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Invited Review

The effectiveness of prolotherapy in treating knee osteoarthritis in adults: a systematic review

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Abstract

Introduction: Osteoarthritis (OA) often leads to symptoms such as pain, stiffness and decreased function. OA is treated with a wide range of modalities, both conservatively and surgically. Prolotherapy has been used to treat various musculoskeletal problems and has shown some promise.

Sources of data: Searches of the electronic databases, PubMed, ISI web of science, PEDro and SPORTDiscus, were conducted for all Level 1–4 studies published from inception through to December 2016.

Areas of agreement: Ten studies were evaluated and results show significant improvement in scores for pain, function and range of motion, both in the short term and long term. Patient satisfaction was also high in these patients (82%).

Areas of controversy: Meta-analysis was not possible due to heterogeneity of outcome measures and populations.

Growing points: Moderate evidence suggests that prolotherapy is safe and can help achieve significant symptomatic control in individuals with OA.

Areas for developing research: Future research should focus on larger sample size, standardization of treatment protocol and basic science evidence.

Key words: knee, osteoarthritis, prolotherapy, regenerative, injection, proliferative, dextrose

Introduction

Osteoarthritis (OA) is an age-related degenerative disease resulting from articular cartilage failure induced by a complex interplay of genetic, metabolic, biochemical and biomechanical factors with secondary components of inflammation leading to degradation of cartilage, bone and synovium.[1] This leads to changes in the joint biomechanics and symptoms such as pain, stiffness and decreased articular function.[2–4]

In industrialized societies, OA is the leading cause of physical disability, increases in health care usage and impaired quality of life. The impact of arthritic conditions is expected to grow as the population both increases and ages in the coming decades.[5] The lifetime risk of symptomatic knee OA is 44.7%,[6] and symptomatic knee disease occurs in ~10% of subjects over the age of 55.[7]

There is no cure for the knee OA, but there are several therapeutic options that might be helpful in reducing symptoms but do very little in changing the biochemical environment or the degree of degeneration.[8] Conservative treatment usually includes strengthening exercises,[10,9] lifestyle changes,[11] simple analgesics (non-steroidal anti-inflammatory drugs),[12] different intra-articular injections[13] and supplements such as chondroitin sulphate and glucosamine.[14] For severe pain, opioids can be also prescribed.[15] If conservative management does not produce an adequate reduction of symptoms, there are different surgical options including total joint replacement. Advanced knee OA is the leading cause of total knee arthroplasty (TKA). In 2005 alone, almost 500 000 TKAs were performed in the USA, at a cost exceeding US$11 billion.[16]

Prolotherapy (prolo, an abbreviation of proliferation) is an alternative therapeutic procedure used for the management of chronic musculoskeletal conditions. Irritant substances, usually hyperosmolar dextrose or morrhuate sodium, are injected either in an intra-articular fashion or as local injections to the attachment of ligaments and tendons.[17] One mechanism of prolotherapy is that the hyperosmolar glucose solutions hyperpolarize nerves by opening their potassium channels, thus decreasing transmission in nociceptive pain fibres.[18] Additionally, hypertonic solutions are thought to produce an inflammatory response through the recruitment of chemical mediators and growth factors that stimulate local healing of injured extra- and intra-articular tissue.[19–21] Furthermore, hypotonic solutions are thought to work by blocking transient receptor potential vanilloid type 1, a membrane cation channel that allows influx of Na^+ and Ca^{2+}.[22] Sodium influx is thought to result in action potential and nociception, whereas calcium results in the release of substance P and calcitonin gene-related peptide.[22] Hence, blocking influx of both cations can theoretically minimize neuropathic pain, oedema and tissue intramuscular compartment pressure.[23] However, further definitive evidence regarding basic science remains developmental.

The most commonly published indication for prolotherapy is mechanical low back pain. Recently, prolotherapy has been reported to be beneficial in the management of chronic tendinopathies[24] and knee OA.[25]

There is an increasing interest in dextrose prolotherapy because of its high safety profile, and potential therapeutic effect in a variety of conditions.[26] Hence, the aim of this systematic review is to provide an evaluation of studies related to the application, effectiveness and safety of dextrose prolotherapy injections to patients with knee OA.

Methods

Strategy for literature search

The systematic review was registered PROSPERO (International Prospective Register of Systematic

Reviews) number 37005. Searches of the electronic databases, PubMed, ISI web of science, PEDro and SPORTDiscus, were conducted by F.H. for all papers published from inception through to December 2016 (Fig. 1).

The search strategy included a wide range of terms for prolotherapy and different terms for OA, aiming for high sensitivity in order to detect all the appropriate literature (Table 1).

Selecting studies for review

Duplicates were removed and relevant titles were selected from the results. This was followed by retrieval of full articles to decide whether to include them, based on the inclusion and exclusion criteria reported in Table 2. Studies were excluded if they were pilot studies or unpublished material with <20 participants or if they assessed outcomes other than pain and function (Table 3). Studies assessing prolotherapy in OA of other joints were excluded if data for the knee joint could not be extracted separately. Reference lists were searched further, and Google Scholar was also used to search cited articles for further relevant articles.

Evaluation of methodological quality

As most of the articles were of an experimental nature, the strength and quality of the evidence was determined using the validated modified Coleman

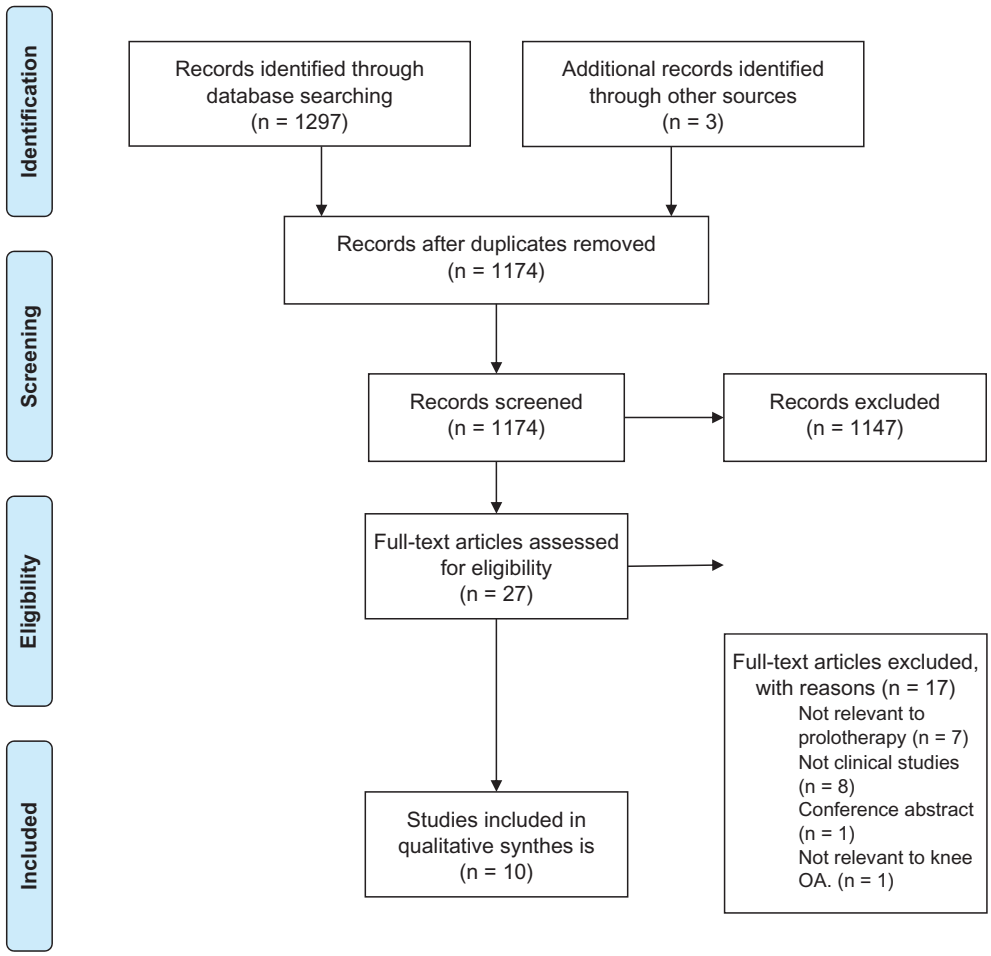

Fig. 1 PRISMA flow diagram of the search results.

Table 1 Electronic database search terms

Terms for prolotherapy
Prolotherapy OR Dextrose OR glucose OR sugar OR regenerative OR proliferation OR injection AND
Terms for knee
Knee OR patellar AND
Terms for OA
osteoarthritis* OR osteo-arthritis* OR Osteoarthrotic OR Osteoarthrosis* OR arthralgia OR degenerate* OR Degenerative joint disease OR gonarthrosis

Table 2 Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Study design	Level 1–4 studies assessing the efficacy of prolotherapy.	Pilot studies ($n < 20$), unpublished material (PhD/MSc thesis), letters to the editor, reviews and conference abstracts.
Participants	Human subjects aged ≥18 years with chronic knee pain/symptoms for at least 6 weeks to ensure true chronicity of symptoms. Studies should also include at least 20 participants to be included and with at least 3 months follow-up.	Animal, cadaver and *in vitro* studies. Studies assessing prolotherapy in other joints/regions, unless knee joint patients were part of the study and results for this subgroup can be extracted separately.
Outcome	Studies assessing pain and function.	Studies assessing outcomes other than pain and function such as imaging findings, biomechanical or microcirculatory outcomes.
Language	English, French, Italian and Spanish.	Languages other than English, French, Italian or Spanish.

Table 3 Excluded studies

Reference	Database	Predominant reason for exclusion
Dávila-Parrilla A, Santaella-Santé B, Otero-López A. Does injection site matter? A randomized controlled trial to evaluate different entry site efficacy of knee intra-articular injections. *BolAsoc Med P R* 2015;107:78–81. PubMed PMID: 26434090	Pubmed	Not relevant to prolotherapy
Park KD, Ahn JK, Lee SC, Lee J, Kim J, Park Y. Comparison of ultrasound-guided intra-articular injections by long axis in plane approach on three different sites of the knee. *Am J Phys Med Rehabil* 2013;92:990–8. doi: 10.1097/PHM.0b013e3182923691. PubMed PMID: 23636088	Pubmed	Not relevant to prolotherapy
Jang SH, Lee SC, Lee JH, Nam SH, Cho KR, Park Y. Comparison of ultrasound (US)-guided intra-articular injections by in-plain and out-of-plain on medial portal of the knee. *Rheumatol Int* 2013;33:1951–9. doi: 10.1007/s00296-012-2660-5. Epub 2013 Jan 25. PubMed PMID: 23354164	Pubmed	Not relevant to prolotherapy
Sibbitt WL Jr, Band PA, Kettwich LG, Chavez-Chiang NR, Delea SL, Bankhurst AD. A randomized controlled trial evaluating the cost-effectiveness of sonographic guidance for intra-articular injection of the osteoarthritic knee. *J Clin Rheumatol* 2011;17:409–15. doi: 10.1097/RHU.0b013e31823a49a4. PubMed PMID: 22089991	Pubmed	Not relevant to prolotherapy

Continued

Table 3 *Continued*

Reference	Database	Predominant reason for exclusion
Goodwin RC, Amjadi F, Parker RD. Short-term analgesic effects of intra-articular injections after knee arthroscopy. *Arthroscopy* 2005;21:307–12. PubMed PMID: 15756184	Pubmed	Not relevant to prolotherapy
Reeves KD, Hassanein KM. Long-term effects of dextrose prolotherapy foranterior cruciate ligament laxity. *Altern Ther Health Med* 2003;9:58–62. PubMed PMID: 12776476	Pubmed	Not relevant to knee OA
Angele P, Madry H, Kon E. Early OA: point of no return or a chance for regenerative approaches. *Knee Surg Sports Traumatol Arthrosc* 2016; 24: 1741–2. doi:10.1007/s00167-016-4156-4	SPORTDiscus	Not a clinical trial
Cheng O, Souzdalnitski D, Vrooman B, Cheng J. Evidence-based knee injections for the management of arthritis. *Pain Med* 2012;13:740–53. doi: 10.1111/j.1526-4637.2012.01394	SPORTDiscus	Not a clinical trial
Rabago D, Nourani B, Mundt M, Zgierska A, Grettie J. Hypertonic dextrose injection (prolotherapy) to multiple tissues for knee osteoarthritis: long term outcomes. *J Bodywork Movement Ther* 2016;20:153. http://dx.doi.org/10.1016/j.jbmt.2015.07.032	SPORTDiscus	Conference abstract
NEW RESEARCH ON INJECTIONS FOR OSTEOARTHRITIC KNEES. Running & Fitnews [serial on the Internet]. (2003, Jan), [cited September 4, 2016]; 21: 1. Available from: SPORTDiscus with Full Text	SPORTDiscus	Not a clinical trial
Jack M Bert, Timothy M Bert. *Nonoperative treatment of unicompartmental arthritis: from bracing to injection, clinics in sports medicine*, Vol. 33, Issue 1, January 2014, Pages 1–10, ISSN 0278–5919, http://dx.doi.org/10.1016/j.csm.2013.08.002	SPORTDiscus	Not relevant to prolotherapy
Kon E, Filardo G, Drobnic M, Madry H, Jelic M, Dijk N, Della Villa. Non-surgical management of early knee osteoarthritis. *Knee Surg Sports Traumatol Arthrosc* 2012;20:436–49	SPORTDiscus	Not a clinical trial
Filardo G, Kon E, Longo U, Madry H, Marchettini P, Marmotti A, Van Assche D, Zanon G, Peretti GM. Non-surgical treatments for the management of early osteoarthritis. *Knee Surg Sports Traumatol Arthrosc* 2016;24:1775–85	SPORTDiscus	Not a clinical trial
Taylor M. Prevention of knee osteoarthritis in athletes using prolotherapy. *J Sci Med Sport* 2003;6:26	SPORTDiscus	Not a clinical trial
Girolamo L, Kon E, Filardo G, Marmotti A, Soler F, Peretti G, Vannini F, Madry H, Chubinskaya. Regenerative approaches for the treatment of early OA. *Knee Surg Sports Traumatol Arthrosc* 2016;24:1826–35	SPORTDiscus	Not a clinical trial
SWEET RELIEF. Shape. Oct 2013: p120. Available from: SPORTDiscus with Full Text. [abstract]	SPORTDiscus	Not a clinical trial
Roman Huber, Ute Prestel, Isabel Bloss, Ulrich Meyer, Rainer Lüdtke. Effectiveness of subcutaneous injections of a cartilage preparation in osteoarthritis of the knee—A randomized, placebo controlled phase II study. *Complement Ther Med* 2010;18:113–8	Web of science	Not relevant to prolotherapy

Methodology Score,[27] with a score of >90 considered to be excellent, 80–90 good, 70–80 fair and <70 poor.

A modification of this score was completed for use assessing conservative intervention by substituting surgical procedure with non-operative procedure for the purposes of this study.[28] There are 10 separate scoring domains that yield a minimum score of 0 and a maximum score of 100 (Table 4). The use of the Coleman Methodology Score modified for conservative

Table 4 Description of the CMS-MCT (B)

	Domains	Subsection allocation	Score
Part A	*Only one score to be given for each of the seven sections*		
	1. Study size: number of patients (*N*) (if multiple follow-ups multiply *N* by number of times subjects followed up)	>60	10
		41–60	7
		20–40	4
		<20, not stated	0
	2. Mean follow-up (months)	>24	5
		12–24	2
		<12, not stated or unclear	0
	3. Number of different non-operative interventions or procedures included in each reported outcome. More than one non-operative interventions or procedures may be assessed but separated outcomes should be reported	One non-operative intervention only	10
		More than one, but >90% subjects undergoing the one intervention	7
		Not stated, unclear, or <90% subjects undergoing the one intervention	0
	4. Type of study	RCT	15
		Prospective cohort	10
		Retrospective cohort	0
	5. Diagnostic certainty (use of pre-operative US, MRI)	In all	5
		In 80%	3
		In <80%	0
	6. Description of non-operative interventions or procedures given	Adequate (technique stated and necessary details given)	5
		Fair	3
		Inadequate, not stated	0
	7. Description of post-intervention rehabilitation	Well described with >80% of patients complying	10
		Well described with 60–80% of patients complying	5
		Protocol not reported or <60–80%	0
Part B	*Scores may be given for each option in each of the three sections if applicable*		
	1. Outcome criteria	Outcome measures clearly defined	2
		Timing of outcome assessments clearly stated (e.g. at best outcome after initial intervention or at follow-up)	2
		Use of outcome criteria that has good reliability	3
		Use of outcome with good sensitivity	3
	2. Procedure for assessing outcomes	Subjects recruited (results not taken from surgeons' files)	5
		Investigator independent of practitioner	4
		Written assessment	3
		Completion of assessment by the subjects themselves with minimal investigator assistance	3
	3. Description of subject selection process	Selection criteria reported and unbiased	5
		Recruitment rate reported >80%	5
		Or <80%	3
		Eligible subjects not included in the study satisfactorily accounted for or 100% recruitment	5

MRI, magnetic resonant imaging; RCT, randomized controlled trial.

therapy (CMS-MCT) attempts to quantify the overall quality of methodology employed in an investigation and provide a relative value on a numerical scale. For the purposes of this study, the score was modified by substituting surgical interventions with conservative treatments, while post-intervention rehabilitation and outcome measurement remained the same.[28] The score is divided into Part A (seven subsections, and only one score may be entered) and Part B (three subsections, and scores may be recorded for each option within each section). Part A is scored by study size, mean follow-up, number of different conservative procedures included in each outcome, design of study, diagnostic certainty, description of conservative procedure given and description of postoperative rehabilitation. Part B is divided into three subsections: (i) outcome criteria (outcome measures clearly defined, timing of outcome assessment is clearly stated, use of outcome criteria that has reported good reliability, use of outcome with good sensitivity); (ii) procedure for assessing outcomes (subjects recruited, investigator independent of surgeon, written assessment, completion of assessment by subjects themselves with minimal investigator assistance); (iii) description of subject selection process (selection criteria reported and unbiased, recruitment rate reported, eligible subjects not included in the study satisfactorily accounted for 100% recruitment).

Two senior orthopaedic surgeons completed the process of scoring all the articles independently. Disagreements were defined as a difference of >2 points from the overall score from each individual article, and disagreements were resolved by consensus.

The overall strength of evidence was then assessed by assigning a level of 1–5 according to the criteria proposed by van Tulder *et al.*,[29] depending on the number and quality of studies (Table 5).

Statistical analysis

To estimate the effect size of any positive effect, we used Cohen's *d* values, which have been shown to be a robust tool for assessing magnitude of effects.[30,31] Cohen's *d* is used when studies report efficacy in terms of continuous measurement, such as pain scores on a rating scale. A Cohen's *d* score of zero means that the treatment and control groups have no differences in effect. A Cohen's *d* greater than zero indicates the degree to which one treatment is more efficacious than the other. Furthermore, a Cohen's *d* of 0.2 is considered as small, 0.5 as medium and 0.8 as large effect.[31,32] A Cohen's *d* score is frequently accompanied by a confidence interval (CI), so that the reliability of the comparison can be assessed.

Results

The initial search returned 1297 studies, with 10 articles meeting the inclusion criteria after a process of screening and full-text retrieval (Table 6). Of the 10 articles included, only 1 was a retrospective study. Furthermore, there were no studies

Table 5 Criteria for the level of evidence existing for each treatment modality

Level of evidence	Criteria
Strong	Consistent findings in multiple high-quality RCTs
Moderate	Consistent findings in multiple low-quality RCTs and/or CCTs and/or one high-quality RCT
Limited	One low-quality RCT and/or CCT
Conflicting	Inconsistent findings among multiple trials (RCTs and/or CCTs)
No evidence	No RCTs or CCTs

CCT, case–control trial; RCT, randomized controlled trial.

Table 6 Included studies

Paper	CMS-MCT (mean)	CMS-MCT
Eslamian *et al.*[8]	66 (SD 1.41)	67/65
Rabago *et al.*[25]	65 (SD 1.41)	66/64
Rabago *et al.*[33]	67 (SD 0)	67/67
Rabago *et al.*[34]	78 (SD 0)	78/78
Rabago *et al.*[35]	62 (SD 0)	62/62
Rabago *et al.*[36]	62 (SD 0)	62/62
Reeves *et al.*[37]	58.5 (SD 0.71)	58/59
Soliman *et al.*[38]	54 (SD 1.41)	55/53
Rahimzadeh *et al.*[39]	64 (SD 1.41)	63/65
Dumais *et al.*[40]	78 (SD 1.41)	77/79

that were scored in the excellent or good range for study methodology, two were scored of fair quality (20%) and the rest were of poor quality (80%). The mean CMS-MCT is 65.45 (range 54.00–78.00, standard deviation (SD) 7.6247, 95% CI 60.00–70.90), which falls in the 'poor quality' range. Data from the 10 studies were extracted and summarized in Table 7.

Population characteristics

The studies reported on a total of 549 patients, of which 345 were females (62.8%) and 204 were males (37.2%). The average age for all participants was 57.7 years. Patients across the 10 studies had varying degrees of symptoms, ranging from mild to severe.

Outcome measures

Studies included had different outcome measures such as the WOMAC score, VAS score, knee pain scale (KPS) score, range of motion measurements, patient satisfaction and radiological assessment.

Summary of results

One study with a population of females showed significant improvement maintained throughout the 24-week period in scores for pain, function and range of motion. Visual analogue score (VAS) for pain was reduced by 45.85% at rest and 44.23% during activity ($P < 0.001$) and a similar pattern was seen in the Western Ontario and McMaster Universities Arthritis Index (WOMAC), which was reduced by 49.58% at 24 weeks ($P < 0.001$).[8] Another trial and a follow-up study showed significant improvement in WOMAC scores at 52 weeks and 3.5 years, beyond the minimal clinical important change (35.8% reduction, $P < 0.05$), and a high patient satisfaction (83%) at 52 weeks.[25,33] Furthermore, these changes were seen as early as 9 weeks, suggesting both short- and long-term effects.[34] Additionally, when prolotherapy was compared with placebo and an exercise-based treatment group, the prolotherapy treatment group showed more promise at 52 weeks with 50% of participants exceeded the minimum clinically significant change in WOMAC scores, compared with 30 and 24% for the placebo and the exercise groups, respectively.[34]

The most recently published investigation showed similar results with the use of 3 months of prolotherapy (with optional treatments at Months 4 and 5), as it resulted in sustained improvement of pain, function and radiological outcomes when compared with physiotherapy alone.[38] Furthermore, the combination of two prolotherapy techniques (Hackett and Lyftgot) resulted in quicker and better improvement in VAS and WOMAC clinical outcomes when compared with use of Hackett technique only.[38]

Following the van Tulder criteria for levels of evidence, our results show moderate evidence suggesting that prolotherapy can help achieve significant symptomatic control in individuals with OA.[29]

Effect size calculations

We performed effect size analysis on our included studies. In one study, prolotherapy was superior to saline at 12 weeks (1.56, 0.06–2.46) and 52 weeks (2.36, 1.46–3.26) in improving total WOMAC scores.[34] When compared with exercise, prolotherapy was again more superior, giving effect size of 2.17 (1.28–3.06).[34] Pain subscale scores followed the similar pattern, showing large effect size of prolotherapy when compared with saline at 52 weeks (1.9, 0.92–2.89). This was also supported by another study, showing a large effect of prolotherapy at 12 weeks (2.5, 1.57–3.43) and 52 weeks (2.37, 1.14–3.59).[36]

Soliman *et al.*[38] compared different techniques of prolotherapy injections in patients who were allocated to Groups 1a (combination of two techniques), 1b (Hackett technique only) and Group 2 (physiotherapy only). Both Groups 1a and 1b were superior to exercise alone, showing large effect size (10.25, 10.04–10.46 and 9.5, 9.28–9.72, respectively).[38] The difference between Groups 1a and 1b was small, favouring the combination Group (1a). Table 8 shows a summary of effect size values and their respective CIs.

Discussion

We pooled data from electronic databases, published from inception until December 2016, and

Table 7 Summaries of the studies reviewed

Study (y)	Design	Sample	Outcome measures	Intervention and dose	Results	MCM score*
Dumais *et al.*[40]	Crossover RCT (open-labelled) between exercise alone and combination of exercise and RIT	36 participants (19 M and 17 F) Chronic knee OA Symptoms ≥6 Mo Age ≥ 18 y (mean 56.75 y)	WOMAC Combined pain score: brief pain inventory, Wong-baker faces scale, simple descriptive intensity scale, and Numeric distress scale Timed up and go	Group A: home-based exercise programme for 32 wks and RIT on wks 0, 4, 8 and 12. RIT included injections of 1cc of 15% dextrose 0.6% lidocaine in the collateral ligaments and intra-articular 5cc injection of 20% dextrose 0.5% lidocaine. Group B: home-based exercise programme for 32 wks in combination with RIT on wks 20, 24, 28 and 32.	Group A (RIT) showed a sig reduction in their WOMAC (−21.8 ± 12.5, $P < 0.001$), whereas that did not change much in Group B (−6.1 ± 13.9, $P = 0.11$). During the last 16 wks, Group A showed improvement in WOMAC (−1.2 ± 10.7, $P = 0.65$) when receiving exercise alone, whereas Group B had a sig decrease in WOMAC scores (−9.3 ± 11.4, $P = 0.006$). After 36 wks, WOMAC scores improved in both groups by 47.3 and 36.2% in Groups A and B, respectively. The improvement attributable to RIT alone corresponds to 29.5% (11.9 points) decrease in WOMAC. Similar patterns seen in the secondary outcomes.	78
Rabago *et al.*[34]	3-arm RCT	90 participants (60 F and 30 M) 40–76 yrs old (mean 56.67 y) Knee OA (mild–severe) Symptoms ≥ 3 Mo Clinical and radiological findings	WOMAC KPS Participant satisfaction	*Group* 1: 6 ml 25% intra-articular and 22.5 ml 15% Extra-articular dextrose injections at 1, 5 and 9 wks with as-needed sessions at wks 13 and 17 ($n = 30$). *Group* 2: as per Group 1 but Saline is injected instead of dextrose ($n = 29$) *Group* 3: home exercises manual and in-person instructions for gradually increased exercise over 20 wks ($n = 31$).	WOMAC scores improved in all groups at 52 wks ($P < 0.01$). However, scores for prolotherapy improved more at 52 wks than those receiving saline injections or home exercises (15.3 ± 3.5 vs. 7.6 ± 3.4 and 8.2 ± 3.3 points, respectively). These sig changes were seen as early as 9 wks post-treatment, across all subscales. 50% of dextrose participants exceeded MCIC for WOMAC, compared to 30% and 24% for saline and exercise groups, respectively.	78

Continued

Table 7 *Continued*

Study (y)	Design	Sample	Outcome measures	Intervention and dose	Results	MCM score*
					KPS improved sig more in the prolotherapy group ($P = 0.05$), leading to high patient satisfaction (91 vs 82 and 89% for Groups 2 and 3, respectively).	
Rabago *et al.*[33]	Single-arm uncontrolled study with 1 y follow-up	36 participants (15 M and 21 F) Aged 40–76 (mean 60 y) Moderate–severe Knee OA Symptoms ≥ 3 Mo Clinical and radiological findings	WOMAC KPS Procedure related pain severity Participant satisfaction	Extra-articular prolotherapy injections of 15% dextrose (22.5 ml) and intra-articular injections of 25% dextrose (6 ml) at 1, 5 and 9 wks (with as-needed treatments at wks 13 and 17).	*WOMAC*: 17.2% improvement 4 wks after first injection (7.6 ± 0.2.4 points, $P < 0.001$), which continued through the 52 wks follow-up, reaching 36.1% (15.9 ± 2.5 points, $P < 0.001$), which exceeds the MCIC. *Analysis showed that females (46–65 yrs) had greater improvement in WOMAC scores.* *KPS*: improvement in both injected ($P < 0.001$) and non-injected knees ($P < 0.05$). *Patient satisfaction* was high (83%)	67
Eslamian *et al.*[8]	Single-arm clinical trial	24 female patients (40 knees) Aged 45–72 (mean 58.37 ± 11.83) Knee OA (moderate or moderate–severe) Symptoms ≥ 3 mo. No response to conservative Tx No history of rheumatological diseases	VAS for pain at rest and at activity Articular ROM WOMAC function scores. *Assessed at 0, 4, 8 and 24 wks*	Intra-articular injection of 8 ml of 20% dextrose water and 2 ml of 1% lidocaine at baseline, 4 wks and 8 wks.	Sig. improvement in scores for pain, function and ROM maintained throughout the 24 wks. *VAS*: baseline mean score at rest and activity was 8.83 (±1.37) and 9.37 (±1.31), respectively. At wk 24, scores decreased to 4.87 (±1.39). Yielding a decrease of 45.86 and 44.23%, respectively ($P < 0.001$). *ROM*: 105.41° (±11.2°) at baseline. At the end of wk 24, ROM increased by 8°. *WOMAC score*: Total score decreased by 30.5 (±14.27) points at 24 wks, leading to 49.58% reduction ($P < 0.001$) as well as a 46.19, 58.12 and 47.85% reduction in pain, stiffness and function subscale scores, respectively.	66

Rabago *et al.*[25]	Open-label follow-up study to an RCT [29] and 2 non-controlled trials [26,28]	65 participants (38 F, 27 M) Mean age 58.7 Mild–severe knee OA Clinical and radiological findings Completed 52 wks prolotherapy in one of three previous studies	WOMAC KPS *Follow-up at baseline, 12 wks, 26 wks, 52 wks and 3.5 yrs*	6 ml of 25% dextrose was injected in the intra-articular and 22 ml of 15% dextrose was injected at extra-articular soft tissue attachments. Sessions delivered at 1, 5 and 9 wks. Optional sessions at wks 13 and 17.	Sig improvement in WOMAC scores, across the three subscales, at all time points in excess of MCIC. Composite scores improved from 13.8 ± 17.4 points (23.6%) at 12 wks, to 20.9 ± 2.8 points ($P < 0.05$; 35.8% improvement) at 2.5 ± 0.6 yrs (range 1.6–3.5 yrs). KPS scores improved progressively through the 2.5 yrs ($P < 0.001$). Subjective perception of change in knee QoL indicated a sig gain and 86% of patients indicated decreased pain (71 ± 26%) compared to baseline.	65
Rahimzadeh *et al.*[39]	RCT	70 patients (30 M and 40 F) Knee OA Age 40–70 y (mean 59.9 y) Clinical and radiological findings	VAS for pain Knee ROM Patient satisfaction	Group 1: intra-articular injection of 5cc of ropivacaine 0.5% together with 4000 IU of EPO. Group 2: fluroscoically guided intra-articular injection of 5cc 0.5% ropivacaine with 5cc dextrose 25%. Group 3: Pulsed radiofrequency.	VAS: mean VAS in Group 1 was 3.15 ± 1.08, 3.15 ± 1.08 and 3.5 ± 1.23 at 2, 4 and 12 wks, respectively. Difference was sig compared with the two other groups ($P \leq 0.005$). Knee ROM in Group 1 was 124 ± 1.50, 124 ± 1.4 and 123 ± 1.53, respectively. This was statistically sig compared with the other groups ($P \leq 0.005$). At 12 wks in the EPO group, 15% were extremely satisfied, 55% were satisfied and 30% were moderately satisfied ($P = 0.005$). Satisfaction for the other groups was lower.	64
Rabago *et al.*[35]	Prospective 3-arm uncontrolled study	38 participants; 18 *prior-control, 15 prior-ineligible and 5 prior-declined in a previous RCT* 21 M and 17 F Mean age 56.8 y	WOMAC KPS Participant satisfaction *52-wk follow-up was conducted*	Extra-articular 15% dextrose and 5% morrhuate sodium injections and a single intra-articular injection of 6 ml 25% dextrose. Treatment delivered at at 1, 5 and 9 wks with as-needed sessions at wks 13 and 17.	*Prior-declined*: most severe baseline WOMAC ($P = 0.02$). There was a score change of 42.9% (19.4 ± 7 points, $P = 0.05$). 75% achieved MCIC. *Prior-control*: WOMAC score change of 19.5% (12.4 ± 3.5 points, $P = 0.002$). 55.6% achieved MCIC.	62

Continued

Table 7 *Continued*

Study (y)	Design	Sample	Outcome measures	Intervention and dose	Results	MCM score*
		Knee OA (mild–severe) Symptoms ≥ 3 Mo Clinical and radiological findings			*Prior-ineligible*: WOMAC score change of 28.4% (17.8 ± 3.9 points, $P = 0.008$). 50% achieved MCIC. *Near maximal improvement seen at 24-wks, which were maintained to 52-wk follow-up.* Similar pattern seen with *KPS* and *patient satisfaction.*	
Rabago *et al.*[36]	2-arm controlled trial	37 participants (16 M and 21 F) Aged 43–71 (mean 55.95 y) Knee OA Symptoms ≥ 3 Mo Clinical and radiological findings	WOMAC at 5, 9, 12, 26, 52 wks. MRI-assessed CV at baseline at 52 wks	Treatment group: 5 monthly injections of intra-articular 25% dextrose and 15% extra-articular dextrose at 1, 5 and 9 wks, with optional sessions at wks 13 and 17. Some participants also had extra-articular 5% morrhuate sodium. Control group: blinded saline injections or gradually increased home-based exercises.	Both groups reported WOMAC improvement. However, it was more sig in the treatment group at 52 wks (17.6 ± 3.2 vs 8.6 ± 5.0 points, $P = 0.05$). Near maximal improvement was seen as early as 9 wks in the treatment group. Both groups experienced reduction in MRI-assessed CV ($P < 0.05$), less so in the treatment group (6.95 vs 7.23%, $P < 0.001$). Those that lost the least CV in the treatment group had the greatest improvement in pain, suggesting pain-specific disease-modifying effect.	62
Reeves *et al.*[37]	Prospective RCT (double-blind)	68 patients and 111 knees—25 knees with ACL laxity. 40 M and 20 F Knee OA ± ACL laxity Average age 63 y Symptoms ≥ 6 Mo	VAS for pain and swelling Frequency of buckling Flexion ROM Radiological joint narrowing and osteophytosis	Treatment group: 3 bi-monthly injections of 9cc of 10% dextrose and 0.75% lidocaine in bacteriostatic water with additional three bi-monthly injections of 10% dextrose. Control: as per treatment group, but without the dextrose.	Sig more benefit from dextrose injection ($P = 0.015$) between 0 and 6 Mo. At 12 Mo (6 injections), the dextrose-treated knees improved in pain (44% decrease), swelling (63% decrease), knee buckling frequency (85% decrease), and in flexion ROM (14° increase).	58.5

		Grade 2 or more joint narrowing or osteophytic changes	KT1000- measured ADD		Lateral patellofemoral cartilage thickness and distal femur width both improved sig ($P = 0.019$ and $P = 0.021$, respectively). ACL laxity: at 12 Mo, dextrose-treated knees with ACL laxity saw sig improvement in pain, swelling and joint flexion ($P = 0.021$). 8/13 of those knees were no longer lax as ADD improved by 57% ($P = 0.025$). However, there was no sig difference at 6 Mo.	
Soliman *et al.*[38]	RCT	128 patients. 96 F and 32 M Age range 35–76 Symptoms ≥6 Mo No statistically sig. difference between groups	VAS score WOMAC Imaging (plain radiographs + ultrasound)	Group 1: intra-articular (5 ml of 25%) and extra-articular (40 ml of 15%) dextrose prolotherapy injections at 1, 2 and 3 Mo. With PRN injections at 4 and 5 Mo ($n = 104$). 1a—both Hackett technique and Lyftgot technique. 1b—Hackett technique only. Group 2: Physiotherapy only ($n = 24$).	Subgroups 1a and 1b reported a sig improvement in VAS, WOMAC and radiological assessment at 12 Mo, compared with their baseline and compared with group 2 ($P \leq 0.001$). 12 Mo mean ± SD of VAS: 1a: 0.32 ± 0.27, Group 1b: 0.44 ± 0.5, Group 2: 9.9 ± 1.65. 12 Mo Mean ± SD of WOMAC: 11.32 ± 10.3 for Group 1a, 18.5 ± 10.25 for Group 1b, and 79.5 ± 22.63 for Group II. Group Ia needed less injections than Ib. Groups 1a and 1b had a statistically sig decrease in the dimensions of ligaments and tendons ($P \leq 0.001$) and a statistically sig increase in the articular cartilage thickness in both compartments ($P \leq 0.001$). The opposite was seen in Group 2 ($P \leq 0.001$).	54

ACL, anterior cruciate ligament; ADD, anterior displacement difference; CV, cartilage volume; EPO, erythropoietin; F, female; IU, international units; M, male; MCIC, minimal clinically important change; ml, millilitre; Mo, Month(s); MRI, magnetic resonant imaging; OA, osteoarthritis; QoL, quality of life; RCT, randomized controlled trial; RIT, regenerative injection therapy; ROM, range of motion; Sig, significant/ly; Tx, treatment; wk, week; y, year(s).

*MCM scores are reported as mean scores.

Table 8 Effect size calculations

Paper	Comparison	Outcome measure	Effect size Mean (SD)*
Rabago *et al.*[34]	Prolotherapy vs saline at 12 weeks	Total WOMAC	1.56 (0.06–2.46)
	Prolotherapy vs saline at 52 weeks	Total WOMAC	2.36 (1.46–3.26)
	Prolotherapy vs exercise at 52 weeks	Total WOMAC	2.17 (1.28–3.05)
	Prolotherapy vs saline at 52 weeks for pain	Pain subscale of WOMAC	1.9 (0.92–2.88)
	Prolotherapy vs exercise at 52 weeks for pain	Pain subscale of WOMAC	1.39 (0.42–2.36)
Rabago *et al.*[36]	Prolotherapy vs saline at 5 weeks	Total WOMAC	0.51 (−0.43–1.45)
	Prolotherapy vs saline at 12 weeks	Total WOMAC	2.50 (1.57–3.43)
	Prolotherapy vs saline at 52 weeks	Total WOMAC	2.37 (1.14–3.59)
	Prolotherapy vs saline at 52 weeks	Pain subscale of WOMAC	3.27 (1.93–4.60)
Soliman *et al.*[38]	Combination of both techniques vs physiotherapy alone	VAS for pain (12 months)	10.25 (10.04–10.46)
	Hackett technique vs physiotherapy alone	VAS for pain (12 months)	9.5 (9.28–9.72)
	Combination of both techniques vs Hackett technique only	VAS for pain (12 months)	0.30 (0.22–0.38)

*Cohen's *d* of 0.2 is considered as small effect, 0.5 as medium effect and 0.8 as large effect.

found that only 10 of 1297 studies originally identified met our inclusion criteria: they were scrutinized for further evaluation. The Coleman Methodology Score, modified for conservative therapy, was used for evaluation of methodological quality. It showed that evaluated studies fall into the 'poor quality' category overall.

In all studies, improvement from baseline was reported.[8,25,34–40] Four studies reported significant improvement comparing with control group.[34,36,37,40] In these studies, dextrose prolotherapy was compared with 0.9% saline and home exercise,[34,36] 0.75% lidocaine[37] and with a home exercise programme only.[40] In one study,[39] dextrose prolotherapy was less efficient than erythropoietin injections and similarly efficient as pulsed radiofrequency therapy. To determine efficacy, most studies measured pain reduction, by using VAS, and functional improvement, using the WOMAC score. Some studies also reported high scores in patients satisfaction with dextrose prolotherapy injections.[25,34,35,39] In terms of degree of improvement, one study showed improvement of 17.2% in WOMAC scores 4 weeks after the first injection session, which continued to improve through the 52-week follow-up period to 36.1% ($P < 0.001$).[33] Several studies showed prolotherapy to be effective. However, most studies did not report analysis on effect size. Cohen's *d* effect size calculations demonstrated that prolotherapy can exert a large positive effect on WOMAC scores and pain subscale scores as soon as 12 weeks following treatment (2.5, 1.57–3.43), which was maintained to 52 weeks (2.37, 1.14–3.59).[34,36] This positive effect lasted as long as 2.5 years following treatment.[25]

Dextrose prolotherapy can be administered in different ways but there are two key techniques in the literature; the perineural or neurofascial prolotherapy (Lyftogt's technique) and the traditional prolotherapy (Hackett's technique).[22,41] The perineural method involves injecting dextrose into the subcutaneous tissues to induce a healing response.[22] The traditional Hackett's method involves injecting into the fibro-osseous junction of ligaments or tendons.[41] The perineural method relies on Hilton's law, which states that nerves supplying a joint are the same ones that supply the muscles moving it as well as the skin

overlying it.[22] A recent study compared a combination of Hackett's and Lyftogt's techniques with Hackett's only and physiotherapy only.[38] The combination of the two techniques yielded the best improvement, followed by the Hackett's prolotherapy, and then by physiotherapy only.[38] Both the combination and the single technique led to significant clinical and imaging improvement when compared with physiotherapy alone: however, the combination was the best option.[38] This was also supported by our effect size analysis, which showed both techniques to be efficacious. However, the difference between the combination of techniques vs Hackett's technique alone was small, nevertheless still favouring the combination of techniques.

There are numerous treatment options for knee OA, documented in systematic reviews and meta-analyses. One of common conservative treatment options was the application of intra-articular steroid injections. Taking into account the considerable heterogeneity between studies, it is not clear whether intra-articular steroid injections provide any clinical benefit after 1–6 weeks.[42] There is high-quality evidence confirming that exercise provides short-term effects, lasting for at least 2–6 months after the cessation of treatment. Also, there is moderate evidence confirming improvement after exercise, in physical function, among patients with knee OA.[43] There is no evidence that transcutaneous electrical stimulation is effective for pain relief. Systematic review included only small trials of doubtful quality that hampered final conclusion.[44] There is low-quality evidence that ultrasound might be beneficial for knee OA, but the magnitude of their effect is unknown.[45] There is no evidence that lateral wedge, neutral wedge or knee bracing is efficient in treatment of knee OA.[46] Viscosupplements are an efficient therapeutic option for treatment of knee OA. They are probably beneficial for pain reduction, functional improvement and patient global assessment, especially 5–13 weeks post-injection.[47] There is a small benefit of non-tramadol opioids, which is overshadowed by a significant increase in risk of adverse effects.[15] There is no evidence that any one non-steroidal anti-inflammatory drug (NSAID) is superior to any other if used in equivalent doses.[48] Adverse effects related to NSAIDs use should be also considered, especially if administered over long periods of time.

There are no 'head to head' studies comparing dextrose prolotherapy with any of the mentioned treatment options, except with home programme exercise,[34,40] where prolotherapy appeared to be more efficient. The great advantage of dextrose prolotherapy is that it is safe, inexpensive, easy to administer, and none of studies included in our systematic review reported any permanent or long lasting adverse effect.

We found only one systematic review with a meta-analysis related to dextrose prolotherapy and knee OA. The review included three randomized and one quasi randomized control trials, and confirmed the efficacy of dextrose prolotherapy as well as high safety profile.[49]

Limitation of study

The main limitations are related to small number of studies selected for this systematic review, their small sample size and the lack of high-quality trials, as 80% of the studies identified were of poor quality. There is great heterogeneity among the studies in term of patients characteristic, study design, concentration of injected ingredients, outcome measures, number of injections, time span between each injection and length of post-treatment follow-up. Only one study measured the association between cartilage volume and functional improvement.[36]

Dextrose prolotherapy is considered a regenerative type of treatment, which is supposed to change the morphology of injected structures and eventually slow down the degenerative process. None of presented studies was able to confirm such assumption, or to provide explanation for possible mechanism of action. The number and location of injected points is based on palpation rather than on objective radiological investigations, so it is always subject to the personal preference of the injector: this may impact on the treatment outcome.

Furthermore, it would have been beneficial to have been able to calculate odds ratios. Unfortunately, the published articles offered no information on the number of participants who responded vs those who did not respond. This could be a point for future studies

to consider, as it will help clinicians to provide statistics that are easy to understand for patients, giving another dimension to effect size.

The strength of this systematic review is that it included a broad database analysis, duplicate study selection, evaluation of methodological quality by two independent reviewers, and comprehensive inclusion and exclusion criteria.

Future studies

Encouraging results, with pain reduction, functional improvement and patient satisfaction, together with high safety profile, provide solid bases for further research that should be focused on standardization of the treatment itself. Optimal volume and concentration of injected substances, the number of treatment sessions and time interval between administration have to be unified. The use of ultrasound may provide more precise assessment of damaged structures and administration of injected substances. RCT comparing dextrose prolotherapy with other injection and non-injection conservative treatments for knee OA would give better insight of the possibility of dextrose prolotherapy being a more wide-spread treatment option. Finally, basic science studies using animal models would provide additional data to help confirm if dextrose prolotherapy can only provide symptom relief or is a truly disease-modifying therapeutic tool.

Conclusion

Dextrose prolotherapy can provide improvement in pain, functional status and patient satisfaction in patients with mild to moderate knee OA, with no long-term or permanent adverse reactions reported. Future research should focus on larger sample size, standardization of treatment protocol and further basic science evidence.

Conflict of interest statement

The authors have no potential conflicts of interest.

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