Systematic Review and Meta-Analysis

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Effects of dextrose prolotherapy on tendinopathy, fasciopathy, and ligament injuries, fact or myth?

A systematic review and meta-analysis

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Abstract

Objectives: Prolotherapy or proliferative therapy is a treatment option for damaged connective tissues involving the injection of a solution (proliferant) which theoretically causes an initial cell injury and a subsequent "proliferant" process of wound healing via modulation of the inflammatory process. Nonetheless, the benefits of dextrose prolotherapy have not been adequately evaluated. Therefore, the present study assesses the effectiveness and superiority of prolotherapy separately in treating dense fibrous connective tissue injuries.

Methods: PubMed, Scopus, and Embase were searched from the earliest record to February 18, 2019. This study included randomized controlled trials which

1. involved adult patients with tendinopathy, fasciopathy, and ligament injuries;
2. compared dextrose prolotherapy to placebo or no treatment or corticosteroid injection;
3. provided quantitative measurements of pain and activity before and after intervention.

Both analysis at individual studies level and pooled meta-analysis were performed.

Results: Ten trials involving 358 participants were included for review. At study level, the majority of comparisons did not reveal significant differences between dextrose prolotherapy and no treatment (or placebo) regarding pain control. The meta-analysis showed dextrose prolotherapy was effective in improving activity only at immediate follow-up (i.e., 0–1 month) (standardized mean difference [SMD]: 0.98; 95% confidence interval [CI]: 0.40–1.50; $I^2 = 0\%$); and superior to corticosteroid injections only in pain reduction at short-term follow-up (i.e., 1–3 month) (SMD: 0.70; 95% CI: 0.14–1.27; $I^2 = 51\%$). No other significant SMDs were found in this analysis.

Conclusions: There is insufficient evidence to support the clinical benefits of dextrose prolotherapy in managing dense fibrous tissue injuries. More high-quality randomized controlled trials are warranted to establish the benefits of dextrose prolotherapy.

Review registration: PROSPERO (CRD42019129044).

Abbreviations: CI = confidence interval, P2G = phenol, glycerin, and glucose, PrT = prolotherapy with hypertonic dextrose, RCT = randomized controlled trial, SD = standard deviations, SMD = standardized mean difference.

Keywords: connective tissue, injections, musculoskeletal diseases, proliferation therapy

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Ethical Statement: All the included studies were conducted in accordance with the Declaration of Helsinki and had ethical approval.

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1. Introduction

Dense fibrous connective tissues, or dense regular connective tissues, are predominantly collagenous tissues with dense and regular orientation of the fibers with respect to each other.[1] They are found in highly fibrous tissues such as ligaments, tendons, fascia, and aponeuroses and are known for their high tensile strength.[2] Unlike skeletal muscle and bone, which are to some degree capable of regeneration, dense fibrous connective tissues heal by the formation of collagen and scar tissue after being injured. The healing process is characterized by angiofibroblastic hyperplasia, including hypercellularity, neovascularization, increased protein synthesis, and matrix disorganization.[3–5] In general, this process is slow,[6] and the resulting fibroblastic scars often possess inferior mechanical and biochemical properties compared to native tissues.[7,8] These factors can contribute to chronic pain and disabilities observed in patients with tendinopathies, fasciopathies, and ligament injuries. So far, experts have not agreed upon an effective treatment that optimizes the healing process.

Several injective medications have been tried to facilitate the healing process after fibrotic tissue injuries. Corticosteroid injection therapies have been used in managing these injuries; however, the lack of inflammation in the healing process, along with poor long-term outcomes[9,10] and adverse effects,[11–13] have led investigators to question the use of corticosteroid injections. Prolotherapy with hypertonic dextrose (PrT) is an available option in clinical practice. Advocates have suggested that such injectates may induce an inflammatory process, initiate the body's wound-healing cascade, and lead to cellular proliferation, collagen deposition, and eventually tissue repair,[14–16] thereby leading to pain reduction and functional improvement. Recently, PrT has become increasingly popular in the United States and internationally in managing various soft tissue problems.[17]

Several reviews have investigated the effectiveness of PrT for individual pathologies such as temporomandibular joint hypermobility[18] and Achilles tendinopathy,[19] and some network meta-analyses have compared all of the injection therapies, including PrT and corticosteroid injections for rotator cuff tendinopathy[20] and lateral epicondylopathy.[21,22] However, no definite conclusion was drawn due to insufficient high-quality randomized controlled trials (RCTs). Though the above-mentioned structures are not histologically identical, they are all made up of dense fibrous connective tissue and share some similarities. For instance, they are composed of abundant parallel-ordered collagen fibers; they rely on the hierarchical structure to resist tension and stretch; and they all have a slow healing process. Pooling studies involving these structures were hence reviewed to provide insights into the effects of PrT on this histologic entity.

Therefore, a systematic review with meta-analysis was conducted to explore both the effectiveness (prolotherapy vs placebo or no treatment) and superiority (prolotherapy vs corticosteroid injection) of PrT regarding pain control and activity improvements in patients with dense fibrous connective tissue injuries.

2. Methods

This review study was reported in accordance with the PRISMA guidelines and registered with PROSPERO (CRD42019129044).

2.1. Eligibility criteria

This study included RCTs published in peer-review journals, and focused on studies which included adult participants diagnosed with dense fibrous connective tissue injuries, including injuries to tendons, ligaments, or fascia, for which they received injection therapy. As prolotherapy may refer to injections of various proliferent agents, this review will limit the scope to hypertonic-dextrose injection. Studies were eligible if they compared the treatment effects of PrT with placebo, no PrT, or corticosteroids, and evaluated either pain or the activity level at follow-up. Co-interventions (e.g., physical therapy) were allowed if they were arranged in the same condition for comparing groups. Injections to irrelevant tissues (e.g., intra-articular, intramuscular, subcutaneous, or perineural) were not considered.

2.2. Study Identification

Relevant articles were searched in the PubMed, Scopus, and Embase databases from the earliest record to February 18, 2019. Main search terms were "(prolotherapy) OR [(dextrose OR glucose) AND (tendin* OR tendon* OR ligament OR fasci* OR joint* OR arthr* OR epicondyl*)]." (See Supplemental Table I, http://links.lww.com/MD/F206, Supplemental file, which displays our search plan). The Cochrane Library and Google Scholar were scrutinized for additional references. Three authors (MWC, CYH, and WKC) searched and evaluated the literature for inclusion of studies based on their titles and abstracts. After pooling studies obtained from different sources and removing duplicates, the full texts of potentially relevant articles were retrieved, and each article was independently evaluated by MWC, CYH, and WKC for eligibility. The involved articles were exported to EndNote 5.4 (Clarivate Analytics) for review.

2.3. Quality assessment

This study assessed the quality of included studies using the Physiotherapy Evidence Database (PEDro) scale. The methodological quality was assessed by ten items regarding random allocation, blinding procedures, and the dropout rate and statistical reporting. Aggregate scores ranged 0 to 10 points with a higher score indicating better quality. Quality was classified as high (6–10), fair (4 or 5), and poor ($\leq$3). Using the Cochrane risk of bias tool, this study assessed seven domains of bias and stratified the risk of bias into low, high and unclear risk. Discrepancies between reviewers at any stage were resolved through discussion and consensus.

2.4. Outcomes

This study investigated the treatment effects on pain reduction and activity improvement. Pain reduction was assessed by the subjective perception of pain severity or satisfaction with the pain condition, including using a visual analogue scale, Likert scale, or any other continuous pain scale. Activity improvement was measured by questionnaires about activities of daily living or disabilities (e.g., Shoulder Pain and Disability Index, Patient-Rated Tennis Elbow Evaluation).

2.5. Data extraction

This study extracted relevant data from each study with a standard data recording form. Data of three time points was

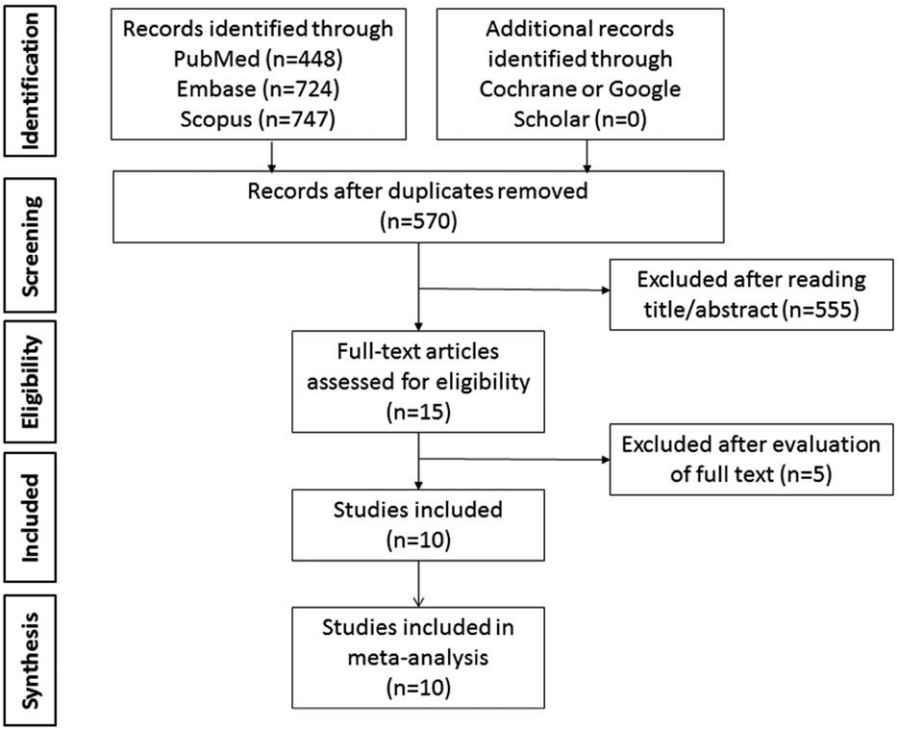

Figure 1. The graph shows the flow of the study selection.

collected to evaluate the immediate (i.e., 0–1 month after the first injection), short-term (i.e., 1–3 months after the first injection), and long-term (i.e., 6–12 months after the first injection) effects of the interventions. If a study included multiple measures within the above-mentioned intervals, the measurements closest to 0, 3, and 12 months after the first injection were selected as the immediate, short-term and long-term follow-up data, respectively. The means, mean changes, and corresponding standard deviations (SDs) of outcomes in the three follow-up periods were extracted. One study can be used only once in one comparison. If a study used PrT in more than one experimental group,[23,24] an estimated mean SD would be calculated by merging means and SDs from the experimental groups. If a study contained a placebo and no-PrT groups as the control groups, the results from the placebo group was used to assess the effectiveness.

2.6. Data analysis

The analyses were performed using Review Manager Software 5.4. Studies comparing PrT to placebo or no PrT were re-analyzed and interpreted individually to understand the effectiveness of PrT on pain control in the short- and long-term at individual studies level. A meta-analysis which pertained to the comparison "PrT vs placebo or no PrT" and "PrT vs corticosteroids" was then conducted separately for the three time points of interest.[25] The meta-analysis aimed to evaluate the overall effectiveness and superiority (compared to corticosteroids) of PrT in respect of pain and activity improvements. Standardized mean differences (SMDs) were obtained to assess the effect size. A random-effects model was used, and a point estimate with a 95% confidence interval (CI) was presented. Heterogeneity across studies was tested using the I^2 test. An I^2 score of >50% indicated significant heterogeneity.

3. Results

Five hundred seventy non-duplicated records were yielded. After exclusion based on the title, abstract, full-text review, and the same study sample, seven effectiveness[23,24,26–30] and three superiority[31–33] (compared to corticosteroids) studies were included for review. Figure 1 displays the flow diagram of study development. In total, 10 studies regarding rotator cuff tendinopathy (n=3), lateral epicondylitis (n=3), temporomandibular joint hypermobility (n=2), Achilles tendinopathy (n=1), and plantar fasciitis (n=1) involving 358 participants were reviewed and analyzed.

Table 1 displays the main characteristics of the included studies. Of the seven effectiveness studies, five were placebo-controlled studies,[23,26–29] and co-interventions of physical therapy were performed in two studies.[26,30] The number of total injections ranged from one to 12, while the interval ranged from once every week to once every month. In one trial,[30] the number of total injections differed from patient to patient and ranged from four to 12. The follow-up period ranged from 6 weeks to 3 years.

PEDro scores ranged from 5 to 10, with medians of 7.3 for effectiveness studies and 6.3 for superiority studies (compared to corticosteroids). (See Table 1 and Supplemental Table ii, http://links.lww.com/MD/F206, Supplementary file, which displays the PEDro scale of each study.) Only three trials[28–30] reported a suitable method for allocation concealment. Three studies[24,30,33] had high risks of bias in the blinding of participants and personnel. Only three[26,28,31] studies presented a successful method of outcome assessor blinding. Most studies reported an adequate description for incomplete results, generating unclear risk in presenting reporting bias. In general, most of the included studies had low-to-moderate risks of bias. (See Supplemental

Table 1

Summary of included studies.

Study	Diagnosis	Study type	Participants	Treatment arms and participants (n) at enrollment		Injection				Follow-up period	Outcomes	PEDro score
						Contents	Dose	Frequency	Total			
Yelland et al. (2011, Australia)[30]	Achilles tendinopathy	Effectiveness	Pain ≥6 weeks ≥18 y/o VISA-A < 80 (sport), or < 70 (no sport)	PrT	(n = 14)	20% glucose/0.1% lignocaine/ 0.1% ropivacaine	0.5–1 mL at each tender point Max. 5 mL	Every week	4–12	12 months	VISA-A score Pain level (7-point Likert scale) PGIC scale Costs and cost-effectiveness	7
				PrT + PT	(n = 14)							
				PT	(n = 15)							
Lin et al. (2018, Taiwan)[28]	Rotator cuff tendinopathy	Effectiveness	Pain > 6 months Confirmed with US > 20 y/o	PrT	(n = 16)	50% dextrose	4 mL		1	6 weeks	Pain level (VAS) SPADI AROM Ultrasonography	10
						NS	1 mL					
				Placebo	(n = 15)	NS	5 mL					
Bertrand et al. (2015, Canada)[26]	Rotator cuff tendinopathy	Effectiveness	Pain > 3 months Confirmed with PE and US 19–75 y/o	PrT + PT	(n = 27)	25% dextrose/0.1% lidocaine/NS	1 mL at each primary injection site 0.5 mL at other tender areas Max. 3 mL	Every month	3	9 months	Pain level (VAS) Satisfaction measurement Ultrasonography (USPRS)	8
				Placebo +PT	(n = 20)	0.1% lidocaine/NS						
				Placebo-superficial + PT	(n = 26)	0.1% lidocaine/NS						
Scarpone et al. (2008, USA)[29]	Lateral epicondylitis	Effectiveness	Pain, ≥6 months 18–65 y/o	PrT	(n = 12)	10.7% dextrose/14.7% sodium motthuate	0.5 mL/tendon insertions Max. 1.5 mL	Every 4 weeks	3	52 weeks	Pain level (Likert scale) Grip strength Isometric resistance strength pain questionnaires	7
				Placebo	(n = 12)	NS						
Rabago et al. (2013, USA)[24]	Lateral epicondylitis	Effectiveness	Pain, ≥3 months VAS ≥4 18–65 y/o	PrT	(n = 8)	50% dextrose	4 mL	Every 4 weeks	3	32 weeks	PRTEE Pain-free grip strength MRI severity score	7
						NS	4 mL					
						1% lidocaine	2 mL					
				PrT-DM	(n = 9)	5% morrhuate sodium	1 mL					
						50% dextrose	1.5 mL					
						NS	2.5 mL					
						1% lidocaine	2 mL					
				No PrT	(n = 10)					16 weeks		
Mustafa et al. (2018, Turkey)[23]	Tmporo-mandibular hypermobility	Effectiveness	18–44 y/o	PrT-10%	(n = 10)	10% dextrose	1.5 mL	Every month	4	4 months	Maximum mouth opening Pain level (VAS) TMJ sounds Frequency of locking episodes	6
						2% lidocaine	1.5 mL					
				PrT-20%	(n = 9)	20% dextrose	1.5 mL					
						2% lidocaine	1.5 mL					
				PrT-30%	(n = 9)	30% dextrose	1.5 mL					
						2% lidocaine	1.5 mL					
				Placebo	(n = 9)	NS	1.5 mL					
						2% lidocaine	1.5 mL					
Comert Kilic et al. (2016, Turkey)[27]	Temporo-mandibular hypermobility	Effectiveness	Confirmed with CBCT > 16 y/o	PrT	(n = 15)	30% dextrose	2 mL	Every month	3	12 months	Pain level (VAS) Maximum mouth opening Lateral and protrusive mandibular motions	6
						NS	2 mL					
						2% articiane or mepivacaine	1 mL					

(*continued*)

Table 1
(continued).

Study	Diagnosis	Study type	Participants	Treatment arms and participants (n) at enrollment		Injection				Follow-up period	Outcomes	PEDro score
						Contents	Dose	Frequency	Total			
				Placebo	(n = 15)	NS	4 mL					
						2% articiane or mepivacaine	1 mL					
Uğurlar et al. (2018, Turkey)	Plantar fasciitis	Superiority	Pain ≥6 months ≥18 y/o VAS > 5 BMI < 30	ESWT	(n = 39)					36 months	Pain level (VAS) FFI-R	5
				PrT	(n = 40)	5 mg/ml bupivacaine	1 mL	Every week	3			
						5% dextrose	3 mL					
						NS	6 mL					
				PRP	(n = 39)							
				CS	(n = 40)	5 mg/mL bupivacaine	2 mL					
						40 mg/mL betamethasone	1 mL					
Cole et al. (2018, Australia)	Rotator cuff tendinopathy	Superiority	Pain ≥3 months > 18 y/o X-ray and US performed	PrT	(n = 17)	50% dextrose	1 mL		1	6 months	Level and frequency of general pain, night pain, and pain at activity Overall shoulder satisfaction ROM Impingement test Shoulder strength	8
						1% lignocaine	1 mL					
				CS	(n = 19)	40 mg/mL methylprednisolone	1 mL					
						1% lignocaine	1 mL					
Carayannopoulos et al. (2011, USA)	Lateral epicondylitis	Superiority	Pain: 3 months-2 years 18–75 y/o	PrT	(n = 8)	1.2% phenol/12.5% glycerine/12.5% dextrose	0.9 ml	Every month	2	6 months	Pain level (VAS) QVAS DASH	6
						Sodium morrhuate	0.1 mL					
						Procaine	1 mL					
				CS	(n = 9)	40 mg/mL methylprednisolone	1 mL					
						Procaine	1 mL					

AROM = active range of motion, BMI = body mass index, CBCT = cone-beam computed tomography, DASH = Disabilities of the Arm, Shoulder and Hand questionnaire, ESWT = extracorporeal shock wave therapy, FFI-R = Foot Function Index-Revised, MRI = magnetic resonance imaging, NPPS = Nirschl Pain Phase Scale, NS = normal saline, PE = physical examination, PF = plantar fasciopathy, PGIC = Patient Global Impression of Change, PrT = prolotherapy, PRTEE = Patient-rated Tennis Elbow Evaluation, PT = physical therapy, QVAS = quadruple visual analog scale, SPADI = Shoulder Pain and Disability Index, USPRS = Ultrasound Shoulder Pathology Rating Scale, VAS = Visual Analogue Scale, VISA-A = Victorian Institute of Sports Assessment—Achilles.

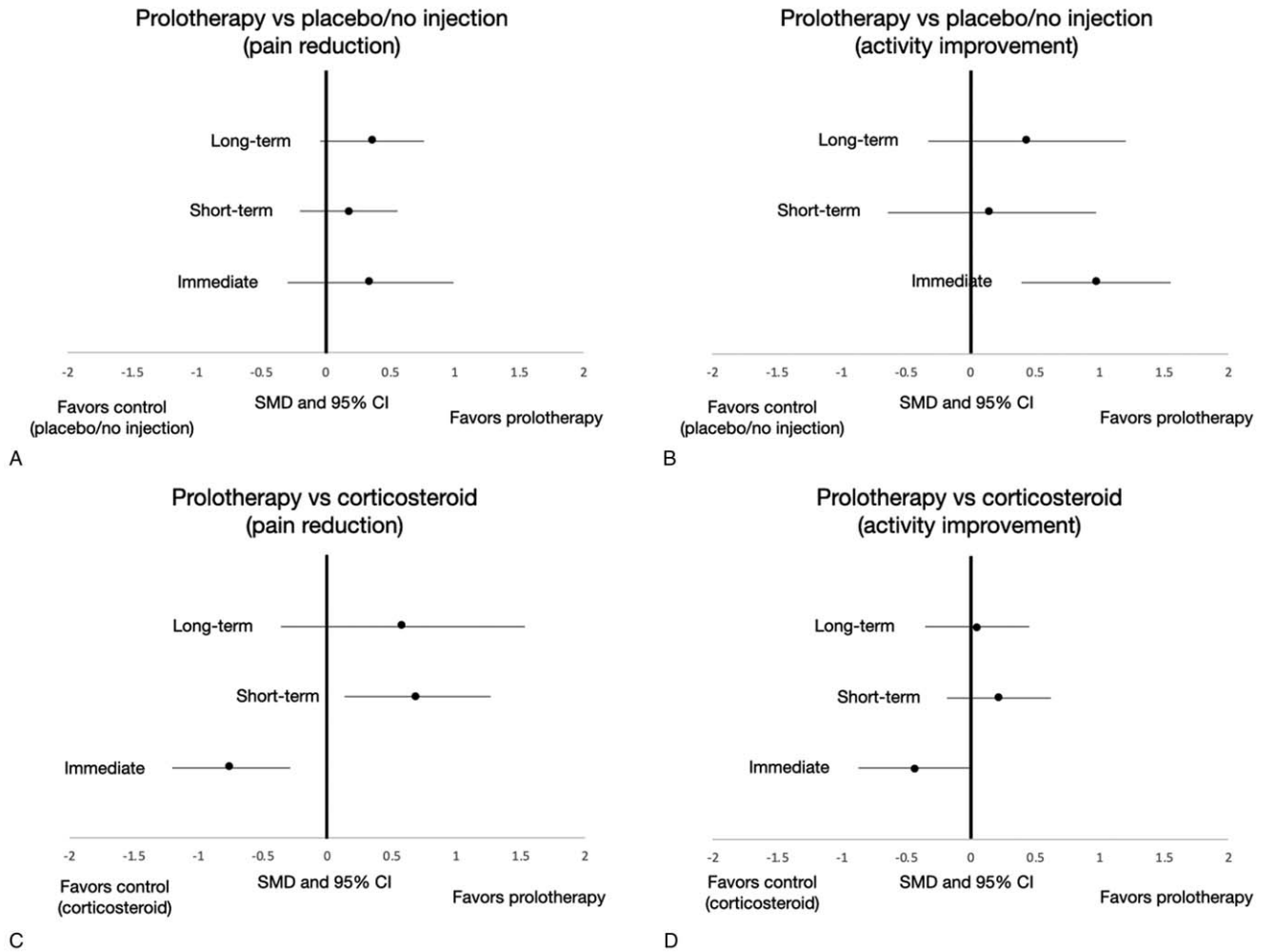

Figure 2. (A–D) The graph summarized the results of this meta-analysis, for (A) effectiveness of prolotherapy (prolotherapy vs placebo or no injection) regarding pain reduction; (B) superiority of prolotherapy (prolotherapy vs corticosteroids) regarding pain reduction; (C) effectiveness of prolotherapy (prolotherapy vs placebo or no injection) regarding activity improvement; and (D) superiority of prolotherapy (prolotherapy vs corticosteroids) regarding activity improvement. Immediate, short-term, and long-term outcomes are shown within each figure (A–D), referring to 0–1, 1–3, and 6–12 months after the first injection, respectively. The forest plots can be reached out in the supplementary file.

Figure a, http://links.lww.com/MD/F206, Supplementary file, which displays the risks of bias of each study.)

The results of study-level evaluation are summarized in the supplementary file (see Supplemental Table iii, http://links.lww.com/MD/F206, Supplementary file, which displays the study-level evaluations of each study). Across comparisons in various disorders, all the study results demonstrated non-significant mean differences between the groups. Two comparisons from one Achilles tendon[30] and one rotator cuff[26] study found significant mean change difference indicating that PrT might be effective in improving pain in the long-term.

Figure 2 outlines the effectiveness and superiority (compared to corticosteroids) of PrT at different time points. No significant SMD was found regarding its effectiveness on pain control at any time point (i.e., immediate, short-term, long-term) (Fig. 2A). PrT was only superior to corticosteroids in the short-term (SMD: 0.70; 95% CI: 0.14–1.27; $I^2 = 51\%$) but inferior in the immediate-term, and not superior in the long-term (Fig. 2B). PrT was effective in improving activity only in the immediate-term (SMD: 0.98; 95% CI: 0.40~1.55; $I^2 = 0\%$) (Fig. 2C), but not superior to corticosteroids at any time point (Fig. 2D). (See Supplemental Figure b to m, http://links.lww.com/MD/F206, Supplementary file, which displays the forest plots of pairwise meta-analysis.)

Considering that histological features of peri-temporomandibular joint soft tissues (i.e., synovial capsule) can differ from the other soft tissues of interest (i.e., ligament, tendon, and fascia), a subgroup analysis was performed after removing two studies[23,27] involving the temporomandibular joint. No change of significance of original SMDs in any outcome categories was found. Sensitivity analyses after removing 2 studies[24,30] without placebo control also did not result in significance changes of original SMDs.

4. Discussion

This review investigated the effects of PrT on various fibrous connective tissue injuries. The majority of included studies were

of moderate-to-high quality and possessed minor-to-moderate risks of bias. The results of the analysis at individual study level and the meta-analysis were inconsistent. In general, the majority of the comparisons of did not yield positive results. Consequently, this study suggests that there is insufficient evidence to support the clinical benefits of PrT in managing fibrous tissue injuries.

Prolotherapy or proliferative therapy is a treatment option for damaged connective tissues involving the injection of a solution (proliferant) which theoretically causes an initial cell injury and a subsequent "proliferant" process of wound healing via modulation of the inflammatory process.[34] Several in vitro studies have shown that cells exposed to hypertonic glucose have an initially decreased viability in terms of decreased cell counts, DNA synthesis, and cellular metabolic activities,[14,16,35] as well as an inflammatory reaction.[15] However, it is unclear whether the subsequent "proliferant" process can lead to better outcomes.

Freeman et al administered various dosages of P2G (namely phenol, glycerin, and glucose) to mouse preosteoblast cells and patellar tendon fibroblasts in vitro. In their best result, only the group treated with 25 μL/mL P2G was associated with a higher cellular viability of preosteoblasts compared to the control group, which was noted only at weeks 2 to 3 during the 6-week observation period. Also, such superiority was not seen in fibroblast viability or collagen production.[16] Martins et al assessed the histology of collagen fibers after administering prolotherapy with 12.5% dextrose into rat Achilles tendons, and found no changes in neovascularization or fibroblasts numbers.[36]

Perhaps the strongest support of prolotherapy came from a Korean language journal.[17] Kim et al reported that chondrocytic tissue filling of 2-mm punch lesions in adult rabbit femoral cartilage was present 6 weeks after injection of 10% dextrose but not after injection of controls.[37] Ahn et al and Kim et al reported that significantly more fibroblasts were recruited after a dextrose injection into injured and non-injured rat Achilles tendons.[38,39] Whether these findings are reproducible and applicable to the human body remains to be seen.

Three of the included trials in this review used imaging methods to assess recovery following prolotherapy. In a trial conducted on patients with lateral epicondylitis, Rabago et al reported no within- or between-group changes in magnetic resonance imaging scores of common extensor tendons despite the better clinical outcomes associated with prolotherapy.[24] Similarly, a trial conducted by Bertrand et al reported no between-group differences in an Ultrasound Shoulder Pathology Rating Scale, while reporting positive effects of prolotherapy on clinical outcomes in patients with rotator cuff tendinopathy.[26] Lin et al also reported no between-group differences in histograms or sonographic morphology in a study involving supraspinatus tendinopathy.[28] In general, histologic and imaging evidence supporting prolotherapy-induced cell proliferation are still lacking, and further studies are required to establish the effects and mechanisms of PrT.

A number of reviews have previously evaluated the effects of prolotherapy on various body parts. A meta-analysis of three temporomandibular joint studies suggested that PrT might lead to significant reductions in mouth opening and associated pain.[18] A network meta-analysis study of rotator cuff tendinopathy including only one prolotherapy trial reported that prolotherapy was effective over 24 weeks.[20] Two network meta-analyses for lateral epicondylitis which respectively included only one and two RCTs suggested that prolotherapy resulted in better outcomes than placebo.[21,22] A meta-analysis study of Achilles tendinopathy including only one RCT stated that eccentric loading exercise combined with prolotherapy provided more-rapid symptomatic improvements than exercise alone in the short term.[19] Given that most of these reviews were based on a limited number of RCTs, they provide very weak evidence as to the effects of prolotherapy.

The present study updated the current knowledge and considered all dense fibrous connective tissue injuries as a whole. However, still only a limited number of high-quality studies explored the beneficial effects of PrT. Considering that prolotherapy is a cheap and convenient treatment option for managing soft-tissue disorders with less probable side effects, more clinical and basic studies are warranted to fully explore its potential benefits.

4.1. Limitations

Several limitations should be addressed. The involved study population differed in diagnosis, durations of symptoms, mechanisms, severity of injuries, and methods of injection, which potentially contributed to the evident heterogeneity. Although the tendons, ligaments, and fascia shared many common features, the surrounding environment, vasculature, and tensile loads within these structures vary. Finally, only three databases were searched, and only a limited number of trials and participants were available for this analysis.

5. Conclusions

There is insufficient evidence to support the clinical benefits of dextrose prolotherapy in managing fibrous tissue injuries, either in aspect of pain management or activity improvement. More high-quality randomized controlled trials are warranted to establish the benefits of prolotherapy.

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Author contributions

The authors' responsibilities were as follows—YNL and MWC conceived of and designed the experiments; MWC, CYH, and WKC searched for relevant studies, conducted quality assessment, and extracted the data; MWC and YNL analyzed the data; MWC and YNL wrote the manuscript; and all authors reviewed and approved the final manuscript.

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