Prolotherapy

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DESCRIPTION

Prolotherapy is a procedure intended to aid in healing and strengthening of the ligaments and tendons by prompting the release of growth factors, such as cytokines, increasing the effectiveness of existing circulating growth factors to stimulate tissue repair or growth. The injecting agent is administered directly into torn or stretched ligaments which induces inflammation and stimulates endogenous repair mechanisms. The mechanism of action is not well-understood but may involve local irritation and/or cell lysis. Prolotherapy may also be referred to as; regenerative injection therapy, proliferant injection, proliferation therapy, prolo, joint sclerotherapy, growth factor stimulation injection, nonsurgical tendon, ligament, and joint reconstruction or prolozone.

Prolotherapy may involve a single or a series of injections of the proliferating agent, which are often diluted with a local anesthetic. Agents used for prolotherapy include zinc sulfate, psyllium seed oil, combinations of dextrose; glycerin; and phenol or dextrose alone. Polidocanol and sodium morrhuate, vascular sclerosants, have also been used to sclerose areas of high intratendinous blood flow associated with tendinopathies. Additional treatments of prolotherapy are purposed, over a period of a few weeks to allow a gradual buildup of tissue to restore the original strength to the area and may relieve pain.

Prolotherapy

Clinical Context and Therapy Purpose
The purpose of prolotherapy in patients who have musculoskeletal pain, osteoarthritic pain, or tendinopathies of the upper or lower limbs is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of prolotherapy improve the net health outcome in those with musculoskeletal pain, osteoarthritic pain, or tendinopathies of the upper or lower limbs?

The following PICO was used to select literature to inform this review.

Patients
The relevant populations of interest are individuals who suffer from musculoskeletal pain, osteoarthritic pain, or upper- or lower-limb tendinopathies.

Interventions
The therapy being considered is prolotherapy.

Injections are administered in an outpatient setting.

Comparators
The following therapies and practices are currently being used to treat musculoskeletal pain, osteoarthritic pain, and upper- or lower-limb tendinopathies: observation and other conservative therapies.

Outcomes
The general outcomes of interest are reductions in pain and medication use, improvements in function, and treatment-related adverse events (mostly mild but in rare instances serious).

Varying by condition, injections are administered over a series of sessions, which can last from several weeks to months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;

To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;

Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Achilles Tendonitis
(2011) Yelland et al. reported a multicenter randomized trial of prolotherapy or exercises for Achilles tendonitis in 43 patients. Inclusion criteria were a diagnosis of unilateral or bilateral mid-portion Achilles tendinosis with pain between 2 cm and 7 cm proximal to the calcaneal attachment in adults older than 18 years with activity-related pain for at least 6 weeks. The sample size was limited by the available resources and slow recruitment rate, resulting in 15 participants in the eccentric loading exercise group, 14 in the prolotherapy group, and 14 in the combined treatment group. Randomization was conducted by a central site and resulted in a lower median duration of pain in the combined treatment group (6 months) than in the exercise alone (21 months) or prolotherapy alone (24 months) groups. An average of 4.4 injections per treatment was directed at tender points in the subcutaneous tissues adjacent to the affected tendon, with 4 to 12 weekly treatments until participants attained pain-free activity or requested to cease treatment. Participants were instructed to perform eccentric loading exercises. Clinical reviews were performed at 3, 6, and 12 weeks to check technique and progress. Mean increases in the validated Victorian Institute of Sport Assessment-Achilles score were 23.7 for exercise alone, 27.5 for prolotherapy alone, and 41.1 for the combined treatment. At 6 weeks and 12 months, these increases were significantly greater for combined treatment (exercise and prolotherapy) than for exercise alone. The predefined minimum clinically important increase of 20 points or more on the Victorian Institute of Sport Assessment-Achilles was obtained by 12 subjects in the combined treatment group and 11 each in the exercise alone and prolotherapy alone groups; the difference was not statistically significant. The percentage of patients achieving full recovery (Victorian Institute of Sport Assessment-Achilles score of ≥90 at 12 months) was 53% for exercise alone, 71% for prolotherapy alone, and 64% for the combined treatment group; but these differences were not significant. This trial was limited by the combination of a small number of subjects per group, unequal durations of pain in the treatment groups at baseline, and minimal differences in the number of patients showing recovery (11/14 vs 12/15, respectively).

Chronic Neck and Back Pain: Systematic Reviews
(2008) A systematic review by Dagenais et al. of the same five studies included in the Cochrane review and by one of the same authors concluded that despite its use for more than 50 years, there is no evidence of efficacy for prolotherapy injections alone for chronic low back pain. The same evidence was evaluated in a systematic review conducted by Chou et al. (2009) for the American Pain Society. In this case, reviewers also concluded that prolotherapy was ineffective when used alone to manage chronic low back pain.

(2007) A Cochrane review by Dagenais et al. evaluated prolotherapy for chronic low back pain and concluded that “When used alone, prolotherapy is not an effective treatment for chronic low back pain.” Reviewers also concluded that, although confounded by cointerventions and heterogeneity of studies, “When combined with spinal manipulation, exercise, and other interventions, prolotherapy may improve chronic low-back pain and disability.”

Chronic Neck and Back Pain: Randomized Controlled Trials
Three randomized trials were identified that focused on the use of injections of dextrose, glycerin, and phenol as a treatment for low back pain. Yelland et al. (2004) reported on a partially blinded RCT of prolotherapy injections, saline injections, and exercises for chronic low back pain in 110 subjects. While decreases in pain and disability were noted in all study groups, there were no significant differences between treatment groups at 12 and 24 months. Therefore, the effects of prolotherapy did not significantly exceed placebo effects.

Klein et al. (1993) reported on a trial that randomized 79 patients with low back pain to a series of 6 weekly injections using either saline or a proliferant solution of dextrose, glycerin, and phenol. Thirty of the 39 patients assigned to the proliferant group achieved a 50% or greater diminution in pain compared with 21 of the 40 in the placebo group. While the incremental benefit of the treatment group was statistically significant (p=.04), blinding of the treatment groups was not maintained because those assigned to the proliferant group experienced a clinically recognizable local inflammatory response.

Ongley et al. (1987) reported on a trial of 81 patients with low back pain who were randomized to spinal manipulation plus prolotherapy or a control group that received less forceful spinal manipulation, less local anesthesia, and placebo injections of saline. Although improved responses were reported for the treatment group, it was not possible to evaluate the contribution of prolotherapy compared with the impact of the different types of spinal manipulation.

Chronic Soft Tissue Injuries: Systematic Reviews
(2021) Goh et al. conducted a systematic review and network meta-analysis of the efficacy of prolotherapy in comparison to other treatments for patients with chronic soft tissue injuries (e.g., tendinopathies and enthesopathies) having a mean symptom duration lasting at least 6 weeks. The review included 91 articles (87 RCTs with 5859 subjects) involving upper limb (74%), lower limb (23%), and truncal/hip (3%) injuries. The "other treatments" within the network meta-analysis were primarily injections such as blood derivatives, corticosteroid, hyaluronic acid, and botulinum toxin. The primary outcome of interest was pain, evaluated mainly at a measurement time point 6 months post-intervention. If a 6-month time point was not available, then measurements of pain at other times were evaluated. Results revealed that prolotherapy had no statistically significant benefits over other therapies with regard to pain relief at all assessed time points. However, prolotherapy was associated with better pain improvement over placebo at selected time points and injuries, primarily shoulder (<4 and >8 months) and elbow (4

to 8 months) injuries. The authors noted that more than 50% of included studies had a high overall risk of bias and some comparisons were connected by a small number of RCTs.

(2020) Chung et al. published a systematic review and meta-analysis involving 10 RCTs (N=358) that analyzed the effects of dextrose prolotherapy on tendinopathy, fasciopathy, and ligament injuries. Included studies compared the effects of hypertonic dextrose prolotherapy to placebo, no prolotherapy, or corticosteroids and evaluated either pain or activity level at follow-up. Results revealed that there were no significant differences between dextrose prolotherapy and no treatment or placebo with regard to pain control for the majority of studies. Dextrose prolotherapy was effective in improving activity only at an immediate follow-up period of 0 to 1 month (standardized mean difference [SMD], 0.98; 95% CI, 0.40 to 1.50) and was superior to steroid injections only in pain reduction at short-term follow-up (1 to 3 months; SMD, 0.70; 95% CI, 0.14 to 1.27). The authors concluded there was insufficient evidence to support the clinical benefits of dextrose prolotherapy in managing dense fibrous tissue injuries.

Lateral Epicondyle Pain: Systematic Reviews

A systematic review by Rabago et al. (2009) evaluated injection therapies for lateral epicondylitis (tennis elbow); 2 RCTs and a prospective case series on prolotherapy were included. One of the randomized trials was referenced as a report from a 2006 conference on complementary and alternative medicine; no authors were listed in the reference, and the trial does not appear to be published in the peer-reviewed literature. The second double-blind, randomized placebo-controlled trial by Scarpone et al. (2008) involved 20 patients who had elbow pain for at least 6 months and failure of conservative therapy (rest, physical therapy, nonsteroidal anti-inflammatory drugs, 2 corticosteroid injections) and who received 3 treatments (over 8 weeks) of prolotherapy or saline injection.19, There was a significant reduction in pain with prolotherapy injection (5.1 to 0.5 on a Likert scale) compared with saline injection (4.5 to 3.5). Isometric strength also improved (13 to 31lb vs. 10 to 11lb, respectively), but there was no difference in grip strength between both groups.

Lateral Epicondyle Pain: Randomized Controlled Trials

Two RCTs were published in 2020 evaluating the efficacy of dextrose prolotherapy in the treatment of lateral epicondylopathy/epicondylalgia. Both of these trials were conducted in Turkey in small patient populations. Table 1 summarizes key study characteristics and Table 2 presents a summary of results. Akcay et al (2020) enrolled 60 subjects with chronic lateral epicondylopathy with randomization to dextrose 15% prolotherapy or normal saline injection.[20,] Results revealed that there was no significant difference between groups in VAS scores at rest or in motion, Disabilities of the Arm, Shoulder, and Hand (DASH) score, and handgrip strength at any time points in terms of improvement ($p>.05$). Dextrose prolotherapy was noted to outperform normal saline with regard to effect on the Patient Rated Tennis Elbow Evaluation (PRTEE). Additionally, a significant percentage of patients in both groups achieved an MCID for all outcome measurements at the end of 12 weeks with no significant difference among the groups in terms of MCID

achievement (p>.05 for VAS at rest and motion, DASH, and PRTEE). Apaydin et al. (2020) compared the effects of dextrose prolotherapy to hyaluronic acid injection in 32 patients with lateral epicondylagia. Overall, dextrose prolotherapy was favored over hyaluronic acid for improvements in pain with activity, at night, and at rest from baseline to 12 weeks. Dextrose prolotherapy was also associated with a significant improvement in in quick-DASH scores. No between-group improvement in grip pain was observed. Results of both studies were limited by a short follow-up time, small sample size, and non-US-based, single center design.

Table 1. Summary of RCT Characteristics

Study	Countries	Sites	Participants	Interventions	
				Active	Comparator
Akcay et al. (2020)	Turkey	1	Adults with chronic lateral epicondylopathy with pain at the lateral side of the elbow lasting a minimum of 3 months despite treatment (N=60)	Dextrose 15% prolotherapy (n=30) injection given at baseline and at the end of the 4th and 8th weeks	Normal saline (n=30) injection given at baseline and at the end of the 4th and 8th weeks
Apaydin et al. (2020)	Turkey	1	Adults with a clinical diagnosis of lateral epicondylagia of at least 6 months duration, pain provoked by palpation and resisted wrist/middle finger extension or gripping, and a score of at least 30/100 on the VAS (N=32)	Dextrose 15% prolotherapy (n=16) injection at weeks 0, 3, and 6	Hyaluronic acid (n=16) injection administered as a single 30 mg dose at baseline

RCT: randomized controlled trial; VAS: visual analog scale

Table 2. Summary of RCT Results

Study	VAS (at rest)	VAS (in motion)	DASH	Pain-Free Grip Strength
Akcay et al. (2020)	12-week follow-up	12-week follow-up	12-week follow-up	12-week follow-up

Dextrose 15% prolotherapy [median (Q1-Q3)]	2.0 (1.0 to 4.0)	3.0 (1.0 to 6.0)	29.1 (5.0 to 55.0)	0.40 (0.30 to 0.42)
Normal saline [median (Q1-Q3)]	3.0 (1.0 to 4.0)	4.0 (3.0 to 6.0)	41.6 (13.0 to 42.5)	0.40 (0.30 to 0.51)
p value (between groups)	NS	NS	NS	NS
Apaydin et al. (2020)	12-week follow-up	12-week follow-up	12-week follow-up	12-week follow-up
Dextrose 15% prolotherapy (mean ± SD)	2.7 ± 1.7	3.18 ± 2.3	28.4 ± 13.4	7.3 ± 6.4
Hyaluronic acid (mean ± SD)	3.8 ± 2.09	4.81 ± 1.2	43.5 ± 17.6	4.8 ± 3.2
p value (between groups)	.04	.04	.04	.38

DASH: Disabilities of the Arm, Shoulder, and Hand; NS: nonsignificant; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analog scale.

(2019) A double-blind RCT reported by Bayat et al. compared dextrose prolotherapy with corticosteroid injection for chronic lateral epicondylitis. Patients (n=28) received a single injection during the treatment period. There was a significant improvement in VAS pain score at 1- and 3- month follow-up in both the prolotherapy group (mean difference: 1.9 and 4.4 points, respectively) and the corticosteroid group (mean difference: 1.5 and 1.9 points, respectively). No difference was observed between groups in VAS score at 1 month (p=0.74); however, prolotherapy resulted in significantly better scores at 3 months (p=0.03). At 1 month follow-up, no statistically significant difference was observed between the prolotherapy and corticosteroid groups in the Quick Disabilities of the Arm, Shoulder, and Hand (QuickDASH) score (24.3 vs 34.8, respectively; p=0.14); however, Quick DASH score was significantly better with prolotherapy compared to corticosteroid at 3 months (score=14.7 vs 34.6, respectively; p=0.01). Results of this study are limited by a short follow-up, use of a single injection regimen, small sample size, and a notable non-significant difference in baseline symptom duration and QuickDASH score.

(2011) Another small (17 subjects) double-blind, randomized trial comparing prolotherapy with corticosteroid injections for chronic lateral epicondylitis was reported by Carayannopoulos et al. Each subject received an injection at baseline followed by a second injection at 1 month. The VAS for pain, quadruple VAS, and DASH were measured at baseline and at 1, 3, and 6 months. Changes of 2 in VAS score and 12 in DASH score were considered clinically significant. Per protocol analysis showed a significant improvement in VAS and DASH scores at both 3 months (2.38 and 19.89) and 6 months (2.63 and 21.76), both respectively, for the prolotherapy group, while the corticosteroid group showed significant improvement for DASH scores at 3 months

(13.33) and 6 months (15.56). The trial was underpowered to detect a significant difference between the prolotherapy and corticosteroid groups for change in VAS, quadruple VAS, or DASH scores.

Osteoarthritis: Systematic Reviews

Wee et al. (2021) published a systematic review and meta-analysis involving 11 RCTs (N=837) that evaluated the use of dextrose prolotherapy in knee osteoarthritis. The included studies compared dextrose prolotherapy to other injectates (active or placebo) or interventions in adults with a knee osteoarthritis diagnosis and included the 3 RCTs of prolotherapy in knee osteoarthritis summarized below [Sert et al. (2020); Rabago et al. (2013); Reeves and Hassanein (2000)]. Study size ranged from 31 to 120 patients. Concentrations of dextrose intra-articular injections ranged from 10% to 25% while extra-articular dextrose injection concentrations ranged from 12.5% to 15%. The number of injections and the intervals between injections were heterogeneous across studies. Overall, the authors concluded that dextrose prolotherapy (as a single 25% intra-articular injection) may confer potential benefits in terms of pain and function for patients with knee osteoarthritis; however, the majority of included studies were at a high risk of bias. The high risk of bias in the included studies was due to deviations from Intended interventions and missing outcome data. Many trials did not discuss how missing data or trial deviations were managed and drop-outs were not clearly defined. The blinding of outcome assessors was also not well documented. For the 2 studies that were of low risk, the authors concluded that dextrose prolotherapy may be considered a treatment option in knee osteoarthritis, particularly in patients with limited treatment alternatives; however, despite good study designs, the study interventions were heterogenous across trials. The authors concluded that more high-quality RCTs are warranted to establish the benefits of this intervention.

Osteoarthritis: Randomized Controlled Trials

(2020) Sert et al. reported on an RCT of prolotherapy in symptomatic knee osteoarthritis refractory to conservative therapy. A total of 66 patients between the ages of 40 to 70 years were randomized to dextrose prolotherapy, saline injection, or a control group. Injections were blinded and given at week 0, 3, and 6, while the control group was not blinded. All groups performed an at home exercise program. At 18 weeks, the primary outcome, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale score was significantly improved in all groups, with the change in the prolotherapy group (-7.2 points) showing a significant improvement compared to the saline (-3.5 points; $p<0.002$) and control groups (-3 points; $p<0.001$). The WOMAC Total Score and pain VAS scores were also significantly improved in all treatment groups at 18 weeks, with a greater improvement in the prolotherapy group (WOMAC: -36 points and VAS: -6 points) compared to the saline group (WOMAC: -22.5 points, $p<0.001$; VAS: -2.8 points, $p<0.001$) and the control group (WOMAC: -9 points, $p=0.002$; VAS: -2.4 points, $p<0.001$). Rates of patients achieving a minimum clinically important difference of a 12-point change in the WOMAC score were not reported. There were no significant differences between the prolotherapy and saline groups on changes in Short Form 36 (SF-36) mental or physical component scores at 18 weeks. This study was

limited by its small sample size and relatively short follow-up. The majority of the included population was composed of women (85.7 to 90.9% of groups) and adhered to the at home exercise regimen (85 to 87% of groups); both of these factors have been shown to increase benefit of prolotherapy limiting generalizability of the findings to all osteoarthritis patients.

(2014) Jahangiri et al. reported on a double-blind, randomized trial that compared prolotherapy with corticosteroid for the treatment of osteoarthritis in the first carpometacarpal joint. Sixty patients were randomized to three monthly prolotherapy injections or two monthly saline injections plus a corticosteroid injection in the third month. The groups were comparable at baseline, with a visual analog scale (VAS) score for pain on pressure of six. Seven in the prolotherapy group and 6.4 in the corticosteroid group. At the six-month follow-up, the pain had decreased more (by »2 cm on the VAS; VAS final score, <2) in the prolotherapy group compared with the corticosteroid-treated group ($p<0.001$). Pain on movement and hand function had also improved to a greater extent in the prolotherapy group.

(2013) Rabago et al. reported on an RCT of prolotherapy for knee osteoarthritis. This trial was supported by the National Center for Complementary and Alternative Medicine. Ninety patients were randomized to blinded injections (3 to 5 treatments with dextrose prolotherapy or saline) or at-home exercise. All 3 groups showed improvements on the composite WOMAC, with significantly greater improvement in the prolotherapy group (15.3 points) than in the saline and exercise groups (7.6 and 8.2 points, respectively). At 52 weeks, 50% of prolotherapy patients achieved the minimum clinically important difference of a 12-point change in the WOMAC score, compared with 30% of saline-treated patients and 24% of exercise participants. Knee pain scores also improved more in the prolotherapy group. Rabago et al (2015) reported on a 2.5-year telephone follow-up from prolotherapy-treated patients in their randomized trial and from 2 uncontrolled open-label studies. The three prolotherapy groups were comparable, having undergone similar treatment courses and showing similar improvements in the WOMAC score at 52 weeks (15.3, 12.4, 15.9 points, respectively). At a mean 2.5-year follow-up (range, 1.5 to 3.5 years), the 65 patients who agreed to participate in this follow-up study had a mean 20.9-point improvement in the WOMAC score. There is a risk of bias due to the open-label design and the relatively high proportion (10%) of prolotherapy-treated patients who declined to participate in the telephone interview.

(2000) Reeves and Hassanein reported on 2 trials that used dextrose to treat osteoarthritis of the knee. The first trial randomized 68 patients with 111 osteoarthritic knees to either 3 bimonthly injections of dextrose or placebo. The patients were evaluated with a VAS for pain and swelling, frequency of leg buckling, goniometrically measured flexion, and radiographic measures of joint narrowing. As presented, the data suggested a significant improvement in both the placebo and the treatment groups, but it is difficult to determine the comparative magnitude of improvement between the groups. For example, for the various outcome measures of pain, it appears that there were probably no clinically significant incremental effects of prolotherapy compared with the placebo group.

However, for other nonpain outcomes (i.e., swelling, buckling, flexion range), prolotherapy might have been associated with a significant incremental improvement. The various outcome measures were combined and assessed using a Hotelling multivariate analysis. With this statistical measurement, prolotherapy demonstrated a statistically superior overall effect (p=.015) compared with the control group. It should be recognized that the statistical significance of this measure was most likely due to the improvements in the nonpain symptoms (i.e., swelling, buckling, flexion range). In summary, it is uncertain whether the incremental improvement in the non-pain-related outcomes of the prolotherapy group compared with the control group is clinically significant.

(2000) In a similarly designed study, Reeves and Hassanein also assessed the effectiveness of prolotherapy as a treatment of osteoarthritic thumb and finger joints. Twenty-seven patients with 150 osteoarthritic joints were randomized to 3 bimonthly injections of dextrose or water. Patients were evaluated with both VAS for pain and goniometric assessment of joint movement. Because patients had a variable number of joints injected (range, 1 to 22), the VAS score for every symptomatic joint in each patient was added together for a total and divided by the number of symptomatic joints to provide an average joint pain score for each patient. There were improvements in pain scores in both the placebo and the treatment groups, but the incremental improvement of the treatment group compared with the placebo group was not statistically significant. Regarding flexion, the treatment group reported statistically significant improvement (p=.043), while the placebo group reported a greater, statistically significant decrease (p=.011). Therefore, the statistically significant difference in flexion between the groups (p=.003) was primarily related to the decrease in the control group, with a smaller contribution related to the positive response in the treatment group. In summary, the clinical significance of an isolated finding of improved flexion without a corresponding significant improvement in pain is uncertain.

Other Musculoskeletal Pain

(2021) Bae et al. reviewed ten studies involving 750 participants were included in the final analysis. Pain scores from 6 months to 1 year after dextrose prolotherapy were significantly reduced compared to saline injection (standardized mean difference [SMD] -0.44; 95% confidence interval [CI] -0.76 to -0.11, P = 0.008) and exercise (SMD -0.42; 95% CI -0.77 to -0.07, P = 0.02). Prolotherapy yielded results similar to platelet-rich plasma or steroid injection, that it showed no significant difference in pain score. Dextrose prolotherapy is more effective in the treatment of chronic pain compared to saline injection or exercise. Its effect was comparable to that of platelet-rich plasma or steroid injection. Adequately powered, homogeneous, and longer-term trials are needed to better elucidate the efficacy of prolotherapy.

(2021) Field et al. noted prolotherapy for hamstring muscle injuries is not suggested for the treatment of acute hamstring injury, pending further research.

(2010) Kim et al. compared intra-articular prolotherapy with intra-articular corticosteroid injection for sacroiliac pain. The double-blind, randomized study included 48 patients with sacroiliac joint pain lasting three months or more, confirmed by 50% or more improvement in response to the local anesthetic block. The injections were performed on a biweekly schedule (maximum of three injections) under fluoroscopic guidance with confirmation of the intra-articular location with an arthrogram. Pain and disability scores were assessed at baseline, 2 weeks, and monthly after completion of treatment. At 2 weeks after treatment, all patients met the primary outcome measure of 50% or more reduction in pain scores, and there was no significant difference between groups. The numeric rating scale score for pain was reduced from 6.3 to 1.4 in the prolotherapy group and from 6.7 to 1.9 in the steroid group. The Oswestry Disability Index score decreased from 33.9 to 11.1 in the prolotherapy group and from 35.7 to 15.5 in the steroid group. Kaplan-Meier survival analysis showed a significantly greater percentage of patients with sustained relief following prolotherapy. At 6 months after treatment, 63.6% of patients in the prolotherapy group reported 50% or more improvement from baseline compared with 27.2% of the steroid group. At 15 months after treatment, 58.7% of patients in the prolotherapy group reported 50% or more relief compared with 10.2% of the steroid group. Key differences between this and other studies on prolotherapy were the selection of patients using a diagnostic sacroiliac joint block and the use of an arthrogram to confirm the location of the injection. Additional trials are needed to confirm the safety and efficacy of this procedure.

Rotator Cuff Tendinopathy

(2021) Kazempour Mofrad et al. compared periarticular (neurofascial) dextrose prolotherapy and physiotherapy for the short-term treatment of chronic rotator cuff tendinopathy in 66 patients with associated symptoms lasting > 3 months. Patients were randomly assigned to physiotherapy, involving 20 minutes of superficial heat using a hot pack followed by transcutaneous electrical nerve stimulation as well as pulsed ultrasound and exercise (n=33), or prolotherapy with hypertonic dextrose 12.5% and 40 mg of 2% lidocaine (n=33). This mixture was injected twice over a 1-week interval around the shoulder joint and to tender joints along the suprascapular nerve. Study outcomes included change in shoulder pain and in a disability index. Overall, 23 patients (70%) in the physiotherapy group and 29 (91%) patients in the prolotherapy group experienced a decrease in pain of 2.8 or greater on a VAS at study end. The difference between the groups was not significant (p=.072). Dextrose prolotherapy was more effective than physiotherapy at alleviating pain at 2 weeks (p<.001) after the intervention; however, both treatments were found to alleviate pain similarly at 3 months (p=.055). Regarding improvement in disability, dextrose prolotherapy was more effective than physiotherapy at 2 weeks and 3 months post-intervention (both p<.001); however, the changes in the physiotherapy group were more sustained. The authors concluded that both treatments were beneficial for chronic rotator cuff tendinopathy, at least in the short term; long-term research is needed to effectively track the pattern of clinical benefits for prolotherapy.

(2019) Lin et al. included all published or unpublished randomized controlled trials (RCTs) comparing diverse injections including corticosteroid, nonsteroidal anti-

inflammatory drugs, hyaluronic acid, botulinum toxin, platelet-rich plasma (PRP), and prolotherapy in patients with rotator cuff tendinopathy. Among the 1495 records screened, 18 studies were included in the meta-analysis. The quality of RCTs was assessed with Cochrane Risk of Bias Tool by two independent raters. The primary outcome was pain reduction, and the secondary outcome was functional improvement. Standardized mean difference (SMD) was used for pairwise and network meta-analysis. In pairwise meta-analysis, corticosteroid was more effective only in the short term in both pain reduction and functional improvement. Network meta-analysis indicated that prolotherapy significantly reduced pain compared with placebo in the long term (over 24wk; SMD: 2.63; 95% confidence interval [CI], 1.88-3.38); meanwhile PRP significantly improved shoulder function compared with placebo in the long term (over 24wk; SMD: 0.44; 95% CI, 0.05-0.84). For patients with rotator cuff tendinopathy, corticosteroid plays a role in the short term (3-6wk) but not in long-term (over 24wk) pain reduction and functional improvement. By contrast, PRP and prolotherapy may yield better outcomes in the long term (over 24wk). On account of heterogeneity, interpreting these results with caution is warranted.

(2016) Bertrand et al. reported on an RCT of prolotherapy in rotator cuff tendinopathy with supraspinatus pathology. A total of 73 participants were randomized to a blinded injection of dextrose prolotherapy (n=27), entheses saline injection (n=20), or superficial saline injection (n=27), all of which were given at months 0, 1, and 2, along with physical therapy. The primary outcome was achieving at least a 2.8-point improvement on the Numeric Rating Scale (NRS), which was obtained by phone by a blinded evaluator. Because the NRS rates pain in only whole numbers, pain levels are typically rated higher than with the VAS. For this reason, the improvement threshold was set as twice the minimal clinically important difference for VAS change in rotator cuff tendinopathy. After 9 months, the primary outcome occurred in 59% of patients in the prolotherapy group, which was significantly higher than in the superficial saline group (27%; p=0.017) and similar to the enthesis saline group (37%; p=0.088). Patient satisfaction at 9 months, assessed using a 10-point satisfaction scale (0=not satisfied, 10=completely satisfied), revealed highest satisfaction in the prolotherapy group (6.7 points), followed by enthesis saline (4.7 points; p=0.079 compared to prolotherapy) and superficial saline (3.9 points; p=0.003 compared to prolotherapy). Scores from the Ultrasound Shoulder Pathology Rating Scale did not differ significantly between groups (p=0.734). Important limitations of this study are the single-center design, which may limit generalizability to all patients. Additionally, the enthesis saline injection group was not sufficiently powered to find a difference from the prolotherapy group. Finally, the use of the NRS as an alternative to the VAS may have biased the measurement of pain improvement.

Soft Tissue Injuries

(2021) Goh et al. reported, a total of 91 articles (87 RCTs; 5859 participants) involving upper limb (74%), lower limb (23%) and truncal/hip (3%) injuries were included. At all-time points, prolotherapy had no statistically significant pain benefits over other therapies. This observation remained unchanged when tested under various assumptions and with exclusion of studies with high risk of bias. Although prolotherapy did not offer

statistically significant functional improvement compared to most therapies, its ES was consistently better than non-injections and corticosteroid injection for both outcomes. At selected time points and for selected injuries, prolotherapy demonstrated potentially better pain improvement over placebo (<4 months: shoulder [ES 0.65; 95% CI 0.00 to 1.30]; 4-8 months: elbow [ES 0.91; 95% CI 0.12 to 1.70]; >8 months: shoulder [ES 2.08; 95% CI 1.49, to 2.68]). Injections generally produced greater ES when combined with non-injection therapy. While clinical outcomes were generally comparable across types of injection therapy, prolotherapy may be used preferentially for selected conditions at selected times.

Temporomandibular Dysfunction

(2020) Zarate et al. reported several intraarticular injections, including dextrose and lidocaine, are reported to reduce pain and dysfunction in temporomandibular dysfunction (TMD) and increase maximal jaw opening; our goal was to determine whether dextrose/lidocaine outperforms sterile water/lidocaine for TMD. Design: Pragmatic randomized controlled trial. Individual were either had Chronic (≥3 months) of moderate-to-severe (≥6/10) jaw or facial pain meeting research-specific TMD criteria. The intervention was blinded intraarticular dextrose prolotherapy (DPT) (20% dextrose/0.2% lidocaine) versus intraarticular lidocaine (0.2% lidocaine in sterile water) at 0, 1, and 2 months. Participants were then unblinded and offered DPT by request for 9 additional months. The Numerical Rating Scale (0-10 points) score for facial pain and jaw dysfunction; percentage achieving ≥50% improvement in pain and dysfunction (0, 3, and 12 months). Secondary: Maximal interincisal opening (MIO; 0 and 3 months). Intention-to-treat analysis was by joint using mixed-model regression. Randomization of 29 participants (25 female, 47 ± 17 years, 43 joints) produced similar groups. Three-month pain and dysfunction improvements were similar, but more DPT-treated joints improved by ≥50% in pain (17/22 vs. 6/21; p = 0.028). The MIO improved in both groups (5.6 ± 5.8 mm vs. 5.1 ± 7.0 mm; p = 0.70). From 3 to 12 months, minimal DPT was received by original DPT and lidocaine recipients, 0.5 ± 0.9 and 0.6 ± 1.5 injections, respectively, with only 2 out of 21 joints in the original lidocaine group receiving more than 1 dextrose injection after 3 months. Twelve-month analysis revealed that joints in the original DPT group improved more in jaw pain (4.8 ± 2.4 points vs. 2.6 ± 2.9 points; p = 0.026) and jaw dysfunction (5.3 ± 2.6 points vs. 2.7 ± 2.3 points; p = 0.013). More DPT than lidocaine-treated joints improved by ≥50% in both pain (19/22 vs. 5/21; p = 0.003) and dysfunction (17/22 vs. 7/21; p = 0.040). There were no adverse events; satisfaction was high. Intraarticular DPT resulted in clinically important and statistically significant improvement in pain and dysfunction at 12 months compared to lidocaine injection.

Summary of Evidence

For individuals who have musculoskeletal pain (e.g., chronic neck, back pain), osteoarthritic pain, or tendinopathies of the upper or lower limbs who receive prolotherapy, the evidence includes small, randomized trials with inconsistent results. Relevant outcomes are symptoms, functional outcomes, and quality of life. The strongest evidence evaluates the use of prolotherapy for the treatment of osteoarthritis, but the clinical significance of the therapeutic results is uncertain. The evidence is insufficient to

determine the technology results in an improvement of the technology on health outcomes.

Practice Guidelines and Position Statements

American Association of Orthopedic Medicine (AAOM)
As of September 2020, American Association of Orthopedic Medicine (AAOM) currently has a recommendation posted online for the use of prolotherapy for back pain, with an unknown original publication date stating the following:

- "…prolotherapy is a safe efficacious therapy for the treatment of selected cases of low back pain and other chronic myofascial pain syndromes. This is based upon basic science data showing the effects of prolotherapy in animal models, clinical studies, a lengthy history of clinical use and efficacy, and increasingly widespread acceptance within the medical community. While we recognize that further basic science and clinical studies need to be done and are currently in process, we believe that prolotherapy is a safe, cost effective and efficacious therapy that can provide back pain treatment and return of function for many patients." (*Accessed September 2022*)

American College of Occupational and Environmental Medicine (ACOEM)
(2021) The ACEOM Guidelines for invasive treatment for low back disorders stats that , prolotherapy injections are Strongly Not Recommended (A), High Confidence for treatment of acute, subacute, or chronic low back pain (LBP) or radicular pain syndromes.

- There are two high-quality and five moderate-quality studies incorporated into this analysis. Prolotherapy injections attempt to address a theoretical cause for chronic LBP. It involves repeated injections of irritating, osmotic, and chemotactic agents (e.g., dextrose, glucose, glycerin, zinc sulphate, phenol, guaiacol, tannic acid, pumice flour, sodium morrhuate), combined with an injectable anesthetic agent to reduce pain, into back structures, especially ligaments, with the theoretical construct that they will strengthen these tissues. The highest quality studies in this considerably heterogeneous literature failed to show benefits. (*Accessed September 2022*)

American Pain Society (APS)
(2009, Updated March 2020) The American Pain Society (APS) updated their evidence-based clinical practice guidelines for patients with chronic low back, nonradicular pain as follows:

- Facet joint corticosteroid injection, prolotherapy (stimulation of an inflammatory response through repeated injections of irritant material), and intradiskal corticosteroid injection are not recommended. (*Accessed September 2022*)

American College of Rheumatology/Arthritis Foundation
(2019) The American College of Rheumatology/Arthritis Foundation guideline for osteoarthritis (OA) of the hand, hip, and knee:

- Conditionally recommends **against** the use of prolotherapy in patients with knee and/or hip OA, A limited number of trials involving a small number of participants have shown small effect sizes of prolotherapy in knee or hip OA. However, injection schedules, injection sites, and comparators have varied substantially between trials.
- This treatment has not been evaluated in hand OA and, therefore, no recommendation is made with regard to OA of the hand. (*Accessed September 2022*).

Regulatory Status
Prolotherapy is a procedure and, therefore, not subject to U.S. Food and Drug Administration (FDA) regulation.

Sclerosing agents have been approved by the FDA for use in treating spider and varicose veins. These sclerosing agents include Asclera® (polidocanol), Varithena® (an injectable polidocanol foam), Sotradecol® (sodium tetradecyl sulfate), Ethamolin® (ethanolamine oleate), and Scleromate® (sodium morrhuate). These agents are not currently approved as joint and ligamentous sclerosing agents.

PRIOR APPROVAL

Not applicable.

POLICY

Prolotherapy is considered **investigational** for the treatment of musculoskeletal pain and/or instability (e.g., laxity/weakness) including, but not limited to the following as the evidence is insufficient to determine that the technology results in an improvement in the net health outcomes:

- Achilles tendinitis
- Chronic neck and back pain
- Lateral epicondyle pain
- Osteoarthritis
- Rotator cuff tendinopathy
- Stimulation of tendon/ligament tissue
- Temporomandibular joint syndrome

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- M0076 Prolotherapy

SELECTED REFERENCES

- 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. The Journal of Alternative and Complementary Medicine 2000; vol 6, No 4: 311-320.
- Reeves KD, Hassanein K. Randomized prospective double-blind placebo-controlled study of dextrose prolotherapy for knee osteoarthritis with or without ACL laxity. The Journal of Alternative and Complementary Medicine 2000;vo.6, No.2:68-7
- Hauser RA. Punishing the pain- Treating chronic pain with prolotherapy. Rehab Management Feb/March 1999;26-30.
- Dechow E, Davies RK, Carr AJ, Thompson PW. A randomized, double-blind, placebo-controlled trial of sclerosing injections in patients with chronic low back pain. Rheumatology (Oxford) 1999 Dec;38(12):1255-9
- Tsatsos G, Mandal R. Prolotherapy in the treatment of foot problems. J Am Podiatr Med Assoc 2002 Jun;92(6):366-8.
- ECRI. Prolotherapy for ligament or tendon pain. Plymouth Meeting (PA): ECRI Health Technology Information Service; 2004 May 14. 8 p. (ECRI Hotline Response). Also available: http://www.ecri.org.
- Linetsky, F. S., Miguel, R., and Torres, F. Treatment of cervicothoracic pain and cervicogenic headaches with regenerative injection therapy. Curr Pain Headache Rep. 2004;8(1):41-8.
- 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(12):1285-90. PMID 21138388
- Scarpone M, Rabago DP, ZZgierska A et al. The efficacy of prolotherapy for lateral epicondylosis: a pilot study. Clin J Sport Med 2008; 18(3):248-54. PMID 18469566
- Rabago D, Best TM, Zgierska A et al. A systematic review of four injection therapies for lateral epicondylosis: prolotherapy, polidocanol, whole blood and platelet rich plasma. Br J Sports Med 2009; 43(7):471-81. PMID 19028733
- Robago D, Zgierska A, Fortney L, et al. Hypertonic dextrose injections (prolotherapy) for knee osteoarthritis: results of a single-arm uncontrolled study with 1-year follow-up. J Altern Complement Med. 2012 Apr;18(4):408-14.
- Carayannopoulos A, Borg-Stein J, Sokolof J, et al. Prolotherapy versus corticosteroid injections for the treatment of lateral epicondylosis: a randomized controlled trial. PM R. 2011 Aug; 3(8): 706-15. PMID 21871414
- 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 Dec; 69(12): 2962-70.
- CMS. National Coverage Determination (NCD) for Prolotherapy, Joint Sclerotherapy and Ligamentous Injections with Sclerosing Agents (150.7). www.cms.gov

- UpToDate. Epicondylitis (Tennis and Golf Elbow). Neeru Jayanthi M.D. Topic last updated January 13, 2014. www.uptodate.com
- UpToDate. Subacute and Chronic Low Back Pain: Nonsurgical Interventional Treatment. Roger Chou M.D. Topic last updated December 5, 2013. www.uptodate.com
- UpToDate. Treatment of Acute Low Back Pain. Christopher L. Knight M.D., Richard A. Deyo, M.D., MPH, Thomas O. Staiger, M.D., Joyce E. Wipf, M.D,, Topic last updated September 26, 2013. www.uptodate.com
- UpToDate. Overview of the Management of Overuse (Chronic) Tendinopathy. Karim Kahn, M.D., Alex Scott, PhD, RPT. www.uptodate.com
- American Association of Orthopaedic Medicine (AAOM). Position Statement. Prolotherapy for the Treatment of Back Pain. Available at: http://www.myctm.org/articles/q4-2006-oa-prolo-position-back-pain.pdf
- American Association of Orthopedic Medicine, Klein RG, Patterson J, et al. Prolotherapy for Back Pain Treatment. n.d.; http://www.aaomed.org/prolotherapy-back-pain. n.d.; http://www.aaomed.org/prolotherapy-back-pain
- American College of Occupational and Environmental Medicine (ACOEM). NGC: 9327 Invasive Treatments for Low Back Disorders Volume 63. Number 4. DOI: 10.1097/JOM.0000000000001983. Available at https://acoem.org/acoem/media/News-Library/Invasive_Treatments_for_Low_Back_Disorders-Apr-2021.pdf
- European Commission Research Directorate General (ECRDG) [website]. European Guidelines for Management of Non-specific Low Back Pain. 2004. Updated June 14, 2005. Available at: http://www.backpaineurope.org/web/files/WG2_Guidelines.pdf.
- Rabago D, Mundt M, Zgierska A, et al. Hypertonic dextrose injection (prolotherapy) for knee osteoarthritis: Long term outcomes. Complement Ther Med. Jun 2015;23(3):388-395. PMID 26051574
- 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. Sep 2014;19(5):737-743. PMID 25158896
- Sanderson, L. Bryant, A. Effectiveness and safety of prolotherapy injections for management of lower limb tendinopathy and fasciopathy: a systematic review. J Foot Ankle Res 2015 Oct (20); 8:57. doi: 10.1186/s13047-015-0114-5
- U.S. National Institutes of Health (NIH). Clinical trials: prolotherapy. Available at: https://www.clinicaltrials.gov/ct2/search.
- Bertrand H, Reeves KD, Bennett CJ, et al. Dextrose Prolotherapy Versus Control Injections in Painful Rotator Cuff Tendinopathy. Arch Phys Med Rehabil. 2016; 97(1):17-25. PMID 26301385
- UpToDate. Chou, R., Atlas, S., Subacute and chronic back pain. Topic last updated October 18, 2017. www.uptodate.com

- Chou R, Atlas SJ, Stanos SP, et al. Nonsurgical interventional therapies for low back pain: a review of the evidence for an American Pain Society clinical practice guideline. Spine (Phila Pa 1976). May 01 2009; 34(10): 1078-93. PMID 19363456
- Hung, C., Hsaio, M., et al. Comparative effectiveness of dextrose prolotherapy versus control injections and exercise in the management of osteoarthritis pain: a systemic review and meta- analysis. Journal of Pain Research. 2016 (6) 847-857.
- Seenauth C, Inouye V, Langland JO. Dextrose prolotherapy for chronic shoulder pain: A case report. Altern Ther Health Med. 2018;24(1):56-60.
- Hassan F, Murrell WD, Refalo A, Maffulli N. Alternatives to Biologics in Management of Knee Osteoarthritis: A Systematic Review. Sports Med Arthrosc Rev. 2018 Jun;26(2):79-85.
- Dagenais S, Yelland MJ, Del Mar C, et al. Prolotherapy injections for chronic low-back pain. Cochrane Database Syst Rev. Apr 18 2007; (2): CD004059. PMID 17443537
- Dagenais S, Mayer J, Haldeman S, et al. Evidence-informed management of chronic low back pain with prolotherapy. Spine J. Jan-Feb 2008; 8(1): 203-12. PMID 18164468
- Dagenais S, Haldeman S, Wooley JR. Intraligamentous injection of sclerosing solutions (prolotherapy) for spinal pain: a critical review of the literature. Spine J. May-Jun 2005; 5(3): 310-28. PMID 15863087
- Rabago D, Best TM, Beamsley M, et al. A systematic review of prolotherapy for chronic musculoskeletal pain. Clin J Sport Med. Sep 2005; 15(5): 376-80. PMID 16162983
- Yelland MJ, Mar C, Pirozzo S, et al. Prolotherapy injections for chronic low-back pain. Cochrane Database Syst Rev. 2004; (2): CD004059. PMID 15106234
- Dagenais S, Ogunseitan O, Haldeman S, et al. Side effects and adverse events related to intraligamentous injection of sclerosing solutions (prolotherapy) for back and neck pain: A survey of practitioners. Arch Phys Med Rehabil. Jul 2006; 87(7): 909-13. PMID 16813776
- Yelland MJ, Glasziou PP, Bogduk N, et al. Prolotherapy injections, saline injections, and exercises for chronic low-back pain: a randomized trial. Spine (Phila Pa 1976). Jan 01 2004; 29(1): 9-16; discussion 16. PMID 14699269
- Reeves KD, Hassanein KM. Long-term effects of dextrose prolotherapy for anterior cruciate ligament laxity. Altern Ther Health Med. May-Jun 2003; 9(3): 58-62. PMID 12776476
- Sert AT, Sen EI, Esmaeilzadeh S, et al. The Effects of Dextrose Prolotherapy in Symptomatic Knee Osteoarthritis: A Randomized Controlled Study. J Altern Complement Med. May 2020; 26(5): 409-417. PMID 32223554
- Rabago D, Patterson JJ, Mundt M, et al. Dextrose prolotherapy for knee osteoarthritis: a randomized controlled trial. Ann Fam Med. May-Jun 2013; 11(3): 229-37. PMID 23690322
- 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. Apr 2011; 45(5): 421-8. PMID 19549615

- Bayat M, Raeissadat SA, Mortazavian Babaki M, et al. Is Dextrose Prolotherapy Superior To Corticosteroid Injection In Patients With Chronic Lateral Epicondylitis?: A Randomized Clinical Trial. Orthop Res Rev. 2019; 11: 167-175. PMID 31819675
- Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Rheumatol. Feb 2020; 72(2): 220-233. PMID 31908163
- Wee TC, Neo EJR, Tan YL. Dextrose prolotherapy in knee osteoarthritis: A systematic review and meta-analysis. J Clin Orthop Trauma. 2021 May 20;19:108-117. doi: 10.1016/j.jcot.2021.05.015. PMID: 34046305; PMCID: PMC8144680.
- Chang, Yu-Ju et al. "Effects of Hyperosmolar Dextrose Injection in Patients With Rotator Cuff Disease and Bursitis: A Randomized Controlled Trial." Archives of physical medicine and rehabilitation vol. 102,2 (2021): 245-250. doi:10.1016/j.apmr.2020.08.010
- Goh, Siew-Li et al. "Efficacy of prolotherapy in comparison to other therapies for chronic soft tissue injuries: A systematic review and network meta-analysis." PloS one vol. 16,5 e0252204. 26 May. 2021, doi:10.1371/journal.pone.0252204
- Giovannetti de Sanctis, Edoardo et al. "The Efficacy of Injections for Partial Rotator Cuff Tears: A Systematic Review." Journal of clinical medicine vol. 10,1 51. 25 Dec. 2020, doi:10.3390/jcm10010051
- Bae, Geonhyeong et al. "Prolotherapy for the patients with chronic musculoskeletal pain: systematic review and meta-analysis." Anesthesia and pain medicine vol. 16,1 (2021): 81-95. doi:10.17085/apm.20078
- Akcay, S. Gurel Kandemir N, Kaya T, et al. "Dextrose Prolotherapy Versus Normal Saline Injection for the Treatment of Lateral Epicondylopathy: A Randomized Controlled Trial." J Altern Complement Med. Dec 2020; 26(12): 1159-1168. PMID 32990454
- American Pain Society. Hills EC. Et al. What are other American Pain Socitey (AOS) treatment guidelines for mechanical low back pain? Mar. 2020. https://www.medscape.com/answers/310353-114261/what-are-other-american-pain-society-aps-treatment-guidelines-for-mechanical-low-back-pain
- Lin, Meng-Ting et al. "Comparative Effectiveness of Injection Therapies in Rotator Cuff Tendinopathy: A Systematic Review, Pairwise and Network Meta-analysis of Randomized Controlled Trials." Archives of physical medicine and rehabilitation vol. 100,2 (2019): 336-349.e15. doi:10.1016/j.apmr.2018.06.028.
- Zarate, Miguel Angel et al. "Dextrose Prolotherapy Versus Lidocaine Injection for Temporomandibular Dysfunction: A Pragmatic Randomized Controlled Trial." Journal of alternative and complementary medicine (New York, N.Y.) vol. 26,11 (2020): 1064-1073. doi:10.1089/acm.2020.0207.
- Fields, KB. Copland, ST. Tipton JS. Hamstring muscle and tendon injuries; Apr. 2021 Available at: https://www.uptodate.com/contents/hamstring-muscle-and-tendon-injuries

- Klein RG, Eek BC, DeLong WB, et al. A randomized double-blind trial of dextrose-glycerine-phenol injections for chronic, low back pain. J Spinal Disord. Feb 1993; 6(1): 23-33. PMID 8439713
- Ongley MJ, Klein RG, Dorman TA, et al. A new approach to the treatment of chronic low back pain. Lancet. Jul 18 1987; 2(8551): 143-6. PMID 2439856
- Sert AT, Sen EI, Esmaeilzadeh S, et al. The Effects of Dextrose Prolotherapy in Symptomatic Knee Osteoarthritis: A Randomized Controlled Study. J Altern Complement Med. May 2020; 26(5): 409-417. PMID 32223554
- Reeves KD, Hassanein K. Randomized prospective double-blind placebo-controlled study of dextrose prolotherapy for knee osteoarthritis with or without ACL laxity. Altern Ther Health Med. Mar 2000; 6(2): 68-74, 77-80. PMID 10710805
- 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. J Altern Complement Med. Aug 2000; 6(4): 311-20. PMID 10976977
- Goh SL, Jaafar Z, Gan YN, et al. Efficacy of prolotherapy in comparison to other therapies for chronic soft tissue injuries: A systematic review and network meta-analysis. PLoS One. 2021; 16(5): e0252204. PMID 34038486
- Chung MW, Hsu CY, Chung WK, et al. Effects of dextrose prolotherapy on tendinopathy, fasciopathy, and ligament injuries, fact or myth?: A systematic review and meta-analysis. Medicine (Baltimore). Nov 13 2020; 99(46): e23201. PMID 33181700
- Apaydin H, Bazancir Z, Altay Z. Injection Therapy in Patients with Lateral Epicondylalgia: Hyaluronic Acid or Dextrose Prolotherapy? A Single-Blind, Randomized Clinical Trial. J Altern Complement Med. Dec 2020; 26(12): 1169-1175. PMID 32931308
- Kazempour Mofrad M, Rezasoltani Z, Dadarkhah A, et al. Periarticular Neurofascial Dextrose Prolotherapy Versus Physiotherapy for the Treatment of Chronic Rotator Cuff Tendinopathy: Randomized Clinical Trial. J Clin Rheumatol. Jun 01 2021; 27(4): 136-142. PMID 32975923
- Centers for Medicare and Medicaid Services. National Coverage Determination (NCD) for PROLOTHERAPY, Joint Sclerotherapy, and Ligamentous Injections with Sclerosing Agents (150.7). 1999; https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=15&ncdver=1&bc=AAAAQAAAAAAA&

POLICY HISTORY		
Date	**Reason**	**Action**
October 2022	Annual Review	Policy Renewed
October 2021	Annual Review	Policy Revised
October 2020	Annual Review	Policy Renewed
October 2019	Annual Review	Policy Revised

October 2018	Annual Review	Policy Revised
October 2017	Annual Review	Policy Renewed
October 2016	Annual Review	Policy Revised
November 2015	Annual Review	Policy Revised
December 2014	Annual Review	Policy Revised
February 2014	Annual Review	Policy Renewed
May 2013	Annual Review	Policy Renewed
June 2012	Annual Review	Policy Renewed
August 2011	Annual Review	Policy Renewed

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
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