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## Prolotherapy: Applications, Mechanism of Action, Controversy and Evidence

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# Prolotherapy: applications, mechanism of action, controversy and evidence.

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## Abstract

Merriam-Webster defines prolotherapy (PROLO) as “an alternative therapy for treating musculoskeletal pain that involves injection of irritant substance (as dextrose) into a ligament or tendon to promote the growth of new tissue”. (2017) Experimental research and multiple clinical trials have generated evidence suggesting that PROLO is effective at treating a variety of musculoskeletal conditions, including tendinopathies, joint instability and ligament laxity. PROLO may also hold a potential to delay or avoid joint replacement and rotator cuff surgeries. Further research is needed to demonstrate the therapeutic effect of PROLO unequivocally.

## Introduction

- The traditional approach to treating acute tendon injuries and chronic tendinopathy is with anti-inflammatories, such as NSAIDs, even though histopathological, biochemical and molecular studies of damaged tendons have not been able to demonstrate classical inflammatory processes or components. In addition to that, at least one study found that the early administration of ibuprofen in the postoperative period was detrimental to tendon healing. (Connizzo et al., 2014)
- Corticosteroid injections continue to be one of the most commonly used approaches in treating tendinopathy and other MSK soft tissue pathology. This treatment is deemed to be very effective and provides relatively fast and often long lasting pain relief. The cytotoxic side effect of corticosteroids includes: degradation of fibroblasts, cellular apoptosis, collagen necrosis, and deterioration of mechanical properties of tendons. (Floyd Dean, Franklin, Murphy, Javaid, & Carr, 2014)
- Surgical intervention.

## Statement of the Problem

- At the present time, PROLO is classified as an alternative and/or complementary therapy. Therefore, it is not on the list of services that are covered by commercial healthcare insurance carriers.
- In 1999, the Centers of Medicare and Medicaid Services (CMS) in their national non-coverage decision denied the request for PROLO coverage citing the lack of conclusive scientific evidence.
- In the last 15 years, a number of randomized controlled trials produced clinically and statistically significant evidence in support of PROLO. The studies were published in a variety of established and recognized medical periodicals.
- Will those new pieces of evidence turn out to be sufficient, compelling and significant enough to sway the position the medical establishment and the insurance carriers hold regarding PROLO?

## Research Questions

- What are the common MSK disorders that can potentially be treated with PROLO?
- What is the proposed mechanism of action behind?
- What clinical studies are available in support of effectiveness and efficacy of PROLO?
- What are the existing alternatives to PROLO and how do they compare with it?

## Literature Review

The information used for this project was retrieved from peer reviewed periodicals that can be located at: PubMed, SPORT Discus and Cochrane. The data regarding the epidemiology and pathogenesis was collected from the Centers for Disease Control and Prevention and the Congressional Budget Office. The policies of the following healthcare insurers were reviewed regarding the coverage of PROLO: Aetna, United Healthgroup, and Blue Cross/Blue Shield. The national non-coverage decision of the Centers of Medicare and Medicaid Services regarding PROLO was utilized for this project.

- MSK conditions are the single most common reason for patients visiting their physician. (CDC)
- MSK conditions identified as amenable to PROLO: injured or torn ligaments and tendons; chronic MSK pain, including low back pain; tendinopathy; rotator cuff injuries, and knee disorders.
- Pathophysiology factors: genetic component, repetitive micro trauma, **no evidences for inflammatory processes or components.**
- Proposed intrinsic regeneration elements: growth factors, cytokines and neuropeptides. (Riley, 2004)
- Proposed mechanism of action of PROLO – trigger of inflammatory reaction: recruitment of granulocytes, monocytes, macrophages and other inflammatory mediators. Polypeptide growth factors attract fibroblasts which deposit new collagen fibers at the site of PROLO therapy. (Freeman et al., 2011) Having been injected with hyperosmolar dextrose solutions, the cell becomes dehydrated and releases lipids from cell membrane that produce growth factors. (Reeves, 2015)
- At the present time, there is **level I and/or level II** evidence demonstrating efficacy of PROLO for treating the following conditions: knee (Rabago et al., 2013) and hand osteoarthritis (Reeves & Hassanein, 2000), Osgood-Schlatter disease (Topol et al., 2011), lateral epicondylitis (Scarpone, Rabago, Zgierska, Arbogast, & Snell, 2008), chronic low back pain (Yelland, Mar, Pirozzo, Schoene, & Vercoe, 2004), anterior cruciate ligament laxity (Reeves & Hassanein, 2003), and rotator cuff tendinopathy (Bertrand et al., 2016).

## Discussion

### • Contemporary Research

Since the mid 1980s, research on PROLO effects has accelerated and the number and methodological quality of studies assessing PROLO have increased dramatically.

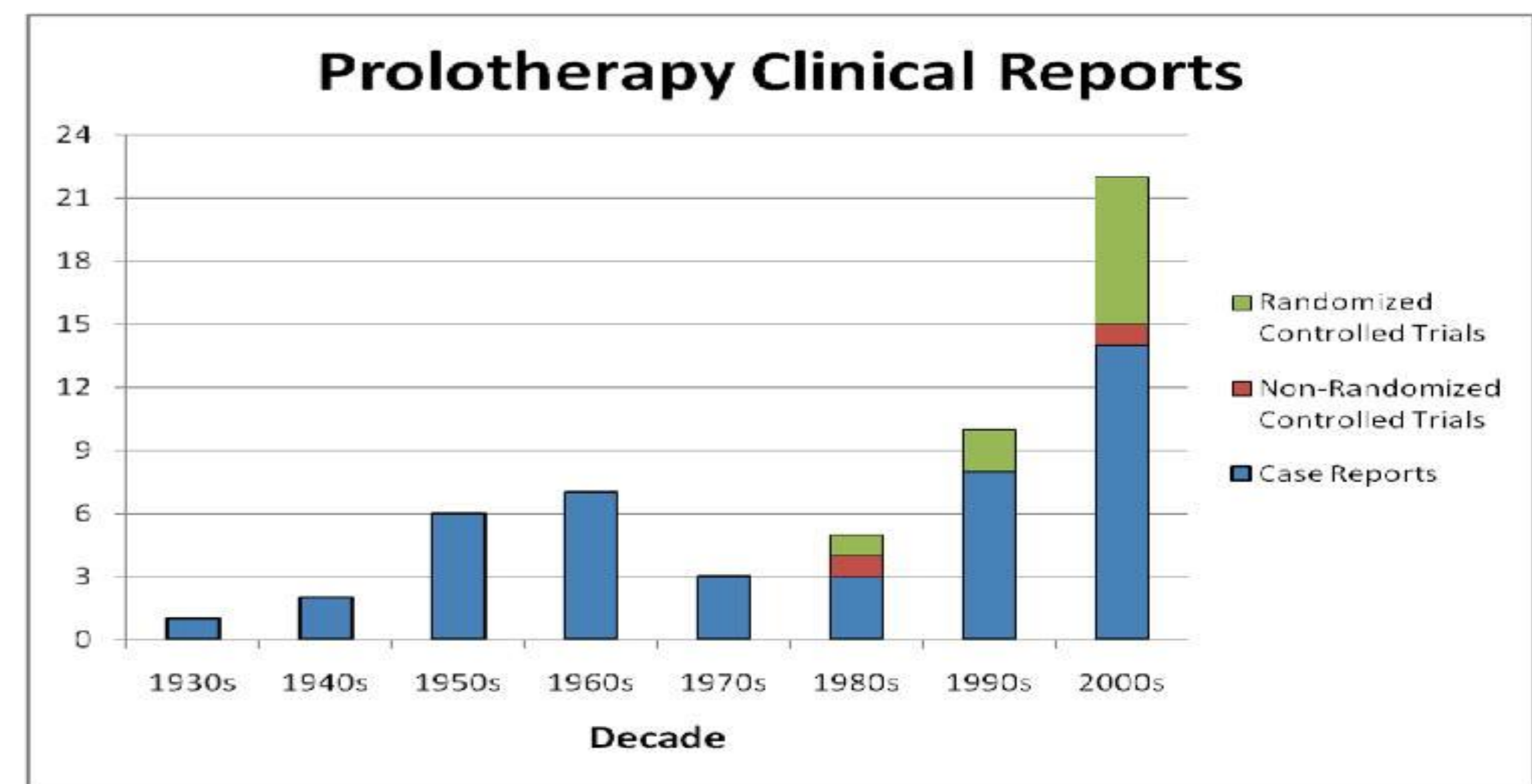


Figure 1. Number of published clinical studies on PROLO since 1937. Adopted from Rabago, D., Slattengren, A., & Zgierska, A. (2010). Prolotherapy in Primary Care Practice. *Primary Care*, 37(1), 65–80. <http://doi.org/10.1016/j.pop.2009.09.013>

### • PROLO for knee osteoarthritis: a randomized controlled trial

Trial parameters: Number of patients 93; duration of the trial 52 weeks; PROLO injections performed at 1,5,9,13,17 weeks; Western Ontario McMaster University Osteoarthritis Index ( WOMAC ) was used as primary outcome measure in evaluating results (WOMAC is scored on a range of 0 to 100 points, with higher scores indicating better knee-related quality of life)

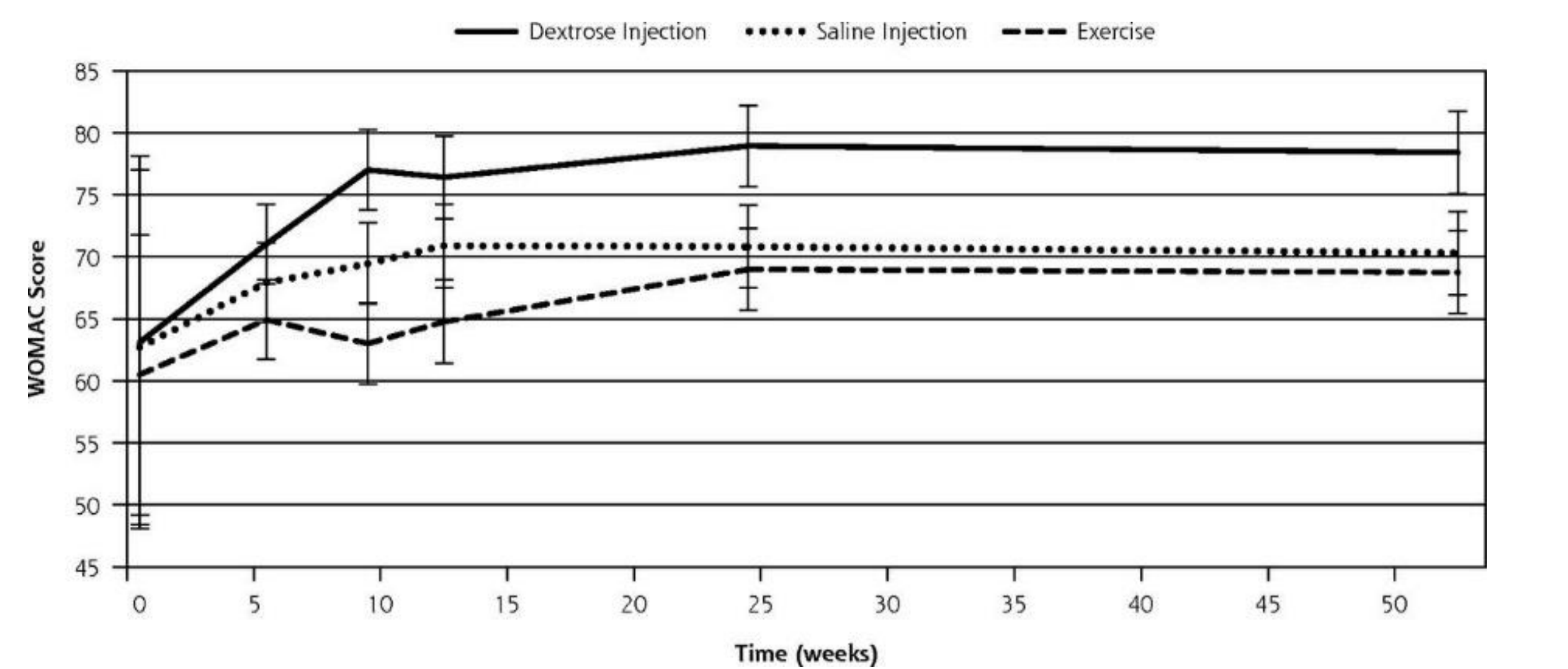


Figure 2. Change in WOMAC composite scores over 52 weeks (± standard error). Nonoverlapping confidence intervals indicate significance of change in dextrose scores compared with change in scores of both saline ( $P<.05$ ) and exercise ( $P<.05$ ) groups. Adopted from Rabago, D., Patterson, J. J., Mundt, M., Kijowski, R., Grettie, J., Segal, N. A., & Zgierska, A. (2013). Dextrose Prolotherapy for Knee Osteoarthritis: A Randomized Controlled Trial. *Annals of Family Medicine*, 11(3), 229–237. <http://doi.org/10.1370/afm.1504>

**RESULTS:** At the end of the tracking period, week 52, there was a statistically significant improvement on the WOMAC score among the participants who received dextrose PROLO injections. The score improved by more than 15 points, which corresponded to 24% compared with the baseline score. These changes exceed the minimal clinical important difference (MCID) on the WOMAC for the knee osteoarthritis, which is set at 12 points.

## Applicability to Clinical Practice

### • Prolotherapy at a glance

What is prolotherapy?	Prolotherapy is an injection-based complementary and alternative medical (CAM) therapy for chronic musculoskeletal pain. This treatment aims to stimulate a natural healing response at the site of painful soft tissue and joints.
What is involved?	Prolotherapy treatment typically involves getting a series of 2–5 monthly injections of a topical anesthetic and a solution of other medicines directly on sore tendon or ligaments, or into painful joints.
What conditions is it used for, and is it effective?	Prolotherapy is generally used for musculoskeletal pain of greater than 3 months. Conditions that have responded well to prolotherapy in published studies include lateral epicondylitis, Achilles tendinopathy, and other overuse injuries involving tendons. Prolotherapy is also likely effective for knee osteoarthritis and low back pain, though studies assessing these conditions are less conclusive.
Is it safe?	Studies indicate that prolotherapy is safe when performed by an experienced practitioner. It does not appear to have a greater risk than other injection techniques, such as steroid injections.
Does it hurt?	No one loves getting a shot, though prolotherapy injections typically hurt less than most immunizations. Most patients related pain quite well with only topical and conservative measures. Physicians can pre-treat with a pain reliever if necessary.

### • Estimated cost of treatment

A typical PROLO protocol consists of 4 to 6 sessions, each separated by intervals of 4 to 6 weeks. At the present time, most insurers do not cover PROLO, and patients pay out-of-pocket. The average cost of PROLO treatment ranges from \$1,125 for wrist/foot/hand disorders to \$2,500 for back pain. (Hauser, Baird 2010)

### • PROLO coverage by insurance

The number of random controlled studies that explore the potential of PROLO continues to grow. Every single one of them has produced positive results supporting PROLO with additional studies needed to establish an unequivocal efficacy. However, most of these studies are self-funded and receive no financial support from any pharmaceutical or medical corporation. Therefore, it will likely take more time for the cumulative solid scientific evidence to reach a point when the insurance policy makers will no longer be able to ignore the PROLO potential. Major healthcare insurers, such as Aetna, United Healthgroup, and Blue Cross/Blue Shield, find the available data insufficient or have not recognized it, thus making PROLO inaccessible for most of the patients.

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