Dextrose Prolotherapy for Musculoskeletal Pain

August 2024

U.S. Department of Veterans Affairs
Veterans Health Administration
Health Systems Research

Recommended citation: Ewart D, Sowerby C, Yang S, et al. Dextrose Prolotherapy for Musculoskeletal Pain: A Systematic Review. Washington, DC: Evidence Synthesis Program, Health Systems Research, Office of Research and Development, Department of Veterans Affairs. VA ESP Project #09-009; 2024.

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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.

ACKNOWLEDGMENTS

The authors are grateful to Becky Baltich Nelson, MLS, MS for literature searching, external peer reviewers, and the following individuals for their contributions to this project:

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

This report was prepared by the Evidence Synthesis Program Center located at the the **Minneapolis VA Health Care System,** directed by Timothy J. Wilt, MD, MPH and Wei Duan-Porter, MD, PhD and funded by the Department of Veterans Affairs, Veterans Health Administration, Health Systems Research.

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.

Main Report

Evidence Synthesis Program

TABLE OF CONTENTS

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

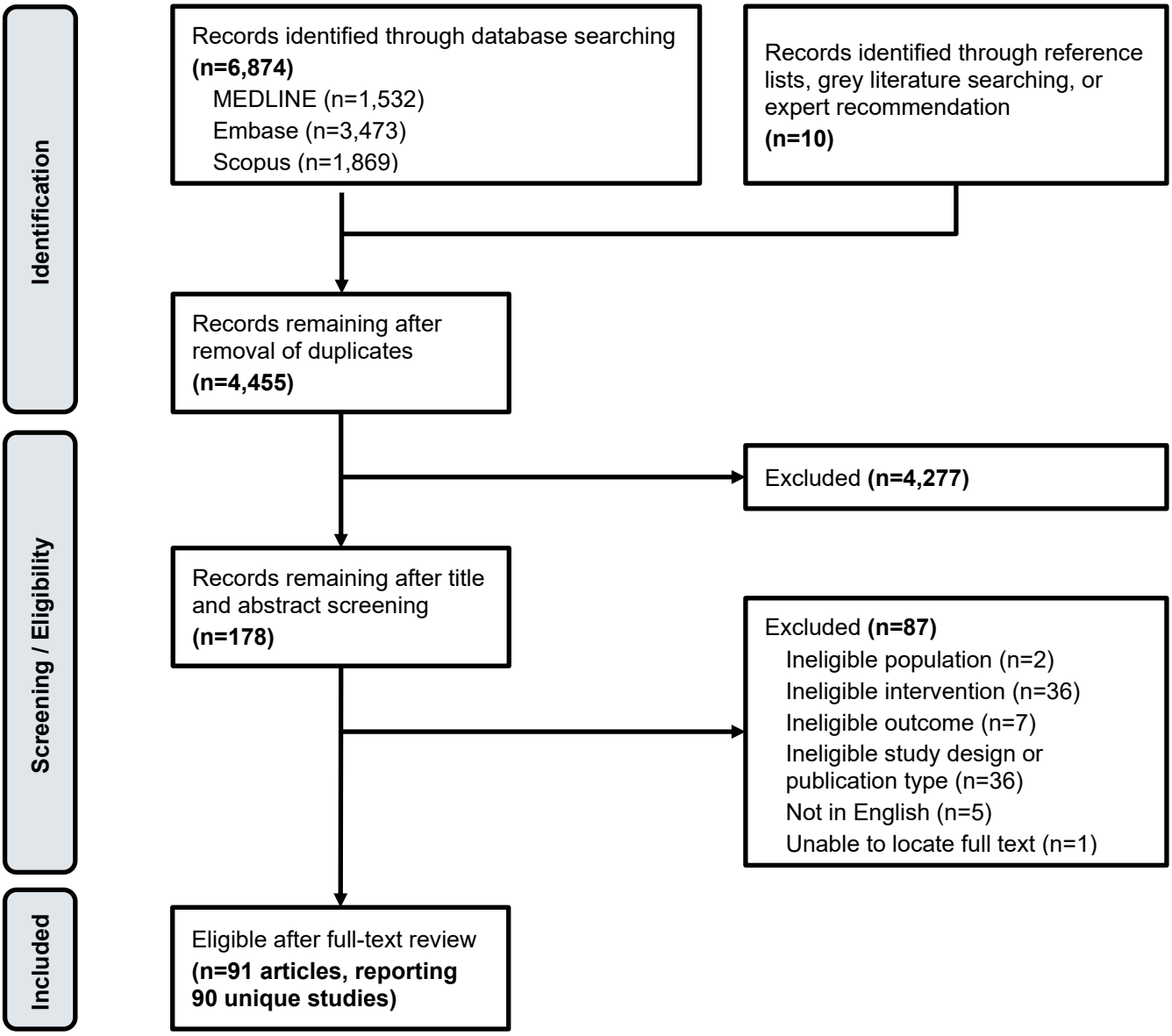


Table 3 provides summary characteristics for all eligible studies, categorized by pain condition. There was wide variation in the dextrose concentration used, as well as the number of injection treatment sessions (range = 1-6) and the overall duration of treatment (up to 5 months). Most studies did not 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).

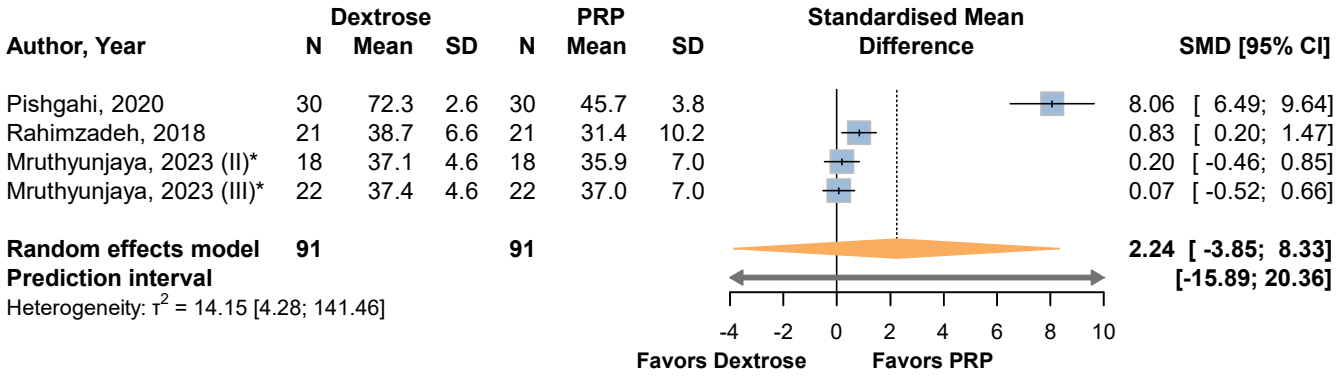
Abbreviations. ADL=activities of daily living; EuroQoL-5D=European Quality of Life-5 dimensions; KOOS=knee injury and osteoarthritis outcome score; mo=month; RCT=randomized controlled trial; RoB=risk of bias; ROM=range of motion.

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

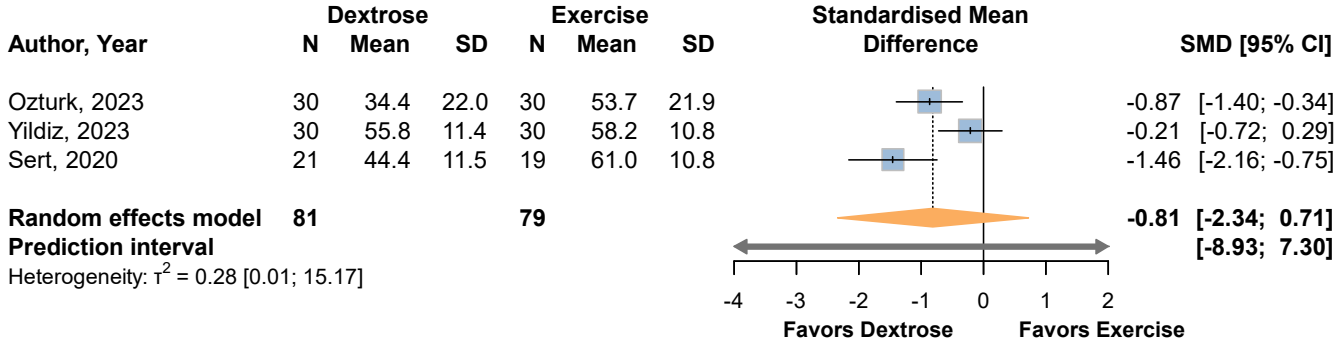
Seven studies (6 RCTs[56,58,59,61-63] and 1 observational study[57]) compared the effects of dextrose prolotherapy with PT and/or home exercise program. Dextrose prolotherapy protocols involved 5-25% intra-articular injections, and 5-20% extra-articular injections, with 1-5 injection sessions over a 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.

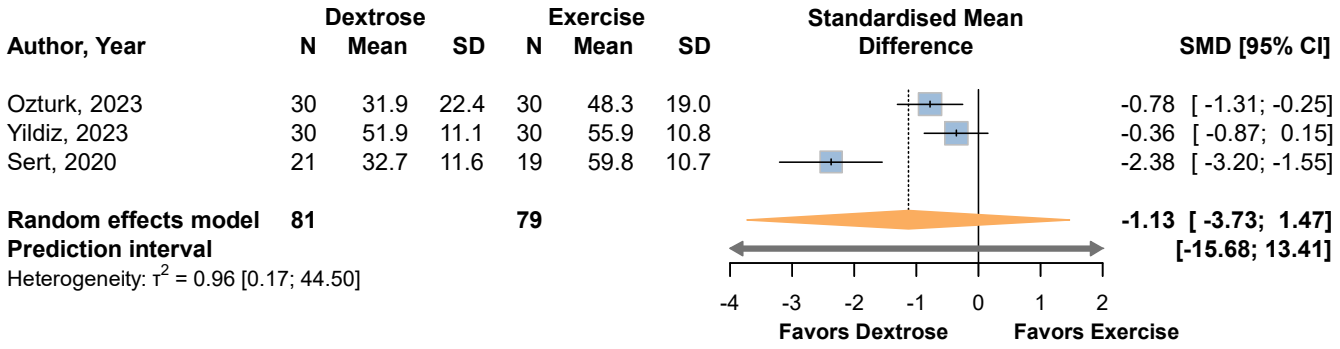
Additionally, Soliman, 2016[57] found that the Hackett plus Lyftogt technique for dextrose prolotherapy injections had lower WOMAC scores (mean 11.3) compared with Hackett technique only (mean 18.5) at 12 months follow-up, but this did not meet MCID (study did not report statistical testing for between-group 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).

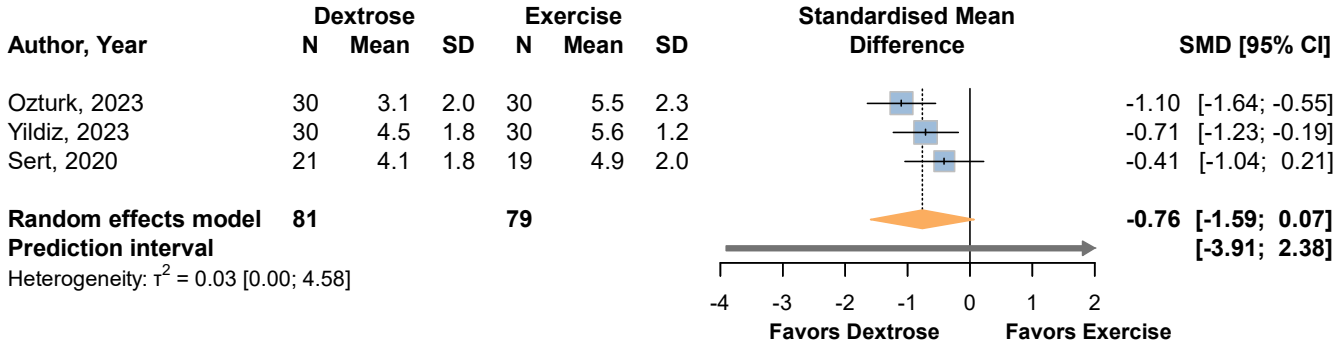
Abbreviations. MD=mean difference; mo=month; PT=physical therapy; RCT=randomized controlled trial; RoB=risk of bias; SF-36=short form health survey; SMD=standardized mean difference; TUG=timed up and go test; VAS=visual analog score; WOMAC= Western Ontario and McMaster Universities Arthritis Index.

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

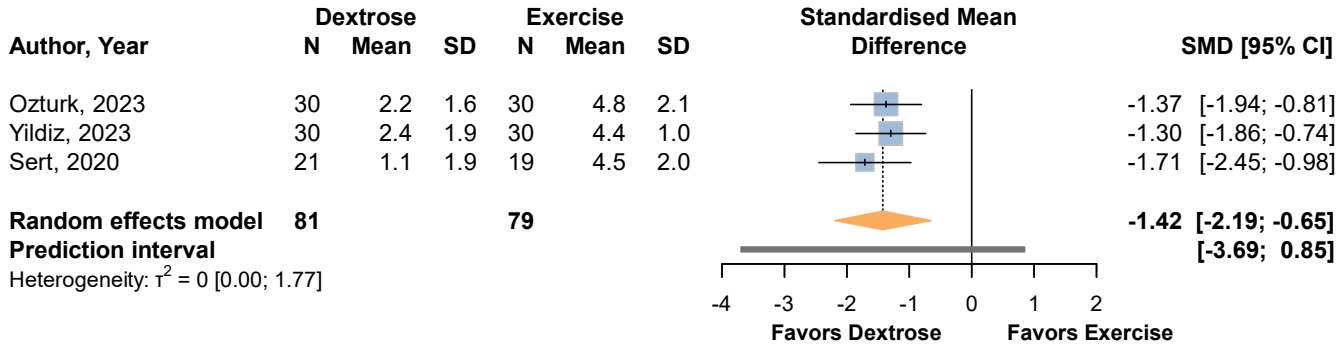
over 3-4 months. Only 3 studies[56,59,62] reported mean scores at short and medium-term follow-up. Pooled estimates were -0.76 (95% CI [-1.59, 0.07]) and -1.42 (95% CI [-2.19, -0.65]) SMD for short and medium-term, respectively (**Figure 4**). While both short and medium-term point estimates favor dextrose 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.

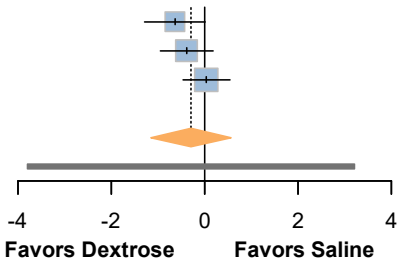
The evidence is very uncertain on the effect of dextrose prolotherapy on adverse events (very low COE, **Table 17**). Two studies addressed adverse events, with Chang, 2021[75] reporting that 1 participant (4%) dropped out of the dextrose prolotherapy group due to “side effect” but providing no further 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]

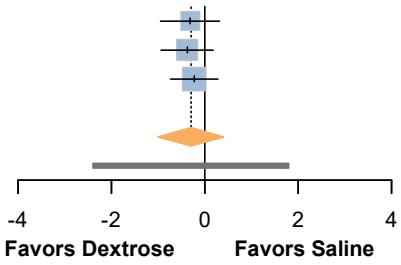


Table 17. Mixed Rotator Cuff Pathology/Subacromial Bursitis COE: Dextrose Prolotherapy versus Normal Saline Injection (With or Without Local Anesthetic)

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.

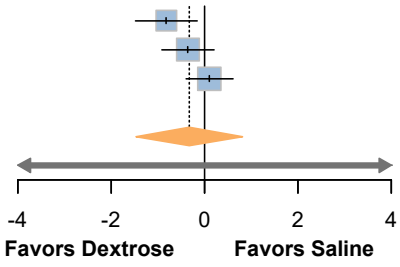
Explanations:

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**).

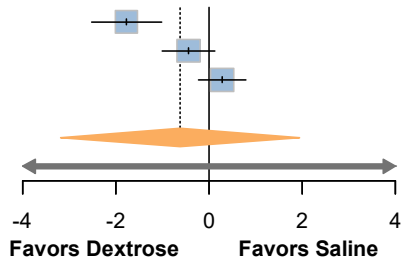
Figure 6. Mixed Rotator Cuff Pathology and/or Subacromial Bursitis: Effect of Dextrose Prolotherapy versus Normal Saline on Pain Intensity or Severity

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]								

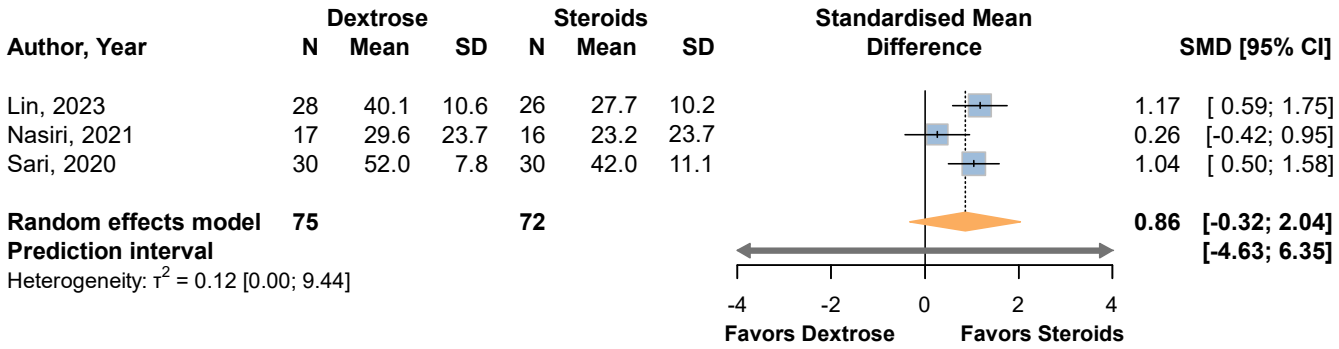
Dextrose Prolotherapy versus Corticosteroid Injection

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.

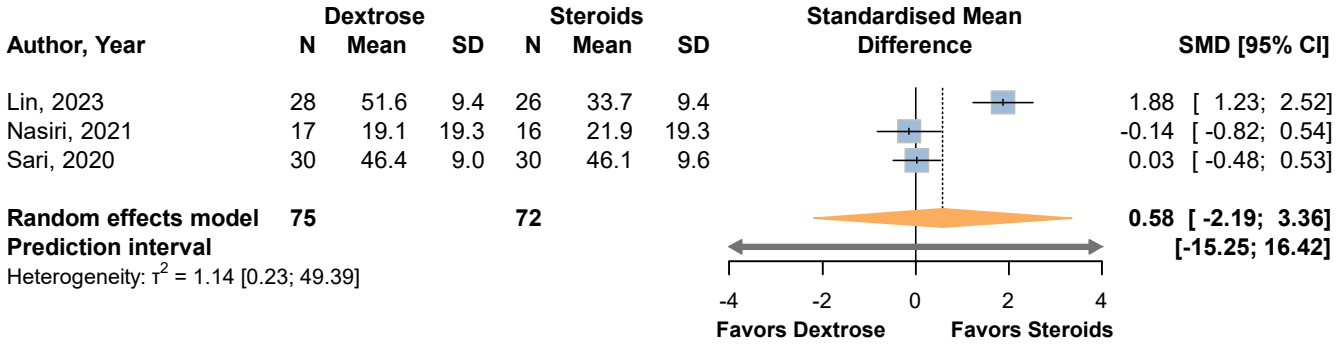
The evidence is very uncertain about the effect of dextrose prolotherapy on pain-related functioning at short- and medium-term follow-up (very low COE) but may result in little to no difference in the long term (low COE, **Table 18**). All 3 trials assessed pain-related functioning, using SPADI,[73,80] 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.

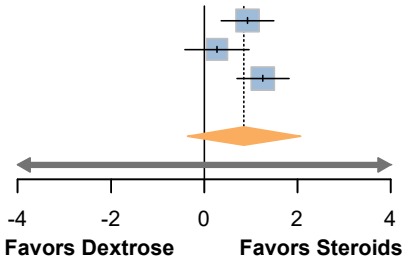
The evidence is very uncertain on the effect of dextrose prolotherapy on adverse events (very low COE, **Table 18**). Only 1 RCT[80] addressed adverse events, reporting that 3 participants (18%) in the

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

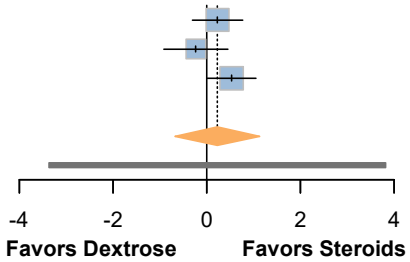
A. Short-Term Follow-Up (3-6 wk)



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).

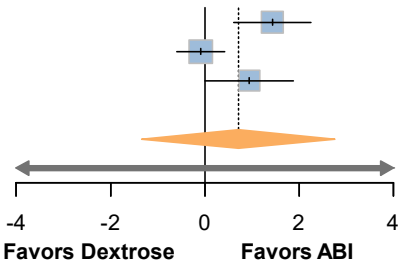
d. Downgraded 1 level for indirectness (no information about how or when adverse event were assessed).
e. Downgraded 2 levels for imprecision (not powered to detect minimum adverse event rate <20%; see Methods for more information).
Abbreviations. MMO=maximum mouth opening; mo=months; NR=not reported; 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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