

Dextrose Prolotherapy

A Narrative Review of Basic Science, Clinical Research, and Best Treatment Recommendations



Kenneth Dean Reeves, MD^{a,b,*}, Regina W.S. Sit, MD^c,
David P. Rabago, MD^d

KEYWORDS

- Prolotherapy • Dextrose • Regenerative medicine • Osteoarthritis, Knee
- Tendinopathy

KEY POINTS

- Animal models suggest specific tissue responses to hypertonic dextrose, including proliferation.
- Clinical benefit in human studies is not explained by proliferation alone; the mechanism of dextrose prolotherapy (DPT) is likely multifactorial.
- DPT is efficacious for knee osteoarthritis and likely efficacious for finger osteoarthritis and Osgood-Schlatter disease.
- Moderate-quality randomized clinical trial (RCT) evidence supports use of DPT in rotator cuff tendinopathy, lateral epicondylitis, plantar fasciopathy and nonsurgical sacroiliac pain.

INTRODUCTION

Prolotherapy is an injection-based treatment of chronic musculoskeletal pain. A general surgeon in the United States, George Hackett, formalized injection protocols in the 1950s, based on 30 years of clinical experience.¹ Prolotherapy has been identified as a regenerative injection therapy² but is differentiated from other regenerative injection therapies, such as platelet-rich plasma (PRP) and stem cell injection by the absence of a biologic agent.

^a Private Practice, 4740 El Monte Roeland Park, KS 66205, USA; ^b Department of Physical Medicine and Rehabilitation, University of Kansas Medical Center, 3901 Rainbow Blvd, Kansas City, KS 66160, USA; ^c The Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, 30-32 Ngan Shing Street, School of Public Health Building, Prince of Wales Hospital, Shatin, New Territory, Hong Kong; ^d Department of Family Medicine and Community Health, University of Wisconsin School of Medicine and Public Health, 1100 Delaplaine Ct, Madison, WI 53715, USA

* Corresponding author. 4740 El Monte, Roeland Park, KS, 66205-1348.

E-mail address: DeanReevesMD@gmail.com

Prolotherapy is increasingly popular in the United States and internationally. The current number of practitioners of prolotherapy in the United States is estimated as several thousand based on conference attendance and physician listings on relevant Web sites, including both independent physicians and members of multispecialty groups. Currently, Prolotherapy Regenerative Medicine is one of the 23 specialty colleges of the American Osteopathic Association (<http://www.prolotherapycollege.org>). Training of doctors of medicine and doctors of osteopathy is primarily outside medical schools, for example, through postgraduate-level conferences and service learning projects through universities, professional organizations, and foundations (www.fammed.wisc.edu/prolotherapy, www.aomed.org, and www.hacketthemwallpatterson.org).

Hypertonic dextrose is the most commonly used prolotherapy solution, with favorable outcomes shown in multiple clinical trials.³ It is inexpensive, readily available, and reported to be safe. This review focuses on the basic science and clinical evidence of prolotherapy using hypertonic dextrose solutions. The term *dextrose* is interchangeable with *glucose* because dextrose is the dexter (right-handed) form of glucose found in animals and humans. For this discussion, the term dextrose is preferred.

METHODS

A search of electronic databases was performed by the University of Kansas library staff, including Medline, Web of Science, and ClinicalTrials.gov, from 1980 to 2016, without language restrictions. Search specifics included (1) prolotherapy; (2) (regenerative OR tendon OR tendinopathy OR ligament OR osteoarthritis) AND (dextrose OR glucose); and (3) dextrose injection from 1980 to 2016. Basic science studies were included in this review if they featured blinded histologic, histochemical, or radiographic outcome assessment. Clinical studies were included if randomized assignment was used and a dextrose arm was included. The strength of each RCT was assessed by 2 reviewers (K.D.R. and R.W.S.S.) using the Cochrane risk of bias tool.⁴ Disagreements were resolved by consensus and presented in descriptive and tabled form.

RESULTS

Of 469 studies identified, 48 met inclusion criteria and were grouped into the following 2 areas: basic science (n = 33) and clinical research (n = 15).

Basic Science Findings

In vitro effects of dextrose on cytokine levels

Transport of dextrose into human cells uses a family of transport proteins, GLUTs 1–4, that interact with cytokines in a crucial way to signal either cell growth or repair.⁵ DNA expression changes favoring production of multiple cytokines have been measured within 20 minutes of exposure to in vitro elevation of pericellular dextrose levels to as little as 30 mM (0.54%)⁶ in a variety of animal and human cells, including fibroblasts,^{6–10} chondrocytes,^{11,12} and nerve cells.^{13,14}

Proliferative tissue changes in diabetic patients who have frequent elevations of pericellular dextrose in the 30-mM range are prominent, such as with diabetic proliferative retinopathy.¹⁵ Such effects are of unclear significance, however, given that elevated glucose levels in cases of diabetes seem to trigger interrelated complex pathophysiological mechanisms,¹⁵ which may vary greatly from the effect of brief and isolated dextrose elevation on injection in either nondiabetics or diabetics. For example, the duration of glucose elevation is important to production of favorable¹⁶ or unfavorable cytokines.¹⁷

Animal studies on cartilage and other soft tissue proliferation

Animal studies on femoral cartilage equivalent Kim and colleagues¹⁸ reported chondrocytic tissue filling of 2-mm punch lesions in adult rabbit femoral cartilage on blinded histologic evaluation 6 weeks after injection of 10% dextrose or platelet-poor plasma but not in controls (noninjected). Histologic images were limited in this Korean language study. Park and colleagues¹⁹ demonstrated a protective effect of injector-blinded weekly 10% dextrose injection versus saline injection in a rabbit osteoarthritis model (anterior cruciate ligament [ACL] transection) on masked Mankin²⁰ grading analysis at 19 weeks. The dextrose injection solution, however, contained amino acids and ascorbic acid as well, so the chondroprotective effect cannot be ascribed to dextrose alone.

Animal studies on Achilles tendon A transient reduction in tensile strength of the healthy rat Achilles tendon was not demonstrable at 0 days, 5 days, or 10 days by Martins and colleagues²¹ after masked injection of 12.5% dextrose compared with normal saline injection or no injection. Injured rat Achilles tendon (transected and sutured) injected with 20% dextrose by Ahn and colleagues²² showed significantly more fibroblasts on blinded histologic review at 4 weeks compared with injured but noninjected control tendons. Kim and colleagues²³ reported that single injection of either 5% dextrose (D5W) or 20% dextrose made hypertonic with saline (1100 mOsm) into non-injured rat Achilles tendon resulted in a significant increase in tendon diameter and fibroblast counts per high-power field (hpf) compared with equimolar (1100-mOsm) saline, suggesting a nonosmolar mechanism of dextrose-induced proliferation. In another study Kim and colleagues²⁴ showed that oral nonsteroidal anti-inflammatory drug (NSAID) (celecoxib) administration did not limit the increase in Achilles diameter or fibroblast count per hpf at 6 weeks, suggesting a noninflammatory mechanism of proliferation.

Animal studies on medial collateral ligament equivalent Jensen and colleagues²⁵ demonstrated an inflammatory response to needling alone or needling with either saline or 15% dextrose in noninjured rat MCL. One measurable difference in the inflammatory responses was that, at 24 hours postdextrose injection, ED2⁺ macrophages and CD43⁺ leukocytes increased compared with saline-injection and needle-stick controls ($P<.05$). Another study by Jensen and colleagues²⁶ using MCL ligaments with a standardized subfailure stretch injury²⁷ showed no significant differences in MCL strength or fibroblast number 3 weeks after injection with 15% dextrose or saline, although the cross-sectional area was significantly increased in the dextrose-injected MCLs ($P<.05$). This time frame was short compared with other animal model studies, perhaps too short to evaluate the effect of dextrose.²¹

Animal studies on transverse carpal ligament equivalent (subsynovial connective tissue) A study by Oh and colleagues²⁸ demonstrated noninflammatory (no neutrophil invasion at 1 week, 2 weeks, 4 weeks, or 8 weeks) collagen bundle thickening at 8 weeks in the transverse carpal ligament rabbit equivalent after a single injection of 0.05 mL of 10% dextrose into the carpal tunnel equivalent (subsynovial space) through a small incision with a 30-gauge needle. This initial study was followed by 3 randomized, masked, 2-arm studies that compared 10% dextrose versus normal saline. One²⁹, two³⁰ or four³¹ injections, given at weekly intervals, were evaluated in successive studies with findings measured at 12 weeks, 12 weeks, and 16 weeks, respectively, after the first dextrose injection. Energy absorption and load to failure of the subsynovial connective tissue (SSCT) were measured using a standardized approach.³² The 3 studies demonstrated consistent and significant increases in tensile load to rupture (**Fig. 1**), total energy

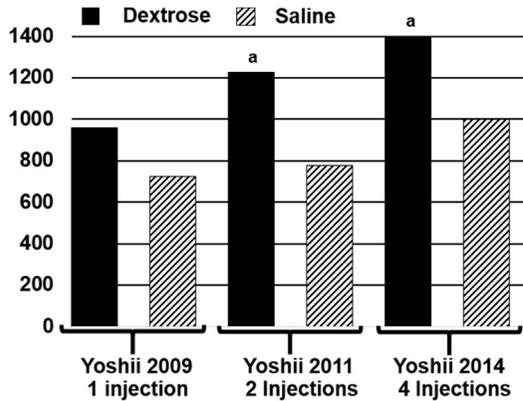


Fig. 1. Tensile load to rupture of the SSCT, comparing forepaws of each rabbit, with randomized injection of either 0.1 mL of 10% dextrose or 0.1 mL of NS on 1, 2, or 4 occasions. ^a $P < .05$.

absorption to rupture (**Fig. 2**), and thickening of the SSCT, presented in **Fig. 3** graphically and by a representative biopsy in **Fig. 4**.

Median nerve flattening was noted in the 2-weekly and 4-weekly injection studies^{30,31} along with a relative increase in latency of the median motor conduction ($P = .08$), edema in the median nerve bundles, a thinner myelin sheath and observation of poorly myelinated nerve fibers, and evidence of wallerian degeneration.³¹ The author's hypothesis that noninflammatory progressive transverse carpal ligament (or equivalent in animal) proliferative thickening (fibrosis) leads to eventual median neuropathy, is supported by these studies.

Human studies on cartilage and other soft tissue proliferation

Human studies on cartilage proliferation Rabago and colleagues³³ reported no changes in cartilage volume on blinded pretreatment and post-treatment MRI knee scans obtained at 1 year between dextrose-injected participants with symptomatic

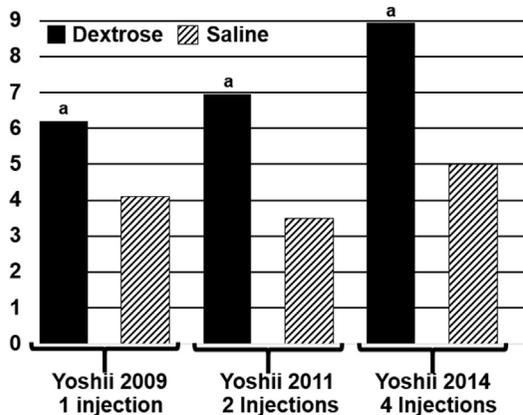


Fig. 2. Total energy absorption to rupture of the SSCT, comparing forepaws of each rabbit with randomized injection of either 0.1 mL of 10% dextrose or 0.1 mL of NS on 1, 2, or 4 occasions. ^a $P < .05$.

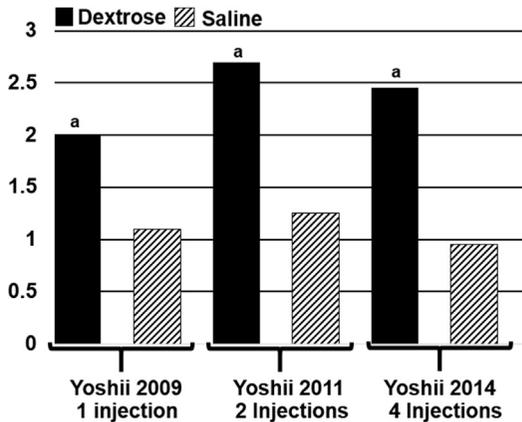


Fig. 3. Thickness of the SSCT in millimeters, comparing forepaws of each rabbit with randomized injection of either 0.1 mL of 10% dextrose or 0.1 mL of NS on 1, 2, or 4 occasions. ^a $P < .05$.

knee osteoarthritis and those who received saline injections or exercise prescription. Direct arthroscopic visualization of the joint surface, however, is superior to MRI evaluation,³⁴ and a recent study by Topol and colleagues³⁵ used pretreatment and post-treatment video-arthroscopy documentation, to compare pre and post treatment denuded femoral cortex surfaces for evidence of cartilage growth. This was by methylene blue stain for chondrocyte growth, with biopsy of new areas of methylene blue uptake after treatment to evaluate for cartilage type (I = fibrocartilage and II = hyaline-like cartilage) by quantitative polarized light microscopy (QPLM) and immunohistologic straining with photographic documentaton of the biopsy defect area. Biopsies were obtained from areas of new uptake of methylene blue with photographic

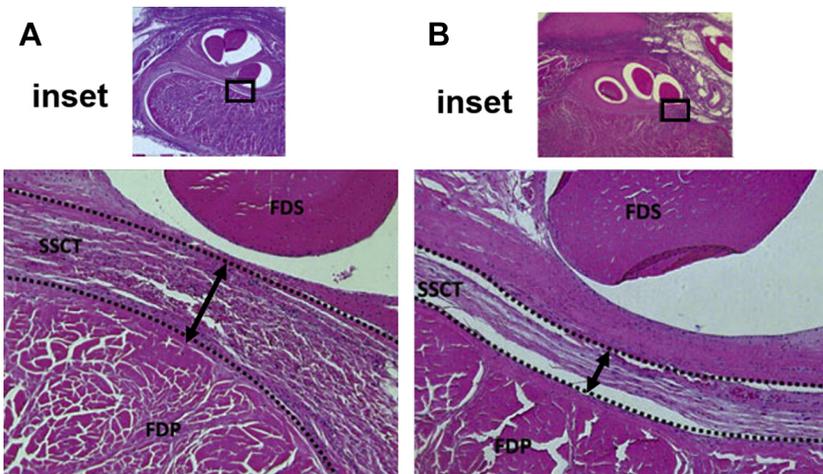


Fig. 4. Representative biopsy showing difference in thickness of the SSCT in a dextrose-injected (A) and saline-injected (B) rabbit forepaw after 4 weekly injections. The main map for A and B includes an outlined area shown below as a magnified inset map. FDP, flexor digitorum profundus; FDS, flexor digitorum superficialis. The *arrow* depicts the thickness of the subsynovial connective tissue (SSCT).

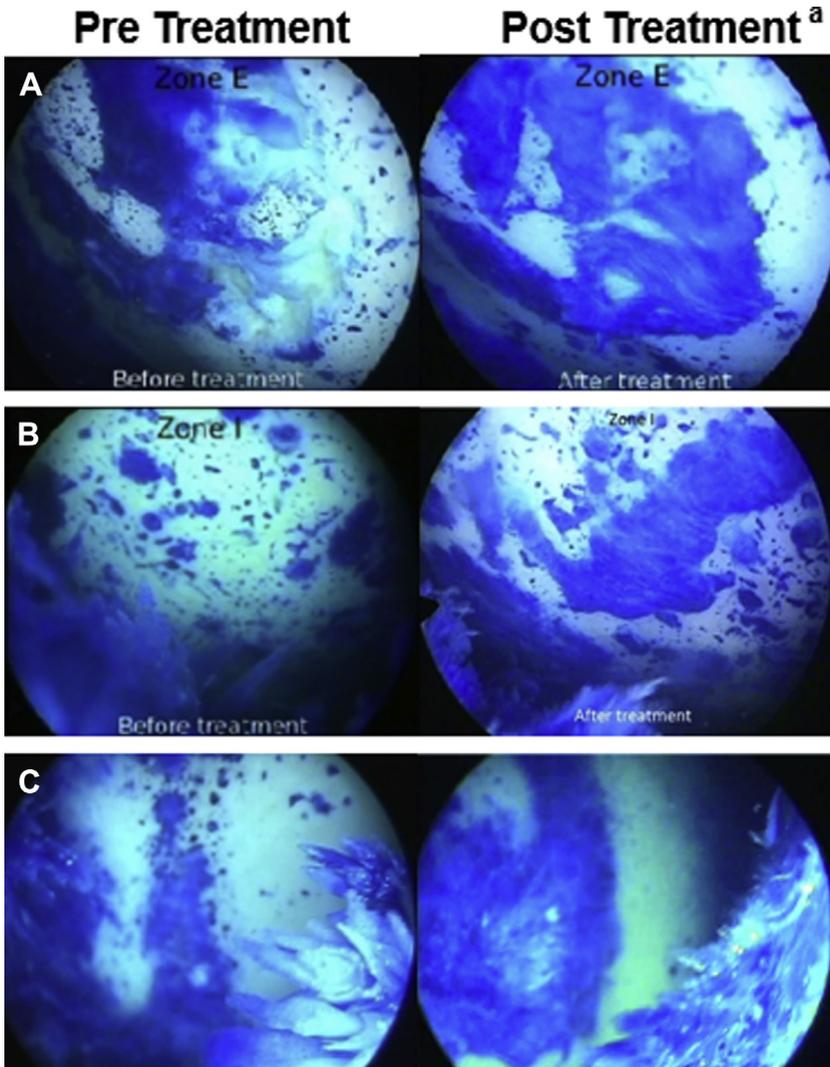


Fig. 5. Prearthroscopy and postarthroscopy showing areas of new methylene blue uptake in representative participants (A–C). ^a Area of new uptake is a combination of fibrocartilage and hyaline-like cartilage, as confirmed by QPLM and immunohistologic staining.

documentation of the biopsy defect area (Fig. 5); QPLM and immunohistologic stains showed a mixture of fibrocartilage and hyaline-like cartilage in the biopsies. Although the study was limited by the small sample size of participants and the lack of a control group, it suggests that dextrose may stimulate or mediate chondrogenesis.

Human studies on ligament or tendon proliferation Several studies have followed clinical and radiographic changes in parallel. Rabago and colleagues³⁶ demonstrated clinical benefit from dextrose injection in lateral epicondylitis in the absence of demonstrable MRI changes at 16 weeks. Bertrand and colleagues³⁷ used a systematic ultrasound rotator cuff tendinopathy grading method³⁸ to evaluate pretreatment

and post-treatment images and showed no significant differences at 9 months despite significant postprolotherapy clinical improvement. Two other second-look ultrasound studies have also indicated improvement in tendinosis, but these studies were not controlled, and standardization of ultrasound imaging is always challenging for clinical studies.^{39,40}

Human studies on a potential sensorineural mechanism

A direct sensorineural effect of dextrose injection has been proposed based on the observation that analgesia results from subcutaneous perineural injection of dextrose along tender peripheral nerves in some chronic pain patients.⁴¹ Hypothesizing a potential analgesic effect of D5W, Maniquis-Smigel and colleagues⁴² conducted a double-blind randomized controlled trial of the effect of epidural injection of D5W versus normal saline in 35 participants with chronic nonsurgical low back pain and buttock or leg pain. A significant analgesic effect was seen in those who received D5W in comparison to those who received normal saline from 15 minutes to 48 hours ($P < .05$). The speed of analgesia onset after epidural⁴² or subcutaneous⁴¹ injection of dextrose suggests a potential direct effect of dextrose on peripheral nerves.⁴¹

The transient receptor potential cation channel subfamily V member 1 (TRPV-1), formerly called the capsaicin receptor, is known to produce nociceptive pain with up-regulation.⁴³ Bertrand and colleagues⁴⁴ stimulated the TRPV-1 receptor using a capsaicin cream model to produce pain. Mannitol-containing cream or a control (vehicle) cream was then applied to the painful area in a double-blind manner. Mannitol is a 6-carbon sugar alcohol chemically related to dextrose. Pain resolution was reported faster with mannitol (Fig. 6). Researchers hypothesized that the TRPV-1 receptors were down-regulated or that other related ion channels or receptors were directly affected.^{44,45}

Summary of basic science-related literature

Key findings from basic science studies are summarized in **Box 1**. Basic science studies suggest that dextrose has independent effects that may promote local healing of chronically injured extra-articular and intra-articular tissue through

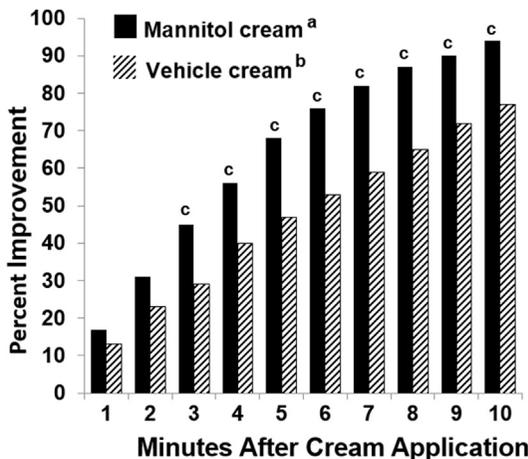


Fig. 6. Minute-by-minute improvement in burning pain after application of mannitol cream or vehicle cream to opposite sides of a lip made to burn by application of capsaicin. ^a Mannitol is similar in structure to dextrose and similar in observed analgesic effect on perineural injection but has minimal sweetness, which is easily masked in cream. ^b Natural degradation occurs in the burning pain on lips after capsaicin application. ^c $P < .05$.

Box 1**Summary of basic science findings from animal or human trials (along with primary/example reference)**

1. Dextrose elevation to as little as 0.6% around fibroblasts and chondrocytes results in a rise in the level of complex proteins (cytokines) responsible to signal growth or breakdown of human tissue *in vitro*.
2. The duration of dextrose elevation *in vitro* influences the balance of cytokines toward repair or disrepair.
3. Dextrose injection (noninflammatory; 10%) may stimulate repair of rabbit femoral cartilage punch lesions.
4. Dextrose injection (10%) may slow the development of osteoarthritis in a rabbit ACL-transection model.
5. Healthy Achilles tendon in rats shows no temporary weakening after direct intratendinous injection.
6. Healthy Achilles tendon in rats shows an increase in tendon diameter and an increase in fibroblast counts by DPT, which is not imitated by equimolar (hypertonic) saline injection and is not altered by administration of an NSAID, suggesting a mechanism of action not based primarily on hyperosmolarity or inflammation.
7. Multiple randomized and saline injection–controlled injections under the transverse carpal ligament equivalent in rabbits demonstrate a consistent and significant thickening of the ligament and an increase in both tensile load to rupture and energy absorption to rupture.
8. An increase in volume of cartilage in the human osteoarthritic knee has not been demonstrated after DPT.
9. A chondrogenic effect of intraarticular dextrose in humans has been demonstrated in a small proof of concept study using second-look arthroscopy with cartilage cell staining and biopsy for immunohistologic evaluation of cartilage type showing a mixture of fibro and hyaline-like cartilage.
10. Clinical studies on lateral epicondylitis with interval MRI testing and rotator cuff tendinopathy with internal ultrasonography have not shown a significant proliferation effect to explain clinical benefits, although evidence for improvement in tendinosis has been suggested in patellar tendinosis and plantar fasciopathy by interval ultrasound examination.

stimulating both inflammatory and noninflammatory pathways; recent studies also suggest a direct sensorineural analgesic mechanism.

Clinical Research

The most important aspects of several studies that exemplify the effects of DPT in discrete conditions—osteoarthritis, tendinopathy, and low back pain—are summarized in this section.

Hand osteoarthritis

Trapeziometacarpal joint Jahangiri and colleagues⁴⁶ compared DPT to steroid injection in a 2-arm blinded trial (**Fig. 7, Table 1**). Participants in both groups with chronic thumb pain and trapeziometacarpal joint (TMCJ) osteoarthritis received 1-mL intra-articular and 1-mL extra-articular injection through the anatomic snuff box at 0 months, 1 month, and 2 months. Effects were assessed at 6 months by a 0 to 10 Visual Analog Scale (VAS) for pain, a Health Assessment Questionnaire Disability Index (HAQ-DI), and lateral pinch strength in pounds by a hydraulic pinch gauge.

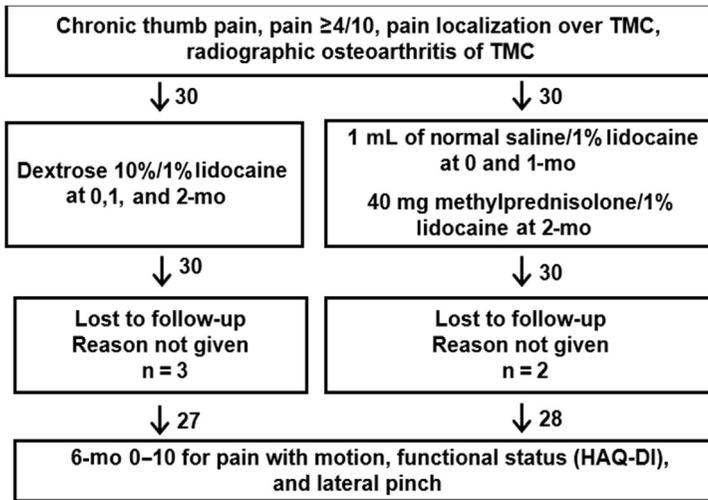


Fig. 7. Flow diagram for Jahangiri et al. (Data from Jahangiri A, Moghaddam FR, Najafi S. Hypertonic dextrose versus corticosteroid local injection for the treatment of osteoarthritis in the first carpometacarpal joint: a double-blind randomized clinical trial. *J Orthop Sci* 2014;19:737–43.)

Participants had statistically similar baseline characteristics. At 6 months the DPT group improved more in pain on movement (3.8 points \pm 0.9 points [76%] vs 2.1 points \pm 1.0 points [46%]; $P = .02$) and hand function (HAQ-DI) function score (3.0 points \pm 2.2 points [65%] vs 1.77 points \pm 1.0 points [41%]; $P = .01$) than the steroid group (Fig. 8).

Trapeziometacarpal joint, proximal interphalangeal joint, or distal interphalangeal joint of fingers 2–4 Reeves and Hassanein⁴⁷ compared DPT to blinded lidocaine injections in a 2-arm blinded trial (Fig. 9, see Table 1). Participants with chronic thumb or finger pain and radiographic hand osteoarthritis received treatment at 0 months, 2 months, and 4 months, with optional open-label dextrose injection after 6 months. All symptomatic joints were treated and participants were analyzed based on the average change across all joints treated, with effects assessed at 6 months (blinded) and 12 months (open label) using a 0 to 10 numeric rating scale (NRS) pain score and flexion range of motion.

Participants were similar statistically at baseline. The DPT group improved more in pain on movement (1.9 points \pm 1.5 points [42%] vs 0.6 points \pm 1.0 points [14%]; $P = .027$) and flexion range of motion (+8.0 \pm 3.6° vs -8.8 \pm 2.9°; $P = <.01$) than the lidocaine group at 6 months (Figs. 10 and 11). DPT administration to the lidocaine group after 6 months resulted in a similar pattern of improvement as the original dextrose group.

Summary of hand osteoarthritis Both HOA studies were double-blind trials but lacked a robust study design (see Table 1); whereas DPT is likely to be efficacious in HOA, higher-quality evidence is needed to confirm the role of DPT.

Intraarticular dextrose versus intraarticular lidocaine Reeves and Hassanein⁴⁸ compared DPT to blinded lidocaine injections in a 2-arm blinded trial using an intraarticular-only injection protocol (Fig. 12, Table 2) Participants with chronic knee

Table 1
Hand osteoarthritis risk of bias table

Source	Sequence Generation	Allocation Concealment	Blinding of Participants and Researchers	Blinding of Outcome Assessment	Incomplete Outcome Data Addressed	Selective Outcome Reporting
Jahangiri et al, ⁴⁶ 2014	Low (A computer-generated randomization)	Low (sequentially numbered sealed envelopes used for assignment)	Unclear (information was not reported)	Unclear (clinician masked to group but who assessed outcome is not stated)	Low (5/60 lost to follow-up; <10%)	Low (clinical trial registration available)
Reeves & Hassanein, ⁴⁷ 2000	Low (a random number table was utilized)	Unclear (clinicians and research coordinator masked. Assignments not made off-site)	Low (the solutions were identical in color and viscosity)	Low (assessor and database coordinator were masked)	Low (lost to follow-up dextrose 2/13 and control 0/14; <10%)	Unclear (no protocol provided)

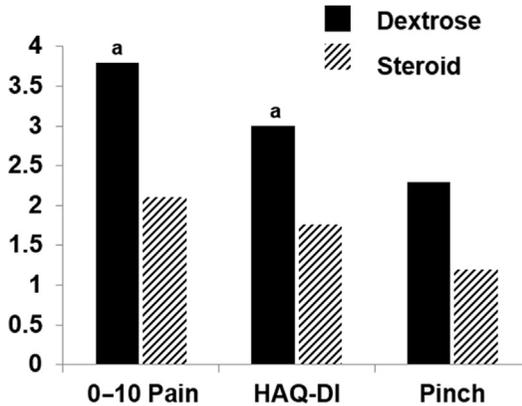


Fig. 8. Numeric improvement at 6-month follow-up on 0 to 10 VAS for pain with movement, 0 to 9 function scale (HAQ-DI hand portion), and lateral grip pinch in pounds comparing DPT and steroid injection. ^a $P < .05$.

pain and Kellgren-Lawrence (KL) stages II-IV radiographic knee osteoarthritis received injections at 0 months, 2 months, and 4 months, with optional open-label dextrose injection after 6 months. Primary measures were 0 to 10 NRS for walking pain and goniometrically measured knee range of motion.

Participants had statistically similar baseline characteristics. Range-of-motion gains favored the DPT group at 6 months ($13.2 \pm 2.1^\circ$ vs $7.7 \pm 2.2^\circ$; $P = .015$). The 2 groups did not have a statistically significant difference in walking pain (**Fig. 13**). The DPT

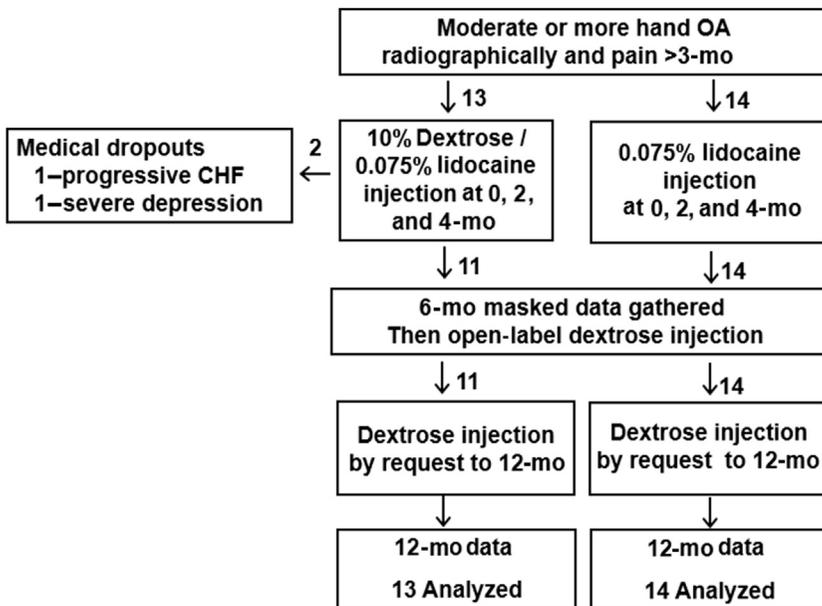


Fig. 9. Flow diagram for Reeves et al hand osteoarthritis clinical trial. (Data from Reeves KD, Hassanein K. Randomized prospective placebo-controlled double-blind study of dextrose prolotherapy for osteoarthritic thumbs and fingers [DIP, PIP and trapeziometacarpal Joints]: evidence of clinical efficacy. *J Altern Complement Med* 2000;6:311-20.)

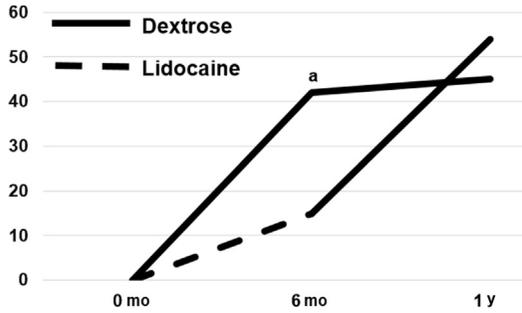


Fig. 10. Percentage improvement in finger movement pain from 0 to 6 months (masked period) after injection of dextrose or lidocaine, and from 6 months to 12 months (open label) after offering dextrose injection to all participants. ^a $P < .05$.

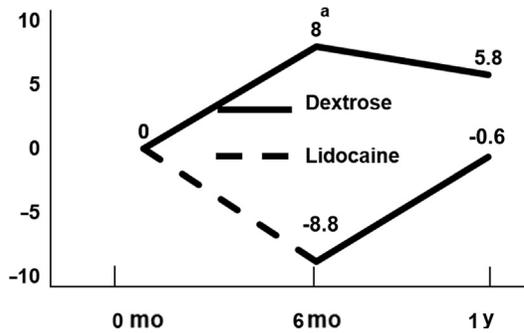


Fig. 11. Improvement in finger flexion range in degrees from 0 to 6 months (masked period) after injection of dextrose or lidocaine, and from 6 months to 12 months (open-label) after offering dextrose injection to all participants. ^a $P < .05$.

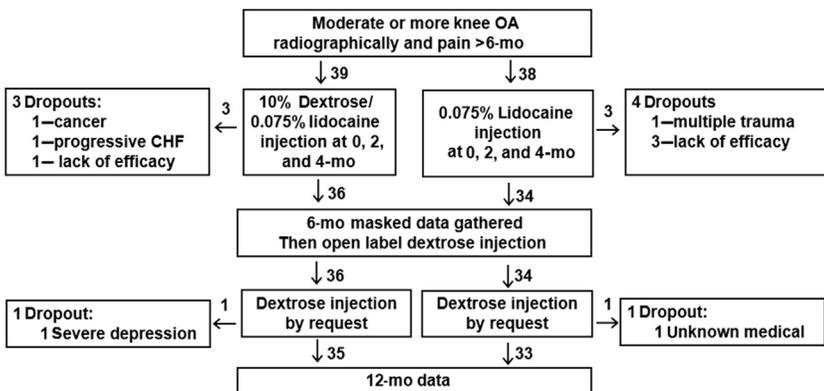


Fig. 12. Flow diagram for Reeves et al knee osteoarthritis clinical trial. (Data from Reeves KD, Hassanein K. Randomized prospective double-blind placebo-controlled study of dextrose prolotherapy for knee osteoarthritis with or without ACL laxity. *J Altern Complement Med* 2000;6:68–80.)

Table 2
Knee osteoarthritis risk of bias table

Source	Sequence Generation	Allocation Concealment	Blinding of Participants and Researchers	Blinding of Outcome Assessment	Incomplete Outcome Data Addressed	Selective Outcome Reporting
Reeves & Hassanein, ⁴⁸ 2000	Low (a random number table was used)	Unclear (relevant information was not reported)	Low (identical control solution was used)	Low (assessor and database coordinator masked)	High (9/77 [11.7%]; >10%).	Unclear (no protocol provided)
Hashemi et al, ⁴⁹ 2015	Unclear (randomization method was not mentioned)	Unclear (relevant information was not reported)	Unclear (relevant information was not reported)	Unclear (relevant information was not reported)	Unclear (relevant information was not reported)	Unclear (no protocol provided)
Dumais et al, ⁵⁰ 2012	Unclear (random sequencing method not described)	Low (opaque sealed envelopes were used)	High (open-label trial)	Low (outcome assessors masked to group)	High (>10% lost to follow-up from each group)	Unclear (no protocol provided)
Rabago et al, ⁵² 2013	Low (random sequence generated by computer)	Low (off-site assignment and opaque sealed envelopes)	Low (both active and control solutions looked similar)	Low (outcome assessor masked to group allocation)	Low (no lost to follow-up cases)	Unclear (no protocol provided)

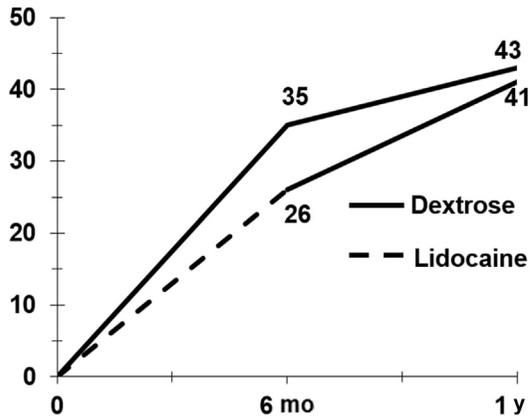


Fig. 13. Percentage improvement in knee pain with walking from 0 months to 6 months (masked period) after injection of dextrose or lidocaine, and from 6 months to 12 months (open label) after offering dextrose injection to all participants.

group, however, showed continuing improvement at 12 months and the lidocaine group, after unblinding, received DPT and also showed continuing improvement to 12 months (see [Fig. 13](#)).

Intraarticular dextrose versus intraarticular ozone Hashemi and colleagues⁴⁹ compared DPT to ozone injection in a 2-arm randomized open-label trial ([Fig. 14](#); see [Table 2](#)). Participants with KL I-II knee osteoarthritis of undocumented duration received 3 treatments at 7-day to 10-day intervals of intra-articular dextrose or intra-articular ozone. Effects were assessed at 3 months using 0 to 10 VAS pain levels and Western Ontario and McMaster Universities Arthritis Index (WOMAC), 0–100 points.

Participants had statistically similar baseline characteristics. At 3-month follow-up, the DPT group and the ozone group did not differ with respect to VAS pain level improvement (4.8 points vs 5.1 points) or WOMAC composite score improvement (25.3 vs 25.2) ([Fig. 15](#)). This is a comparison, however, of 2 active treatment groups, both of which demonstrated significant improvement in pain and WOMAC scores compared with the pretreatment baseline.

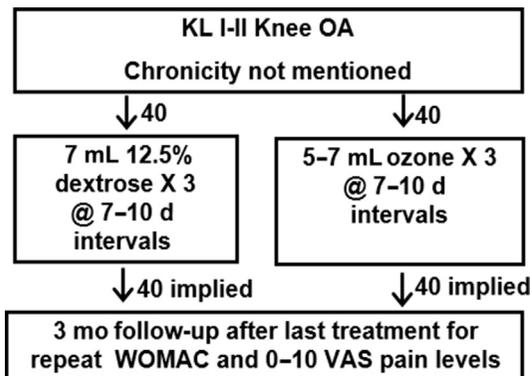


Fig. 14. Flow diagram for Hashemi et al. (Data from Hashemi M, Jalili P, Mennati S, et al. The effects of prolotherapy with hypertonic dextrose versus prolozone [intraarticular ozone] in patients with knee osteoarthritis. *Anesth Pain Med* 2015;5:e27584.)

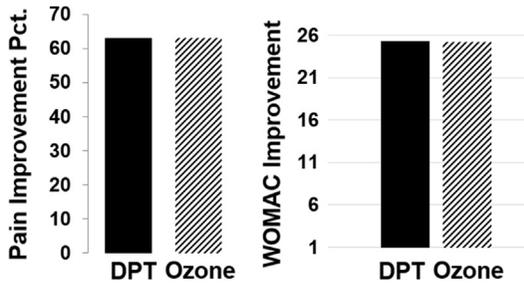


Fig. 15. Percentage improvement in 0 to 10 knee pain intensity 3 months after 3 intra-articular injections of dextrose or ozone.

Exercise plus intraarticular and collateral ligament dextrose injection versus exercise alone Dumais and colleagues⁵⁰ compared DPT plus a home-based physical therapy program to home-based physical therapy alone in a randomized crossover trial (Fig. 16; see Table 2). Participants with chronic knee pain and any KL grading received injections at 0 weeks, 4 weeks, 8 weeks, and 12 weeks of 20% dextrose intra-articularly and 15% dextrose in collateral ligaments versus therapy only. Assessments were performed at week 16. After that, the 2 arms crossed over with a second assessment at week 36.

Participants had statistically similar baseline characteristics, and 86% were KL III or IV. Improvement in composite WOMAC score was significantly more in the group receiving DPT for period 1 (21.8 ± 12.5 vs 6.1 ± 13.9 ; $P < .05$) and period 2 (9.3 ± 11.4 vs 1.2 ± 10.7 ; $P < .05$) with an overall significance of $P < .001$ using a standard statistical method of crossover design analysis⁵¹ (Fig. 17).

Intraarticular and multiple extraarticular dextrose or saline injection versus exercise alone Rabago and colleagues⁵² conducted a 3-arm RCT comparing DPT to normal saline injection and a home-based exercise group (Fig. 18; see Table 2). Participants with chronic knee pain and any radiological evidence of osteoarthritis by KL grading were randomized to receive injection at 1 weeks, 5 weeks, and 9 weeks with optional treatments at 13 and 17 weeks consistent with a published protocol.⁵³ Effects were

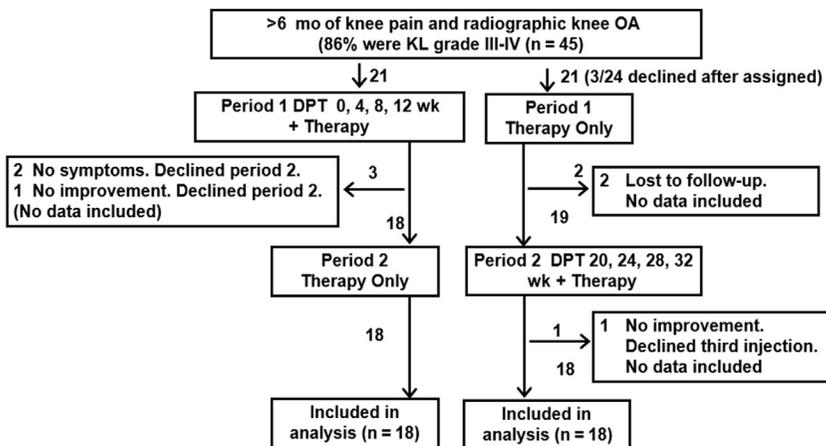


Fig. 16. Flow diagram for Dumais et al. (Data from Dumais R, Benoit C, Dumais A, et al. Effect of regenerative injection therapy on function and pain in patients with knee osteoarthritis: a randomized crossover study. *Pain Med* 2012;13:990–9.)

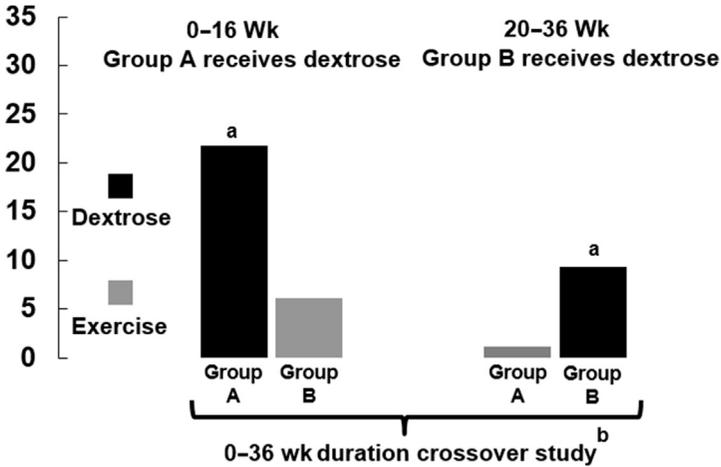


Fig. 17. Ordinal improvement in WOMAC Score during period 1 (0–16 weeks) and period 2 (20–36 weeks) of Dumais and colleagues' crossover trial of knee osteoarthritis treatment.⁵⁰
^a Change in DPT group greater than change in group receiving exercise alone ($P < .05$).
^b Change in DPT group greater than change in group receiving exercise along during the entire 0 to 36-week period ($P < .001$).

assessed using the WOMAC questionnaire at 0 weeks, 5 weeks, 9 weeks, 12 weeks, 26 weeks, and 52 weeks.

Participants had statistically similar baseline characteristics and 63% were rated KL III–IV. By 9 weeks, participants receiving DPT reported substantial improvement in the WOMAC composite score (13.91 ± 3.2 points) compared with both control therapies (Fig. 19). Maximum benefits were recorded by 24 weeks and persisted through 52 weeks. At 52 weeks, the DPT group improved more than either the saline injection or exercise groups in WOMAC composite score (15.3 ± 3.3 vs 7.6 ± 3.4 vs 8.2 ± 3.3 , respectively; $P < .05$) (see Fig. 19).

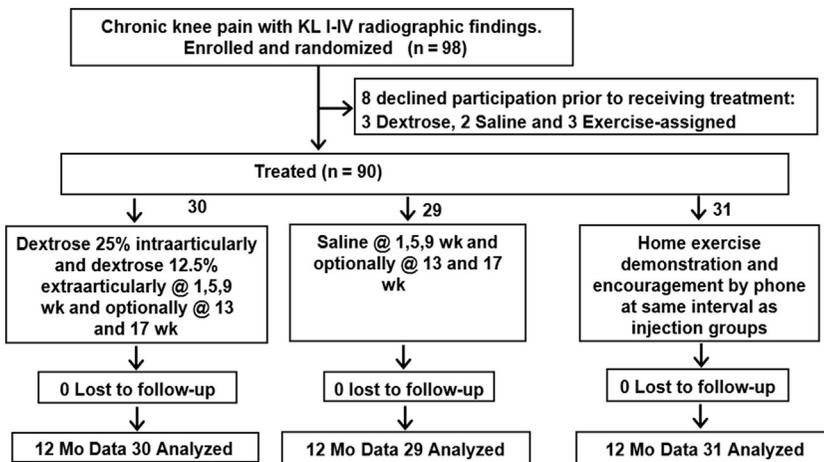


Fig. 18. Flow diagram from Rabago et al knee osteoarthritis clinical trial. (Data from Rabago D, Patterson JJ, Mundt M, et al. Dextrose prolotherapy for knee osteoarthritis: a randomized controlled trial. *Ann Fam Med* 2013;11:229–37.)

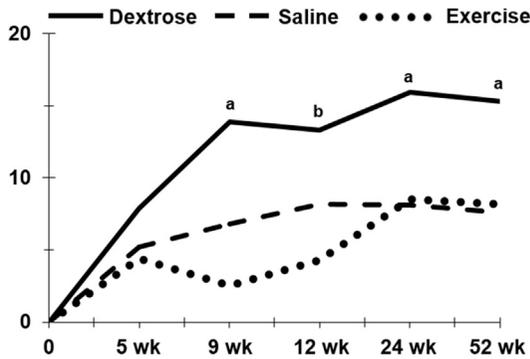


Fig. 19. Improvement in WOMAC score comparing dextrose injection, saline injection and home-based exercise in knee OA. ^a Change in DPT group greater than change in either saline or exercise group. ($P < .05$). ^b Change in DPT group greater than change in exercise group ($P < .05$). Change in DPT group not significantly greater than in the saline group.

Summary of knee osteoarthritis The role of DPT in knee osteoarthritis is supported by level I evidence in the form of a systemic review and meta-analysis published in 2016.⁵⁴ A standardized mean difference was used to evaluate the effect size. Four RCTs were included in the review.^{33,48,50,52} Analysis of pooled data indicated that peri-articular and intra-articular hypertonic dextrose knee injections in 3 to 5 sessions have a statistically significant and clinically relevant effect in the improvement of WOMAC composite score (0.81; 95% CI, 0.18–1.45, $P = .012$; $I_2 = 53.6\%$); functional subscale (0.78; 95% CI, 0.25–1.30; $P = .001$; $I_2 = 34.5\%$); and pain subscale (0.62; 95% CI, 0.04–1.20; $P = .035$; $I_2 = 46.2\%$) at 12 to 16 weeks compared with formal at-home exercise. Benefits, generally higher than the minimal clinically important difference (MCID), were sustained to 1 year.

Low back pain or sacroiliac pain

Low back pain Yelland and colleagues⁵⁵ compared DPT to normal saline injection in addition to either exercise or usual care in a factorial design (Fig. 20, Table 3). Participants with chronic back pain and failure of conservative treatment received 6 treatments at 2-week intervals and then as needed at 4 months, 6 months, 12 months, and 24 months, consistent with a published protocol.⁵⁶ Participants were masked to solution type for the 24-month period of the study. Effects were assessed using the Roland-Morris (R-M) disability score and a 0 to 100 VAS for pain. Data were collected at 12 months and 24 months.

Participants had statistically similar baseline characteristics. At 12 months, no statistical difference was found between exercise and normal activity. DPT and not significant (NS) groups also did not differ in terms of the change in R-M disability score (5.5 ± 0.9 ; 36% vs 4.5 ± 0.8 ; 26%; $P = .60$) or pain intensity measured by a VAS (18.6 ± 3.2 points; 36% vs 18.4 ± 4.0 points; 33%; $P = .93$). However, 12-month improvements exceeded the minimally important change for the R-M disability score (30% or 5.0)⁵⁷ in the dextrose group and the 0 to 100 VAS pain score (20% or 15 points)⁵⁷ in both groups (Fig. 21). Greater than 50% pain reduction was observed in 46% and 36% of dextrose and saline groups respectively at 12 months. Improvements were durable to 24 months.

Sacroiliac pain Kim and colleagues⁵⁸ compared DPT to steroid injection in a 2-arm blinded trial (Fig. 22, see Table 3). Participants with pain more than 3 months localized below the posterior superior iliac spine with positive Patrick or Gaeslen test, and pain

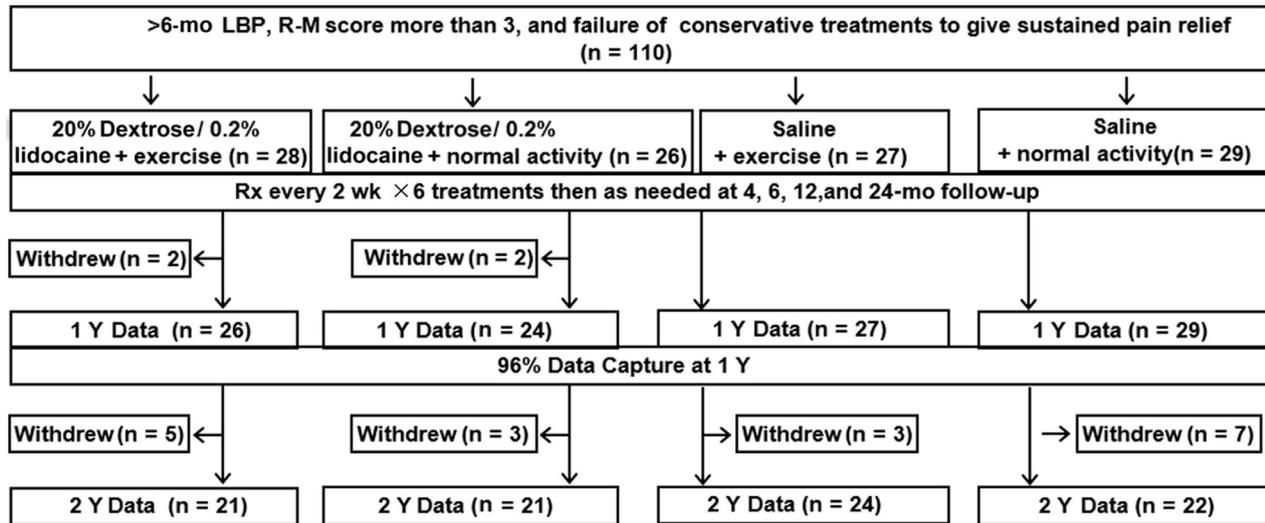


Fig. 20. Flow diagram for Yelland et al low back pain study. (Data from Yelland MJ, Glasziou PP, Bogduk N, et al. Prolotherapy injections, saline injections, and exercises for chronic low-back pain: a randomized trial. Spine 2004;29:9–16.)

Table 3
Low back pain and sacroiliac pain risk of bias table

Source	Sequence Generation	Allocation Concealment	Blinding of Participants and Researchers	Blinding of Outcome Assessment	Incomplete Outcome Data Addressed	Selective Outcome Reporting
Yelland et al, ⁵⁵ 2004	Low (computer-generated random number system)	Low (off-site randomization)	Low (off-site solution preparation)	Low (assessors masked)	Low 4% loss of data to 1 y (Intention to treat utilized)	Unclear (no protocol was provided)
Kim et al, ⁵⁸ 2010	Low (computer-generated random table)	Unclear (relevant information was not reported)	Low (researcher and patient masked. Injector not masked but no other interaction with participant)	Low (outcome assessor was blinded)	Low (only 2/48 lost to follow-up)	Unclear (no protocol was provided)

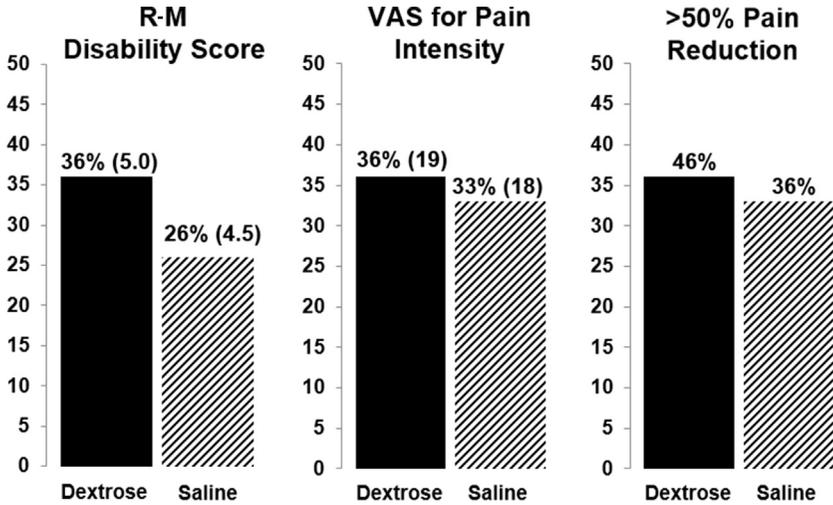


Fig. 21. Percentage improvement in R-M disability score, percentage improvement in VAS for pain intensity at 12 months, and percentage of participants with more than 50% pain reduction.

reduction more than 50% with fluoroscopic injection of 0.25% levobupivacaine, were recruited in this study. Injections were performed at 0 weeks, 2 weeks, and 4 weeks or until pain improvement more than 90% was reached. The primary measure was a 0 to 10 NRS pain scale and data were collected pretreatment and 2 weeks, 6 months, 10 months, and 15 months after the last injection.

Participants had statistically similar baseline characteristics. The dextrose group received more injections than the steroid group (2.7 ± 1.1 vs 1.5 ± 0.8) to achieve an initial 90% improvement. Fig. 23 reinforces the diagnostic specificity for SI joint pain source, with greater than or equal to 50% pain reduction achieved by all participants at 2 weeks post-treatment. **By 6 months, significantly more participants in the dextrose group than steroid group remained more than 50% improved. At 9 months**

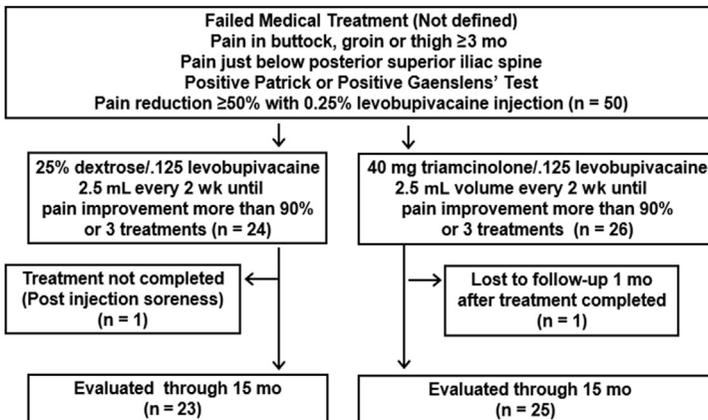


Fig. 22. Flow diagram for Kim et al sacroiliac clinical trial. (Data from Kim WM, Lee HG, Jeong CW, et al. A randomized controlled trial of intra-articular prolotherapy versus steroid injection for sacroiliac joint pain. J Altern Complement Med 2010;16:1285-90.)

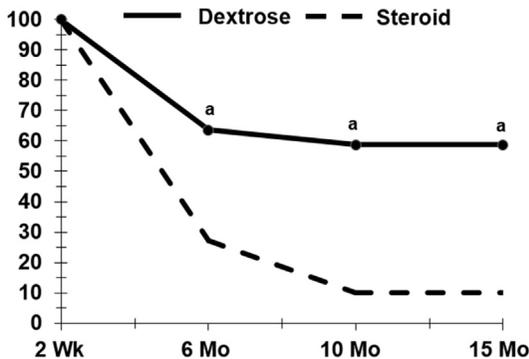


Fig. 23. Percentage of participants with greater than or equal to 50% pain reduction at 2, 6, 10, and 15 months after treatment completion for sacroiliac pain. ^a Change in DPT group greater than change in steroid group ($P < .01$).

the between group difference was maximal, ($58.7 \pm 20.8\%$ vs $10.2 \pm 16.9\%$; $P < .01$) and was sustained to follow-up at 15 months (Fig. 23).

Summary of low back pain and sacroiliac pain A Cochrane review by Dagenais and colleagues⁵⁹ in 2007 evaluated the role of prolotherapy in low back pain. The review included 5 eligible studies^{55,60–63} and concluded that prolotherapy alone is not effective for chronic low back pain; however, 4 of the 5 studies^{60–63} used a mixture of prolotherapy solutions containing dextrose, glycerine, and phenol, which may not allow full evaluation of DPT alone in low back pain. **More high-quality RCTs using DPT alone are needed to confirm or refute DPT efficacy in lumbosacral pain.** However, **intrarticular injection of dextrose into symptomatic SI joints appears to result in significant and sustained benefit in comparison injection of steroid.**⁵⁸

Osgood-Schlatter disease

Topol and colleagues⁶⁴ conducted a 3-arm RCT comparing usual-care with double-blind injection of 1% lidocaine solution with or without 12.5% dextrose (Fig. 24, Table 4). Preteens and teens with chronic anterior knee pain localized to the tibial tuberosity with a single leg squat received treatment at 0 months, 1 months, and 2 months, and all groups were offered dextrose injection after 3 months by request. The primary measure for assessment was the 0 to 7 Nirschl Pain Phase Scale (NPPS),^{65,66} chosen because a score of 0 indicates both no pain and no stiffness, consistent with full symptom resolution. A 0 to 10 NRS pain score was the secondary measure. Data were collected at 3 months (blinded) and 1 year (open-label).

Participants had statistically similar baseline characteristics. DPT resulted in more improvement of the NPPS score at 3 months than either lidocaine injection or usual care (3.9 ± 0.3 points vs 2.4 ± 0.3 points vs $1.2 \pm .4$ points, respectively; $P < .05$) and lidocaine injection was superior to usual care ($P < .05$) (Fig. 25). **At 1 year, 32/38 (84%) of knees treated with DPT were asymptomatic (NPPS = 0) compared with 6/13 (46%) or 2/14 (14%) of knees receiving lidocaine injection or usual care throughout the year (see Fig. 25).**

Temporomandibular subluxation with pain

Multiple needling with either dextrose plus mepivacaine or mepivacaine alone-
Study 1 Refai and colleagues⁶⁷ compared DPT with mepivacaine to mepivacaine-

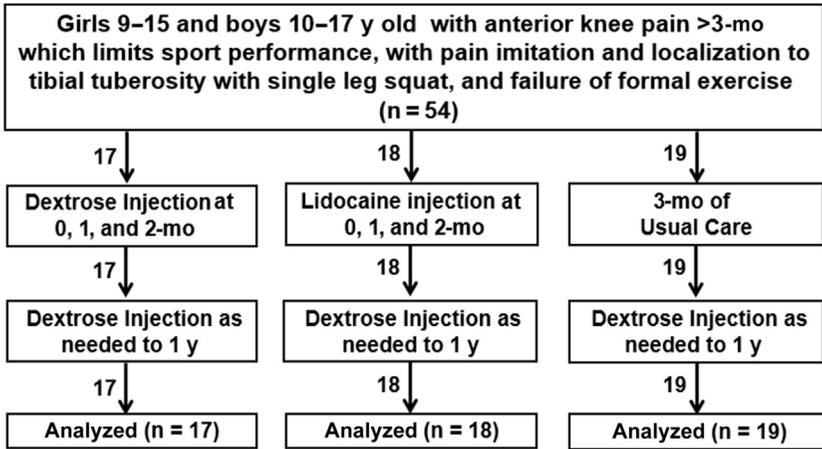


Fig. 24. Flow diagram for Topol et al. (Data from Topol GA, Podesta LA, Reeves KD, et al. Hyperosmolar dextrose injection for recalcitrant Osgood-Schlatter disease. *Pediatrics* 2011;128:e1121–8.)

only injection in a 2-arm blinded trial (**Fig. 26, Table 5**) Participants with symptoms of temporomandibular joint (TMJ) locking and facial pain, with CT confirmation of an anteriorly positioned condyle with wide mouth opening received treatment at 0 weeks, 6 weeks, 12 weeks, and 18 weeks, which involved needle insertion into superior and inferior capsular attachments, superficial to the TMJ capsule and joint capsule, and into the superior joint space. Effects were assessed by maximal interincisal opening in millimeters, 0 to 10 VAS for pain with palpation, and in the number of locking episodes per month. Data collection was 3 months after the last injection.

Participants had similar baseline characteristics. Three months after the last treatment, the dextrose group significantly improved in laxity, as reflected in a reduction of excess interincisal opening (dextrose 7 mm [8.6%] vs mepivacaine 0 mm [0%]; $P = .039$). At 3 months, 5/6 (83%) of participants in each group no longer had any pain with palpation of the TMJ, and locking episodes were no longer reported in 6/6 dextrose and 5/6 mepivacaine recipients, with no statistically significant difference between groups (**Fig. 27**).

Multiple needling with either dextrose plus mepivacaine or mepivacaine alone—Study 2 Kilic and Güngörmüş⁶⁸ also compared DPT with mepivacaine to mepivacaine-only injection in a 2-arm blinded trial (**Fig. 28, see Table 5**). Participants with symptoms of TMJ locking, facial pain, and CT confirmation of an anteriorly positioned condyle with wide mouth opening received injection at 0 weeks, 4 weeks, and 8 weeks into the superior and inferior capsular attachments, posterior disk attachment, stylomandibular ligament, and superior joint space. Effects were assessed by maximal interincisal opening in millimeters and 0 to 10 VAS for participant self-reported pain (not pain with examiner's palpation). The number of subluxations was not monitored. Data were collected at 0 and 12 months.

Participants had statistically similar baseline characteristics. At 1-year follow-up, excess mouth opening was improved significantly but equally in both dextrose and mepivacaine groups (−2.9 mm vs −2.7 mm; $P > .05$). Jaw pain substantially improved in each group (dextrose 79% and mepivacaine 68%) with no significant difference between the 2 groups (**Fig. 29**).

Table 4
Osgood-Schlatter disease risk of bias table

Source	Sequence Generation	Allocation Concealment	Blinding of Participants and Researchers	Blinding of Outcome Assessment	Incomplete Outcome Data Addressed	Selective Outcome Reporting
Topol et al, ⁶⁴ 2011	Low (a random numbers table was used for assignment)	Unclear (relevant information was not reported)	Low (identical control solution prepared in manner that blinded the subjects and treating/evaluating physicians)	Low (outcome assessor blinded)	Low (no loss to follow-up)	Unclear (no protocol was provided)

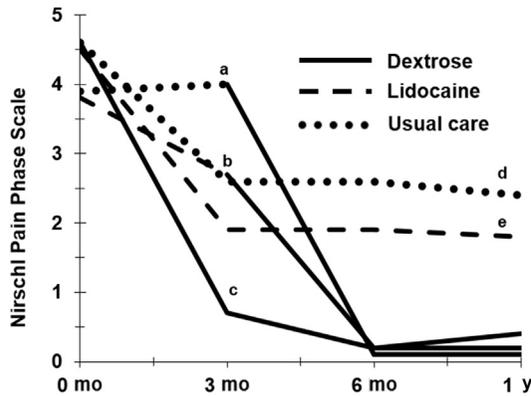


Fig. 25. Improvement in NPPS from 0 to 3 months (masked period) after injection of dextrose, injection of lidocaine, or usual care and improvement pattern from 3 months to 12 months after offering dextrose injection to all participants with Osgood-Schlatter disease. ^a Conversion of a dotted line to a solid line represents the mean NPPS score pattern of participants who received usual care for 3 months and then chose to receive dextrose injection beginning at 3 months. ^b Conversion of a dashed line to a solid line represents the mean NPPS score pattern of participants who received lidocaine injection for 3 months and then chose to receive dextrose injection beginning at 3 months. ^c NPPS change in DPT group from 0 to 3 months was greater than the NPPS change with lidocaine injection ($P < .01$) or usual care ($P < .001$). The DPT group more likely to be symptom free with sport (NPPS = 0) at 3 months than with lidocaine ($P < .01$) or usual care ($P < .001$). NPPS change in lidocaine group greater than change with usual care ($P = .024$). ^d Dextrose-treated knees more frequently asymptomatic with sport 1 year than knees treated with exercise only ($P < .001$). ^e Dextrose-treated knees more frequently asymptomatic with sport 1 year than knees treated with lidocaine only ($P = .024$).

Summary of temporomandibular dysfunction The studies discussed previously suggest that DPT does not perform better than mepivacaine injection alone in improving TMJ pain and laxity, although pain relief was substantial and laxity reduction measurable in both injection groups in each study, suggesting a potential therapeutic effect of

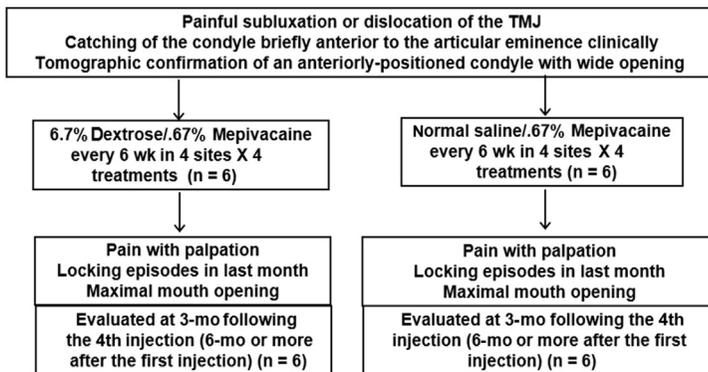


Fig. 26. Flow diagram for Refai et al. (Data from Refai H, Altahhan O, Elsharkawy R. The efficacy of dextrose prolotherapy for temporomandibular joint hypermobility: a preliminary prospective, randomized, double-blind, placebo-controlled clinical trial. *J Oral Maxillofac Surg* 2011;69:2962–70.)

Table 5
Temporomandibular dysfunction painful subluxation risk of bias table

Source	Sequence Generation	Allocation Concealment	Blinding of Participants and Researchers	Blinding of Outcome Assessment	Incomplete Outcome Data Addressed	Selective Outcome Reporting
Rafai et al, ⁵⁷ 2011	Unclear (random sequence mentioned but method was not described)	Unclear (relevant information was not reported)	Low (the solutions were identical in color)	Low (outcome assessor blinded)	Unclear (relevant information was not reported)	Unclear (no protocol was provided)
Kilic & Güngörmüş, ⁶⁸ 2016	Unclear (random sequence mentioned but method was not described)	Unclear (relevant information was not reported)	Unclear (relevant information was not reported)	Unclear (relevant information was not reported)	High (4/30 [13.3%] lost to follow-up and intention to treat not used)	Unclear (no protocol was provided)

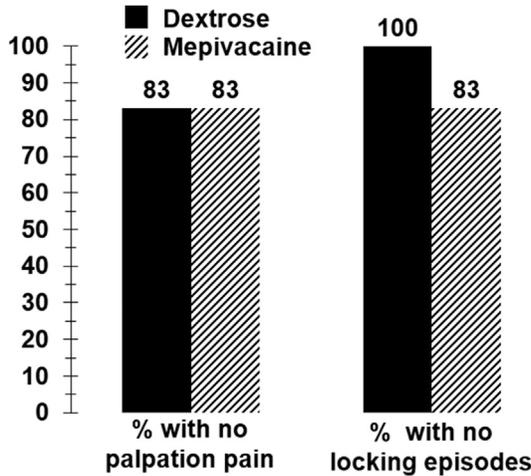


Fig. 27. Percentage of participants with no palpation pain and with no locking episodes 3 months after treatment completion in participants with TMD hypermobility and locking.

injection alone. Both studies had a high risk of bias (see Table 5). Larger double-blinded RCTs with more robust methods should be conducted to confirm the efficacy of DPT in the TMJ and preferably include those with other types of TMD, because those with painful hyperlaxity are a subset of the those with TMD. One such larger RCT has recently reported favorable preliminary results.⁶⁹

Tendinopathy

Achilles tendinosis Yelland and colleagues⁷⁰ compared DPT to eccentric loading exercises (ELEs) and to combined DPT and ELEs in a 3-arm randomized trial (Fig. 30, Table 6). ELE is a standard-of-care treatment of Achilles tendinosis with a high success rate.^{71,72} Participants had 6 weeks or more of midsubstance Achilles tendinopathy, and clinical severity on the Victorian Institute of Sport Assessment-Achilles

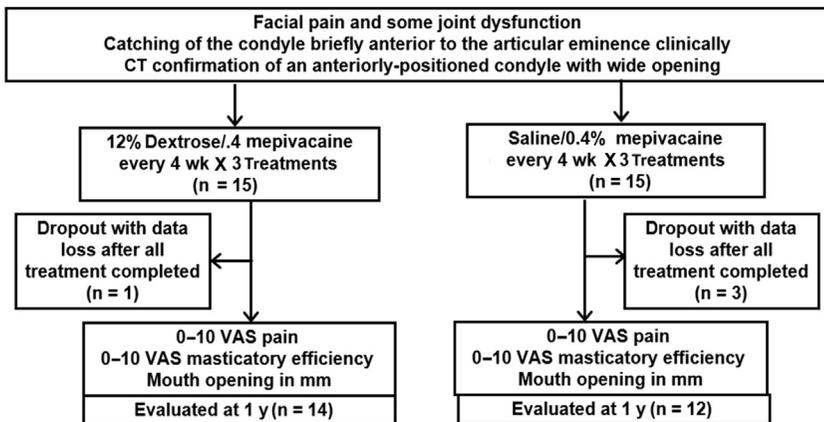


Fig. 28. Flow diagram for Kilic et al. (Data from Kilic SC, Güngörmüş M. Is dextrose prolotherapy superior to placebo for the treatment of temporomandibular joint hypermobility? A randomized clinical trial. *Int J Oral Maxillofac Surg* 2016;45(7):813-9.)

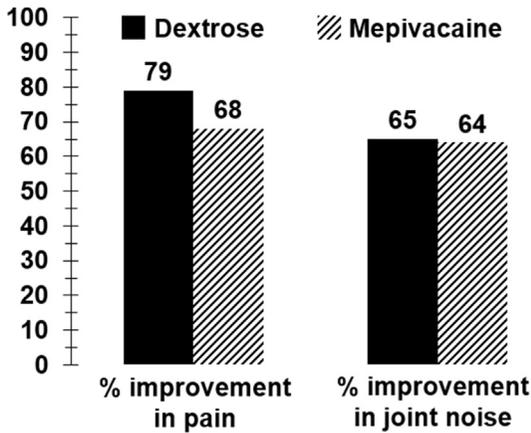


Fig. 29. Percentage improvement in a 0 to 10 VAS for jaw pain and a 0 to 10 VAS for joint noise 1 year after treatment completion in participants with TMD hypermobility and locking.

(VISA-A) score of less than 80 for athletes and less than 70 for nonathletes (higher scores are better). The primary effect measure was the 0 to 100 point VISA-A, measured to 12 months. Injection-treated participants received 9.5 ± 2.8 weekly peritendinous subcutaneous injections according to a published protocol⁷³; ELE participants performed eccentric training for 12 weeks according to a published protocol,⁷⁴ and combined treatment participants received 8.7 ± 2.9 DPT injections with ELE.

Participants had statistically similar baseline characteristics. By 12 months the improvement in VISA-A scores was more in the combined treatment than ELE-only group (41.1 ± 11.8 vs 23.7 ± 8.1 ; $P = .007$) (Fig. 31) with intermediate results for the DPT-only group (27.5 ± 14.7). One partial Achilles tear occurred in the ELE group.

Lateral epicondylitis Rabago and colleagues³⁶ compared DPT versus injection of dextrose plus sodium morrhuate versus delayed treatment in a 3-arm trial with

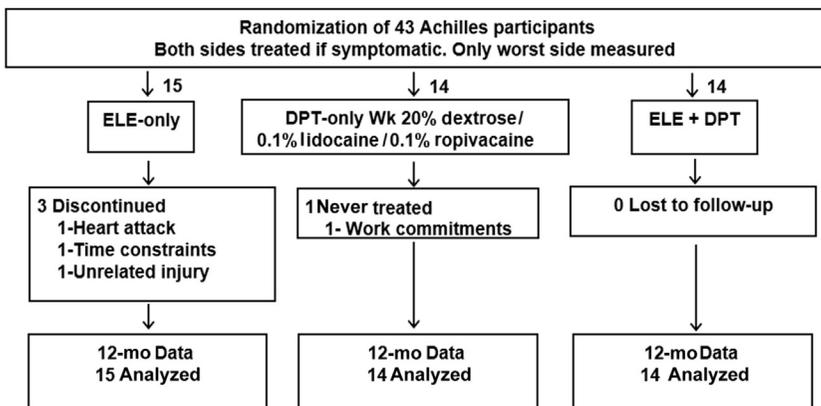


Fig. 30. Flow diagram for Yelland et al Achilles tendinosis clinical trial. (Data from Yelland MJ, Sweeting KR, Lyftogt JA, et al. Prolotherapy injections and eccentric loading exercises for painful Achilles tendinosis: a randomised trial. Br J Sports Med 2011;45:421-8.)

Table 6

Tendinopathy risk of bias table

Source	Sequence Generation	Allocation Concealment	Blinding of Participants and Researchers	Blinding of Outcome Assessment	Incomplete Outcome Data Addressed	Selective Outcome Reporting
Yelland et al, ⁷⁰ 2011	Low (computer-generated random table)	Low (randomization generated and administered by a separate statistics center)	High (open-label trial)	Low (outcome assessor blinded)	Low (4/43 [$<10\%$] dropped out, but intention to treat used)	Unclear (no protocol was provided)
Rabago et al, ³⁶ 2013	Low (computer-generated randomization)	Low (randomization generated and administered by a separate statistical center)	Unclear (relevant information was not reported)	Low (outcome assessor blinded, identical solution)	Low (no lost to follow-up)	Measures agree with (clinical trial registration)
Kim & Lee, ⁷⁶ 2014	High (randomization by odd and even sequence number)	High (predictable allocation sequence)	High (PRP and dextrose were 2 different modalities)	Unclear (relevant information was not reported)	Low (0/11 dextrose and 1/10 PRP lost to follow-up)	Unclear (no protocol provided)
Bertrand et al, ³⁷ 2016	Low (randomization by blocks of 3)	Low (allocation by off-site pharmacists)	Low (the solutions were identical, participants and injectors blinded)	Low (outcome assessor blinded)	Low (loss to follow-up: 5/77 [6.5%] Intention to treat used)	Low (measures agree with clinical trial registration)

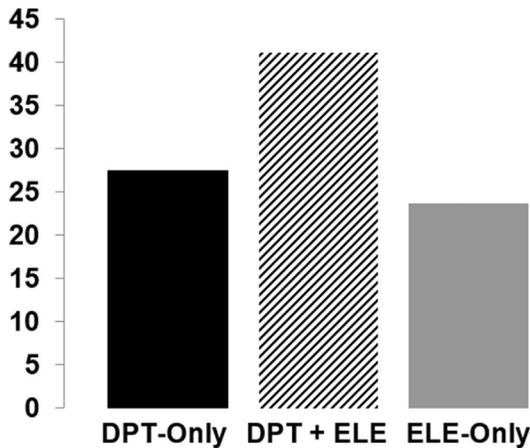


Fig. 31. Improvement in VISA-A score at 12 months comparing DPT versus combination DPT + ELE versus ELE-only in participants with Achilles tendinopathy.

masked injection arms (Fig. 32, see Table 6). Participants received treatment at 1 week, 4 weeks, and 8 weeks with data collection at 16 weeks, at which time those in the wait-and-see group were offered DPT as their incentive for participation. The prolotherapy groups were then followed to 32 weeks. Effects were assessed using the composite Patient Rated Tennis Elbow Evaluation (PRTEE) score, which has pain (5-item) and function (10-item) subscales⁷⁵ and dynamometer-measured grip strength in pounds.

At 16 weeks, the dextrose-morrhuate group improved significantly more than the wait-and-see group on the composite PRTEE (17.5 [54%] vs 9.3 [18%]; $P < .05$) (Fig. 33), and the dextrose group outperformed the wait-and-see group on the function subscale of the PRTEE (7.3 vs 5.4; $P < .05$), and further improvement was noted at 32 weeks. Grip strength improvement at 16 weeks in the dextrose group was significantly greater than either the dextrose-morrhuate or wait-and-see groups (65.0 pounds vs 0.9 pounds vs 18.7 pounds, respectively; $P < .05$) (Fig. 34). At 32 weeks, the difference between the 2 injection groups was no longer significant for grip strength improvement (69.5 pounds [dextrose] vs 38.6 pounds [dextrose-morrhuate]; $P > .05$) (see Fig. 34).

Plantar fasciosis Kim and colleagues compared DPT to injection of autologous PRP in a 2-arm blinded trial (Fig. 35, see Table 6). Participants with chronic medial arch pain imitated with palpation over the plantar fascia origin and failure of conservative treatments, such as NSAIDs, stretching PT, night split, arch supports, or steroid injection received injection at 0 and 2 weeks. Effects were assessed using the Foot Function Index (FFI).^{77,78} Data were collected before the first injection, and 2 weeks, 10 weeks, and 28 weeks after the last injection.

The 2 groups were statistically similar at baseline. The between-group difference in improvement on the FFI did not reach statistical significance at any point in time (Fig. 36). This is a comparison, however, of 2 active treatment groups, both of which resulted in clinically significant improvement at more than twice the minimal perceptible change of 11.9 for the FFI⁷⁹ in these participants with a mean pain duration of 2.9 years.

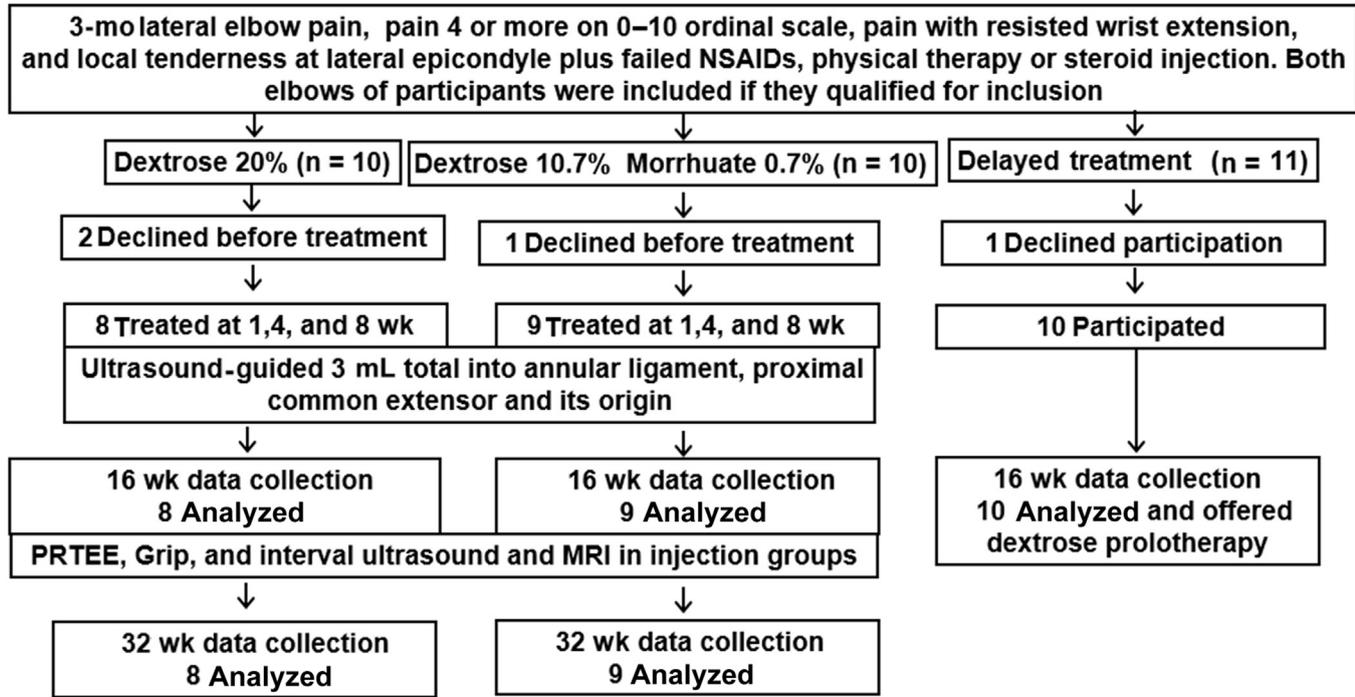


Fig. 32. Flow diagram for Rabago et al lateral epicondylitis clinical trial. (Data from Rabago D, Lee KS, Ryan M, et al. Hypertonic dextrose and morrhuate sodium injections [prolotherapy] for lateral epicondylitis [tennis elbow]: results of a single-blind, pilot-level, randomized controlled trial. Am J Phys Med Rehabil 2013;92:587–96.)

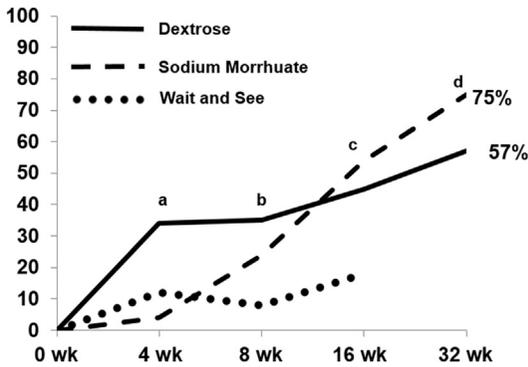


Fig. 33. Percentage improvement in composite PRTEE over time in treatment of lateral epicondylitis. ^a Change in DPT group greater than change in dextrose-morrhuate injection group and wait-and-see group ($P<.05$). ^b Change in DPT group greater than change in the wait-and-see group ($P<.05$) but not greater than change in the dextrose-morrhuate group. ^c Change in the dextrose morrhuate group greater than change in the wait-and-see group ($P<.05$). Change in the DPT group greater than wait-and-see group on functional component of PRTEE. No significant difference between DPT and dextrose-morrhuate. Change in DPT group significantly greater than baseline ($P<.05$). ^d No significant difference between DPT and dextrose-morrhuate. Change in DPT and dextrose-morrhuate group significantly greater than baseline ($P<.05$).

Rotator cuff tendinopathy Bertrand and colleagues³⁷ conducted a 3-arm blinded RCT comparing DPT (group 1) to lidocaine alone on painful entheses (group 2) to lidocaine alone with superficial injections over painful entheses without touching the entheses (group 3) (Fig. 37, see Table 6). Participants with chronic shoulder pain and confirmation of rotator cuff tendinopathy by clinical examination and ultrasound

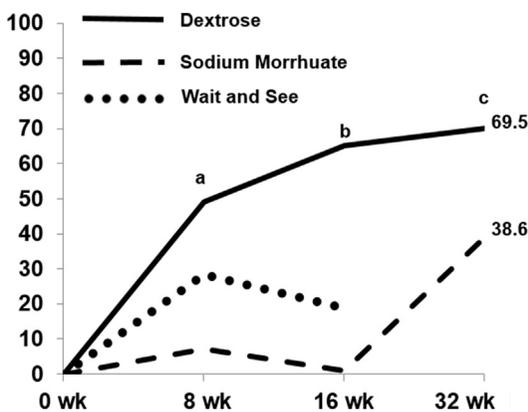


Fig. 34. Improvement in grip strength over time in pounds. ^a Change in DPT group greater than change in dextrose-morrhuate injection group and wait-and-see group ($P<.05$). ^b Change in DPT group greater than change in dextrose-morrhuate injection group and wait-and-see group ($P<.05$). Change in DPT group significantly greater than baseline ($P<.05$). ^c No significant difference between DPT and dextrose-morrhuate. Change in DPT group significantly greater than baseline ($P<.05$).

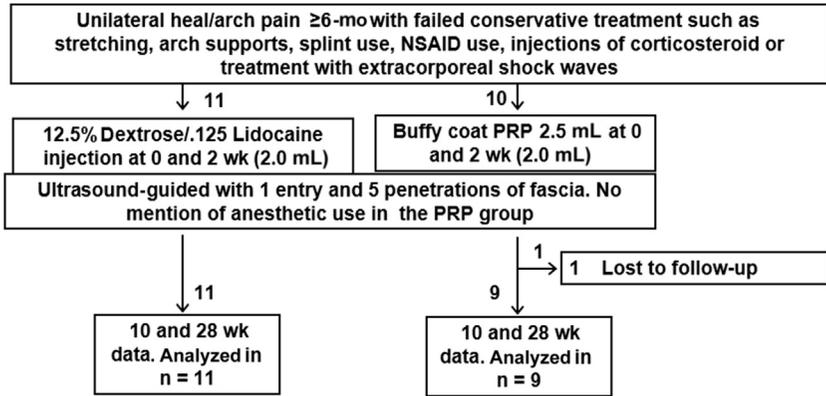


Fig. 35. Flow diagram for Kim et al plantar fasciosis clinical trial. (Data from Kim E, Lee JH. Autologous platelet-rich plasma versus dextrose prolotherapy for the treatment of chronic recalcitrant plantar fasciitis. *PM R* 2014;6:152–8.)

confirmation received injections at 0 months, 1 months, and 2 months, and all received physical therapy during the period of injection. The primary outcome measure was achieving an improvement in maximal current shoulder pain greater than or equal to 2.8 points on a 0 to 10 VAS score, which is twice the MCID for shoulder pain improvement in rotator cuff tendinopathy.³⁰ Data were collected at 0 and 9 months for pain improvement and for 0 to 10 participant satisfaction (10 = completely satisfied.)

Participants had statistically similar baseline characteristics. A post-treatment questionnaire indicated that blinding of participants was effective. The percentage of participants reaching shoulder pain improvement greater than or equal to 2.8 points on the 0 to 10 VAS at 9 months favored DPT over the superficial lidocaine injection control (59% vs 27%; $P = .017$) (Fig. 38) but not the lidocaine entheses injection group (59% vs 37%; $P = .088$). Patient satisfaction was greater in the DPT group than with superficial lidocaine injection (6.7 ± 3.2 vs 3.9 ± 3.1 ; $P = .003$) but not compared with lidocaine entheses injection (6.7 ± 3.2 vs 4.7 ± 4.1 ; $P = .079$).

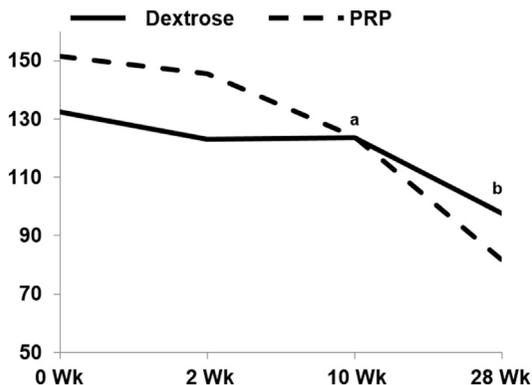


Fig. 36. Change in FFI from 0 to 28 weeks. ^a Change in PRP group significantly better than baseline ($P < .05$). No significant difference between PRP and DPT. ^b Change in PRP and DPT group significantly better than baseline ($P < .05$). No significant difference between PRP and DPT.

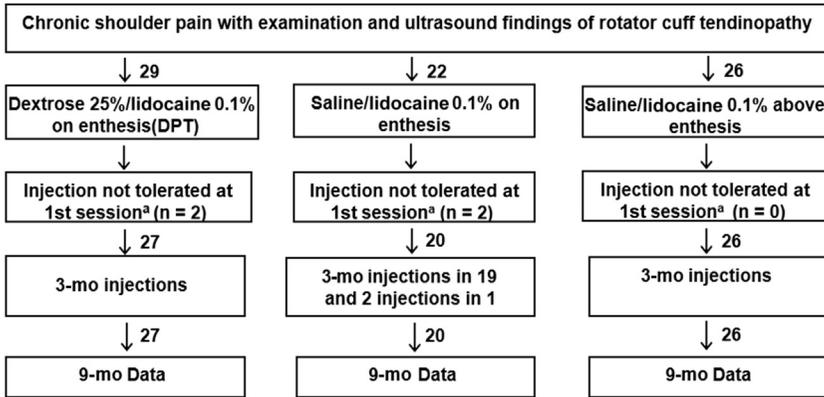


Fig. 37. Flow diagram for Bertrand et al. ^a Anesthetic blebs were not used to enhance the ability to blind between superficial and deep injection groups. Several patients could not tolerate injection. (Data from Bertrand H, Reeves KD, Bennett CJ, et al. Dextrose prolotherapy versus control injections in painful rotator cuff tendinopathy. Arch Phys Med Rehabil 2016;97:17–25.)

Summary of tendinopathy Studies show that prolotherapy is effective in both reducing pain and improving function for lower limb tendinopathy and fasciopathy, with no study reporting a mean negative or non significant outcome after prolotherapy injection; DPT injections provides equal or superior short-term, intermediate-term, and long-term results to alternative treatment modalities, including ELEs for Achilles tendinopathy, plantar fasciopathy treatment with PRP, and usual care or lignocaine injections for Osgood-Schlatter disease. The use of DPT on rotator cuff tendinopathy needs more study to confirm its role.

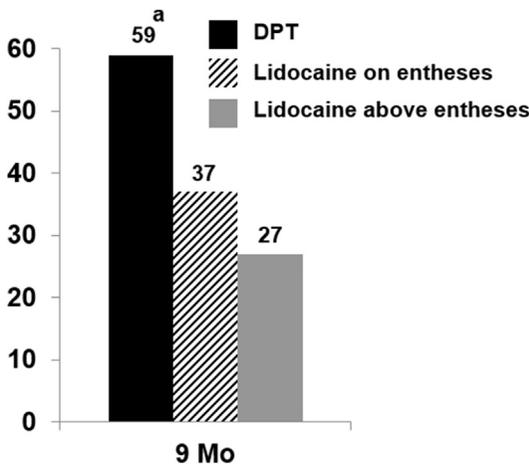


Fig. 38. Percentage of participants improving greater than or equal to 2.8 points on the 0 to 10 VAS at 9 months. ^a Percentage of DPT participants favored DPT over the superficial lidocaine injection control ($P = .017$) but not the lidocaine entheses injection group ($P = .088$).

CONTRAINDICATIONS, SIDE EFFECTS, AND ADVERSE EVENTS

Contraindications

The few absolute contraindications for DPT include local abscess, cellulitis, or septic arthritis. Knowledge of a patient's anticoagulation status is important, however, because injection at the facet level is contraindicated in the anticoagulated patient.⁸¹

Box 2

Summary of findings from controlled clinical trials in humans (Strength of Recommendation Taxonomy scale)

1. Finger/thumb osteoarthritis: 2 RCT results; 1 found that 10% dextrose results in superior pain reduction and functional improvement compared with corticosteroid injection in trapeziometacarpal (TMC) OA, and the second found that DPT improves pain and joint flexibility significantly more than anesthetic injection in symptomatic TMC thumb and 2nd through 5th finger proximal interphalangeal (PIP) and distal interphalangeal (DIP) osteoarthritis (B).
2. Knee osteoarthritis: 3 RCT results; 1 study found that DPT improves knee range of motion in advanced knee osteoarthritis, 1 that DPT plus exercise improves pain, function, and stiffness significantly more than exercise alone, and 1 that DPT improves function and pain levels significantly in comparison with both injection control and exercise. A recently published meta-analysis concluded that the effects of DPT are both positive and significantly beneficial in symptomatic knee osteoarthritis (A).
3. Low back pain: 1 study found that DPT is not superior to injection of multiple entheses with saline, although treatment in both groups resulted in significant and sustainable functional gains to 1 year (B).
4. Sacroiliac pain: 1 study found that intraarticular injection of dextrose compared with steroid injection resulted in superior long-term pain reduction in those with a diagnostic-injection-confirmed sacroiliac pain source (B).
5. Osgood-Schlatter disease: 1 study found that DPT significantly improves the frequency of unrestricted sport and asymptomatic sport compared with usual-care exercise and lidocaine injection. (A)
6. Temporomandibular dysfunction with painful laxity: only 1 of 2 studies showed that DPT reduced laxity in painful lax TMJs in comparison with anesthetic injection. Jaw pain and subluxation improved markedly in both treatment groups in each study, for reasons unclear, but potentially a needling effect on multiple entheses (B).
7. Achilles tendinopathy: 1 study found that DPT combined with standard-of-care therapy (ELEs) results in better functional outcomes and improved pain reduction at 12 months than ELEs alone (B).
8. Lateral epicondylitis: 1 study found that DPT and DPT/morrhuate improve function and pain levels in comparison with a delayed treatment control group (B).
9. Plantar fasciosis: 1 study found that DPT and PRP injection both result in clinically significant functional improvement in a treatment comparison study (B).
10. Rotator cuff tendinopathy: 1 study found that, in patients who receive physical therapy, DPT results in improved pain reduction at 9 months compared with superficial anesthetic control injection (B).

Per Ebell and colleagues⁸⁵ article on SORT, where A = good quality and consistent patient-oriented evidence, B = limited quality of inconsistent patient-oriented evidence, and C = usual practice, consensus, disease-oriented evidence, opinion, or case series evidence.

Common Side Effects

Pain with injection is common, although this may be minimized considerably with use of anesthetic blebs, coupled with tumescent type anesthetic injection through such blebs. Mild bleeding also occurs with injection. Postinjection soreness is common, typically waning by the second day,⁵³ and mild or limited analgesic use may be helpful for some patients.⁵² A self-limited pain flare may occur, typically managed with acetaminophen. NSAIDs are not routinely used postprocedure, due to theoretic interference with 1 or more DPT mechanisms, although histologic evidence does not support that theory.²⁴

Adverse Events

Dagenais and colleagues⁸² reported the largest survey to date of adverse events associated with prolotherapy to the spine. They sought responses from 308 practicing prolotherapists, with a response rate of 50%. Of the 472 adverse events reported, 174 were spinal headaches, with 123 pneumothoraces, 73 systemic reactions, 54 nerve damage events, 27 hemorrhages, 9 nonsevere spinal cord insults to spinal cord and 2 disk injuries. Their conclusion was that adverse effects are similar to other needling procedures about the spine.

No adverse effects were noted in the randomized trials reviewed in this article. The authors' review for other reports in peer-reviewed literature of DPT-related complications revealed 1 case report of isolated partial R arm numbness related to improper technique in a cervical injection⁸³ and 1 case report of epidural abscess time-related to perispinal proliferant injection.⁸⁴ Despite the rarity of such events, complications after DPT directly relate to the training of the injector and consistency in use of customary antiseptic precautions.⁸⁵ As prolotherapy progressively moves toward

Box 3

Best practice recommendations with strength of recommendation per Strength of Recommendation Taxonomy scale

1. TMC/finger osteoarthritis: in chronic TMC osteoarthritis DPT is preferable to steroid injection, and in symptomatic PIP and DIP arthritis DPT may reduce pain and stiffness (B).
2. Knee osteoarthritis: DPT should be considered, because its effects are both positive and significantly beneficial in symptomatic knee osteoarthritis (A).
3. Low back pain: no definite recommendations can be made based on literature available.
4. Sacroiliac pain: DPT is preferable to steroid injection in those with sacroiliac pain confirmed by diagnostic injection.
5. Osgood-Schlatter disease: consider DPT for adolescents with Osgood-Schlatter disease who have persistent pain or limitation of sport despite physical therapy.
6. Temporomandibular dysfunction with painful laxity: no definite recommendations can be made based on literature available.
7. Achilles tendinopathy: the combination of DPT and ELEs may be utilized as potentially superior to either treatment alone.
8. Lateral epicondylitis: DPT may improve pain and function in those who have failed NSAIDs, standard physical therapy or steroid injection.
9. Plantar fasciosis: DPT may improve functional status in plantar fasciosis.
10. Rotator cuff tendinopathy: consider DPT administration in combination with physical therapy, or with insufficient or nonsustained response to physical therapy.

routine incorporation in university training programs, systemization of methods is expected to further reduce adverse events.

SUMMARY OF CURRENT LITERATURE STATUS, STRENGTH OF RECOMMENDATION EVIDENCE, AND BEST TREATMENT RECOMMENDATIONS

Box 2 is a summary of clinical findings from the RCTs published at the time of this writing along with their Strength of Recommendation Taxonomy (SORT).⁸⁶ **Box 3** lists the current best practice recommendations for use of DPT for osteoarthritis, low back pain and sacroiliac pain, Osgood-Schlatter disease, TMD, and various enthesopathies (Achilles, lateral epicondylitis, and rotator cuff).

INCORPORATING PROLOTHERAPY INTO PRACTICE

DPT is a treatment method with broad applications and this article cannot address methods in any detail. Methods of prolotherapy are described in several textbooks.^{1,87,88} Training in DPT is not typically available in medical school and residency programs. More commonly, post graduate training is available through conference settings including the University of Wisconsin Prolotherapy Education and Research Lab (UW-PEARL; <http://www.fammed.wisc.edu/prolotherapy/research>) in concert with the Hackett Hemwall Foundation (www.hacketthemwall.org/WELCOME.html), the American Association of Orthopaedic Medicine (www.aaomed.org), and the American Osteopathic Association of Prolotherapy Regenerative Medicine (www.prolotherapycollege.org)

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