Dextrose Prolotherapy for Musculoskeletal Pain

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Appendix

APPENDIX A. SEARCH STRATEGIES

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

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

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

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

APPENDIX B. ONGOING AND COMPLETED TRIALS (WITHOUT PUBLICATIONS)

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

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

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

APPENDIX C. EXCLUDED STUDIES

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

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

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

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

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

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

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

APPENDIX D. PEER REVIEW COMMENTS AND RESPONSES

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

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

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

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

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

APPENDIX E. RISK OF BIAS ASSESSMENTS

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

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

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

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

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

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

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

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

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

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

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

APPENDIX F. KNEE OSTEOARTHRITIS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX G. PLANTAR FASCIITIS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX H. SHOULDER PAIN

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX I. LATERAL ELBOW TENDINOPATHY

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

†Mean differences reported by study.

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

APPENDIX J. CHRONIC LOW BACK PAIN (LBP)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

‡23 items from RMDQ.

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

‖Authors assessed VAS on a scale of 0 (no pain) to 10 (unbearable pain).

¶Authors assessed VAS on a scale of 0 (no pain) to 100 (unbearable pain).

QAuthors assessed VAS on a scale of 0 (no pain) to 8 (unbearable pain).

ǂAuthors assessed VAS on a scale of 0 (no pain) to 7.5 (unbearable pain).

ƻAuthors assessed VAS on a scale that was undefined.

Abbreviations. AE=adverse event; DPQ=Dallas Pain Questionnaire; DPT=dextrose prolotherapy; h=hour; IDET=Intradiscal Electrothermal Therapy; kg=kilogram; lbs=pounds; LBP=low back pain; LDLPC=left dorso-lateral prefrontal cortex; mg=milligram; ml=milliliter; mm=millimeter; mo=month; NHS=National Health Service; NR=not reported; NRS=Numeric Rating Scale; NS=not significant; ODI=Oswestry Disability Index; RMDQ=Roland Morris Disability Questionnaire; RoB=risk of bias; ROM=range of motion; rTMS=repetitive transcranial magnetic stimulation; SD=standard deviation; SI=sacroiliac; SIJ=Sacroiliac Joint Dysfunction; VAS=Visual Analogue Scale; WDI=Waddell Disability Index; wk=week; yr=year.

Appendix Table 13. Detailed Results for All Eligible Chronic Low Back Pain Studies

Author, Year Risk of Bias	Outcome Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
Injections in L4-S1 and Sacroiliac Areas				
Dechow, 1999[100] High	Pain-related functioning or interference ODI 1, 3, 6 mo	**Dextrose Prolotherapy** Baseline: 33.99 (NR) 1 mo: 35.92 (NR) 3 mo: 36.02 (NR) 6 mo: 35.22 (NR)	**Normal Saline** Baseline: 33.06 (NR) 1 mo: 33.06 (NR) 3 mo: 33.59 (NR) 6 mo: 34.56 (NR)	**Arm 1 vs. Arm 2** 1 mo: 2.86, p=NR 3 mo: 2.43, p=NR 6 mo: 0.66, p=NR
	Physical performance Modified Schober Test 1, 3, 6 mo	**Dextrose Prolotherapy** Baseline: 4.83 (NR) 1 mo: 5.52 (4.86) 3 mo: 5.45 (5.1) 6 mo: 5.4 (4.8)	**Normal Saline** Baseline: 5.28 (NR) 1 mo: 5.49 (NR) 3 mo: 5.23 (NR) 6 mo: 5.77 (NR)	**Arm 1 vs. Arm 2** 1 mo: 0.03, p=NR 3 mo: 0.22, p=NR 6 mo: -0.37, p=NR
	Pain severity or intensity VAS† 1, 3, 6 mo	**Dextrose Prolotherapy** Baseline: 5.39 (NR) 1 mo: 5.2 (NR) 3 mo: 5.1 (NR) 6 mo: 5.19 (NR)	**Normal Saline** Baseline: 5.31 (NR) 1 mo: 4.77 (NR) 3 mo: 5.28 (NR) 6 mo: 4.47 (NR)	**Arm 1 vs. Arm 2** 1 mo: 0.43, p=NR 3 mo: -0.18, p=NR 6 mo: 0.72, p=NR
	Adverse events 6 mo	*"A few subjects reported a transient increase in back pain following the injections, but…no differences between the treatment and control groups and no other significant adverse reactions."* (AE not defined)		
Klein, 1993[101] High	Pain-related functioning or interference RMDQ 6 mo	**Dextrose Prolotherapy** Baseline: 9.36 (3.6) 6 mo: 4.04 (3.71)	**Normal Saline** Baseline: 8.25 (3.3) 6 mo: 4.38 (4.05)	**Arm 1 vs. Arm 2** 6 mo: -0.34, p=0.068
	Physical performance B-200 Triaxial Dynamometer ROM: Rotation, Flexion-Extension, Side Flexion 6 mo	**Dextrose Prolotherapy** Baseline: 81.9 (11.8) 6 mo, Rotation: 91.8 (8.6) 6 mo, Flexion-Extension: 100.5 (11.1) 6 mo, Side Flexion: 78.2 (11.4)	**Normal Saline** Baseline: 84.0 (9.9) 6 mo, Rotation: 93.8 (6.2) 6 mo, Flexion-Extension: 102.3 (11.7) 6 mo, Side Flexion: 78.1 (11.7)	**Arm 1 vs. Arm 2** 6 mo, Rotation: -2, p=NR 6 mo, Flexion-Extension: -1.80, p=NR 6 mo, Side Flexion: 0.10, p=NR
	Physical performance B-200 Triaxial Dynamometer Isometric Strength: Rotation, Flexion, Extension, Side Flexion 6 mo	**Dextrose Prolotherapy** Baseline: 68.7 (33.2) 6 mo, Rotation: 57.1 (24.1) 6 mo, Flexion: 81.6 (43.3) 6 mo, Extension: 100.7 (40.5) 6 mo, Side Flexion: 92.9 (39.0)	**Normal Saline** Baseline: 78.9 (42.1) 6 mo, Rotation: 63.7 (27.7) 6 mo, Flexion: 96.2 (49.6) 6 mo, Extension: 120.2 (53.2) 6 mo, Side Flexion: 108.5 (47.3)	**Arm 1 vs. Arm 2** 6 mo, Rotation: -6.60, p=NR 6 mo, Flexion: -14.60, p=NR 6 mo, Extension: -19.5, p=NR 6 mo, Side Flexion: -15.60, p=NR

Author, Year Risk of Bias	Outcome Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
	B-200 Triaxial Dynamometer Angular Velocity: Rotation 50% Resistance, Rotation 25% Resistance, Flexion-Extension 50% Resistance, Flexion-Extension 25% Resistance, Side Flexion 50% Resistance, Side Flexion 25% Resistance 6 mo	**Dextrose Prolotherapy** Baseline: 105.4 (33.7) 6 mo, Rotation 50%: 92.0 (28.6) 6 mo, Rotation 25%: 121.4 (34.7) 6 mo, Flexion-Extension 50%: 115.2 (34.7) 6 mo, Flexion-Extension 25%: 129.1 (39.3) 6 mo, Side Flexion 50%: 105.9 (35.5) 6 mo, Side Flexion 25%: 129.2 (41.6)	**Normal Saline** Baseline: 109.6 (31.0) 6 mo, Rotation 50%: 94.6 (26.0) 6 mo, Rotation 25%: 122.9 (26.1) 6 mo, Flexion-Extension 50%: 123.7 (32.3) 6 mo, Flexion-Extension 25%: 135.0 (35.4) 6 mo, Side Flexion 50%: 112.8 (35.2) 6 mo, Side Flexion 25%: 131.2 (38.7)	**Arm 1 vs. Arm 2** 6 mo, Rotation 50%: -2.60, p=NR 6 mo, Rotation 25%: -1.5, p=NR 6 mo, Flexion-Extension 50%: -8.5, p=NR 6 mo, Flexion-Extension 25%: -5.90, p=NR 6 mo, Side Flexion 50%: -6.90, p=NR 6 mo, Side Flexion 25%: -2, p=NR
	Pain severity or intensity VAS‡ 6 mo	**Dextrose Prolotherapy** Baseline: 4.88 (1.3) 6 mo: 2.85 (1.88)	**Normal Saline** Baseline: 4.56 (1.12) 6 mo: 2.29 (1.67)	**Arm 1 vs. Arm 2** 6 mo: 0.56, p=0.056
	Adverse events 6 mo	*"one in each group… [developed] lumbar puncture headaches…during the course of treatment, lasting approximately 3 days each before spontaneously abating without sequelae… All patients complained of varying degrees of stiffness and soreness for 1-3 days following injection, but in no case was this severe enough…to discontinue treatment."*		
Ongley, 1987[102] Some concerns	Pain-related functioning or interference Modified RMDQ/WDI¶ 1, 3, 6 mo	**Dextrose Prolotherapy** Baseline: 11.45 (NR) 1 mo: 4.00 (NR) 3 mo: 4.70 (NR) 6 mo: 3.43 (NR)	**Normal Saline** Baseline: 11.82 (NR) 1 mo: 8.37 (NR) 3 mo: 8.49 (NR) 6 mo: 8.29 (NR)	**Arm 1 vs. Arm 2** 1 mo: -4.37, p=<0.001 3 mo: -3.79, p=<0.004 6 mo: -4.86, p=<0.001
	Pain severity or intensity VAS‖ 1, 3, 6 mo	**Dextrose Prolotherapy** Baseline: 3.78 (NR) 1 mo: 2.13 (NR) 3 mo: 1.77 (NR) 6 mo: 1.50 (NR)	**Normal Saline** Baseline: 3.99 (0.19) 1 mo: 3.06 (0.29) 3 mo: 2.93 (0.25) 6 mo: 3.08 (0.28)	**Arm 1 vs. Arm 2** 1 mo: -0.93, p=<0.01 3 mo: -1.16, p=<0.001 6 mo: -1.58, p=<0.001
	Adverse events 6 mo	**Dextrose Prolotherapy** 2 with increased menstrual bleeding, 2 with post-menopausal bleeding (at 4 wk)	**Normal Saline** 1 with increased menstrual bleeding, 1 withdrew after the second day of injections due to severe headache and cough (resolved 1 wk later)	*"Patients in both groups complained of pain and stiffness for 12-24 h after each injection…[, not] severe enough to necessitate bed rest or absence from work."*
Yelland, 2004[99] High	Pain-related functioning or interference Modified RMDQ** §§ 12, 24 mo	**Dextrose Prolotherapy** Baseline: 13.7 (5.0) 12 mo: 8.0 (NR) 24 mo: 8.6 (NR)	**Normal Saline** Baseline: 14.3 (4.5) 12 mo: 9.8 (NR) 24 mo: 9.4 (NR)	**Arm 1 vs. Arm 2** 12 mo: -1.8, p=NR 24 mo: -0.8, p=NR
	Health-related quality of life SF-12 PCS††	**Dextrose Prolotherapy** Baseline: 35.2 (9.9)	**Normal Saline** Baseline: 32.1 (7.1)	**Arm 1 vs. Arm 2** 12, 24 mo: NR, p=NR

Author, Year Risk of Bias	Outcome Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
	12, 24 mo	12, 24 mo: NR	12, 24 mo: NR	
	Health-related quality of life SF-12 MCS[††] 12, 24 mo	**Dextrose Prolotherapy** Baseline: 47.6 (12.7) 12, 24 mo: NR	**Normal Saline** Baseline: 49.6 (12.4) 12, 24 mo: NR	**Arm 1 vs. Arm 2** 12, 24 mo: NR, p=NR
	Pain severity or intensity VAS[‡‡] [§§] 12, 24 mo	**Dextrose Prolotherapy** Baseline: 51.9 (19.3) 12 mo: 33.21 (NR) 24 mo: 32.83 (NR)	**Normal Saline** Baseline: 55.0 (20.7) 12 mo: 36.79 (NR) 24 mo: 37.17 (NR)	**Arm 1 vs. Arm 2** 12 mo: -3.58, p=NR 24 mo: -4.34, p=NR
	Adverse events 24 mo	*"Incidence of potential adverse effects did not differ between groups."* (Range of potential AE were described for total participants but proportion by arm NR and no separation by severity; potential AE included increased pain in back or legs, nausea or diarrhea, headaches, etc.)		
Non-specific Low Back Pain: Intradiscal or Facet Joint Injections				
Yildirim, 2021[105] Moderate	Pain-related functioning or interference ODI 3 mo	**Dextrose Prolotherapy** Baseline: 55.93 (10.74) 3 mo: 39.13 (8.11)	**Steroid Injectable** Baseline: 56.59 (10.47) 3 mo: 32.85 (7.50)	**Arm 1 vs. Arm 2** 3 mo: 6.28, p=0.000
	Pain severity or intensity VAS[¶¶] 1, 15 day, 3 mo	**Dextrose Prolotherapy** Baseline: 7.57 (0.98) 1 day: 3.48 (1.06) 15 day: 2.80 (0.85) 3 mo: 3.11 (1.02)	**Steroid Injectable** Baseline: 8.45 (0.69) 1 day: 1.67 (0.88) 15 day: 3.02 (1.45) 3 mo: 5.38 (1.99)	**Arm 1 vs. Arm 2** 1 day: 1.81, p=0.000 15 day: -0.22, p=0.225 3 mo: -2.27, p=0.000
Sacroiliac Joint Dysfunction (focal)				
Kim, 2010[107] Some concerns	Pain-related functioning or interference ODI 2 wk	**Dextrose Prolotherapy** Baseline: 33.9 (15.5) 2 wk: 11.1 (10.0)	**Steroid Injectable** Baseline: 35.7 (20.4) 2 wk: 15.5 (10.7)	**Arm 1 vs. Arm 2** 2 wk: -4.40, p=NR
	Pain severity or intensity NRS 2 wk	**Dextrose Prolotherapy** Baseline: 6.3 (NR) 2 wk: 1.4 (1.1)	**Steroid Injectable** Baseline: 6.7 () 2 wk: 1.9 (0.9)	**Arm 1 vs. Arm 2** 2 wk: -0.50, p=NR
Raissi, 2022[106] Some concerns	Pain-related Functioning DPQ 2, 8 wk	**Dextrose Prolotherapy** Baseline: 217.89 (72.87) 2 wk: 182.94 (84.62) 8 wk: 195.83 (47.41)	**Steroid Injectable** Baseline: 208.56 (70.69) 2 wk: 165.54 (62.12) 8 wk: 158.83 (78.81)	**Arm 1 vs. Arm 2** 2 wk: 17.40, p=NR 8 wk: 37.00, p=NR
	Pain severity or intensity	**Dextrose Prolotherapy**	**Steroid Injectable**	**Arm 1 vs. Arm 2**

Author, Year Risk of Bias	Outcome Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
	VAS† 2, 8 wk, 9 mo	Baseline: 8.17 (1.54) 2 wk: 4.50 (2.12) 8 wk: 4.11 (1.45) 9 mo: 2.67 (1.24)	Baseline: 7.76 (1.70) 2 wk: 3.71 (2.12) 8 wk: 4.48 (2.60) 9 mo: 2.62 (1.63)	2 wk: 0.79, p=NR 8 wk: -0.37, p=NR 9 mo: 0.05, p=NR

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

†Authors assessed VAS on a scale of 0 (no pain) to 10 (unbearable pain).

‡Authors assessed VAS on a scale of 0 (no pain) to 8 (unbearable pain).

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

‖Authors assessed VAS on a scale of 0 (no pain) to 7.5 (unbearable pain).

**23 items from modified RMDQ. Study reported mean (SE) change scores.

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

‡‡Authors assessed VAS on a scale of 0 (no pain) to 100 (unbearable pain).

¶¶Authors assessed VAS on a scale that was undefined.

§§Authors reported VAS and modified RMDQ scores graphically. Review team extracted results using Plot Digitizer.

Abbreviations. DPQ=Dallas Pain Questionnaire; MCS=Mental Component Summary; mo=month; NR=not reported; NS=not significant; NRS=Numeric Rating Scale; ODI=Oswestry Disability Index; PCS=Physical Component Summary; RMDQ=Roland Morris Disability Questionnaire; ROM=range of motion; SD=standard deviation; VAS=Visual Analogue Scale; WDI=Waddell Disability Index; wk=week.

APPENDIX K. TEMPOROMANDIBULAR JOINT (TMJ) DISORDERS

Appendix Table 14. Detailed Study Characteristics for All Eligible TMJ Studies

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported**
Normal or Restricted Mobility				
Elwerfelli, 2019[108] NR Serious 6 Weeks Egypt (1) NR	**Inclusion:** Clinical signs and symptoms of TMJ internal derangement; diagnosed based on clinical data and MRI findings; failed prior conservative, non-surgical treatment (*eg,* NSAIDs, soft diet, moist heat, habit modification, and occlusal splint ≥4 wk); TMJ pain with one of the following criteria: joint noises, limited mouth opening (<35 mm), impeded lateral movement, deviation toward the affected side of the opening and protrusion movements **Exclusion:** Previous TMJ surgical intervention; previous joint fractures; TMJ ankyloses; current chemotherapy or radiotherapy; compromising conditions (*eg*, osteoporosis, organ transplantation); systemic immunological destruction disease (*eg,* osteoarthritis); receiving anticoagulation treatment or aspirin within 48 hours; corticosteroid injection; uncontrolled diabetes millets; TMJ infection	**Dextrose prolotherapy:** *N*=7 Age, mean (SD): NR % Female NR Clinic or health care facility Single injection Arthrocentesis with normal saline followed by 2 mL 50% dextrose into superior joint space. First entry mark was 10 mm from the tragus and the second mark was 2 mm below. Used 20-G needle to inject 2 mL saline at first point, then another 20-G at the second point to establish a free flow through the joint space. Both needles inserted about 1.5 cm deep. 50 mL total of normal saline solution was used to lavage. Other treatments: Postoperative instructions included soft diet and home physiotherapy (*eg*, moist heat and ROM exercises every 6 hr daily). Prescribed medication: 250 mg Amoxicillin and 250	**Saline/Local anesthetic:** *N*=7 Age, mean (SD): NR % Female NR Clinic or health care facility Single injection Arthrocentesis with 2 mL normal saline alone; procedure as described for Arm 1 Other treatments: Same as Arm 1	**Primary outcome NR** **Physical performance (1 day; 1, 2, 3, 4, 5, 6 wk)** • MMO **Adverse events** **Other outcomes:** • Pain severity or intensity

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported**
		mg Flucloxacillin (Flumox 500 mg) and paracetamol 665 mg to be taken every 8 hr/day for 1 wk.		
Fouda, 2018[109] NR High 3 Months Egypt (1) NR	**Inclusion:** Unilateral symptoms of pain; clicking sounds; normal range of mouth opening; MRI showed displacement of the disc with reduction **Exclusion:** History of previous operations in TMJ region; bilateral symptoms; coexisting conditions (*eg,* rheumatic disease or neurological disorders); physiotherapy within the previous 3 mo; coagulation or bleeding problems; treatment with radiotherapy, chemotherapy, or anticoagulants	**Dextrose prolotherapy:** *N*=18 Age, mean (SD): NR % Female NR Clinic or health care facility 4 injections, each 1 wk apart 22% dextrose + 0.2% mepivacaine into outer capsule. 25% hypertonic dextrose solution 1.5 mL mixed with 2% mepivacaine hydrochloride plus 1:20000 levonordefrin 0.2 mL using 22-G needle. Arm 1 received intra-articular injection into outer capsule through the midpoint of the condylar head with the patient's mouth wide open so that the solution was given subcutaneously. Other treatments: None reported	**Dextrose prolotherapy:** *N*=18 Age, mean (SD): NR % Female NR Clinic or health care facility 4 injections, each 1 wk apart Injection solution same as Arm 1. Arm 2 received intra-articular injection into superior joint space after the condylar head had been palpated with the patient's mouth closed and the upper surface of the condylar head marked. The needle was introduced from the bottom upwards until it touched the upper bony surface of the glenoid fossa, and then the solution was injected. Other treatments: None reported **Dextrose prolotherapy:** *N*=18 Age, mean (SD): NR % Female NR	**Benefits of treatment:** internal derangement and pain **Physical performance (2 wk, 3 mo)** • MMO **Adverse events** **Other outcomes**: • Pain severity or intensity

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported**
			Clinic or health care facility 4 injections, each 1 wk apart Injection solution same as Arm 1. Arm 3 received intra-articular injection into inferior joint space after the condylar head had been palpated and the upper surface marked with the patient's mouth closed. The needle was introduced from the top downwards until it touched the upper bony surface of the condylar head, after which the solution was injected. Other treatments: None reported **Dextrose prolotherapy:** *N*=18 Age, mean (SD): NR % Female NR Clinic or health care facility 4 injections, each 1 wk apart Injection solution same as Arm 1. Arm 4 received intra-articular injection into retrodiscal tissues through the space left behind the condylar head between the tragus of the ear and the	

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported**
			posterior surface of the condylar head with the patient's mouth wide open. Other treatments: None reported	
Haggag, 2022[110] NR High 6 Months Egypt (1) None	**Inclusion:** Disc displacement with reduction; DDWR with arthralgia (joint pain); limited unassisted mouth opening; failed prior conservative therapies; absence of any medical condition that could interfere with healing. **Exclusion:** Persistent pain in any other anatomical site greater than that in the TMJ area; long-term intake of NSAIDs or corticosteroids; active rheumatoid conditions; active infection or malignancy in TMJ area; any previous injection or operation in the TMJ region.	**Dextrose prolotherapy**: *N*=15 Age, mean (SD): 22.7 (NR) 100% Female Clinic or health care facility Max 4 injections, each 1 wk apart Bilateral auriculotemporal nerve block using 0.5 mL of 4% articaine with 1:100,000 epinephrine followed by 2 injections: one in the superior joint space and the other in the retrodiscal tissue. First injection: mouth was kept widely open and the skin over the affected joint was penetrated with the injection needle 10 mm anterior to the tragus of the ear and 2 mm below the trago-canthal line. Needle was directed anteromedially until it contacted the medial wall of the glenoid fossa. After negative aspiration, 1 mL of 25% dextrose was injected. For retrodiscal tissue injection: mouth was opened about 10 mm and the injection needle was inserted just anterior to the tragus of the ear and directed anteromedially to a depth of 20 mm. After	**Saline/Local anesthetic:** *N*=15 Age, mean (SD): 23.9 (NR) 100% Female Clinic or health care facility Max 4 injections, each 1 wk apart Intra-articular injections of normal saline solution in each joint, following same procedure as Arm 1. Other treatments: Same as Arm 1	To assess the efficacy of dextrose prolotherapy on the clinical signs and symptoms of patients having DDWR **Physical performance (3, 6 mo)** • MMO **Other outcomes:** • Pain severity or intensity

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported**
		negative aspiration, 1 mL of 25% dextrose solution was injected. Other treatments: For postoperative pain, patients were instructed to take an analgesic such as paracetamol. All patients were discouraged to use any oral devices or to have any dental work for malocclusion during the 6-mo period of follow up.		
Hassanien, 2020[111] NR High 8 Weeks Egypt (1) NR	**Inclusion:** TMJ pain; sounds during mandibular movements (clicking, popping); functional disability; age range 16-40 yr old. **Exclusion:** Taking corticosteroids; previous treatment of TMJ pain (*eg*, occlusal splints); pregnancy; medical conditions that interfere with treatment, such as cardiac diseases and patients on pace makers.	**Dextrose prolotherapy:** *N*=10 Age, mean (SD): NR % Female NR Clinic or health care facility 3 injections at 2 wk intervals (*ie*, baseline, 2 wk, and 4 wk) 3 mL 12.5% dextrose + 0.5% lidocaine into posterior joint space then anterior disc attachment. Posterior joint space injection: palpated as the depression forms immediately anterior to the tragus of the ear as the condyle moves forward and down when the patient opened the mouth. Then, a bite block was placed. The needle was directed medially and slightly anteriorly and penetrated to nearly its full length before encountering the medial wall of the fossa. Following aspiration, 1 mL of prolotherapy solution	**Other non-injectable:** *N*=10 Age, mean (SD): NR % Female NR Clinic or health care facility 3x/wk for 4 consecutive wk Each joint received active application of low level laser therapy using Ga-Al-As diode laser. The anatomic landmarks were located by asking the patient to open widely to allow drawing of the articular fossa and then to close lightly on the posterior teeth to draw the condyle within the glenoid fossa. The therapeutic LLLT (wavelength of 980 nanometers, output power of 0.2 Watt, total energy of 12 J and exposure time 60 seconds) application was achieved using a laser beam delivered through a handheld single laser probe on the	**Pain severity at rest (VAS)** **Physical performance (2, 4 wk)** • MMO **Other outcomes:** • Pain severity or intensity

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes Measurement tool(s) (Time points)** **Other Outcomes Reported**
		was deposited. Anterior disc attachment: palpated as the slight depression just anterior to the condyle when the mouth is closed. The bite block is removed and the patient is instructed to close gently. Then, the needle is directed medially and slightly anteriorly to its full length. Following aspiration, another 1 mL of prolotherapy solution was injected here. Other treatments: Restriction from NSAIDs 1-2 days before treatment and 10-14 days after treatment. After the injection, the patients were cautioned against taking anti-inflammatory agents to relieve the discomfort.	affected TMJ; anterior, superior, posterior and lateral to the condyle. The laser beam was continuously delivered from the tip of the laser applicator to the target surfaces. Other treatments: None reported	
Louw, 2019[112] NCT01706172 Some concerns 3 Months Canada (1) NR	**Inclusion:** Adults aged 19-80 yr with moderately severe and chronic (>3 mo) pain and jaw dysfunction, indicated by NRS score ≥6. Dysfunction was defined as "difficulty chewing, jaw fatigue with eating, tension in jaw, or grinding of teeth." **Exclusion:** Allergy to lidocaine, dental problems, or sinus pathology potentially contributing to pain; pain in any other anatomical site persistently greater than that in the TMJ area; long-term intake of NSAIDs or corticosteroids; active rheumatological conditions.	**Dextrose prolotherapy:** *N*=22 Age, mean (SD): 44 (14.1) 73% Female Clinic or health care facility 3 injections, each 1 mo apart 20% dextrose + 0.2% lidocaine. Closed-mouth approach with the jaw relaxed. The point of needle entry was 1 cm below the apex of the zygomatic arch, with a 45° cranial and 10° posterior angulation measured using a 1-in 30-G needle	**Saline/Local anesthetic:** *N*=20 Age, mean (SD): 50 (13.4) 96% Female Clinic or health care facility 3 injections, each 1 mo apart 0.2% lidocaine, using same technique as Arm 1 Other treatments: Same as Arm 1	**Pain intensity and severity of jaw dysfunction as assessed by NRS** **Pain-related functioning (3 mo)** • NRS-Dysfunction **Physical performance (3 mo)** • MMO **Other outcomes:** • Pain severity or intensity

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported**
		Other treatments: Patients were advised to use acetaminophen or NSAIDs as well as local application of ice for postprocedure pain.		
Mahmoud, 2018[113] NR High 13 Months Egypt (1) NR	**Inclusion:** Internal derangement, age range 20-50 yr **Exclusion:** Haematologic disorders (platelet function disorders & anticoagulation therapy); renal and/or hepatic insufficiency; prosthetic joint replacement; allergic to any components of the injectable solution.	**Dextrose prolotherapy**: *N*=15 Age, mean (SD): NR 60% Female Clinic or health care facility 3 injections (2 wk apart), as reported in abstract and beginning of methods 25% dextrose + 2% lidocaine into a 3-mL syringe for each TMJ into posterior joint space, then anterior disc attachment, and finally the attachment of masseter muscle. Patients were asked to open their mouth and a needle was inserted 10 mm in front of tragus and 2 mm below lateral cantho-tragal line. Posterior joint space: palpated as the depth of the depression that forms immediately anterior to tragus of ear as the condyle translates forward and down. Then, a bite block was placed. The needle was directed medially and slightly anteriorly and penetrated to nearly its full length before encountering medial wall of the fossa. Following aspiration, 1 mL of prolotherapy solution is deposited. Anterior disc attachment: palpated as the slight depression just anterior to condyle	**HA:** *N*=15 Age, mean (SD): NR 66.7% Female Clinic or health care facility 1 injection Arthrocentesis followed by hyaluronic acid injected intra-articularly Other treatments: None reported **Other injectable:** *N*=15 Age, mean (SD): NR 60% Female Clinic or health care facility Single injection 1 mL of platelet rich plasma was injected intra-articular.	**Primary outcome NR** **Physical performance (1, 3, 6, 12 mo)** • MMO **Other outcomes:** • Pain severity or intensity

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported**
		when mouth is closed. The bite block was removed and the patient was instructed to close gently. Then, needle was directed medially and angulated slightly anteriorly to, or nearly to, its full one-inch length. Following aspiration, another 1mL of prolotherapy solution was injected here. Masseter attachment: palpated along inferior border of zygomatic arch while patient clenched teeth. Then, the patient was told to relax jaw and the final 1 mL was injected, again at or near the full one-inch length of the needle. If the opposite joint is affected, the same procedure is repeated on opposite joint. Other treatments: None reported	Other treatments: None reported	
Priyadarshini, 2021[114] NR High 1 Yr India (1) NR	**Inclusion:** Internal derangement of the TMJ confirmed by MRI; Healthy patients with Wilkes stage II and III TMJ internal derangement; aged range 18-50 yr. **Exclusion:** History of previous TMJ surgery; allergy to corn products.	**Dextrose prolotherapy:** *N*=17 Age, mean (SD): 31.76 (NR) 58.8% Female Clinic or health care facility 4 injections over 3 mo 50% dextrose (0.75 mL) + 2% lignocaine with adrenaline (1.5 mL) and bacteriostatic water (0.75 mL) drawn into a 5 mL syringe and mixed prior to injection using a 26-G needle. The patient was positioned semi-supine. Prolotherapy solution was injected at three target sites:	**Other non-injectable:** *N*=17 Age, mean (SD): 28.35 (NR) 70.6% Female Home 12 hr/day for up to 3 mo Anterior bite planes, which produced a posterior open bite of 2 mm. Other treatments: None reported	**Primary outcome NR** **Physical performance (1, 3, 6, 12 mo)** • MMO **Other outcomes:** • Pain severity or intensity

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported**
		1) Posterior joint space: palpated as the depression formed anterior to the tragus of the ear following wide mouth opening, and a bite block was placed in the posterior interocclusal space. The needle was directed medially and slightly anteriorly to avoid penetration of the ear and deposited 1 mL of prolotherapy solution. 2) Anterior disc attachment to the lateral pterygoid muscle: palpated as the depression felt anterior to the condyle after closing the mouth. The needle injected another 1 mL of prolotherapy solution. 3) Masseter attachment: Palpated along the inferior border of the zygomatic arch. Last 1 mL of prolotherapy solution was injected into the most tender area. Other treatments: Soft diet and tablet paracetamol (500 mg) 2x/day for 2 days following injection.		
Zarate, 2020[115] NCT01617356 Low 3 Months Argentina (1) Self financed by the authors	**Inclusion:** Adults age 19–80 yr; ≥3 mo of symptoms meeting RDC/TMD criteria; met baseline jaw pain and dysfunction severity criteria defined by NRS ≥6. Eligibility was “per TMJ;” both TMJs could be treated if both met criteria. **Exclusion:** Other painful dental problems; previous injections of any type for treatment of TMD symptoms; symptomatic sinus pathology; other	**Dextrose prolotherapy:** *N*=15 Age, mean (SD): 44.9 (15.1) 87% Female Pain duration (mo) in past yr (SD): 5.3 (4.6) Clinic or health care facility 3 injections, each 1 mo apart	**Saline/Local anesthetic:** *N*=14 Age, mean (SD): 50.1 (18.0) 86% Female Pain duration (mo) in past yr (SD): 6.8 (7.2) Clinic or health care facility 3 injections, each 1 mo apart	**Pain intensity and jaw dysfunction by NRS (0-10)** **Pain-related functioning (3 mo)** • NRS (dysfunction) **Physical performance (3 mo)** • MMO **Adverse events** **Other outcomes:**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes Measurement tool(s) (Time points)** **Other Outcomes Reported**
	pain greater than TMD-associated facial pain; active rheumatologic conditions; ongoing use of NSAIDs or corticosteroids.	20% dextrose + 0.2% lidocaine. Relaxed, closed-mouth approach. The injector's index finger was placed in the depression under the zygomatic arch, against the zygoma, and a curved line was drawn approximating the bottom of the arch. The posterior location of the mandible was confirmed by mouth opening and closing, with the head of the mandible passing anteriorly underneath the injector's finger and then resuming its posterior position. 27-G needle entry was 1 cm below the apex of the zygomatic arch with slight (<15°) posterior angulation and 45° of cephalad angulation. Injection of 1 mL was at ~25mm depth. Other treatments: Instructed to avoid NSAIDs; advised to use acetaminophen as needed and follow routine post-injection precautions. Other types of TMD care were discouraged. Participants who had oral devices at baseline were allowed to continue their use.	0.2% lidocaine in sterile water, same injection procedure as Arm 1 Other treatments: Same as Arm 1	• Pain severity or intensity
Hypermobility				
Arafat, 2019[116] NR High 7 Months	**Inclusion**: Diagnosis of subluxation (hypermobility) based on clinical finding of excessive abnormal excursion of the condyle associated with pain and sound and radiographic imaging (tomogram) showing presence of condyles anterior to the	**Dextrose prolotherapy**: *N*=15 Age, mean (SD): NR % Female NR Clinic or health care facility	**ABI/ACS**: *N*=15 Age, mean (SD): NR % Female NR Clinic or health care facility	**Primary outcome NR** **Physical performance (2 wk; 3, 6 mo)** • MMO **Adverse events**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported**
Egypt (1) NR	articular eminence in the open-mouth position. **Exclusion**: Drug-induced hypermobility; previous treatment (either conservative or surgical) on the TMJ; any medical condition that could interfere with the treatment.	2-3 injections 2 wk apart 6.7% dextrose + 0.67% mepivacaine. First injection point was placed 1 cm in front of the mid-tragus 2 mm below the canthal-tragus line. The second point was placed 1 cm below the first one. Used 18-G needle to inject dextrose solution 3 mL (10% dextrose 2 mL and 2% mepivacaine with 1:20,000 levonordefrin1 mL). The needle was inserted at the first point in an antero-superior direction to the glenoid fossa where the capsule was attached, and 0.7 mL of the solution was injected. The needle was then directed downwards and medially to the superior joint space, and 1 mL was injected. Then, the needle was removed and reinserted at the second point where the capsule was attached to the condylar neck, and 0.7 mL of the solution was injected. Finally, the needle was then directed superficial to the capsule of the TMJ, and the remaining 0.6 mL of the solution was injected with withdrawal of the needle. The same procedure was performed on the contralateral TMJ. Other treatments: Applied an elastic bandage around the patient's head for 2 wk. Patients were instructed to restrict the mouth opening and to eat soft food for 2 wk. NSAIDs were prescribed during the first postoperative wk.	1-2 injections (2 wk apart) Autologous blood injection: The point of the articular fossa was found on this line, 10mm anterior to the tragus of the ear and 2mm inferior to the line. At this point, an 18-G needle was inserted at this site into the superior joint space. 3 mL of blood was withdrawn from the patient's anticubital fossa; 2 mL of blood was injected into the superior joint space and 1 mL was injected into the outer surface of the TMJ capsule. The same procedure was performed on the contralateral TMJ. Other treatments: Same as Arm 1	**Other outcomes:** • Pain severity or intensity
Bhargava, 2023[117]	**Inclusion**:	**Dextrose prolotherapy**: *N*=30	**ABI/ACS**: *N*=30	**Primary outcome NR**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported**
NR High 1 Yr India (1) Self-funded project by the investigators through TMJ Consultancy Services, Bhopal, Madhya Pradesh, India.	Age >15 yr; history of symptomatic chronic joint sub-luxation, confirmed with clinical evaluation and imaging study. **Exclusion**: Noncompliance for follow-up, up to one yr post-operatively; previous conservative/surgical management to TMJ; history of psychiatric disorders; connective tissue disorders; known systemic disease; long-term use of steroids or NSAIDs.	Age, mean (SD): NR 53% Female Clinic or health care facility Every 6 wk as needed 8% dextrose + bupivacaine, 3 mL per joint. Patient positioned so back and neck were at 45°. Auriculotemporal nerve block was administered using 1.5 mL of local anesthetic (Lignocaine HCl with 1:2,00,000 Adrenaline), then used 26-G needle to inject 1 mL heavy bupivacaine-dextrose solution into the joint space posterior to the mandibular condyle. The same needle was redirected after a latency period of 300–420 s to the superior joint space. A 24-G needle was inserted into the superior joint cavity, 20 mm anterior to tragus and 10 mm inferior to cantho-tragal line followed by lavage using 50–100 mL normal saline from the inflow needle to confirm the needle location and wash out the inflammatory mediators. The outflow or the second needle was removed after the lavage. Other treatments: Patients were instructed to minimize mandibular function post-operatively for 10-14 days and to	Age, mean (SD): NR 40% Female Clinic or health care facility Every 6 wk as needed Patient positioned so back and neck were at 45°. Auriculotemporal nerve block was administered using 1.5 mL of local anesthetic (Lignocaine HCl with 1:2,00,000 Adrenaline), then followed People's University protocol for ABI in chronic recurrent TMJ sub-luxation. 3 mL of whole autologous blood was drawn from the anti-cubital fossa, 1 mL of the blood was deposited in the superior joint space via inflow needle, 2 mL in the peri-capsular and retro-discal region followed by placement of a pressure dressing. Other treatments: Same as Arm 1	**Physical performance (6, 12 mo)** • MMO **Adverse events** **Other outcomes:** • Pain severity or intensity

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported**
		consume soft diet and small morsels of food with limited mouth opening. Prescribed Ultracet (Tramadol + Paracetamol) tablet for the pain management and Cefixime (200 mg) tablet 2x/day for 5 days. Instructed to avoid NSAIDs.		
Chhapane, 2023[118] Clinical Trials Registry of India: CTRI/2020/10/028382 High 1 Yr India (1) NR	**Inclusion**: Age ≥18 yr; multiple episodes of TMJ dislocation (uni- or bilateral); position of the condyle with relation to the articular eminence on wide mouth opening was assessed by radiography (Orthopantomogram) and a transpharyngeal TMJ view (in open and closed mouth positions). Signs and symptoms associated TMJ dislocation such as the presence of clicking sounds, crepitus, hypermobility, increased mouth opening, and level of pre-auricular pain were also recorded, but were not strict criteria for inclusion. **Exclusion**: Connective tissue syndromes; psychological abnormalities; bleeding disorders; pregnancy; allergy to anesthetics.	**Dextrose prolotherapy**: *N*=16 Age, mean (SD): NR % Female NR Clinic or health care facility Single injection 50% dextrose after lignocaine with adrenaline. Auriculotemporal nerve block by local infiltration of lignocaine with 1:200000 adrenaline. Located articular fossa 10 mm anterior to the tragus of the ear and 2 mm inferior to the cantho-tragal line. Inserted 18-G needle into the superior joint space. Lavaged with Ringer's lactate, then injected 2 mL of 50% dextrose into the upper joint space and 1 mL aroumd the pericapsular tissues. Other treatments: Rehab exercises to gradually control range of mouth opening were initiated after 2 wk. Patients were	**Other injectable**: *N*=16 Age, mean (SD): NR % Female NR Clinic or health care facility Single injection 3 mL of autologous blood was withdrawn from the patient's cubital fossa, 2 mL was injected into the upper joint space and 1 mL was injected into the pericapsular tissues. Same injection procedure as Arm 1. Other treatments: Same as Arm 1	**Primary outcome NR** **Physical performance (1, 2 wk; 1, 3, 6, 12 mo)** • MMO **Other outcomes:** • Pain severity or intensity

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported**
		advised to perform these exercises in front of the mirror for a more fine-tuned control and to ensure the correctness of the technique.		
Comert Kilic, 2016[119] NR High 12 Months Turkey (1) None	**Inclusion**: Hypermobility diagnosed with clinical and CBCT evaluations; complaints of joint sounds, open-locking, and facial pain; age >16 yr; completion of study protocol; adequate existing clinical and CBCT data at baseline and follow-up. **Exclusion**: Haematological or neurological disorder; inflammatory or connective tissue disease; malignant disease in the head and neck region; degenerative TMJ; previous TMJ treatment or craniofacial surgery; existing parafunctional habits; inadequate existing data at baseline or follow-up.	**Dextrose prolotherapy**: *N*=15 Age, mean (SD): 32.36 (13.45) 71% Female Clinic or health care facility 3 injections, each 1 mo apart 1 mL injections of 12% dextrose solution in each of the 5 injection areas. Solution consisted of 2 mL 30% dextrose, 2 mL saline, and 1 mL 2% articaine or mepivacaine. Injected in the following order: posterior disk attachment, superior joint space, superior and inferior capsular attachments, and stylomandibular ligament. Other treatments: Patients instructed to take muscle relaxant and analgesic (paracetamol) drugs after the injections. Wide mouth opening was prohibited during the treatment and follow-up period.	**Saline/Local anesthetic**: *N*=15 Age, mean (SD): 29.0 (9.24) 75% Female Clinic or health care facility 3 injections, each 1 mo apart 1 mL injections of placebo solution in each of the five injection areas. Solution consisted of 4 mL saline and 1 mL 2% articaine or mepivacaine. Same injection sites and order as Arm 1. Other treatments: Same as Arm 1	**Primary outcome NR** **Physical performance (12 mo)** • MMO **Adverse events** **Other outcomes:** • Pain severity or intensity
Mustafa, 2018[120] NR	**Inclusion** Painful subluxation or dislocation of the TMJ; history of open locking; complaints of joint sounds and facial	**Dextrose prolotherapy**: *N*=10 Age, mean (SD): 23.6 (7.32)	**Dextrose prolotherapy**: *N*=10 Age, mean (SD): 27.1 (7.67)	**Primary outcome NR** **Physical performance (1, 2, 3, 4 mo)**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes Measurement tool(s) (Time points)** **Other Outcomes Reported**
High 4 Months Turkey (1) NR	pain. Diagnosis of TMJ hypermobility based on the patient's history and the clinical recognition of an excessive abnormal excursion of the condyle. **Exclusion**: Presence of medical conditions that may interfere with healing process; neurological disorders; allergy to anesthetic or proliferant solutions.	70% Female Clinic or health care facility 4 injections, each 1 mo apart 1.5 mL 10% dextrose with 1.5 mL 1% lidocaine injected into 4 areas: 1) Posterior disc attachment: patient opened mouth about 10mm and 30-G needle inserted just anterior to the tragus of the ear and directed anteromedially to a depth of 20 mm, where 1mL of solution deposited. 2) Superior joint space: patient opened mouth wide and needle inserted about 10 mm anterior to the tragus of the ear and 2mm below the tragocanthal line, then directed anteromedially to contact with medial wall of glenoid fossa where 1mL of solution was deposited. 3) Superior capsular attachment: 0.5 mL of solution was applied to the lateral margin of the glenoid fossa. 4) Inferior capsular attachment: 0.5 mL of solution was applied to the condylar neck. Other treatments: All patients were instructed to take a paracetamol in case of additional pain without any NSAID. Patients were also instructed to avoid wide mouth opening during the treatment period.	88.9% Female Clinic or health care facility 4 injections, each 1 mo apart 1.5 mL 20% dextrose with 1.5 mL 1% lidocaine. Same injection technique as Arm 1. Other treatments: Same as Arm 1 **Dextrose prolotherapy**: *N*=10 Age, mean (SD): 24.5 (4.21) 66.7% Female Clinic or health care facility 4 injections, each 1 mo apart 1.5 mL 30% dextrose with 1.5 mL 1% lidocaine. Same injection technique as Arm 1. Other treatments: Same as Arm 1 **Saline/Local anesthetic**: *N*=10	• MMO **Other outcomes:** • Pain severity or intensity

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported**
			Age, mean (SD): 25.3 (7.43) 55.6% Female Clinic or health care facility 4 injections, each 1 mo apart 3 mL 1% lidocaine solution (1.5 mL 0.9% saline and 1.5 mL of 2% lidocaine HCl). Same injection technique as Arm 1. Other treatments: Same as Arm 1	
Pandey, 2022[121] NR Serious 6 Months India (1) None	**Inclusion**: Bilateral chronic recurrent TMJ dislocations with MMO >40 mm; recurrent dislocation of TMJ >2x/wk; pain and sounds in joints; age 18-60 yr. **Exclusion**: Any previous invasive procedures on TMJ.	**Dextrose prolotherapy**: *N*=10 Age, mean (SD): 34.1 (10.5) % Female NR Clinic or health care facility Single injection 25% dextrose into upper joint space (2 mL) and around capsule 1 mL). External auditory meatus was blocked with cotton soaked in Neosporin ointment, and auriculo-temporal nerve block was given (1:200,000 LA with Adrenaline). Inserted 18-G needle into superior joint space after drawing a cantho-tragal line and marking	**ABI/ACS**: *N*=10 Age, mean (SD): 34.8 (7.7) % Female NR Clinic or health care facility Single injection 3 mL of autologous blood was withdrawn from the patient's anticubital fossa, out of which 2 mL was injected into the upper joint space and 1 mL was injected around the capsule (pericapsular tissues). This procedure was then repeated on the opposite side	**Primary outcome NR** **Physical performance (1, 2 wk; 1, 3, 6 mo)** • MMO **Other outcomes:** • Pain severity or intensity

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported**
		a point 10 mm anterior to tragus and 2 mm below the cantho-tragal line and injected 2 mL, then injected 1 mL around the capsule (pericapsular tissues). The same procedures were repeated on the opposite joint. Other treatments: Placed bandage for the first wk and patients were instructed to avoid wide mouth opening. All patients were advised to follow a soft diet for 2 wk. Antibiotics (Tab Amoxicillin) and non-steroidal anti-inflammatory drugs were prescribed for 5 days.	in the same manner. Same injection procedure as Arm 1. Other treatments: Same as Arm 1	
Refai, 2011[122] NR High 7.5 Months Egypt (1) NR	**Inclusion**: Bilateral TMJ symptomatic hypermobility; diagnosis of painful subluxation or dislocation of the TMJ; willingness to follow instructions. **Exclusion**: Medical conditions that may significantly interfere with healing.	**Dextrose prolotherapy**: *N*=6 Age, mean (SD): 23.0 (NR) 100% Female Clinic or health care facility 4 injections, each 6 wk apart 6.7% dextrose + 0.7 mepivacaine (2 mL of 10% dextrose and 1 mL of 2% mepivacaine). Patient opened mouth wide to allow drawing of the articular fossa and then to close lightly on the posterior teeth to draw the condyle within the glenoid fossa. Typically, each joint had 3 injection sites. Superior capsular attachment on the lateral margin of the glenoid fossa, where 0.8 mL was injected. Inferior	**Saline/Local anesthetic**: *N*=6 Age, mean (SD): 29.8 (NR) 66.7% Female Clinic or health care facility 4 injections, each 6 wk apart 0.67% mepivacaine (2 mL of saline solution and 1 mL of 2% mepivacaine). Same injection technique as Arm 1. Other treatments: Same as Arm 1	**Primary outcome NR** **Physical performance (6, 12, 18 wk; 7.5 mo)** • MMO **Adverse events**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes Measurement tool(s) (Time points)** **Other Outcomes Reported**
		capsular attachment on the condylar neck, where 0.8 mL was injected. The needle was then directed superficial to the TMJ capsule, and 0.4 mL was injected. Superior joint space was approached with the needle directed superiorly and anteriorly toward the apex of the fossa, where contact was made with the periosteum and 1 mL was injected. Other treatments: Post-injection, patients were instructed to reduce or stop other pain medications and therapies as much as the pain would allow and to follow a soft diet for 2 wk.		
Saadat, 2018[123] NR High 6 Months Egypt (1) NR	**Inclusion**: Age 20-40 yr; recurrent dislocation of TMJ more >2 times in the last mo. **Exclusion**: Neurological conditions; parafunctional habits; allergy to lidocaine and dextrose; Ehler Danlos syndrome; use of anticoagulant drugs.	**Dextrose prolotherapy**: *N*=8 Age, mean (SD): 29.1 (NR) 62.5% Female Clinic or health care facility Single injection 25% dextrose in retrodiscal tissue. Drew line from the tragus of the ear to the outer canthus of the eye and marked first point 10 mm anterior to the tragus of the ear along the tragocanthal line and then marked a second point 10 mm inferior to the first point on line perpendicular to the tragocanthal line. Auriculotemporal nerve block was achieved using 2 mL of 2%	**Dextrose prolotherapy**: *N*=8 Age, mean (SD): 29.5 (NR) 75% Female Clinic or health care facility Single injection 25% dextrose injected into the superior joint space. Auriculotemporal nerve block was achieved using 2 mL of 2% lidocaine. Asked patient to close anterior teeth on bite block to gain access to the superior joint space. Marked injection site between tragus of ear and posterior aspect of condyle and directed needle superiorly and anteriorly	**Primary outcome NR** **Physical performance (2 wk; 1, 3, 6 mo)** • MMO **Other outcomes:** • Pain severity or intensity

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics and clinical information** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments**	**Primary Outcome** **Prioritized Outcomes** **Measurement tool(s) (Time points)** **Other Outcomes Reported**
		lidocaine. Then injected 2 mL of 25% dextrose prolotherapy solution. The needle was directed to the surface of the condylar neck until 5 mm deep and 0.5 mL was deposited, then the needle was advanced along the back of condyle to a depth of 25 mm, where 0.5 mL was deposited. The needle then withdrawn 5mm and the remaining 1.0 mL were gradually injected. Other treatments: None reported	towards the apex of the glenoid fossa into the superior joint space until contact of the needle with the periosteum was reached. 2 mL of 25% dextrose solution was gradually injected in the superior joint space. Other treatments: None reported	

Abbreviations. ABI=autologous blood injection; ACS=autologous conditioned serum; CBCT=cone beam computed tomography; cm=centimeter; DDWR=disc displacement with reduction; G=gauge; Ga-Al-As=Gallium-Aluminum-Arsenide; HCl=hydrogen chloride; LLLT=low level laser therapy; mg=milligram; mL=milliliter; mm=millimeter; MMO=maximum mouth opening; mo=month; MRI=magnetic resonance imaging; NR=not reported; NRS=numerical rating scale; NSAID=nonsteroidal anti-inflammatory drug; RDC=research diagnostic criteria; ROM=range of motion; SD=standard deviation; TMD=temporomandibular dysfunction; TMJ=temporomandibular joint; VAS=visual analog scale; wk=week; yr=year.

Appendix Table 15. Detailed Results for All Eligible TMJ Studies

Author, Year Risk of Bias	Outcome Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
Normal or Restricted Mobility				
Elwerfelli, 2019[108] Serious	Physical performance MMO 1 day 1, 2, 3, 4, 5, 6 wk	**Dextrose prolotherapy 50% + arthrocentesis + saline lavage** Baseline: 23.14 (3.53) 1 day: 34.43 (1.62) 1 wk: 40.29 (1.98) 2 wk: 41.86 (2.67) 3 wk: 44.71 (1.25) 4 wk: 45.29 (1.25) 5 wk: 45.29 (1.25) 6 wk: 45.29 (1.25)	**Arthrocentesis + saline lavage** Baseline: 24.43 (2.82) 1 day: 34.14 (2.54) 1 wk: 39.57 (2.57) 2 wk: 39.43 (2.70) 3 wk: 41.0 (1.25) 4 wk: 41.43 (3.26) 5 wk: 41.57 (3.05) 6 wk: 41.57 (3.05)	**Arm 1 vs. Arm 2** 1 day: 0.3, p=0.806 1 wk: 0.7, p=0.571 2 wk: 2.4, p=0.117 3 wk: 3.7, p=0.035 4 wk: 3.9, p=0.020 5 wk: 3.7, p=0.018 6 wk: 3.7, p=0.018 Avg. increase (%): Dextrose: 83.40% Arthrocentesis + lavage: 64.02%
	Pain severity or intensity VAS 6 wk	**Dextrose prolotherapy 50% + arthrocentesis + saline lavage** Baseline: NR 6 wk: NR	**Arthrocentesis + saline lavage** Baseline: NR 6 wk: NR	**Arm 1 vs. Arm 2** Mean difference between arms NR Avg. reduction (%): Dextrose: 93.38% Arthrocentesis + lavage: 91.23% Statistical comparison of postoperative pain intensity was not significant
	Adverse events *N*/A Follow-up NR	*"Postoperative complication was recorded in this study; Three female patients in group-B [arthrocentesis alone] have been reported mild preauricular swelling in immediate postoperative phase. One female patient in group-B [arthrocentesis alone] reported difficult closure of the eyelid." (AE not defined)*		
Fouda, 2018[109] High	Physical performance MMO 2 wk 3 mo	**Dextrose prolotherapy 22% (outer capsule)** Baseline: 36.2 (6.8) 2 wk: 29.3 (3.9) 3 mo: 29.6 (3.8)	**Dextrose prolotherapy 22% (superior joint space)** Baseline: 35.6 (5.5) 2 wk: 37.1 (4.4) 3 mo: 36.0 (4.2) **Dextrose prolotherapy 22% (inferior joint space)** Baseline: 34.6 (2.4) 2 wk: 36.6 (1.4) 3 mo: 36.8 (1.2)	**Arm 1 vs. Arm 2** 2 wk: -7.8, NR 3 mo: -6.4, NR **Arm 1 vs. Arm 3** 2 wk: -7.3, NR 3 mo: -7.2, NR **Arm 1 vs. Arm 4** 2 wk: -10.7, NR

Author, Year Risk of Bias	Outcome Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
			Dextrose prolotherapy 22% (retrodiscal tissues) Baseline: 35.7 (9.4) 2 wk: 40 (5.6) 3 mo: 40.1 (5.3)	3 mo: -10.5, NR p<0.0005 between all 4 groups at both time points
	Pain severity or intensity VAS 2 wk 3 mo	**Dextrose prolotherapy 22% (outer capsule)** Baseline: 4.7 (3.3) 2 wk: 4.4 (1.7) 3 mo: 4.1 (2.9)	**Dextrose prolotherapy 22% (superior joint space)** Baseline: 3.7 (2.7) 2 wk: 3.4 (3.0) 3 mo: 2.9 (3.1) **Dextrose prolotherapy 22% (inferior joint space)** Baseline: 6.6 (2.5) 2 wk: 2.8 (2.8) 3 mo: 1.8 (2.1) **Dextrose prolotherapy 22% (retrodiscal tissues)** Baseline: 6.4 (2.7) 2 wk: 1.7 (2.1) 3 mo: 1.0 (1.7)	**Arm 1 vs. Arm 2** 2 wk: 1.0, NR 3 mo: 1.2, NR **Arm 1 vs. Arm 3** 2 wk: 1.6, NR 3 mo: 2.3, NR **Arm 1 vs. Arm 4** 2 wk: 2.7, NR 3 mo: 3.1, NR p-value between all 4 groups: 2 wk: p=0.014 3 mo: p=0.003
	Adverse events *N*/A 3 mo	*"Unwanted side effects in the form of painful injections and burning sensations were reported in 18 of the 72 patients. Two patients in group 4 [site of injection-retrodiscal tissues] developed paralysis of the temporal branch of the facial nerve, accompanied by a temporary inability to blink."*		
Haggag, 2022[110] High	Physical performance MMO 1, 3, 6 mo	**Dextrose prolotherapy 25%**† Baseline: 27.5 1 mo: 40.8 3 mo: 41.3 6 mo: 41.7	**Normal saline (with local anesthetic)** † Baseline: 25.7 1 mo: 35.3 3 mo: 29.7 6 mo: 29.1	**Arm 1 vs. Arm 2** 1 mo: 5.5, p=0.041 3 mo: 11.6, p<0.001 6 mo: 12.6, p<0.001
	Pain severity or intensity NRS - Pain 1, 3, 6 mo	**Dextrose prolotherapy 25%** Baseline: 8.1 1 mo: 2.3 3 mo: 2.3 6 mo: 2.1	**Normal saline (with local anesthetic)** Baseline: 7.3 1 mo: 3.7 3 mo: 5.6 6 mo: 6.3	**Arm 1 vs. Arm 2** 1 mo: -1.4, p=0.015 3 mo: -3.3, p<0.001 6 mo: -4.2, p<0.001

Author, Year **Risk of Bias**	**Outcome** **Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, p-value*** **Other results reported**
Hassanien, 2020[111] High	Physical performance MMO 2, 4 wk	**Dextrose prolotherapy 12.5%** Baseline: 35.213 (3.776) 2 wk: 39.488 (2.713) 4 wk: 43.375 (1.707)	**Laser** Baseline: 32.750 (0.463) 2 wk: 35.250 (1.282) 4 wk: 37.375 (1.923)	**Arm 1 vs. Arm 2** 2 wk: 4.2, p=0.001 4 wk: 6.0, p≤0.001
	Pain severity or intensity VAS 2, 4 wk	**Dextrose prolotherapy 12.5%** Baseline: 5.88 (2.36) 2 wk: 3.75 (1.58) 4 wk: 2.13 (0.99)	**Laser** Baseline: 4.38 (1.51) 2 wk: 4.38 (2.07) 4 wk: 3.50 (2.27)	**Arm 1 vs. Arm 2** 2 wk: -0.6, NR 4 wk: -1.4, p=0.138
Louw, 2019[112] Some concerns	Pain-related functioning NRS - Dysfunction 3 mo	**Dextrose prolotherapy 20%** Baseline: 7.2 (1.1) 1 mo: NR 2 mo: NR 3 mo: NR Change from baseline: 1 mo: 1.5 (1.9) 2 mo: 2.8 (2.7) 3 mo: 3.5 (2.8)	**Water (with local anesthetic)** Baseline: 6.7 (0.9) 1 mo: NR 2 mo: NR 3 mo: NR Change from baseline: 1 mo: 0.2 (0.5) 2 mo: 0.8 (1.3) 3 mo: 1.0 (2.1)	**Arm 1 vs. Arm 2** Mean time point scores and difference between arms NR
	Physical performance MMO 3 mo	**Dextrose prolotherapy 20%** Baseline: 43.7 (5.7) 3 mo: NR Change from baseline: 3 mo: 1.5 (4.1)	**Water (with local anesthetic)** Baseline: 39.0 (6.9) 3 mo: NR Change from baseline: 3 mo: -1.8 (5.1)	**Arm 1 vs. Arm 2** Mean time point scores and difference between arms NR
	Pain severity or intensity NRS - Pain 1, 2, 3 mo	**Dextrose prolotherapy 20%** Baseline: 7.8 (1.2) 1 mo: NR 2 mo: NR 3 mo: NR Change from baseline: 1 mo: 2.2 (1.8) 2 mo: 3.3 (2.9) 3 mo: 4.3 (2.9)	**Water (with local anesthetic)** Baseline: 8.2 (1.2) 1 mo: NR 2 mo: NR 3 mo: NR Change from baseline: 1 mo: 0.9 (1.4) 2 mo: 1.8 (2.3) 3 mo: 1.8 (2.7)	**Arm 1 vs. Arm 2** Mean time point scores and difference between arms NR
Mahmoud, 2018[113]	Physical performance	**Dextrose prolotherapy 12.5%†**	**Arthrocentesis + HA†**	**Arm 1 vs. Arm 2**

Author, Year **Risk of Bias**	**Outcome** **Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, p-value*** **Other results reported**
High	MMO 1, 3, 6, 12 mo	Baseline: 36.7 1 mo: 40.5 3 mo: 41.5 6 mo: 39.8 12 mo: 39.1	Baseline: 34.6 1 mo: 39.7 3 mo: 39.8 6 mo: 38.9 12 mo: 38.7	1 mo: 0.8, p>0.05 3 mo: 1.7, p>0.05 6 mo: 0.9, p>0.05 12 mo: 0.4, p>0.05
			PRP† Baseline:41.3 1 mo: 38.0 3 mo: 35.9 6 mo: 33.8 12 mo: 33.7	**Arm 1 vs. Arm 3** 1 mo: 2.5, p>0.05 3 mo: 5.6, p<0.05 6 mo: 6.0, p<0.05 12 mo: 5.4, p<0.05
	Pain severity or intensity VAS 1, 3, 6, 12 mo	**Dextrose prolotherapy 12.5%†** Baseline: 9.9 1 mo: 4.2 3 mo: 3.3 6 mo: 3.7 12 mo: 3.7	**Arthrocentesis + HA†** Baseline: 9.9 1 mo: 4.3 3 mo: 3.6 6 mo: 3.7 12 mo: 3.7	**Arm 1 vs. Arm 2** 1 mo: -0.1, p>0.05 3 mo: -0.3, p>0.05 6 mo: 0, p>0.05 12 mo: 0, p>0.05
			PRP Baseline: 10.0† 1 mo: 5.3 3 mo: 3.1 6 mo: 1.6 12 mo: 1.1	**Arm 1 vs. Arm 3** 1 mo: -1.1, p>0.05 3 mo: 0.2, p>0.05 6 mo: 2.1, p<0.05 12 mo: 2.6, p<0.05
Priyadarshini, 2021[114] High	Physical performance MMO 1, 3, 6, 12 mo	**Dextrose prolotherapy 12.5%** Baseline: 36.06 (11.003) 1 mo: 40.65 (8.246) 3 mo: 41.18 (8.017) 6 mo: 41.35 (7.960) 12 mo: 41.29 (7.967)	**Occlusal splints** Baseline: 33.88 (9.130) 1 mo: 34.71 (8.402) 3 mo: 34.65 (8.389) 6 mo: 34.82 (8.346) 12 mo: 35.06 (7.967)	**Arm 1 vs. Arm 2** 1 mo: 5.9, p=0.046 3 mo: 6.5, p=0.027 6 mo: 6.5, p=0.026 12 mo: 6.2, p=0.032
	Pain severity or intensity NRS - Pain 1, 3, 6, 12 mo	**Dextrose prolotherapy 12.5%** Baseline: 5.76 (1.95) 1 mo: 0.59 (0.51) 3 mo: 0.59 (0.51) 6 mo: 0.47 (0.51) 12 mo: 0.47 (0.51)	**Occlusal splints** Baseline: 5.35 (1.935) 1 mo: 3.47 (2.04) 3 mo: 3.41 (1.94) 6 mo: 3.41 (1.87) 12 mo: 3.29 (0.51)	**Arm 1 vs. Arm 2** 1 mo: -2.9, p≤0.001 3 mo: -2.8, p≤0.001 6 mo: -2.9, p≤0.001 12 mo: -2.8, p≤0.001

Author, Year Risk of Bias	Outcome Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
Zarate, 2020[115] Low	Pain-related functioning NRS - Dysfunction 3 mo	**Dextrose prolotherapy 20%** Baseline: 7.4 (1.0) 1 mo: 4.0 (2.7) 2 mo: 3.9 (2.7) 3 mo: 3.4 (2.5)	**Water (with local anesthetic)** Baseline: 7.1 (0.9) 1 mo: 5.9 (1.5) 2 mo: 4.6 (2.2) 3 mo: 4.0 (2.2)	**Arm 1 vs. Arm 2** 1 mo: -1.9, p=0.006 2 mo: -0.7, p=0.34 3 mo: -0.6, p=0.74
	Physical performance MMO 3 mo	**Dextrose prolotherapy 20%** Baseline: 38.7 (10.6) 3 mo: 43.4 (9.8)	**Water (with local anesthetic)** Baseline: 42.4 (9.27) 3 mo: 47.8 (7.8)	**Arm 1 vs. Arm 2** 3 mo: -4.4, p=0.20
	Pain severity or intensity NRS - Pain 3 mo	**Dextrose prolotherapy 20%** Baseline: 7.2 (1.1) 1 mo: 4.4 (2.4) 2 mo: 4.4 (2.4) 3 mo: 2.9 (2.6)	**Water (with local anesthetic)** Baseline: 7.2 (0.8) 1 mo: 5.4 (2.1) 2 mo: 4.6 (2.2) 3 mo: 4.3 (2.6)	**Arm 1 vs. Arm 2** 1 mo: -1.0, p=0.19 2 mo: -0.2, p=0.69 3 mo: -1.4, p=0.19
	Adverse events *N*/A Unclear	*"There were no adverse events."*		
TMJ with Hypermobility				
Arafat, 2019[116] High	Physical performance MMO 2 wk 3, 6 mo	**Dextrose prolotherapy 6.7%** Baseline: 43.27 (1.53) 2 wk: 36.67 (1.72) 3 mo: 34.4 (1.1) 6 mo: 34.3 (1.2)	**ABI** Baseline: 43.53 (1.55) 2 wk: 34 (2.07) 3 mo: 32.2 (1.6) 6 mo: 32.3 (1.5)	**Arm 1 vs. Arm 2** 2 wk: 2.7, p<0.001 3 mo: 2.2, p<0.001 6 mo: 2, p<0.001
	Pain severity or intensity VAS 2 wk 3, 6 mo	**Dextrose prolotherapy 6.7%** Baseline: NR 2 wk: NR 1 mo: NR 3 mo: 0 (median) 6 mo: 0 (median)	**ABI** Baseline: NR 2 wk: NR 1 mo: NR 3 mo: 0 (median) 6 mo: 0 (median)	**Arm 1 vs. Arm 2** 2 wk: Dextrose had a higher VAS score, p≤ 0.001 1 mo: Dextrose had a higher VAS score, p≤ 0.001 3 mo: 0 (median) 6 mo: 0 (median)
	Adverse events *N*/A Unclear	*"There were no incidences of facial nerve palsy in patients of group A [autologous blood], while there were transient facial palsy seen in 5 cases of group B [dextrose prolotherapy] which resolved 2 hours post-operatively as the effect of local anesthesia subsided."*		
Bhargava, 2023[117] High	Physical performance MMO	**Dextrose prolotherapy 8%** Baseline: 43.3 (7.5)	**ABI** Baseline: 42.9 (6.9)	**Arm 1 vs. Arm 2** 6 mo: -0.5, NR

Author, Year **Risk of Bias**	**Outcome** **Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, p-value*** **Other results reported**
	6, 12 mo	6 mo: 38.5 (5.4) 12 mo: 37.9 (2.0)	6 mo: 39 (5.8) 12 mo: 38.4 (2.6)	12 mo: -0.5, NR
	Pain severity or intensity VAS 6, 12 mo	**Dextrose prolotherapy 8%** Baseline: 8.4 (8.9) 6 mo: 5.7 (1.5) 12 mo: 4 (1.2)	**ABI** Baseline: 8.9 (9.9) 6 mo: 6.2 (1.9) 12 mo: 4.7 (1.2)	**Arm 1 vs. Arm 2** 6 mo: -0.5, NR 12 mo: -0.7, NR
	Adverse events *N*/A 12 mo	*"No complications/adverse reactions were recorded in any of the patient among both the groups."* (AE not defined)		
Chhapane, 2023[118] High	Physical performance MMO 1, 2 wk 1, 3, 6 mo 1 yr	**Dextrose prolotherapy 50%** Baseline: 23.56 (3.847) 1 wk: 25.50 (3.266) 2 wk: 26.93 (2.658) 1 mo: 27.60 (2.667) 3 mo: 28.73 (2.631) 6 mo: 29.60 (2.165) 1 yr: 30.60 (2.558)	**ABI** Baseline: 22.75 (3.768) 1 wk: 25.38 (4.113) 2 wk: 27.56 (4.427) 1 mo: 29.00 (4.147) 3 mo: 30.75 (2.631) 6 mo: 32.81 (3.468) 1 yr: 36.88 (2.217)	**Arm 1 vs. Arm 2** 1 wk: 0.1, p=.925 2 wk: -0.6, p=.638 1 mo: -1.4, p=.276 3 mo: -2.0, p=0.77 6 mo: -3.2, p=.005 1 yr: -6.3, p=.000
	Pain severity or intensity VAS 1, 2 wk 1, 3, 6 mo 1 yr	**Dextrose prolotherapy 50%**† Baseline: 5.1 1 wk: 2.2 2 wk: 0.4 1 mo: 0.7 3 mo: 0.6 7 mo: 0.5 1 yr: 0.3	**ABI**† Baseline: 5.5 1 wk: 2.1 2 wk: 1.1 1 mo: 0.5 3 mo: 0.3 7 mo: 0.2 1 yr: 0.3	**Arm 1 vs. Arm 2** 1 wk: 0.1, p≥0.05 2 wk: -0.7, p≥0.05 1 mo: 0.2, p≥0.05 3 mo: 0.3, p≥0.05 7 mo: 0.3, p≥0.05 1 yr: 0, p≥0.05
Comert Kilic, 2016[119] High	Physical performance MMO 12 mo	**Dextrose prolotherapy 12%** Baseline: 46.14 (6.89) 12 mo: 43.29 (5.92)	**Normal saline (with local anesthetic)** Baseline: 46.33 (3.47) 12 mo: 43.67 (5.65)	**Arm 1 vs. Arm 2** 12 mo: -0.4, NR
	Pain severity or intensity VAS 12 mo	**Dextrose prolotherapy 12%** Baseline: 4.3 (2.57) 12 mo: 0.89 (1.45)	**Normal saline (with local anesthetic)** Baseline: 5.39 (2.09) 12 mo: 1.72 (1.58)	**Arm 1 vs. Arm 2** 12 mo: -0.8, NR
	Adverse events *N*/A 12 mo	*"Some side effects were observed in four of the 14 patients in the prolotherapy group. Paresthesia spreading to the zygomatic arch and pre-auricular regions was observed in three patients, and this recovered over the course of a month with the use of prescribed*		

Author, Year Risk of Bias	Outcome Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up, p-value* Other results reported
		drugs including vitamin B. A transient blepharospasm occurred in one patient, which recovered after a few weeks. No other complications were observed during the treatment and follow-up periods."		
Mustafa, 2018[120] High	Physical performance MMO 1, 2, 3, 4 mo	**Dextrose prolotherapy 5%** Baseline: 54.30 (5.92) 1 mo: 43.80 (3.31) 2 mo: 40.90 (4.72) 3 mo: 39.70 (4.49) 4 mo: 39.40 (4.19)	**Dextrose prolotherapy 10%** Baseline: 52.11 (6.90) 1 mo: 44.22 (6.57) 2 mo: 44.88 (5.86) 3 mo: 42.33 (5.70) 4 mo: 41.22 (4.19) **Dextrose prolotherapy 15%** Baseline: 54.00 (7.41) 1 mo: 45.22 (3.33) 2 mo: 42.55 (9.38) 3 mo: 39.88 (4.83) 4 mo: 39.44 (4.55) **Normal saline (with local anesthetic)** Baseline: 52.33 (6.63) 1 mo: 44.66 (3.31) 2 mo: 44.77 (5.40) 3 mo: 43.44 (4.27) 4 mo: 43.33 (4.24)	**Arm 1 vs. Arm 2** 1 mo: -0.9 2 mo: -3.9 3 mo: -3.7 4 mo: -3.9 **Arm 1 vs. Arm 3** 1 mo: -0.4 2 mo: 0.1 3 mo: -1.1 4 mo: -2.1 **Arm 1 vs. Arm 4** 1 mo: 0.6 2 mo: -2.2 3 mo: -3.6 4 mo: -3.9 p≥0.05 between all 4 groups at all time points
	Pain severity or intensity VAS 1, 2, 3, 4 mo	**Dextrose prolotherapy 5%** Baseline: 5.25 (2.84) 1 mo: 2.60 (1.86) 2 mo: 2.00 (1.56) 3 mo: 0.95 (0.68) 4 mo: 0.70 (0.67)	**Dextrose prolotherapy 10%** Baseline: 5.66 (1.95) 1 mo: 2.55 (1.94) 2 mo: 1.66 (1.87) 3 mo: 1.11 (1.05) 4 mo: 0.55 (0.67) **Dextrose prolotherapy 15%** Baseline:5.33 (2.29) 1 mo: 3.50 (1.82) 2 mo: 2.72 (1.52) 3 mo: 1.16 (0.35) 4 mo: 0.88 (0.60) **Normal Saline (with local anesthetic)**	**Arm 1 vs. Arm 2** 1 mo: -0.6 2 mo: -0.6 3 mo: -1.1 4 mo: -1.1 **Arm 1 vs. Arm 3** 1 mo: -0.7 2 mo: -0.9 3 mo: -0.9 4 mo: -1.2 **Arm 1 vs. Arm 4** 1 mo: 0.3 2 mo: 0.2

Author, Year **Risk of Bias**	**Outcome** **Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, p-value*** **Other results reported**
			Baseline: 4.38 (3.14) 1 mo: 3.22 (2.93) 2 mo: 2.55 (2.12) 3 mo: 2.05 (2.24) 4 mo: 1.77 (1.64)	3 mo: -0.9 4 mo: -0.9 p≥0.05 between all 4 groups at all time points
Pandey, 2022[121] Serious	Physical performance MMO 1, 2 wk 1, 3, 6 mo	**Dextrose prolotherapy 25%** Baseline: 46.95 (1.38) 1 wk: 19.35 (3.62) 2 wk: 29.85 (3.28) 1 mo: 36.55 (1.59) 3 mo: 39.1 (1.37) 6 mo: 40.2 (1.55)	**ABI** Baseline: 46.7 (1.81) 1 wk: 18.85 (2.65) 2 wk: 26.57 (2.40) 1 mo: 33.75 (1.72) 3 mo: 27.35 (1.37) 6 mo: 38.5 (1.89)	**Arm 1 vs. Arm 2** 1 wk: 0.5, p=0.708 2 wk: 3.3, p=0.029 1 mo: 2.8, p=0.002 3 mo: 11.8, p=0.012 6 mo: 1.7, p=0.049
	Pain severity or intensity VAS 1, 2 wk 1, 3, 6 mo	**Dextrose prolotherapy 25%†** Baseline: 5.4 (1.3) 1 wk: 3.1 2 wk: 1.5 1 mo: 1.1 3 mo: 1 6 mo: 0.8 (0.8)	**ABI†** Baseline: 5.1 (1.5) 1 wk: 3.8 2 wk: 3.3 1 mo: 2.4 3 mo: 1.9 6 mo: 1.7 (0.5)	**Arm 1 vs. Arm 2** 1 wk: -0.7, p>0.05 2 wk: -1.8, p<0.05 1 mo: -1.3, p<0.05 3 mo: -0.9, p<0.05 6 mo: -0.9, p<0.05
Refai, 2011[122] High	Physical performance MMO 6, 12, 18 wk 7.5 mo	**Dextrose prolotherapy 6.7%** Baseline: 5.03 (0.43) 6 wk: 4.72 (0.54) 12 wk: 4.53 (0.50) 18 wk: 4.35 (0.35) 7.5 mo: 4.33 (0.45)	**Normal saline (with local anesthetic)** Baseline: 4.97 (0.49) 6 wk: 4.93 (0.54) 12 wk: 4.88 (0.52) 18 wk: 4.93 (0.51) 7.5 mo: 4.97 (0.45)	**Arm 1 vs. Arm 2** 6 wk: -0.2, p=0.503 12 wk: -0.4, p=0.262 18 wk: -0.6, p=0.043 7.5 mo: -0.6, p=0.039
	Adverse events /A Unclear	*"All patients tolerated the TMJ injection well without serious complications. Discomfort after injection did not appear to vary between groups. Three patients in each group had mild pain after injection. After the first injection, 4 patients in the active group and 2 in the placebo group complained of an itching sensation at the site of injection. This sensation disappeared spontaneously after a few days without any treatment. Some patients had transient facial palsy due to the anesthetic inclusion in the injected solution. The anesthetic effect diminished within 60 to 90 minutes postoperatively."*		
Saadat, 2018[123] High	Physical performance MMO 2 wk 1, 3, 6 mo	**Dextrose prolotherapy 25% (retrodiscal tissues)** Baseline: 4.325 (0.260) 2 wk: 3.613 (0.323) 1 mo: 3.875 (0.260) 3 mo: 3.929 (0.450)	**Dextrose prolotherapy 25% (superior joint space)** Baseline: 4.150 (0.393) 2 wk: 3.700 (0.289) 1 mo: 3.729 (0.382) 3 mo: 3.933 (0.301)	**Arm 1 vs. Arm 2** 2 wk: -0.09, p=0.592 1 mo: 0.1, p=0.396 3 mo: -0.004, p=0.983 6 mo: 0.1, p=0.657

Author, Year **Risk of Bias**	**Outcome** **Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up, p-value*** **Other results reported**
		6 mo: 3.929 (0.450)	6 mo: 3.833 (0.450)	
	Pain severity or intensity VAS 2 wk 1, 3, 6 mo	**Dextrose prolotherapy 25% (retrodiscal tissues)** Baseline: NR 2 wk: 5.87 (0.79)	**Dextrose prolotherapy 25% (superior joint space)** Baseline: NR 2 wk: 7.37 (0.64)	**Arm 1 vs. Arm 2** 2 wk: -1.5, p=0.001

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

†Data abstracted by review team from figures in article.

Abbreviations. ABI=autologous blood injection; AE=adverse event; avg=average; HA=hyaluronic acid; MMO=maximum mouth opening; mo=month; N/A=not applicable; NR=not reported; NRS=numerical rating scale; PRP=platelet rich plasma; SD=standard deviation; TMJ=temporomandibular joint; VAS=visual analog scale; wk=week; wk=week; yr=year.

APPENDIX L. OTHER PAIN CONDITIONS

Appendix Table 16. Detailed Study Characteristics for All Eligible Studies on Other Pain Conditions

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
Non-arthritis Knee Pain				
Babaei-Ghazani, 2023[125] IRCT20151017024572N22 Some concerns 8 Weeks Iran (3) NR	**Inclusion**: "Inclusion criteria were: The clinical diagnosis of pes anserine bursitis by a physiatrist based on the presence of pain and tenderness and occasionally local swelling on the inferomedial side of the knee below the medial joint line, and age 18 to 70 years old." **Exclusion**: "Exclusion criteria were: previous knee surgery, prior local soft tissue injection of [pes anserine bursitis] in the last six months, previous physical therapy in the last three months, pregnancy, coagulopathy, and anticoagulation therapy, current infection on the skin or soft tissue at or near the site of intervention, positive physical examination for knee meniscus or ligaments tear, severe underlying diseases such as uncontrolled diabetes (Hemoglobin A1c level greater than 9.0%) or rheumatologic	**Dextrose prolotherapy**: *N*=25 Age, mean (SD): 59.3 (8.9) 82.6% Female Clinic or health care facility 1 injection "One milliliter of 2% lidocaine was used for local anesthesia in all patients. [Using a 22-gauge needle] prolotherapy with 2 ml of 20% dextrose was done under sterile conditions into the pes anserine bursa under ultrasound guidance..." Other treatments: None reported	**Corticosteroid Injection**: *N*=25 Age, mean (SD): 64.3 (10.1) 92% Female Clinic or health care facility 1 injection “40 mg of triamcinolone acetonide (1 milliliter) was…injected into the pes anserine bursa under ultrasound guidance." Other treatments: None reported **Oxygen-ozone**: *N*=25 Age, mean (SD): 60 (8.32) 79.2% Female	**Primary outcome NR** **Pain-related functioning (1, 8 wk)** • WOMAC (total, pain, stiffness, function) **Other outcomes:** • Pain severity or intensity: VAS (1, 8 wk)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
	disorders, previous allergic reaction history to corticosteroid, dextrose, O2-O3 and, local anesthetic."		Clinic or health care facility “5 ml of O2-O3 with a 15 microgram concentration was injected.” Other treatments: None reported	
Cho, 2017[128] NR Serious 12 Weeks Korea (1) NR	**Inclusion**: “diagnosed with chronic patellar tendinopathy.” **Exclusion**: NR	**Dextrose prolotherapy**: *N*=10 Age, mean (SD): 32.5 (9.4) 60% Female Clinic or health care facility 4 weeks (3 injections) Prolotherapy: "[An] ultrasound-guided 10 mL injection of a solution of 12.5% glucose (Dextrose) and 0.5% lidocaine was administered…into the tendon-bone junction and the tender peritendinous soft tissues." Other treatments: “The use of non-narcotic anti-inflammatory drugs and corticosteroids was restricted during the treatment period.”	**Prolotherapy and rehabilitation**: *N*=10 Age, mean (SD): 32.2 (10.3) 30% Female Clinic or health care facility 4 weeks (3 injections) Prolotherapy + Rehab: Injection protocol the same as arm 1; exercise protocol the same as arm 3. Other treatments: Same as Arm 1 **Exercise/PT**: *N*=10 Age, mean (SD): 34.6 (8.0) 50% Female	**Primary outcome NR** **Pain-related functioning (6, 12 wk)** • VISA-P **Physical performance (6, 12 wk)** • Knee extensor/flexor **Other outcomes:** • Pain severity or intensity (6, 12 wk)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
			Setting not reported 12 weeks (3x/wk) EG: Rehab exercise: "The exercise program…consisted of a warm-up, functional exercise, and assistive exercise. Specifically, the warm-up was composed of light walking and static stretching of the lower extremities. The functional exercise was composed of exercise including strong eccentric muscle contractions of the hip and quadriceps muscles. The assistive exercise was composed of a gastrocnemius muscle strength exercise and a balance strengthening exercise of the lower extremities." Other treatments: Same as Arm 1	
Wu, 2022[135] NR High 12 Months China (1)	**Inclusion**: "Only patients who had been in the army for more than 1 year had knee pain and exhibited irregular ossification of the tibial tubercle and ossification fragments in the patellar tendon insertion, as demonstrated by X-ray/or MRI examination. The study included patients who stopped participating in army training generally after at	**Dextrose prolotherapy**: *N*=35 Age, mean (SD): 21.9 (4.8) 0% Female Clinic or health care facility 2 months (3 injections)	**Saline/Local anesthetic**: *N*=35 Age, mean (SD): 21.7 (4.4) 0% Female Clinic or health care facility 2 months (3 injections)	**VISA-P score at 3 months after enrollment** **Pain-related functioning (3, 6, 12 wk)** • VISA-P **Adverse events**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
NR	least 1 month of conservative treatment." **Exclusion**: "We excluded those who withdrew from active service within 3 months and those with OSD in both knees or other diseases that could cause knee pain."	Dextrose: "12.5% dextrose solution (1 ml 50% dextrose, 2 ml 1% lidocaine, and 1 ml sterile water); Under ultrasound guidance, 1 ml of the solution was injected into the superficial layer of the patellar tendon at the pain site, and 1 ml of the solution was injected into the deep layer of the patellar tendon at the pain site." Other treatments: None reported	Saline: "saline solution (2 ml saline and 2 ml 1% lidocaine)…under ultrasound guidance." Other injection details were the same as group 1. Other treatments: None reported	
Other Foot Pain (not plantar fasciitis)				
Akpancar, 2019[131] NR Critical 12 Months Turkey (1) NR	**Inclusion**: "Patients whose ages varied between 18 and 70 years, who had at least 6 months of symptomatic OLT [osteochondral lesions of the talus] refractory (patients who had pain, stiffness, disability, and dissatisfaction after treatment) to at least 3 months of standard care modalities (temporary immobilization, use of analgesics and anti-inflammatory drugs, partial weight bearing and orthotic provision) and who had grade I, II, or III lesions in their standard ankle radiographies" **Exclusion**:	**Dextrose prolotherapy**: *N*=27 Age, mean (SD): 57.7 (11.1) 70.4% Female Clinic or health care facility 3 injections, duration unclear ("3 sessions (one session in 3 weeks)") 2 mL 25% dextrose for intra-articular, 2ml 13.5% dextrose (1.8 mL 15% dextrose+ 0.2 mL lidocaine) for tibial edge and talar dome adjacent the joint surface	**PRP**: *N*=22 Age, mean (SD): 54.0 (11.5) 72.7% Female Clinic or health care facility 3 injections, duration unclear (as noted for dextrose arm) 2 mL PRP intra-articular and 2 mL PRP for tibial edge and talar dome adjacent to the joint surface) Other treatments:	**Primary outcome NR** **Pain-related functioning (21 days; 3, 6, 12 mo)** • AOS **Adverse events** **Other outcomes:** • Pain severity or intensity • Cost

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
	"Patients with rheumatic or systemic diseases, patients who had active or chronic infection in the treatment area, previous operation history on ankle, other ankle problems accompanying OLT which may cause pain and loss of function in the ankle and pregnant patients"	Other treatments:		
Hadianfard, 2023[126] NR Some concerns 8 Weeks Iran (1) None	**Inclusion**: Hallux rigidus: "Patients aged 30-65 years and complaining of pain or decreased range of motion in the first MTP for at lease 3 months without response to other conservative therapies..." **Exclusion**: "patients with severe stage of degenerative disease in the first MTP according to the anterior-posterior and lateral views of radiography performed before treatment (grades III and IV). Diabetes, rheumatologic disease, history of previous trauma or operation of the first MTP, infections, lumbar radiculopathies, anomalies, nonsteroidal anti-inflammatory drug consumption, coagulopathies, pregnancy, and history of previous local injection of this joint in recent six months."	**Dextrose prolotherapy**: *N*=16 Age, mean (SD): 49.8 (9.3) 87.5% Female Clinic or health care facility Single session 25% dextrose 2 ml (+1% lidocaine): "mixture of 1 cc dextrose 50% and 1 cc of lidocaine 2%" Injection "with a 2 cc syringe (23 gauge)...inserted from the medial side of the joint while the solution was injected in both plantar and dorsal directions." Other treatments:	**Corticosteroid Injection**: *N*=16 Age, mean (SD): 46.9 (9.8) 81.3% Female Clinic or health care facility Single session methylprednisolone acetate 40 mg (+ 1% lidocaine): "1 cc methylprednisolone (40 mg) and 1 cc of lidocaine 2%" same injection method Other treatments:	**Primary outcome NR** **Pain-related functioning (1, 4, 8 wk)** • MOXFQ **Other outcomes:** • Pain severity or intensity

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
Yelland, 2011[129] ACTRN: 12606000179538 Some concerns 12 Months Australia (5) Musculoskeletal Research Foundation of Australia, the Australian Podiatry Education and Research Foundation and the Griffith University Office of Research	**Inclusion**: "diagnosis of unilateral or bilateral midportion Achilles tendinosis with pain between 2 and 7 cm proximal to the calcaneal attachment in adults >18 years with activity-related pain for at least 6 weeks. The clinical severity of the tendinosis had to yield a score on the Victorian Institute of Sport Assessment—Achilles (VISA-A) of <80 of a maximum of 100 for participants involved in sport and <70 of 90 for people not involved in sport.,, ultrasound findings of mid-portion tendinosis..." **Exclusion**: "previous steroid or prolotherapy injections or surgery to the affected tendon, previous completion of >50% of the Achilles ELE protocol and any allergies or medical conditions that might limit completion of trial treatments."	**Dextrose prolotherapy**: *N*=14 Age, mean (SD): 48 (41-54) % Female NR Clinic or health care facility Weekly for 4-12 treatments. "The number of treatments was determined by the time it took to reach a pain-free activity or until the participant requested to cease treatment." 20% dextrose 5 ml: "injected tender points in the subcutaneous tissues adjacent to the affected tendon with a solution consisting of 20% glucose/0.1% lignocaine/0.1% ropivacaine using the technique described by Lyftogt. The tender points were most commonly the anterolateral and anteromedial margins of the tendon and on the most posterior aspect of the tendon 2–7 cm from the calcaneus attachment. At each point, 0.5–1 ml of solution was used to a maximum total of 5 ml." Other treatments:	**Exercise/PT**: *N*=15 Age, mean (SD): 46 (40-58) % Female NR Clinic or health care facility " exercises... twice daily in three sets of 15 repetitions with the knee straight and three sets of 15 repetitions with the knee bent for a period of 12 weeks." ELE protocol: "Eccentric loading exercises... participants were instructed by a doctor or podiatrist in the ELE protocol described by Alfredson et al [Alfredson H, Pietilä T, Jonsson P, et al. Heavy-load eccentric calf muscle training for the treatment of chronic Achilles tendinosis. Am J Sports Med 1998;26:360–6.)... participants are told that the exercises may be painful but not to exceed an intensity of 4/10. As the pain eases over time, load is progressively increased by adding weights to a backpack. The participants had an initial training session and then reviews at 3, 6 and 12 weeks to check technique and progress. Written instructions for the exercises were supplied, and the participants kept a	**Victorian Institute of Sport Assessment—Achilles (VISA-A)** **Pain-related functioning (6 wk; 3, 6, 12 mo)** • VISA-A **Adverse events** **Other outcomes:** • Cost

Author, Year Registry # Risk of Bias Follow-up Duration Location (# Sites) Funding source	Inclusion/Exclusion Criteria	Intervention: *N* Randomized Demographics Setting Frequency; Duration Detailed Intervention Characteristics Other treatments/co-interventions	Comparator(s): *N* Randomized Demographics Setting Frequency; Duration Detailed Comparator Characteristics Other treatments/co-interventions	Primary Outcome Prioritized Outcomes • Measurement tool(s) (Time points) Other Outcomes Reported
		Combined: *N*=14 Age, mean (SD): 46 (40-57) % Female NR Clinic or health care facility; Home Combined dextrose prolotherapy + ELE (as described above) Other treatments:	diary to document exercise load and compliance." Other treatments:	
Hand Pain Conditions				
Hooper, 2011[136] NR Some concerns 12 Months Canada (1) "This study was funded in part by a grant from the Calgary Health Region."	**Inclusion:** 18-50 years, wrist pain ≥6 months, PRWE score ≥20, normal X-ray, no other systemic illness, discontinue anti-inflammatory medication, no other wrist pathology on examination **Exclusion:** NR	**Dextrose prolotherapy**: *N*=20 Age, mean (SD): 33.0 (8.5) 75% Female Clinic Max of 6 sessions, each 1 month apart 20% dextrose 5 ml (+0.6% lidocaine), injected into at least three sites including: scaphotrapezium, perilunate region, scaphotrapezoid, first carpometacarpal, radioulnar, or	**Saline/Local anesthetic**: *N*=30 Age, mean (SD): 35.4 (8.5) 68% Female Clinic Max of 6 sessions, each 1 month apart 1% lidocaine 5 mL as per intervention protocol Other treatments: Same as Arm 1	**PRWE** **Pain-related functioning (3,12 mo)** • PRWE **Physical performance** • Grip strength • Flexion • Extension • Supination • Pronation **Adverse events** **Other outcomes:**

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
		peritriquetral. Injected using a peppering technique Other treatments: No "antiinflammatory medication for up to 1 month after last treatment."		• Pain severity or intensity: 10-point VAS
Jahangiri, 2014[127] IRCT201011025088N1 Some concerns 6 Months Iran (1) NR	**Inclusion:** >40 years, CMCI1 pain ≥3 months, pain intensity >30 mm on 100-point VAS, evidence of osteoarthritis on radiograph **Exclusion:** "history of fracture or other hand pathologies… within 6 months before the study… diabetes, blood coagulation disorders, neuropathy, corticosteroid injection [≤3 months], and contraindications to steroid injection. Pregnant or breast feeding mothers, participants who were taking NSAIDs or wearing a brace at the time of the study, and patients with a history of injection into their CMC1 within the last [≤6 months]."	**Dextrose prolotherapy**: *N*=30 Age, mean (SD): 63.9 (9.4) 77% Female Clinic 3 sessions, each 1 month apart 10% dextrose (+2% lidocaine),injected "toward the ulnar side of the extensor pollicis brevis and just proximal to the base of the first metacapral in the snuffbox." Other treatments: "Participants were also instructed not to use a brace, physiotherapy, and analgesic medications."	**Corticosteroid Injection,** *N*=19 Age, mean (SD): 63.3 (10.1) 70% Female Clinic 3 sessions, each 1 month apart 40 mg methylprednisolon acetate (+ 2% lidocaine) as per intervention protocol Other treatments: Same as Arm 1	**VAS** **Physical performance** • Lateral Pinch Strength **Adverse events** **Other outcomes:** • Pain severity & intensity: 10-point VAS
Ustun, 2023[132] NCT03839108 Some concerns	**Inclusion:** 40-70 years, bilateral hand osteoarthritis by ACR diagnosis **Exclusion:**	**Dextrose prolotherapy**: *N*=23 Age, mean (SD): 59.5 (6.9) 100% Female	**Paraffin wax**, *N*=23 Age, mean (SD): 60.4 (7.4) 100% Female	**Primary outcome NR** **Physical performance** • DHI

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
Turkey (1) "This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors."	"carpal tunnel syndrome, de Quervain tenosynovitis, Dupuytren's contracture, inflammatory arthritis, secondary OA due to rheumatoid arthritis, chondrocalcinosis, psoriatic arthritis, hemochromatosis or trigger finger… history of upper extremity surgery, patients with neurological disorders, and those who received physiotherapy or joint injections [≤6 months] were omitted."	Clinic Single injection 15% dextrose ml NR, "injected into the periarticular ligaments of the symptomatic proximal interphalangeal, distal interphalangeal, and carpometacarpal joints" Other treatments: None reported	Clinic 10 sessions, 20 minutes a day, 5 days a week, for 2 weeks Both hands were dipped into "melted wax bath at 52°C 10 times. Patients were instructed to keep their hands open and their wrists in a neutral position." Other treatments None reported	**Adverse events** **Other outcomes:** • Pain severity or intensity: 10-point VAS
Other conditions				
Abd Elghany, 2019[133] NR Moderate 1 Months Egypt (1) NR	**Inclusion**: " Patients met ACR 2010 preliminary diagnostic criteria for fibromyalgia syndrome." **Exclusion**: "Excluded were patients with secondary fibromyalgia, patients with systemic disease or chronic arthritis such as RA, SLE, pregnant and nursing women, patients with bleeding tendency or using anticoagulant, patients with active infection or cancer, complete rupture of a tendon or alignment, patients with muscle diseases, diabetes mellitus, thyroid dysfunction, patients with seizures or abnormal brain	**Dextrose prolotherapy**: *N*=60 Age, mean (SD): NR (NR) NR% Female Clinic or health care facility 3 injections bi-weekly 25% DPT: "The injected solution consisted of 25% dextrose to make a 12.5% soft tissue solution (1/2 volume of 10 ml syringe), xylocaine 0.3% (1 ml of 3% xylocaine over 10 ml solution); bacteriostatic water was	**Other non-injectable**: *N*=60 Age, mean (SD): NR (NR) NR% Female Clinic or health care facility 3 injections bi-weekly rTMS: "Brain repetitive transcranial magnetic stimulation (rTMS) is another therapeutic modality for fibromyalgia. It modifies cortical and deep brain areas, through an electromagnetic field generated over the scalp, by	**VAS** **Pain-related functioning** • FIQR*† (0 day, 1 mo) **Other outcomes:** • Pain Severity & Intensity: VAS*‡ (0 day, 1 mo)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
	electrical activity, primary psychiatric or neurological disorders, patients with pacemakers, recent head trauma, auditory problems or drug abuse."	recommended as a diluent. 0.5–1 ml of solution was injected in each trigger point as well as tender ligaments and tendinous insertion points. The prolotherapist used his fingertip to palpate potential pain referral sources for the patient's clinical complaints. Injection sites were cervical inter-transverse ligaments, posterior-superior trapezius, infraspinatus, common extensors, iliolumbar, and sacroiliac ligament." Other treatments: None reported	decreasing or increasing cortical excitability (when using low- or high-frequency protocols). The TMS machine used was the Magstim 200 repetitive pulse stimulator by Magstim Company, Whitland Wales, UK. The cortical target was DLPFC, a functional, rather than anatomical, structure. This region lies in the middle frontal gyrus (i.e., lateral part of Brodmann's area), 9 and 46, and it is considered the end point for the dorsal pathway that tells the brain how to interact with the stimuli [8]. The same stimulation frequency was used for all patients, parameters of antidepressant and anti-nociceptive effects were: 10 Hertz – pulse train duration (on time) five seconds, inter-train interval (off time) ten seconds (15 second cycle time). Additionally, stimulation-train duration and inter-stimulus intervals were determined such that they comply with current published rTMS safety guidelines." Other treatments: None reported	
Gul, 2020[130] NR Some concerns 12 Months	**Inclusion**: "Patients whose ages varied between 18 years and 80 years, who had at least 6 months of symptomatic osteoarthritis secondary to DDH refractory to at least 3 months of standard care modalities (weight loss, temporary	**Dextrose prolotherapy**: *N*=20 Age, mean (SD): 45.74 (16.86) 60% Female	**Exercise/PT**: *N*=21 Age, mean (SD): 47.56 (13.8) 66.67% Female	**Primary outcome NR** **Adverse events** **Other outcomes:** • Pain severity or intensity: VAS*¶ (21 day, 3, 6, 12 mo)

Author, Year **Registry #** **Risk of Bias** **Follow-up Duration** **Location (# Sites)** **Funding source**	**Inclusion/Exclusion Criteria**	**Intervention:** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Intervention Characteristics** **Other treatments/co-interventions**	**Comparator(s):** ***N* Randomized** **Demographics** **Setting** **Frequency; Duration** **Detailed Comparator Characteristics** **Other treatments/co-interventions**	**Primary Outcome** **Prioritized Outcomes** • **Measurement tool(s) (Time points)** **Other Outcomes Reported**
Turkey (1) NR	immobilization, use of analgesics and anti-inflammatory drugs, partial weight-bearing heel risers, orthotic provision, and physical therapy) and who had Crowe Type I–IV lesions in their standard anteroposterior hip radiographic and waiting list for total hip arthroplasty (THA) surgery at Tokat State Hospital were included in the study." **Exclusion**: "Patients with systemic or rheumatic diseases, active or chronic infection in the affected hip, hip problems accompanying DDH that may cause pain and loss of function in the hip and other chronic hip diseases, patients who had undergone surgery for joint preserving or arthroplasty of the hip, who had rheumatologic or neurological diseases that affect hip functions and pregnant patients were excluded from the study."	Clinic or health care facility 1 injection every 21 days repeated up to 6 times 15% DPT: "Injections were applied in supine position. A maximum of 8 mL dextrose solution (7.2 mL 15% dextrose and 0.8 mL lidocaine mixture) were injected into iliopsoas and adductor tendon insertions. In patients with type I and II DDH, a mixture containing 7.2 mL 25% dextrose and 0.8 mL lidocaine were applied to the hip joint with anterosuperior, parasagittal approach [22]. A proper needle position was confirmed by ultrasonographic visualization of the injected solution. The injections were applied in lateral decubitus position and the hip was in a neutral position. A maximum of 12 mL dextrose solution (10.8 mL 15% dextrose and 1.2 mL lidocaine mixture) were injected to gluteus medius, gluteus minimus insertions; then, the hip was given a flexion position for the piriformis insertion injection." Other treatments: "Patients were instructed to take 500 mg of acetaminophen up to 4 times a day if necessary. The use of anti-	Clinic or health care facility 1 injection every 21 days repeated up to 6 times Exercise (supervised & at-home): "All patients received standard 12-week rehabilitation protocol and supervised progressive resistance training consisting of 30 training sessions (5 sessions per 2 weeks, an average of 45–60 minutes per season). All patients started with a warm-up on a stationary bicycle for 10 minutes. Then they performed leg press, hamstring curl and knee extension with double-legged, hip flexion with single-legged and lunges. Sets were performed 3 to 4 times with 8 repetitions. The intensity of all exercises increased progressively to a maximum of 12 repetitions. Eight repetitions of 3 sets were performed in the first 2 weeks and 4 sets in the last 2 weeks. If the sets were performed with 2 or more repetitions from the target of the maximum repetitions number, then the load was increased. All sessions were supervised by a physiotherapist or by a sports medicine physician to provide adequate loading and progression. A home exercise plan with similar exercises 3 times a day was adopted to the patients for other days. Also, the	

Author, Year Registry # Risk of Bias Follow-up Duration Location (# Sites) Funding source	Inclusion/Exclusion Criteria	Intervention: *N* Randomized Demographics Setting Frequency; Duration Detailed Intervention Characteristics Other treatments/co-interventions	Comparator(s): *N* Randomized Demographics Setting Frequency; Duration Detailed Comparator Characteristics Other treatments/co-interventions	Primary Outcome Prioritized Outcomes • Measurement tool(s) (Time points) Other Outcomes Reported
		inflammatory drugs was not allowed. Hot pack application to the injected areas was suggested 3 times a day during the first 3 days after the treatment."	home exercise plan was advised after the 12-week rehabilitation program." Other treatments: None reported	
Senturk, 2017[134] NR Serious 4 Weeks Turkey (1) NR	**Inclusion**: "They had no history of trauma to the thorax or symptoms of systemic disease. Patient evaluation included a complete history, X-ray chest, electrocardiography, physical examination, complete blood count." **Exclusion**: NR	**Dextrose prolotherapy**: *N*=21 Age, mean (SD): 45.4 (13.5) 66.7% Female Clinic or health care facility 1 injection 20% DPT: "The affected costochondral joint was injected with a combination of 8 ml of 20% dextrose and 2 ml of 2% lidocaine into the chest wall. Twenty-one of them had received one local injections." Other treatments: None reported	**NSAID:** *N*=13 Age, mean (SD): 47.7 (15) 76.9% Female Home 1 injection "...treated analgesia by NSAID's (Naproxen Sodium) dose is approximately 10 mg/kg given orally in 2 divided doses (i.e., 5 mg/kg given twice a day)." Other treatments: None reported	**VAS*¶** **Adverse events** **Other outcomes:** • Pain severity or intensity: VAS*¶ (1 day, 1, 4 wk)

Notes. *No established MCID for outcome; direction of effect based on statistically significant difference reported by study.
†Fibromyalgia Impact Questionnaire Revised (FIQR) was measured on a weighted scale of 3 domains with a maximum score of 100, lower values indicating improvement
‡Authors assessed VAS on a scale of 0 (no pain) to 100 (unbearable pain).
¶Authors assessed VAS on a scale of 0 (no pain) to 10 (unbearable pain).
Abbreviations. ACR=American College of Rheumatology; AE=adverse event; DDH=development dysplasia of the hip; DHI=Duruoz Hand Index; DLPFC=dorsolateral prefrontal cortex; DPT=dextrose prolotherapy; kg=kilogram; mg=milligram; mL=milliliter; mo=month; NR=not reported; NS=not significant; NSAID=nonsteroidal anti-

inflammatory drug; PrT=prolotherapy; PWRE=Patient rated wrist evaluation; RA= rheumatoid arthritis; rTMS=repetitive transcranial magnetic stimulation; SD=standard deviation; SLE=systemic lupus erythematosus; THA= total hip arthroplasty; VAS=Visual Analog Scale; wk=week.

Appendix Table 17. Detailed Results for All Eligible Studies on Other Pain Conditions

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up P-value* Other results reported
Non-arthritis Knee Pain				
Babaei-Ghazani, 2023[125] Some concerns	Pain-related functioning WOMAC Total 1, 8 wk	**Dextrose prolotherapy** Baseline: 59.3 (16.8) 1 wk: 56.7 (21.5) 8 wk: 38.1 (15.5)	**Corticosteroid** Baseline: 63.2 (13.3) 1 wk: 44.1 (21.0) 8 wk: 48.0 (19.2)	**Dextrose prolotherapy vs. Corticosteroid** 1 wk: 12.6, p=NR 8 wk: -9.9, p=NR
			Oxygen/ozone Baseline: 58.6 (11.2) 1 wk: 43.2 (16.8) 8 wk: 33.0 (15.3)	**Dextrose prolotherapy vs. Oxygen/ozone** 1 wk: 13.5, p=NR 8 wk: 5.1, p=NR
	Pain intensity or severity WOMAC Pain 1, 8 wk	**Dextrose prolotherapy** Baseline: 11.8 (4.1) 1 wk: 11.4 (4.6) 8 wk: 7.1 (3.5)	**Corticosteroid** Baseline: 13.5 (3.7) 1 wk: 8.6 (4.5) 8 wk: 10.1 (4.9)	**Dextrose prolotherapy vs. Corticosteroid** 1 wk: 2.8, p=NR 8 wk: -3.0, p=NR
			Oxygen/ozone Baseline: 12.2 (2.3) 1 wk: 7.95 (3.7) 8 wk: 6.3 (3.5)	**Dextrose prolotherapy vs. Oxygen/ozone** 1 wk: 3.5, p=NR 8 wk: 0.8, p=NR
	Pain-related functioning WOMAC Stiffness 1, 8 wk	**Dextrose prolotherapy** Baseline: 4.2 (1.8) 1 wk: 3.2 (1.8) 8 wk: 2.5 (1.7)	**Corticosteroid** Baseline: 3.9 (2.5) 1 wk: 3.2 (2.0) 8 wk: 3.5 (2.3)	**Dextrose prolotherapy vs. Corticosteroid** 1 wk: 0.0, p=NR 8 wk: -1.0, p=NR
			Oxygen/ozone Baseline: 4.0 (1.5) 1 wk: 3.7 (1.4) 8 wk: 2.4 (1.8)	**Dextrose prolotherapy vs. Oxygen/ozone** 1 wk: -0.5, p=NR 8 wk: 0.1, p=NR
	Pain-related functioning WOMAC Physical Function 1, 8 wk	**Dextrose prolotherapy** Baseline: 43.3 (12.4) 1 wk: 42.2 (16.9) 8 wk: 28.5 (11.5)	**Corticosteroid** Baseline: 45.8 (8.9) 1 wk: 32.3 (15.98) 8 wk: 34.5 (12.9)	**Dextrose prolotherapy vs. Corticosteroid** 1 wk: 9.9, p=NR 8 wk: -6.0, p=NR
			Oxygen/ozone Baseline: 41.6 (8.9) 1 wk: 29.8 (14.3) 8 wk: 22.9 (12.4)	**Dextrose prolotherapy vs. Oxygen/ozone** 1 wk: 12.4, p=NR 8 wk: 5.6, p=NR

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up** **P-value*** **Other results reported**
	Pain severity or intensity VAS 1, 8 wk	**Dextrose prolotherapy** Baseline: 7.6 (1.31) 1 wk: 7.25 (1.77) 8 wk: 3.5 (1.85)	**Corticosteroid** Baseline: 8.04 (1.33) 1 wk: 4.53 (2.71) 8 wk: 5.07 (2.55)	**Dextrose prolotherapy vs. Corticosteroid** 1 wk: 2.7, p=NR 8 wk: -1.6, p=NR
			Oxygen/ozone Baseline: 7.6 (1.31) 1 wk: 4.83 (2.53) 8 wk: 3.88 (2.59)	**Dextrose prolotherapy vs. Oxygen/ozone** 1 wk: 2.4, p=NR 8 wk: -0.4, p=NR
Cho, 2017[128] Serious	Pain-related functioning VISA-P 6, 12 wk	**Dextrose prolotherapy** Baseline: 52.4 (9.7) 6 wk: 57.2 (12.8) 12 wk: 62.6 (11.1)	**Dextrose prolotherapy + Exercise** Baseline: 58.7 (12.1) 6 wk: 67.6 (12.6) 12 wk: 79.0 (9.18)	**Dextrose prolotherapy vs. Dextrose prolotherapy + Exercise** 6 wk: -10.4 12 wk: -16.4 p<0.05 (across time points)
			Exercise Baseline: 59.9 (13.8) 6 wk: 73.7 (11.9) 12 wk: 78.1 (10.6)	**Dextrose prolotherapy vs. Exercise** 6 wk: -16.5 12 wk: -15.5 p<0.05 (across time points)
				Dextrose prolotherapy + Exercise vs. Exercise 6 wk: -6.1 12 wk: 0.9 P=NS (across time points)
	Physical performance Knee extensor strength 6, 12 wk	**Dextrose prolotherapy** Baseline: 206.8 (46.3) 6 wk: 501.8 (46.9) 12 wk: 183.5 (38.1)	**Dextrose prolotherapy + Exercise** Baseline: 227.0 (52.9) 6 wk: 253.7 (62.7) 12 wk: 252.9 (52.9)	**Dextrose prolotherapy vs. Dextrose prolotherapy + Exercise** 6 wk: 248.1, p=NR 12 wk: -69.4, p=NR
			Exercise Baseline: 197.1 (61.5) 6 wk: 208.6 (52.2) 12 wk: 225.4 (47.9)	**Dextrose prolotherapy vs. Exercise** 6 wk: 293.2, p=NR 12 wk: -41.9, p=NR
				Dextrose prolotherapy + Exercise vs. Exercise 6 wk: 45.1, p=NR 12 wk: 27.5, p=NR
	Physical performance Knee flexor strength 6, 12 wk	**Dextrose prolotherapy** Baseline: 96.0 (24.2) 6 wk: 105.7 (33.6) 12 wk: 95.3 (29.1)	**Dextrose prolotherapy + Exercise** Baseline: 106.8 (21.8) 6 wk: 117.8 (24.3) 12 wk: 129.3 (27.2)	**Dextrose prolotherapy vs. Dextrose prolotherapy + Exercise** 6 wk: -12.1, p=NR 12 wk: -34.0, p=NR

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up** **P-value*** **Other results reported**
			Exercise Baseline: 100.7 (32.9) 6 wk: 115.0 (26.5) 12 wk: 116.4 (24.4)	**Dextrose prolotherapy vs. Exercise** 6 wk: -9.3, p=NR 12 wk: -21.1, p=NR
				Dextrose prolotherapy + Exercise vs. Exercise 6 wk: 2.8, p=NR 12 wk: 12.9, p=NR
	Pain severity or intensity VAS 6, 12 wk	**Dextrose prolotherapy** Baseline: 6.8 (1.2) 6 wk: 5.2 (0.8) 12 wk: 4.5 (1.1)	**Dextrose prolotherapy + Exercise** Baseline: 6.7 (0.5) 6 wk: 3.6 (1.4) 12 wk: 2.5 (1.2)	**Dextrose prolotherapy vs. Dextrose prolotherapy + Exercise** 6 wk: 1.6 12 wk: 2.0 p<0.05 (across time points)
			Exercise Baseline: 6.4 (0.7) 6 wk: 4.5 (1.1) 12 wk: 3.1 (1.6)	**Dextrose prolotherapy vs. Exercise** 6 wk: 0.7 12 wk: 1.4 p<0.05 (across time points)
				Dextrose prolotherapy + Exercise vs. Exercise 6 wk: -0.9 12 wk: -0.6 P=NS (across time points)
Wu, 2022[135] High	Pain-related functioning VISA-P 3 wk 6, 12 mo	**Dextrose prolotherapy** Baseline: 49.1 (5.9) 3 wk: 76.2 (1.1) 6 mo: 80.8 (1.1) 12 mo: 83.1 (1.3)	**Saline** Baseline: 49.4 (5.7) 3 wk: 50.8 (1.1) 6 mo: 74.6 (1.1) 12 mo: 77.6 (1.3)	**Dextrose prolotherapy vs. Saline** 3 wk: 25.4, p=<.0001 6 mo: 6.2, p=<.0001 12 mo: 5.5, p=0.0026
	Adverse events 12 mo	*"No adverse events were reported in either group"*		
Other Foot Pain (not plantar fasciitis)				
Akpancar, 2019[131] Critical	Pain-related functioning AOS 21 days 3, 6, 12 mo	**Dextrose prolotherapy** Baseline: 129.4 (20.0) 21 days: 75.2 (23.3) 3 mo: 51.4 (28.3) 6 mo: 36.9 (25.8) 12 mo: 29.9 (25.9)	**PRP** Baseline:137.4 (20.9) 21 days: 86.5 (28.0) 3 mo: 49.9 (20.5) 6 mo: 33.3 (15.6) 12 mo: 30.1 (19.5)	**Arm 1 vs. Arm 2** 21 days: -11.3, p=0.13 3 mo: 1.5, p=0.84 6 mo: 3.6, p=0.57 12 mo: -0.2, p=0.98
	Pain severity or intensity VAS	**Dextrose prolotherapy** Baseline: 7.2 (1.5)	**PRP** Baseline: 7.7(1.4)	**Arm 1 vs. Arm 2** 21 days: -0.7, p=0.10

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up** **P-value*** **Other results reported**
	21 Days 3, 6, 12 mo	21 days: 4.0 (1.6) 3 mo: 2.5 (1.8) 6 mo: 1.7 (1.7) 12 mo: 1.3 (1.8)	21 days: 4.7 (1.4) 3 mo: 2.6 (1.0) 6 mo: 1.6 (1.2) 12 mo: 1.4 (1.4)	3 mo: -0.1, p=0.91 6 mo: 0.1, p=0.89 12 mo: -0.1, p=0.81
	Adverse events 12 mo	*"Patients did not suffer from any side effects such as infection, fever, hematoma, or rupture. Only 3 patients reported extreme pain 1 or 2 days after injection in the prolotherapy group, which was alleviated after 2 days of non-weight bearing."* (of note, study excluded participants who could not complete all 3 injections or who were lost to follow-up at any time within the 12 mo of follow-up)		
	Cost 12 mo	*"The average cost of PrT to the hospital was 30 Turkish Liras (TL) ($6.8) per session, and average cost of PRP to the hospital was 250 TL ($56.8) per session."*		
Hadianfard, 2023[126] Some concerns	Pain-related functioning MOXFQ 1, 4, 8 wk	**Dextrose prolotherapy** Baseline: 45.5 (NR) 1 wk: 29.1 (NR) 4 wk: 33.1 (NR) 8 wk: 33.1 (NR)	**Corticosteroid** Baseline: 49.6 (NR) 1 wk: 28.6 (NR) 4 wk: 33.1 (NR) 8 wk: 33.8 (NR)	**Arm 1 vs. Arm 2** 1 wk: -0.5, p=0.93 4 wk: 0.0, p=1.0 8 wk: -0.7, p=0.82
	Pain severity or intensity VAS 1, 4, 8 wk	**Dextrose prolotherapy** Baseline: 5.7 (NR) 1 wk: 2.5 (NR) 4 wk: 2.7 (NR) 8 wk: 2.8 (NR)	**Corticosteroid** Baseline: 6.1 (NR) 1 wk: 2.3 (NR) 4 wk: 2.4 (NR) 8 wk: 2.7 (NR)	**Arm 1 vs. Arm 2** 1 wk: 0.2, p=0.32 4 wk: 0.3, p=0.30 8 wk: 0.1, p=0.70
Yelland, 2011[129] Some concerns	Pain-related functioning VISA-A 6 wk, 3, 6, 12 mo	**Dextrose prolotherapy** Baseline: 59.7 (NR) 6 wk: 71.7 (NR) 3 mo: 80.6 (NR) 6 mo: 86.6 (NR) 12 mo: 87.4 (NR) **Dextrose prolotherapy + exercise/PT** Baseline: 50.3 (NR) 6 wk: 74.5 (NR) 3 mo: 76.4 (NR) 6 mo: 81.6 (NR) 12 mo: 91.5 (NR)	**Exercise/ELE:** Baseline: 57.6 (NR) 6 wk: 70.3 (NR) 3 mo: 79.7 (NR) 6 mo: 76.3 (NR) 12 mo: 81.5 (NR)	**Arm 1 vs. Arm 3** 6 wk: 1.4, p=NR 3 mo: 0.9, p=NR 6 mo: 10.3, p=NR 12 mo: 5.9, p=NR **Arm 2 vs. Arm 3** 6 wk: 4.2, p=0.005 3 mo: -3.3, p=NR 6 mo: 5.3, p=NR 12 mo: 10.0, p=0.007
	Adverse events 12 mo	*"One adverse event was reported in the trial. A participant in the ELE group had a partial calf tear while playing tennis. An independent sports physician did not attribute this to the ELE programme."*		

Author, Year Risk of Bias	Effect Measure Time point(s)	Intervention Baseline mean (SD) Time point mean (SD)	Comparator(s) Baseline mean (SD) Time point mean (SD)	Mean Difference at Follow-up P-value* Other results reported
	Cost 12 mo	*"Compared with ELE, prolotherapy cost an additional $90 in total and combined treatment cost $191 (table 3). For those additional costs, an additional 5.2% of the participants achieved a ≥20-point improvement in VISA-A score from prolotherapy at 12 months, whereas for the combined treatment, an additional 13% achieved this response. From the ICERs, it is apparent that combined treatment offers the best value for money (ie, the additional cost per responder is less than prolotherapy alone)."*		
Hand Pain Conditions				
Hooper, 2011[136] Some concerns	Pain-related functioning PRWE 3, 12 mo	**Prolotherapy** Baseline: 43.4 (11.9) 3 mo: NR 12 mo: NR	**Corticosteroid** Baseline: 42.2 (14.9) 3 mo: NR 12 mo: NR	**Arm 1 vs. Arm 2** 3 mo: NR 12 mo: NR Difference in differences: 3 mo: p=0.48 12 mo: p=0.04
	Physical performance Grip strength, flexion, extension, supination, pronation 12 mo	**Prolotherapy** Baseline: NR 12 mo: NR	**Corticosteroid** Baseline: NR 12 mo: NR	**Arm 1 vs. Arm 2** 12 mo: NR Difference in differences: Grip strength 12 mo: NR, p=0.40 Flexion 12 mo: NR, p=0.50 Extension 12 mo: NR, p=0.59 Supination 12 mo: NR, p=0.53 Pronation 12 mo: NR, p=0.90 Ulnar deviation 12 mo: NR, p=0.65 Radial deviation 12 mo: NR, p=0.22
Jahangiri, 2014[127] Some concerns	Pain-related functioning HAQDI 1, 2, 6 mo	**Prolotherapy** Baseline: 4.6 (1.8) 1 mo: NR 2 mo: NR 6 mo: NR	**Corticosteroid** Baseline: 4.37 (1.4) 1 mo: NR 2 mo: NR 6 mo: NR	**Arm 1 vs. Arm 2** 1, 2, 6 mo: NR Difference in differences: 1 mo: -0.5, p=0.15 2 mo: -1.0, p=0.01 6 mo: -1.0, p=0.01

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up** **P-value*** **Other results reported**
	Lateral pinch strength 1, 2, 6 mo	**Prolotherapy** Baseline: 9.6 (3.4) 1 mo: NR 2 mo: NR 6 mo: NR	**Corticosteroid** Baseline: 11.6 (3.6) 1 mo: NR 2 mo: NR 6 mo: NR	**Arm 1 vs. Arm 2** 1, 2, 6 mo: NR Difference in differences: 1 mo: -2.9, p=0.005 2 mo: -1.1, p=0.25 6 mo: -0.8, p=0.45
	Pain severity or VAS 1, 2, 6 mo	**Prolotherapy** Baseline: 5.0 (2.1) 1 mo: NR 2 mo: NR 6 mo: NR	**Corticosteroid** Baseline: 4.5 (1.6) 1 mo: NR 2 mo: NR 6 mo: NR	**Arm 1 vs. Arm 2** 1, 2, 6 mo: NR Difference in differences: 1 mo: 0.7, p=0.14 2 mo: -1.0, p=0.02 6 mo: -1.1, p=0.02
	Adverse events 6 mo	*"The participants did not report any significant side effects. However, three patients experienced transient increases in pain at the site of injection which subsided within several days. There was no sign of infection or any other complication at the site of injections."*		
Ustun, 2023[132] Some concerns	Physical performance DHI 2 wk, 1, 3 mo	**Prolotherapy** Baseline: 16.76 (10.73) 2 wk: 9.43 (7.49) 1 mo: 5.86 (4.22) 3 mo: 5.57 (3.57)	**Paraffin wav** Baseline: 8.90 (5.38) 2 wk: 4.52 (4.23) 1 mo: 4.00 (3.38) 3 mo: 3.90 (3.69)	**Arm 1 vs. Arm 2** 2 wk: 4.91, p=0.004 1 mo: 1.86, p=0.20 3 mo: 1.67, p=0.064
	Pain severity or intensity VAS 2 wk, 1, 3 mo	**Prolotherapy** Baseline: 3.86 (1.96) 2 wk: 2.29 (1.85) 1 mo: 2.86 (1.90) 3 mo: 2.86 (1.15)	**Paraffin wav** Baseline: 3.95 (1.63) 2 wk: 3.00 (1.97) 1 mo: 2.90 (1.48) 3 mo: 2.52 (1.75)	**Arm 1 vs. Arm 2** 2 wk: -0.71, p=0.22 1 mo: -0.04, p=0.69 3 mo: 0.34, p=0.46
	Pain severity or intensity VAS 2 wk, 1, 3 mo	**Prolotherapy** Baseline: 5.67 (1.39) 2 wk: 4.24 (1.37) 1 mo: 3.71 (1.85) 3 mo: 3.52 (1.29)	**Paraffin wav** Baseline: 5.33 (1.39) 2 wk: 4.00 (1.97) 1 mo: 3.57 (1.75) 3 mo: 3.33 (1.85)	**Arm 1 vs. Arm 2** 2 wk: 0.24, p=0.99 1 mo: 0.14, p=79 3 mo: 0.19, p=0.65
	Adverse events 3 mo	*"1 discontinued due to adverse events"*		
Other conditions				
Abd Elghany, 2019[133] Moderate	Pain related functioning or interference	**Dextrose prolotherapy** Baseline: 61.95 (9.75)	**rTMS** Baseline: 65.00 (8.64)	**Arm 1 vs. Arm 2** 1 mo: -4.01, p=0.294

Author, Year **Risk of Bias**	**Effect Measure** **Time point(s)**	**Intervention** **Baseline mean (SD)** **Time point mean (SD)**	**Comparator(s)** **Baseline mean (SD)** **Time point mean (SD)**	**Mean Difference at Follow-up** **P-value*** **Other results reported**
	FIQR 1 mo 1 mo	1 mo: 48.42 (8.87) 2 mo: 31.23 (10.67)	1 mo: 52.43 (11.27) 2 mo: 51.71 (12.57)	2 mo: -20.48, p=<0.001
	Pain severity or intensity VAS 1 mo 1 mo	**Dextrose prolotherapy** Baseline: 82.67 (6.19) 1 mo: 57.47 (9.57) 2 mo: 33.71 (11.32)	**rTMS** Baseline: 71.43 (10.69) 1 mo: 51.43 (10.69) 2 mo: 33.71 (11.32)	**Arm 1 vs. Arm 2** 1 mo: 6.04, p=0.112 2 mo: -13.43, p=<0.001
Gul, 2020[130] Some concerns	Pain severity or intensity VAS¶ 21 day 3 mo 6 mo 12 mo	**Dextrose prolotherapy** Baseline: 7.83 (1.19) 21 day: 4.65 (1.40) 3 mo: 3.82 (2.05) 6 mo: 3.17 (2.44) 12 mo: 3.26 (2.32)	**Exercise** Baseline: 7.43 (1.12) 21 day: 5.52 (1.08) 3 mo: 3.82 (2.05) 6 mo: 4.56 (2.33) 12 mo: 3.26 (2.32)	**Arm 1 vs. Arm 2** 21 day: -0.87, p=0.024 3 mo: -1.00, p=0.045 6 mo: -1.39, p=0.027 12 mo: -1.26, p=0.011
	Adverse events 12 mo	*"Serious complications such as cellulitis, septic joint arthritis, osteomyelitis or bleeding were not observed in any patient."*		
Senturk, 2017[134] Serious	Pain severity or intensity VAS 1 day 1 wk 4 wk	**Dextrose prolotherapy** Baseline: 7.1 (1.2) 1 day: 2.2 (0.9) 1 wk: 2.1 (1.0) 4 wk: 1.5 (0.7)	**NSAID** Baseline: 7.2 (1.2) 1 day: 2.6 (1.0) 1 wk: 2.1 (1.0) 4 wk: 2.6 (0.8)	**Arm 1 vs. Arm 2** 1 day: -0.40, p=NR 1 wk: -0.70, p=NR 4 wk: -1.10, p=0.001
	Adverse events 4 wk	*"Complications during the course of treatment included superficial skin pigmentation (n=1) for the prolotherapy group."*		

Notes. *No established MCID for outcome; direction of effect based on statistically significant difference reported by study.
Abbreviations. ACR=American College of Rheumatology; AE=adverse event; DDH=development dysplasia of the hip; DHI=Duruoz Hand Index; DLPFC=dorsolateral prefrontal cortex; DPT=dextrose prolotherapy; kg=kilogram; mg=milligram; mL=milliliter; mo=month; NR=not reported; NS=not significant; NSAID=nonsteroidal anti-inflammatory drug; PrT=prolotherapy; PT=physical therapy; PWRE=Patient rated wrist evaluation; RA= rheumatoid arthritis; rTMS=repetitive transcranial magnetic stimulation; SD=standard deviation; SLE=systemic lupus erythematosus; THA= total hip arthroplasty; VAS=Visual Analog Scale; wk=week.