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Dextrose Prolotherapy for Muscle, Tendon and Ligament Injury or Pathology: A Systematic Review

Sholahuddin Rhatomy[1*], Evlin Margaretha[2] and Rizki Rahmadian[3]

[1]Department of Orthopaedics and Traumatology, Dr. Soeradji Tirtonegoro General Hospital, Klaten, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia.
[2]Department of Anesthesiology and Intensive Care, Faculty of Medicine, Baiturrahmah University, Padang, Indonesia.
[3]Department of Orthopaedics and Traumatology, Dr. M Jamil General Hospital, Padang, Faculty of Medicine, University of Andalas, Padang, Indonesia.

Authors' contributions

This work was carried out in collaboration among all authors. Authors SR and RR designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors SR and EM managed the analyses of the study. Author SR managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Prolotherapy with dextrose has recently gained attention as a potential treatment for muscle, ligament or tendon pathology/injury.
Questions/Purpose: This review aimed to: 1) evaluate the main outcome of dextrose prolotherapy treatment for muscle, ligament or tendon pathology/injury; 2) determine the concentrations of dextrose and protocol of injection; and 3) assess complications or adverse effects after dextrose prolotherapy.
Methods: Four electronic databases were searched for related published articles. Articles that met the following criteria were included in this review: 1) articles on peer-reviewed level 1 to 4 studies; 2) articles published in English; 3) articles on dextrose prolotherapy study for tendon or ligament or muscle injury/pathology; and 5) articles that describe dose of dextrose. Published articles that met this inclusion criteria were included in this systematic review.

**Corresponding author: E-mail: doktergustomrhatomy@yahoo.com;*

Results: Twenty four studies fulfilled inclusion criteria,consisting of seventeen clinical studies, four animal studies and three invitro studies. Eleven studies reported there were improvement of functional outcome after dextrose prolotherapy. Three Studies reported improvement of patient satisfaction after dextroprolotherapy in supraspinatus tear, Achilles tendinopathy. And patellar tendinopathy, meniscus tear and anterior tibiofibular ligament tear. Three studies reported there are increasing of neovascularization in Achilles tendinopathy and patellar tendinopathy in animal studies, increasing of inflammatory response in animal studies and *in vitro* studies and increasing of cell proliferation and collagen production. Nine studies (52%) use dextrose 25% concentration. A few adverse effects were reported and minor effect, such as discomfort Minor soreness, extreme pain, skin burns 2nd grade, hypotension, Deep Vein Thrombosis (DVT) (patient has history DVT).
Conclusions: Dextrose Prolotherapy is a potentially effective treatment for patients with muscle, tendon or ligament tear or pathology. Efficacy in long term follow-up, as single therapy or first-line therapy cannot be determined from the current literature.

Keywords: Dextrose; prolotherapy; muscle; tendon; ligament.

1. INTRODUCTION

Musculoskeletal injuries are the most common cause of chronic pain and decreased body function [1]. In the United States, soft tissue trauma accounts for 45% of injuries reported in the orthopedic clinical settings. Among physically active individuals, at least 80% of musculoskeletal injuries are directly related to physical activity, and more than 85% of injuries sustained by athletes are soft tissue injuries [2]. Accordingly, effective treatment of soft tissue trauma is essential for physically active individuals and competitive athletes. Prolotherapy, sometimes abbreviated as (PrT) is a therapeutic alternative for a musculoskeletal injury or pathology [1,2].

Previous study found that injection of a hypertonic sugar solution around ligaments could reduce back pain related to weakened articular ligaments. Hackett believed that the proliferant solution would stimulate the production of fibrous tissue, thereby strengthening the ligaments. He noted that the treatment provided satisfactory results immediately [3].

Prolotherapy is believed to strengthen damaged ligaments or tendons through the stimulation of fibrous tissue synthesis. Frequency of prolotherapy administration generally includes 3–6 times around the involved tendon and ligament attachment sites at 4–6-week intervals. The treatment response will vary according to injury severity, which determines the amount of collagen synthesis that is necessary for tissue repair. Concomitant administration of therapeutic exercise is recommended to enhance the effectiveness of the injection [4].

The most common prolotherapy used in clinical practice is dextrose. Based on previous studies, the most frequently used dextrose concentration ranges from 10% to 25%. Dextrose is chosen because it is water soluble and safe to inject into many areas and can be used in large volume.

Dextrose has been accepted generally by the Food and Drug Administration United States, but not specifically for prolotherapy [5-7]. The action mechanism of dextrose works by dehydrating cells at the injection site, causing inflammation, which will attract granulocytes and macrophages and enhance the healing process [5].

There are still only a small number of studies about dextrose prolotherapy and there is no consensus on the protocol for treatment such as concentration, volume of injection, frequency of injection, or time interval for treatment of muscle, tendon and ligament injury/pathology. The aim of this systematic review was to evaluate the main outcomes and adverse effects of dextrose prolotherapy as a treatment of muscle, tendon and ligament injury/pathology and determine the most effective dose of dextrose for prolotherapy.

2. METHODS

2.1 Outcomes Measure

To assess the outcomes of dextrose prolotherapy for muscle, tendon and ligament injury, we: 1) evaluated the main outcome after dextrose prolotherapy treatment, 2) determined concentrations of dextrose and protocol of injection; and 3) assessed complications or adverse effects after dextrose prolotherapy.

2.2 Literature Search and Study Selection

PubMed (Medline), Embase, Scopus, and the Cochrane library were searched from database inception until August 25th, 2020 to study about dextrose prolotherapy injection for muscle, tendon and ligament injury. The search terms: "prolotherapy" or "dextrose" and "muscle" or "ligament" or "tendon" were used.

2.3 Eligibility Criteria

Inclusion criteria were: 1) articles on peer-reviewed level 1 to 4 studies; 2) articles published in English; 3) articles on dextrose prolotherapy study for tendon or ligament or muscle injury/pathology; and 4) articles that describe dose of dextrose. Published articles that met these inclusion criteria were included in this systematic review.

Non-English articles, duplicate articles, literature reviews, articles on studies that involve cadaveric investigation, biomechanical study, letters to editors, instructional courses, and technical notes were excluded. We also excluded articles with incomplete information on diagnosis, examination, follow-up duration, clinical postoperative outcomes, and no statistical analysis.

2.4 Study Screening and Data Abstraction

Two authors (S.R and R.R) independently screened study and extracted data. Disagreements were resolved by discussion between the two review authors. If no agreement could be reached, consultation with a third author was done. The reference lists of all included studies were also screened for additional articles relevant to this review.

This study included in vitro or in vivo, animal studies, case reports, case series, prospective or retrospective studies, and randomized or non-randomized control trial studies. The data from the articles were extracted using a predesigned form which included sample size, age, intervention, concentration of dextrose, time interval, main outcome and complications or adverse effects. Raw data for continuous outcome measures were extracted at all reported follow-up times (if available), including means and standard deviations (SDs).

2.5 Quality Assessment and Risk of Bias

The methodological quality was evaluated using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (6). Two authors (S.R and R.R) independently performed all the assessments. Coleman Methodology Score (CMS) was used to quantify the quality of the article. The article's methodology was assessed by CMS with a total score ranging from 0 to 100. The higher CMS score of the article, the more valid the article because it was free from biases and confounding factors [7]. To avoid bias, the included and excluded article were reviewed and re-assessed by all of the researchers, if there was any disagreement between them.

3. RESULTS

3.1 Study Selection

5,091 articles were obtained from the database literature searching and 4,229 articles were excluded based on the titles or due to duplication. A total of 862 articles were eligible for further screening. Seven-hundred-and-forty-six articles were excluded because they did not match the inclusion criteria resulting in a total of 116 articles. Ninety-two articles were excluded after full-text screening was performed. We excluded these articles due to: Dextrose prolotherapy fused other than tendon or ligament or muscle (n=82), they were either technical notes, short communications, or reviews (n=7), they were cadaveric, or biomechanical studies (n=3). Accordingly, 24 full articles were included in this systematic qualitative review. The flow chart of article selection is shown in Fig. 1.

3.2 Characteristics of Selected Studies

Seven studies (28%) were randomized control trials, seven studies (28%) were prospective studies, two were case series, four were animal studies, and three were laboratory in vitro studies. These clinical studies included 730 patients. There were 364 male (55.4 %) and 293 female (44.6 %) patients. Three studies did not describe the gender distribution (73 patients). The average age at the time of study was 6.9 month (range, 45 days - 29 month). The average follow-up duration was 7.4 months (range, 45 days- 28 months). The clinical studies evaluated the effect of dextrose prolotherapy on supraspinatus tendon in 6 studies (35%), Achilles tendon in 6 studies (35%), and the other studies were done on patellar tendon, plantar fascia, anterior cruciate ligament and acromion enthesopathy. There were four animal studies that all used rats for subjects, and 2 studies focused to evaluate medial collateral ligament,

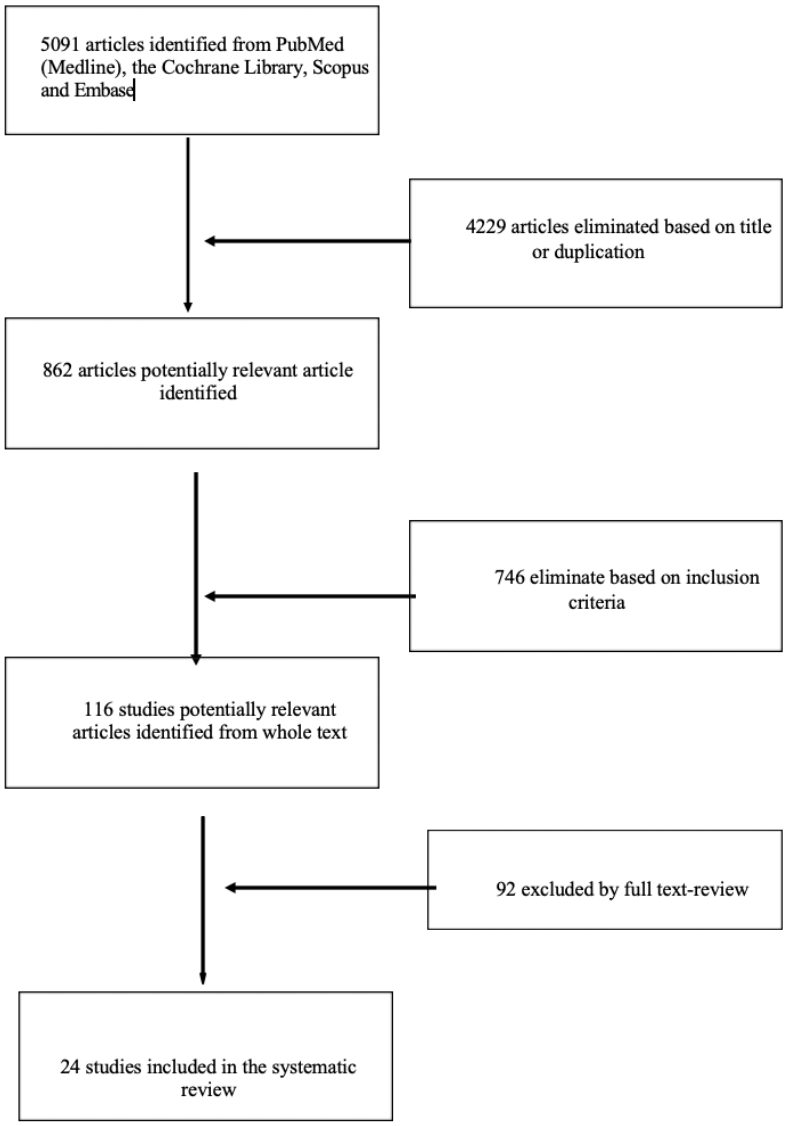

Fig. 1. Flow chart of study process selection

Achilles tendon in 1 study and gastrocnemius muscle in 1 study. Also, there were three in vitro studies that included 2 studies using human hamstring and/or Achilles tendon and adult human fibroblasts and one study used rat patellar tendon fibroblasts (Table 1).

3.3 Main Outcomes

3.3.1 Pain visual analog scale score

All of studies reported about good improvement of pain using the VAS score after dextrose prolotherapy treatment. A total of 6 studies reported improvement in supraspinatus tendon tear or pathology [8-13], 6 studies reported in Achilles tendon cases [4,14-18] and the other studies reported improvement in pain VAS score in treatment of patellar tendon, meniscus, acromion enthesopathy, anterior cruciate ligament laxity and anterior tibiofibular ligament injury [19-23].

3.3.2 Functional outcome

Eleven studies reported there were improvement of functional outcome after dextrose prolotherapy [9-11,13-15,18,19,21-23]. Five studies used a special scoring to evaluate the outcome. Seven et al. used the Shoulder Pain and Disability Index

(SPADIs) and the Western Ontario Rotator Cuff (WORC) to evaluate supraspinatus tear [9], George et al. used the Disability of Arm and Shoulder (DASH) to evaluate supraspinatus tear [10], Lee et al. and Lin et al. used the Shoulder Pain and Disability Index (SPADIs) to evaluate supraspinatus tearing [11,13], and Kim et al. used the Foot Functional Index total to evaluate outcome in plantar fasciitis [21].

3.3.3 Patient satisfaction

Three studies reported improvement of patient satisfaction after dextroprolotherapy in supraspinatus tear [8], Achilles tendinopathy [15], and patellar tendinopathy, meniscus tear and anterior tibiofibular ligament tear [19].

3.3.4 Neo vascularization

Three studies reported there was increasing of neovascularization after dextroprolotherapy in Achilles tendinopathy [16,17] and patellar tendinopathy [22].

3.3.5 Inflammatory response

Three studies reported there was increasing of inflammatory response after dextrose prolotherapy in vivo/animal studies [24,25] and in vitro study [26].

3.3.6 Cell proliferation

Freeman et al. reported that there were increasing of cell proliferation and collagen production after dextrose treatment [27].

3.4 Concentration of Dextrose and Injection Protocol

There are nine studies (52%) used the concentration of dextrose with 25% [8,9,12,14,16,17,22,23,28] while three studies each used concentrations with 20% [11,15,18] or 15% [19-21]. The other two studies used concentrations of 10% [23] and 16.5% [13]. Most of study (15 studies/88%) reported dextrose mixed with lidocaine, and only one study used a mix with saline [8] or marcaine [28].

Five studies (29.4%) performed prolotherapy monthly [8,18,19,20,23] and four studies performed it with only a single injection [10-12,14]. Four studies performed prolotherapy every 1 week or 2 weeks [9,13,15,21]. Additionally, three studies performed it every 6 weeks [16,17,22].

Table 1. Overview of clinical study

No	Author, year, country	Type of study
1	Bertrand et al., 2015, Canada [8]	Randomized controlled Trial
2	Seven et al., 2017, Turkey [9]	Randomized controlled Trial
3	George et al., 2018, Malaysia [10]	Randomized controlled Trial
4	Lin et al., 2018,Taiwan [11]	Randomized controlled Trial
5	Cole et al., 2017, Australia [12]	Randomized Controlled Trial
6	Buchanan et al., 2016, USA [14]	Prospective study
7	Lyftogt et al., 2005, New Zealand [15]	Prospective study
8	Maxwell et al., 2007, Canada [16]	Prospective study
9	Ryan et al., 2010, Canada [17]	Prospective study
10	Fullerton et al., 2008, USA [19]	Case series
11	Hsieh et al., 2018, Taiwan [20]	Prospective study
12	Kim et al., 2014, Korea [21]	Randomized Controlled Trial
13	Lee et al., 2015, Korea [13]	Retrospective case-control study
14	Chan et al., 2017, UK [28]	Case series
15	Ryan et al., 2011, USA [22]	Prospective study
16	Yelland et al., 2009, Australia [18]	Randomized Controlled Trial
17	Reeves et al., 2003, USA [23]	Prospective study
18	Jensen, et al., 2008, USA [24]	Animal Study
19	Jensen, et al., 2008, USA [29]	Animal Study
20	Martins et al., 2011, Brazil [25]	Animal Study
21	Tsai et al., 2018, Taiwan [30]	Animal Study
22	Freeman et al., 2011, USA [27]	*In vitro* Study
23	Güran et al., 2018, Turkey [31]	*In vitro* Study
24	Ekwueme et al., 2017, USA [26]	*In vitro* Study

Table 2. Clinical studies results

No	Author	Site	Sample size (pts) and Sex (M:F)	Age, years (SD/range)	Intervention	Dose of dextrose	Results	Follow-up	Complication reported
1	Bertrand et al. [8]	Supraspinatus tendinosis/tear	73 46:27	51 (13)	Three monthly injections with dextrose, injection on entheses with saline or above entheses with saline. All solutions included 0.1% lidocaine.	25% dextrose + 0.1% lidocaine/saline	- 59% of dextrose patient showed ≥2.8 decrease of pain compared with Enthesis-Saline (37%; P=.088) and Superficial-Saline (27%; *p*=.017). - Dextrose group satisfaction was 6.7±3.2 compared with Enthesis-Saline (4.7±4.1; *p*=.079) and Superficial-Saline (3.9±3.1; *p*=.003).	9 month	Discomfort and Minor soreness
2	Seven et al. [9]	Chronic rotator cuff lesions	101 42:59	51(12)	Two groups: - control group; exercise - prolotherapy group; dextrose injection	4 ml; a mixture 3.6 mL of 25% dextrose and 0.4 mL lidocaine	A significant difference in : - VAS at baseline, weeks 3, 6, and 12, and last follow-up. - SPADIs and WORC at weeks 6 and 12 and the last follow-up. - Shoulder abduction and flexion at week 12 and last follow-up, and in internal rotation at last follow-up. No significant in external rotation at any follow-up period. Prolotherapy group : 92.9% patient reported excellent or good outcomes	12 month	Extreme pain prolotherapy group (3 patients). Skin burns (1 patient) and Hypotension (1 patient)

No	Author	Site	Sample size (pts) and Sex (M:F)	Age, years (SD/range)	Intervention	Dose of dextrose	Results	Follow-up	Complication reported
3	George et al. [10]	Supraspinatus Tendinosis	12 NR	59 (NR)	Prolotherapy group: dextrose injection Control group: Standard physiotherapy	0,5-1ml (12.5% dextrose, 0.5% lignocaine)	1. 20-degree improvement in abduction ROM (p = 0.03) 2. Decrease in DASH pain score of 2 or greater, compared to controls. (not statistical significance). 3. Sleep score improvement (significant statistically different). 4. Dextrose group showed improvement in echogenicity within the area of tendinosis	12 Week	None
4	Lin et al.[11]	Chronic Supraspinatus Tendinopathy	31 19:12	49 (6)	- Intervention group: dextrose 20% injection - Control group: 5% normal saline injection	5 ml of 20% Dextrose solution (4 ml 50% dextrose+1 ml normal saline)	- A significant improvement in the VAS (p=0.001), SPADI scores (p=0.017), shoulder AROM of flexion (p=0.039), and abduction (p=0.043) - No differences in the histograms and morphological changes (thickness) before and after injection in both groups.	6 Week	None
5	Cole et al.[12]	Supraspinatus Tendinopathy	36 27:9	51 (16)	- Prolotherapy group - Corticosteroid group	1mL of 50% glucose (25 g/50 mL) (Glucose 50%) and 1mL of 1% lignocaine	- Pain with overhead activities was significantly reduced at the 3-month follow-up in the prolotherapy group and at the 6-month follow-	6 Month	None

No	Author	Site	Sample size (pts) and Sex (M:F)	Age, years (SD/range)	Intervention	Dose of dextrose	Results	Follow-up	Complication reported
						hydrochloride = 25% glucose prolotherapy solution.	up for both the prolotherapy and corticosteroid groups.		
6	Buchanan et al.[14]	insertional Achilles calcific tendinosis	10 7:3	47 (NR)	Dextrose injection of the distal calcaneal tendon	2 mL mixture of 1 mL of 1% lidocaine and 1 mL of 50% dextrose is placed in a syringe	- Five patients reported drastic pain relief and return to normal gait and sports activity within 8 weeks. - The average pain level by VAS at rest was 1/10 with two patients reporting complete pain relief at rest. - The average pain level by VAS with sport activity was reported as a 3/10. - The average VISA-A score was 84, indicating a sizeable clinical improvement in pain and function. - All patients no recurrence of previous pain levels and symptoms.	NR	None
7	Lyftogt et al. [15]	Achilles tendinopathy	16 pts (19 Achilles Tendinopathies) 12:4	48 (range 37-59).	Injection with 20% dextrose and 0.1% lignocaine	1 ml of prolotherapy diluent consisting of dextrose 20% + lignocaine 0.1%	- Fourteen patients were satisfied with the results of the treatment and returned to pre-injury levels of activity. - One patient was referred for surgery.	12 Month	None

No	Author	Site	Sample size (pts) and Sex (M:F)	Age, years (SD/range)	Intervention	Dose of dextrose	Results	Follow-up	Complication reported
							- 14 patients reaching VAS=0 at the end of treatment, 11 remained at VAS=0 at follow up.		
8	Maxwell et al. [16]	Chronic Achilles Tendinosis	36 25:11	52,6 (23-82)	25% dextrose injection every 6 weeks	1 mL of 2% lignocaine (20 mg/mL) and 1 mL of 50% dextrose (25 g/50 mL) (dextrose monohydrate, 500 mg), giving a 25% dextrose solution.	- There was a mean percentage reduction for VAS for pain rest of 88.2% ($p < 0.0001$) - VAS pain during normal daily activity of 84.0% ($p < 0.0001$) - VAS pain during or after sporting or other physical activity of 78.1% ($p < 0.0001$). - The mean tendon thickness decreased from 11.7 to 11.1 mm ($p < 0.007$). - Echogenicity improved in six tendons (18%) - Neovascularity was unchanged in 11 tendons (33%) but decreased in 18 tendons (55%); no neovascularity was present before or after treatment in the four remaining tendons. - Follow-up telephone interviews	12 months	None

No	Author	Site	Sample size (pts) and Sex (M:F)	Age, years (SD/range)	Intervention	Dose of dextrose	Results	Follow-up	Complication reported
							revealed that 20 patients were still asymptomatic, nine patients had mild symptoms, and one patient had moderate symptoms.		
9	Ryan et al. [21]	Chronic Achilles Tendinosis	99 pts (108 tendons) 58:41	54.0 ± 10.8	Less than 0.5 mL was injected at any one site.	1 mL of 2% lignocaine (20 mg/mL) and 1 mL of 50% dextrose (25g/50 mL) (dextrose monohydrate 500 mg) giving a 25% dextrose solution.	- There was a significant improvement in pain scores for both midportion (rest: 34.1 ± 27.7–3.3 ± 7.4, activities of daily living (ADL): 50.2 ± 25.6–9.5 ±16.2, and sport: 70.7 ± 23.3–16.7 ± 22.0) and insertional (rest: 33.0 ± 26.5–2.7 ± 6.0, ADL: 51.3 ± 25.4–10.0 ± 16.3, and sport: 69.6 ± 24.5–17.7 ± 29.1) - There were reductions in the size and severity of hypoechoic regions and improvements in neovascularity.	28.6 months	None
10	Fullerton, BD [13]	Patellar tendinopathy, anterior talofibular ligament sprain, medial meniscus tear	3 1:2	36,6	Injection dextrose at pathologic site	(15% dextrose/0.3% lidocaine)	Good clinical and sonography and MRI outcome	More than 1 year	None
11	Hsieh PC et al. [28]	Acromial Enthesopathy	31 10:21	57.4 ± 10.4	Injecting 10 mL of a 15% dextrose solution into	50% dextrose diluted to a final concentration of	- Twenty of the 31 patients reported pain reduction	61.8 days	None

No	Author	Site	Sample size (pts) and Sex (M:F)	Age, years (SD/range)	Intervention	Dose of dextrose	Results	Follow-up	Complication reported
					the acromial enthesis of the deltoid or acromioclavicular joint capsule aseptically, in 2 sessions, separated 1-month interval.	approximately 15% with a mixture of 2% lidocaine and distilled water	- The mean VAS score reduction ± SD was 4.3 ± 2.6 (pretreatment, 6.8 ± 1.5; posttreatment, 2.5 ± 2.1; $p < .01$).		
12	Kim E et al. [22]	Plantar Fasciitis	21 11:10	Dextrose Prolotherapy (DP) group :37.8 (19-51) PRP Group: 36.2 (20-57)	2 injections into the plantar fascia under ultrasound guidance at an interval of 2 weeks, either with 2 mL of autologous PRP or 2 mL of 15% dextrose/lidocaine solution.	combination of 1.5 mL of 20% dextrose and 0.5 mL of 0.5% lidocaine, resulting in a 15% dextrose solution, within a 2.5-mL syringe	- The mean Foot Functional Index total and subcategory score improvements were greater in the PRP group compared the Dextrose group (improvement with PRP vs DP, total: 30.4% vs 15.1%, pain: 29.7% vs 17.1%, disability: 26.6% vs 14.5%, activity limitation: 28.0% vs 12.4%). (no statistically significant difference) - Both groups showed significant improvements in the pain and disability subcategories.	6 month	None
13	Lee D H et al. [18]	Rotator Cuff disease	110 40 : 70	Treatment group : 54.1±7.8, Control group : 55.8±6.6	Prolotherapy group : 16.5% dextrose 10 ml solution Control group : conservative	16.5% dextrose 10 ml solution (mixture of 20% DW 8 cc and 1% lidocaine 2 ml)	There were improvement in VAS score, SPADI score, isometric strength of shoulder abductor, and shoulder AROM of flexion, abduction, and external	1 years	None

No	Author	Site	Sample size (pts) and Sex (M:F)	Age, years (SD/range)	Intervention	Dose of dextrose	Results	Follow-up	Complication reported
					treatment		rotation in the treatment group. There were no adverse events.		
14	Chan O et al. [23]	Achilles Tendon	43 27:16	41 (11.3)	Injected with 0.4ml-1.5ml (mean 0.8ml) of 50% dextrose and 0.5% Marcaine mixed in a 1:1 ratio.	0.4ml-1.5ml (mean 0.8ml) of 50% dextrose and 0.5% Marcaine mixed in a 1:1 ratio	- 30 patients (70%) responded with VISA-A scores increasing by 31 (30.5) points after 3 months (p<0.05) and by 40 (29.3) points after 12.60 (7.0) months (p<0.05). - After 5.2 (2.3) weeks, echogenicity was significantly reduced (p<0.05) and 27% of tears were no longer detectable.		One patient (with a history of previous DVTs) suffered a DVT two weeks after the injection
15	Ryan M et al. [24]	Patellar tendinopathy	47 pts (49 tendon) 39:6	NR	Injection of 25% dextrose with lidocaine into the area of tendinopathy .	25% dextrose (1 ml 2% lidocaine (20 mg/ml) and 1 ml 50% dextrose (25 g/50 ml) (dextrose monohydrate in a 2.5 ml syringe 500 mg)	- Subjects reported a reduction in pain across the three VAS items (rest 38.4±25–18.7±18.4; ADL 51.1±22.9–25.8±20.1; sport 78.1±15.7–38.8±26.1; p<0.01). - There was improvement in neovascularity following the dextrose injection.	45 weeks	None
16	Yelland MJ et al. [29]	Achilles Trendinosis	43	46 (40–57)	Participants were randomised to a 12-week program of eccentric loading exercises (ELE) (n=15), or	20% glucose/0.1% lignocaine/0.1% ropivacaine weekly for four to 12	- At 12 months: the minimum clinically important change (MCIC) for VISA-A were 73% for ELE, 79% for prolotherapy and 86% for combined	12 Month	None

No	Author	Site	Sample size (pts) and Sex (M:F)	Age, years (SD/range)	Intervention	Dose of dextrose	Results	Follow-up	Complication reported
					prolotherapy injections of hypertonic glucose with lignocaine alongside the affected tendon (n=14) or combined treatment (n=14).	treatments	treatment. - Mean (95% CI) increases in VISA-A scores at 12 months were 23.7 (15.6 to 31.9) for ELE, 27.5 (12.8 to 42.2) for prolotherapy and 41.1 (29.3 to 52.9) for combined treatment. - Compared with ELE, reductions in stiffness and limitation of activity occurred earlier with prolotherapy and reductions in pain, stiffness and limitation of activity occurred earlier with combined treatment.		
17	Reeves KD et al. [25]	Anterior Cruciate ligament laxity	18	68	Intraarticular injection of 6-9 cc of 10% dextrose at months 0, 2 ,4, 6, and 10. Injection with 6 cc of 25% dextrose at 12 months. Then, depending on patient preference, injection of either 10% or 25% dextrose every 2-4 months (based on patient	10% dextrose and 25% dextrose .	- KT1000 measurement : 6 knees measured as normal (not loose) after 6 months, 9 measured as normal after 1 year (6 injections), and 10 measured as normal at 3 years. - 3 year follow-up, pain at rest, pain with walking, and pain with stair use had improved - Individual paired t tests indicated subjective swelling improved 63% (p = .017), flexion range of	36 month	Discomfort after injection

No	Author	Site	Sample size (pts) and Sex (M:F)	Age, years (SD/range)	Intervention	Dose of dextrose	Results	Follow-up	Complication reported
					preference) through 36 months.		motion improved by 10.5 degrees (p = .002), and KT1000 ADD improved by 71% (p = .002).		

SD: Standard Deviation, pts: patients, M: male, F: female, NR: Not Reported. VAS: The Visual Analog Scale, SPADI: Shoulder Pain And Disability Index, AROM: active range of motion, VISA A: The Victorian Institute of Sport Assessment-Achilles questionnaire, PRP: Platelet Rich plasma

Table 3. Animal studies results

Author	Animal	Site	Intervention	Dose of dextrose	Outcomes
Jensen, K T et al. [30]	Rat	Medial Collateral Ligament	- MCL of 84 Sprague- Dawley rats were injected one time at both the tibial and femoral insertions. - IHC to determine the inflammatory response at three locations (tibial and femoral insertions and midsubstance) 6, 24, and 72 h after dextrose injection compared to saline- and no-injection controls and collagenase (positive control) - qPCR was used to analyze gene expression	15% Dextrose	- Inflammation (CD43) increased after prolotherapy injection compared to no-injection control but did not increase consistently compared to saline and needlestick control injections. - This response varied by both location and proliferant. - Inflammation was observed at 6 and 24 h post-injection but was resolved by 72 h compared to no-injection controls (p<0.05). - Prolotherapy injections created an inflammatory response, the response was variable and overall, not uniformly different from that caused by saline injections or needlestick procedures
Jensen, KT et al. [27]	Rat	Medial Collateral Ligament	Twenty-four rats were bilaterally MCL stretch-injured, and the induced laxity was measured. After 2 weeks, 32 MCLs were injected twice, 1 week apart, with either dextrose or saline control; 16 MCLs received no injection. Seven uninjured rats (14 MCLs) were additional controls. Two weeks after the second injection, ligament laxity, mechanical properties	15% Dextrose	- Cross-sectional area of dextrose-injected MCLs was increased 30% and 90% compared with saline and uninjured controls, respectively (p < .05). - Collagen fibril diameter and density were decreased in injured ligaments compared with uninjured controls (p < .05), but collagen fibril characteristics were not different between injured groups.

Author	Animal	Site	Intervention	Dose of dextrose	Outcomes
			(n = 8), and collagen fibril diameter and density (n = 3) were assessed.		
Martins et al. [31]	Rat	Achilles Tendon	15 received 12.5% dextrose (group I); 15 were treated with corticosteroid injection (group II); and 15 were given 0.9% saline injection (group III), all into the right Achilles tendon, whereas 13 animals received no injections (group IV). Three doses of each substance (groups I, II, and III) were given at a 5-day interval. Collagen fiber color was quantitatively assessed in three samples from each group and in five samples from the control group using picrosirius red staining under polarized and nonpolarized light.	12.5% dextrose	- There was no statistical difference across the groups with respect to maximum load at failure (n.s.) and absorbed energy (n.s.). With respect to tendon rupture, - there was no difference between the myotendinous and the tendinous regions (n.s.). - Hematoxylin–eosin staining revealed statistical significance in lymphocytic inflammatory infiltrate (p = 0.008) and in parallel fiber orientation (p = 0.003) when comparing groups to the control group, without significance for either neovascularization (n.s.) or the presence of fibroblasts (n.s.). - There was no significant difference between the percentage of mature (n.s.) and immature (n.s.) fibers
Tsai SW et al. [26]	Rat	Gastrocnemius Muscle	Mice were separated into five groups, including a normal control (NC), post-injury with no treatment (mass-drop injury, MDI), post-injury with 10% dextrose (MDI + 10% dextrose), post-injury with 20% dextrose (MDI + 20% dextrose), and post-injury with 30% dextrose (MDI + 30% dextrose). The gastrocnemius muscles of the mice were subjected to an MDI, and muscle samples were collected at 7 days post-injury.	10%,20% and 30% Dextrose	- The serum creatine kinase (CK), blood urea nitrogen (BUN), creatinine (CREA), and low-density lipoprotein (LDH) of the MDI-alone group were significantly higher than those of the normal control group (p<0.05). - However, levels of serum CK, BUN, CREA, and lactate dehydrogenase (LDH) significantly decreased with different concentrations of dextrose. - Dextrose suppressed the macrophage response (F4/80 protein decreased) and promoted muscle satellite cell regeneration (desmin protein increased).

IHC: Immunohistochemistry, CD: Cluster of Differentiation

Table 4. *In vitro* studies results

Author	Subject	Studied Cells	Intervention	Dose of dextrose	Outcomes
Freeman JW et al. [32]	Rat	Mouse preosteoblast cells (MC3T3-E1 cells) and mouse patellar tendon fibroblasts	P2G was administered to mouse preosteoblast cells (MC3T3-E1, ATCC, Manassas, Va) in various dosages	P2G is a solution composed of 2% phenol, 25% dextrose, and 25%glycerin in a sufficient quantity of sterile water for injection	- Trichrome staining : an increasing in collagen production - The cell numbers and amounts of collagen from the treated groups never surpassed those of the untreated groups, although collagen production was comparable in fibroblasts. - There is an effective proliferant dosage and point to a local response to the proliferant that increases cell proliferation and collagen production.
Şefik Güran et al [33]	Human	Adult human fibroblasts	The effects of dextrose solution (1%, 5%, 10%-low doses, 15%, 20% and 25%-high doses) in vitro, using human fibroblast culture. Total RNA extraction and cDNA synthesis were performed. The gene expression levels of angiogenic and apoptotic factors were analyzed by using real-time PCR.	1%, 5%, 10%-low doses, 15%, 20% and 25%-high doses)	- High doses dextrose concentrations, up to 80% of fibroblasts were died because of toxic conditions. - Viable fibroblast cell ratios were decreased proportionally due to the dextrose concentration. - Low dextrose concentrations increased gene expressions in angiogenic (VEGF A, PDGFA, PDGF B, IGF 1) and in apoptotic factors (CASP3 and CASP8) in fibroblasts.
Ekwueme EC et al. [34]	Human	Human hamstring and Achilles tendon Cells	- Assess the effect of dextrose and P2G proliferant treatment on cell mitochondrial activity compared with nontreated tenocytes. - Quantitative PCR, ELISA, and a reporter cell line assessed the expression of several key markers involved in tendon development and inflammation.	50% (v/v) dextrose	- Decreasing of tenocyte metabolic activity, P2G more pronounced effect (75% ± 7% versus 95% ± 7% of untreated control cell metabolic levels) - Gene expression: upregulation of key proinflammatory markers; IL-8 and cyclooxygenase-2 and downregulation of collagen type I. - A reporter cell line : decreasing of TGF-b bioactivity. - ELISA : elevated PGE2

P2G: Combination of phenol, glycerin, and glucose,R: Polymerase Chain Reaction, ELISA: The Enzyme-linked Immunosorbent Assay, IL: interleukin, TGF: Transforming Growth Factor, PGE2: prostaglandin E2, VEGF: Vascular Endothelial Growth Factor, PDGF: Platelet-derived Growth Factor, IGF: Insulin-like Growth Factor, CASP: Caspase

3.5 Complications / Adverse Effects

Only four studies reported adverse effects after dextrose prolotherapy and all of the adverse effects were minor effects, such as discomfort [8], minor soreness [8], extreme pain [9], skin burns grade 2nd because of improper use of hot water bags and local anaesthetic effect of the injections [9], hypotension [9] and Deep Vein Thrombosis (DVT), in a patient who has a history of DVT [28].

4. DISCUSSION

This review suggests that dextrose prolotherapy for treatment of muscle, ligament and tendon tear or pathology, demonstrates potential results in decreasing pain, improving range of motion, and function outcomes, at least in the short term follow-up, and increasing of cell proliferation and neovascularization in *in vitro* study. Single or serial injections of dextrose showed improvements of clinical outcomes and may be a promising treatment for long term follow-up. High quality of research is needed with specific populations with soft tissue problems (tendon, ligament and muscle) to determine the best protocol for treatment of soft tissue problem including time interval of injections, volume, concentration of dextrose solution, and location of injection.

Prolotherapy for musculoskeletal pain has been used in practice as an adjuvant treatment for decades [5]. Thus, in this review, we found that most of studies were clinical studies (70.8%), which indicated this treatment has been used for many years, and most of clinical studies involved supraspinatus tendinopathy or tearing and Achilles tendinopathy. Tendinopathy of the supraspinatus and Achilles tendon is a common problem in adult patients and often is the cause of pain that disturbs their daily activity. This is caused by overuse and repetitive loads on the tendon, such as in sports activity [9,12,18].

The main purpose of dextrose prolotherapy treatment is to decrease of pain and improve functional outcomes [9]. In our study, all of the studies reported decreased pain after treatment and most of studies (eleven studies) reported functional improvement after follow up. Reduction in pain is closely related to improvements in the functional clinical outcome. By significantly reducing pain, it will help physiotherapy programs and at the same time improve patients' functional outcome. Cole et al. showed that injection of dextrose prolotherapy for the supraspinatus tendon can reduce pain and improve functional outcome over a 6-month period. There was no adverse effects on tendon structure and, in fact, prolotherapy groups showed significant improvements in ultrasound characteristics of the supraspinatus tendon, decreasing pain, with increased range of motion and strength of muscle [32].

In previous review study, dextrose prolotherapy improved patient satisfaction in as many as 82% of cases in treating knee osteoarthritis [33]. In our study, there were two studies that evaluated patient satisfaction. Lyftogt et al. reported that fourteen patients (29.1%) were satisfied and can return to pre-injury levels of activity [15].

Most of the studies on dextrose prolotherapy for musculoskeletal conditions, were for chronic, painful overused tendon conditions. Despite different anatomical locations, the tendinopathies of repetitive and overuse injuries have similar characteristics. The process of tendinopathy of the Achilles tendon, common elbow extensors and patellar tendons have almost the same histological, sonographic and clinical features. The main role of dextrose prolotherapy is to reduce pain significantly, so that the patient can undergo physiotherapy optimally and improve their functional ability and range of motion [5]. In our review, there were three studies that reported increased neovascularization, collagenization, and cell proliferation after treatment [16,17,22].

In vitro studies on human fibroblasts and chondrocytes using extracellular 0.5% dextrose showed that there were increasing of cell proliferation and production of numerous growth factors, such as platelet-derived growth factor, transforming growth factor β, epidermal growth factor, basic fibroblast growth factor, insulin-like growth factor and connective tissue growth factor. These growth factors have important role for regeneration and structural integrity of tendons, ligaments, and muscles [5,27]. One in vitro study showed that these growth factors can promote the prominent expression of types 1 and 3 collagen in tenocytes and prevent fibrous tissue. These mechanism could be an inexpensive method of soft tissue regeneration, and that may be more cost effective and promising for the long term follow-up [5,27].

In clinical settings, many studies showed that dextrose concentrations higher than 10% can enhance the inflammatory process, while

concentrations less than 10% are considered noninflammatory [5]. In this review, there were three studies that showed the similar effect of increasing inflammatory response after treatment with 15%, 30%, and 50% of dextrose [25,26,29]. Other outcomes were reported by Freeman et al. that explained there are increasing cell proliferation and collagen production after dextrose treatment [27].

In this review, dextrose concentrations that were more often used to treat soft tissue problems were 15%, 20% and 25% and most of them were mixed with lidocaine and performed as a single injection. This is similar with previous review that evaluated dextrose prolotherapy for musculoskeletal pain, and found that the most common prolotherapy agent used in clinical practice is dextrose, with concentrations ranging from 12.5% to 25% [5].

Few adverse effects or complications after prolotherapy have been reported in the previous studies. Simon et al. reported adverse events related to prolotherapy for back and neck pain, such as temporary post injection pain, stiffness, and bruising [34]. In this review, we found that only four studies reported adverse effects after dextrose prolotherapy, and all of the adverse effects were minor effects, such as discomfort [8], minor soreness [8], extreme pain for one or two days [9], grade 2nd skin burns because of improper use of hot water bags and local anaesthetic effect [9], while the other reported adverse effects were hypotension [9], and Deep Vein Thrombosis/DVT in a patient with a history of DVT [28].

5. CONCLUSION

Dextrose prolotherapy is a potentially effective treatment for patients with muscle, tendon or ligament tear or pathology. Efficacy in long term follow-up, as single therapy or first-line therapy, and long term outcomes cannot be determined from the current literature.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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