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Prolotherapy for Osteoarthritis and Tendinopathy: a Descriptive Review

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Abstract
Purpose of Review Osteoarthritis and overuse tendinopathy are common chronic conditions of high societal and patient burden. The precise etiology of pain and disability in both conditions is multifactorial and not well understood. Patients are often refractory to conservative therapy. The development of new therapeutic options in both conditions is a public health priority. Prolotherapy is an injection-based outpatient regenerative therapy for chronic musculoskeletal conditions, including osteoarthritis and tendinopathy. The authors reviewed the basic science and clinical literature associated with prolotherapy for these conditions.
Recent Findings Systematic review, including meta-analysis, and randomized controlled trials suggest that prolotherapy may be associated with symptom improvement in mild to moderate symptomatic knee osteoarthritis and overuse tendinopathy.
Summary Although the mechanism of action is not well understood and is likely multifactorial, a growing body of literature suggests that prolotherapy for knee osteoarthritis may be appropriate for the treatment of symptoms associated with knee osteoarthritis in carefully selected patients who are refractory to conservative therapy and deserves further basic and clinical science investigation for the treatment of osteoarthritis and tendinopathy.

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Introduction

Osteoarthritis and tendinopathy are frequent sources of musculoskeletal pain and disability. Common to both is a multifactorial etiology, and a pressing need to find new therapeutic options. Prolotherapy has been assessed for both conditions; recent evidence suggests that prolotherapy has a role in the routine care of both osteoarthritis and tendinopathy.

Osteoarthritis, the most common form of arthritis [1], is a leading cause of disability in the USA and the world [1–3]. Incidence in the USA of symptomatic knee osteoarthritis (KOA) is up to 6% of those 30 years and older [4, 5]; among persons ages 30 to 65, incidence increases up to tenfold [6]. The societal and personal burden of disease is high due to utilization of health care resources, time off work, and individual morbidity [1, 7]. Intra-articular cartilage, bone and synovium, and extra-articular structures are all targets of the degenerative mechanisms and their sequelae. The search for effective non-surgical treatment for KOA has been challenging. In 2007, the agency is Agency for Healthcare Research and Quality (AHRC) assessed treatment options and found each lacking sufficient evidence for recommendation [8]; more recent evaluation provides a similar assessment [9]. Tendinopathy is likewise problematic; the etiology of pain and disability in tendinopathy is thought to originate from an underlying non-inflammatory injury resulting from repetitive motion or overuse and is associated with degenerative tissue [10, 11, 12].

Prolotherapy

Prolotherapy is an injection-based therapy for chronic musculoskeletal pain conditions including osteoarthritis and overuse tendinopathy [13]. It has been used in allopathic medicine since at least 1937 [14]. George Hackett, MD, developed contemporary injection techniques based on clinical experience and research [15]. While a variety of injectants have been used since, hypertonic dextrose is the most commonly used and best studied. Used as an injectant, hypertonic dextrose is hypothesized to stimulate native healing of damaged intra-articular and peri-articular soft tissue, including cartilage, ligaments, tendons, and fascial structures. It has been termed a "regenerative" injection therapy due to these purported effects [16].

Treatment with prolotherapy typically consists of injections 2 to 6 weeks apart over several months. Subsequent local irritation, inflammation, and anabolic tissue healing [17, 18] are thought to occur, improving joint stability and biomechanics, ultimately decreasing pain [15, 19]. While a pain-control mechanism at the tissue level is not well elucidated, the overall mechanism is likely multifactorial, involving several tissue types and planes, and associated with needle and tissue displacement effects of the injection procedure itself, in addition to injectant-related effects. Hypertonic dextrose is typically used in two strengths: 15% for peri-articular injections of tendon and ligament attachments and 25% dextrose for intra-articular injections; 1% lidocaine without epinephrine and saline are typical diluents. These dextrose concentrations are anecdotally, rather than empirically, derived over decades of use by physicians who practice prolotherapy. Needle size is pragmatically determined and varies mainly by tissue target; the smallest needle that can reach the target tissue is used to minimize needle trauma and minimize injection-related pain.

Basic Science

Animal and human studies suggest an injectant-specific biological effect and have focused on inflammation, ligament size and strength, sensorineural effects, and cartilage growth. Dextrose produces a local inflammatory response in uninjured rat knee ligaments [20]. In stretch-injured medial collateral rat ligaments, dextrose-injected tissue showed a significantly larger cross-sectional area compared to non-injured and injured saline-injected controls [21]. In a rabbit model, flexor retinaculum tissue showed greater load absorption (strength) and tissue thickness than saline injected controls [22]. Dextrose may also act directly on sensory nerves by an unclear mechanism. In one clinical trial, participants with painful mid-substance Achilles tendinopathy receiving exercise or palpation-guided dextrose injections to tender peri-tendinous tissue reported improvement compared to exercise alone ($p.$ = .007) [23].

Clinical Science

Prolotherapy is used in an array of specialties to treat pain in many chronic conditions. In the twentieth century, published data supporting its use was generally limited to case reports and retrospective and prospective case series reporting successful outcomes [13]. Favorable outcomes in these studies were limited by biases inherent to study design. Evidence from more rigorous studies suggests that prolotherapy is effective for finger joint osteoarthritis, KOA, and tendinopathy.

Prolotherapy for Knee and Finger Joint Osteoarthritis

Early Work

Two early osteoarthritis randomized controlled trials (RCTs) reported improved outcomes after prolotherapy. Participants meeting clinical and radiological criteria for finger joint and KOA were randomized to either prolotherapy (10% dextrose and lidocaine) or control injections (lidocaine and bacteriostatic water) [24, 25]. Dextrose recipients with finger joint osteoarthritis reported significantly decreased pain with movement (as assessed by 0–10 visual analog scale (VAS)) and improved flexion range compared with controls (as assessed by goniometry) at 6-month follow up. An early RCT reported improvement of VAS-assessed knee pain at rest, walking, and stair-climbing at 6 months compared with control lidocaine/bacteriostatic water control injections. All participants reported improvements in goniometrically assessed knee flexion. Both studies were limited by the use of non-validated outcome measures and use of basic statistical analyses. However, they suggested further research was warranted.

Recent Work

Recent studies assessing prolotherapy for KOA have used more rigorous methods. They used a protocol which placed injectants at both intra- and extra-articular structures and a validated outcome measure, the Western Ontario and McMaster Universities Arthritis Index (WOMAC) questionnaire, as the primary outcome measure. Both design elements facilitate direct comparison of results across studies. A participant-reported improvement of approximately 12 points on a 0–100 point WOMAC scale is clinically important to patients [26, 27]. A prospective case series first reported an effect size of prolotherapy compared to baseline status [28]. Researchers enrolled 36 participants who met the American College of Rheumatology case definition of KOA [29]. Injections were given at 1, 5, and 9 weeks; optional treatments were provided at 13 and 17 weeks. Dextrose (22 mL, 15%)

was injected at attachments of peri-articular soft tissue structures and in the intra-articular space (6 mL, 25%). Participants reported improved WOMAC scores through 9 weeks that remained stable through 52 weeks, with an average score improvement of 15.9 ± 2.5 points. Female sex, middle age (46–65 years), and BMI ≤25 kg/m^2 were associated with larger improvement. Four (11%) participants reported worse WOMAC scores at 52 weeks than at baseline. This is consistent with anecdotal clinical experience and suggests that most, but not all, patients with KOA respond to prolotherapy. This was the first study to suggest that a "whole joint" (intra- and extra-articular) injection protocol may be effective for KOA and informed sample size calculations for future RCTs. It was also the first study to publish a detailed, illustrated injection protocol. The study was limited primarily by the lack of control group. A subsequent open-label RCT assessed participants in two groups with a two-period crossover [30]. The study compared at-home exercise with prolotherapy. Forty-five participants were assigned to 32 weeks of home exercise and received treatment using an injection protocol that employed intra-articular and peri-articular injections to the attachments of supportive soft tissue structures, similar to that used by Rabago et al. [31]. Group A received four monthly prolotherapy sessions in the first period of the study, starting at week 0, while Group B received four sessions starting in the second period at week 20. Group A participants reported a statistically significant improvement in composite WOMAC scores. Group B did not improve with exercise alone, but WOMAC scores improved by 11.9 points attributable to prolotherapy ($p. < 0.05$) treatment started in the second period at week 20 and assessed at 32 weeks. Group A's WOMAC scores did not improve within the second period of the trial. This study suggested that prolotherapy is effective treatment for symptomatic KOA compared to at-home exercise. The unmasked nature of the study does not allow determination of whether positive outcomes resulted from dextrose alone or whether treatment-provider bias or needle-based procedural effects may have affected score change.

A three-arm RCT compared dextrose prolotherapy to two active control therapies, masked saline injections, and a 20-week home exercise regimen [32••]. Identical-appearing dextrose and sham saline control syringes were filled and masked at an outside research pharmacy using a paper sleeve and delivered to the treating physician on the day of the procedure. The integrity of masking was assessed using a questionnaire. Eligibility criteria, active intervention, assessment, and 52 week follow-up mirrored previous prospective case series [28]. Masked allocation was maintained among injection participants and all study personnel, resulting in an assessment of the effects of dextrose alone. Prolotherapy participants reported improvements of 13.91 ± 3.2 points on the WOMAC questionnaire at 9 weeks post-enrollment, which improved through 52 weeks to 15.32 ± 3.3 points, while participants receiving saline and home exercise reported 7.6 ± 3.4 and 8.2 ± 3.3 point improvements, respectively ($P. < 0.05$). In addition, the effect size of dextrose exceeded 12 points, exceeding the minimally clinically important improvement threshold [26, 27]. This study was the first to provide evidence that dextrose is associated with independent clinical efficacy. The effect size of prolotherapy compared with other active therapies is difficult to determine because no head-to-head studies have been conducted. However, self-reported outcomes for prolotherapy for KOA appear to be consistent with those of two other injection therapies. Platelet-rich plasma (PRP) and hyaluronic acid (HA) injection were recently assessed in a 12-month clinical trial; there were no differences between the two therapies in several self-reported outcome measures, including the International Knee Documentation Committee (IKDC; 0–100 points) measure. PRP and HA participants reported effects of 13.8 and 14.6 points, respectively, similar to that reported by recipients of prolotherapy [33].

Positive quantitative studies prompted the conduct of a systematic review with meta-analysis. Searching relevant databases, Sit et al. reviewed 143 abstracts and found that two were eligible for meta-analysis. [34••, 30, 32••] Data from the two studies were pooled, and prolotherapy was found to be superior to exercise alone by a standardized mean difference (SMD) of 0.81, 0.78, and 0.62 on the WOMAC composite, function, and pain subscale scores, respectively ($p. < 0.05$ in each case). Although moderate heterogeneity existed in each study, these pooled data suggest a potent effect of prolotherapy compared with at-home exercise.

Mechanism of Action The mechanism of prolotherapy in KOA has been investigated in two clinical trials. A hypothesized mechanism is regeneration or proliferation of tissue. Rabago et al. analyzed a subset of participants recruited from two studies [32••, 35] to assess whether prolotherapy slows or reverses MRI-assessed intra-articular cartilage volume loss in the context of clinical change [36•]. Compared to control, at 52 weeks post-enrollment, prolotherapy participants reported larger WOMAC score gains. However, WOMAC scores and cartilage volume were not correlated at baseline or any follow-up time point. Prolotherapy in this study did not produce an MRI-assessed regenerative effect. However, in the prolotherapy group, cartilage volume stability predicted pain score change. Prolotherapy participants losing the least cartilage volume during 52 weeks reported the largest pain score improvement; stiffness and function subscales among prolotherapy participants did not improve, nor did any control group subscales. The finding that only pain scores improved, but not function and stiffness scores, in prolotherapy participants with stable cartilage volume suggests that prolotherapy's mechanism of action may include pain-specific effects.

Arthroscopic visualization and biopsy have the potential to detect subtle tissue change more accurately than MRI [37]. A

recent pilot study of six participants with severe KOA assessed the effect of serial intra-articular dextrose injection using pre- and post-treatment video arthroscopy with biopsy to evaluate potential cartilage growth using quantitative polarized light microscopy [38•]. The medial condyle of the affected knee in each of six participants was divided into nine zones (54 total zones). Arthroscopic assessment showed modest cartilage growth in 19 of 54 areas evaluated before and after dextrose injections; biopsy showed metabolically active cartilage consistent with fibro- and hyaline-like cartilage. Although the study was limited by small sample size and lack of control group, it suggests that dextrose may have a role in altering chondrogenesis.

Long-Term and Qualitative Outcomes The long-term quantitative and qualitative effects of prolotherapy for KOA have been assessed. An open-label follow-up study tracked a sample of participants recruited from three prior studies [32••, 28, 35] to determine the duration of improvement on the WOMAC measure [39•]. Sixty-five participants with 2.5 ± 0.6 years (range 1.6–3.5 years) follow-up after initial enrollment reported an average composite WOMAC score improvement of 20.9 ± 22.6 points. Further analysis however revealed that the cohort contained both "responders" and "non-responders." Most participants ("responders"; 53/65; 82%) reported improved composite WOMAC scores at 2.5 ± 0.6 years of 28.3 ± 17.5 points. A minority of participants ("non-responders;" 12/65; 18%) worsened by 12.1 ± 7.9 points. Baseline characteristics did not predict responsiveness. This study is consistent with anecdotal observation regarding responsiveness to prolotherapy for KOA in that approximately 20% of study participants had little or no response to prolotherapy, and that approximately 80% report a robust positive response that endures for at least 1 year.

Qualitative outcomes associated with prolotherapy for KOA have also been investigated. Twenty-two participants from one of three clinical trials [28, 32••, 35] were interviewed using semi-structured in-depth interviews 52 weeks post-enrollment [40•]. Content analysis by co-authors identified themes; they included overall improvement of knee symptoms, good safety profile, the importance of pre-procedure counseling, and a willingness to recommend prolotherapy to others. A minority of participants noted improved function but had minimal improvement in pain, and 18% (*n.* = 4) noted no improvement in pain.

Prolotherapy for Tendinopathy

Researchers have assessed prolotherapy for six overuse tendon disorders: lateral epicondylosis, Achilles tendinopathy, Osgood-Schlatter disease, rotator cuff and hip adductor tendinopathies, and plantar fasciopathy.

Lateral Epicondylosis

Lateral epicondylosis (LE) is a common condition of the upper extremity. It has an incidence of 4–7/1000 patients per year [41–43]. Societal and patient costs are large [44, 45]. Two pilot-level RCTs suggest that prolotherapy may be effective for LE. A two-arm study compared prolotherapy with a solution containing dextrose and morrhuate sodium to masked saline injections. Twenty adults (10 per group) had at least 6 months of severe LE refractory to rest, corticosteroid injections, and non-steroidal anti-inflammatory medications (NSAIDs) [46]. On a 0–10 point visual analog scale of elbow pain at rest, prolotherapy participants reported a decrease of 4.6 points at 16 weeks, compared to 1.0 points for controls. Prolotherapy participants also showed improved isometric strength compared to controls and grip strength compared to baseline status. These findings were corroborated in a second pilot-level study using the validated Patient-Rated Tennis Elbow Evaluation (PRTEE), which is scored using a composite score and pain and function subscales [47]. This unmasked RCT randomized 18 participants (22 elbows) with lateral epicondylosis to prolotherapy with dextrose and watchful waiting. Participants receiving prolotherapy reported improved composite PRTEE scores (16 and 32 weeks), pain subscale scores (16 and 32 weeks), and function subscale scores (32 weeks) compared to baseline status and at 8 weeks compared to watchful waiting. While both studies suggest efficacy, they are limited by small sample size. Data from both studies were used to inform methods of an ongoing, more definitive study [48].

Osgood Schlatter Disease

Osgood Schlatter Disease is a tendinopathy of the patellar tendon at the tibial tubercle in children 9–17 years old who are often engaged in kicking sports. Historically understood as a self-limited condition resolving spontaneously with growth, it can become chronic; morbidity associated with pain and rest absence from sport is substantial. Researchers in a three-arm study assessed prolotherapy using the standard criterion "return to asymptomatic sport" [49]. Prolotherapy with lidocaine was compared to masked lidocaine injections alone and supervised usual care, including strengthening and stretching, at 3 and 12 months among 54 student athletes with 65 injured knees. Among participants with two knees in the study, both knees received the same therapy. The injection groups were unmasked at 3 months and saline participants were crossed over to prolotherapy. At 3 months, most participants in both

injection groups had full return to their sports (100 and 91%) as compared with 60% of children treated with usual care ($P. < .05$). At 12 months, 32 of 38 (84%) of prolotherapy-treated knees were pain-free, compared with 6 of 13 (46%) lidocaine-treated knees and 2 of 14 (14%) usual care knees ($P. < .05$ for both comparisons).

Rotator Cuff Tendinopathy

Among adults with rotator cuff tendinopathy, researchers in a three-arm masked RCT ($N. = 73$) compared prolotherapy and control solution placed at the entheses of rotator cuff tendons, with superficially placed control solution [50]. Participants received three monthly injections and simultaneous, individualized physical therapy. The primary outcome was the percentage of participants reporting 2.8 or more points of change on a 0–10 visual analog pain scale. Data were collected at 0 and 9 months. Fifty-nine percent of prolotherapy participants reported at least 2.8 points of change compared with 37% of participants receiving saline at the enthesis ($P. = .088$) and 27% of participants receiving superficial saline injections ($P. = .017$).

Hip Adductor Tendinopathy

Symptomatic hip adductor tendinopathy with groin pain is common among athletes in kicking sports [51]. Topol et al. conducted a case series assessing prolotherapy for hip adductor tendinopathy [52]. Twenty-four male athletes with 15.5 months of groin pain refractory to conservative care received prolotherapy at the symphysis pubis and the thigh and suprapubic abdominal attachments of the adductor tendon. Participants received three prolotherapy sessions. At 17 months, participants reported 5.3 points of improvement on a 0–10 VAS scale. Among 24 subjects, 20 were pain free and 22 returned to sports unrestricted.

Achilles Tendinopathy

Achilles tendinopathy is a common disabling overuse injury seen among athletes and the general population [53]. Maxwell et al. conducted a well-designed case series ($N. = 36$) to assess whether dextrose, injected under ultrasound guidance, would decrease pain (VAS), be satisfactory (percent satisfied), and change ultrasound-based measures of tendon thickness, hypoechogenicity, and neovascularity [54]. At 6 weeks after conclusion of injections, participants reported improvement in VAS-assessed pain severity at rest (88%), during activities of daily living (84%), and during sport activities (78%). Satisfaction with injections was assessed at an average 12 month follow up (4.5–28 months) but was incomplete; 19 participants reported a satisfaction level of 95–100%, nine reported a satisfaction level of 70–90%, and one had moderate symptoms and described 50% satisfaction. Tendon thickness decreased significantly; however, hypoechogenicity and neovascularity were not correlated with self-reported outcomes, suggesting the causal relationship between ultrasound-imaged tissue characteristics, and the degree of clinical improvement remains unclear.

Plantar Fasciopathy

Plantar fasciopathy, a common age-related injury especially common among runners, accounts for 15% of all adult foot complaints requiring professional consultation [55, 56]. There is limited evidence supporting the general effectiveness of any one standard of care approach, including steroid injections [57]. Ryan et al. assessed dextrose injections for chronic plantar fasciitis refractory to one or more prior conservative care therapies including at-home physiotherapy, extracorporeal shock wave therapy, orthotics, massage, non-steroidal anti-inflammatory drugs, or corticosteroid injections [58]. Twenty adults with an average of 21 months of heel pain underwent ultrasound-guided dextrose injections. Pain scores were assessed using a 0–100-point VAS at baseline and at 12 months. Compared to baseline status, significant improvement in pain severity was seen at rest (26.5 points), during activities of daily living (49.7 points), and during sport activities (56.5 points). Sixteen of 20 subjects reported good or excellent treatment effects.

Safety, Contraindications, and Practical Considerations

Prolotherapy for KOA and tendinopathy appears to be safe; none of the studies reported adverse events though they were not powered to detect rare events. There are few absolute contraindications to dextrose prolotherapy; they include joint or skin infection, active flare of a rheumatological condition, allergy to corn, and use of immunosuppressive medications. Relative contraindications include acute fracture, acute gout, bleeding disorders, and use of anticoagulants. Like any medical procedure, the safe practice of prolotherapy requires training. It is not typically taught in medical school or residency; rather, prolotherapy is taught via peer learning and in conference, workshop, and formal continuing medical education (CME) settings. A growing number of fellowships in Sports and Rehabilitation Medicine also provide training. Therefore, recommendations are anecdotal. Two organizations, the Hackett-Hemwall-Patterson Foundation and the American Association of Orthopedic Medicine, provide CME eligible

Table 1 Educational and informational prolotherapy resources

Name/URL	Comments
Hackett-Hemwall Patterson Foundation List of Prolotherapists http://hhpfoundation.org/	The Hackett-Hemwall-Patterson Foundation is a non-profit medical foundation whose mission is to provide high-quality treatment of musculoskeletal problems to underserved people around the world. Physicians listed on the site have completed the foundation's high-volume continuing medical education experience in prolotherapy.
Commercial Prolotherapy Physician Listing http://www.getprolo.com	This site lists physicians by state who perform prolotherapy. It includes contact information and a short biography and prolotherapy credentials. Physicians pay to list themselves on this site.
American Association of Orthopedic Medicine http://www.aaomed.org	The American Association of Orthopedic Medicine is a non-profit organization which provides information and educational programs on comprehensive non-surgical musculoskeletal treatment including prolotherapy. This searchable site lists AAOM members who perform prolotherapy.
University of Wisconsin Prolotherapy Education and Research Lab (UW PEARL; http://www.fammed.wisc.edu/prolotherapy/)	The UW PEARL is a university-based collaboration between primary care and specialty clinicians and basic scientists to further education and research of prolotherapy.

coursework and training in the USA. Physicians interested in learning more about prolotherapy have access to a variety of resources (Table 1). The Hackett-Hemwall-Patterson Foundation is developing protocol standards based on consensus expert opinion. Illustrated descriptions of prolotherapy procedures consistent with the studies described have been published [15, 28, 59, 60].

Conclusions

These studies assessing prolotherapy and its mechanisms of action in osteoarthritis and tendinopathy suggest that prolotherapy can result in improvement in symptoms in some patients with osteoarthritis, especially KOA, and tendinopathy who are refractory to conservative care. They also suggest the need for further research involving self-reported measures, and also radiological, functional, and cellular biomarker assessments. Interpretation of positive results is limited by methodological shortcomings, including small sample size, inadequate control groups, and lack of masking. Likewise, the utility of prolotherapy in the larger context of regenerative injection therapy, including PRP and stem cell injection, is unclear and requires further investigation.

Compliance with Ethical Standards

Conflict of Interest Dr. Rabago is president of the Hackett Hemwall Patterson Foundation, a non-profit (501c3) organization that provides prolotherapy teaching and service. Dr. Nourani has nothing to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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