of the study."		
Ongley, 1987[102] NR Some concerns 6 mo United States of America (1) NR	**Inclusion**: "...back pain of more than one year in duration that had not responded to previous conservative (non-surgical) treatment....All patients accepted for the study had full clinical evaluation as well as lumbar spine and pelvic X-rays and laboratory tests to rule out infectious, neoplastic, metabolic, or inflammatory causes of back pain." **Exclusion**: "Patients were not interviewed if they were less than 21 or more than 70 years old, if they were pregnant or contemplating pregnancy, if they had litigation pending, if they had	**Dextrose Prolotherapy**: *N*=40 Age, mean (SD): 45 (2.08) 55% Female Clinic or health care facility 1 of 6 injections at each site (0.2-0.4 ml injections per site) every week for 5 weeks 12.5% DPT + triamcinolone + home exercise program: "For US guidance, the transducer was positioned transverse to the sacral hiatus (sacral cornea) and then moved slightly lateral to reach the sacrum's outer edge until the joint appeared in the US field (in plane method)...using	**Normal Saline:** *N*=41 Age, mean (SD): 43.3 (1.66) 51.2% Female Clinic or health care facility 1 of 6 injections at each site (0.2-0.4 ml injections per site) every week for 5 weeks Saline + home exercise program: "Patients in the placebo group received sterile 0.9% saline. All patients were given 10 mg diazepam intravenously for relaxation and amnesia before the start of treatment...The placebo patients were injected at the same entry site(s) with	**Primary outcome NR** **Pain-related functioning (1, 3, 6 mo)** • Modified RMDQ/WDI*† **Adverse events** **Other outcomes:** • Pain severity or intensity: VAS*ǂ (1, 3, 6 mo)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and Clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported** **Measurement tools(s) (Time points)**
	an unsettled worker's compensation claim, or if they were on disability pay…body weight more than 25% over ideal (making injections technically more difficult), insulin-dependent diabetes, coronary artery disease, and debilitating medical conditions…excluded if they had fewer than 4 positive responses on the disability pain questionnaire...Patients were examined neurologically to rule out central and peripheral nervous system disease including acute radiculopathy."	the spinal needle Gauge 22 through an inferomedial approach, i.e, one inch medial and below the PSIS (Figure 1). Initially, each patient received 2 ml of 2.5% bupivacaine intra-articular injection as a confirmatory test for SIJ dysfunction. 2.5 ml of dextrose 20% solution was injected into the prolotherapy group." Other treatments: "Patients were advised to stop all pain medications except paracetamol (Acetaminophen) and to avoid all other ancillary forms of treatment for back pain during the course of this study. Patients in both groups were instructed in a specific series of flexion exercises. These exercises were continued during the injection period and for at least six months afterwards."	0.5% lignocaine, but no more than 10 ml was used. The placebo patients were injected with lignocaine alone. Patients in the placebo group received a manipulation in which they were placed on their side and pressure was applied from behind to the torso and buttocks simultaneously. About 85% of patients in both groups requested and were given premedication with intravenous diazepam, with or without pethidine, to lessen the discomfort of the weekly injections." Other treatments: Same as Arm 1	
Yelland, 2004[99] NR High 24 mo Australia (1)	**Inclusion**: "Inclusion criteria were age 21 to 70 years, low-back pain present on more than half the days in the past 6 months, modified Roland-Morris disability questionnaire21 score more than three, and failure of conservative treatment(s) to give sustained pain relief."	**Dextrose Prolotherapy**: *N*=54 Age, mean (SD): 51.5 (10.6) 40.7% Female Clinic or health care facility 10 injections per visit every 2 weeks repeated up to 6 times	**Normal Saline:** *N*=56 Age, mean (SD): 49.4 (10.4) 44.6% Female Clinic or health care facility 10 injections per visit every 2 weeks repeated up to 6 times	**VAS &** RMDQ **Pai-related functioning (12, 24 mo)** • RMDQ‡ **Health-related quality of life (12, 24 mo)** • SF-12 Physical & Mental*¶ **Adverse events**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and Clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported** **Measurement tools(s) (Time points)**
"Australian General Practice Evaluation Program, the Australian Association of Musculoskeletal Medicine, and the Musculoskeletal Research Foundation of Australia."	**Exclusion**: "Exclusion criteria were acute exacerbation of pain, lumbar spinal stenosis or radiculopathy, osteoarthritis or aseptic necrosis of the hip, cancer, inflammatory arthritis, previous spinal surgery or prolotherapy, body mass index more than 33 for women and 35 for men (making injections technically difficult), unresolved litigation or workers' compensation claims, 31 fibromyalgia, more than three of Waddell's nonorganic signs 29 of back pain, and pregnancy or intended pregnancy."	20% DPT + home exercise program (factorial design): "The injected solution consisted of 25% dextrose to make a 12.5% soft tissue solution (1/2 volume of 10 ml syringe), xylocaine 0.3% (1 ml of 3% xylocaine over 10 ml solution); bacteriostatic water was recommended as a diluent. 0.5–1 ml of solution was injected in each trigger point as well as tender ligaments and tendinous insertion points. The prolotherapist used his fingertip to palpate potential pain referral sources for the patient's clinical complaints. Injection sites were cervical inter-transverse ligaments, posterior-superior trapezius, infraspinatus, common extensors, iliolumbar, and sacroiliac ligament." Other treatments: "For all participants, analgesics, heat, and general activity were recommended for postinjection pain and stiffness, but the use of anti-inflammatory medications were discouraged. All participants were supplied with a daily supplement of zinc 30 mg, manganese 22.5 mg, beta-carotene 3 mg, pyridoxine 15 mg, and vitamin C 1,000 mg for 6-month treatment period."	Saline + home exercise program (factorial design): "The control injections contained normal (0.9%) saline...Injections were performed through an anesthetized wheel of skin over each site after first contacting bone to confirm their position. Approximately 3 ml solution was infiltrated at each site and a maximum of 10 sites treated at each visit. If no improvement was noted by the fifth session, the deeper interosseous sacroiliac ligaments on the affected side or sides were also treated. Exercise group participants were taught two sagittal loading exercises to be performed in standing-alternating flexion and extension of the hips to midrange with the spine held straight, and flexion of the lumbar spine with the hips stationary...All participants were encouraged to continue all their pretrial activities and exercises." Other treatments: Same as Arm 1	**Other outcomes:** • Pain severity or intensity: VAS*¶ (12, 24 mo)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and Clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes Measurement tool(s) (Time points)** **Other Outcomes Reported Measurement tools(s) (Time points)**
Intradiscal or Facet Joint Injections				
Derby, 2004[104] NR Serious 18 mo United States of America (1) NR	**Inclusion**: "Patients with putative chronic discogenic LBP…Participants included patients who underwent IDET during the same period that restorative injections were performed. All patients presented with LBP of discogenic origin established via discography of the lumbar spine within the past 6 months. All patients failed to respond to previous conservative treatment including nerve blocks, with non-focal neurologic examination, disc protrusion =<2 mm, single level pathology, and positive discogram with annular tear." **Exclusion**: "Subjects with allergy to any contrast media, iodine, or cephalosporin antibiotics were excluded. We excluded patients with unstable medical conditions, instability and spondylolisthesis, severe spinal stenosis, and reduced disc height >50%. Patients	**Dextrose prolotherapy**: *N*=35 Age, mean (SD): 42 (NR) 51.4% Female Clinic or health care facility 1 injection 16.7% DPT, fluoroscopy-guided: "A compounding pharmacist using sterile technique and USP grade pharmaceuticals prepared the solutions which consisted of 0.5% chondroitin sulfate, 20% glucosamine hydrochloride, 12% DMSO and 2% bupivacaine. These concentrations were based upon the solubility and tolerance characteristics of the constituents. This solution was then mixed with equal parts non-ionic contrast and 50% dextrose at the time of injection. To avoid patient discomfort, the injection was performed during diagnostic discography. An intradiscal injection of 1-2 cc of solution was utilized at each involved disc level as determined by discography. Injections were	**Other Non-Injectable**: *N*=74 Age, mean (SD): 41.57 (NR) 56.8% Female Clinic or health care facility 1 injection Intradiscal electrothermal treatment (IDET), fluoroscopy-guided: "Prior to injection a fluoroscopic examination of the spine was performed to confirm segmentation and determine the appropriate level for needle placement. Using standard discographic practices, a 17-gauge introducer was placed into the center of the disc. Position was confirmed by fluoroscopy in oblique, antero-posterior (AP), and lateral views. A navigable intradiscal catheter with a 6-cm active electrothermal tip (SpineCATH, Oratec Interventions, Menlo Park, CA) was then advanced and passed diametrically across the nucleus pulposus until it contacted the inner antero-lateral annulus. With continued insertion the electrode deflected	**Primary outcome NR** **Adverse events**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and Clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes Measurement tool(s) (Time points)** **Other Outcomes Reported Measurement tools(s) (Time points)**
	who could not speak English were also excluded for accuracy of outcome."	performed using fluoroscopic guidance. If leakage of contrast into the epidural space was noted, the injection was terminated. Prophylactic antibiotics and standard discographic monitoring and sedation procedures were used." Other treatments: "Following the procedure, patients were given a lumbar support brace to deter movements that might elevate intradiscal pressure (e.g., forward bending) and were instructed to forego intense physical training for a period of 6 months. In the first month, permitted activities included walking and gentle leg stretches. Over the next 5 months, the intensity of exercise was gradually increased until patients engaged in normal activities by 6 months."	circumferentially back towards the insertion side, with its circuitous route encompassing the inner perimeter of the annulus. After satisfactory catheter placement, an ORA-50 S ElectroThermal Spine Generator was attached and gradually heated to 90 degrees C over 16.5 minutes. Once coagulation was complete, cefazolin antibiotic and 0.5% bupivacaine were administered intradiscally for antimicrobial prophylaxis and post-procedure analgesia, respectively." Other treatments: Same as Arm 1	
Yildirim, 2021[105] NR Moderate 3 mo Turkey (1)	**Inclusion**: "In our study, patients with chronic low back pain were examined before and after different methods of treatment to assess treatment effective ness…Data from patients who were treated for chronic low back pain in our clinic between 2013 and 2019 and who were treated with local	**Dextrose prolotherapy**: *N*=87 Age, mean (SD): 60.01 (12.475) 64.4% Female Clinic or health care facility 1 injection	**Steroid Injectable**: *N*=91 Age, mean (SD): 57.32 (12.774) 76.9% Female Clinic or health care facility 1 injection	**VAS & ODI** **Pain-related functioning (3 mo)** • ODI **Other outcomes:** • Pain severity or intensity: VAS[*b] (1, 15 day, 3 mo)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and Clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes Measurement tool(s) (Time points)** **Other Outcomes Reported Measurement tools(s) (Time points)**
"During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct con nection with the research subject, nor from a company that pro vides or produces medical instruments and materials which may negatively affect the evaluation process of this study."	treatment without surgical indication..." **Exclusion**: NR	5 ml 25% DPT, single-level facet joint capsule Other treatments: None reported	20 mg of methylprednisolone combined with 2-4 mL of 0.25% bupivacaine, single-level facet joint injection Other treatments: None reported	
Sacroiliac Joint Injections				
Kim, 2010[107] NR Some concerns 15 mo South Korea (1) “No financial support was provided for this study.”	**Inclusion**: "…history of pain lasting 2 months or longer in the buttock, groin, or thigh, regardless of associated lower extremity symptoms. Positive physical examination included tenderness over the area just below the posterior superior iliac spine, the Patrick test, or Gaenslen’s test...diagnostic local anesthetic intra-articular injection using 2.5mL of 0.25% levobupivacaine was performed to confirm SI joint pain. A decrease in pain intensity of at least 50%, measured by the numeric rating scale was deemed a positive response. Patients diagnosed with SI joint pain	**Dextrose Prolotherapy**: *N*=23 Age, mean (SD): 58.7 (13) 70% Female Clinic or health care facility 1 injection every other week repeated up to 3 times 25% DPT, fluoroscopy-guided: "The experimental (proliferant) solution consisted of dextrose, 25%; glycerine, 25%; and phenol, 2.4%, made up to 100% with pyrogen-free water. Fifteen milliliters of this solution were combined with 15 ml of 1/2%	**Steroid Injectable**: *N*=25 Age, mean (SD): 61.6 (15.2) 72% Female Clinic or health care facility 1 injection every other week repeated up to 3 times Triamcinolone, fluoroscopy-guided: "A similar treatment schedule (injection into the SI joint every other week and repeated this up to 3 times, if the symptoms improved by more than 90% by NRS on the second or third visit the next procedure was canceled)	**NRS** **Pain-related functioning (2 wk)** • ODI **Adverse events** **Other outcomes:** • Pain severity or intensity: NRS (2 wk)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and Clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes Measurement tool(s) (Time points)** **Other Outcomes Reported Measurement tools(s) (Time points)**
	and who failed medical treatment for an additional 1 month were prospectively enrolled." **Exclusion**: "Exclusion criteria were cancer, fractures, inflammatory arthritis, infection, unresolved litigation or workers' compensation claims, fibromyalgia, and pregnancy."	lidocaine to make up the maximum total volume of 30 ml of solution available for each of the six weekly double-blind injection sessions on the experimental group. The initial day of treatment prior to instituting the double-blind phase consisted of identifying the L4-5 and L5-S1 midline interspinous spaces by palpation. Lidocaine wheals were raised lateral to the midline at each of these levels, approximately over the apophyseal joint capsules bilaterally. Lidocaine wheals were also raised just medial to the posterior superior iliac spines, allowing access to the posterior sacroiliac and interosseous ligaments. Wheals were also placed bilaterally over the iliac crests at the point of insertion of the iliolumbar ligaments and dorsolumbar fascia. Using 1/2-1 ml at each injection site, 50-60 ml of 1/2% lidocaine were infiltrated into these sites on the initial day of treatment...Body landmarks were lightly touched with the needle tip and aspiration was performed before each injection to be certain the fibro-osseous junctions were being contacted and that intrathecal injections were avoided. The interspinous and supraspinous ligaments were injected obliquely to minimized the risk of intrathecal injections potentially associated with a	was administered in the steroid group, but the injected drug was triamcinolone acetonide 40 mg in 0.125% levobupivacaine 2.5 mL). Patients were positioned prone, with the C-arm slightly tilted cephalad, to displace the posteroinferior portion of the SI joint inferiorly from the anterior aspect. Then, the C-arm was orbited back and forth such that the medial joint line (the posterior portion of SI joint) and the edge of the sacrum are clearly identified. After the skin was draped and anesthetized slightly caudal to the most inferior aspect of the SI joint, a 22-gauge spinal needle was inserted into the joint. Then, the needle was advanced upward into the base of the joint while being checked for the depth of the tip on the lateral fluoroscopic view. After confirmation of the intra-articular position using an arthrogram, with 0.2–0.5mL of contrast medium, the drug for diagnosis or therapy was injected." Other treatments: Same as Arm 1	

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and Clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported** **Measurement tools(s) (Time points)**
		vertical midline approach. If any foci of tissue hypersensitivity were located on the initial day of treatment these areas were infiltrated with a maximum of 20 mg of triamcinolone for each patient. Only those patients with hyperirritable foci, defined as an exaggerated withdrawal response to light palpation, were injected with corticosteroid. Corticosteroid administration was limited to the 1st day of treatment prior to beginning the double-blind phase of the study." Other treatments: "For managing postprocedure pain, an oral tramadol and acetaminophen containing tablet and tizanidine hydrochloride were prescribed for 7 days to all patients. Analgesics being administered before the study were stopped prior to the first session and for the duration of the study. However, adequate medications were provided for patients with recurring severe SI joint pain."		
Raissi, 2022[106] IRCT20170910036107N2 Some concerns 9 mo	**Inclusion**: "The primary diagnosis of the patients was based on at least two months of unilateral typical hip, thigh, and groin pain. Patients were included in the study if they had not responded to	**Dextrose Prolotherapy**: *N*=18 Age, mean (SD): 50.72 (7.3) 72.2% Female	**Steroid Injectable**: *N*=18 Age, mean (SD): 52.44 (7.6) 66.7% Female	**VAS & DPQ** **Pain-related functioning (2, 8 wk)** • DPQ **Adverse events**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and Clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported** **Measurement tools(s) (Time points)**
Iran (1) NR	pharmacological treatments for at least one month. Tenderness below the Posterior Superior Iliac Spine (PSIS) and at least one positive Patrick or Gaenslen test were consistent clinical examinations in favor of a SI origin pathology; given that these tests are not specific, a significant reduction in pain (greater than 50% of the baseline level) immediately following an anesthetic injection (2 ml of bupivacaine 2.5%), measured at 100 mm Visual Analog Scale (VAS), was considered a confirmatory tool for the diagnosis of SIJ dysfunction." **Exclusion**: "Our exclusion criteria were history of surgery, trauma, or any invasive procedure in the lumbosacral region during the past 6 months, and abnormal complete blood count or impaired coagulation tests. Pregnant women, patients on immunosuppressive medications, and those with an underlying systemic	Clinic or health care facility 1 injection 20% DPT, ultrasound-guided + home exercises: "The index injections contained 20% glucose/0.2% lignocaine (with 4 ml 50% glucose, 1 ml 2%lignocaine, and 5 ml water in each 10-ml syringe). Injections were performed through an anesthetized wheel of skin over each site after first contacting bone to confirm their position. Approximately, 3 ml solution was infiltrated at each site and a maximum of 10 sites treated at each visit. If no improvement was noted by the fifth session, the deeper interosseous sacroiliac ligaments on the affected side or sides were also treated. Exercise group participants were taught two sagittal loading exercises to be performed in standing-alternating flexion and extension of the hips to midrange with the spine held straight, and flexion of the lumbar spine with the hips stationary...All participants were encouraged to continue all their pretrial activities and exercises."	Clinic or health care facility 1 injection Triamcinolone, ultrasound-guided + home exercises: "For US guidance, the transducer was positioned transverse to the sacral hiatus (sacral cornea) and then moved slightly lateral to reach the sacrum's outer edge until the joint appeared in the US field (in plane method)...using the spinal needle Gauge 22 through an inferomedial approach, i.e, one inch medial and below the PSIS. Initially, each patient received 2 ml of 2.5% bupivacaine intra-articular injection as a confirmatory test for SIJ dysfunction. 2.5 ml of triamcinolone 40 mg/ml was injected into the steroid group." Other treatments: Same as Arm 1	**Other outcomes:** • Pain severity or intensity: VAS*‖ (2, 8 wk, 9 mo)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and Clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported** **Measurement tools(s) (Time points)**
	inflammatory disease were also excluded. Furthermore, patients with a history of infections, fibromyalgia, cancer, or concurrent lumbosacral radiculopathy were excluded."	Other treatments: "A program of stretching exercises and Acetaminophen consumption was recommended to control potential post-injection reactions."		

Notes. *No established MCID for outcome; direction of effect based on statistically significant difference reported by study.

†Authors assessed disability using a combined measure of 24 items from Roland-Morris Disability Questionnaire (RMDQ) and 9 questions from Waddell Disability Index.

‡23 items from RMDQ.

¶Study only reported change in SF-12 scores, no mean scores at follow-up time points.

‖Authors assessed VAS on a scale of 0 (no pain) to 10 (unbearable pain).

¶Authors assessed VAS on a scale of 0 (no pain) to 100 (unbearable pain).

QAuthors assessed VAS on a scale of 0 (no pain) to 8 (unbearable pain).

ǂAuthors assessed VAS on a scale of 0 (no pain) to 7.5 (unbearable pain).

ƻAuthors assessed VAS on a scale that was undefined.

Abbreviations. AE=adverse event; DPQ=Dallas Pain Questionnaire; DPT=dextrose prolotherapy; h=hour; IDET=Intradiscal Electrothermal Therapy; kg=kilogram; lbs=pounds; LBP=low back pain; LDLPC=left dorso-lateral prefrontal cortex; mg=milligram; ml=milliliter; mm=millimeter; mo=month; NHS=National Health Service; NR=not reported; NRS=Numeric Rating Scale; NS=not significant; ODI=Oswestry Disability Index; RMDQ=Roland Morris Disability Questionnaire; RoB=risk of bias; ROM=range of motion; rTMS=repetitive transcranial magnetic stimulation; SD=standard deviation; SI=sacroiliac; SIJ=Sacroiliac Joint Dysfunction; VAS=Visual Analogue Scale; WDI=Waddell Disability Index; wk=week; yr=year.

Appendix Table 13. Detailed Results for All Eligible Chronic Low Back Pain Studies

Author, Year Risk of Bias	Outcome Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
Injections in L4-S1 and Sacroiliac Areas				
Dechow, 1999[100] High	Pain-related functioning or interference ODI 1, 3, 6 mo	**Dextrose Prolotherapy** Baseline: 33.99 (NR) 1 mo: 35.92 (NR) 3 mo: 36.02 (NR) 6 mo: 35.22 (NR)	**Normal Saline** Baseline: 33.06 (NR) 1 mo: 33.06 (NR) 3 mo: 33.59 (NR) 6 mo: 34.56 (NR)	**Arm 1 vs. Arm 2** 1 mo: 2.86, p=NR 3 mo: 2.43, p=NR 6 mo: 0.66, p=NR
	Physical performance Modified Schober Test 1, 3, 6 mo	**Dextrose Prolotherapy** Baseline: 4.83 (NR) 1 mo: 5.52 (4.86) 3 mo: 5.45 (5.1) 6 mo: 5.4 (4.8)	**Normal Saline** Baseline: 5.28 (NR) 1 mo: 5.49 (NR) 3 mo: 5.23 (NR) 6 mo: 5.77 (NR)	**Arm 1 vs. Arm 2** 1 mo: 0.03, p=NR 3 mo: 0.22, p=NR 6 mo: -0.37, p=NR
	Pain severity or intensity VAS† 1, 3, 6 mo	**Dextrose Prolotherapy** Baseline: 5.39 (NR) 1 mo: 5.2 (NR) 3 mo: 5.1 (NR) 6 mo: 5.19 (NR)	**Normal Saline** Baseline: 5.31 (NR) 1 mo: 4.77 (NR) 3 mo: 5.28 (NR) 6 mo: 4.47 (NR)	**Arm 1 vs. Arm 2** 1 mo: 0.43, p=NR 3 mo: -0.18, p=NR 6 mo: 0.72, p=NR
	Adverse events 6 mo	*"A few subjects reported a transient increase in back pain following the injections, but…no differences between the treatment and control groups and no other significant adverse reactions."* (AE not defined)		
Klein, 1993[101] High	Pain-related functioning or interference RMDQ 6 mo	**Dextrose Prolotherapy** Baseline: 9.36 (3.6) 6 mo: 4.04 (3.71)	**Normal Saline** Baseline: 8.25 (3.3) 6 mo: 4.38 (4.05)	**Arm 1 vs. Arm 2** 6 mo: -0.34, p=0.068
	Physical performance B-200 Triaxial Dynamometer ROM: Rotation, Flexion-Extension, Side Flexion 6 mo	**Dextrose Prolotherapy** Baseline: 81.9 (11.8) 6 mo, Rotation: 91.8 (8.6) 6 mo, Flexion-Extension: 100.5 (11.1) 6 mo, Side Flexion: 78.2 (11.4)	**Normal Saline** Baseline: 84.0 (9.9) 6 mo, Rotation: 93.8 (6.2) 6 mo, Flexion-Extension: 102.3 (11.7) 6 mo, Side Flexion: 78.1 (11.7)	**Arm 1 vs. Arm 2** 6 mo, Rotation: -2, p=NR 6 mo, Flexion-Extension: -1.80, p=NR 6 mo, Side Flexion: 0.10, p=NR
	Physical performance B-200 Triaxial Dynamometer Isometric Strength: Rotation, Flexion, Extension, Side Flexion 6 mo	**Dextrose Prolotherapy** Baseline: 68.7 (33.2) 6 mo, Rotation: 57.1 (24.1) 6 mo, Flexion: 81.6 (43.3) 6 mo, Extension: 100.7 (40.5) 6 mo, Side Flexion: 92.9 (39.0)	**Normal Saline** Baseline: 78.9 (42.1) 6 mo, Rotation: 63.7 (27.7) 6 mo, Flexion: 96.2 (49.6) 6 mo, Extension: 120.2 (53.2) 6 mo, Side Flexion: 108.5 (47.3)	**Arm 1 vs. Arm 2** 6 mo, Rotation: -6.60, p=NR 6 mo, Flexion: -14.60, p=NR 6 mo, Extension: -19.5, p=NR 6 mo, Side Flexion: -15.60, p=NR

Author, Year Risk of Bias	Outcome Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
	B-200 Triaxial Dynamometer Angular Velocity: Rotation 50% Resistance, Rotation 25% Resistance, Flexion-Extension 50% Resistance, Flexion-Extension 25% Resistance, Side Flexion 50% Resistance, Side Flexion 25% Resistance 6 mo	**Dextrose Prolotherapy** Baseline: 105.4 (33.7) 6 mo, Rotation 50%: 92.0 (28.6) 6 mo, Rotation 25%: 121.4 (34.7) 6 mo, Flexion-Extension 50%: 115.2 (34.7) 6 mo, Flexion-Extension 25%: 129.1 (39.3) 6 mo, Side Flexion 50%: 105.9 (35.5) 6 mo, Side Flexion 25%: 129.2 (41.6)	**Normal Saline** Baseline: 109.6 (31.0) 6 mo, Rotation 50%: 94.6 (26.0) 6 mo, Rotation 25%: 122.9 (26.1) 6 mo, Flexion-Extension 50%: 123.7 (32.3) 6 mo, Flexion-Extension 25%: 135.0 (35.4) 6 mo, Side Flexion 50%: 112.8 (35.2) 6 mo, Side Flexion 25%: 131.2 (38.7)	**Arm 1 vs. Arm 2** 6 mo, Rotation 50%: -2.60, p=NR 6 mo, Rotation 25%: -1.5, p=NR 6 mo, Flexion-Extension 50%: -8.5, p=NR 6 mo, Flexion-Extension 25%: -5.90, p=NR 6 mo, Side Flexion 50%: -6.90, p=NR 6 mo, Side Flexion 25%: -2, p=NR
	Pain severity or intensity VAS‡ 6 mo	**Dextrose Prolotherapy** Baseline: 4.88 (1.3) 6 mo: 2.85 (1.88)	**Normal Saline** Baseline: 4.56 (1.12) 6 mo: 2.29 (1.67)	**Arm 1 vs. Arm 2** 6 mo: 0.56, p=0.056
	Adverse events 6 mo	*"one in each group… [developed] lumbar puncture headaches…during the course of treatment, lasting approximately 3 days each before spontaneously abating without sequelae… All patients complained of varying degrees of stiffness and soreness for 1-3 days following injection, but in no case was this severe enough…to discontinue treatment."*		
Ongley, 1987[102] Some concerns	Pain-related functioning or interference Modified RMDQ/WDI¶ 1, 3, 6 mo	**Dextrose Prolotherapy** Baseline: 11.45 (NR) 1 mo: 4.00 (NR) 3 mo: 4.70 (NR) 6 mo: 3.43 (NR)	**Normal Saline** Baseline: 11.82 (NR) 1 mo: 8.37 (NR) 3 mo: 8.49 (NR) 6 mo: 8.29 (NR)	**Arm 1 vs. Arm 2** 1 mo: -4.37, p=<0.001 3 mo: -3.79, p=<0.004 6 mo: -4.86, p=<0.001
	Pain severity or intensity VAS‖ 1, 3, 6 mo	**Dextrose Prolotherapy** Baseline: 3.78 (NR) 1 mo: 2.13 (NR) 3 mo: 1.77 (NR) 6 mo: 1.50 (NR)	**Normal Saline** Baseline: 3.99 (0.19) 1 mo: 3.06 (0.29) 3 mo: 2.93 (0.25) 6 mo: 3.08 (0.28)	**Arm 1 vs. Arm 2** 1 mo: -0.93, p=<0.01 3 mo: -1.16, p=<0.001 6 mo: -1.58, p=<0.001
	Adverse events 6 mo	**Dextrose Prolotherapy** 2 with increased menstrual bleeding, 2 with post-menopausal bleeding (at 4 wk)	**Normal Saline** 1 with increased menstrual bleeding, 1 withdrew after the second day of injections due to severe headache and cough (resolved 1 wk later)	*"Patients in both groups complained of pain and stiffness for 12-24 h after each injection…[, not] severe enough to necessitate bed rest or absence from work."*
Yelland, 2004[99] High	Pain-related functioning or interference Modified RMDQ** §§ 12, 24 mo	**Dextrose Prolotherapy** Baseline: 13.7 (5.0) 12 mo: 8.0 (NR) 24 mo: 8.6 (NR)	**Normal Saline** Baseline: 14.3 (4.5) 12 mo: 9.8 (NR) 24 mo: 9.4 (NR)	**Arm 1 vs. Arm 2** 12 mo: -1.8, p=NR 24 mo: -0.8, p=NR
	Health-related quality of life SF-12 PCS††	**Dextrose Prolotherapy** Baseline: 35.2 (9.9)	**Normal Saline** Baseline: 32.1 (7.1)	**Arm 1 vs. Arm 2** 12, 24 mo: NR, p=NR

Author, Year Risk of Bias	Outcome Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
	12, 24 mo	12, 24 mo: NR	12, 24 mo: NR	
	Health-related quality of life SF-12 MCS[††] 12, 24 mo	**Dextrose Prolotherapy** Baseline: 47.6 (12.7) 12, 24 mo: NR	**Normal Saline** Baseline: 49.6 (12.4) 12, 24 mo: NR	**Arm 1 vs. Arm 2** 12, 24 mo: NR, p=NR
	Pain severity or intensity VAS[‡‡] [§§] 12, 24 mo	**Dextrose Prolotherapy** Baseline: 51.9 (19.3) 12 mo: 33.21 (NR) 24 mo: 32.83 (NR)	**Normal Saline** Baseline: 55.0 (20.7) 12 mo: 36.79 (NR) 24 mo: 37.17 (NR)	**Arm 1 vs. Arm 2** 12 mo: -3.58, p=NR 24 mo: -4.34, p=NR
	Adverse events 24 mo	*"Incidence of potential adverse effects did not differ between groups."* (Range of potential AE were described for total participants but proportion by arm NR and no separation by severity; potential AE included increased pain in back or legs, nausea or diarrhea, headaches, etc.)		
Non-specific Low Back Pain: Intradiscal or Facet Joint Injections				
Yildirim, 2021[105] Moderate	Pain-related functioning or interference ODI 3 mo	**Dextrose Prolotherapy** Baseline: 55.93 (10.74) 3 mo: 39.13 (8.11)	**Steroid Injectable** Baseline: 56.59 (10.47) 3 mo: 32.85 (7.50)	**Arm 1 vs. Arm 2** 3 mo: 6.28, p=0.000
	Pain severity or intensity VAS[¶¶] 1, 15 day, 3 mo	**Dextrose Prolotherapy** Baseline: 7.57 (0.98) 1 day: 3.48 (1.06) 15 day: 2.80 (0.85) 3 mo: 3.11 (1.02)	**Steroid Injectable** Baseline: 8.45 (0.69) 1 day: 1.67 (0.88) 15 day: 3.02 (1.45) 3 mo: 5.38 (1.99)	**Arm 1 vs. Arm 2** 1 day: 1.81, p=0.000 15 day: -0.22, p=0.225 3 mo: -2.27, p=0.000
Sacroiliac Joint Dysfunction (focal)				
Kim, 2010[107] Some concerns	Pain-related functioning or interference ODI 2 wk	**Dextrose Prolotherapy** Baseline: 33.9 (15.5) 2 wk: 11.1 (10.0)	**Steroid Injectable** Baseline: 35.7 (20.4) 2 wk: 15.5 (10.7)	**Arm 1 vs. Arm 2** 2 wk: -4.40, p=NR
	Pain severity or intensity NRS 2 wk	**Dextrose Prolotherapy** Baseline: 6.3 (NR) 2 wk: 1.4 (1.1)	**Steroid Injectable** Baseline: 6.7 () 2 wk: 1.9 (0.9)	**Arm 1 vs. Arm 2** 2 wk: -0.50, p=NR
Raissi, 2022[106] Some concerns	Pain-related Functioning DPQ 2, 8 wk	**Dextrose Prolotherapy** Baseline: 217.89 (72.87) 2 wk: 182.94 (84.62) 8 wk: 195.83 (47.41)	**Steroid Injectable** Baseline: 208.56 (70.69) 2 wk: 165.54 (62.12) 8 wk: 158.83 (78.81)	**Arm 1 vs. Arm 2** 2 wk: 17.40, p=NR 8 wk: 37.00, p=NR
	Pain severity or intensity	**Dextrose Prolotherapy**	**Steroid Injectable**	**Arm 1 vs. Arm 2**

Author, Year Risk of Bias	Outcome Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
	VAS† 2, 8 wk, 9 mo	Baseline: 8.17 (1.54) 2 wk: 4.50 (2.12) 8 wk: 4.11 (1.45) 9 mo: 2.67 (1.24)	Baseline: 7.76 (1.70) 2 wk: 3.71 (2.12) 8 wk: 4.48 (2.60) 9 mo: 2.62 (1.63)	2 wk: 0.79, p=NR 8 wk: -0.37, p=NR 9 mo: 0.05, p=NR

Notes. *Mean differences calculated by review team; p-values reported by study (otherwise NR).

†Authors assessed VAS on a scale of 0 (no pain) to 10 (unbearable pain).

‡Authors assessed VAS on a scale of 0 (no pain) to 8 (unbearable pain).

¶Authors assessed disability using a combined measure of 24 items from Roland-Morris Disability Questionnaire (RMDQ) and 9 questions from Waddell Disability Index.

‖Authors assessed VAS on a scale of 0 (no pain) to 7.5 (unbearable pain).

**23 items from modified RMDQ. Study reported mean (SE) change scores.

††Study only reported change in SF-12 scores, no mean scores at follow-up time points.

‡‡Authors assessed VAS on a scale of 0 (no pain) to 100 (unbearable pain).

¶¶Authors assessed VAS on a scale that was undefined.

§§Authors reported VAS and modified RMDQ scores graphically. Review team extracted results using Plot Digitizer.

Abbreviations. DPQ=Dallas Pain Questionnaire; MCS=Mental Component Summary; mo=month; NR=not reported; NS=not significant; NRS=Numeric Rating Scale; ODI=Oswestry Disability Index; PCS=Physical Component Summary; RMDQ=Roland Morris Disability Questionnaire; ROM=range of motion; SD=standard deviation; VAS=Visual Analogue Scale; WDI=Waddell Disability Index; wk=week.

APPENDIX K. TEMPOROMANDIBULAR JOINT (TMJ) DISORDERS

Appendix Table 14. Detailed Study Characteristics for All Eligible TMJ Studies

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported**
Normal or Restricted Mobility				
Elwerfelli, 2019[108] NR Serious 6 Weeks Egypt (1) NR	**Inclusion:** Clinical signs and symptoms of TMJ internal derangement; diagnosed based on clinical data and MRI findings; failed prior conservative, non-surgical treatment (*eg,* NSAIDs, soft diet, moist heat, habit modification, and occlusal splint ≥4 wk); TMJ pain with one of the following criteria: joint noises, limited mouth opening (<35 mm), impeded lateral movement, deviation toward the affected side of the opening and protrusion movements **Exclusion:** Previous TMJ surgical intervention; previous joint fractures; TMJ ankyloses; current chemotherapy or radiotherapy; compromising conditions (*eg*, osteoporosis, organ transplantation); systemic immunological destruction disease (*eg,* osteoarthritis); receiving anticoagulation treatment or aspirin within 48 hours; corticosteroid injection; uncontrolled diabetes millets; TMJ infection	**Dextrose prolotherapy:** *N*=7 Age, mean (SD): NR % Female NR Clinic or health care facility Single injection Arthrocentesis with normal saline followed by 2 mL 50% dextrose into superior joint space. First entry mark was 10 mm from the tragus and the second mark was 2 mm below. Used 20-G needle to inject 2 mL saline at first point, then another 20-G at the second point to establish a free flow through the joint space. Both needles inserted about 1.5 cm deep. 50 mL total of normal saline solution was used to lavage. Other treatments: Postoperative instructions included soft diet and home physiotherapy (*eg*, moist heat and ROM exercises every 6 hr daily). Prescribed medication: 250 mg Amoxicillin and 250	**Saline/Local anesthetic:** *N*=7 Age, mean (SD): NR % Female NR Clinic or health care facility Single injection Arthrocentesis with 2 mL normal saline alone; procedure as described for Arm 1 Other treatments: Same as Arm 1	**Primary outcome NR** **Physical performance (1 day; 1, 2, 3, 4, 5, 6 wk)** • MMO **Adverse events** **Other outcomes:** • Pain severity or intensity

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported**
		mg Flucloxacillin (Flumox 500 mg) and paracetamol 665 mg to be taken every 8 hr/day for 1 wk.		
Fouda, 2018[109] NR High 3 Months Egypt (1) NR	**Inclusion:** Unilateral symptoms of pain; clicking sounds; normal range of mouth opening; MRI showed displacement of the disc with reduction **Exclusion:** History of previous operations in TMJ region; bilateral symptoms; coexisting conditions (*eg,* rheumatic disease or neurological disorders); physiotherapy within the previous 3 mo; coagulation or bleeding problems; treatment with radiotherapy, chemotherapy, or anticoagulants	**Dextrose prolotherapy:** *N*=18 Age, mean (SD): NR % Female NR Clinic or health care facility 4 injections, each 1 wk apart 22% dextrose + 0.2% mepivacaine into outer capsule. 25% hypertonic dextrose solution 1.5 mL mixed with 2% mepivacaine hydrochloride plus 1:20000 levonordefrin 0.2 mL using 22-G needle. Arm 1 received intra-articular injection into outer capsule through the midpoint of the condylar head with the patient's mouth wide open so that the solution was given subcutaneously. Other treatments: None reported	**Dextrose prolotherapy:** *N*=18 Age, mean (SD): NR % Female NR Clinic or health care facility 4 injections, each 1 wk apart Injection solution same as Arm 1. Arm 2 received intra-articular injection into superior joint space after the condylar head had been palpated with the patient's mouth closed and the upper surface of the condylar head marked. The needle was introduced from the bottom upwards until it touched the upper bony surface of the glenoid fossa, and then the solution was injected. Other treatments: None reported **Dextrose prolotherapy:** *N*=18 Age, mean (SD): NR % Female NR	**Benefits of treatment:** internal derangement and pain **Physical performance (2 wk, 3 mo)** • MMO **Adverse events** **Other outcomes**: • Pain severity or intensity

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported**
			Clinic or health care facility 4 injections, each 1 wk apart Injection solution same as Arm 1. Arm 3 received intra-articular injection into inferior joint space after the condylar head had been palpated and the upper surface marked with the patient's mouth closed. The needle was introduced from the top downwards until it touched the upper bony surface of the condylar head, after which the solution was injected. Other treatments: None reported **Dextrose prolotherapy:** *N*=18 Age, mean (SD): NR % Female NR Clinic or health care facility 4 injections, each 1 wk apart Injection solution same as Arm 1. Arm 4 received intra-articular injection into retrodiscal tissues through the space left behind the condylar head between the tragus of the ear and the	

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported**
			posterior surface of the condylar head with the patient's mouth wide open. Other treatments: None reported	
Haggag, 2022[110] NR High 6 Months Egypt (1) None	**Inclusion:** Disc displacement with reduction; DDWR with arthralgia (joint pain); limited unassisted mouth opening; failed prior conservative therapies; absence of any medical condition that could interfere with healing. **Exclusion:** Persistent pain in any other anatomical site greater than that in the TMJ area; long-term intake of NSAIDs or corticosteroids; active rheumatoid conditions; active infection or malignancy in TMJ area; any previous injection or operation in the TMJ region.	**Dextrose prolotherapy**: *N*=15 Age, mean (SD): 22.7 (NR) 100% Female Clinic or health care facility Max 4 injections, each 1 wk apart Bilateral auriculotemporal nerve block using 0.5 mL of 4% articaine with 1:100,000 epinephrine followed by 2 injections: one in the superior joint space and the other in the retrodiscal tissue. First injection: mouth was kept widely open and the skin over the affected joint was penetrated with the injection needle 10 mm anterior to the tragus of the ear and 2 mm below the trago-canthal line. Needle was directed anteromedially until it contacted the medial wall of the glenoid fossa. After negative aspiration, 1 mL of 25% dextrose was injected. For retrodiscal tissue injection: mouth was opened about 10 mm and the injection needle was inserted just anterior to the tragus of the ear and directed anteromedially to a depth of 20 mm. After	**Saline/Local anesthetic:** *N*=15 Age, mean (SD): 23.9 (NR) 100% Female Clinic or health care facility Max 4 injections, each 1 wk apart Intra-articular injections of normal saline solution in each joint, following same procedure as Arm 1. Other treatments: Same as Arm 1	To assess the efficacy of dextrose prolotherapy on the clinical signs and symptoms of patients having DDWR **Physical performance (3, 6 mo)** • MMO **Other outcomes:** • Pain severity or intensity

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		negative aspiration, 1 mL of 25% dextrose solution was injected. Other treatments: For postoperative pain, patients were instructed to take an analgesic such as paracetamol. All patients were discouraged to use any oral devices or to have any dental work for malocclusion during the 6-mo period of follow up.		
Hassanien, 2020[111] NR High 8 Weeks Egypt (1) NR	**Inclusion:** TMJ pain; sounds during mandibular movements (clicking, popping); functional disability; age range 16-40 yr old. **Exclusion:** Taking corticosteroids; previous treatment of TMJ pain (*eg*, occlusal splints); pregnancy; medical conditions that interfere with treatment, such as cardiac diseases and patients on pace makers.	**Dextrose prolotherapy:** *N*=10 Age, mean (SD): NR % Female NR Clinic or health care facility 3 injections at 2 wk intervals (*ie*, baseline, 2 wk, and 4 wk) 3 mL 12.5% dextrose + 0.5% lidocaine into posterior joint space then anterior disc attachment. Posterior joint space injection: palpated as the depression forms immediately anterior to the tragus of the ear as the condyle moves forward and down when the patient opened the mouth. Then, a bite block was placed. The needle was directed medially and slightly anteriorly and penetrated to nearly its full length before encountering the medial wall of the fossa. Following aspiration, 1 mL of prolotherapy solution	**Other non-injectable:** *N*=10 Age, mean (SD): NR % Female NR Clinic or health care facility 3x/wk for 4 consecutive wk Each joint received active application of low level laser therapy using Ga-Al-As diode laser. The anatomic landmarks were located by asking the patient to open widely to allow drawing of the articular fossa and then to close lightly on the posterior teeth to draw the condyle within the glenoid fossa. The therapeutic LLLT (wavelength of 980 nanometers, output power of 0.2 Watt, total energy of 12 J and exposure time 60 seconds) application was achieved using a laser beam delivered through a handheld single laser probe on the	**Pain severity at rest (VAS)** **Physical performance (2, 4 wk)** • MMO **Other outcomes:** • Pain severity or intensity

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		was deposited. Anterior disc attachment: palpated as the slight depression just anterior to the condyle when the mouth is closed. The bite block is removed and the patient is instructed to close gently. Then, the needle is directed medially and slightly anteriorly to its full length. Following aspiration, another 1 mL of prolotherapy solution was injected here. Other treatments: Restriction from NSAIDs 1-2 days before treatment and 10-14 days after treatment. After the injection, the patients were cautioned against taking anti-inflammatory agents to relieve the discomfort.	affected TMJ; anterior, superior, posterior and lateral to the condyle. The laser beam was continuously delivered from the tip of the laser applicator to the target surfaces. Other treatments: None reported	
Louw, 2019[112] NCT01706172 Some concerns 3 Months Canada (1) NR	**Inclusion:** Adults aged 19-80 yr with moderately severe and chronic (>3 mo) pain and jaw dysfunction, indicated by NRS score ≥6. Dysfunction was defined as "difficulty chewing, jaw fatigue with eating, tension in jaw, or grinding of teeth." **Exclusion:** Allergy to lidocaine, dental problems, or sinus pathology potentially contributing to pain; pain in any other anatomical site persistently greater than that in the TMJ area; long-term intake of NSAIDs or corticosteroids; active rheumatological conditions.	**Dextrose prolotherapy:** *N*=22 Age, mean (SD): 44 (14.1) 73% Female Clinic or health care facility 3 injections, each 1 mo apart 20% dextrose + 0.2% lidocaine. Closed-mouth approach with the jaw relaxed. The point of needle entry was 1 cm below the apex of the zygomatic arch, with a 45° cranial and 10° posterior angulation measured using a 1-in 30-G needle	**Saline/Local anesthetic:** *N*=20 Age, mean (SD): 50 (13.4) 96% Female Clinic or health care facility 3 injections, each 1 mo apart 0.2% lidocaine, using same technique as Arm 1 Other treatments: Same as Arm 1	**Pain intensity and severity of jaw dysfunction as assessed by NRS** **Pain-related functioning (3 mo)** • NRS-Dysfunction **Physical performance (3 mo)** • MMO **Other outcomes:** • Pain severity or intensity

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		Other treatments: Patients were advised to use acetaminophen or NSAIDs as well as local application of ice for postprocedure pain.		
Mahmoud, 2018[113] NR High 13 Months Egypt (1) NR	**Inclusion:** Internal derangement, age range 20-50 yr **Exclusion:** Haematologic disorders (platelet function disorders & anticoagulation therapy); renal and/or hepatic insufficiency; prosthetic joint replacement; allergic to any components of the injectable solution.	**Dextrose prolotherapy**: *N*=15 Age, mean (SD): NR 60% Female Clinic or health care facility 3 injections (2 wk apart), as reported in abstract and beginning of methods 25% dextrose + 2% lidocaine into a 3-mL syringe for each TMJ into posterior joint space, then anterior disc attachment, and finally the attachment of masseter muscle. Patients were asked to open their mouth and a needle was inserted 10 mm in front of tragus and 2 mm below lateral cantho-tragal line. Posterior joint space: palpated as the depth of the depression that forms immediately anterior to tragus of ear as the condyle translates forward and down. Then, a bite block was placed. The needle was directed medially and slightly anteriorly and penetrated to nearly its full length before encountering medial wall of the fossa. Following aspiration, 1 mL of prolotherapy solution is deposited. Anterior disc attachment: palpated as the slight depression just anterior to condyle	**HA:** *N*=15 Age, mean (SD): NR 66.7% Female Clinic or health care facility 1 injection Arthrocentesis followed by hyaluronic acid injected intra-articularly Other treatments: None reported **Other injectable:** *N*=15 Age, mean (SD): NR 60% Female Clinic or health care facility Single injection 1 mL of platelet rich plasma was injected intra-articular.	**Primary outcome NR** **Physical performance (1, 3, 6, 12 mo)** • MMO **Other outcomes:** • Pain severity or intensity

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		when mouth is closed. The bite block was removed and the patient was instructed to close gently. Then, needle was directed medially and angulated slightly anteriorly to, or nearly to, its full one-inch length. Following aspiration, another 1mL of prolotherapy solution was injected here. Masseter attachment: palpated along inferior border of zygomatic arch while patient clenched teeth. Then, the patient was told to relax jaw and the final 1 mL was injected, again at or near the full one-inch length of the needle. If the opposite joint is affected, the same procedure is repeated on opposite joint. Other treatments: None reported	Other treatments: None reported	
Priyadarshini, 2021[114] NR High 1 Yr India (1) NR	**Inclusion:** Internal derangement of the TMJ confirmed by MRI; Healthy patients with Wilkes stage II and III TMJ internal derangement; aged range 18-50 yr. **Exclusion:** History of previous TMJ surgery; allergy to corn products.	**Dextrose prolotherapy:** *N*=17 Age, mean (SD): 31.76 (NR) 58.8% Female Clinic or health care facility 4 injections over 3 mo 50% dextrose (0.75 mL) + 2% lignocaine with adrenaline (1.5 mL) and bacteriostatic water (0.75 mL) drawn into a 5 mL syringe and mixed prior to injection using a 26-G needle. The patient was positioned semi-supine. Prolotherapy solution was injected at three target sites:	**Other non-injectable:** *N*=17 Age, mean (SD): 28.35 (NR) 70.6% Female Home 12 hr/day for up to 3 mo Anterior bite planes, which produced a posterior open bite of 2 mm. Other treatments: None reported	**Primary outcome NR** **Physical performance (1, 3, 6, 12 mo)** • MMO **Other outcomes:** • Pain severity or intensity

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		1) Posterior joint space: palpated as the depression formed anterior to the tragus of the ear following wide mouth opening, and a bite block was placed in the posterior interocclusal space. The needle was directed medially and slightly anteriorly to avoid penetration of the ear and deposited 1 mL of prolotherapy solution. 2) Anterior disc attachment to the lateral pterygoid muscle: palpated as the depression felt anterior to the condyle after closing the mouth. The needle injected another 1 mL of prolotherapy solution. 3) Masseter attachment: Palpated along the inferior border of the zygomatic arch. Last 1 mL of prolotherapy solution was injected into the most tender area. Other treatments: Soft diet and tablet paracetamol (500 mg) 2x/day for 2 days following injection.		
Zarate, 2020[115] NCT01617356 Low 3 Months Argentina (1) Self financed by the authors	**Inclusion:** Adults age 19–80 yr; ≥3 mo of symptoms meeting RDC/TMD criteria; met baseline jaw pain and dysfunction severity criteria defined by NRS ≥6. Eligibility was “per TMJ;” both TMJs could be treated if both met criteria. **Exclusion:** Other painful dental problems; previous injections of any type for treatment of TMD symptoms; symptomatic sinus pathology; other	**Dextrose prolotherapy:** *N*=15 Age, mean (SD): 44.9 (15.1) 87% Female Pain duration (mo) in past yr (SD): 5.3 (4.6) Clinic or health care facility 3 injections, each 1 mo apart	**Saline/Local anesthetic:** *N*=14 Age, mean (SD): 50.1 (18.0) 86% Female Pain duration (mo) in past yr (SD): 6.8 (7.2) Clinic or health care facility 3 injections, each 1 mo apart	**Pain intensity and jaw dysfunction by NRS (0-10)** **Pain-related functioning (3 mo)** • NRS (dysfunction) **Physical performance (3 mo)** • MMO **Adverse events** **Other outcomes:**

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	pain greater than TMD-associated facial pain; active rheumatologic conditions; ongoing use of NSAIDs or corticosteroids.	20% dextrose + 0.2% lidocaine. Relaxed, closed-mouth approach. The injector's index finger was placed in the depression under the zygomatic arch, against the zygoma, and a curved line was drawn approximating the bottom of the arch. The posterior location of the mandible was confirmed by mouth opening and closing, with the head of the mandible passing anteriorly underneath the injector's finger and then resuming its posterior position. 27-G needle entry was 1 cm below the apex of the zygomatic arch with slight (<15°) posterior angulation and 45° of cephalad angulation. Injection of 1 mL was at ~25mm depth. Other treatments: Instructed to avoid NSAIDs; advised to use acetaminophen as needed and follow routine post-injection precautions. Other types of TMD care were discouraged. Participants who had oral devices at baseline were allowed to continue their use.	0.2% lidocaine in sterile water, same injection procedure as Arm 1 Other treatments: Same as Arm 1	• Pain severity or intensity
Hypermobility				
Arafat, 2019[116] NR High 7 Months	**Inclusion**: Diagnosis of subluxation (hypermobility) based on clinical finding of excessive abnormal excursion of the condyle associated with pain and sound and radiographic imaging (tomogram) showing presence of condyles anterior to the	**Dextrose prolotherapy**: *N*=15 Age, mean (SD): NR % Female NR Clinic or health care facility	**ABI/ACS**: *N*=15 Age, mean (SD): NR % Female NR Clinic or health care facility	**Primary outcome NR** **Physical performance (2 wk; 3, 6 mo)** • MMO **Adverse events**

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Egypt (1) NR	articular eminence in the open-mouth position. **Exclusion**: Drug-induced hypermobility; previous treatment (either conservative or surgical) on the TMJ; any medical condition that could interfere with the treatment.	2-3 injections 2 wk apart 6.7% dextrose + 0.67% mepivacaine. First injection point was placed 1 cm in front of the mid-tragus 2 mm below the canthal-tragus line. The second point was placed 1 cm below the first one. Used 18-G needle to inject dextrose solution 3 mL (10% dextrose 2 mL and 2% mepivacaine with 1:20,000 levonordefrin1 mL). The needle was inserted at the first point in an antero-superior direction to the glenoid fossa where the capsule was attached, and 0.7 mL of the solution was injected. The needle was then directed downwards and medially to the superior joint space, and 1 mL was injected. Then, the needle was removed and reinserted at the second point where the capsule was attached to the condylar neck, and 0.7 mL of the solution was injected. Finally, the needle was then directed superficial to the capsule of the TMJ, and the remaining 0.6 mL of the solution was injected with withdrawal of the needle. The same procedure was performed on the contralateral TMJ. Other treatments: Applied an elastic bandage around the patient's head for 2 wk. Patients were instructed to restrict the mouth opening and to eat soft food for 2 wk. NSAIDs were prescribed during the first postoperative wk.	1-2 injections (2 wk apart) Autologous blood injection: The point of the articular fossa was found on this line, 10mm anterior to the tragus of the ear and 2mm inferior to the line. At this point, an 18-G needle was inserted at this site into the superior joint space. 3 mL of blood was withdrawn from the patient's anticubital fossa; 2 mL of blood was injected into the superior joint space and 1 mL was injected into the outer surface of the TMJ capsule. The same procedure was performed on the contralateral TMJ. Other treatments: Same as Arm 1	**Other outcomes:** • Pain severity or intensity
Bhargava, 2023[117]	**Inclusion**:	**Dextrose prolotherapy**: *N*=30	**ABI/ACS**: *N*=30	**Primary outcome NR**

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NR High 1 Yr India (1) Self-funded project by the investigators through TMJ Consultancy Services, Bhopal, Madhya Pradesh, India.	Age >15 yr; history of symptomatic chronic joint sub-luxation, confirmed with clinical evaluation and imaging study. **Exclusion**: Noncompliance for follow-up, up to one yr post-operatively; previous conservative/surgical management to TMJ; history of psychiatric disorders; connective tissue disorders; known systemic disease; long-term use of steroids or NSAIDs.	Age, mean (SD): NR 53% Female Clinic or health care facility Every 6 wk as needed 8% dextrose + bupivacaine, 3 mL per joint. Patient positioned so back and neck were at 45°. Auriculotemporal nerve block was administered using 1.5 mL of local anesthetic (Lignocaine HCl with 1:2,00,000 Adrenaline), then used 26-G needle to inject 1 mL heavy bupivacaine-dextrose solution into the joint space posterior to the mandibular condyle. The same needle was redirected after a latency period of 300–420 s to the superior joint space. A 24-G needle was inserted into the superior joint cavity, 20 mm anterior to tragus and 10 mm inferior to cantho-tragal line followed by lavage using 50–100 mL normal saline from the inflow needle to confirm the needle location and wash out the inflammatory mediators. The outflow or the second needle was removed after the lavage. Other treatments: Patients were instructed to minimize mandibular function post-operatively for 10-14 days and to	Age, mean (SD): NR 40% Female Clinic or health care facility Every 6 wk as needed Patient positioned so back and neck were at 45°. Auriculotemporal nerve block was administered using 1.5 mL of local anesthetic (Lignocaine HCl with 1:2,00,000 Adrenaline), then followed People's University protocol for ABI in chronic recurrent TMJ sub-luxation. 3 mL of whole autologous blood was drawn from the anti-cubital fossa, 1 mL of the blood was deposited in the superior joint space via inflow needle, 2 mL in the peri-capsular and retro-discal region followed by placement of a pressure dressing. Other treatments: Same as Arm 1	**Physical performance (6, 12 mo)** • MMO **Adverse events** **Other outcomes:** • Pain severity or intensity

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		consume soft diet and small morsels of food with limited mouth opening. Prescribed Ultracet (Tramadol + Paracetamol) tablet for the pain management and Cefixime (200 mg) tablet 2x/day for 5 days. Instructed to avoid NSAIDs.		
Chhapane, 2023[118] Clinical Trials Registry of India: CTRI/2020/10/028382 High 1 Yr India (1) NR	**Inclusion**: Age ≥18 yr; multiple episodes of TMJ dislocation (uni- or bilateral); position of the condyle with relation to the articular eminence on wide mouth opening was assessed by radiography (Orthopantomogram) and a transpharyngeal TMJ view (in open and closed mouth positions). Signs and symptoms associated TMJ dislocation such as the presence of clicking sounds, crepitus, hypermobility, increased mouth opening, and level of pre-auricular pain were also recorded, but were not strict criteria for inclusion. **Exclusion**: Connective tissue syndromes; psychological abnormalities; bleeding disorders; pregnancy; allergy to anesthetics.	**Dextrose prolotherapy**: *N*=16 Age, mean (SD): NR % Female NR Clinic or health care facility Single injection 50% dextrose after lignocaine with adrenaline. Auriculotemporal nerve block by local infiltration of lignocaine with 1:200000 adrenaline. Located articular fossa 10 mm anterior to the tragus of the ear and 2 mm inferior to the cantho-tragal line. Inserted 18-G needle into the superior joint space. Lavaged with Ringer's lactate, then injected 2 mL of 50% dextrose into the upper joint space and 1 mL aroumd the pericapsular tissues. Other treatments: Rehab exercises to gradually control range of mouth opening were initiated after 2 wk. Patients were	**Other injectable**: *N*=16 Age, mean (SD): NR % Female NR Clinic or health care facility Single injection 3 mL of autologous blood was withdrawn from the patient's cubital fossa, 2 mL was injected into the upper joint space and 1 mL was injected into the pericapsular tissues. Same injection procedure as Arm 1. Other treatments: Same as Arm 1	**Primary outcome NR** **Physical performance (1, 2 wk; 1, 3, 6, 12 mo)** • MMO **Other outcomes:** • Pain severity or intensity

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		advised to perform these exercises in front of the mirror for a more fine-tuned control and to ensure the correctness of the technique.		
Comert Kilic, 2016[119] NR High 12 Months Turkey (1) None	**Inclusion**: Hypermobility diagnosed with clinical and CBCT evaluations; complaints of joint sounds, open-locking, and facial pain; age >16 yr; completion of study protocol; adequate existing clinical and CBCT data at baseline and follow-up. **Exclusion**: Haematological or neurological disorder; inflammatory or connective tissue disease; malignant disease in the head and neck region; degenerative TMJ; previous TMJ treatment or craniofacial surgery; existing parafunctional habits; inadequate existing data at baseline or follow-up.	**Dextrose prolotherapy**: *N*=15 Age, mean (SD): 32.36 (13.45) 71% Female Clinic or health care facility 3 injections, each 1 mo apart 1 mL injections of 12% dextrose solution in each of the 5 injection areas. Solution consisted of 2 mL 30% dextrose, 2 mL saline, and 1 mL 2% articaine or mepivacaine. Injected in the following order: posterior disk attachment, superior joint space, superior and inferior capsular attachments, and stylomandibular ligament. Other treatments: Patients instructed to take muscle relaxant and analgesic (paracetamol) drugs after the injections. Wide mouth opening was prohibited during the treatment and follow-up period.	**Saline/Local anesthetic**: *N*=15 Age, mean (SD): 29.0 (9.24) 75% Female Clinic or health care facility 3 injections, each 1 mo apart 1 mL injections of placebo solution in each of the five injection areas. Solution consisted of 4 mL saline and 1 mL 2% articaine or mepivacaine. Same injection sites and order as Arm 1. Other treatments: Same as Arm 1	**Primary outcome NR** **Physical performance (12 mo)** • MMO **Adverse events** **Other outcomes:** • Pain severity or intensity
Mustafa, 2018[120] NR	**Inclusion** Painful subluxation or dislocation of the TMJ; history of open locking; complaints of joint sounds and facial	**Dextrose prolotherapy**: *N*=10 Age, mean (SD): 23.6 (7.32)	**Dextrose prolotherapy**: *N*=10 Age, mean (SD): 27.1 (7.67)	**Primary outcome NR** **Physical performance (1, 2, 3, 4 mo)**

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High 4 Months Turkey (1) NR	pain. Diagnosis of TMJ hypermobility based on the patient's history and the clinical recognition of an excessive abnormal excursion of the condyle. **Exclusion**: Presence of medical conditions that may interfere with healing process; neurological disorders; allergy to anesthetic or proliferant solutions.	70% Female Clinic or health care facility 4 injections, each 1 mo apart 1.5 mL 10% dextrose with 1.5 mL 1% lidocaine injected into 4 areas: 1) Posterior disc attachment: patient opened mouth about 10mm and 30-G needle inserted just anterior to the tragus of the ear and directed anteromedially to a depth of 20 mm, where 1mL of solution deposited. 2) Superior joint space: patient opened mouth wide and needle inserted about 10 mm anterior to the tragus of the ear and 2mm below the tragocanthal line, then directed anteromedially to contact with medial wall of glenoid fossa where 1mL of solution was deposited. 3) Superior capsular attachment: 0.5 mL of solution was applied to the lateral margin of the glenoid fossa. 4) Inferior capsular attachment: 0.5 mL of solution was applied to the condylar neck. Other treatments: All patients were instructed to take a paracetamol in case of additional pain without any NSAID. Patients were also instructed to avoid wide mouth opening during the treatment period.	88.9% Female Clinic or health care facility 4 injections, each 1 mo apart 1.5 mL 20% dextrose with 1.5 mL 1% lidocaine. Same injection technique as Arm 1. Other treatments: Same as Arm 1 **Dextrose prolotherapy**: *N*=10 Age, mean (SD): 24.5 (4.21) 66.7% Female Clinic or health care facility 4 injections, each 1 mo apart 1.5 mL 30% dextrose with 1.5 mL 1% lidocaine. Same injection technique as Arm 1. Other treatments: Same as Arm 1 **Saline/Local anesthetic**: *N*=10	• MMO **Other outcomes:** • Pain severity or intensity

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			Age, mean (SD): 25.3 (7.43) 55.6% Female Clinic or health care facility 4 injections, each 1 mo apart 3 mL 1% lidocaine solution (1.5 mL 0.9% saline and 1.5 mL of 2% lidocaine HCl). Same injection technique as Arm 1. Other treatments: Same as Arm 1	
Pandey, 2022[121] NR Serious 6 Months India (1) None	**Inclusion**: Bilateral chronic recurrent TMJ dislocations with MMO >40 mm; recurrent dislocation of TMJ >2x/wk; pain and sounds in joints; age 18-60 yr. **Exclusion**: Any previous invasive procedures on TMJ.	**Dextrose prolotherapy**: *N*=10 Age, mean (SD): 34.1 (10.5) % Female NR Clinic or health care facility Single injection 25% dextrose into upper joint space (2 mL) and around capsule 1 mL). External auditory meatus was blocked with cotton soaked in Neosporin ointment, and auriculo-temporal nerve block was given (1:200,000 LA with Adrenaline). Inserted 18-G needle into superior joint space after drawing a cantho-tragal line and marking	**ABI/ACS**: *N*=10 Age, mean (SD): 34.8 (7.7) % Female NR Clinic or health care facility Single injection 3 mL of autologous blood was withdrawn from the patient's anticubital fossa, out of which 2 mL was injected into the upper joint space and 1 mL was injected around the capsule (pericapsular tissues). This procedure was then repeated on the opposite side	**Primary outcome NR** **Physical performance (1, 2 wk; 1, 3, 6 mo)** • MMO **Other outcomes:** • Pain severity or intensity

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported**
		a point 10 mm anterior to tragus and 2 mm below the cantho-tragal line and injected 2 mL, then injected 1 mL around the capsule (pericapsular tissues). The same procedures were repeated on the opposite joint. Other treatments: Placed bandage for the first wk and patients were instructed to avoid wide mouth opening. All patients were advised to follow a soft diet for 2 wk. Antibiotics (Tab Amoxicillin) and non-steroidal anti-inflammatory drugs were prescribed for 5 days.	in the same manner. Same injection procedure as Arm 1. Other treatments: Same as Arm 1	
Refai, 2011[122] NR High 7.5 Months Egypt (1) NR	**Inclusion**: Bilateral TMJ symptomatic hypermobility; diagnosis of painful subluxation or dislocation of the TMJ; willingness to follow instructions. **Exclusion**: Medical conditions that may significantly interfere with healing.	**Dextrose prolotherapy**: *N*=6 Age, mean (SD): 23.0 (NR) 100% Female Clinic or health care facility 4 injections, each 6 wk apart 6.7% dextrose + 0.7 mepivacaine (2 mL of 10% dextrose and 1 mL of 2% mepivacaine). Patient opened mouth wide to allow drawing of the articular fossa and then to close lightly on the posterior teeth to draw the condyle within the glenoid fossa. Typically, each joint had 3 injection sites. Superior capsular attachment on the lateral margin of the glenoid fossa, where 0.8 mL was injected. Inferior	**Saline/Local anesthetic**: *N*=6 Age, mean (SD): 29.8 (NR) 66.7% Female Clinic or health care facility 4 injections, each 6 wk apart 0.67% mepivacaine (2 mL of saline solution and 1 mL of 2% mepivacaine). Same injection technique as Arm 1. Other treatments: Same as Arm 1	**Primary outcome NR** **Physical performance (6, 12, 18 wk; 7.5 mo)** • MMO **Adverse events**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes Measurement tool(s) (Time points)** **Other Outcomes Reported**
		capsular attachment on the condylar neck, where 0.8 mL was injected. The needle was then directed superficial to the TMJ capsule, and 0.4 mL was injected. Superior joint space was approached with the needle directed superiorly and anteriorly toward the apex of the fossa, where contact was made with the periosteum and 1 mL was injected. Other treatments: Post-injection, patients were instructed to reduce or stop other pain medications and therapies as much as the pain would allow and to follow a soft diet for 2 wk.		
Saadat, 2018[123] NR High 6 Months Egypt (1) NR	**Inclusion**: Age 20-40 yr; recurrent dislocation of TMJ more >2 times in the last mo. **Exclusion**: Neurological conditions; parafunctional habits; allergy to lidocaine and dextrose; Ehler Danlos syndrome; use of anticoagulant drugs.	**Dextrose prolotherapy**: *N*=8 Age, mean (SD): 29.1 (NR) 62.5% Female Clinic or health care facility Single injection 25% dextrose in retrodiscal tissue. Drew line from the tragus of the ear to the outer canthus of the eye and marked first point 10 mm anterior to the tragus of the ear along the tragocanthal line and then marked a second point 10 mm inferior to the first point on line perpendicular to the tragocanthal line. Auriculotemporal nerve block was achieved using 2 mL of 2%	**Dextrose prolotherapy**: *N*=8 Age, mean (SD): 29.5 (NR) 75% Female Clinic or health care facility Single injection 25% dextrose injected into the superior joint space. Auriculotemporal nerve block was achieved using 2 mL of 2% lidocaine. Asked patient to close anterior teeth on bite block to gain access to the superior joint space. Marked injection site between tragus of ear and posterior aspect of condyle and directed needle superiorly and anteriorly	**Primary outcome NR** **Physical performance (2 wk; 1, 3, 6 mo)** • MMO **Other outcomes:** • Pain severity or intensity

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported**
		lidocaine. Then injected 2 mL of 25% dextrose prolotherapy solution. The needle was directed to the surface of the condylar neck until 5 mm deep and 0.5 mL was deposited, then the needle was advanced along the back of condyle to a depth of 25 mm, where 0.5 mL was deposited. The needle then withdrawn 5mm and the remaining 1.0 mL were gradually injected. Other treatments: None reported	towards the apex of the glenoid fossa into the superior joint space until contact of the needle with the periosteum was reached. 2 mL of 25% dextrose solution was gradually injected in the superior joint space. Other treatments: None reported	

Abbreviations. ABI=autologous blood injection; ACS=autologous conditioned serum; CBCT=cone beam computed tomography; cm=centimeter; DDWR=disc displacement with reduction; G=gauge; Ga-Al-As=Gallium-Aluminum-Arsenide; HCl=hydrogen chloride; LLLT=low level laser therapy; mg=milligram; mL=milliliter; mm=millimeter; MMO=maximum mouth opening; mo=month; MRI=magnetic resonance imaging; NR=not reported; NRS=numerical rating scale; NSAID=nonsteroidal anti-inflammatory drug; RDC=research diagnostic criteria; ROM=range of motion; SD=standard deviation; TMD=temporomandibular dysfunction; TMJ=temporomandibular joint; VAS=visual analog scale; wk=week; yr=year.

Appendix Table 15. Detailed Results for All Eligible TMJ Studies

Author, Year Risk of Bias	Outcome Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
Normal or Restricted Mobility				
Elwerfelli, 2019[108] Serious	Physical performance MMO 1 day 1, 2, 3, 4, 5, 6 wk	**Dextrose prolotherapy 50% + arthrocentesis + saline lavage** Baseline: 23.14 (3.53) 1 day: 34.43 (1.62) 1 wk: 40.29 (1.98) 2 wk: 41.86 (2.67) 3 wk: 44.71 (1.25) 4 wk: 45.29 (1.25) 5 wk: 45.29 (1.25) 6 wk: 45.29 (1.25)	**Arthrocentesis + saline lavage** Baseline: 24.43 (2.82) 1 day: 34.14 (2.54) 1 wk: 39.57 (2.57) 2 wk: 39.43 (2.70) 3 wk: 41.0 (1.25) 4 wk: 41.43 (3.26) 5 wk: 41.57 (3.05) 6 wk: 41.57 (3.05)	**Arm 1 vs. Arm 2** 1 day: 0.3, p=0.806 1 wk: 0.7, p=0.571 2 wk: 2.4, p=0.117 3 wk: 3.7, p=0.035 4 wk: 3.9, p=0.020 5 wk: 3.7, p=0.018 6 wk: 3.7, p=0.018 Avg. increase (%): Dextrose: 83.40% Arthrocentesis + lavage: 64.02%
	Pain severity or intensity VAS 6 wk	**Dextrose prolotherapy 50% + arthrocentesis + saline lavage** Baseline: NR 6 wk: NR	**Arthrocentesis + saline lavage** Baseline: NR 6 wk: NR	**Arm 1 vs. Arm 2** Mean difference between arms NR Avg. reduction (%): Dextrose: 93.38% Arthrocentesis + lavage: 91.23% Statistical comparison of postoperative pain intensity was not significant
	Adverse events *N*/A Follow-up NR	*"Postoperative complication was recorded in this study; Three female patients in group-B [arthrocentesis alone] have been reported mild preauricular swelling in immediate postoperative phase. One female patient in group-B [arthrocentesis alone] reported difficult closure of the eyelid." (AE not defined)*		
Fouda, 2018[109] High	Physical performance MMO 2 wk 3 mo	**Dextrose prolotherapy 22% (outer capsule)** Baseline: 36.2 (6.8) 2 wk: 29.3 (3.9) 3 mo: 29.6 (3.8)	**Dextrose prolotherapy 22% (superior joint space)** Baseline: 35.6 (5.5) 2 wk: 37.1 (4.4) 3 mo: 36.0 (4.2) **Dextrose prolotherapy 22% (inferior joint space)** Baseline: 34.6 (2.4) 2 wk: 36.6 (1.4) 3 mo: 36.8 (1.2)	**Arm 1 vs. Arm 2** 2 wk: -7.8, NR 3 mo: -6.4, NR **Arm 1 vs. Arm 3** 2 wk: -7.3, NR 3 mo: -7.2, NR **Arm 1 vs. Arm 4** 2 wk: -10.7, NR

Author, Year Risk of Bias	Outcome Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
			Dextrose prolotherapy 22% (retrodiscal tissues) Baseline: 35.7 (9.4) 2 wk: 40 (5.6) 3 mo: 40.1 (5.3)	3 mo: -10.5, NR p<0.0005 between all 4 groups at both time points
	Pain severity or intensity VAS 2 wk 3 mo	**Dextrose prolotherapy 22% (outer capsule)** Baseline: 4.7 (3.3) 2 wk: 4.4 (1.7) 3 mo: 4.1 (2.9)	**Dextrose prolotherapy 22% (superior joint space)** Baseline: 3.7 (2.7) 2 wk: 3.4 (3.0) 3 mo: 2.9 (3.1) **Dextrose prolotherapy 22% (inferior joint space)** Baseline: 6.6 (2.5) 2 wk: 2.8 (2.8) 3 mo: 1.8 (2.1) **Dextrose prolotherapy 22% (retrodiscal tissues)** Baseline: 6.4 (2.7) 2 wk: 1.7 (2.1) 3 mo: 1.0 (1.7)	**Arm 1 vs. Arm 2** 2 wk: 1.0, NR 3 mo: 1.2, NR **Arm 1 vs. Arm 3** 2 wk: 1.6, NR 3 mo: 2.3, NR **Arm 1 vs. Arm 4** 2 wk: 2.7, NR 3 mo: 3.1, NR p-value between all 4 groups: 2 wk: p=0.014 3 mo: p=0.003
	Adverse events *N*/A 3 mo	*"Unwanted side effects in the form of painful injections and burning sensations were reported in 18 of the 72 patients. Two patients in group 4 [site of injection-retrodiscal tissues] developed paralysis of the temporal branch of the facial nerve, accompanied by a temporary inability to blink."*		
Haggag, 2022[110] High	Physical performance MMO 1, 3, 6 mo	**Dextrose prolotherapy 25%**† Baseline: 27.5 1 mo: 40.8 3 mo: 41.3 6 mo: 41.7	**Normal saline (with local anesthetic)** † Baseline: 25.7 1 mo: 35.3 3 mo: 29.7 6 mo: 29.1	**Arm 1 vs. Arm 2** 1 mo: 5.5, p=0.041 3 mo: 11.6, p<0.001 6 mo: 12.6, p<0.001
	Pain severity or intensity NRS - Pain 1, 3, 6 mo	**Dextrose prolotherapy 25%** Baseline: 8.1 1 mo: 2.3 3 mo: 2.3 6 mo: 2.1	**Normal saline (with local anesthetic)** Baseline: 7.3 1 mo: 3.7 3 mo: 5.6 6 mo: 6.3	**Arm 1 vs. Arm 2** 1 mo: -1.4, p=0.015 3 mo: -3.3, p<0.001 6 mo: -4.2, p<0.001

Author, Year **Risk of Bias**	**Outcome** **Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, p-value*** **Other results reported**
Hassanien, 2020[111] High	Physical performance MMO 2, 4 wk	**Dextrose prolotherapy 12.5%** Baseline: 35.213 (3.776) 2 wk: 39.488 (2.713) 4 wk: 43.375 (1.707)	**Laser** Baseline: 32.750 (0.463) 2 wk: 35.250 (1.282) 4 wk: 37.375 (1.923)	**Arm 1 vs. Arm 2** 2 wk: 4.2, p=0.001 4 wk: 6.0, p≤0.001
	Pain severity or intensity VAS 2, 4 wk	**Dextrose prolotherapy 12.5%** Baseline: 5.88 (2.36) 2 wk: 3.75 (1.58) 4 wk: 2.13 (0.99)	**Laser** Baseline: 4.38 (1.51) 2 wk: 4.38 (2.07) 4 wk: 3.50 (2.27)	**Arm 1 vs. Arm 2** 2 wk: -0.6, NR 4 wk: -1.4, p=0.138
Louw, 2019[112] Some concerns	Pain-related functioning NRS - Dysfunction 3 mo	**Dextrose prolotherapy 20%** Baseline: 7.2 (1.1) 1 mo: NR 2 mo: NR 3 mo: NR Change from baseline: 1 mo: 1.5 (1.9) 2 mo: 2.8 (2.7) 3 mo: 3.5 (2.8)	**Water (with local anesthetic)** Baseline: 6.7 (0.9) 1 mo: NR 2 mo: NR 3 mo: NR Change from baseline: 1 mo: 0.2 (0.5) 2 mo: 0.8 (1.3) 3 mo: 1.0 (2.1)	**Arm 1 vs. Arm 2** Mean time point scores and difference between arms NR
	Physical performance MMO 3 mo	**Dextrose prolotherapy 20%** Baseline: 43.7 (5.7) 3 mo: NR Change from baseline: 3 mo: 1.5 (4.1)	**Water (with local anesthetic)** Baseline: 39.0 (6.9) 3 mo: NR Change from baseline: 3 mo: -1.8 (5.1)	**Arm 1 vs. Arm 2** Mean time point scores and difference between arms NR
	Pain severity or intensity NRS - Pain 1, 2, 3 mo	**Dextrose prolotherapy 20%** Baseline: 7.8 (1.2) 1 mo: NR 2 mo: NR 3 mo: NR Change from baseline: 1 mo: 2.2 (1.8) 2 mo: 3.3 (2.9) 3 mo: 4.3 (2.9)	**Water (with local anesthetic)** Baseline: 8.2 (1.2) 1 mo: NR 2 mo: NR 3 mo: NR Change from baseline: 1 mo: 0.9 (1.4) 2 mo: 1.8 (2.3) 3 mo: 1.8 (2.7)	**Arm 1 vs. Arm 2** Mean time point scores and difference between arms NR
Mahmoud, 2018[113]	Physical performance	**Dextrose prolotherapy 12.5%†**	**Arthrocentesis + HA†**	**Arm 1 vs. Arm 2**

Author, Year **Risk of Bias**	**Outcome** **Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, p-value*** **Other results reported**
High	MMO 1, 3, 6, 12 mo	Baseline: 36.7 1 mo: 40.5 3 mo: 41.5 6 mo: 39.8 12 mo: 39.1	Baseline: 34.6 1 mo: 39.7 3 mo: 39.8 6 mo: 38.9 12 mo: 38.7	1 mo: 0.8, p>0.05 3 mo: 1.7, p>0.05 6 mo: 0.9, p>0.05 12 mo: 0.4, p>0.05
			PRP† Baseline:41.3 1 mo: 38.0 3 mo: 35.9 6 mo: 33.8 12 mo: 33.7	**Arm 1 vs. Arm 3** 1 mo: 2.5, p>0.05 3 mo: 5.6, p<0.05 6 mo: 6.0, p<0.05 12 mo: 5.4, p<0.05
	Pain severity or intensity VAS 1, 3, 6, 12 mo	**Dextrose prolotherapy 12.5%†** Baseline: 9.9 1 mo: 4.2 3 mo: 3.3 6 mo: 3.7 12 mo: 3.7	**Arthrocentesis + HA†** Baseline: 9.9 1 mo: 4.3 3 mo: 3.6 6 mo: 3.7 12 mo: 3.7	**Arm 1 vs. Arm 2** 1 mo: -0.1, p>0.05 3 mo: -0.3, p>0.05 6 mo: 0, p>0.05 12 mo: 0, p>0.05
			PRP Baseline: 10.0† 1 mo: 5.3 3 mo: 3.1 6 mo: 1.6 12 mo: 1.1	**Arm 1 vs. Arm 3** 1 mo: -1.1, p>0.05 3 mo: 0.2, p>0.05 6 mo: 2.1, p<0.05 12 mo: 2.6, p<0.05
Priyadarshini, 2021[114] High	Physical performance MMO 1, 3, 6, 12 mo	**Dextrose prolotherapy 12.5%** Baseline: 36.06 (11.003) 1 mo: 40.65 (8.246) 3 mo: 41.18 (8.017) 6 mo: 41.35 (7.960) 12 mo: 41.29 (7.967)	**Occlusal splints** Baseline: 33.88 (9.130) 1 mo: 34.71 (8.402) 3 mo: 34.65 (8.389) 6 mo: 34.82 (8.346) 12 mo: 35.06 (7.967)	**Arm 1 vs. Arm 2** 1 mo: 5.9, p=0.046 3 mo: 6.5, p=0.027 6 mo: 6.5, p=0.026 12 mo: 6.2, p=0.032
	Pain severity or intensity NRS - Pain 1, 3, 6, 12 mo	**Dextrose prolotherapy 12.5%** Baseline: 5.76 (1.95) 1 mo: 0.59 (0.51) 3 mo: 0.59 (0.51) 6 mo: 0.47 (0.51) 12 mo: 0.47 (0.51)	**Occlusal splints** Baseline: 5.35 (1.935) 1 mo: 3.47 (2.04) 3 mo: 3.41 (1.94) 6 mo: 3.41 (1.87) 12 mo: 3.29 (0.51)	**Arm 1 vs. Arm 2** 1 mo: -2.9, p≤0.001 3 mo: -2.8, p≤0.001 6 mo: -2.9, p≤0.001 12 mo: -2.8, p≤0.001

Author, Year Risk of Bias	Outcome Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
Zarate, 2020[115] Low	Pain-related functioning NRS - Dysfunction 3 mo	**Dextrose prolotherapy 20%** Baseline: 7.4 (1.0) 1 mo: 4.0 (2.7) 2 mo: 3.9 (2.7) 3 mo: 3.4 (2.5)	**Water (with local anesthetic)** Baseline: 7.1 (0.9) 1 mo: 5.9 (1.5) 2 mo: 4.6 (2.2) 3 mo: 4.0 (2.2)	**Arm 1 vs. Arm 2** 1 mo: -1.9, p=0.006 2 mo: -0.7, p=0.34 3 mo: -0.6, p=0.74
	Physical performance MMO 3 mo	**Dextrose prolotherapy 20%** Baseline: 38.7 (10.6) 3 mo: 43.4 (9.8)	**Water (with local anesthetic)** Baseline: 42.4 (9.27) 3 mo: 47.8 (7.8)	**Arm 1 vs. Arm 2** 3 mo: -4.4, p=0.20
	Pain severity or intensity NRS - Pain 3 mo	**Dextrose prolotherapy 20%** Baseline: 7.2 (1.1) 1 mo: 4.4 (2.4) 2 mo: 4.4 (2.4) 3 mo: 2.9 (2.6)	**Water (with local anesthetic)** Baseline: 7.2 (0.8) 1 mo: 5.4 (2.1) 2 mo: 4.6 (2.2) 3 mo: 4.3 (2.6)	**Arm 1 vs. Arm 2** 1 mo: -1.0, p=0.19 2 mo: -0.2, p=0.69 3 mo: -1.4, p=0.19
	Adverse events *N*/A Unclear	*"There were no adverse events."*		
TMJ with Hypermobility				
Arafat, 2019[116] High	Physical performance MMO 2 wk 3, 6 mo	**Dextrose prolotherapy 6.7%** Baseline: 43.27 (1.53) 2 wk: 36.67 (1.72) 3 mo: 34.4 (1.1) 6 mo: 34.3 (1.2)	**ABI** Baseline: 43.53 (1.55) 2 wk: 34 (2.07) 3 mo: 32.2 (1.6) 6 mo: 32.3 (1.5)	**Arm 1 vs. Arm 2** 2 wk: 2.7, p<0.001 3 mo: 2.2, p<0.001 6 mo: 2, p<0.001
	Pain severity or intensity VAS 2 wk 3, 6 mo	**Dextrose prolotherapy 6.7%** Baseline: NR 2 wk: NR 1 mo: NR 3 mo: 0 (median) 6 mo: 0 (median)	**ABI** Baseline: NR 2 wk: NR 1 mo: NR 3 mo: 0 (median) 6 mo: 0 (median)	**Arm 1 vs. Arm 2** 2 wk: Dextrose had a higher VAS score, p≤ 0.001 1 mo: Dextrose had a higher VAS score, p≤ 0.001 3 mo: 0 (median) 6 mo: 0 (median)
	Adverse events *N*/A Unclear	*"There were no incidences of facial nerve palsy in patients of group A [autologous blood], while there were transient facial palsy seen in 5 cases of group B [dextrose prolotherapy] which resolved 2 hours post-operatively as the effect of local anesthesia subsided."*		
Bhargava, 2023[117] High	Physical performance MMO	**Dextrose prolotherapy 8%** Baseline: 43.3 (7.5)	**ABI** Baseline: 42.9 (6.9)	**Arm 1 vs. Arm 2** 6 mo: -0.5, NR

Author, Year **Risk of Bias**	**Outcome** **Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, p-value*** **Other results reported**
	6, 12 mo	6 mo: 38.5 (5.4) 12 mo: 37.9 (2.0)	6 mo: 39 (5.8) 12 mo: 38.4 (2.6)	12 mo: -0.5, NR
	Pain severity or intensity VAS 6, 12 mo	**Dextrose prolotherapy 8%** Baseline: 8.4 (8.9) 6 mo: 5.7 (1.5) 12 mo: 4 (1.2)	**ABI** Baseline: 8.9 (9.9) 6 mo: 6.2 (1.9) 12 mo: 4.7 (1.2)	**Arm 1 vs. Arm 2** 6 mo: -0.5, NR 12 mo: -0.7, NR
	Adverse events *N*/A 12 mo	*"No complications/adverse reactions were recorded in any of the patient among both the groups."* (AE not defined)		
Chhapane, 2023[118] High	Physical performance MMO 1, 2 wk 1, 3, 6 mo 1 yr	**Dextrose prolotherapy 50%** Baseline: 23.56 (3.847) 1 wk: 25.50 (3.266) 2 wk: 26.93 (2.658) 1 mo: 27.60 (2.667) 3 mo: 28.73 (2.631) 6 mo: 29.60 (2.165) 1 yr: 30.60 (2.558)	**ABI** Baseline: 22.75 (3.768) 1 wk: 25.38 (4.113) 2 wk: 27.56 (4.427) 1 mo: 29.00 (4.147) 3 mo: 30.75 (2.631) 6 mo: 32.81 (3.468) 1 yr: 36.88 (2.217)	**Arm 1 vs. Arm 2** 1 wk: 0.1, p=.925 2 wk: -0.6, p=.638 1 mo: -1.4, p=.276 3 mo: -2.0, p=0.77 6 mo: -3.2, p=.005 1 yr: -6.3, p=.000
	Pain severity or intensity VAS 1, 2 wk 1, 3, 6 mo 1 yr	**Dextrose prolotherapy 50%**† Baseline: 5.1 1 wk: 2.2 2 wk: 0.4 1 mo: 0.7 3 mo: 0.6 7 mo: 0.5 1 yr: 0.3	**ABI**† Baseline: 5.5 1 wk: 2.1 2 wk: 1.1 1 mo: 0.5 3 mo: 0.3 7 mo: 0.2 1 yr: 0.3	**Arm 1 vs. Arm 2** 1 wk: 0.1, p≥0.05 2 wk: -0.7, p≥0.05 1 mo: 0.2, p≥0.05 3 mo: 0.3, p≥0.05 7 mo: 0.3, p≥0.05 1 yr: 0, p≥0.05
Comert Kilic, 2016[119] High	Physical performance MMO 12 mo	**Dextrose prolotherapy 12%** Baseline: 46.14 (6.89) 12 mo: 43.29 (5.92)	**Normal saline (with local anesthetic)** Baseline: 46.33 (3.47) 12 mo: 43.67 (5.65)	**Arm 1 vs. Arm 2** 12 mo: -0.4, NR
	Pain severity or intensity VAS 12 mo	**Dextrose prolotherapy 12%** Baseline: 4.3 (2.57) 12 mo: 0.89 (1.45)	**Normal saline (with local anesthetic)** Baseline: 5.39 (2.09) 12 mo: 1.72 (1.58)	**Arm 1 vs. Arm 2** 12 mo: -0.8, NR
	Adverse events *N*/A 12 mo	*"Some side effects were observed in four of the 14 patients in the prolotherapy group. Paresthesia spreading to the zygomatic arch and pre-auricular regions was observed in three patients, and this recovered over the course of a month with the use of prescribed*		

Author, Year Risk of Bias	Outcome Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
		drugs including vitamin B. A transient blepharospasm occurred in one patient, which recovered after a few weeks. No other complications were observed during the treatment and follow-up periods."		
Mustafa, 2018[120] High	Physical performance MMO 1, 2, 3, 4 mo	**Dextrose prolotherapy 5%** Baseline: 54.30 (5.92) 1 mo: 43.80 (3.31) 2 mo: 40.90 (4.72) 3 mo: 39.70 (4.49) 4 mo: 39.40 (4.19)	**Dextrose prolotherapy 10%** Baseline: 52.11 (6.90) 1 mo: 44.22 (6.57) 2 mo: 44.88 (5.86) 3 mo: 42.33 (5.70) 4 mo: 41.22 (4.19) **Dextrose prolotherapy 15%** Baseline: 54.00 (7.41) 1 mo: 45.22 (3.33) 2 mo: 42.55 (9.38) 3 mo: 39.88 (4.83) 4 mo: 39.44 (4.55) **Normal saline (with local anesthetic)** Baseline: 52.33 (6.63) 1 mo: 44.66 (3.31) 2 mo: 44.77 (5.40) 3 mo: 43.44 (4.27) 4 mo: 43.33 (4.24)	**Arm 1 vs. Arm 2** 1 mo: -0.9 2 mo: -3.9 3 mo: -3.7 4 mo: -3.9 **Arm 1 vs. Arm 3** 1 mo: -0.4 2 mo: 0.1 3 mo: -1.1 4 mo: -2.1 **Arm 1 vs. Arm 4** 1 mo: 0.6 2 mo: -2.2 3 mo: -3.6 4 mo: -3.9 p≥0.05 between all 4 groups at all time points
	Pain severity or intensity VAS 1, 2, 3, 4 mo	**Dextrose prolotherapy 5%** Baseline: 5.25 (2.84) 1 mo: 2.60 (1.86) 2 mo: 2.00 (1.56) 3 mo: 0.95 (0.68) 4 mo: 0.70 (0.67)	**Dextrose prolotherapy 10%** Baseline: 5.66 (1.95) 1 mo: 2.55 (1.94) 2 mo: 1.66 (1.87) 3 mo: 1.11 (1.05) 4 mo: 0.55 (0.67) **Dextrose prolotherapy 15%** Baseline:5.33 (2.29) 1 mo: 3.50 (1.82) 2 mo: 2.72 (1.52) 3 mo: 1.16 (0.35) 4 mo: 0.88 (0.60) **Normal Saline (with local anesthetic)**	**Arm 1 vs. Arm 2** 1 mo: -0.6 2 mo: -0.6 3 mo: -1.1 4 mo: -1.1 **Arm 1 vs. Arm 3** 1 mo: -0.7 2 mo: -0.9 3 mo: -0.9 4 mo: -1.2 **Arm 1 vs. Arm 4** 1 mo: 0.3 2 mo: 0.2

Author, Year **Risk of Bias**	**Outcome** **Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, p-value*** **Other results reported**
			Baseline: 4.38 (3.14) 1 mo: 3.22 (2.93) 2 mo: 2.55 (2.12) 3 mo: 2.05 (2.24) 4 mo: 1.77 (1.64)	3 mo: -0.9 4 mo: -0.9 p≥0.05 between all 4 groups at all time points
Pandey, 2022[121] Serious	Physical performance MMO 1, 2 wk 1, 3, 6 mo	**Dextrose prolotherapy 25%** Baseline: 46.95 (1.38) 1 wk: 19.35 (3.62) 2 wk: 29.85 (3.28) 1 mo: 36.55 (1.59) 3 mo: 39.1 (1.37) 6 mo: 40.2 (1.55)	**ABI** Baseline: 46.7 (1.81) 1 wk: 18.85 (2.65) 2 wk: 26.57 (2.40) 1 mo: 33.75 (1.72) 3 mo: 27.35 (1.37) 6 mo: 38.5 (1.89)	**Arm 1 vs. Arm 2** 1 wk: 0.5, p=0.708 2 wk: 3.3, p=0.029 1 mo: 2.8, p=0.002 3 mo: 11.8, p=0.012 6 mo: 1.7, p=0.049
	Pain severity or intensity VAS 1, 2 wk 1, 3, 6 mo	**Dextrose prolotherapy 25%†** Baseline: 5.4 (1.3) 1 wk: 3.1 2 wk: 1.5 1 mo: 1.1 3 mo: 1 6 mo: 0.8 (0.8)	**ABI†** Baseline: 5.1 (1.5) 1 wk: 3.8 2 wk: 3.3 1 mo: 2.4 3 mo: 1.9 6 mo: 1.7 (0.5)	**Arm 1 vs. Arm 2** 1 wk: -0.7, p>0.05 2 wk: -1.8, p<0.05 1 mo: -1.3, p<0.05 3 mo: -0.9, p<0.05 6 mo: -0.9, p<0.05
Refai, 2011[122] High	Physical performance MMO 6, 12, 18 wk 7.5 mo	**Dextrose prolotherapy 6.7%** Baseline: 5.03 (0.43) 6 wk: 4.72 (0.54) 12 wk: 4.53 (0.50) 18 wk: 4.35 (0.35) 7.5 mo: 4.33 (0.45)	**Normal saline (with local anesthetic)** Baseline: 4.97 (0.49) 6 wk: 4.93 (0.54) 12 wk: 4.88 (0.52) 18 wk: 4.93 (0.51) 7.5 mo: 4.97 (0.45)	**Arm 1 vs. Arm 2** 6 wk: -0.2, p=0.503 12 wk: -0.4, p=0.262 18 wk: -0.6, p=0.043 7.5 mo: -0.6, p=0.039
	Adverse events /A Unclear	*"All patients tolerated the TMJ injection well without serious complications. Discomfort after injection did not appear to vary between groups. Three patients in each group had mild pain after injection. After the first injection, 4 patients in the active group and 2 in the placebo group complained of an itching sensation at the site of injection. This sensation disappeared spontaneously after a few days without any treatment. Some patients had transient facial palsy due to the anesthetic inclusion in the injected solution. The anesthetic effect diminished within 60 to 90 minutes postoperatively."*		
Saadat, 2018[123] High	Physical performance MMO 2 wk 1, 3, 6 mo	**Dextrose prolotherapy 25% (retrodiscal tissues)** Baseline: 4.325 (0.260) 2 wk: 3.613 (0.323) 1 mo: 3.875 (0.260) 3 mo: 3.929 (0.450)	**Dextrose prolotherapy 25% (superior joint space)** Baseline: 4.150 (0.393) 2 wk: 3.700 (0.289) 1 mo: 3.729 (0.382) 3 mo: 3.933 (0.301)	**Arm 1 vs. Arm 2** 2 wk: -0.09, p=0.592 1 mo: 0.1, p=0.396 3 mo: -0.004, p=0.983 6 mo: 0.1, p=0.657

Author, Year **Risk of Bias**	**Outcome** **Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, p-value*** **Other results reported**
		6 mo: 3.929 (0.450)	6 mo: 3.833 (0.450)	
	Pain severity or intensity VAS 2 wk 1, 3, 6 mo	**Dextrose prolotherapy 25% (retrodiscal tissues)** Baseline: NR 2 wk: 5.87 (0.79)	**Dextrose prolotherapy 25% (superior joint space)** Baseline: NR 2 wk: 7.37 (0.64)	**Arm 1 vs. Arm 2** 2 wk: -1.5, p=0.001

Notes. *Mean differences calculated by review team; p-values reported by study (otherwise NR)

†Data abstracted by review team from figures in article.

Abbreviations. ABI=autologous blood injection; AE=adverse event; avg=average; HA=hyaluronic acid; MMO=maximum mouth opening; mo=month; N/A=not applicable; NR=not reported; NRS=numerical rating scale; PRP=platelet rich plasma; SD=standard deviation; TMJ=temporomandibular joint; VAS=visual analog scale; wk=week; wk=week; yr=year.

APPENDIX L. OTHER PAIN CONDITIONS

Appendix Table 16. Detailed Study Characteristics for All Eligible Studies on Other Pain Conditions

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
Non-arthritis Knee Pain				
Babaei-Ghazani, 2023[125] IRCT20151017024572N22 Some concerns 8 Weeks Iran (3) NR	**Inclusion**: "Inclusion criteria were: The clinical diagnosis of pes anserine bursitis by a physiatrist based on the presence of pain and tenderness and occasionally local swelling on the inferomedial side of the knee below the medial joint line, and age 18 to 70 years old." **Exclusion**: "Exclusion criteria were: previous knee surgery, prior local soft tissue injection of [pes anserine bursitis] in the last six months, previous physical therapy in the last three months, pregnancy, coagulopathy, and anticoagulation therapy, current infection on the skin or soft tissue at or near the site of intervention, positive physical examination for knee meniscus or ligaments tear, severe underlying diseases such as uncontrolled diabetes (Hemoglobin A1c level greater than 9.0%) or rheumatologic	**Dextrose prolotherapy**: *N*=25 Age, mean (SD): 59.3 (8.9) 82.6% Female Clinic or health care facility 1 injection "One milliliter of 2% lidocaine was used for local anesthesia in all patients. [Using a 22-gauge needle] prolotherapy with 2 ml of 20% dextrose was done under sterile conditions into the pes anserine bursa under ultrasound guidance..." Other treatments: None reported	**Corticosteroid Injection**: *N*=25 Age, mean (SD): 64.3 (10.1) 92% Female Clinic or health care facility 1 injection “40 mg of triamcinolone acetonide (1 milliliter) was…injected into the pes anserine bursa under ultrasound guidance." Other treatments: None reported **Oxygen-ozone**: *N*=25 Age, mean (SD): 60 (8.32) 79.2% Female	**Primary outcome NR** **Pain-related functioning (1, 8 wk)** • WOMAC (total, pain, stiffness, function) **Other outcomes:** • Pain severity or intensity: VAS (1, 8 wk)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
	disorders, previous allergic reaction history to corticosteroid, dextrose, O2-O3 and, local anesthetic."		Clinic or health care facility “5 ml of O2-O3 with a 15 microgram concentration was injected.” Other treatments: None reported	
Cho, 2017[128] NR Serious 12 Weeks Korea (1) NR	**Inclusion**: “diagnosed with chronic patellar tendinopathy.” **Exclusion**: NR	**Dextrose prolotherapy**: *N*=10 Age, mean (SD): 32.5 (9.4) 60% Female Clinic or health care facility 4 weeks (3 injections) Prolotherapy: "[An] ultrasound-guided 10 mL injection of a solution of 12.5% glucose (Dextrose) and 0.5% lidocaine was administered…into the tendon-bone junction and the tender peritendinous soft tissues." Other treatments: “The use of non-narcotic anti-inflammatory drugs and corticosteroids was restricted during the treatment period.”	**Prolotherapy and rehabilitation**: *N*=10 Age, mean (SD): 32.2 (10.3) 30% Female Clinic or health care facility 4 weeks (3 injections) Prolotherapy + Rehab: Injection protocol the same as arm 1; exercise protocol the same as arm 3. Other treatments: Same as Arm 1 **Exercise/PT**: *N*=10 Age, mean (SD): 34.6 (8.0) 50% Female	**Primary outcome NR** **Pain-related functioning (6, 12 wk)** • VISA-P **Physical performance (6, 12 wk)** • Knee extensor/flexor **Other outcomes:** • Pain severity or intensity (6, 12 wk)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
			Setting not reported 12 weeks (3x/wk) EG: Rehab exercise: "The exercise program…consisted of a warm-up, functional exercise, and assistive exercise. Specifically, the warm-up was composed of light walking and static stretching of the lower extremities. The functional exercise was composed of exercise including strong eccentric muscle contractions of the hip and quadriceps muscles. The assistive exercise was composed of a gastrocnemius muscle strength exercise and a balance strengthening exercise of the lower extremities." Other treatments: Same as Arm 1	
Wu, 2022[135] NR High 12 Months China (1)	**Inclusion**: "Only patients who had been in the army for more than 1 year had knee pain and exhibited irregular ossification of the tibial tubercle and ossification fragments in the patellar tendon insertion, as demonstrated by X-ray/or MRI examination. The study included patients who stopped participating in army training generally after at	**Dextrose prolotherapy**: *N*=35 Age, mean (SD): 21.9 (4.8) 0% Female Clinic or health care facility 2 months (3 injections)	**Saline/Local anesthetic**: *N*=35 Age, mean (SD): 21.7 (4.4) 0% Female Clinic or health care facility 2 months (3 injections)	**VISA-P score at 3 months after enrollment** **Pain-related functioning (3, 6, 12 wk)** • VISA-P **Adverse events**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
NR	least 1 month of conservative treatment." **Exclusion**: "We excluded those who withdrew from active service within 3 months and those with OSD in both knees or other diseases that could cause knee pain."	Dextrose: "12.5% dextrose solution (1 ml 50% dextrose, 2 ml 1% lidocaine, and 1 ml sterile water); Under ultrasound guidance, 1 ml of the solution was injected into the superficial layer of the patellar tendon at the pain site, and 1 ml of the solution was injected into the deep layer of the patellar tendon at the pain site." Other treatments: None reported	Saline: "saline solution (2 ml saline and 2 ml 1% lidocaine)…under ultrasound guidance." Other injection details were the same as group 1. Other treatments: None reported	
Other Foot Pain (not plantar fasciitis)				
Akpancar, 2019[131] NR Critical 12 Months Turkey (1) NR	**Inclusion**: "Patients whose ages varied between 18 and 70 years, who had at least 6 months of symptomatic OLT [osteochondral lesions of the talus] refractory (patients who had pain, stiffness, disability, and dissatisfaction after treatment) to at least 3 months of standard care modalities (temporary immobilization, use of analgesics and anti-inflammatory drugs, partial weight bearing and orthotic provision) and who had grade I, II, or III lesions in their standard ankle radiographies" **Exclusion**:	**Dextrose prolotherapy**: *N*=27 Age, mean (SD): 57.7 (11.1) 70.4% Female Clinic or health care facility 3 injections, duration unclear ("3 sessions (one session in 3 weeks)") 2 mL 25% dextrose for intra-articular, 2ml 13.5% dextrose (1.8 mL 15% dextrose+ 0.2 mL lidocaine) for tibial edge and talar dome adjacent the joint surface	**PRP**: *N*=22 Age, mean (SD): 54.0 (11.5) 72.7% Female Clinic or health care facility 3 injections, duration unclear (as noted for dextrose arm) 2 mL PRP intra-articular and 2 mL PRP for tibial edge and talar dome adjacent to the joint surface) Other treatments:	**Primary outcome NR** **Pain-related functioning (21 days; 3, 6, 12 mo)** • AOS **Adverse events** **Other outcomes:** • Pain severity or intensity • Cost

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
	"Patients with rheumatic or systemic diseases, patients who had active or chronic infection in the treatment area, previous operation history on ankle, other ankle problems accompanying OLT which may cause pain and loss of function in the ankle and pregnant patients"	Other treatments:		
Hadianfard, 2023[126] NR Some concerns 8 Weeks Iran (1) None	**Inclusion**: Hallux rigidus: "Patients aged 30-65 years and complaining of pain or decreased range of motion in the first MTP for at lease 3 months without response to other conservative therapies..." **Exclusion**: "patients with severe stage of degenerative disease in the first MTP according to the anterior-posterior and lateral views of radiography performed before treatment (grades III and IV). Diabetes, rheumatologic disease, history of previous trauma or operation of the first MTP, infections, lumbar radiculopathies, anomalies, nonsteroidal anti-inflammatory drug consumption, coagulopathies, pregnancy, and history of previous local injection of this joint in recent six months."	**Dextrose prolotherapy**: *N*=16 Age, mean (SD): 49.8 (9.3) 87.5% Female Clinic or health care facility Single session 25% dextrose 2 ml (+1% lidocaine): "mixture of 1 cc dextrose 50% and 1 cc of lidocaine 2%" Injection "with a 2 cc syringe (23 gauge)...inserted from the medial side of the joint while the solution was injected in both plantar and dorsal directions." Other treatments:	**Corticosteroid Injection**: *N*=16 Age, mean (SD): 46.9 (9.8) 81.3% Female Clinic or health care facility Single session methylprednisolone acetate 40 mg (+ 1% lidocaine): "1 cc methylprednisolone (40 mg) and 1 cc of lidocaine 2%" same injection method Other treatments:	**Primary outcome NR** **Pain-related functioning (1, 4, 8 wk)** • MOXFQ **Other outcomes:** • Pain severity or intensity

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
Yelland, 2011[129] ACTRN: 12606000179538 Some concerns 12 Months Australia (5) Musculoskeletal Research Foundation of Australia, the Australian Podiatry Education and Research Foundation and the Griffith University Office of Research	**Inclusion**: "diagnosis of unilateral or bilateral midportion Achilles tendinosis with pain between 2 and 7 cm proximal to the calcaneal attachment in adults >18 years with activity-related pain for at least 6 weeks. The clinical severity of the tendinosis had to yield a score on the Victorian Institute of Sport Assessment—Achilles (VISA-A) of <80 of a maximum of 100 for participants involved in sport and <70 of 90 for people not involved in sport.,, ultrasound findings of mid-portion tendinosis..." **Exclusion**: "previous steroid or prolotherapy injections or surgery to the affected tendon, previous completion of >50% of the Achilles ELE protocol and any allergies or medical conditions that might limit completion of trial treatments."	**Dextrose prolotherapy**: *N*=14 Age, mean (SD): 48 (41-54) % Female NR Clinic or health care facility Weekly for 4-12 treatments. "The number of treatments was determined by the time it took to reach a pain-free activity or until the participant requested to cease treatment." 20% dextrose 5 ml: "injected tender points in the subcutaneous tissues adjacent to the affected tendon with a solution consisting of 20% glucose/0.1% lignocaine/0.1% ropivacaine using the technique described by Lyftogt. The tender points were most commonly the anterolateral and anteromedial margins of the tendon and on the most posterior aspect of the tendon 2–7 cm from the calcaneus attachment. At each point, 0.5–1 ml of solution was used to a maximum total of 5 ml." Other treatments:	**Exercise/PT**: *N*=15 Age, mean (SD): 46 (40-58) % Female NR Clinic or health care facility " exercises... twice daily in three sets of 15 repetitions with the knee straight and three sets of 15 repetitions with the knee bent for a period of 12 weeks." ELE protocol: "Eccentric loading exercises... participants were instructed by a doctor or podiatrist in the ELE protocol described by Alfredson et al [Alfredson H, Pietilä T, Jonsson P, et al. Heavy-load eccentric calf muscle training for the treatment of chronic Achilles tendinosis. Am J Sports Med 1998;26:360–6.)... participants are told that the exercises may be painful but not to exceed an intensity of 4/10. As the pain eases over time, load is progressively increased by adding weights to a backpack. The participants had an initial training session and then reviews at 3, 6 and 12 weeks to check technique and progress. Written instructions for the exercises were supplied, and the participants kept a	**Victorian Institute of Sport Assessment—Achilles (VISA-A)** **Pain-related functioning (6 wk; 3, 6, 12 mo)** • VISA-A **Adverse events** **Other outcomes:** • Cost

Author, Year Registry # Risk of Bias Follow-up Duration Location (# Sites) Funding source	Inclusion/Exclusion Criteria	Intervention: *N* Randomized Demographics Setting Frequency; Duration Detailed Intervention Characteristics Other treatments/co-interventions	Comparator(s): *N* Randomized Demographics Setting Frequency; Duration Detailed Comparator Characteristics Other treatments/co-interventions	Primary Outcome Prioritized Outcomes • Measurement tool(s) (Time points) Other Outcomes Reported
		Combined: *N*=14 Age, mean (SD): 46 (40-57) % Female NR Clinic or health care facility; Home Combined dextrose prolotherapy + ELE (as described above) Other treatments:	diary to document exercise load and compliance." Other treatments:	
Hand Pain Conditions				
Hooper, 2011[136] NR Some concerns 12 Months Canada (1) "This study was funded in part by a grant from the Calgary Health Region."	**Inclusion:** 18-50 years, wrist pain ≥6 months, PRWE score ≥20, normal X-ray, no other systemic illness, discontinue anti-inflammatory medication, no other wrist pathology on examination **Exclusion:** NR	**Dextrose prolotherapy**: *N*=20 Age, mean (SD): 33.0 (8.5) 75% Female Clinic Max of 6 sessions, each 1 month apart 20% dextrose 5 ml (+0.6% lidocaine), injected into at least three sites including: scaphotrapezium, perilunate region, scaphotrapezoid, first carpometacarpal, radioulnar, or	**Saline/Local anesthetic**: *N*=30 Age, mean (SD): 35.4 (8.5) 68% Female Clinic Max of 6 sessions, each 1 month apart 1% lidocaine 5 mL as per intervention protocol Other treatments: Same as Arm 1	**PRWE** **Pain-related functioning (3,12 mo)** • PRWE **Physical performance** • Grip strength • Flexion • Extension • Supination • Pronation **Adverse events** **Other outcomes:**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
		peritriquetral. Injected using a peppering technique Other treatments: No "antiinflammatory medication for up to 1 month after last treatment."		• Pain severity or intensity: 10-point VAS
Jahangiri, 2014[127] IRCT201011025088N1 Some concerns 6 Months Iran (1) NR	**Inclusion:** >40 years, CMCI1 pain ≥3 months, pain intensity >30 mm on 100-point VAS, evidence of osteoarthritis on radiograph **Exclusion:** "history of fracture or other hand pathologies… within 6 months before the study… diabetes, blood coagulation disorders, neuropathy, corticosteroid injection [≤3 months], and contraindications to steroid injection. Pregnant or breast feeding mothers, participants who were taking NSAIDs or wearing a brace at the time of the study, and patients with a history of injection into their CMC1 within the last [≤6 months]."	**Dextrose prolotherapy**: *N*=30 Age, mean (SD): 63.9 (9.4) 77% Female Clinic 3 sessions, each 1 month apart 10% dextrose (+2% lidocaine),injected "toward the ulnar side of the extensor pollicis brevis and just proximal to the base of the first metacapral in the snuffbox." Other treatments: "Participants were also instructed not to use a brace, physiotherapy, and analgesic medications."	**Corticosteroid Injection,** *N*=19 Age, mean (SD): 63.3 (10.1) 70% Female Clinic 3 sessions, each 1 month apart 40 mg methylprednisolon acetate (+ 2% lidocaine) as per intervention protocol Other treatments: Same as Arm 1	**VAS** **Physical performance** • Lateral Pinch Strength **Adverse events** **Other outcomes:** • Pain severity & intensity: 10-point VAS
Ustun, 2023[132] NCT03839108 Some concerns	**Inclusion:** 40-70 years, bilateral hand osteoarthritis by ACR diagnosis **Exclusion:**	**Dextrose prolotherapy**: *N*=23 Age, mean (SD): 59.5 (6.9) 100% Female	**Paraffin wax**, *N*=23 Age, mean (SD): 60.4 (7.4) 100% Female	**Primary outcome NR** **Physical performance** • DHI

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
Turkey (1) "This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors."	"carpal tunnel syndrome, de Quervain tenosynovitis, Dupuytren's contracture, inflammatory arthritis, secondary OA due to rheumatoid arthritis, chondrocalcinosis, psoriatic arthritis, hemochromatosis or trigger finger… history of upper extremity surgery, patients with neurological disorders, and those who received physiotherapy or joint injections [≤6 months] were omitted."	Clinic Single injection 15% dextrose ml NR, "injected into the periarticular ligaments of the symptomatic proximal interphalangeal, distal interphalangeal, and carpometacarpal joints" Other treatments: None reported	Clinic 10 sessions, 20 minutes a day, 5 days a week, for 2 weeks Both hands were dipped into "melted wax bath at 52°C 10 times. Patients were instructed to keep their hands open and their wrists in a neutral position." Other treatments None reported	**Adverse events** **Other outcomes:** • Pain severity or intensity: 10-point VAS
Other conditions				
Abd Elghany, 2019[133] NR Moderate 1 Months Egypt (1) NR	**Inclusion**: " Patients met ACR 2010 preliminary diagnostic criteria for fibromyalgia syndrome." **Exclusion**: "Excluded were patients with secondary fibromyalgia, patients with systemic disease or chronic arthritis such as RA, SLE, pregnant and nursing women, patients with bleeding tendency or using anticoagulant, patients with active infection or cancer, complete rupture of a tendon or alignment, patients with muscle diseases, diabetes mellitus, thyroid dysfunction, patients with seizures or abnormal brain	**Dextrose prolotherapy**: *N*=60 Age, mean (SD): NR (NR) NR% Female Clinic or health care facility 3 injections bi-weekly 25% DPT: "The injected solution consisted of 25% dextrose to make a 12.5% soft tissue solution (1/2 volume of 10 ml syringe), xylocaine 0.3% (1 ml of 3% xylocaine over 10 ml solution); bacteriostatic water was	**Other non-injectable**: *N*=60 Age, mean (SD): NR (NR) NR% Female Clinic or health care facility 3 injections bi-weekly rTMS: "Brain repetitive transcranial magnetic stimulation (rTMS) is another therapeutic modality for fibromyalgia. It modifies cortical and deep brain areas, through an electromagnetic field generated over the scalp, by	**VAS** **Pain-related functioning** • FIQR*† (0 day, 1 mo) **Other outcomes:** • Pain Severity & Intensity: VAS*‡ (0 day, 1 mo)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
	electrical activity, primary psychiatric or neurological disorders, patients with pacemakers, recent head trauma, auditory problems or drug abuse."	recommended as a diluent. 0.5–1 ml of solution was injected in each trigger point as well as tender ligaments and tendinous insertion points. The prolotherapist used his fingertip to palpate potential pain referral sources for the patient's clinical complaints. Injection sites were cervical inter-transverse ligaments, posterior-superior trapezius, infraspinatus, common extensors, iliolumbar, and sacroiliac ligament." Other treatments: None reported	decreasing or increasing cortical excitability (when using low- or high-frequency protocols). The TMS machine used was the Magstim 200 repetitive pulse stimulator by Magstim Company, Whitland Wales, UK. The cortical target was DLPFC, a functional, rather than anatomical, structure. This region lies in the middle frontal gyrus (i.e., lateral part of Brodmann's area), 9 and 46, and it is considered the end point for the dorsal pathway that tells the brain how to interact with the stimuli [8]. The same stimulation frequency was used for all patients, parameters of antidepressant and anti-nociceptive effects were: 10 Hertz – pulse train duration (on time) five seconds, inter-train interval (off time) ten seconds (15 second cycle time). Additionally, stimulation-train duration and inter-stimulus intervals were determined such that they comply with current published rTMS safety guidelines." Other treatments: None reported	
Gul, 2020[130] NR Some concerns 12 Months	**Inclusion**: "Patients whose ages varied between 18 years and 80 years, who had at least 6 months of symptomatic osteoarthritis secondary to DDH refractory to at least 3 months of standard care modalities (weight loss, temporary	**Dextrose prolotherapy**: *N*=20 Age, mean (SD): 45.74 (16.86) 60% Female	**Exercise/PT**: *N*=21 Age, mean (SD): 47.56 (13.8) 66.67% Female	**Primary outcome NR** **Adverse events** **Other outcomes:** • Pain severity or intensity: VAS*¶ (21 day, 3, 6, 12 mo)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
Turkey (1) NR	immobilization, use of analgesics and anti-inflammatory drugs, partial weight-bearing heel risers, orthotic provision, and physical therapy) and who had Crowe Type I–IV lesions in their standard anteroposterior hip radiographic and waiting list for total hip arthroplasty (THA) surgery at Tokat State Hospital were included in the study." **Exclusion**: "Patients with systemic or rheumatic diseases, active or chronic infection in the affected hip, hip problems accompanying DDH that may cause pain and loss of function in the hip and other chronic hip diseases, patients who had undergone surgery for joint preserving or arthroplasty of the hip, who had rheumatologic or neurological diseases that affect hip functions and pregnant patients were excluded from the study."	Clinic or health care facility 1 injection every 21 days repeated up to 6 times 15% DPT: "Injections were applied in supine position. A maximum of 8 mL dextrose solution (7.2 mL 15% dextrose and 0.8 mL lidocaine mixture) were injected into iliopsoas and adductor tendon insertions. In patients with type I and II DDH, a mixture containing 7.2 mL 25% dextrose and 0.8 mL lidocaine were applied to the hip joint with anterosuperior, parasagittal approach [22]. A proper needle position was confirmed by ultrasonographic visualization of the injected solution. The injections were applied in lateral decubitus position and the hip was in a neutral position. A maximum of 12 mL dextrose solution (10.8 mL 15% dextrose and 1.2 mL lidocaine mixture) were injected to gluteus medius, gluteus minimus insertions; then, the hip was given a flexion position for the piriformis insertion injection." Other treatments: "Patients were instructed to take 500 mg of acetaminophen up to 4 times a day if necessary. The use of anti-	Clinic or health care facility 1 injection every 21 days repeated up to 6 times Exercise (supervised & at-home): "All patients received standard 12-week rehabilitation protocol and supervised progressive resistance training consisting of 30 training sessions (5 sessions per 2 weeks, an average of 45–60 minutes per season). All patients started with a warm-up on a stationary bicycle for 10 minutes. Then they performed leg press, hamstring curl and knee extension with double-legged, hip flexion with single-legged and lunges. Sets were performed 3 to 4 times with 8 repetitions. The intensity of all exercises increased progressively to a maximum of 12 repetitions. Eight repetitions of 3 sets were performed in the first 2 weeks and 4 sets in the last 2 weeks. If the sets were performed with 2 or more repetitions from the target of the maximum repetitions number, then the load was increased. All sessions were supervised by a physiotherapist or by a sports medicine physician to provide adequate loading and progression. A home exercise plan with similar exercises 3 times a day was adopted to the patients for other days. Also, the	

Author, Year Registry # Risk of Bias Follow-up Duration Location (# Sites) Funding source	Inclusion/Exclusion Criteria	Intervention: *N* Randomized Demographics Setting Frequency; Duration Detailed Intervention Characteristics Other treatments/co-interventions	Comparator(s): *N* Randomized Demographics Setting Frequency; Duration Detailed Comparator Characteristics Other treatments/co-interventions	Primary Outcome Prioritized Outcomes • Measurement tool(s) (Time points) Other Outcomes Reported
		inflammatory drugs was not allowed. Hot pack application to the injected areas was suggested 3 times a day during the first 3 days after the treatment."	home exercise plan was advised after the 12-week rehabilitation program." Other treatments: None reported	
Senturk, 2017[134] NR Serious 4 Weeks Turkey (1) NR	**Inclusion**: "They had no history of trauma to the thorax or symptoms of systemic disease. Patient evaluation included a complete history, X-ray chest, electrocardiography, physical examination, complete blood count." **Exclusion**: NR	**Dextrose prolotherapy**: *N*=21 Age, mean (SD): 45.4 (13.5) 66.7% Female Clinic or health care facility 1 injection 20% DPT: "The affected costochondral joint was injected with a combination of 8 ml of 20% dextrose and 2 ml of 2% lidocaine into the chest wall. Twenty-one of them had received one local injections." Other treatments: None reported	**NSAID:** *N*=13 Age, mean (SD): 47.7 (15) 76.9% Female Home 1 injection "...treated analgesia by NSAID's (Naproxen Sodium) dose is approximately 10 mg/kg given orally in 2 divided doses (i.e., 5 mg/kg given twice a day)." Other treatments: None reported	**VAS*¶** **Adverse events** **Other outcomes:** • Pain severity or intensity: VAS*¶ (1 day, 1, 4 wk)

Notes. *No established MCID for outcome; direction of effect based on statistically significant difference reported by study.
†Fibromyalgia Impact Questionnaire Revised (FIQR) was measured on a weighted scale of 3 domains with a maximum score of 100, lower values indicating improvement
‡Authors assessed VAS on a scale of 0 (no pain) to 100 (unbearable pain).
¶Authors assessed VAS on a scale of 0 (no pain) to 10 (unbearable pain).
Abbreviations. ACR=American College of Rheumatology; AE=adverse event; DDH=development dysplasia of the hip; DHI=Duruoz Hand Index; DLPFC=dorsolateral prefrontal cortex; DPT=dextrose prolotherapy; kg=kilogram; mg=milligram; mL=milliliter; mo=month; NR=not reported; NS=not significant; NSAID=nonsteroidal anti-

inflammatory drug; PrT=prolotherapy; PWRE=Patient rated wrist evaluation; RA= rheumatoid arthritis; rTMS=repetitive transcranial magnetic stimulation; SD=standard deviation; SLE=systemic lupus erythematosus; THA= total hip arthroplasty; VAS=Visual Analog Scale; wk=week.

Appendix Table 17. Detailed Results for All Eligible Studies on Other Pain Conditions

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up P-value* Other results reported
Non-arthritis Knee Pain				
Babaei-Ghazani, 2023[125] Some concerns	Pain-related functioning WOMAC Total 1, 8 wk	**Dextrose prolotherapy** Baseline: 59.3 (16.8) 1 wk: 56.7 (21.5) 8 wk: 38.1 (15.5)	**Corticosteroid** Baseline: 63.2 (13.3) 1 wk: 44.1 (21.0) 8 wk: 48.0 (19.2)	**Dextrose prolotherapy vs. Corticosteroid** 1 wk: 12.6, p=NR 8 wk: -9.9, p=NR
			Oxygen/ozone Baseline: 58.6 (11.2) 1 wk: 43.2 (16.8) 8 wk: 33.0 (15.3)	**Dextrose prolotherapy vs. Oxygen/ozone** 1 wk: 13.5, p=NR 8 wk: 5.1, p=NR
	Pain intensity or severity WOMAC Pain 1, 8 wk	**Dextrose prolotherapy** Baseline: 11.8 (4.1) 1 wk: 11.4 (4.6) 8 wk: 7.1 (3.5)	**Corticosteroid** Baseline: 13.5 (3.7) 1 wk: 8.6 (4.5) 8 wk: 10.1 (4.9)	**Dextrose prolotherapy vs. Corticosteroid** 1 wk: 2.8, p=NR 8 wk: -3.0, p=NR
			Oxygen/ozone Baseline: 12.2 (2.3) 1 wk: 7.95 (3.7) 8 wk: 6.3 (3.5)	**Dextrose prolotherapy vs. Oxygen/ozone** 1 wk: 3.5, p=NR 8 wk: 0.8, p=NR
	Pain-related functioning WOMAC Stiffness 1, 8 wk	**Dextrose prolotherapy** Baseline: 4.2 (1.8) 1 wk: 3.2 (1.8) 8 wk: 2.5 (1.7)	**Corticosteroid** Baseline: 3.9 (2.5) 1 wk: 3.2 (2.0) 8 wk: 3.5 (2.3)	**Dextrose prolotherapy vs. Corticosteroid** 1 wk: 0.0, p=NR 8 wk: -1.0, p=NR
			Oxygen/ozone Baseline: 4.0 (1.5) 1 wk: 3.7 (1.4) 8 wk: 2.4 (1.8)	**Dextrose prolotherapy vs. Oxygen/ozone** 1 wk: -0.5, p=NR 8 wk: 0.1, p=NR
	Pain-related functioning WOMAC Physical Function 1, 8 wk	**Dextrose prolotherapy** Baseline: 43.3 (12.4) 1 wk: 42.2 (16.9) 8 wk: 28.5 (11.5)	**Corticosteroid** Baseline: 45.8 (8.9) 1 wk: 32.3 (15.98) 8 wk: 34.5 (12.9)	**Dextrose prolotherapy vs. Corticosteroid** 1 wk: 9.9, p=NR 8 wk: -6.0, p=NR
			Oxygen/ozone Baseline: 41.6 (8.9) 1 wk: 29.8 (14.3) 8 wk: 22.9 (12.4)	**Dextrose prolotherapy vs. Oxygen/ozone** 1 wk: 12.4, p=NR 8 wk: 5.6, p=NR

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up** **P-value*** **Other results reported**
	Pain severity or intensity VAS 1, 8 wk	**Dextrose prolotherapy** Baseline: 7.6 (1.31) 1 wk: 7.25 (1.77) 8 wk: 3.5 (1.85)	**Corticosteroid** Baseline: 8.04 (1.33) 1 wk: 4.53 (2.71) 8 wk: 5.07 (2.55)	**Dextrose prolotherapy vs. Corticosteroid** 1 wk: 2.7, p=NR 8 wk: -1.6, p=NR
			Oxygen/ozone Baseline: 7.6 (1.31) 1 wk: 4.83 (2.53) 8 wk: 3.88 (2.59)	**Dextrose prolotherapy vs. Oxygen/ozone** 1 wk: 2.4, p=NR 8 wk: -0.4, p=NR
Cho, 2017[128] Serious	Pain-related functioning VISA-P 6, 12 wk	**Dextrose prolotherapy** Baseline: 52.4 (9.7) 6 wk: 57.2 (12.8) 12 wk: 62.6 (11.1)	**Dextrose prolotherapy + Exercise** Baseline: 58.7 (12.1) 6 wk: 67.6 (12.6) 12 wk: 79.0 (9.18)	**Dextrose prolotherapy vs. Dextrose prolotherapy + Exercise** 6 wk: -10.4 12 wk: -16.4 p<0.05 (across time points)
			Exercise Baseline: 59.9 (13.8) 6 wk: 73.7 (11.9) 12 wk: 78.1 (10.6)	**Dextrose prolotherapy vs. Exercise** 6 wk: -16.5 12 wk: -15.5 p<0.05 (across time points)
				Dextrose prolotherapy + Exercise vs. Exercise 6 wk: -6.1 12 wk: 0.9 P=NS (across time points)
	Physical performance Knee extensor strength 6, 12 wk	**Dextrose prolotherapy** Baseline: 206.8 (46.3) 6 wk: 501.8 (46.9) 12 wk: 183.5 (38.1)	**Dextrose prolotherapy + Exercise** Baseline: 227.0 (52.9) 6 wk: 253.7 (62.7) 12 wk: 252.9 (52.9)	**Dextrose prolotherapy vs. Dextrose prolotherapy + Exercise** 6 wk: 248.1, p=NR 12 wk: -69.4, p=NR
			Exercise Baseline: 197.1 (61.5) 6 wk: 208.6 (52.2) 12 wk: 225.4 (47.9)	**Dextrose prolotherapy vs. Exercise** 6 wk: 293.2, p=NR 12 wk: -41.9, p=NR
				Dextrose prolotherapy + Exercise vs. Exercise 6 wk: 45.1, p=NR 12 wk: 27.5, p=NR
	Physical performance Knee flexor strength 6, 12 wk	**Dextrose prolotherapy** Baseline: 96.0 (24.2) 6 wk: 105.7 (33.6) 12 wk: 95.3 (29.1)	**Dextrose prolotherapy + Exercise** Baseline: 106.8 (21.8) 6 wk: 117.8 (24.3) 12 wk: 129.3 (27.2)	**Dextrose prolotherapy vs. Dextrose prolotherapy + Exercise** 6 wk: -12.1, p=NR 12 wk: -34.0, p=NR

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up** **P-value*** **Other results reported**
			Exercise Baseline: 100.7 (32.9) 6 wk: 115.0 (26.5) 12 wk: 116.4 (24.4)	**Dextrose prolotherapy vs. Exercise** 6 wk: -9.3, p=NR 12 wk: -21.1, p=NR
				Dextrose prolotherapy + Exercise vs. Exercise 6 wk: 2.8, p=NR 12 wk: 12.9, p=NR
	Pain severity or intensity VAS 6, 12 wk	**Dextrose prolotherapy** Baseline: 6.8 (1.2) 6 wk: 5.2 (0.8) 12 wk: 4.5 (1.1)	**Dextrose prolotherapy + Exercise** Baseline: 6.7 (0.5) 6 wk: 3.6 (1.4) 12 wk: 2.5 (1.2)	**Dextrose prolotherapy vs. Dextrose prolotherapy + Exercise** 6 wk: 1.6 12 wk: 2.0 p<0.05 (across time points)
			Exercise Baseline: 6.4 (0.7) 6 wk: 4.5 (1.1) 12 wk: 3.1 (1.6)	**Dextrose prolotherapy vs. Exercise** 6 wk: 0.7 12 wk: 1.4 p<0.05 (across time points)
				Dextrose prolotherapy + Exercise vs. Exercise 6 wk: -0.9 12 wk: -0.6 P=NS (across time points)
Wu, 2022[135] High	Pain-related functioning VISA-P 3 wk 6, 12 mo	**Dextrose prolotherapy** Baseline: 49.1 (5.9) 3 wk: 76.2 (1.1) 6 mo: 80.8 (1.1) 12 mo: 83.1 (1.3)	**Saline** Baseline: 49.4 (5.7) 3 wk: 50.8 (1.1) 6 mo: 74.6 (1.1) 12 mo: 77.6 (1.3)	**Dextrose prolotherapy vs. Saline** 3 wk: 25.4, p=<.0001 6 mo: 6.2, p=<.0001 12 mo: 5.5, p=0.0026
	Adverse events 12 mo	*"No adverse events were reported in either group"*		
Other Foot Pain (not plantar fasciitis)				
Akpancar, 2019[131] Critical	Pain-related functioning AOS 21 days 3, 6, 12 mo	**Dextrose prolotherapy** Baseline: 129.4 (20.0) 21 days: 75.2 (23.3) 3 mo: 51.4 (28.3) 6 mo: 36.9 (25.8) 12 mo: 29.9 (25.9)	**PRP** Baseline:137.4 (20.9) 21 days: 86.5 (28.0) 3 mo: 49.9 (20.5) 6 mo: 33.3 (15.6) 12 mo: 30.1 (19.5)	**Arm 1 vs. Arm 2** 21 days: -11.3, p=0.13 3 mo: 1.5, p=0.84 6 mo: 3.6, p=0.57 12 mo: -0.2, p=0.98
	Pain severity or intensity VAS	**Dextrose prolotherapy** Baseline: 7.2 (1.5)	**PRP** Baseline: 7.7(1.4)	**Arm 1 vs. Arm 2** 21 days: -0.7, p=0.10

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up** **P-value*** **Other results reported**
	21 Days 3, 6, 12 mo	21 days: 4.0 (1.6) 3 mo: 2.5 (1.8) 6 mo: 1.7 (1.7) 12 mo: 1.3 (1.8)	21 days: 4.7 (1.4) 3 mo: 2.6 (1.0) 6 mo: 1.6 (1.2) 12 mo: 1.4 (1.4)	3 mo: -0.1, p=0.91 6 mo: 0.1, p=0.89 12 mo: -0.1, p=0.81
	Adverse events 12 mo	*"Patients did not suffer from any side effects such as infection, fever, hematoma, or rupture. Only 3 patients reported extreme pain 1 or 2 days after injection in the prolotherapy group, which was alleviated after 2 days of non-weight bearing."* (of note, study excluded participants who could not complete all 3 injections or who were lost to follow-up at any time within the 12 mo of follow-up)		
	Cost 12 mo	*"The average cost of PrT to the hospital was 30 Turkish Liras (TL) ($6.8) per session, and average cost of PRP to the hospital was 250 TL ($56.8) per session."*		
Hadianfard, 2023[126] Some concerns	Pain-related functioning MOXFQ 1, 4, 8 wk	**Dextrose prolotherapy** Baseline: 45.5 (NR) 1 wk: 29.1 (NR) 4 wk: 33.1 (NR) 8 wk: 33.1 (NR)	**Corticosteroid** Baseline: 49.6 (NR) 1 wk: 28.6 (NR) 4 wk: 33.1 (NR) 8 wk: 33.8 (NR)	**Arm 1 vs. Arm 2** 1 wk: -0.5, p=0.93 4 wk: 0.0, p=1.0 8 wk: -0.7, p=0.82
	Pain severity or intensity VAS 1, 4, 8 wk	**Dextrose prolotherapy** Baseline: 5.7 (NR) 1 wk: 2.5 (NR) 4 wk: 2.7 (NR) 8 wk: 2.8 (NR)	**Corticosteroid** Baseline: 6.1 (NR) 1 wk: 2.3 (NR) 4 wk: 2.4 (NR) 8 wk: 2.7 (NR)	**Arm 1 vs. Arm 2** 1 wk: 0.2, p=0.32 4 wk: 0.3, p=0.30 8 wk: 0.1, p=0.70
Yelland, 2011[129] Some concerns	Pain-related functioning VISA-A 6 wk, 3, 6, 12 mo	**Dextrose prolotherapy** Baseline: 59.7 (NR) 6 wk: 71.7 (NR) 3 mo: 80.6 (NR) 6 mo: 86.6 (NR) 12 mo: 87.4 (NR) **Dextrose prolotherapy + exercise/PT** Baseline: 50.3 (NR) 6 wk: 74.5 (NR) 3 mo: 76.4 (NR) 6 mo: 81.6 (NR) 12 mo: 91.5 (NR)	**Exercise/ELE:** Baseline: 57.6 (NR) 6 wk: 70.3 (NR) 3 mo: 79.7 (NR) 6 mo: 76.3 (NR) 12 mo: 81.5 (NR)	**Arm 1 vs. Arm 3** 6 wk: 1.4, p=NR 3 mo: 0.9, p=NR 6 mo: 10.3, p=NR 12 mo: 5.9, p=NR **Arm 2 vs. Arm 3** 6 wk: 4.2, p=0.005 3 mo: -3.3, p=NR 6 mo: 5.3, p=NR 12 mo: 10.0, p=0.007
	Adverse events 12 mo	*"One adverse event was reported in the trial. A participant in the ELE group had a partial calf tear while playing tennis. An independent sports physician did not attribute this to the ELE programme."*		

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up P-value* Other results reported
	Cost 12 mo	*"Compared with ELE, prolotherapy cost an additional $90 in total and combined treatment cost $191 (table 3). For those additional costs, an additional 5.2% of the participants achieved a ≥20-point improvement in VISA-A score from prolotherapy at 12 months, whereas for the combined treatment, an additional 13% achieved this response. From the ICERs, it is apparent that combined treatment offers the best value for money (ie, the additional cost per responder is less than prolotherapy alone)."*		
Hand Pain Conditions				
Hooper, 2011[136] Some concerns	Pain-related functioning PRWE 3, 12 mo	**Prolotherapy** Baseline: 43.4 (11.9) 3 mo: NR 12 mo: NR	**Corticosteroid** Baseline: 42.2 (14.9) 3 mo: NR 12 mo: NR	**Arm 1 vs. Arm 2** 3 mo: NR 12 mo: NR Difference in differences: 3 mo: p=0.48 12 mo: p=0.04
	Physical performance Grip strength, flexion, extension, supination, pronation 12 mo	**Prolotherapy** Baseline: NR 12 mo: NR	**Corticosteroid** Baseline: NR 12 mo: NR	**Arm 1 vs. Arm 2** 12 mo: NR Difference in differences: Grip strength 12 mo: NR, p=0.40 Flexion 12 mo: NR, p=0.50 Extension 12 mo: NR, p=0.59 Supination 12 mo: NR, p=0.53 Pronation 12 mo: NR, p=0.90 Ulnar deviation 12 mo: NR, p=0.65 Radial deviation 12 mo: NR, p=0.22
Jahangiri, 2014[127] Some concerns	Pain-related functioning HAQDI 1, 2, 6 mo	**Prolotherapy** Baseline: 4.6 (1.8) 1 mo: NR 2 mo: NR 6 mo: NR	**Corticosteroid** Baseline: 4.37 (1.4) 1 mo: NR 2 mo: NR 6 mo: NR	**Arm 1 vs. Arm 2** 1, 2, 6 mo: NR Difference in differences: 1 mo: -0.5, p=0.15 2 mo: -1.0, p=0.01 6 mo: -1.0, p=0.01

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up** **P-value*** **Other results reported**
	Lateral pinch strength 1, 2, 6 mo	**Prolotherapy** Baseline: 9.6 (3.4) 1 mo: NR 2 mo: NR 6 mo: NR	**Corticosteroid** Baseline: 11.6 (3.6) 1 mo: NR 2 mo: NR 6 mo: NR	**Arm 1 vs. Arm 2** 1, 2, 6 mo: NR Difference in differences: 1 mo: -2.9, p=0.005 2 mo: -1.1, p=0.25 6 mo: -0.8, p=0.45
	Pain severity or VAS 1, 2, 6 mo	**Prolotherapy** Baseline: 5.0 (2.1) 1 mo: NR 2 mo: NR 6 mo: NR	**Corticosteroid** Baseline: 4.5 (1.6) 1 mo: NR 2 mo: NR 6 mo: NR	**Arm 1 vs. Arm 2** 1, 2, 6 mo: NR Difference in differences: 1 mo: 0.7, p=0.14 2 mo: -1.0, p=0.02 6 mo: -1.1, p=0.02
	Adverse events 6 mo	*"The participants did not report any significant side effects. However, three patients experienced transient increases in pain at the site of injection which subsided within several days. There was no sign of infection or any other complication at the site of injections."*		
Ustun, 2023[132] Some concerns	Physical performance DHI 2 wk, 1, 3 mo	**Prolotherapy** Baseline: 16.76 (10.73) 2 wk: 9.43 (7.49) 1 mo: 5.86 (4.22) 3 mo: 5.57 (3.57)	**Paraffin wav** Baseline: 8.90 (5.38) 2 wk: 4.52 (4.23) 1 mo: 4.00 (3.38) 3 mo: 3.90 (3.69)	**Arm 1 vs. Arm 2** 2 wk: 4.91, p=0.004 1 mo: 1.86, p=0.20 3 mo: 1.67, p=0.064
	Pain severity or intensity VAS 2 wk, 1, 3 mo	**Prolotherapy** Baseline: 3.86 (1.96) 2 wk: 2.29 (1.85) 1 mo: 2.86 (1.90) 3 mo: 2.86 (1.15)	**Paraffin wav** Baseline: 3.95 (1.63) 2 wk: 3.00 (1.97) 1 mo: 2.90 (1.48) 3 mo: 2.52 (1.75)	**Arm 1 vs. Arm 2** 2 wk: -0.71, p=0.22 1 mo: -0.04, p=0.69 3 mo: 0.34, p=0.46
	Pain severity or intensity VAS 2 wk, 1, 3 mo	**Prolotherapy** Baseline: 5.67 (1.39) 2 wk: 4.24 (1.37) 1 mo: 3.71 (1.85) 3 mo: 3.52 (1.29)	**Paraffin wav** Baseline: 5.33 (1.39) 2 wk: 4.00 (1.97) 1 mo: 3.57 (1.75) 3 mo: 3.33 (1.85)	**Arm 1 vs. Arm 2** 2 wk: 0.24, p=0.99 1 mo: 0.14, p=79 3 mo: 0.19, p=0.65
	Adverse events 3 mo	*"1 discontinued due to adverse events"*		
Other conditions				
Abd Elghany, 2019[133] Moderate	Pain related functioning or interference	**Dextrose prolotherapy** Baseline: 61.95 (9.75)	**rTMS** Baseline: 65.00 (8.64)	**Arm 1 vs. Arm 2** 1 mo: -4.01, p=0.294

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up** **P-value*** **Other results reported**
	FIQR 1 mo 1 mo	1 mo: 48.42 (8.87) 2 mo: 31.23 (10.67)	1 mo: 52.43 (11.27) 2 mo: 51.71 (12.57)	2 mo: -20.48, p=<0.001
	Pain severity or intensity VAS 1 mo 1 mo	**Dextrose prolotherapy** Baseline: 82.67 (6.19) 1 mo: 57.47 (9.57) 2 mo: 33.71 (11.32)	**rTMS** Baseline: 71.43 (10.69) 1 mo: 51.43 (10.69) 2 mo: 33.71 (11.32)	**Arm 1 vs. Arm 2** 1 mo: 6.04, p=0.112 2 mo: -13.43, p=<0.001
Gul, 2020[130] Some concerns	Pain severity or intensity VAS¶ 21 day 3 mo 6 mo 12 mo	**Dextrose prolotherapy** Baseline: 7.83 (1.19) 21 day: 4.65 (1.40) 3 mo: 3.82 (2.05) 6 mo: 3.17 (2.44) 12 mo: 3.26 (2.32)	**Exercise** Baseline: 7.43 (1.12) 21 day: 5.52 (1.08) 3 mo: 3.82 (2.05) 6 mo: 4.56 (2.33) 12 mo: 3.26 (2.32)	**Arm 1 vs. Arm 2** 21 day: -0.87, p=0.024 3 mo: -1.00, p=0.045 6 mo: -1.39, p=0.027 12 mo: -1.26, p=0.011
	Adverse events 12 mo	*"Serious complications such as cellulitis, septic joint arthritis, osteomyelitis or bleeding were not observed in any patient."*		
Senturk, 2017[134] Serious	Pain severity or intensity VAS 1 day 1 wk 4 wk	**Dextrose prolotherapy** Baseline: 7.1 (1.2) 1 day: 2.2 (0.9) 1 wk: 2.1 (1.0) 4 wk: 1.5 (0.7)	**NSAID** Baseline: 7.2 (1.2) 1 day: 2.6 (1.0) 1 wk: 2.1 (1.0) 4 wk: 2.6 (0.8)	**Arm 1 vs. Arm 2** 1 day: -0.40, p=NR 1 wk: -0.70, p=NR 4 wk: -1.10, p=0.001
	Adverse events 4 wk	*"Complications during the course of treatment included superficial skin pigmentation (n=1) for the prolotherapy group."*		

Notes. *No established MCID for outcome; direction of effect based on statistically significant difference reported by study.
Abbreviations. ACR=American College of Rheumatology; AE=adverse event; DDH=development dysplasia of the hip; DHI=Duruoz Hand Index; DLPFC=dorsolateral prefrontal cortex; DPT=dextrose prolotherapy; kg=kilogram; mg=milligram; mL=milliliter; mo=month; NR=not reported; NS=not significant; NSAID=nonsteroidal anti-inflammatory drug; PrT=prolotherapy; PT=physical therapy; PWRE=Patient rated wrist evaluation; RA= rheumatoid arthritis; rTMS=repetitive transcranial magnetic stimulation; SD=standard deviation; SLE=systemic lupus erythematosus; THA= total hip arthroplasty; VAS=Visual Analog Scale; wk=week.