TITLE: **Prolotherapy for the Management of Musculoskeletal Pain: A Review of the Clinical Effectiveness**

DATE: 4 November 2014

CONTEXT AND POLICY ISSUES

Chronic musculoskeletal disorders including low back pain, tendinopathy, and osteoarthritis are degenerative diseases and overuse injuries that affect quality of life and have a cost in an aging and working society.[1-3] One in eight Canadians report having chronic back problems and most Canadians will have back pain at some point in their lifetime.[3] Canadians among the 30 to 49 age group have highest prevalence (1 in 10) of repetitive strain injury that limit their normal activities.[3] Nearly four million Canadians have had arthritis and other rheumatic conditions, and three out of five people with arthritis are younger than 65 years.[3] These conditions are often associated with loss of productivity and reduced performance while at work. It was estimated that musculoskeletal disorders cost Canada over $20.6 billion in 2005.[3]

Various injection therapies have been used for the treatment of musculoskeletal conditions. These include combinations of corticosteroid and anesthetic, platelet-rich plasma, autologous whole blood, dry needling, and acupuncture.[4] Prolotherapy (termed from proliferant therapy) has emerged as an alternative and cost-effective treatment option for chronic musculoskeletal injuries.[4] It involves the injection of small amount of irritant solutions during several treatment sessions into tender ligaments, tendons and adjacent joint spaces to induce local inflammation, which promotes musculoskeletal repair via the stimulation of growth factors in the inflammatory healing cascade.[1] Although prolotherapy techniques and injected solutions vary by condition, clinical severity and physician preferences, the most common injected solution is dextrose (12.5% to 25%); sodium morrhuate is used slightly less often.[4,5] Injection of a solution of greater than 10% dextrose is believed to cause an osmotic gradient outside the cells leading to cell lysis, with the net effect being an influx of growth factors and inflammatory cells that initiate wound-healing cascades at the specific areas.[3] This, in turn, results in the repair, health, and growth of tendons, ligaments and other soft tissues.[4] In addition, increase in dextrose concentration in animal models was found to cause an increase in cell protein synthesis, DNA synthesis, cell volume, and proliferation.[6] Since it uses the body's self-healing mechanisms to improve structure and function of the ligaments and tendons, prolotherapy is considered to be a low-risk injection therapy.[6] Prolotherapy appears to be safe, with few adverse events or contraindications, making it an attractive alternative to other treatments.

This aim of this report is to review the clinical effectiveness of prolotherapy for management of musculoskeletal pain.

RESEARCH QUESTION

1. What is the clinical effectiveness of prolotherapy for the management of musculoskeletal pain?

KEY FINDINGS

Evidence from studies of limited quality suggests that dextrose prolotherapy for the management of musculoskeletal pain including low back pain, tendinopathy, and osteoarthritis may provide pain relief and improve physical function compared with saline injection control, exercise alone, or before prolotherapy treatment.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 10), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and October 3, 2014.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to the selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with chronic musculoskeletal pain including low back pain, tendinopathy, and osteoarthritis.
Intervention	Prolotherapy (hypertonic dextrose, phenol-glycerine-glucose, and morrhuate sodium)
Comparator	Standard of care
Outcomes	Clinical effectiveness, pain reduction, improved physical function
Study designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), and non-randomized studies

Exclusion Criteria

Articles were excluded if they did not satisfy the selection criteria in Table 1, if they were published prior to 2009, duplicate publications of the same study, or included in selected health technology assessment of systematic review.

Critical Appraisal of Individual Studies

The quality of included HTAs and systematic reviews was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.[7] RCT and non-randomized study quality was evaluated using the Downs and Black instrument.[8] A numeric score was not calculated for each study. Instead, strengths and weaknesses of each study were summarized and described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 190 citations. Upon screening titles and abstracts, 159 citations were excluded and 31 potentially relevant articles were retrieved for full-text review. No additional relevant reports were retrieved from grey literature or hand searching. After full-text review, 16 studies were included. The process of study selection is outlined in the PRISMA flowchart (Appendix 1).

Summary of Study Characteristics

The characteristics of 16 studies including one systematic review,[9] seven RCTs,[10-16] and eight case series[17-24] are presented in Appendix 2. Of the 16 included studies, there were three studies on low back pain (one RCT[16] and two case series[22,24]), six studies on tendinopathy (one systematic review,[9] three RCTs,[12,14,15] and two case series[21,23]) including lateral epicondylosis,[9,12,14] Achilles tendinosis[15,23] and patellar tendinopathy,[21] and seven studies on hand and knee osteoarthritis (three RCT,[10,11,13] and four case series[17-20]). Characteristics of included studies are presented in Appendix 2.

A. Low back Pain:

Three studies were conducted in South Korea,[16] Australia,[22] and Canada.[24]

The double-blind RCT by Kim et al., 2010[16] included 50 adult patients (mean age 42 years), who had sacroiliac joint pain and failed medical treatment for one month. The intervention group was prolotherapy (dextrose-levobupivacaine, n=24) compared with a steroid group (triamcinolone acetonide, n=26). Patients received a maximum of three injections at 0, 2 and 4 weeks. Follow-up was done at 0, 2 weeks and monthly after completion of treatment. Long-term follow up reached up to 15 months. Pain scores and disability scores were measured by visual analog scales (VAS). A power calculation was conducted and the study had sufficient power to detect a clinical important effect (P<0.05). A per protocol approach was used for data analysis.

The prospective case series by Cusi et al., 2010[22] included 25 adult patients (age ranging from 26 to 67 years), who had localized and/or radiating low back pain; the symptoms persisted for at least six months. Patients received three injections of prolotherapy (dextrose-bupivicaine), six weeks apart. Outcome measures included clinical examination scores (0 to 9) and functional scores including the Quebec Back Pain Disability Scale, Roland-Morris Back Pain Questionnaire and Roland-Morris 24 Multiform Questionnaire. Follow-up visits were at 0, 3, 12, and 24 months.

The retrospective case series by Watson et al., 2010[24] included chart reviews of 190 adult patients (mean age 48 years), who had low back pain of at least three months and failed to respond to standard treatments. Only charts of patients who reported a decrease in their pain

following lidocaine injection were included. The number of prolotherapy (dextrose-lidocaine) injections varied among patients. Patients were followed up for at least one year. The outcome measures were pain score and quality of life, which were quantified by non-validated VAS.

B. Tendinopathy:
Of the six studies, the systematic review[9] was multinational (Canada, Sweden, USA), while three RCTs[12,14,15] and case series[21] were from the USA, and one case series was from Canada.[23]

The systematic review by Rabago et al., 2009[9] appraised the evidence of four injection therapies (prolotherapy, polidocanol, whole blood and platelet rich plasma) for lateral epicondylosis. Three studies (two RCTs and one case series) were included for prolotherapy. All three studies had small sample size (RCTs [N=24, 8]; case series [N=20]). Patients were adults with ages ranging from 19 to 63 years, who had lateral epicondylosis with pain which varied from at least 3 months to 1.9 years. The two RCTs compared prolotherapy injection (dextrose-morrhuate or dextrose-lidocaine) with saline injection. The case series compared before and after prolotherapy injection (dextrose-lidocaine). Follow-up times of the RCTs were 16 weeks and 9 weeks, while the case series had a mean of 19 months follow-up. Pain scores were obtained using a VAS (0 to 10) or McGill Pain questionnaire (0 to 45). Other clinical outcomes included isometric strength, grip strength, physical composite score of SF-36, or subject satisfaction.

The single-blinded RCT by Rabago et al., 2013[12] included 31 adult patients (age ranging from 18 to 65 years), who had lateral epicondylosis with elbow pain for at least three months and failed at least one of the common treatments (NSAIDs, physician initiated therapy or corticosteroid injection). The study had three parallel groups comparing prolotherapy with dextrose (n=8; 10 elbows) versus dextrose–morrhuate (n=9; 10 elbows) versus wait-list control (n=10; 12 elbows). Only patients in the prolotherapy groups were blinded while injector and assessor were not. Patients in the prolotherapy groups received three injection sessions at 1, 4 ad 8 weeks. Patients from all three groups were followed up at 4, 8, 16 weeks; patients in the prolotherapy groups were additionally followed up at week 32. The primary outcome was composite score on the Patient-Rated Tennis Elbow Evaluation (PRTEE 0 to 100), with subscales of pain (5 items) and function (10 items). The minimal clinically important difference (MCID) for PRTEE was 11 points or 37% improvement from baseline. Other outcomes were epicondylosis identified by MRI and ultrasound assessment and satisfaction rating (0 to 5). The study had a sample size calculation (N=30; 10 participants per group) with 80% power ($P<0.05$). The data were analyzed using intention-to-treat (ITT) analysis and a last observation carried forward (LOCF) approach was used for missing data.

The double-blinded RCT by Carayannopoulos et al., 2011[14] included 24 adult patients (age range 18 to 75 years), who had elbow pain for 3 months to 2 years in the region of lateral epicondyle. The study compared prolotherapy with dextrose-morrhuate-procaine versus corticosteroid (methylprednisone). Patients received two injections one month apart, and were followed up at 0, 1, 3 months at a clinician's office and at 6 months by telephone. The primary outcome was pain severity (0 to 10 VAS). Other outcomes included quadruple VAS (0 to 10 QVAS) and the Disability of the Arm, Shoulder and Hand (0 to 5, DASH) scale. The study did not meet sample size calculation requirements and the results were purely exploratory. A per protocol approach was used for data analysis.

The single-blinded RCT by Yelland et al., 2011[15] included 43 adult patients (age ranging from 40 to 58 years) with painful Achilles tendinosis. The intervention group was prolotherapy (dextrose-lignocaine/ropivacaine; n=14) compared with exercise (n=15) and a combination of prolotherapy and exercise (n=14). Prolotherapy injections were done weekly for four to 12 treatments and the exercise was instructed by a doctor or podiatrist. Follow-ups were at baseline, 6 weeks, 3 months, 6 months and 12 months. The primary outcome was the Victorian Institute of Sport Assessment-Achilles (VISA-A) questionnaire (0 to 100) with an MCID of 20 points. Other outcomes included treatment satisfaction (Likert scales 0 to 7), a Patient Global Impression of Change (PGIC) scale (0 to 10), with an MCID of 1.75 points for pain, 1.75 points for stiffness, and 2.0 points for limitation of activity. The study did not have a power calculation, and only the assessor was blinded, an ITT approach was used for data analysis, and missing data was addressed using LOCF strategy.

The prospective case series by Ryan et al., 2010[23] included 99 adult patients (mean age 54 years) experiencing pain for greater than 6 months at either the Achilles tendon insertion or midportion. The intervention was prolotherapy with dextrose-lignocaine. Patients had a median of 5 (ranging from 1 to 13) injection consultations spaced by a mean of 5.6 weeks apart. Follow-up was given at a mean of 28 weeks (range 5 to 73 weeks). Long-term follow-up from 12 to 48 months was conducted by telephone. The main outcome measure was pain score (0 to 100 VAS) with subscales for pain at rest (VAS1), daily activity (VAS2), and sport (VAS3).

The prospective case series by Ryan et al., 2011[21] included 47 adult patients (mean age 38.3 years) who had patellar tendinopathy with symptoms persisting for at least 6 months, and who failed standard therapy. The intervention was prolotherapy with dextrose-lidocaine. Patients received 2 to 8 injections (median: 4 injections) spaced by a mean of 6.4 weeks. Follow-up was given at every 6 weeks up to 45 weeks post-treatment injection. Outcome measures included pain score (VAS) and ultrasound examination.

C. Osteoarthritis:

Seven studies on prolotherapy for knee osteoarthritis were conducted in Iran,[10] USA,[11,17-19] Canada[13] and Germany.[20]

The double-blinded RCT by Jahangiri et al., 2014[10] included 60 adult patients (>40 years) with osteoarthritis in the first carpometacarpal joint based on radiographic criteria. Pain persisted at least 3 months. The intervention group was prolotherapy (dextrose-lidocaine; n=30) compared with injection of prednisone-lidocaine (n=30). Patients received monthly injections for 3 months. Of note, patients in the prednisone group received saline injection for the first 2 months, then prednisone in the third month. Follow-up was given at 0, 1, 2, and 6 months. The primary outcome was subjective pain intensity (0 to 9 VAS). Other outcomes included pain on joint movement (0 to 9 VAS), hand function (HAQ-DI 0 to 3 VAS), and pinching (HAQ-DI 0 to 3 VAS). The study had a power calculation set at 80% with $p<0.05$. A per protocol approach was used for data analysis.

The double-blinded RCT by Rabago et al., 2013[11] included 90 adult patients (age ranging from 40 to 76 years), who had knee osteoarthritis within 5 years of study enrolment, tenderness of one or more anterior knee structure, and moderate-to-severe knee pain for at least 3 months. Intervention was prolotherapy (dextrose-lidocaine; n=30) versus saline injection (n=29) versus exercise (n=31). Injections were given at 1, 5, 9 weeks with additional sessions at 13 and 17 weeks as per physician's recommendations and participants' preference. Exercise was home-based according to instructions in a provided pamphlet. Patients were followed up in person at

0, 5, 9, and 12 weeks, and by telephone at 26 and 52 weeks. The primary outcome was knee-related quality of life (0 to 100 WOMAC; Western Ontario McMaster University Osteroarthritis Index), with pain, stiffness and functional subscales. The MCID for WOMAC was 12 points of change on a 0 to 100 VAS. Other outcome measures included knee pain scale (KPS: 0 to 4 ordinal scale for keen pain frequency; 0 to 5 ordinal scale for severity), procedure-related pain (1 to 7 ordinal scale), opioid medication use, and treatment satisfaction. The study had a sample size calculation (32 participants per group) with 80% power to detect a 20% difference (P<0.05). The analysis was done by ITT.

The open-labeled cross-over RCT by Dumais et al., 2012[13] included 45 adult patients (mean age 57 years), who had knee osteoarthritis with pain in the knee for at least 6 months. The intervention was prolotherapy (dextrose-lidocaine) versus home-based exercise. There were two groups, both undertaking exercise throughout the 32 week study period. In Group A (n=21) patients received dextrose injections on weeks 0, 4, 8, 12. Group B (n=24): patients received dextrose injections on weeks 20, 24, 28 and 32. The primary outcome was knee-related quality of life (0 to 100 WOMAC), with pain, stiffness, and functional subscales. The MCID for WOMAC was 12 points of change on a 0 to 100 VAS. Other outcome measures included brief pain inventory, (0 to 10), Wong-Baker Rating scale (0 to 5), simple descriptive intensity scale (0 to 10), combined pain score, functional capacity and severity on knee osteoarthritis (Kellgren-Lawrence grading scale). The study had a sample size calculation (minimum 36 participants total) with 80% power to detect a treatment effect (P<0.05).

The retrospective case series by Hauser et al., 2014[17] reviewed the charts of 61 adult patients (age ranging from 18 to 82 years), who had pain for at least three months due to chondromalacia patella, which is primarily the result of age-related knee osteoarthritis. Patients had to complete prolotherapy (dextrose-procaine) injections (24 to 40 injections per treated knee at each session). Treatment intervals were every 4 to 6 weeks. Patients were followed up by telephone after the first day, and at one month and three months. Outcome measures included pain level (0 to 10 VAS), functional level (levels of stiffness and crepitus, 0 to 10 VAS), and pain medication use before and after prolotherapy.

The case series by Rabago et al., 2014[18] included 38 adult patients from a previous RCT who had at least three months knee osteoarthritis. The cohort consisted of prior-decline (those who declined to participate the previous RCT) patients (n=5), prior control patients (n=18) and prior ineligible (those who were excluded from previous RCT) patients (n=15). The symptoms of these patients ranged from mild to severe. All patients received prolotherapy injections of dextrose-morrhuate-lidocaine at 1, 5, and 9 weeks with as-needed treatment at weeks 13 and 17. Patients were followed up at one year. The primary outcome was knee-related quality of life (0 to 100 WOMAC), with pain, stiffness, and functional subscales. The MCID for WOMAC was 12 points of change on a 0 to 100 VAS. Other outcome measures included the knee pain scale (KPS: 0 to 4 ordinal scale for keen pain frequency; 0 to 5 ordinal scale for severity), procedure-related pain (1 to 7 ordinal scale), opioid medication use, and treatment satisfaction. Analysis was done by ITT.

The prospective case series by Rabago et al., 2012[19] included 36 adults patients (age ranging from 40 to 76 years) with at least three months of knee osteoarthritis. Patients received prolotherapy of dextrose-lidocaine at 1, 5, and 9 weeks, and were followed up at 0, 5, 9, 12, 24 and 52 weeks. The primary outcome was knee-related quality of life (0 to 100 WOMAC), with pain, stiffness and functional subscales. The MCID for WOMAC was 12 points of change on a 0 to 100 VAS. Other outcome measures included the knee pain scale (KPS: 0 to 4 ordinal scale

for keen pain frequency; 0 to 5 ordinal scale for severity), procedure-related pain (1 to 7 ordinal scale), opioid medication use and treatment satisfaction. Analysis was by per protocol.

The retrospective case series by Schaumburger et al., 2012[20] reviewed charts of 92 adult patients (age ranging from 18 to 76 years), who had knee arthritis (recurrent knee joint effusion) of heterogeneous etiology. Patients had received prolotherapy of morrhuate-mepivacaine-triamcinolone. The mean follow-up was 29.8 months. Outcome measures included pain score (0 to 10 VAS), Knee Injury and Osteoarthritis Outcome score (KOOS), and Lysholm and Gillquist score.

Summary of Critical Appraisal

The individual strengths and limitations of the systematic review, seven RCTs and eight observational studies are presented in Appendix 3.

The quality of the systematic review met most items of the AMSTAR checklist, including duplicate study selection and data extraction, a comprehensive literature search, a list of included and excluded studies, reporting of the characteristics of included studies, quality assessment of the included studies, and a statement of conflict of interest. However, the likelihood of publication bias was not assessed, it was unclear if the research question and inclusion criteria had been established before the conduct of the review, and it was unclear if grey literature was included in the literature search.

Strengths of all RCTs were mostly on reporting. Internal validity such as time of follow-up and statistical tests used to assess main outcome were appropriate in most studies. A number of studies did not blind the injector and assessor to treatment, used non-validated outcome measures, did not use adequate adjustment for confounding in the analyses, or did not take into account of loss of patients to follow-up. Although the staff, places and facilities where patients were treated, were representative of the treatment that majority of patients would receive, all studies lacked generalizability (external validity) in that it was difficult to determine if the participants were representative of the entire population from which they were recruited.

All the observational studies were uncontrolled case series of either prospective or retrospective design. They suffered substantial limitations in reporting, internal validity, external validity and power. In reporting, the baseline characteristics of patients included in the study and the baseline characteristics of patients lost to follow-up were not described in most studies. For internal validity, there was no attempt to blind those measuring the main outcomes of the intervention. For external validity, all studies lacked generalizability that it was difficult to determine if the participants were representative of the entire population from which they were recruited. All studies also lacked a sample size determination and had no power calculation for the primary outcome.

Summary of Findings

The summary of results of the two included studies is presented in Appendix 4.

A. Low back Pain:
In the double-blind RCT by Kim et al., 2010,[16] there were no differences between dextrose prolotherapy injection and steroid injection after two weeks of treatment for pain improvement (78% vs. 71%) and disability improvement (68% vs. 59%). However, at 6 months after

treatment, 64% of patients in the dextrose group maintained a positive response compared to 27% in the steroid group (*P*<0.01); and after 15 months, 59% of patients in the dextrose group maintained a positive response compared to 10% in the steroid group (*P*<0.01). It was concluded that "*intra-articular prolotherapy provided significant relief of sacroiliac joint pain, and its effects lasted longer than those of steroid injections*." Limitations of this study included small sample size, no ITT analysis, non-validated instruments with unknown MCID, and more frequent injection of dextrose than steroid (2.7 versus 1.5) to achieve pain relief of ≥90% from baseline.

In the prospective case series by Cusi et al., 2010,[22] prolotherapy of dextrose in combination with exercise significantly improved clinical examination scores (*P*<0.001) and functional questionnaire scores including Quebec pain disability scores (*P*<0.001 at 3 months, *P*<0.002 at 12 months and *P*<0.006 at 24 months), Roland-Morris back pain questionnaire scores (*P*=0.001 at 3 months, *P*<0.047 at 12 months and *P*<0.035 at 24 months), and Roland-Morris 24 multiform questionnaire scores (*P*=0.001 at 3 months, *P*<0.016 at 12 months and *P*=0.012 at 24 months). Not all patients attended each follow-up visit. It was concluded that "*the use of prolotherapy in combination with a specific exercise programme in private practice has shown improvement in clinical outcome scores for all the patients who attended follow-up visits*." Limitations of this study included small sample size, lack of control group and risk of selection and assessment biases.

In the retrospective case series by Watson et al., 2010,[24] patients received a mean of 10.3 ± 9.6 dextrose prolotherapy treatments. Of 190 patients, 140 had one year or more follow-up with data analysis. The results showed that both pain and quality of life scores were significantly improved at least one year after prolotherapy treatment (*P*<0.05). It was concluded that "*prolotherapy can be an effective treatment for low back pain from presumed ligamentous dysfunction for some patients when performed by a skilled practitioner*." The limitations of this study included the use of non-validated outcome measures, lack of control, high rate of withdrawals (26%), retrospective design, and risk of selection bias. The most common reasons for discontinuation of treatment included a plateau in progress, lack of response to treatment, and financial considerations.

In summary, evidence from RCTs and case series with several limitations suggested that dextrose prolotherapy treatment of low back pain might provide significant pain relief, which lasted longer than corticosteroid treatment.

B. Tendinopathy:

In the systematic review by Rabago et al., 2009,[9] the results from one RCT showed that prolotherapy with dextrose-morrhuate injections significantly improved pain at 16 weeks compared with saline injection (90% versus 20%, *P*<0.001). In another RCT, the improvement in the disease specific questionnaire at 9 weeks was numerically higher with dextrose-lidocaine prolotherapy compared with saline injection (66% versus 11.5%, *P*=0.09). In a case series, prolotherapy with dextrose-lidocaine showed significant pain improvement at mean 19 months compared to baseline (*P*<0.05). It was concluded that "*there is strong pilot level evidence supporting the use of prolotherapy in the treatment of lateral epicondylosis*." One of the limitations of this systematic review was that meta-analysis was not conducted due to substantial heterogeneity of the included studies. Of the included studies, there were only three studies on dextrose prolotherapy, with small sample size, published before 2009.

The results from the single-blinded RCT by Rabago et al., 2013[12] showed that both prolotherapy treatment using either dextrose or dextrose-morrhuate significantly improved the composite

scores of PRTEE (Patient-Rated Tennis Elbow Evaluation) compared to baseline at 16 weeks (*P*<0.05) in patients with lateral epicodylosis. The improvement exceeded the MCID for PRTEE and was greater than the waitlist control (41.1% vs. 53.3% vs 18.3% for dextrose vs dextrose-morrhuate vs. waitlist). The improvement was maintained up to 32 weeks (57.1% vs. 74.9% for dextrose vs dextrose-morrhuate). Similar results were obtained for subscales of pain and function. There were no significant differences between dextrose and dextrose-morrhuate. Satisfaction was high at both 16 weeks (75% in dextrose and 78% in dextrose-morrhuate) and 32 weeks (75% in dextrose and 89% in dextrose-morrhuate). It was concluded that "*prolotherapy resulted in safe, significant improvement of elbow pain and function compared to baseline status and wait-and-see control*." Limitations of this study included small sample size and short term follow-up. There was a risk of placebo effect due to lack of injection control, and performance and detection biases because the injector and assessor were not blinded.

In the double-blinded RCT by Carayannopoulos et al., 2011,[14] 17 out of 24 patients with lateral epicondylosis remained at 6-month follow-up (8 in the dextrose group and 9 in the corticosteroid group). There were no significant differences in the amount of change between dextrose prolotherapy and corticosteroid treatment for lateral epicondylosis at 3 or 6 months with any of the three scales (VAS, QVAS and DASH). There was also no significant change in grip strength within or between groups. It was concluded that "*prolotherapy may be a useful alternative to corticosteroid injection, and may provide a basis for undertaking larger, more definitive studies."* Limitations of this study included small sample size, high dropout rate, lack of power to detect a significant difference, short term follow-up and lack of placebo injection.

In the single-blinded RCT by Yelland et al., 2011,[15] all three groups (dextrose-lignocaine, eccentric loading exercise, and combination of dextrose and exercise) of patients with Achilles tendinosis showed significant improvements in VISA-A scores at all times (up to 12 months) compared to baseline (P<0.0005); the exercise group had slightly lower scores, but not a statistically significant difference compared to the other groups. Similar results were obtained for pain, stiffness, limitation activities, satisfaction ratings, and PGIC (Patient Global Impression of Change) ratings. Overall, there were no significant differences between groups or between groups over time for these outcomes. It was concluded that, "*for achilles tendinosis, prolotherapy and particularly eccentric loading exercise (ELE) combined with prolotherapy give more rapid improvements in symptoms than ELE alone but long-term VISA-A scores are similar*." Limitations of this study included small sample size, no sample size determination and no placebo control. There was risk of attention bias due to the open-label design for patients and doctors who performed injection.

In the prospective case series by Ryan et al., 2010,[23] data from 69 out of 99 patients with chronic insertional and midportion Achilles tendinosis were included in the final follow-up. There were significant improvements in pain scores for both the insertional (*P*<0.05) and midportion (*P*<0.001) of the Achilles tendon from baseline to follow-up for all VAS items (i.e., at rest, daily activity, and sport) for both short- and long-term (28.6 months) follow-up. Improvements in pain correlated with improvements in the size and severity of regions detected by sonographic examination. It was concluded that "*dextrose injections appear to present a low-cost and safe treatment alternative with good-long-term evidence for reducing pain from pathology at either the insertion or midportion of the Achilles tendon*." Limitations of this study included a lack of control group, no blinding, loss to follow-up (30%), no validation of the clinical outcome measures, and risk of selection and assessment biases.

The prospective case series by Ryan et al., 2011[21] showed that dextrose prolotherapy injection for treatment of patellar tendinopathy significantly improved VAS scores for pain (at rest, daily living and sport) at 45-week follow-up (*P*<0.001). VAS pain scores correlated with changes to echotexture severity. It was concluded that "*ultrasound-guided prolotherapy injections resulted in significant and clinically meaningful reductions in pain in patients with patellar tendinopathy. Tendon structure also improved substantially following injections; changes in hypoechoic severity were significantly correlated with pain outcomes."* Limitations of this study included a small sample size (n=47), lack of control group, lack of blinding of the radiologist, no reporting on losses to follow-up, lack of validation of the clinical outcome measures, short term follow-up, and the risk of selection and assessment biases.

In summary, evidence from poor quality studies with multiple limitations suggests that dextrose prolotherapy might provide improvement in pain caused by tendinopathy including lateral epicondylosis, Achilles tendinosis and patellar tendinopathy.

C. Osteoarthritis:

In the double-blinded RCT by Jahangiri et al., 2014,[10] dextrose prolotherapy for treatment of osteoarthritis in the first carpometacarpal joint led to a significant improvement in change in mean VAS for severity of pain on pressure compared to corticosteroid at month 6 (*P*=0.001). Dextrose also resulted in a significant improvement in pain on movement (*P*=0.02) and hand function (*P*=0.01) compared with corticosteroid at month 6, but not at the first two months after injection. It was concluded that "*for the long term, dextrose seems to be more advantageous"* compared to corticosteroid. Limitations of this study included small sample size, lack of control injection, and short-term follow-up. Of note, patients in corticosteroid group got their treatment only in the 3rd session (3rd month) [the first two sessions were saline placebo injections], while those in dextrose group received three doses of dextrose monthly. Therefore, during the first two months, dextrose was actually compared with saline and there were no differences in pain or function scores between dextrose and placebo injections.

In the double-blinded RCT by Rabago et al., 2013,[11] dextrose injection resulted in significant improvement (*P*<0.05) in knee-related quality of life (WOMAC) including pain, stiffness and functional subscales compared to saline injection or exercise at all-time points of follow-up (9 through 52 weeks). Knee pain scale (KPS) pain frequency scores (9 through 52 weeks, *P*<0.05) and KPS pain severity score (24 through 52 weeks, *P*<0.05) were statistically significantly reduced in dextrose group compared with saline and exercise groups. It was concluded that "*prolotherapy resulted in clinically meaningful sustained improvement of pain, function, and stiffness scores for knee osteoarthritis compared with blinded saline injections and at-home exercises*." Limitations of this study included a small sample size in each group, and limited generalizability due to numerous exclusion criteria.

In the open-labeled cross-over RCT by Dumais et al., 2012,[13] dextrose prolotherapy alone given to patients with knee osteoarthritis showed significant improvement (*P*=0.002) in WOMAC scores compared to exercise alone during the first 16 weeks. All secondary outcomes (brief pain inventory, Wong-Baker rating scale, simple descriptive intensity scale, combined pain score, time Up-and-Go test and Kellgren-Lawrence grading scale) also improved statistically significantly in the dextrose prolotherapy group during the first 16 weeks. During the second phase of the study, the WOMAC scores improved in the patients in the exercise group who received dextrose prolotherapy. It was concluded that "*the use of regenerative injection therapy is associated with a marked reduction in symptoms, which was sustained for over 24 weeks*." Limitations of this study included small sample size, no ITT analysis, lack of sufficient power for

secondary outcomes, no saline injection control, and lack of generalizability as the study had relatively younger, heavier, and more male patients with higher severity of knee osteoarthritis than in other clinical practices.

In the retrospective case series by Hauser et al., 2014,[17] patients with knee osteoarthritis (chondromalacia patella) receiving dextrose-morrhuate prolotherapy had statistically significant decreases in pain at rest, during daily activities, and exercise compared to baseline (P<0.0001). Range of motion, stiffness and crepitus also significantly decreased (P<0.0001). Sustained improvement of over 75% was reported in 85% of patients. The requirement of pain medication was reduced after prolotherapy. It was concluded that "*prolotherapy in the treatment of chondromalecia patella is associated with substantial gains in pain relief and functionality*." The limitations of this study included small sample size, unclear validation of the instruments used to measure pain and disability, and risk of self-reporting and selection biases.

In the case series by Rabago et al., 2014,[18] patients with knee osteoarthritis of different characteristics (prior-control, prior-decline, prior-ineligible) recruited from a previous RCT reported statistically significant improvement in WOMAC and KPS scores after receiving dextrose-morrhuate prolotherapy (P≤0.05). Patients reported consistent improvement across WOMAC subscales, which were achieved near maximum by weeks 24 and remained through 52 weeks. It was concluded that "*prolotherapy with dextrose and morrhuate sodium resulted in substantial, significant, and sustained improvement on validates pain, function, and stiffness measures in participants with mild-to-moderate knee osteoarthritis compared to baseline status."* Limitations of this study included small sample size, lack of comparison group, and the risk of bias from recruiting patients previously involved in a prolotherapy study.

In the prospective case series by Rabago et al., 2012,[19] patients with knee osteoarthritis receiving dextrose prolotherapy had improved WOMAC scores 4 weeks after first injection (7.6 ± 2.4 points; 17.2%) and continued to improve through 52-weeks of follow-up (15.9 ± 2.5 points, P<0.001, 36.1%). KSP scores also improved in both injected knees (P<0.001) and uninjected knees (P<0.05). It was concluded that "*prolotherapy resulted in safe, significant, and sustained improvement on validated pain, function, and stiffness measures in participants with knee osteoarthritis."* Limitations of this study included small sample size, lack of comparison group, and risk of assessment and selection bias.

In the retrospective case series by Schaumburger et al., 2012,[20] patients with knee arthritis of different etiology who had received morrhuate prolotherapy had significant improvement in pain score at final follow-up (before: 6.9 ± 3.2 versus after: 3.7 ± 0.57, P<0.05). Activity level improved in 62% of patients. 57% of patients reached excellent or good results in the Lysholm and Gillquist score for knee function. 92% of patients had improved Knee Injury and Osteoarthritis score after treatment with morrhuate. It was concluded that "*the intra-articular application of sodium morrhuate is an effective and safe measure in the treatment of recurrent symptomatic knee joint effusions in young patients suffering from recurrent knee joint effusions."* Limitations of this study included high rate of dropout (22.3%), lack of control group, moderate improvement, no validation of the clinical outcome measures, and risk of selection bias.

In summary, evidence from limited quality studies suggests that dextrose, dextrose-morrhuate or morrhuate prolotherapy for treatment of knee osteoarthritis might improve in pain and function of the knee. The benefit of dextrose prolotherapy for treatment of hand osteoarthritis was unclear.

Limitations

Generally, most studies, including RCTs and case series, had several limitations including small sample size, lack of validation of the clinical outcome measures (with unclear MCIDs), and short-term follow-up. All the observational studies were either prospective case series or retrospective case series, which lack a control group, making it difficult to attribute improvements to the treatment rather than other factors. There was high risk of assessment and selection biases in many studies as injectors and assessors were not blinded and loss of follow-up was high or not reported. Patients might receive special attention with prolotherapy treatment in a trial setting which may not be reflective of real world practice, and some patients were recruited from previous prolotherapy studies that may have introduced bias in either direction depending on the experience of the patients.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

In this review, 16 studies involving prolotherapy using dextrose, dextrose-morrhuate or morrhuate for the treatment of low back pain, tendinopathy and osteoarthritis were identified. Evidence was from one systematic review, seven RCTs, and eight case series (prospective and retrospective). The number of injections, concentrations of injectant, mixtures and procedures varied markedly between studies. Most studies showed that prolotherapy significantly improved pain and physical function over various times of follow-up compared with saline injection control, exercise alone or before treatment. However, the results should be interpreted with caution due to several limitations of the included studies. The benefit of prolotherapy over corticosteroid injection remains unclear. Well-controlled studies with large sample size, long-term follow-up, optimized technique and procedure, and validated outcome measures are still needed.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

REFERENCES

1. Rabago D, Slattengren A, Zgierska A. Prolotherapy in primary care practice. Prim Care [Internet]. 2010 Mar [cited 2014 Oct 6];37(1):65-80. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2831229

2. McGee R, Bevan S, Quadrello T. Fit for Work? Musculoskeletal Disorders and the Canadian labour market [Internet]. London: The Work Foundation; 2009 May. [cited 2014 Oct 24]. Available from: http://www.conferenceboard.ca/Libraries/NETWORK_PUBLIC/CCDPM_report2_jul2011.sflb

3. Hauser RA, Hauser MA, Baird NM. Evidence-based use of dextrose prolotherapy for musculoskeletal pain: a scientific literature review. Journal of Prolotherapy [Internet]. 2011 Dec [cited 2014 Oct 24];3(4):765-89. Available from: http://www.journalofprolotherapy.com/pdfs/issue_12/issue_12_03_evidence_based_prolo.pdf

4. Distel LM, Best TM. Prolotherapy: a clinical review of its role in treating chronic musculoskeletal pain. Pm r. 2011 Jun;3(6 Suppl 1):S78-S81.

5. Zhou H, Hu K, Ding Y. Modified dextrose prolotherapy for recurrent temporomandibular joint dislocation. Br J Oral Maxillofac Surg. 2014 Jan;52(1):63-6.

6. Goswami A. Prolotherapy. J Pain Palliat Care Pharmacother. 2012 Dec;26(4):376-8.

7. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007;7:10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf

8. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun;52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf

9. Rabago D, Best TM, Zgierska AE, Zeisig E, Ryan M, Crane D. A systematic review of four injection therapies for lateral epicondylosis: prolotherapy, polidocanol, whole blood and platelet-rich plasma. Br J Sports Med [Internet]. 2009 Jul [cited 2014 Oct 6];43(7):471-81. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2755040

10. Jahangiri A, Moghaddam FR, Najafi S. Hypertonic dextrose versus corticosteroid local injection for the treatment of osteoarthritis in the first carpometacarpal joint: a double-blind randomized clinical trial. J Orthop Sci. 2014 Sep;19(5):737-43.

11. Rabago D, Patterson JJ, Mundt M, Kijowski R, Grettie J, Segal NA, et al. Dextrose prolotherapy for knee osteoarthritis: a randomized controlled trial. Ann Fam Med [Internet]. 2013 May [cited 2014 Oct 6];11(3):229-37. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3659139

12. Rabago D, Lee KS, Ryan M, Chourasia AO, Sesto ME, Zgierska A, et al. Hypertonic dextrose and morrhuate sodium injections (prolotherapy) for lateral epicondylosis (tennis elbow): results of a single-blind, pilot-level, randomized controlled trial. Am J Phys Med Rehabil [Internet]. 2013 Jul [cited 2014 Oct 8];92(7):587-96. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3700532

13. Dumais R, Benoit C, Dumais A, Babin L, Bordage R, de Arcos C, et al. Effect of regenerative injection therapy on function and pain in patients with knee osteoarthritis: a randomized crossover study. Pain Med. 2012 Aug;13(8):990-9.

14. Carayannopoulos A, Borg-Stein J, Sokolof J, Meleger A, Rosenberg D. Prolotherapy versus corticosteroid injections for the treatment of lateral epicondylosis: a randomized controlled trial. Pm r. 2011 Aug;3(8):706-15.

15. Yelland MJ, Sweeting KR, Lyftogt JA, Ng SK, Scuffham PA, Evans KA. Prolotherapy injections and eccentric loading exercises for painful Achilles tendinosis: a randomised trial. Br J Sports Med. 2011 Apr;45(5):421-8.

16. Kim WM, Lee HG, Jeong CW, Kim CM, Yoon MH. A randomized controlled trial of intra-articular prolotherapy versus steroid injection for sacroiliac joint pain. J Altern Complement Med. 2010 Dec;16(12):1285-90.

17. Hauser RA, Sprague IS. Outcomes of prolotherapy in chondromalacia patella patients: improvements in pain level and function. Clin Med Insights Arthritis Musculoskelet Disord [Internet]. 2014 [cited 2014 Oct 6];7:13-20. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3937178

18. Rabago D, Patterson JJ, Mundt M, Zgierska A, Fortney L, Grettie J, et al. Dextrose and morrhuate sodium injections (prolotherapy) for knee osteoarthritis: a prospective open-label trial. J Altern Complement Med. 2014 May;20(5):383-91.

19. Rabago D, Zgierska A, Fortney L, Kijowski R, Mundt M, Ryan M, et al. Hypertonic dextrose injections (prolotherapy) for knee osteoarthritis: results of a single-arm uncontrolled study with 1-year follow-up. J Altern Complement Med [Internet]. 2012 Apr [cited 2014 Oct 8];18(4):408-14. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3326267

20. Schaumburger J, Trum S, Anders S, Beckmann J, Winkler S, Springorum HR, et al. Chemical synovectomy with sodium morrhuate in the treatment of symptomatic recurrent knee joint effusion. Rheumatol Int. 2012 Oct;32(10):3113-7.

21. Ryan M, Wong A, Rabago D, Lee K, Taunton J. Ultrasound-guided injections of hyperosmolar dextrose for overuse patellar tendinopathy: a pilot study. Br J Sports Med. 2011 Sep;45(12):972-7.

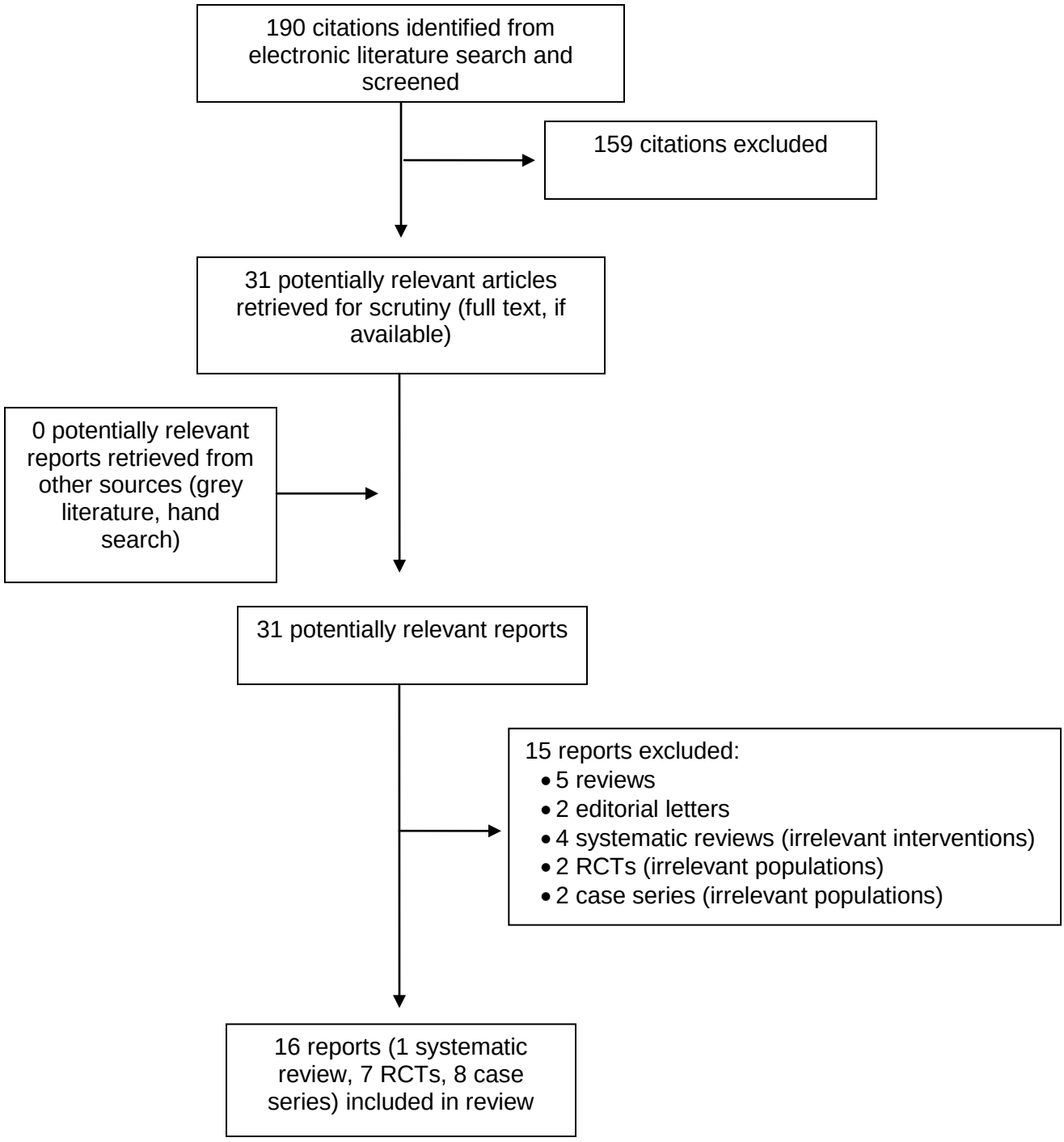
22. Cusi M, Saunders J, Hungerford B, Wisbey-Roth T, Lucas P, Wilson S. The use of prolotherapy in the sacroiliac joint. Br J Sports Med. 2010 Feb;44(2):100-4.

23. Ryan M, Wong A, Taunton J. Favorable outcomes after sonographically guided intratendinous injection of hyperosmolar dextrose for chronic insertional and midportion achilles tendinosis. AJR Am J Roentgenol [Internet]. 2010 Apr [cited 14 A.D. Feb

8];194(4):1047-53. Available from: http://www.ajronline.org/doi/pdfplus/10.2214/AJR.09.3255

24. Watson JD, Shay BL. Treatment of chronic low-back pain: a 1-year or greater follow-up. J Altern Complement Med. 2010 Sep;16(9):951-8.

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Clinical Studies

First Author, Year, Country	Study/Patient Characteristics	Condition / Treatments	Clinical outcomes Measured
Systematic reviews			
Rabago et al., 2009[9] USA, Sweden, Canada	• Two RCTs (N=24, 8) and one prospective case series (N=20) • Adult patients (19-63 years) • Intervention: o RCT1: 0, 4, 8 weeks o RCT2: 0, 3, 6 weeks o Case series: weekly sessions for 8 weeks • Follow-up: o RCT1: 8, 16, 52 weeks o RCT2: 9 weeks o Case series: mean 19 months	Lateral epicondylosis RCT1: • Dextrose + morrhuate vs. saline RCT2: • Dextrose + lidocaine vs. saline Case series: • Dextrose + lidocaine vs. baseline	RCT1: • Resting elbow pain (0 to10 VAS) • Isometric strength • Grip strength • Continuity of improvement at 52 weeks RCT2: • McGill Pain Questionnaire (0 to 45) • Physical composite score of SF-36 Case series: • Elbow pain (0 to10 VAS) • Subject satisfaction (yes/no)
RCTs			
Jahangiri et al., 2014[10] Iran	DB RCT, assessor blinded (N=60) Two parallel groups: • Dextrose (n=30) • Prednisone (n=30) • Inclusion: o Adults (>40 years) with osteoarthritis in the first carpometacarpal joint based on radiographic criteria o Pain persisted at least 3 months • Exclusion: o Fracture or other hand pathologies o Diabetes, blood coagulation disorders, neuropathy, corticosteroid injection at least 3 months, pregnant, or NSAID use • Intervention: injected monthly for 3 months o Prednisone: injected saline for the first 2 months, then prednisone in the 3rd month o Dextrose: three injections given monthly • Follow-up: 0,1, 2, 6 months	Carpometacarpal osteoarthritis Dextrose + lidocaine vs. prednisone + lidocaine	1° outcome: Subjective pain intensity (0 to 9 VAS) 2° outcomes: • Pain on joint movement (0 to 9 VAS) • Hand function (HAQ-DI, 0 to 3 VAS) • Pinching (HAQ-DI, 0 to 3 VAS) Statistics: • Power calculations • No ITT analysis

First Author, Year, Country	Study/Patient Characteristics	Condition / Treatments	Clinical outcomes Measured
Rabago et al., 2013[11] USA	DB RCT (N=90) • Three parallel groups: o Dextrose (n=30) o Saline (n=29) o Exercise (n=31) • Inclusion: o Adults 40-76 years o Knee osteoarthritis within 5 years o Tenderness of 1 or more anterior knee structure o moderate-to-severe knee pain for at least 3 months • Exclusion: o Pregnancy, diabetes, anticoagulation therapy, history of total knee replacement, prior knee prolotherapy, any knee injection within 3 months, inflammatory or post-infectious knee arthritis, daily use of opioid medication, BMI greater than 40 kg/m^2, and severe comorbidity. • Intervention: o Injection: 1, 5, 9 weeks. Additional sessions at 13 and 17 weeks per physician's recommendations and participants' preference. o Exercise: at home according to instructions in pamphlet. Follow-up with telephone calls. • Follow-up: WOMAC and KPS were collected in person and before any procedure at 0, 5, 9, 12 weeks, and by phone at 26 and 52 weeks.	Knee osteoarthritis Dextrose + lidocaine vs. saline vs. home-based exercise	1^o outcome: knee-related quality of life (0 to100 WOMAC; pain, stiffness and functional subscales; MCID 12 points of change on 0 to100 VAS) 2^o outcomes: knee pain scale (KPS: 0 to 4 ordinal scale for knee pain frequency; 0 to 5 ordinal scale for severity); with higher values indicating worse symptoms. 3^o outcomes: • Procedure-related pain (1 to 7 ordinal scale) • Opioid medication use (yes/no) • Treatment satisfaction (yes/no) Statistics: • Power calculations • ITT analysis
Rabago et al., 2013[12] USA	SB RCT (N=31) Three parallel groups: blinded prolotherapy • Dextrose (n=8; 10 elbows) • Dextrose + morrhuate (n=9; 10 elbows) • Waitlist (n=10; 12 elbows) • Inclusion: o Adults (18 to 65 years)	Lateral epicondylosis Dextrose vs. dextrose + morrhuate vs. waitlist control	1^o outcome: • Composite score on the Patient-Rated Tennis Elbow Evaluation, PRTEE (0-100); subscales pain (5 items), function (10 items) • MCID for PRTEE was

First Author, Year, Country	Study/Patient Characteristics	Condition / Treatments	Clinical outcomes Measured
	with elbow pain for at least 3 months from lateral epicondyle o Failed at least one of the three most common treatments (NSAIDs, physician initiated therapy or corticosteroid injection) • Exclusion: o Prior elbow prolotherapy o Other elbow injection-based therapies in the last 3 months o Other concurrent extremity pathology o Prior extremity surgery o Pregnancy o Comorbidity precluding participation o Bleeding disorders o Use of chronic opioid, anticoagulant or immunosuppressive medication • Intervention: o Injection: 1, 4, 8 weeks • Follow-up: o Week 4, 8, 16 for all three groups o Week 32 for prolotherapy only		11-point or 37% improvement from baseline 2° outcomes: MRI and ultrasound assessment 3° outcomes: Satisfaction rating (0 to 5) Statistics: • Power calculations • ITT analysis • LOCF was used for missing data
Dumais et al., 2012[13] Canada	OL RCT, crossover (N=45) Two groups: • Group A (n=21): received dextrose injection on weeks 0, 4, 8, 12 and in combination with home-based exercise for 32 weeks • Group B (n=24): received home-based exercise for 32 weeks in combination with dextrose injection on weeks 20, 24, 28 and 32. • Inclusion: o Adults (≥18 years) with knee osteoarthritis) o Pain in the knee for ≥6 months • Exclusion: o Previous operation on the referring knee o Infection of the skin	Knee osteoarthritis Dextrose + lidocaine vs. home-based exercise	1° outcome: knee-related quality of life (0 to100 WOMAC; pain, stiffness and functional subscales; MCID 12 points of change on 0 to100 VAS) 2° outcomes: • Brief Pain Inventory (0 to 10) • Wong-Baker Rating Scale (0 to 5) • Simple descriptive intensity scale (0 to 10) • Combined pain score • The time Up-and-Go Test (evaluate functional capacity) • Kellgren-Lawrence grading scale (severity of knee osteoarthritis)

First Author, Year, Country	Study/Patient Characteristics	Condition / Treatments	Clinical outcomes Measured
	surrounding the knee or of the articulation o Abnormal coagulation o Pregnancy or breast-feeding • Intervention: o Injection given on weeks 0, 4, 8, and 12 for group A and on weeks 20, 24, 28 and 32 for group B • Follow-up: every 4 weeks up to week 36.		Statistics: Power calculations No ITT analysis
Carayannopuolos et al., 2011[14] USA	DB RCT (N=24) Two groups: • Dextrose (n=11) • Corticosteroid (n=13) • Inclusion: o Adults (18 to 75 years) with elbow pain (3 months to 2 years) in the region of lateral epicondyle • Exclusion: o Steroid injections within 6 months before study o Other arm/forearm pathology o Use of narcotic for pain management for more than 1 month o Previous prolotherapy • Intervention: two injections, 1 month apart • Follow-up: 0, 1, 3 months in office; 6 months by phone	Lateral epicondylosis Dextrose + morrhuate + procaine vs. methylprednisolone	1° outcome: Pain severity (0 to 10 VAS) 2° outcomes: Quadruple visual analog scale (0 to 10 QVAS) Disability of the Arm, Shoulder, and Hand (0 to 5 DASH) Statistics: • Exploratory analysis, since recruitment did not meet sample size calculations • No ITT analysis
Yelland et al., 2011[15] Australia	SB RCT (N=43) Three groups: • Dextrose (n=14) • Exercise (n=15) • Combination (n=14) • Inclusion: o Adults (40 to 58 years) with painful Achilles tendinosis • Exclusion: o Previous steroid or prolotherapy injections o Surgery to the affected tendon • Intervention: o Prolotherapy: injection weekly for four to 12 treatments	Achilles tendinosis Dextrose + lignocaine/ropivacaine vs. exercise vs. combination	1° outcome: VISA-A questionnaire (0 to 100); MCID = 20; fully recovered as attaining a score of ≥90. 2° outcomes: • Treatment satisfaction (Likert scales 0 to 7) • Patient Global Impression of Change (PGIC) scale (0 to 10); MCID 1.75 for pain, 1.75 for stiffness, 2.0 for limitation of activities. Statistics:

First Author, Year, Country	Study/Patient Characteristics	Condition / Treatments	Clinical outcomes Measured
	○ Exercise: Instructed by doctor or podiatrist. Performed twice daily in three sets of 15 repetitions with the knee straight and three sets of 15 repetitions with the knee bent for a period of 12 weeks. • Follow-up: 0, 6 weeks, 3 months, 6 months, 12months.		• ITT analysis • No power calculations • Assessor blinded only • LOCF for missing data
Kim et al., 2010[16] South Korea	DB RCT (N=50) Two groups: • Dextrose (n=24) • Steroid (N=26) • Inclusion: ○ Adults (mean age 42 years) with sacroiliac joint pain ○ Failed medical treatment for 1 month • Exclusion: ○ Cancer, fractures, inflammatory arthritis, infection, fibromyalgia, and pregnancy • Intervention: Max 3 injections: 0, 2, 4 weeks • Follow-up: 0, 2 weeks, and monthly after completion of treatment	Low-back pain Dextrose + levobupivacaine vs. steroid (triamcinolone acetonide)	Pain score (0 to 10) and disability score (Oswestry disability index, 0 to 100%) <u>Main outcome</u>: cumulative incidence of sustained pain relief, defined as maintenance of a 50% or more improvement in the numeric rating scale from baseline, without analgesic medication, at the monthly follow-up session <u>Statistics</u>: Power calculations No ITT analysis
Observational studies			
Hauser et al., 2014[17] USA	Retrospective case series (N=61; 69 knees) • Inclusion: ○ Adults (18 to 82 years) with chondromalacia patella, pain at least 3 months ○ Completion of prolotherapy injections (24 to 40 injections per treated knee per session) ○ No NSAID use, no corticosteroid injections, no physical therapy ○ Completion of follow-up visits ○ Completion of questionnaire • Exclusion: ○ Other conditions affected	Chondromalacia patella Dextrose + procaine + sarapin	• Pain level (0 to 10 VAS) • Function level (levels of stiffness and crepitus; 0 to 10 VAS) • Pain medication before and after prolotherapy <u>Statistics</u>: Level of significant set at $p<0.0001$

First Author, Year, Country	Study/Patient Characteristics	Condition / Treatments	Clinical outcomes Measured
	patellar or knee • Intervention: treatment intervals every 4 to 6 weeks • Follow-up: by phone calls (first day, 1 month, 3 months)		
Rabago et al., 2014[18] USA	Case series (N = 38) • Inclusion: o Cohort consisted of patients from previous RCT (prior-decline (n=5); prior-control (n=18); prior ineligible (n=15) o Prior-decline = severe patients • Intervention: injection sessions at 1, 5, and 9 weeks with as needed treatment at weeks 13 and 17. • Follow-up: 1 year	Knee osteoarthritis Dextrose + morrhuate + lidocaine	1° outcome: knee-related quality of life (0 to100 WOMAC; pain, stiffness and functional subscales; MCID 12 points of change on 0 to100 VAS) 2° outcomes: knee pain scale (KPS: 0 to 4 ordinal scale for knee pain frequency; 0 to 5 ordinal scale for severity); with higher values indicating worse symptoms. 3° outcomes: • Procedure-related pain (1 to 7 ordinal scale) • Opioid medication use (yes/no) • Treatment satisfaction (yes/no) Statistics: ITT analysis
Rabago et al., 2012[19] USA	Case series (N=36) • Inclusion: o Adults (40 to 76 years) with at least 3 months of knee osteoarthritis • Exclusion: o Significant co-morbidity o Knee replacement o Prolotherapy or other knee injection o Daily use of opioid medication o Inflammatory or post-infectious knee arthritis • Intervention: injections at 1, 5, and 9 weeks post-entry • Follow-up: 0, 5, 9, 12, 24, and 52 weeks	Knee osteoarthritis Dextrose + lidocaine	1° outcome: knee-related quality of life (0 to100 WOMAC; pain, stiffness and functional subscales; MCID 12 points of change on 0 to100 VAS) 2° outcomes: knee pain scale (KPS: 0 to 4 ordinal scale for knee pain frequency; 0 to 5 ordinal scale for severity); with higher values indicating worse symptoms. 3° outcomes: • Procedure-related pain (1 to 7 ordinal scale) • Opioid medication use (yes/no) • Treatment satisfaction

First Author, Year, Country	Study/Patient Characteristics	Condition / Treatments	Clinical outcomes Measured
			(yes/no) Statistics: No ITT analysis
Schaumburger et al., 2012[20] Germany	Retrospective case series (N=92 patients) • Inclusion: o Adults (18 to 76 years) with knee arthritis of heterogeneous etiology • Mean follow-up: 29.8 months • 2 died, 27 (22.3%) lost to follow-up	Knee arthritis (recurrent knee joint effusion) Morrhuate + mepivacaine + triamcinolone	• Pain score (0 to 10 VAS) • Knee Injury and Osteoarthritis Outcome Score (KOOS) • Lysholm and Gillquist score Statistics: Level of significant set at $p<0.05$
Ryan et al., 2011[21] USA, Canada	Case series (N=47) • Inclusion: o Adults (mean age 38.3 years) who failed conservative treatment o Symptom duration: 21.8 ± 16.6 months • Intervention: 2 to 8 injections • Follow-up: every 6 weeks up to 45 weeks post-treatment initiation	Patellar tendinopathy Dextrose + lidocaine	• Pain score (VAS) • Ultrasound-based outcomes Statistics: Level of significant set at $p<0.05$
Cusi et al., 2010[22] Australia	Case series (N=25) • Inclusion: o Adults (26 to 67 years) with localized and/or radiating low back or buttock pain o Symptoms persisted for at least 6 months • Exclusion: o Acute radiculopathy, infection, pregnancy, inflammatory conditions, and malignancy • Intervention: 3 injections, 6 weeks apart • Follow-up: 0, 3, 12, 24 months	Low-back Pain Dextrose + bupivicaine	• Clinical examination scores (0 to 9) • Functional questionnaire scores o Quebec Back Pain Disability Scale o Roland-Morris Back Pain Questionnaire o Roland-Morris 24 Multiform Questionnaire Statistics: Level of significant set at $p<0.05$
Ryan et al., 2010[23] Canada	Case series (N=99 patients, 108 tendons) • Inclusion: o Adults (mean age 54 years) experiencing pain for greater than 6 months at either Achilles tendon insertion or midportion	Achilles tendinosis Dextrose + lignocaine	• Pain score (0 to 100 VAS); at rest, daily activity and sport • Sonography examination Statistics: Level of significant set at

First Author, Year, Country	Study/Patient Characteristics	Condition / Treatments	Clinical outcomes Measured
	• Intervention: median 5 (1 to 13) injection consultations spaced 5.6 ± 3.1 weeks apart • Follow-up: o Pretest to posttest: 28 weeks (range 5 to 73 weeks) o Long term (telephone interview): 12 to 48 months		$p<0.05$
Watson et al., 2010[24] Canada	Retrospective Case series (N=190) • Inclusion: o Adults (mean age 48 years) with low-back pain of at least 3 months o Failed to respond standard treatments o Only charts of patients who reported a decrease in their pain following the lidocaine injection were included • Exclusion: • Pregnancy, surgical causes of low-back pain • Intervention: number of injections and injection sites varied among patients • Follow-up: 1 year or more	Low-back pain Dextrose + lidocaine	• 1° outcome: Pain score (0 to 10 VAS) • 2° outcome: QoL (0 to 10 VAS) Statistics: Level of significant set at $p\leq0.05$

DB = double-blinded; FFI = foot function index; HAQ-DI = heath assessment questionnaire disability index; ITT = intention-to-treat; KPS = knee pain scale; LOCF = last observation carried forward; MCID = minimal clinically important difference; NR = not reported; OL = open-labelled; PGIC = Patient Global Impression of Change; PRTEE = Patient-Rated Tennis Elbow Evaluation; RCT = randomized controlled trial; SB = single-blinded; VAS = visual analog scale; WOMAC = Western Ontario McMaster University Osteoarthritis Index

APPENDIX 3: Critical Appraisal of Clinical Studies

Author, year	Strengths	Limitations
Systematic review		
Rabago et al., 2009[9]	• There was duplicate study selection and data extraction. • A comprehensive literature search was performed. • Lists of included (not excluded, but rather described) studies were provided. • The characteristics of the included studies were provided. • The scientific quality of the included studies was assessed and documented. • The scientific quality of the included studies was used appropriately in formulating conclusions. • The conflict of interest was included.	• It was unclear if the research question and inclusion criteria had been established before the conduct of the review. • It was unclear if grey literature was included in the literature search.
RCT		
Jahangiri et al., 2014[10] DB RCT	*Reporting* • The objective was clearly described • The main outcome measures were clearly described • The baseline characteristics of the patients included in the study were clearly described • The main findings of the study were clearly described • The study provided estimates of the random variability in the data for the main outcomes (standard deviation and confidence intervals) • Adverse events were reported • Actual probability values were reported *External validity* • Participants asked to participate in the study were representative of the entire population from which they were recruited • The staff, places and facilities where the patients were treated, were representative of the treatment majority of patients received *Internal validity - bias* • Follow-up was the same for all participants • Patients and physician were blinded (double-blinded) • Statistical tests used to assess the main outcome were appropriate	*Reporting* • List of principle confounders was not provided *External validity* • Unable to determine if the participants were representative of the entire population from which they were recruited *Internal validity - bias* • Unable to determine if the main outcome measures used were accurate (valid and reliable) *Internal validity – confounding (selection bias* • Unable to determine if there was adequate adjustment for confounding in the analyses from which the main findings were drawn (no ITT) • Unable to determine if losses of patients to follow-up were taken into account

Author, year	Strengths	Limitations
	Internal validity – confounding (selection bias • The patients in different intervention groups were recruited from the same population • The patients in different intervention groups were recruited over the same period of time • Patients were randomized to the intervention groups • The randomized intervention assignment was concealed from both patients and health care staff until recruitment was complete and irrevocable *Power* • The study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%	
Rabago et al., 2013[11] DB RCT	*Reporting* • The objective was clearly described • The main outcome measures were clearly described • The baseline characteristics of the patients included in the study were clearly described • The main findings of the study were clearly described • The study provided estimates of the random variability in the data for the main outcomes (standard deviation) • Adverse events were reported • Actual probability values were reported *External validity* • Participants asked to participate in the study were representative of the entire population from which they were recruited • The staff, places and facilities where the patients were treated, were representative of the treatment majority of patients received *Internal validity - bias* • Follow-up was the same for all participants • Patients and physician were blinded (double-blinded) • Statistical tests used to assess the main outcome were appropriate • The main outcome measures used	*Reporting* • List of principle confounders was not provided *External validity* • Unable to determine if the participants were representative of the entire population from which they were recruited *Internal validity – confounding (selection bias* • Unable to determine if the randomized intervention assignment was concealed from both patients and health care staff until recruitment was complete and irrevocable

Author, year	Strengths	Limitations
	were accurate (valid and reliable) *Internal validity – confounding (selection bias* • The patients in different intervention groups were recruited from the same population • The patients in different intervention groups were recruited over the same period of time • Patients were randomized to the intervention groups • There was adequate adjustment for confounding in the analyses from which the main findings were drawn (ITT) • Losses of patients to follow-up were taken into account *Power* • The study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%	
Rabago et al., 2013[12] SB RCT	*Reporting* • The objective was clearly described • The main outcome measures were clearly described • The baseline characteristics of the patients included in the study were clearly described • The main findings of the study were clearly described • The study provided estimates of the random variability in the data for the main outcomes (standard deviation) • Adverse events were reported • Actual probability values were reported *External validity* • Participants asked to participate in the study were representative of the entire population from which they were recruited • The staff, places and facilities where the patients were treated, were representative of the treatment majority of patients received *Internal validity - bias* • Follow-up was the same for all participants • Statistical tests used to assess the main outcome were appropriate • The main outcome measures used	*Reporting* • List of principle confounders was not provided *External validity* • Unable to determine if the participants were representative of the entire population from which they were recruited *Internal validity - bias* • Injector and assessor were not blinded (patients blinded only) *Internal validity – confounding (selection bias* • Unable to determine if the randomized intervention assignment was concealed from both patients and health care staff until recruitment was complete and irrevocable

Author, year	Strengths	Limitations
	were accurate (valid and reliable) *Internal validity – confounding (selection bias* • The patients in different intervention groups were recruited from the same population • The patients in different intervention groups were recruited over the same period of time • Patients were randomized to the intervention groups • There was adequate adjustment for confounding in the analyses from which the main findings were drawn (ITT) • Losses of patients to follow-up were taken into account *Power* • The study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%	
Dumais et al., 2012[13] OL RCT	*Reporting* • The objective was clearly described • The main outcome measures were clearly described • The baseline characteristics of the patients included in the study were clearly described • The main findings of the study were clearly described • The study provided estimates of the random variability in the data for the main outcomes (standard deviation and confidence intervals) • Adverse events were reported • Actual probability values were reported *External validity* • Participants asked to participate in the study were representative of the entire population from which they were recruited • The staff, places and facilities where the patients were treated, were representative of the treatment majority of patients received *Internal validity - bias* • Follow-up was the same for all participants • Statistical tests used to assess the main outcome were appropriate	*Reporting* • List of principle confounders was not provided *External validity* • Unable to determine if the participants were representative of the entire population from which they were recruited *Internal validity - bias* • Patients and physician were not blinded (open-labeled) *Internal validity – confounding (selection bias* • Unable to determine if there was adequate adjustment for confounding in the analyses from which the main findings were drawn (no ITT) • Unable to determine if losses of patients to follow-up were taken into account

Author, year	Strengths	Limitations
	• The main outcome measures used were accurate (valid and reliable) *Internal validity – confounding (selection bias* • The patients in different intervention groups were recruited from the same population • The patients in different intervention groups were recruited over the same period of time • Patients were randomized to the intervention groups • The randomized intervention assignment was concealed from both patients and health care staff until recruitment was complete and irrevocable *Power* • The study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%	
Carayannopuolos et al., 2011[14] USA DB RCT	*Reporting* • The objective was clearly described • The main outcome measures were clearly described • The baseline characteristics of the patients included in the study were clearly described • The main findings of the study were clearly described • The study provided estimates of the random variability in the data for the main outcomes (standard deviation) • Adverse events were reported • Actual probability values were reported *External validity* • Participants asked to participate in the study were representative of the entire population from which they were recruited • The staff, places and facilities where the patients were treated, were representative of the treatment majority of patients received *Internal validity - bias* • Follow-up was the same for all participants • Patients and physician were blinded (double-blinded) • Statistical tests used to assess the	*Reporting* • List of principle confounders was not provided *External validity* • Unable to determine if the participants were representative of the entire population from which they were recruited *Internal validity - bias* • Unable to determine if the main outcome measures used were accurate (valid and reliable) *Internal validity – confounding (selection bias* • Unable to determine if the randomized intervention assignment was concealed from both patients and health care staff until recruitment was complete and irrevocable • Unable to determine if there was adequate adjustment for confounding in the analyses from which the main findings were drawn (ITT) • Unable to determine if losses of patients to follow-up were taken into account *Power* • The study did not have sufficient

Author, year	Strengths	Limitations
	main outcome were appropriate *Internal validity – confounding (selection bias* • The patients in different intervention groups were recruited from the same population • The patients in different intervention groups were recruited over the same period of time • Patients were randomized to the intervention groups	power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%
Yelland et al., 2011[15] SB RCT	*Reporting* • The objective was clearly described • The main outcome measures were clearly described • The baseline characteristics of the patients included in the study were clearly described • The main findings of the study were clearly described • The study provided estimates of the random variability in the data for the main outcomes (standard deviation and confidence intervals) • Actual probability values were reported *External validity* • Participants asked to participate in the study were representative of the entire population from which they were recruited • The staff, places and facilities where the patients were treated, were representative of the treatment majority of patients received *Internal validity - bias* • Follow-up was the same for all participants • Statistical tests used to assess the main outcome were appropriate • The main outcome measures used were accurate (valid and reliable) *Internal validity – confounding (selection bias* • The patients in different intervention groups were recruited from the same population • The patients in different intervention groups were recruited over the same period of time • Patients were randomized to the intervention groups • There was adequate adjustment for	*Reporting* • List of principle confounders was not provided • Adverse events were not reported *External validity* • Unable to determine if the participants were representative of the entire population from which they were recruited *Internal validity - bias* • Injector and patients were not blinded (assessor blinded only) *Internal validity – confounding (selection bias* • Unable to determine if the randomized intervention assignment was concealed from both patients and health care staff until recruitment was complete and irrevocable • Unable to determine if losses of patients to follow-up were taken into account *Power* • The study did not have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%

Author, year	Strengths	Limitations
	confounding in the analyses from which the main findings were drawn (ITT)	
Kim et al., 2010[16] DB RCT	*Reporting* • The objective was clearly described • The main outcome measures were clearly described • The baseline characteristics of the patients included in the study were clearly described • The main findings of the study were clearly described • The study provided estimates of the random variability in the data for the main outcomes (standard deviation and confidence intervals) • Adverse events were reported • Actual probability values were reported *External validity* • Participants asked to participate in the study were representative of the entire population from which they were recruited • The staff, places and facilities where the patients were treated, were representative of the treatment majority of patients received *Internal validity - bias* • Follow-up was the same for all participants • Patients and physician were blinded (double-blinded) • Statistical tests used to assess the main outcome were appropriate *Internal validity – confounding (selection bias* • The patients in different intervention groups were recruited from the same population • The patients in different intervention groups were recruited over the same period of time • Patients were randomized to the intervention groups *Power* • The study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%	*Reporting* • List of principle confounders was not provided *External validity* • Unable to determine if the participants were representative of the entire population from which they were recruited *Internal validity - bias* • Unable to determine if the main outcome measures used were accurate (valid and reliable) *Internal validity – confounding (selection bias* • Unable to determine if the randomized intervention assignment was concealed from both patients and health care staff until recruitment was complete and irrevocable • Unable to determine if there was adequate adjustment for confounding in the analyses from which the main findings were drawn (ITT) • Unable to determine if losses of patients to follow-up were taken into account

Author, year	Strengths	Limitations
Observational studies		
Hauser et al., 2014[17] Retrospective case series	*Reporting* • The objective was clearly described • The main outcome measures were clearly described • Adverse events were reported *Internal validity - bias* Follow-up was the same for all participants	*Reporting* • The baseline characteristics of the patients included in the study were not described • The characteristics of patients lost to follow-up were not described • Actual probability values were not reported *External validity* • Unable to determine if the participants were representative of the entire population from which they were recruited *Internal validity – bias* • Attempt was not made to blind those measuring the main outcomes of the intervention *Power* • A power calculation was not reported for the primary outcome • The study did not have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%
Rabago et al., 2014[18] Case series	*Reporting* • The objective was clearly described • The main outcome measures were clearly described • The baseline characteristics of the patients included in the study were described • Adverse events were reported • Actual probability values were reported *Internal validity - bias* Follow-up was the same for all participants	*Reporting* • The characteristics of patients lost to follow-up were not described *External validity* • Unable to determine if the participants were representative of the entire population from which they were recruited *Internal validity – bias* • Attempt was not made to blind those measuring the main outcomes of the intervention *Power* • A power calculation was not reported for the primary outcome • The study did not have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%
Rabago et al., 2012[19] Case series	*Reporting* • The objective was clearly described • The main outcome measures were clearly described • The baseline characteristics of the	*Reporting* • The characteristics of patients lost to follow-up were not described • *External validity*

Author, year	Strengths	Limitations
	patients included in the study were not described • Adverse events were reported • Actual probability values were not reported *Internal validity - bias* Follow-up was the same for all participants	• Unable to determine if the participants were representative of the entire population from which they were recruited *Internal validity – bias* • Attempt was not made to blind those measuring the main outcomes of the intervention *Power* • A power calculation was not reported for the primary outcome • The study did not have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%
Schaumburger et al., 2012[20] Retrospective case series	*Reporting* • The objective was clearly described • The main outcome measures were clearly described • Adverse events were reported *Internal validity - bias* Follow-up was the same for all participants	*Reporting* • The baseline characteristics of the patients included in the study were not described • The characteristics of patients lost to follow-up were not described • Actual probability values were not reported *External validity* • Unable to determine if the participants were representative of the entire population from which they were recruited *Internal validity – bias* • Attempt was not made to blind those measuring the main outcomes of the intervention *Power* • A power calculation was not reported for the primary outcome • The study did not have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%
Ryan et al., 2011[21] Case series	*Reporting* • The objective was clearly described • The main outcome measures were clearly described *Internal validity - bias* Follow-up was the same for all participants	*Reporting* • The baseline characteristics of the patients included in the study were not described • The characteristics of patients lost to follow-up were not described • Adverse events were not reported • Actual probability values were not reported *External validity*

Author, year	Strengths	Limitations
		• Unable to determine if the participants were representative of the entire population from which they were recruited *Internal validity – bias* • Attempt was not made to blind those measuring the main outcomes of the intervention *Power* • A power calculation was not reported for the primary outcome • The study did not have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%
Cusi et al., 2010[22] Case series	*Reporting* • The objective was clearly described • The main outcome measures were clearly described • Actual probability values were not reported *Internal validity - bias* Follow-up was the same for all participants	*Reporting* • The baseline characteristics of the patients included in the study were not described • The characteristics of patients lost to follow-up were not described • Adverse events were not reported *External validity* • Unable to determine if the participants were representative of the entire population from which they were recruited *Internal validity – bias* • Attempt was not made to blind those measuring the main outcomes of the intervention *Power* • A power calculation was not reported for the primary outcome • The study did not have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%
Ryan et al., 2010[23] Case series	*Reporting* • The objective was clearly described • The main outcome measures were clearly described • Actual probability values were reported	*Reporting* • The baseline characteristics of the patients included in the study were not described • The characteristics of patients lost to follow-up were not described • Adverse events were reported *Internal validity - bias* • Follow-up was not the same for all participants *External validity*

Author, year	Strengths	Limitations
		• Unable to determine if the participants were representative of the entire population from which they were recruited *Internal validity – bias* • Attempt was not made to blind those measuring the main outcomes of the intervention *Power* • A power calculation was not reported for the primary outcome • The study did not have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%
Watson et al., 2010[24] Retrospective case series	*Reporting* • The objective was clearly described • The main outcome measures were clearly described • The baseline characteristics of the patients included in the study were not described • Adverse events were reported *Internal validity - bias* Follow-up was the same for all participants	*Reporting* • The characteristics of patients lost to follow-up were not described • Actual probability values were not reported *External validity* • Unable to determine if the participants were representative of the entire population from which they were recruited *Internal validity – bias* • Attempt was not made to blind those measuring the main outcomes of the intervention *Power* • A power calculation was not reported for the primary outcome • The study did not have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%

APPENDIX 4: Summary of Results of Clinical Studies

Author, year, type of study, country, design	Condition / Treatments	Results
Systematic Review		
Rabago et al., 2009[9] USA, Sweden, Canada SR (3 studies)	Lateral epicondylosis RCT1: • Dextrose (10.7%) + morrhuate (14.7%) vs. saline RCT2: • Dextrose (15%) + lidocaine (0.1%) vs. saline Case series: • Glucose (20%) + lidocaine (0.1%) vs. baseline	RCT1: • Pain improvement at 16 weeks compared to baseline: active 90% vs. control 22% (p<0.001) RCT2: • Improvement in disease specific questionnaire at 9 weeks compared to baseline: active 66% vs. control 11.5% (p=0.09) Case series: • Pain improvement at mean 19 months compared to baseline: 94% (p<0.05)
Authors' conclusions: *"There is strong pilot level evidence supporting the use of prolotherapy … in the treatment of lateral epicondylosis"* p.472		
RCTs		
Jahangiri et al., 2014[10] Iran DB RCT, assessor blinded (N=60)	Carpometacarpal osteoarthritis Dextrose + lidocaine vs. prednisone + lidocaine	• Change in mean VAS for severity of pain on pressure was significantly more favorable for dextrose compared to prednisone at month 6 (p=0.001) • Dextrose resulted in significant improvement in pain on movement (mean difference [95% CI] = 1.1 [0.2, 2.0]; p=0.02) and hand function (mean difference [95% CI] = 1.0 [0.2, 1.8]; p=0.01) • Limitations: o patients in group lidocaine got their treatment only in the 3rd session (3rd month), while those in dextrose group received three doses of dextrose monthly. o no ITT analysis o short-term (6 months)
Authors' conclusions: *"For the long term, dextrose seems to be more advantageous"* compared to corticosteroid. P. 737		
Rabago et al., 2013[11] USA DB RCT (N=90)	Knee osteoarthritis Dextrose + lidocaine vs. saline vs. exercise	• WOMAC improved by 12 or more points at 52 weeks: - dextrose (15 of 30, 50%), saline (10 of 29, 30%); exercise (8 of 31; 24%) - dextrose vs. saline (15.32 vs. 7.59 points, p=0.022) - dextrose vs. exercise (15.32 vs. 8.24 points, p=0.034) • Dextrose consistently showed improvement across WOMAC subscales, achieved near max at 26 weeks and maintained through 52 weeks. - Most improvements were on function subscale - dextrose vs. saline (16.25 vs. 5.46 points, p<0.001) - dextrose vs. exercise (16.25 vs. 7.31 points, p=0.009) • Significant differences were also observed at 9 weeks and 24 weeks for dextrose compared with saline and exercise.

Author, year, type of study, country, design	Condition / Treatments	Results
		• KPS pain frequency scores (9 through 52 weeks, $p<0.05$) and KPS pain severity score (24 through 52 weeks, $p<0.05$) were significantly reduced in dextrose group compared with saline and exercise groups. • No side effects or adverse events • Limitations: • Small sample size • Limited generalizability by numerous exclusion criteria
Authors' conclusions: *"Prolotherapy resulted in clinically meaningful sustained improvement of pain, function, and stiffness scores for knee osteoarthritis compared with blinded saline injections and at-home exercises"* p.229		
Rabago et al., 2013[12] USA SB RCT (N=31)	Lateral epicondylosis Dextrose vs. dextrose + morrhuate vs. waitlist control	• At 16 weeks, prolotherapy with dextrose or dextrose/morrhuate showed significant improvement in composite scores of PRTEE compared to baseline. The improvement in prolotherapy exceeded MCID and greater than waitlist group ($p<0.05$) o Dextrose (41.1%, $p<0.05$) o Dextrose + morrhuate (53.5%, $p<0.05$) o Waitlist (18.3%) • At 32 weeks, the improvement from prolotherapy maintained o Dextrose (57.1%, $p<0.05$) o Dextrose + morrhuate (74.9%, $p<0.05$) o Waitlist (not applicable) • Similar results were obtained for subscales of pain and function • No significant differences between dextrose and dextrose/morrhuate • No within or between group differences in MRI severity scores • Satisfaction ("somewhat" or "very") at 16 weeks o Dextrose (75%) o Dextrose + morrhuate (78%) • Satisfaction ("somewhat" or "very") at 32 weeks o Dextrose (75%) o Dextrose + morrhuate (89%) • Grip strength was improved in dextrose group (8, 16, 32 weeks), but did not change in waitlist (16 weeks) and in dextrose/morrhuate (16, 32 weeks) • Limitations: o Small sample size o No blinded injection control (placebo effect) o Injector and assessor were not blinded (performance and detection bias) o Short term follow-up (16 and 32 weeks)
Authors' conclusions: *"Prolotherapy resulted in safe, significant improvement of elbow pain and function compared to baseline status and wait-and-see control. This pilot study suggests the need for a definitive trial"* p. 588		
Dumais et al., 2012[13] Canada	Knee osteoarthritis Dextrose + lidocaine vs.	• Overall estimation: dextrose prolotherapy alone showed improvement in WOMAC scores by 29.5% compared to exercise alone.

Author, year, type of study, country, design	Condition / Treatments	Results
OL RCT, crossover (N=45)	home-based exercise	• Similar observations can be made for each of the WOMAC subscales. • All secondary outcomes improved significantly in group A during first 16 weeks. • Limitations: o Small sample size o Lack of sufficient power for secondary outcomes o No ITT analysis (lost to follow-up) o No saline injection control o Lack of generalizability (younger, heavier, and more male patients)
Authors' conclusions: *"The use of regenerative injection therapy is associated with a marked reduction in symptoms, which was sustained over 24 weeks"* p. 990		
Carayannopuolos et al., 2011[14] USA DB RCT (N=24)	Lateral epicondylosis Dextrose + morrhuate + procaine vs. methylprednisolone	• 17 patients remained at 6-month follow-up (8 dextrose, 9 corticosteroid) • VAS improvement from baseline to month 6: o Dextrose: 2.63 ± 2.39 (p = 0.017) o Corticosteroid: 1.72 ± 4.41 (p = 0.28) • QVAS improvement from baseline to month 6: o Dextrose: 8.38 ± 8.96 (p = 0.03) o Corticosteroid: 8.78 ± 8.74 (p = 0.017) • DASH improvement from baseline to month 3: o Dextrose: 19.89 ± 16.93 (p = 0.0013) o Corticosteroid: 13.33 ± 16.46 (p = 0.04) • No significant differences in the amount of change between dextrose and corticosteroid at 3 or 6 months with any of the 3 scales • No significant change in grip strength within or between groups • Limitations: o Small sample size o High dropout rate o Lack of power o Short term follow-up o No placebo injection
Authors' conclusions: *"prolotherapy may be a useful alternative to corticosteroid injection, and may provide a basis for undertaking larger, more definitive studies"* p. 713		
Yelland et al., 2011[15] Australia SB RCT (N=43)	Achilles tendinosis Dextrose + lignocaine/ropivacaine vs. exercise vs. combination	• All three groups showed significant improvements in VISA-A scores at all times compared to baseline ($p<0.0005$) • There were no significant differences between groups or between groups over time • Same results were obtained for pain, stiffness and limitation activities. Overall, all three groups showed significant decrease in these outcomes with no difference between groups. • There were no significant differences in satisfaction ratings or PGIC ratings between groups over time. • Limitations: o Small sample size o No sample size determination

Author, year, type of study, country, design	Condition / Treatments	Results
		o Open-label for patients and doctor who performed injection o No placebo control o Possible attention bias
Authors' conclusions: *"For Achilles tendinosis, prolotherapy and particularly eccentric loading exercise (ELE) combined with prolotherapy give more rapid improvements in symptoms than ELE alone but long-term VISA-A scores are similar"* p.421		
Kim et al., 2010[16] South Korea DB RCT (N=50)	Low back pain Dextrose + levobupivacaine vs. steroid (triamcinolone acetonide)	• Number of injections: dextrose 2.7 ± 1.1 vs steroid 1.5 ± 0.8 • At 2 weeks after treatment: o Pain improvement compared with baseline: dextrose 78% vs. steroid 71% (NS) o Disability improvement compared with baseline: dextrose 68% vs. steroid 59% (NS) o No significant differences between groups for pain or disability after 2 weeks of treatment • At 6 months after treatment, 64% patients in dextrose group remained positive response compared to 27% in the steroid group (p<0.01) • At 15 months after treatment, 59% patients in dextrose group remained positive response compared to 10% in the steroid group (p<0.01) • Limitations: o Small sample size o No ITT analysis o Unclear if instruments used to measure pain and disability were validated o Unclear about the MCID o More frequent injection of dextrose (2.7) than steroid (1.5) to achieve pain relief of ≥90% from baseline
Authors' conclusions: *"Intra-articular prolotherapy provided significant relief of sacroiliac joint pain, and its effects lasted longer than those of steroid injections. Further studies are needed to confirm the safety of the procedure and to validate an appropriate injection protocol"* p. 1285		
Observational studies		
Hauser et al., 2014[17] USA Retrospective case series (N=61; 69 knees)	Chondromalacia patella Dextrose + procaine + sarapin	After prolotherapy: • Statistically significant decreased in pain at rest, during daily activities and exercise (p<0.0001) • Range of motion significantly increased (p<0.0001) • Stiffness and crepitus significantly decreased (p<0.0001) • 85% of patients reported sustained improvement of over 75% • Require of pain medication was reduced • Limitations: o Small sample size o Unclear if instruments used to measure pain and disability were validated o Self-reporting bias (by phone) o Lack of objective data o Risk of selection bias

Author, year, type of study, country, design	Condition / Treatments	Results
Authors' conclusions: *"…prolotherapy in the treatment of chondromalecia patella is associated with substantial gains in pain relief and functionality."* p. 19		
Rabago et al., 2014[18] USA Case series (N = 38)	Knee osteoarthritis Dextrose + morrhuate + lidocaine	After prolotherapy: • Participants in all 3 groups reported improvement in WOMAC score o Prior-control: 12.4 ± 3.5 points (19.5%, *p*=0.002) o Prior-decline: 19.4 ± 7.0 (42.9%, *p*=0.05) o Prior-ineligible: 17.8 ± 3.9 (28.4%, *p*=0.008) • 55.6% of prior-control, 75% of prior-decline, and 50% of prior-ineligible reported score improvement in excess of 12-point MCID • Similar pattern for KSP scores • Improvement by 24 weeks and remained stable through 52 weeks • Satisfaction was high and no adverse events • Limitations: o Small sample size o Lack of comparison group o Different in patient baseline characteristics o Risk of bias from recruiting patients previously involved in prolotherapy study
Authors' conclusions: *"Prolotherapy with dextrose and morrhuate sodium resulted in substantial, significant, and sustained improvement on validates pain, function, and stiffness measures in participants with mild-to-moderate knee osteoarthritis compared to baseline status. Prolotherapy performed by a trained operator may be an appropriate therapy for selected patients who have moderate-to-severe knee osteoarthritis and who are refractory to conservative care."* p. 390		
Rabago et al., 2012[19] USA Case series (N=36)	Knee osteoarthritis Dextrose + lidocaine	After prolotherapy: • WOMAC score improved 4 weeks after first injection session (7.6 ± 2.4 points, 17.2%) • WOMAC score continued improved through 52-week follow-up (15.9 ± 2.5 points, *p*<0.001, 36.1%) • KPS scores improved in both injected knees (*p*<0.001) and uninjected knees (*p*<0.05) • Satisfaction was high and no adverse events: 83% would recommend prolotherapy • Limitations: o Small sample size o Lack of comparison group o The assessment of participant satisfaction was indirect (risk of bias) o Radiographs were not available for all participants o Six patients had completed a prior prolotherapy (risk of selection bias)
Authors' conclusions: *"Prolotherapy resulted in safe, significant, and sustained improvement on validated pain, function, and stiffness measures in participants with knee osteoarthritis. Prolotherapy performed by an experienced operator may be an appropriate therapy for selected patients with moderate-to-severe knee osteoarthritis who are refractory to conservative care"* p. 413		
Schaumburger et al., 2012[20] Germany	Knee arthritis (recurrent knee joint effusion) Morrhuate + mepivacaine	• Mean follow-up: 29.8 months • 2 died, 27 (22.3%) lost to follow-up • 53 of 92 patients (57%) reported satisfaction • Pain (VAS score) was significantly improved at final

Author, year, type of study, country, design	Condition / Treatments	Results
Retrospective case series (N=92)	+ triamcinolone	follow-up (3.7 vs. 6.9, *p*<0.05) • Activity level improved in 62% of patients • 57% reached excellent or good results in Lysholm and Gillquist score (knee function) • 92% had improved Knee Injury and Osteoarthritis score after treatment with sodium morrhuate • Limitations: o High rate of dropout o Risk of selection bias o Lack of control o Moderate improvement o No validation of the clinical outcome measures
Authors' conclusions: *"The intra-articular application of sodium morrhuate is an effective and safe measure in the treatment of recurrent symptomatic knee joint effusions in young patients suffering from recurrent knee joint effusions"* p. 3113		
Ryan et al., 2011[21] USA, Canada Case series (N=47)	Patellar tendinopathy Dextrose + lidocaine	• Median number of injections: 4 ± 3.4 (range 2 to 8) spaced a mean of 6.4 weeks ± 5.5 days • Mean follow-up: 45 weeks ± 36 • VAS scores for pain (at rest, daily living, sport) significantly improved at 45-week follow-up (*p*<0.001) • VAS pain scores correlated with changes to echotexture severity • Limitations: o Small sample size o Lack of control group o Lack of blinding of radiologist o No report on loss of follow-up o Risk of selection and assessment biases o No validation of the clinical outcome measures o Short follow-up
Authors' conclusions: *"Ultrasound-guided prolotherapy injections resulted in significant and clinically meaningful reductions in pain in patients with patellar tendinopathy. Tendon structure also improved substantially following injections; changes in hypoechoic severity were significantly correlated with pain outcomes."* p. 976		
Cusi et al., 2010[22] Australia Case series (N=25)	Low-back Pain Dextrose + bupivicaine	• No all patients attended follow-up visits (3 months [n=15 to 19], 12 months [n=12 to 19], 24 months [n=7] • Clinical scores were significantly improved at 3 months, 12 months and 24 months (*p*<0.001) • Quebec pain disability scores significantly improved at 3 months (*p*<0.001), 12 months (*p*<0.002) and 24 months (*p*<0.006) • Roland-Morris back pain questionnaire scores significantly improved at 3 months (*p*=0.001), 12 months (*p*<0.047) and 24 months (*p*<0.035) • Roland-Morris 24 multiform questionnaire scores significantly improved at 3 months (*p*=0.001), 12 months (*p*<0.016) and 24 months (*p*=0.012 • Limitations: o Small sample size o Lack of control group o Risk of selection and assessment biases

Author, year, type of study, country, design	Condition / Treatments	Results
Authors' conclusions: *"This descriptive study of the use of prolotherapy in combination with a specific exercise programme in private practice has shown improvement in clinical outcome scores for all the patients who attended follow-up visits"* p.103		
Ryan et al., 2010[23] Canada Case series (N=99 patients, 108 tendons)	Achilles tendinosis Dextrose + lignocaine	• A median number of 5 (range 1 to 13) injection consultations, spaced average of 6 weeks apart • Average elapse time from pretest to posttest was 28 weeks (range 5 to 73 weeks) • Data of 69 patients (73 tendons, 68%) were included in the final follow-up • There was significant improvement in pain scores for both insertional (p<0.05) and midportion (p<0.001) patients from baseline to follow-up for all VAS items (i.e., at rest, daily activity, and sport) for both short and long-term of follow-up (28.6 months) • Improvements in pain correlated with improvements in some aspects of the sonographic appearance of the Achilles tendon • Limitations: o Lack of control group o No blinding o Loss of follow-up o Risk of selection and assessment biases o No validation of the clinical outcome measures
Authors' conclusions: *"Dextrose injections appear to present a low-cost and safe treatment alternative with good-long-term evidence for reducing pain from pathology at either the insertion or midportion of the Achilles tendon"* p.1047		
Watson et al., 2010[24] Canada Retrospective case series (N=190)	Low-back pain Dextrose + lidocaine	• 140 patients had 1 year or more follow-up with data analysis • Patients received a mean 10.3 ± 9.6 treatments • Both pain and QoL scores were significantly improved at least 1 year after the last treatment (p<0.05) • Pain score (post vs. pre): 4.0 ± 2.9 vs. 6.2 ± 2.1 points • QoL score (post vs. pre): 3.7 ± 2.8 vs. 6.9 ± 2.2 points • Limitations: o Retrospective design and the use of non-validated outcome measures o Lack of control o High rate of withdrawal (26%) o Risk of selection bias
Authors' conclusions: *"prolotherapy using a variety of proliferants can be an effective treatment for low back pain from presumed ligamentous dysfunction for some patients when performed by a skilled practitioner"* p.951		

DB = double-blinded; FFI = foot function index; HAQ-DI = heath assessment questionnaire disability index; ITT = intention-to-treat; KPS = knee pain scale; LOCF = last observation carried forward; MCID = minimal clinically important difference; NR = not reported; OL = open-labelled; PGIC = Patient Global Impression of Change; PRTEE = Patient-Rated Tennis Elbow Evaluation; QoL = quality of life; RCT = randomized controlled trial; SB = single-blinded; VAS = visual analog scale; WOMAC = Western Ontario McMaster University Osteoarthritis Index