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Prolotherapy for Knee Osteoarthritis: A Descriptive Review

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Abstract Knee osteoarthritis (KOA) is a common chronic disease of high patient and societal impact. The etiology is multifactorial; pain sources include both intra- and extra-articular tissues. A number of alternative therapies have been assessed for KOA. Patients are often refractory to best-practice conservative management, and the development of new therapy has been called for by national health services groups. Prolotherapy is an outpatient therapy for chronic musculoskeletal pain including KOA. Protocols include injection at attachments of soft-tissue supportive structures such as ligaments and tendons, and within intra-articular spaces. Although the understanding of mechanism is not well understood, a small but growing body of literature suggests that prolotherapy may be appropriate therapy for carefully selected patients refractory to conventional treatment. This article summarizes evidence from basic and clinical science for use of prolotherapy among patients with KOA.

Keywords Knee osteoarthritis · KOA · Prolotherapy · Chronic pain · Rehabilitation · Review

Introduction

Knee osteoarthritis (KOA) is a common and age-related chronic joint disease [1]; 33.6 % of those 65 years of age and older will eventually develop KOA [2], conferring a substantial expense for patients and society. Disability arises primarily from pain affecting activities of daily living, which results in decreased quality of life and a high economic impact through absenteeism and utilization of health care resources.

Treatment options for KOA are limited. A review by the Agency for Healthcare Research and Quality (AHRC) noted that evidence for several common therapies including glucosamine, chondroitin, intra-articular viscosupplementation, and arthroscopic lavage did not demonstrate clinical benefit [3]. Non-surgical therapy [4] and oral supplements [5, 6] have also not shown uniform efficacy. Clinical guidelines reflect the paucity of effective conservative therapy [7]. Total knee replacement for advanced KOA is effective but costly. The number of knee replacements in developed nations is rising; in the US the number of total knee replacements performed annually quadrupled to over 700,000 between 1990 and 2010, with the most dramatic rise among 45 to 65 year olds [8]. Knee replacement can result in peri- and post-operative adverse events, including stiffness, infection, deep venous thrombosis, and supracondylar femur fracture [9].

Given the paucity of effective therapy, organizations such as the AHRC and the Institute of Medicine (now National Academy of Medicine) have prioritized research and development of new therapies to treat KOA [3, 10]. Successful therapy would reduce pain and improve physical function, leading to improved quality of life, and decreased direct and indirect health care costs [7]. Effective conservative therapy could also slow the rate of knee replacement, reducing health care expenditures.

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Prolotherapy: Early History

Prolotherapy is an injection-based therapy for chronic musculoskeletal pain conditions including KOA that has received increased attention over the past decade. Originally termed "sclerotherapy" due to early use of scar-forming sclerosants, the technique has been practiced for at least 75 years [11]. In the 1950s, "sclerotherapy" was replaced by "prolotherapy" based on the observation that newer injectants resulted in the hypertrophy of ligamentous tissue [12•]. Due to the purported effects of prolotherapy on degenerative tissue, including revitalization and reorganization, it has also been categorized as a "regenerative" injection therapy by some researchers [13].

Prolotherapy is not typically taught in medical school or residency programs, and there is no single society that has standardized injection protocols. However, there are clinically based protocols that are relatively uniform; treatment commonly consists of multiple injection sessions conducted every 2–6 weeks over the course of several months. Hypertonic dextrose (15–25 %) is the most common solution and is injected at sites of tender ligament and tendon attachments, and in adjacent joint spaces [14]. Injected solutions are hypothesized to cause local irritation with subsequent inflammation and anabolic tissue healing, theoretically improving joint stability, biomechanics, function, and ultimately decreasing pain [12•, 15].

Proposed Mechanism of Action

Animal model studies suggest an injectant-specific biological effect focusing on inflammation, and ligamentous size and strength. Dextrose has been reported to create a local inflammatory response in a rat knee ligament model [16]. Injured rat medial collateral ligaments injected with dextrose had a larger cross-sectional area compared to both non-injured and injured saline-injected controls [17•]. Flexor retinaculum tissue in a rabbit model showed increased strength and tissue thickness relative to saline-injected controls [18]. Dextrose is also hypothesized to have a pain-specific sensorineural effect associated with neuro-inflammation, currently understood to play a role in osteoarthritic pain [19•–22]. Injected dextrose may act on relevant pain receptors to reduce neurogenic inflammation and decrease subsequent pain; however, this hypothesized clinical mechanism has not been objectively studied at the tissue and cellular level [19•].

Clinical Evidence

Evidence assessing efficacy and effectiveness has been mixed. Prolotherapy is performed for many chronic pain conditions in a variety of pain-related specialties. Publication of data supporting its use in the twentieth century was largely limited to reports of individual successful cases and retrospective and prospective case series [23•]. Reports noted favorable outcomes but were limited by biases inherent to modest study design. The first randomized controlled trials (RCT) assessed prolotherapy for chronic low back pain. Initially, positive results in two studies were offset by two subsequent trials, one of which was of high methodological quality, suggesting a more modest effect [23•, 24].

However, growing clinical trial evidence from three research groups suggests that prolotherapy for KOA may be more effective. Prolotherapy has been used for knee pain since the mid-twentieth century and has been assessed in early case reports [25]. Reeves et al. [26] were the first to report improvement of knee symptoms in response to prolotherapy in an RCT (Table 1). Participants with knee pain and radiologic evidence of KOA were randomly assigned to receive three prolotherapy sessions using a single anteromedial injection of either 10 % dextrose and lidocaine (treatment group) or control injection with lidocaine and bacteriostatic water at 0, 2, and 4 months. Participants in both groups reported improvements in pain and swelling, number of buckling episodes, and flexion-related range of motion. Results showed that improvements were statistically significant compared to baseline status, but were not significantly different between groups. Follow-up data suggested improved radiologic features of OA on plain X-ray films; Reeves et al. reported increased patellofemoral cartilage thickness, suggesting potential disease modification. However, the ability of plain radiographs to quantify cartilage thickness is questionable, limiting the impact of these findings. Nevertheless, this study provided early trial data suggesting further research was warranted.

Subsequent studies have used a more comprehensive injection protocol that stems from the belief that prolotherapy injections effect change in both intra- and extra-articular structures. This is consistent with the contemporary understanding of KOA as a "whole joint" condition, with pathophysiology and pain generators in a variety of structures inside and outside the joint space. Building on prior published work and clinical experience, Rabago et al. established an academic working group to assess the effect of prolotherapy for KOA in a series of related studies (Prolotherapy Education and Research Lab; http://www.fammed.wisc.edu/prolotherapy/research).

The first pilot-level study sought to establish an effect size for prolotherapy compared to baseline status on a multidimensional validated outcome measure [27•]. The Western Ontairo McMaster Universities Arthritis Index (WOMAC) was selected as the primary outcome measure for these studies. The WOMAC is a patient-reported outcome questionnaire; pain, stiffness, and function subscales

Table 1 Description of clinical trials assessing prolotherapy for knee osteoarthritis

Study/Type	Participants	Intervention	Injectant/Control	Follow-up/outcome measures	Results	Comments
Reeves et al. 2000[26] RCT	*N* = 68 participants, 111 knees KOA ≥ Grade 2, ≥ 6 months knee pain	Injections at 0, 2, and 4 months for PrT and Control Additional injections for PrT group at 6, 8, and 10 months	PrT IA: 9 mL D10% Control IA: 9 mL Lidocaine	6 months (0-100 VAS); Knee pain at rest, walking, and with stairs 12 months (0-100 VAS); Knee pain at rest, walking, and with stairs	0-6 months: Both groups improved in pain, swelling, buckling episodes, and flexion 0-12 months: PrT group had improvements in pain, swelling, buckling episodes, and flexion	No between-group differences from 0 to 6 months First study to suggest IA dextrose PrT benefits symptoms of KOA 8 of 13 PrT participants had improved ACL laxity
Rabago et al. 2012[27] Prospective uncontrolled case series	*N* = 36 participants, 58 knees Age 40—76 years KOA ≥ Grade 2, ≥ 3 months knee pain Excluded BMI ≥ 45 kg/m^2 and uncontrolled diabetes (HgA1c > 7.5%)	Injections at 1, 5, and 9 weeks Optional injections at 13 and 17 weeks	PrT IA: 6 mL D25% EA: ≤ 22.5 mL D15%	WOMAC scores at 0, 5, 9, 12, 26, and 52 weeks	WOMAC scores improved by 15.9 ± 2.5 points (36.1%)	First study to show EA and IA PrT as a safe and good therapeutic option for symptomatic KOA with a duration of at least 1 year Females 46—65 years with BMI ≤ 25 kg/m^2 had the largest improvement in WOMAC 89% of participants would recommend PrT for KOA 4 (11%) of participants reported worse WOMAC scores at 52 weeks
Dumais et al. 2012[32] RCT with crossover	*N* = 45 participants, 45 knees Age ≥ 18 years KOA ≥ 6 months Participants assigned to either Group A or Group B	Home exercise for both groups x 32 weeks Weeks 0—16 Group A: PrT at weeks 0, 4, 8, and 12 weeks Group B: no injections Weeks 16—32 Group B: PrT at 20, 24, 28, and 32 weeks Group A: no injections	PrT IA: 5 mL D20% EA: 8 mL D15%	WOMAC scores every 4 weeks from 0 to 32 weeks	Weeks 0—16: Group A WOMAC improved 21.1 points (47.3%) from baseline; improvements were sustained through 32 weeks Weeks 0—32: Group B WOMAC improved 11.9 points attributable to PrT	First study showing improvement using IA and EA PrT with a control injection group One participant was stopped from completing the trial due to diffuse bilateral lower extremity edema probably due to a cardiovascular condition
Rabago et al. 2013[33] Double-blind RCT	*N* = 90 participants Age 40—76 KOA ≥ 3 months Excluded BMI ≥ 40 kg/m^2, diabetes	Injections at weeks 1, 5, and 9 Optional injections at weeks 13 and 17	PrT IA: 6 mL D25% EA: ≤ 22.5 mL D15% Saline Control IA: 6 mL EA: ≤ 22.5 mL Home Exercise Weeks 0—20+	WOMAC scores at weeks 0, 5, 9, 12, 26, and 52	PrT group had significant WOMAC score improvement of 13.9 ± 3.2 at week 9 relative to control injections WOMAC scores were maintained at 52 weeks, 15.32 ± 3.3 points	PrT group had statistically significant WOMAC score improvement at week 9 relative to control injection group PrT group achieved maximum benefit by week 26 and persisted through 52 weeks First double-blind study evaluating prolotherapy and showed good clinical outcome

Table 1 continued

Rabago et al. 2013[19] MRI outcomes	*N* = 37 participants Age 40—76 KOA diagnosis consistent with ACR guidelines, ≥ 3 months knee pain	Injections at weeks 1, 5, and 9 Optional injections at weeks 13 and 17	PrT IA: 6 mL D25% EA: ≤ 22.5 mL D15% Saline Control IA: 6 mL EA: ≤ 22.5 mL	MRI at baseline and 52 weeks WOMAC scores at weeks 0, 5, 9, 12, 26, and 52	WOMAC scores of PrT group were slightly lower (experiencing more severe pain) at baseline Neither control nor PrT slowed rate of cartilage loss PrT participants with the least cartilage volume loss had greatest improvement in pain scores; this correlation was not seen in the control group	Best responders to PrT had least cartilage volume loss Every 1% loss in cartilage volume was associated with 2.7% less improvement in WOMAC pain scores
Rabago et al. 2014[36] Prospective 3-arm open-label case series	*N* = 38 participants, 57 knees Age 40—76 57.3 ± 5.5 years KOA diagnosis consistent with ACR guidelines, ≥ 3 months knee pain Avg. ≥ 5 years of knee pain Excluded BMI ≥ 45 kg/m^2, uncontrolled diabetes (HgA1c > 7.5%)	Injections at weeks 1, 5, and 9 Optional injections at weeks 13 and 17 After week 1, participants had the option of adding morrhuate sodium to the EA injections	PrT IA: 6 mL D25% 1st EA: ≤ 22.5 mL D15% Subsequent EA: ≤ 22.5 mL D15% OR ≤ 22.5 mL D15% + morrhuate sodium 5%	WOMAC at 0, 5, 9, 12, 26, and 52 weeks	Participants divided into three groups and analyzed separately given different recruitment origin; WOMAC change scores at 52 weeks were 12.4 ± 3.5, 17.8 ± 3.9, and 19.4 ± 7.0 points per group at 52 weeks	All participants received dextrose PrT at the first visit Participants did a step-up selection to include dextrose + morrhuate sodium in subsequent injections if they did not achieve desired benefit from previous injection Participants who had the most severe WOMAC scores improved the most Near maximum improvement by 24 weeks with continued effect through 52 weeks This study reflects a more generalized population
Rabago et al. 2015[38] Long-term outcomes	*N* = 65 participants, 95 knees 58.7 ± SD 7.4 years 77% with BMI ≥ 25 kg/m^2 Avg. duration of 97.7 ± 91.2 months of knee pain prior to PrT injection	Injections at weeks 1, 5, and 9 Optional injections at weeks 13 and 17	PrT IA: 6 mL D25% EA: ≤ 22.5 mL D15%	WOMAC scores at weeks 0, 5, 9, 12, 26, 52, and 120 weeks	Total WOMAC score improvement over 2.5 years for all participants: 20.9 ± 22.6 (35.6%) 62% (40/65) improved ≥ 12 points 82% (53/65) had improvements in WOMAC scores	Participants who improved (53/65, 82%, "responders") had a mean WOMAC improvement 28.3 ± 17.5 points Minority of participants (12/65, 18%, "non-responders") worsened by 12.1 ± 7.9 points 86% (56/65) of participants reported decreased knee pain Uninjected knees also improved from PrT

Dextrose injections include lidocaine + sterile water or normal saline

Control injections are composed of lidocaine + sterile water or normal saline

PrT prolotherapy, *RCT* randomized controlled trial, *WOMAC* Western Ontairo McMaster Universities Arthritis Index, *VAS* Visual Analogue Scale, *KOA* knee osteoarthritis, *IA* intra-articular, *EA* extra-articular, *D* Dextrose

are aggregated in a composite score [28]. Using a consistent outcome measure enables direct comparison of results across studies in this and other research groups. An improvement of approximately 12 points on a normalized 100 point WOMAC scale has been reported to be clinically important to patients [29, 30]. The prospective open-label case series enrolled adults aged 40–76 years with at least 3 months of knee pain who met clinical criteria of KOA, as

defined by the American College of Rheumatology [31], and had X-rays confirming the presence of KOA. Thirty-six participants received injections at 1, 5, and 9 weeks with optional treatments at 13 and 17 weeks, and received up to 22.5 mL of 15 % dextrose to extra-articular soft-tissue structures and 6 mL of 25 % dextrose to the intra-articular space using an anteromedial approach. WOMAC data were collected at 0, 5, 9, 12, 26, and 52 weeks. Participants reported an average score improvement at 52 weeks on the composite WOMAC scale of 15.9 ± 2.5 points, exceeding the clinical importance benchmark. Females aged 46–65 years with BMI $\leq$ 25 kg/m^2 reported the largest improvement. Consistent with clinical experience, four (11 %) participants reported worse WOMAC scores at 52 weeks, suggesting most but not all participants with KOA respond to prolotherapy. Only expected injection-related side effects and no adverse events were reported. Satisfaction was high. This study was the first to suggest that a "whole joint" prolotherapy injection protocol using both intra- and extra-articular dextrose injections might be effective for KOA. The primary limitation was the lack of control group.

Dumais et al. addressed this limitation by conducting a randomized open-label trial assessing participants in two groups with a two-period crossover [32••]. The study compared prolotherapy to at-home exercise and assessed outcomes using composite WOMAC score change (Table 1). Forty-five participants were randomized to one of two groups. All participants were assigned to 32 weeks of home exercise and received treatment using an injection protocol similar to Rabago et al. [28]. Group A received dextrose prolotherapy injections at 0, 4, 8, and 12 weeks. Group B received equivalent injections at 20, 24, 28, and 32 weeks. During the first period, weeks 0–16, Group A participants reported a statistically significant improvement in composite WOMAC scores. Group B did not improve with exercise alone. During the second period of the study, Group B received prolotherapy and reported statistically significant improvements in WOMAC scores (11.9 points) attributable to injection. Group A's WOMAC scores remained improved, but showed no other change within the second period of the trial. This study suggested that prolotherapy is effective treatment for symptomatic KOA compared to unblinded control therapy. However, given the unblinded nature of the study, it was not possible to determine whether positive outcomes were a result of dextrose alone, treatment-provider bias, or non-dextrose procedural effects, such as the doctor–patient relationship, needle effects, or tissue-level pressure/volume effects.

Rabago et al. attempted to build on these findings in a study that compared prolotherapy to two control therapies in a three-arm randomized controlled trial [33••]. The trial compared dextrose prolotherapy to blinded control saline injections and a 20-week home exercise regimen. Overall eligibility criteria, outcome assessment using WOMAC scores, and study follow-up through 52 weeks were similar to the initial study; the injection protocol was identical to that of the pilot study. Participants had statistically similar baseline characteristics demonstrating effective randomization. Blinding was maintained among injection participants, the injector, and all other study personnel; injection allocation groups were unmasked after data analysis. By week 9, participants receiving prolotherapy reported substantial improvement in WOMAC scores (13.91 ± 3.2 points) compared to both control therapies. These improved scores were maintained at the 52-week follow-up (15.32 ± 3.3 points). Differences between the active treatment group and both control groups were statistically significant and clinically important. Maximum benefits were recorded by 26 weeks and persisted through 52 weeks; side effects were expected as the result of needle effects. There were no adverse events. This study added to the scientific understanding of prolotherapy and its effects through use of a blinded injection group. Clinical and statistical superiority in the prolotherapy group compared to the blinded injection and control group suggested that dextrose is biologically active.

Rabago et al. have conducted three additional studies on prolotherapy for KOA. The first of these assessed prolotherapy in participants who more broadly represented those in real clinical practice than did those in prior studies. Initial studies were limited by injection and cohort-related characteristics. Although dextrose is the most commonly used prolotherapy injectant, prolotherapists often use other injectants, including the sclerosant morrhuate sodium, and adjust the injection strategy to individual patient needs [14, 34, 35]. Other injectants are anecdotally perceived to be "stronger" and used in refractory cases, but the evidence base supporting their use is limited. The RCT cohort also excluded participants with a body mass index of more than 40 kg/m^2 and those with diabetes, limiting generalizability [33••]. Researchers therefore made three changes to the study protocol while maintaining other procedural aspects of the study. Eligibility criteria were relaxed to include participants with body mass index of up to 45 kg/m^2, and diabetes mellitus with a glycosylated hemoglobin up to 7.5 %. The injection protocol was identical with one exception; participants who reported minimal or no improvement after the first session could select a combined solution of dextrose and morrhuate sodium in each subsequent injection session.

Participants were recruited from the community and sources associated with prior studies by Rabago et al., and were analyzed in three groups: the control groups of the prior RCT; those who were eligible for, but declined enrollment in the RCT; and those ineligible for the prior RCT. Given the differences in the recruitment sources, data

were not pooled for analysis [36]. The baseline severity of KOA as assessed by WOMAC composite scores for these three cohorts was equal to or greater than that of prior studies. The first prolotherapy session for each participant used dextrose solution consistent with prior studies; from sessions 2 through 5, participants progressively selected the combination injectant. Participants in each group reported improved WOMAC composite scores at 1 year compared to their baseline score ($p < .05$). The range of improvement varied between 12.4 ± 3.5 points among participants from the control groups of the RCT, to 19.4 ± 7.0 and 17.8 ± 3.9 points among participants from the community who declined RCT enrollment or were ineligible, respectively. The study concluded that prolotherapy with an additional agent, in a population slightly more generalizable, appears to be effective compared to baseline status.

Given that a hallmark of KOA is intra-articular cartilage volume loss, and the purported mechanism of action of prolotherapy involves regeneration, Rabago et al. assessed a subsample of participants in two studies [33••, 36] to determine whether prolotherapy in these KOA patients slows or reverses cartilage volume loss as assessed by MRI [37] in the context of clinical change, again assessed by the WOMAC [19•]. At the 52-week follow-up, prolotherapy participants reported larger improvements in the WOMAC composite score compared with the control group. However, cartilage volume and WOMAC scores were not correlated at baseline or any follow-up time points. Prolotherapy in this study did not have a proliferant or regenerative effect as assessed by MRI. Nevertheless, cartilage volume stability predicted pain score change in the prolotherapy group. Prolotherapy participants who lost the least cartilage volume over 52 weeks reported the greatest improvement in pain scores; such gains were not reported in other WOMAC subscales (stiffness and function) among prolotherapy participants, nor in any control group outcomes. Although limited, these objective findings suggest that the mechanism of action of prolotherapy may include pain-specific neural effects.

The long-term effects of prolotherapy have also been assessed. Rabago et al. conducted an open-label follow-up study that tracked a subsample of participants from all three prior studies [27•, 33••, 36] to determine whether adults with symptomatic KOA who received prolotherapy will continue to report improvement on the WOMAC measure up to 3.5 years after initiating treatment [38•]. Sixty-five participants were contacted at an average 2.5 ± 0.6 years (range 1.6–3.5 years) after initial enrollment and reported an average improvement in composite WOMAC score of 20.9 ± 22.6 points. On the whole, the cohort continued to improve over time. However, further analysis revealed that the cohort was divided between "responders" and "non-responders." The majority of participants (53/65, 82 %) reported improved composite WOMAC scores at the long-term follow-up. Their mean composite WOMAC score increase was 28.3 ± 17.5 points. A minority of participants ("non-responders," 12/65, 18 %) actually worsened by 12.1 ± 7.9 points. This study is consistent with anecdotal clinical observation that approximately 20 % of patients with KOA do not respond to prolotherapy. In this study, no baseline characteristics predicted responsiveness.

Contraindications and Common Side Effects

There are few absolute contraindications to prolotherapy for KOA; they include acute localized infections, acute gouty arthritis, acute fracture, and acute flare of rheumatoid arthritis. Corn allergy is a contraindication for dextrose prolotherapy, but appears to be uncommon. Needle effects include pain and mild bleeding and a sense of fullness and numbness around the injection site. Such side effects are typically self-limited. A mild to moderate post-procedural pain flare occurred in studies by Rabago et al. in approximately 10 % of participants, and may last 1–5 days [33••]. Post-procedural pain generally responds well to oral acetaminophen. Some practitioners prescribe ice, low-dose hydrocodone/acetaminophen, or oxycodone for pain flares during the first 3 days after treatment. Non-steroidal anti-inflammatory medications are generally avoided due to their potential inhibition of the inflammatory and healing cascade. Regular activities can be progressively resumed over the course of 1–2 weeks post procedure.

Adverse Events

Prolotherapy for KOA performed by an experienced injector appears safe. None of the studies reviewed reported adverse events. However, injecting irritant solutions in tendons, ligaments, and joints raises safety concerns. Existing studies have not been powered to detect uncommon adverse events. Theoretical risks of the injection procedure and its injectants include infection, allergic reaction, lightheadedness, and nerve damage. All injections should be performed with universal precautions. Patients should be prone or supine to limit the effect of vaso-vagal episodes.

Clinical Summary

Reports by three research teams assessing prolotherapy for KOA suggest safety, efficacy, and effectiveness in the short and long term. However, data are limited by small sample size and study heterogeneity. Indeed, differences in

injection technique exist between practitioners depending on training venue. Prolotherapy is taught in conference, workshop, and other formal continuing medical education (CME) settings, and via peer learning, and is typically performed by MDs or DOs. Two organizations, the Hackett–Hemwall–Patterson Foundation and the American Association of Orthopaedic Medicine, provide formal conference-based coursework in the US.

Research Summary

Research on prolotherapy injection techniques, solutions, and their effect on symptomatic KOA has grown over the past two decades; clinical and basic science of prolotherapy suggest that it can be confidently used by trained clinicians. However, determination of the optimal clinical utility of prolotherapy for KOA will require confirmation in larger studies that include objectively assessed function, biomechanical and imaging outcome measures. Understanding of the basic science regarding the mechanism of action is limited and will likely grow as the understanding of relevant anatomy increases. Particularly important areas include the rapidly growing science of neuro-inflammation and the role of fascial disruption in the pathophysiology of KOA. An especially important area of study is the determination of phenotypic characteristics of patients who respond well to prolotherapy. Potential markers predicting responsiveness include baseline self-reported KOA severity; objectively assessed ligament laxity and knee alignment; intra-articular tissue characteristics; extra-articular soft-tissue character assessed by palpation and ultrasound; serum and synovial fluid biomarkers; and MRI characteristics.

Coverage in the US is typically not provided by third party payers; however, the Unity plan in the authors' practice in Madison, Wisconsin recently included coverage of prolotherapy on a "prior authorization" basis for patients refractory to other conservative care. The effect of such programs on dissemination of prolotherapy to a larger population is not known. However, given the low cost and apparent benefits of this procedure, prolotherapy has the potential to substantively impact the patient and societal burden of KOA.

Conclusion

The evaluation of prolotherapy for KOA is early in development. A series of clinical trials, including two of high quality, suggests both efficacy and effectiveness for a broad range of KOA severity grades. The mechanism of action of prolotherapy is not well elucidated; animal model and limited human trial data suggest an inflammatory response with direct tissue effects and possible neural effects. Prolotherapy performed by a trained clinician appears to be an effective treatment option for patients with KOA refractory to conservative care. Many questions remain unaddressed, including mechanism of action, effect on objectively assessed functional status and imaging outcomes, and the degree to which prolotherapy can be disseminated to routine clinical settings.

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Compliance with Ethics Guidelines

Conflict of Interest Bobby Nourani and David Rabago declare that they have no conflict of interest.

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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- • Of importance
- •• Of major importance

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