Prolotherapy in the Treatment of Sports-Related Tendinopathies

A Systematic Review of Randomized Controlled Trials

Salvatore Capotosto,*† MD, Alireza K. Nazemi,‡ MD, MS, David E. Komatsu,§ PhD, and James Penna,§ MD
Investigation performed at the Department of Orthopedics and Rehabilitation, Stony Brook University Hospital, Stony Brook, New York, USA

Background: As sports have increased in popularity, the incidence of tendinopathy has also grown dramatically. Nonoperative techniques and treatments used to address these pathologies continue to evolve and improve. One such treatment, prolotherapy (PrT), has become increasingly popular and may provide patients with an alternative nonoperative treatment option.

Purpose: To review high-quality randomized controlled trials (RCTs) that analyzed PrT treatments for the most common tendinopathies. Specifically, this review aims to provide meaningful data regarding methods and outcomes for each condition treated and guide professionals who are considering PrT as a treatment option.

Study Design: Systematic review; Level of evidence, 2.

Methods: All RCTs published in English between January 1, 1980, and July 30, 2021, and reported in Embase, Medline, and Web of Science databases were reviewed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. After the initial search, a total of 3264 articles were identified. Studies analyzing sports medicine injuries and musculoskeletal pathologies using an RCT design were included, while case-reports, case-studies, reviews, and observational studies were excluded. Two independent researchers reviewed the search results, and conflicts were resolved by discussion of inclusion and exclusion criteria among all authors. The articles' quality was evaluated using the Cochrane tool for assessing the risk of bias. Statistical analysis and graphical representations were performed using SPSS Version 28.00.

Results: A total of 20 articles, including 1136 patients, met the inclusion criteria and were included in the study. Overall, in 85% of the studies, PrT was found to be effective in the treatment of tendinopathy. Specifically, PrT was superior to or as effective as the control in 83% (10/12) of the studies analyzing lateral epicondylitis (LE) and rotator cuff (RC) tendinopathies and in 88% (7/8) of the studies on plantar fasciitis (PF), Osgood-Schlatter disease (OSD), and Achilles tendinosis (AT). LE, RC, and PF tendinopathies were the most studied conditions (17/20 studies), while AT and OSD were the least studied (3/20 studies). Of the studies, 95% (19/20) used dextrose solutions, with only 1 using solutions of 2.5% phenol, 25% glycerin, and 25% dextrose in sterile water.

Conclusion: Our systematic review suggests that PrT appears to be a promising alternative treatment for common tendinopathies. Most studies used a hypertonic dextrose solution. Even though further, larger randomized controlled trials comparing PrT with other orthobiologics would be beneficial, based on this review, sports medicine physiciansmay safely pursue PrT as an additional component of conservative treatment.

Keywords: Biologic healing enhancement; muscle injuries; physical therapy/rehabilitation; prolotherapy; tendinopathy; dextrose; hypertonic glucose; sclerotherapy

With an increased portion of the US population practicing high–calorie burning activities,[17] there is the need to account for the associated growth of sports-related injuries.[14,16,31,32] This compels health care professionals to consider nonsurgical approaches to sports-related disorders, as they can be cost-effective, safer, and less invasive than surgical options.[22] Prolotherapy (PrT) is a promising treatment for a wide variety of common musculoskeletal conditions, including lateral epicondylitis (LE),[1] rotator cuff

The Orthopaedic Journal of Sports Medicine, 12(11), 23259671241275087
DOI: 10.1177/23259671241275087

(RC) tendinopathy,[4] plantar fasciitis (PF),[20] and Osgood-Schlatter disease (OSD).[34] Prolotherapy solutions may be divided into 3 main classes: irritants (phenol, guaiacol, tannic acid, and phenol-glycerin-glucose), osmotics (dextrose), and chemotactics (sodium morrhuate).[7] At the core of their mechanism of action is the initiation of the inflammatory cascade, consequent recruitment of macrophage and fibroblast at the site of injection, and collagen deposition. This deposition is thought to aid in the strengthening and regeneration of damaged tendons, ligaments, and cartilage.[19,36,49] The first class, irritants, are compounds containing phenolic hydroxyl groups. These are readily oxidized within body tissues, damaging the cells' membranes, and initiating the inflammatory cascade.[7,18] On the other hand, chemotactic agents are biosynthetic precursors able to directly attract inflammatory cells at the site of injections. Finally, osmotic agents such as hypertonic dextrose are the most widely used. These create a hypertonic environment causing the lysis of cells whose content releases growth factors and proteins able to recruit granulocytes and fibroblasts.[7,19,36,49] Because of its proposed regenerative actions, PrT has been used in the treatment of various tendinopathies.[4,9,15,24,29,44] Despite these studies, a review of high-quality evidence and protocols for PrT administration in tendinopathy is lacking. This systematic review aimed to provide a summary of the current applications of PrT in the treatment of sports-related tendinopathies and provide an assessment of bias within these studies. We hypothesized that PrT would improve pain and functional scores in the treatment of tendinopathy.

METHODS

A systematic review of English-language papers published between January 1, 1980, and July 30, 2021, was performed using Embase, Medline, and Web of Science databases. Emtree terms, Medical Subject Headings terms, and keywords included were sclerotherapy, PrT, sports medicine, sports injuries, and musculoskeletal pain/injuries. Other keywords included orthopaedics, orthopaedic injuries, and tendinopathies. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[35] were followed (Figure 1). Inclusion criteria were randomized controlled trials (RCTs) written in English and reporting on PrT injections for sports medicine injuries or other orthopaedic pathologies. Exclusion criteria were non-English language papers, papers focusing on nonmusculoskeletal problems, review articles, case reports, animal studies, symposia, conference abstracts, and letters to the editor. Duplicates were eliminated through Endnote. The remaining articles were screened by titles, followed by abstracts, and then by full-text analysis. Most of the initial articles screened by titles and abstracts were not focused on PrT applications for the treatment of orthopaedic pathologies. The remaining excluded articles comprised non-RCTs (prospective and retrospective cohort studies, case studies, conference abstracts) and treatment of intra-articular and spine pathologies. Data were extracted using an Excel spreadsheet (Microsoft 2023) to record the following characteristics: author, year, journal, title, and abstract. Under the supervision of a senior sports medicine orthopaedic surgeon (J.P.) and an experienced bioengineer with a doctorate (D.E.K.), 2 researchers including a fifth-year orthopaedic surgery resident (A.K.N.) and a medical student (S.C.) independently performed the screening. If conflicts arose, articles and selective criteria were simultaneously reviewed by the senior attending surgeon (J.P.), bioengineer with PhD (D.E.K.), resident (A.K.N.), and student (S.C.) using Rayyan software (Rayyan Systems Inc). Agreement on articles' inclusion was reached by all the authors. The articles' quality was evaluated using the Cochrane tool for assessing the risk of bias.[23] Statistical analysis (descriptive statistics and frequency values) and graphical representations were created using SPSS Version 28.00 (IBM Corp).

RESULTS

Application of the inclusion and exclusion criteria yielded 20 RCTs.[§] The included studies were subsequently grouped based on the pathology treated, resulting in 6 studies on LE,[1,2,5,13,38,50] 6 on RC injuries,[4,9,15,24,29,44] 5 on PF,[6,20,26,30,47] 2 on OSD,[34,46] and 1 on Achilles tendinosis (AT).[51] Overall, PrT was found superior to control in all outcomes in 25% of the studies, superior to control in specific outcomes such as pain and function scores in 30% of the studies, as effective as the control in 30% of the studies, while inferior to control in 15% of the studies (Figure 2). Patients' Baseline Characteristics are summarized in Table 1.

Lateral Epicondylitis

Six studies examined the effectiveness of PrT in treating LE.[1,2,5,13,38,50] The most utilized solution was dextrose

[§]References 1, 2, 4-6, 9, 13, 15, 20, 24, 26, 29, 30, 34, 38, 44, 46, 47, 50, 51.

*Address correspondence to Salvatore Capotosto, MD,Mount Sinai Hospital, 1 Gustave L. Levy Place, New York, NY 10029, USA(email: salvatore.capotosto@mountsinai.org) (Twitter/X: @CapotostoS).
[†]Department of Orthopedic Surgery, Mount Sinai Hospital, New York, USA.
[‡]Cedars-Sinai Kerlan-Jobe Institute, Los Angeles, California, USA.
[§]Department of Orthopedics and Rehabilitation, Stony Brook University Hospital, Stony Brook, New York, USA.
Presented at the 2023 AOSSM Annual Meeting, Washington, DC, July 2023.
Final revision submitted October 23, 2023; accepted February 2, 2024.
One or more of the authors has declared the following potential conflict of interest or source of funding: A.K.N. has received education payments from Gotham Surgical Solutions & Devices. J.P. has received education payments from Gotham Surgical Solutions & Devices. AOSSM checks author disclosures against the Open Payments Database (OPD). AOSSM has not conducted an independent investigation on the OPD and disclaims any liability or responsibility relating thereto.

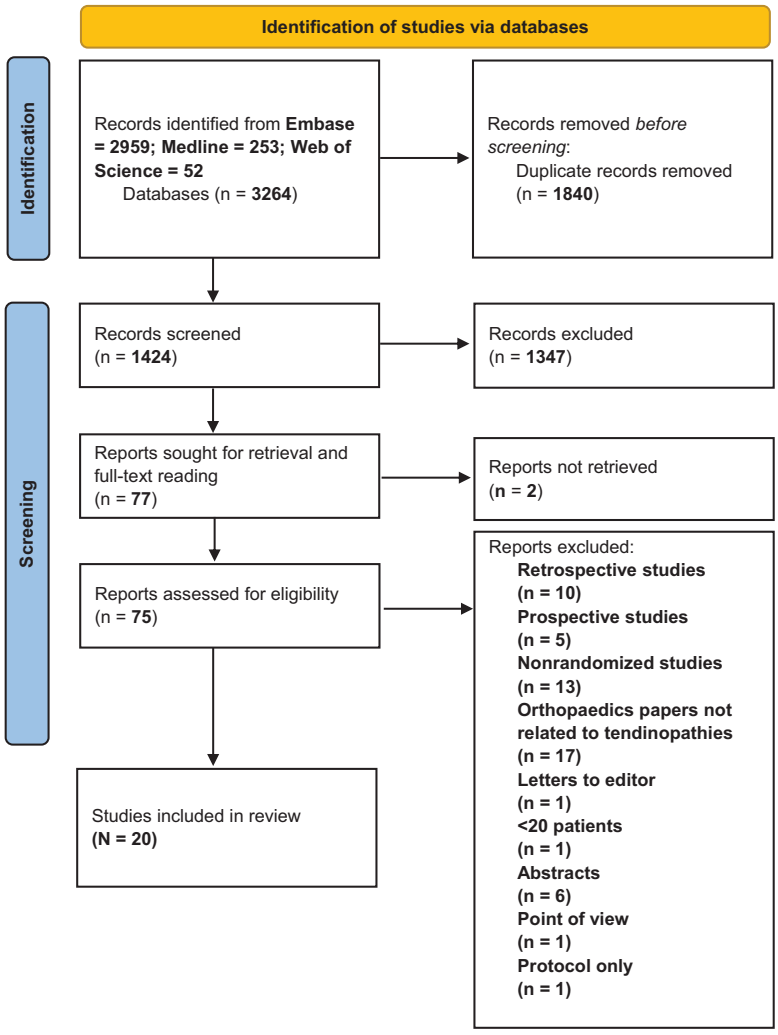

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines followed for systematic screening and selection of relevant articles.

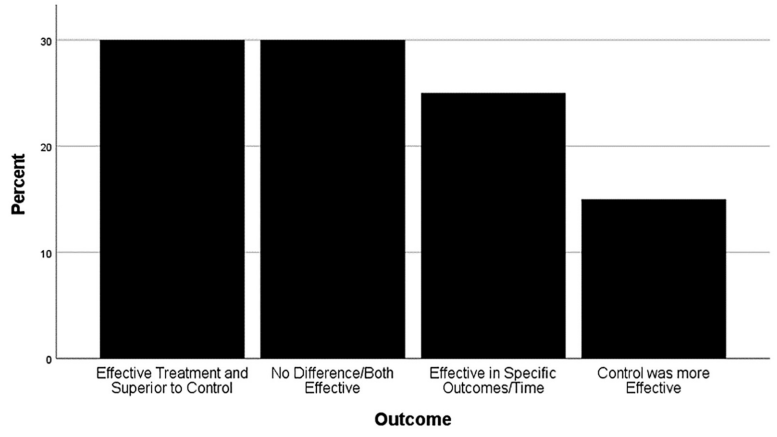

Figure 2. Effectiveness of prolotherapy treatment compared with controls.

TABLE 1
Patients' Baseline Characteristics[a]

Patients' Characteristics	Value	Range (total)
Sex ratio, F:M (18 studies/ 1071 patients)	1:1	N/A
Number of patients (20 studies/ 1136 patients)	1136	17-120
Age, y (20 studies/1136 patients)	43.8	44.4-57.8
Symptom duration, mo (15 studies/898)	23.8	5.5-64.3
Visual analog scale baseline (15 studies/898 patients)	6.6	3.4-7.8

[a]Ranges reported as minimum and maximum for the studies examined. F, female; M, male; N/A, not available.

(95%; 19/20 studies),[1,2,5,38] with limited use of phenol-glycerin-glucose (5%; 1/20 of the studies).[13] For LE, PrT was superior to control in 50% of the cases (3/6 studies) and equal to control in 33.3% (2/6 studies) of the cases, while it was inferior to control in 16.7% of the cases (1/6 studies). The preferred method of injection was administering the solution at the lateral epicondyle, annular ligament, radial collateral ligament, and/or at the most tender points. Rabago et al[38] injected solutions of dextrose and dextrose plus morrhuate (PrT groups) in 2 distinct treatment groups while the control population was counseled about lifestyle changes and activity modification. The PrT groups showed improved patient-related tennis elbow evaluation (PRTEE) composite and subscale scores of 41.1% and 53.5%, respectively, and both groups achieved more than the minimal clinically important difference (MCID) at 16 weeks. In contrast, the control group showed no significant improvements in PRTEE scores nor met the MCID. Additionally, the dextrose plus morrhuate group demonstrated greater improvements in grip strength at 8 and 16 weeks when compared to the dextrose only and control group ($P < .05$). Another study[5] showed improvements in the PrT group (15% dextrose solution) over hyaluronic acid (HA) injections in pain with activity, pain at night, pain at rest, and the shortened version of Disabilities of the Arm, Shoulder and Hand (QuickDASH) (all $P < .05$). However, no difference was found for grip pain ($P = .38$). Interestingly, Ahadi et al[1] injected a 20% dextrose solution into the point of maximal tenderness and compared it with extracorporeal shock wave therapy (ESWT) administered at weekly intervals. At 4 and 8 weeks, visual analog scale (VAS) and QuickDASH scores were superior in the control group, leading the authors to conclude that ESWT was more effective in treating LE pain and restoring function.

RC Tendinopathy

Six studies examined the effectiveness of PrT on RC injuries.[4,9,15,24,29,44] All the studies utilized dextrose solutions. For the RC, PrT was superior to control in 66.7% of the cases (4/6 studies) and equal to control in 16.7% (1/6 studies) of the cases, while it was not clinically significant in 16.7% of the studies (1/6). Five (83%) studies analyzed included patients with partial RC tears <1.2 cm, calcific tendinosis, and chronic shoulder pain, while 1 study[15] included patients with bursitis. Multiple methods of injection were used for RC tendinopathy ranging from neurofascial injections[24] to injections at the muscle insertions[44] or points of maximal tenderness.[15] Two RCTs, Kazempour et al[24] and Lin et al,[28] demonstrated superior improvements for the PrT groups in alleviating overall pain, as well as improving Shoulder Pain and Disability Index (SPADI) scores and shoulder active range of motion (ROM) 2 weeks after injection when compared with physical therapy (PT) and saline, respectively. The injections done by Kazempour et al were extra-articular neurofascial injections performed superficially in the anterior, posterior, and lateral sides of the shoulder along the suprascapular nerve (0.5-1 mL). Tender points were also injected with ultrasound-guided myofascial injections (2 mL). Intra-articular injections were avoided.[24] Using a different approach, Lin et al[28] injected the dextrose solution subacromially into the supraspinatus tendon insertion site using ultrasound guidance. In another RCT, Seven et al[44] compared a 25% dextrose solution with a PT protocol by performing injections into the subacromial bursa, supraspinatus, infraspinatus, teres minor insertion along the greater tuberosity, and tendons inserting on the coracoid process using ultrasound guidance. The study showed improvements in both groups, and the authors concluded that PrT is an easily applicable and satisfying auxiliary method for the treatment of chronic RC lesions. Chang et al[15] injected a 15% dextrose solution into the point of maximal tenderness and compared it with normal saline plus xylocaine. At 3 months, both the treatment and the control groups showed significant improvement in VAS, active ROM, and SPADI scores compared with the control (all $P < .05$). A major limitation of this study was the short follow-up period.

Plantar Fasciitis

Five RCTs have examined the potential of PrT in the treatment of PF.[6,20,26,30,47] For PF, PrT was superior to control in 60.0% of the cases (3/5 studies) and equal to control in 40.0% (2/5 studies) of the cases, while it was inferior to control in none of the studies examined. Injections were made at the insertion of the plantar fascia over the media calcaneus. Kim and Lee[26] and Mansiz-Kaplan et al[30] compared dextrose PrT with platelet-rich plasma (PRP) and saline injection to evaluate their effectiveness in improving VAS, Foot Function Index (FFI), and plantar fascial thickness. Both studies concluded that there were improvements in VAS during activity and at rest, as well as improvements in FFI and plantar fascial thickness. In contrast, Uğurlar et al[47] compared PrT dextrose injections with corticosteroids to PRP injections and ESWT. The outcomes compared were VAS and revised FFI. The authors concluded that corticosteroids and ESWT were more effective than PrT at 3 and 6 months respectively, but there were no differences between groups at the 36-month follow-up.

Osgood-Schlatter Disease

Two RCTs have been performed to evaluate PrT injections in treating OSD.[34,46] Of the 2 studies, PrT was superior to the control in one[34] while as effective as the control in the other.[46] Nakase et al[34] compared 20% dextrose solution with saline plus lidocaine injections. Both solutions were injected under ultrasound guidance into the deep and superficial infrapatellar bursa and infrapatellar fat pad. They concluded that there were no differences between dextrose PrT and lidocaine plus saline injections. The mean Victorian Institute of Sport Assessment (VISA) improved in both groups ($P < .01$). On the other hand, Topol et al[46] performed 4 injections of 0.5 mL of a 12.5% dextrose solution starting at the most distal point of tenderness (tibial tubercle) and moving proximally toward the patellar tendon, which showed greater improvements in the dextrose-treated patients compared with PT or lidocaine-only groups. Outcomes measured were Nirschl Pain Phase Scale and symptom reduction. The authors concluded that dextrose injections were safe, well tolerated, and resulted in more rapid and frequent achievement of return to asymptomatic sport than PT and nonsteroidal anti-inflammatory drugs (NSAIDs) alone.[46]

Achilles Tendinosis

Yelland et al[51] injected a hypertonic glucose PrT solution in patients with AT, comparing it with eccentric loading exercise (ELE) and a combined ELE/PrT treatment. The injections were made at the tender points mostly anteromedial and anterolateral to the tendon 2 to 7 cm from the calcaneal insertion. The outcome measured was the VISA–Achilles questionnaire, with a MCID of 20 points. PrT and the combined treatment were more effective than ELE in treating AT with mean increases in the VISA–Achilles score of 27.5 and 41.1, respectively, versus 23.7 in the ELE-only group ($P = .003$).

Risk of Bias

The risk of bias was overall low. In particular, all studies except Apaydin et al,[5] Ersen et al,[20] and Nakase et al,[34] who did not clearly describe their randomization process, provided detailed information regarding random sequence generation and allocation concealment. Blinding was clearly described in most of the studies with the exception of Ahadi et al,[1] Asheghan et al,[6] Ersen et al, Kim and Lee,[26] Uğurlar et al,[47] and Yelland et al.[51] In Ahadi et al, participants were not blinded but the outcome assessor was. On the other hand, in both Kim and Lee and Yelland et al, participants were blinded but the outcome assessors were not. In both Ersen et al and Uğurlar et al, there was not a clear description of the blinding process. In Asheghan et al, it was not possible to blind either the participants or the outcome assessors due to the nature of the treatments—an injection versus ESWT. Finally, all the studies comprehensively reported relevant clinical outcomes and were at low risk for other biases.

DISCUSSION

This systematic review identified 20 articles, of which all were RCTs aimed to assess the efficacy of PrT injections for common tendinopathies. Results were promising in 17 of the 20 studies examined (85%) with some variations among the conditions treated.

When compared with HA, saline, corticosteroids, and PT for the treatment of LE and PF, PrT showed promising results, outperforming or equivalent to control groups.[2,5,13,38,50] However, in 2 studies,[1,47] ESWT yielded better outcomes than the PrT treatment. It is worth mentioning that even though Uğurlar et al[47] demonstrated superiority of ESWT for PF at 6 months, this did not endure at 36 months, where there was no difference between groups. When PrT was compared with corticosteroids, saline, ESWT, and PT in the treatment of RC tendinopathy,[4,9,15,24,29,44] it provided superior or equal results. Only 1 study, that reported by Chang et al,[15] showed insufficient evidence when compared with saline solution; however, in contrast to the other papers that analyzed tendinopathies, this study analyzed the effects of PrT on subacromial bursitis and was limited by a short follow-up.

For the other 2 conditions examined, OSD[34,46] and AT,[51] PrT use demonstrated mixed outcomes. Although Nakase et al[34] did not establish superiority of PrT to lidocaine/saline injections, patients treated with PrT reported significant improvements in the VISA score. AT is currently understudied, with only 1 study reported as of the time of this review.[51] In this study, the control group, which proved to be superior, was still treated with PrT but in combination with eccentric loading exercise; therefore, for AT, PrT treatment remains worthy of further investigation.

PrT is a broad term that applies to the injection of an irritant into an injured structure to promote a healing response.[18] The most used solution for PrT includes hyperosmolar dextrose.[18] It is thought that PrT acts through 2 main pathways: chemical and mechanical. Indeed, dextrose may act directly through a sensorineural mechanism by the opening of potassium channels in nerve fibers, resulting in their hyperpolarization and inhibition.[12] Additionally, dextrose has been shown to positively modulate inhibitory glycine receptors, which mediate and inhibit the propagation of nociceptive signals to higher cortical structures.[11] Its hyperpolarizing and modulatory effects would support its analgesic potential reported by patients.

In addition to its analgesic mechanism, PrT solutions induce immune responses at the injection sites, which stimulate hypertrophy and hyperplasia of injured tissues through the recruitment of granulocytes, macrophages, and fibroblasts, and subsequent collagen deposition.[7] This enables the natural creation of a stronger extracellular matrix, enhancing the structure of tendons and ligaments and potentially contributing to joint stability.[18] The mechanical effect of PrT, a hypertonic solution, is proposed to be through its induced “osmotic shock” and dehydration of cells.[7] Specifically, synoviocytes are dehydrated and damaged, initiating an inflammatory reaction and a wound-healing cascade. The release of chemotactic agents from the lysed cells attracts granulocytes and macrophages.

This initiates the recruitment of fibroblasts, which begin secreting collagen directly for tendons and ligaments.[21,48] Interestingly, if inducing an inflammatory response is at the core of PrT treatment, it is reasonable to postulate that anything interfering with its physiology would limit the healing process. Indeed, practitioners have observed a diminished clinical result of PrT when NSAIDS are prescribed to alleviate the discomfort of PrT injections.[7]

Understanding the pathology of tendinopathy, including the distinction between tendinitis and tendinosis, is crucial for comprehending the regenerative effects of PrT. Tendinitis involves inflammation caused by excessive loads on the musculotendinous unit, while tendinosis results in the degeneration of tendons from chronic overuse.[8] Biopsy is necessary for a complete differentiation, but both are generally referred to as tendinopathy. Many cases are erroneously classified as tendinitis when they are, in fact, tendinosis. For example, tennis elbow is usually reported as tendinitis of the extensor carpi radialis brevis; however, no signs of chronic or acute inflammation have been found on pathological surgical specimens.[10] This would provide a mechanistic and molecular explanation supporting the use of PrT, which may induce a positive healing response in tendons and ligaments. Similarly, AT is mainly characterized by noninflammatory processes[42]; however, contrary to LE, there is more variation to the possible etiologies of Achilles tendon disorders,[37] and further studies delineating these pathologies would be beneficial.

In the treatment of PF, it has been shown that repeated corticosteroid injections into the plantar fascia are associated with heel pad atrophy and plantar fascial rupture.[43] This association has not been reported for PrT, but additional long-term studies would help better determine if a relationship does exist. In OSD, the pathophysiology occurs at the tendon insertion. This traction apophysitis is theorized to be either due to the fragmentation of the tibial tubercle or an inflammation of the patellar tendon itself.[27] The inflammation theory is supported by a study in which only one-third of patients with symptomatic OSD had an ossicle present on imaging, while 100% of patients showed signaling changes and changes to the tendon shape and appearance.[40] Therefore, this pathology remains within the scope of the discussion regarding tendinopathy. Further studies regarding the safety and efficacy of PrT in pediatric musculotendinous conditions are warranted.

Studies on RC tendinopathy have shown mixed results with subacromial injections. Corticosteroids have been effective at short-term pain relief, between 4 and 8 weeks, but have not demonstrated superiority to placebo over the long term.[33] Seemingly, orthobiologics have not been significantly different than placebo. An RCT by Kesikburun et al[25] found no difference between PRP injections and placebo for chronic RC tendinopathy. Scarpone et al[41] analyzed the efficacy of PRP injection in RC tendinopathy refractory to corticosteroids and PT, showing improved pain control and functional outcomes. However, this study did not include a control group for comparison. Due to the rising interest in orthobiologics, further studies including a PRP group may also be beneficial in determining the comparative efficacy of PrT.

Limitations

Limitations of the study include the potential for publication bias where only analysis resulting in positive outcomes is reported. Additionally, a large number of the RCTs included in the analysis were from nonorthopaedic journals, and a clear conclusion about PrT is challenging to achieve because of the high heterogeneity between studies. Indeed, there were important variations regarding the dextrose solutions utilized (eg, 12.5% vs 15% vs 25%) and control groups (eg, HA vs steroids vs saline). With regard to injection techniques, the most variation was seen in the treatment of RC tendinopathies, where injections were made at the insertion of the RC muscles, into the subacromial bursa, or with the addition of neurofascial injections along the suprascapular nerve. Despite these limitations, the studies are of higher-level evidence due to their prospective nature, randomization, and inclusion of control groups. Furthermore, the mean age across the studies, excluding OSD, was 43.8 years. In the OSD studies, the mean age was 12.8 years. This corresponds with the increase in pediatric tendinopathy as children approach the age of 18 years[45] and the greater prevalence of adult tendinopathy in older patients.[3]

CONCLUSION

Our systematic review suggests that PrT appears to be a promising alternative treatment for common tendinopathies, both acute and chronic, including LE, RC tendinopathy, PF, and AT. No significant adverse events or prolonged complications were reported in any of the RCTs evaluated. It is worth noting, however, that PrT should be managed by an experienced practitioner to avoid potential injury to surrounding neurovascular structures.[39]

ACKNOWLEDGMENT

The authors thank the Department of Orthopedics and Rehabilitation at Stony Brook University Hospital for their continuous support and dedication to research and innovation.

ORCID iD

Salvatore Capotosto https://orcid.org/0000-0002-5914-6560

Supplemental Material for this article is available at https://journals.sagepub.com/doi/full/10.1177/23259671241275087#supplementary-materials.

REFERENCES

1. Ahadi T, Esmaeili Jamkarani M, Raissi GR, Mansoori K, Emami Razavi SZ, Sajadi S. Prolotherapy vs radial extracorporeal shock wave therapy in the short-term treatment of lateral epicondylosis: a randomized clinical trial. *Pain Med*. 2019;20(9):1745-1749.

2. Akcay S, Kandemir NG, Kaya T, Dogan N, Eren M. Dextrose prolotherapy versus normal saline injection for the treatment of lateral epicondylopathy: a randomized controlled trial. *J Altern Complement Med*. 2020;26(12):1159-1168.
3. Albers IS, Zwerver J, Diercks RL, Dekker JH, Van den Akker-Scheek I. Incidence and prevalence of lower extremity tendinopathy in a Dutch general practice population: a cross sectional study. *BMC Musculoskelet Disord*. 2016;17:16.
4. Amanollahi A, Asheghan M, Hashemi SE. Subacromial corticosteroid injection versus subcutaneous 5% dextrose in patients with chronic rotator cuff tendinopathy: a short-term randomized clinical trial. *Interv Med Appl Sci*. 2020;11(3):154-160.
5. 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*. 2020;26(12):1169-1175.
6. Asheghan M, Hashemi SE, Hollisaz MT, Roumizade P, Hosseini SM, Ghanjal A. Dextrose prolotherapy versus radial extracorporeal shock wave therapy in the treatment of chronic plantar fasciitis: a randomized, controlled clinical trial. *Foot Ankle Surg*. 2021;27(6):643-649.
7. Banks AR. A rationale for prolotherapy. *J Orthop Med*. 1991;13(3):54-59.
8. Bass E. Tendinopathy: why the difference between tendinitis and tendinosis matters. *Int J Ther Massage Bodywork*. 2012;5(1):14-17.
9. Bertrand H, Reeves KD, Bennett CJ, Bicknell S, Cheng AL. Dextrose prolotherapy versus control injections in painful rotator cuff tendinopathy. *Arch Rehabil Res Clin Transl*. 2016;97(1):17-25.
10. Boyer MI, Hastings H. Lateral tennis elbow: ''Is there any science out there?'' *J Shoulder Elbow Surg*. 1999;8(5):481-491.
11. Breitinger U, Breitinger HG. Augmentation of glycine receptor alpha3 currents suggests a mechanism for glucose-mediated analgesia. *Neurosci Lett*. 2016;612:110-115.
12. Burdakov D, Jensen LT, Alexopoulos H, et al. Tandem-pore K+ channels mediate inhibition of orexin neurons by glucose. *Neuron*. 2006;50(5):711-722.
13. Carayannopoulos A, Borg-Stein J, Sokolof J, Meleger A, Rosenberg D. Prolotherapy versus corticosteroid injections for the treatment of lateral epicondylosis: a randomized controlled trial. *PM R*. 2011;3(8):706-715.
14. Centers for Disease and Control. Nonfatal traumatic brain injuries related to sports and recreation activities among persons aged ≤19 years—United States, 2001-2009. *MMWR*. 2011;60(39):1337-1342.
15. Chang YJ, Chang FH, Hou PH, Tseng KH, Lin YN. Effects of hyperosmolar dextrose injection in patients with rotator cuff disease and bursitis: a randomized controlled trial. *Arch Rehabil Res Clin Transl*. 2021;102(2):245-250.
16. Conn JM, Annest JL, Gilchrist J. Sports and recreation related injury episodes in the US population, 1997-99. *Inj Prev*. 2003;9(2):117-123.
17. Council PA. The Physical Activity Council's annual study tracking sports, fitness, and recreation participation in the US. Published 2016. Accessed 2021.
18. DeChellis DM, Cortazzo MH. Regenerative medicine in the field of pain medicine: prolotherapy, platelet-rich plasma therapy, and stem cell therapy—theory and evidence. *Tech Reg Anesth Pain Manag*. 2011;15(2):74-80.
19. Desai MJ, Mansfield JT, Robinson DM, Miller BC, Borg-Stein J. Regenerative medicine for axial and radicular spine-related pain: a narrative review. *Pain Pract*. 2020;20(4):437-453.
20. Ersen Ö, Koca K, Akpancar S, et al. A randomized-controlled trial of prolotherapy injections in the treatment of plantar fasciitis. *Turk J Phys Med Rehabil*. 2018;64(1):59-65.
21. Hackett GS, Henderson DG. Joint stabilization; an experimental, histologic study with comments on the clinical application in ligament proliferation. *Am J Surg*. 1955;89(5):968-973.
22. Hauser RA, Lackner JB, Steilen-Matias D, Harris DK. A systematic review of dextrose prolotherapy for chronic musculoskeletal pain. *Clin Med Insights Arthritis Musculoskelet Disord*. 2016;9:139-159.
23. Higgins JP, Altman DG, Gøtzsche PC, et al; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:5928.
24. Kazempour M, Rezasoltani Z, Dadarkhah A, Kazempour R, Abdorrazaghi F, Azizi S. Periarticular neurofascial dextrose prolotherapy versus physiotherapy for the treatment of chronic rotator cuff tendinopathy: randomized clinical trial. *J Clin Rheumatol*. 2021;27(4):136-142.
25. Kesikburun S, Tan AK, Yilmaz B, Yaşar E, Yazicioğlu K. Platelet-rich plasma injections in the treatment of chronic rotator cuff tendinopathy: a randomized controlled trial with 1-year follow-up. *Am J Sports Med*. 2013;41(11):2609-2616.
26. Kim E, Lee JH. Autologous platelet-rich plasma versus dextrose prolotherapy for the treatment of chronic recalcitrant plantar fasciitis. *PM R*. 2014;6(2):152-158.
27. Ladenhauf HN, Seitlinger G, Green DW. Osgood-Schlatter disease: a 2020 update of a common knee condition in children. *Curr Opin Pediatr*. 2020;32(1):107-112.
28. Lin CL, Huang CC, Huang SW. Effects of hypertonic dextrose injection in chronic supraspinatus tendinopathy of the shoulder: a randomized placebo-controlled trial. *Eur J Phys Rehabil Med*. 2019;55(4):480-487.
29. Lin MT, Chiang CF, Wu CH, Huang YT, Tu YK, Wang TG. Comparative effectiveness of injection therapies in rotator cuff tendinopathy: a systematic review, pairwise and network meta-analysis of randomized controlled trials. *Arch Rehabil Res Clin Transl*. 2019;100(2):336-349.
30. Mansiz-Kaplan B, Nacir B, Pervane-Vural S, Duyur-Cakit B, Genc H. Effect of dextrose prolotherapy on pain intensity, disability, and plantar fascia thickness in unilateral plantar fasciitis: a randomized, controlled, double-blind study. *Arch Rehabil Res Clin Transl*. 2020;99(4):318-324.
31. Meehan WP, Mannix R. A substantial proportion of life-threatening injuries are sport-related. *Pediatr Emerg Care*. 2013;29(5):624-627.
32. Merkel DL. Youth sport: positive and negative impact on young athletes. *Open Access J Sports Med*. 2013;4:151-160.
33. Mohamadi A, Chan JJ, Claessen FM, Ring D, Chen NC. Corticosteroid injections give small and transient pain relief in rotator cuff tendinosis: a meta-analysis. *Clin Orthop Relat Res*. 2017;475(1):232-243.
34. Nakase J, Oshima T, Takata Y, Shimozaki K, Asai K, Tsuchiya H. No superiority of dextrose injections over placebo injections for Osgood-Schlatter disease: a prospective randomized double-blind study. *Arch Orthop Trauma Surg*. 2020;140(2):197-202.
35. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:N7.
36. Pattinson B. Extended review of the 5th edition of ligament and tendon relaxation treated by prolotherapy. *J Orthop Med*. 1992;14(2):64-66.
37. Puddu G, Ippolito E, Postacchini F. A classification of Achilles tendon disease. *Am J Sports Med*. 1976;4(4):145-150.
38. Rabago D, Lee KS, Ryan M, et al. Hypertonic dextrose and morrhuate sodium injections (prolotherapy) for lateral epicondylosis (tennis elbow): results of a single-blind, pilot-level, randomized controlled trial. *Am J Phys Med Rehabil*. 2013;92(7):587-596.
39. Rabago D, Slattengren A, Zgierska A. Prolotherapy in primary care practice. *Prim Care*. 2010;37(1):65-80.
40. Rosenberg ZS, Kawelblum M, Cheung YY, Beltran J, Lehman WB, Grant AD. Osgood-Schlatter lesion: fracture or tendinitis? Scintigraphic, CT, and MR imaging features. *Radiology*. 1992;185(3):853-858.
41. Scarpone M, Rabago D, Snell E, et al. Effectiveness of platelet-rich plasma injection for rotator cuff tendinopathy: a prospective open-label study. *Glob Adv Health Med*. 2013;2(2):26-31.
42. Schepsis AA, Jones H, Haas AL. Achilles tendon disorders in athletes. *Am J Sports Med*. 2002;30(2):287-305.
43. Sellman JR. Plantar fascia rupture associated with corticosteroid injection. *Foot Ankle Int*. 1994;15(7):376-381.
44. Seven MM, Ersen O, Akpancar S, et al. Effectiveness of prolotherapy in the treatment of chronic rotator cuff lesions. *Orthop Traumatol Surg Res*. 2017;103(3):427-433.

45. Simpson M, Rio E, Cook J. At what age do children and adolescents develop lower limb tendon pathology or tendinopathy? A systematic review and meta-analysis. *Sports Med*. 2016;46(4):545-557.
46. Topol GA, Podesta LA, Reeves KD, Raya MF, Fullerton BD, Yeh HW. Hyperosmolar dextrose injection for recalcitrant Osgood-Schlatter disease. *Pediatrics*. 2011;128(5):e1121-e1128.
47. Uğurlar M, Sönmez MM, Uğurlar ÖY, Adıyeke L, Yıldırım H, Eren OT. Effectiveness of four different treatment modalities in the treatment of chronic plantar fasciitis during a 36-month follow-up period: a randomized controlled trial. *J Foot Ankle Surg*. 2018;57(5):913-918.
48. Vora AMD, Borg-Stein JMD, Nguyen RTMD. Regenerative injection therapy for osteoarthritis: fundamental concepts and evidence-based review. *PM R*. 2012;4(5):S104-S109.
49. Woo MS, Park J, Ok SH, et al. The proper concentrations of dextrose and lidocaine in regenerative injection therapy: in vitro study. *Korean J Pain*. 2021;34(1):19-26.
50. Yelland M, Rabago D, Ryan M, et al. Prolotherapy injections and physiotherapy used singly and in combination for lateral epicondylalgia: a single-blinded randomised clinical trial. *BMC Musculoskelet Disord*. 2019;20(1):509.
51. Yelland MJ, Sweeting KR, Lyftogt JA, Ng SK, Scuffham PA, Evans KA. Prolotherapy injections and eccentric loading exercises for painful Achilles tendinosis: a randomised trial. *Br J Sports Med*. 2011;45(5):421-428.