

ABSTRACT

Objective: To evaluate, through a scientific review of the current literature, the efficacy of dextrose Prolotherapy in treating musculoskeletal pain.

Data Sources: All possible internet sources, especially online medical databases including PUBMED, PREMEDLINE, EMBASE, AMED, HEALTHLINE, OMNIMEDICALSEARCH, MEDSCAPE and MEDLINE, were searched through October 2011 for scientific articles on dextrose Prolotherapy. The bibliographies of retrieved articles were also searched.

Study Selection: All published studies that could be found on human subjects that included at least five subjects and at least one outcome measure related to pain intensity were included. Nonhuman studies and those studies (human and nonhuman) on Prolotherapy involving other solutions besides dextrose were excluded.

Main Results: Data from forty-four case series, two nonrandomized controlled trials (NRCT) and nine randomized controlled trials (RCT) were included in this review. A total of 2,443 patients were treated which included 2,181 in the case series, 27 in the NRCT and 235 in the RCT. In the 27 case series, involving 1,478 musculoskeletal structures treated, that used VAS or NRS in monitoring the response to treatment, dextrose Prolotherapy caused a decline of over 4.4 points (0 to 10 scale). Seven of nine double-blind placebo-controlled studies showed statistically significant improvements in pain and/or function with dextrose Prolotherapy over placebo for myofascial pain syndrome, sacroiliac pain, knee osteoarthritis, Osgood-Schlatter disease and Achilles tendinosis. There is level 1 and 2 evidence to support the use of dextrose Prolotherapy for osteoarthritis pain and function, tendinopathies, myofascial pain syndrome, and sacroiliac ligament pain. There is level 3 evidence in support of the use of dextrose Prolotherapy for diffuse musculoskeletal pain involving the spine, pelvis and peripheral joints. Using the U.S. Preventative Services Task Force guidelines there is fair to good evidence to support the use of dextrose Prolotherapy for musculoskeletal pain.

Conclusion: This scientific literature review shows there is level 1 and 2 evidence to support the use of dextrose Prolotherapy for osteoarthritic pain and function, tendinopathies, myofascial pain syndrome, sacroiliac pain, and myofascial pain syndrome. There is level 3 evidence in support of the use of dextrose Prolotherapy for diffuse musculoskeletal pain involving the spine, pelvis and peripheral joints. Dextrose Prolotherapy should be recommended for such musculoskeletal conditions as tendinopathy, ligament sprains, Osgood-Schlatter disease and degenerative joint disease, including osteoarthritis.

Journal of Prolotherapy. 2011;3(4):765-789.

KEYWORDS: chronic musculoskeletal pain, clinical evidence, degenerative joint disease, dextrose Prolotherapy, level of evidence, ligament laxity, Osgood-Schlatter disease, osteoarthritis, scientific literature review, tendinopathy.

Evidence-Based Use of Dextrose Prolotherapy for Musculoskeletal Pain: A Scientific Literature Review

Ross A. Hauser, MD,
Marion A. Hauser, MS, RD,
Nicole M. Baird, CHFP

Introduction

Chronic musculoskeletal disease is a major cause of pain and reduced quality of life. In 2005, 107.7 million adults, one in two aged 18 and over, reported suffering from a musculoskeletal condition lasting three months or longer during the past year. In addition, nearly 15 million adults reported they were unable to perform at least one common activity, such as self-care, walking, or rising from a chair, on a regular basis due to their musculoskeletal condition.¹

In 2004, the estimated cost for treatment of patients with musculoskeletal conditions was \$510 billion; however if one also includes the indirect cost, primarily of lost wages, this adds another \$339 billion, resulting in total cost attributed to patients with musculoskeletal disease of \$849 billion, or 7.7 percent of the gross national product.² In addition, musculoskeletal diseases accounted for the majority of both lost work and bad days due to health conditions.

Musculoskeletal diseases occur more frequently as people age. Aging of the U.S. population, higher rates of diagnoses and treatment, increasing medical cost and the cost of higher earnings loss all contribute to the rising burden of musculoskeletal diseases. For instance, currently 27 million Americans are affected by osteoarthritis (OA), up from 21 million in 1990. By the year 2030, it is expected that more than 67 million Americans will have arthritis.³ OA and its related conditions cost the U.S. economy nearly \$128 billion per year in medical care and indirect expenses, including lost wages and productivity.⁴ A major component of the economic burden associated with the treatment of arthritis relates to surgical joint replacements of the hips and knees.

In 2004, the national bill of hospital charges for hip and knee replacements was \$26 billion, and hospital cost was \$9.1 billion.⁵ Musculoskeletal procedures, including hip and knee replacements account for 10% of all hospital care in the United States. From 1997 to 2005, the number of knee replacements climbed by 60%, from 328,000 to 555,800 annually. The number of hip replacements rose from 290,700 to 383,500 procedures.⁶ The number of these procedures is expected to increase at an alarming rate to nearly 600,000 hip replacements and 1.4 million knee replacements by the year 2015.^{5,7} By 2030, it is estimated that the annual number of hip and knee replacements will increase to 1.85 and 3.48 million, respectively.⁸ Costs for other forms of musculoskeletal care are also spiraling out of control. For instance, Medicare spending for inpatient back surgery more than doubled over the decade from 1992-2003, while some surgeries including lumbar fusion increased more than 500%.⁹ Unless treatment methods change, it is certain that the costs for musculoskeletal surgical procedures will escalate.

Prolotherapy has emerged as a cost-effective treatment option for chronic musculoskeletal and arthritic pain. It involves the injection of a small amount of solution into multiple painful ligament and tendon insertions (entheses), typical trigger points, as well as into the adjacent joint spaces to induce healing of the injured structures. It is presumed to work by stimulating weakened structures such as ligaments and tendons to strengthen, tighten and heal by the induced proliferation of cells. George S. Hackett, MD, a trauma surgeon from Canton, Ohio, who coined the term in the mid 1950s describes it this way, "The treatment consists of the injection of a solution within the relaxed ligament and tendon which will stimulate the production of new fibrous tissue and bone cells that will strengthen the 'weld' of fibrous tissue and bone to stabilize the articulation and permanently eliminate the disability... My definition of Prolotherapy as applied medically in the treatment of skeletal disability is 'the rehabilitation of an incompetent structure by the generation of new cellular tissue.'"^{10, 11} Though the exact process by which Prolotherapy decreases pain and reduces skeletal disability is debated, Prolotherapy has been found historically to induce ligament and tendon hypertrophy^{12, 13} and strengthening,^{14, 15} stabilize unstable joints such as the sacroiliac joint, cervical spine and temporomandibular joint¹⁶⁻¹⁸; as well as eliminate musculoskeletal pain in all joints of the body including the knees, shoulders, and ankles,^{19, 20} and induce musculoskeletal repair via the stimulation of growth factors via the inflammatory healing cascade,²¹⁻²⁵

as well as reduce neurogenic inflammation.^{26, 27} While there are many solutions that can be used in Prolotherapy, including pumice, P2G (dextrose, phenol, glycerin), sodium morrhuate and more recently, platelet rich plasma, stem cell, and lipoaspirate, the most common solution used is dextrose.²⁸⁻³³ Gustav A. Hemwall, MD, is credited as the first doctor to use just dextrose by itself as the proliferant for Prolotherapy, when Synlasol (fatty acid derivative) was no longer available.³⁴ This is why dextrose Prolotherapy case studies do not start appearing in the medical literature until the early 1980s, whereas other Prolotherapy articles and case reports using other proliferants appear much earlier.^{35, 36} Typical concentrations of dextrose used in Prolotherapy are from five to twenty-five percent.^{37, 38}

Dextrose Prolotherapy is presumed to work by several mechanisms including a direct, an osmotic, and inflammatory growth effect. Dextrose injections below a 10% solution directly stimulate proliferation of cells and tissue without causing a histological inflammatory reaction.^{24, 25} When dextrose is injected in greater than 10% solution it is presumed to be causing an osmotic (concentrated) gradient outside of the cells where it is injected. This causes some cells to lose water and lyse with the net effect being an influx of growth factors and inflammatory cells that initiates the wound-healing cascade to that specific area. Dextrose is an ideal proliferant because it is water soluble and a normal component of blood chemistry, which can be injected safely into multiple areas and in large quantity. The presumed net result is the deposition of new collagen into injured structures, such as ligaments and tendons.

A normal human cell contains only 0.1% dextrose.³⁹ Increased glucose concentration (dextrose) causes an increase in cell protein synthesis, DNA synthesis, cell volume and proliferation.⁴⁰⁻⁴³ When exposed to an extracellular d-glucose (dextrose) concentration of as little as 0.5%, normal human cells begin to proliferate and produce a number of growth factors, including platelet-derived growth factor,⁴⁴ transforming growth factor-beta (TGF- β),^{45, 46} epidermal growth factor,⁴⁷ basic fibroblast growth factor,⁴⁸ insulin-like growth factor,⁴⁹ and connective tissue growth factor.⁵⁰ These are some of the growth factors that are pertinent to the repair, health and growth of tendons, ligaments and other soft tissues.⁴⁸⁻⁵² Dextrose injected into tissues has been found in animal and human studies to stimulate inflammation,⁵³ ligament size,⁵⁴ tendon hypertrophy,⁵⁵⁻⁵⁷ extracellular matrix,⁵⁵⁻⁵⁹ fibroblastic proliferation,^{53, 57-59} and repair of articular cartilage defects.^{60, 61} It has also been shown to

induce healing over a wide range of percent concentrations, protect injured cartilage,⁶⁰⁻⁶² and cause biological effects by inflammatory and noninflammatory mechanisms.^{55, 56, 60-64}

Dextrose Prolotherapy, if widely used, could have a tremendous impact on reducing musculoskeletal pain, disability and cost because of the following: nine to twenty percent of adults in the United States experience chronic pain^{65, 66}; of these 89% have some degree of long-term or short-term disability⁶⁷; nearly all chronic pain patients have substantially reduced health-related quality of life⁶⁸; ligament injuries often fail to heal completely⁶⁹; unresolved ligament tears and sprains can completely alter joint mechanics^{70, 71}; ligament and tendon injuries account for 45% of all musculoskeletal injuries in the United States⁷²; ligament laxity and its associated joint instability is a leading cause of spinal and joint degeneration⁷³⁻⁷⁵; and when hypermobility is sought it is the most common finding among patients presenting to a rheumatologist.⁷⁶ To help determine the efficacy for dextrose Prolotherapy to treat these and other musculoskeletal conditions, we undertook this scientific literature review.

OBJECTIVE

The objective of this scientific literature review was to evaluate the evidence-based outcomes on the use of dextrose Prolotherapy for musculoskeletal pain.

Musculoskeletal Pain – persistent pain secondary to injury involving the musculoskeletal system including the bones, muscles, ligaments, tendons, menisci, labrum, nerves and/or joints.

METHODS

All research articles, case series and case reports, nonrandomized and randomized controlled studies involving at least five human subjects that involved dextrose Prolotherapy injections were included. Only those that used exclusively dextrose as the proliferant and/or an anesthetic were included. Dextrose Prolotherapy articles that used P2G, which includes phenol, glycerin and dextrose and sodium morrhuate were excluded, as were those in which patients also received high velocity manipulation. All other forms of Prolotherapy, including those using pumice, platelet rich plasma, bone marrow, lipoaspirate, and stem cells were also excluded. When patients were educated on specific types of exercises to perform, this information

is provided in the analysis. All data was obtained by a thorough search of electronic databases including the most common medical search engines including PUBMED, OMNIMEDICALHEALTHLINE, MEDLINE, EMBASE, AMED, CINAHL and MEDSCAPE. To be included, at least one outcome measure related to pain intensity, such as the visual analog scale (VAS) or numerical rating scale (NRS) had to be measured. The primary outcome for this review was relief of musculoskeletal pain with dextrose Prolotherapy injections. The search found references in both the English and Korean languages. Research articles and case studies were found in American, Korean, British and Australian medical journals.

RESULTS

The search identified 44 case series, two nonrandomized controlled studies and nine randomized controlled studies that used exclusively dextrose as the proliferant. The heterogeneity of the 55 studies was not formally assessed. Since most of the case studies used either a visual analog scale or numerical pain scale to determine before and after response with dextrose Prolotherapy the pooling of data was possible. Final recommendations were based on the minimum improvement standard for clinically significant change found in the scientific literature, as well as U.S. Preventative Task Force guidelines of levels of evidence.

Case Reports and Case Studies of Dextrose Prolotherapy

A summary of the 44 case reports and case series included evaluation of 2,296 reported treated areas in 2,181 patients.

CHRONIC MUSCULOSKELETAL PAIN

Kim, Shin and Seo⁷⁸ report on treating 67 patients with chronic musculoskeletal pain (average of 5.48 years) with two monthly sessions of 15% dextrose Prolotherapy. The VAS showed a statistically significant reduction of pain from 7.0 to 4.31 after the first set of injections and went down to 2.55 after the second series of injections. (See Table 1.) Kim et al.⁷⁹ did a similar report on 20 patients with chronic musculoskeletal pain treated once with a 12.5% dextrose solution. This study showed that one dextrose Prolotherapy treatment reduced VAS by 80% (ratio of pre/post VAS of 0.36).

Table 1. VAS before and after Prolotherapy by body part.
Adapted from: Kim BK, Shin JY, Seo KM. The effect of Prolotherapy for the chronic pain of musculoskeletal system. *The Journal of the Korean Academy of Rehabilitation Medicine*. 2001;25:128-133. Table 3.

VAS (Visual Analog Scale)			
	Before Tx.	After 1st Tx.	After 2nd Tx.
Occipital	7.50	3.20	2.40
C-spine	6.50	3.13	2.25
Shoulder	7.50	3.64	1.79
Elbow	6.50	3.71	2.36
L-spine	7.12	4.96	2.90
Knee	6.77	4.12	2.58
Ankle	6.17	5.00	2.33
Finger	8.00	6.50	2.50

Hauser et al. published 11 studies on the use of dextrose Prolotherapy for chronic musculoskeletal pain. These compiled studies represent 709 patients treated at a charity clinic who had on average 55 months of pain with 42% of the patients stating a medical doctor had told them that there was nothing else they could do for the pain.⁸⁰⁻⁹⁰ The average patient received four quarterly treatments with a 12.5% dextrose Prolotherapy solution. Overall pain levels decreased from 6.3 to 2.2 (NRS 1-10 scale) reaching statistical significance using a matched sample paired *t*-test. (See Table 2.) The patients were followed on average 19 months after their last Prolotherapy session, and in total, 89% of people received greater than 50% pain relief with Prolotherapy.

Table 2. Use of Prolotherapy for pain in individual joints.
Prolotherapy caused a statistically significant decline in pain.⁸⁰⁻⁹⁰

Area treated	Average pain level prior to Prolotherapy	Average pain level after Prolotherapy	Percent of patients who reported > 50% pain relief
Ankle	7.9	1.6	90%
Back	5.6	2.7	89%
Elbow	5.1	1.6	94%
Foot	7.1	2.3	84%
Hand	5.9	2.6	82%
Hip	7.0	2.4	89%
Knee	6.5	2.5	88%
Neck	5.6	2.3	89%
Shoulder	7.1	2.3	87%
TMJ	5.9	2.5	93%
Wrist	5.5	1.4	90%
Overall Average	6.3	2.2	89%

Lyftogt, in 2005, treated 127 patients with chronic musculoskeletal pain (74 knees, 33 shoulders and 20 elbows) with subcutaneous dextrose Prolotherapy.⁹¹ The treatment protocol consisted of weekly injections into all active trigger points and injected subcutaneously with 0.50 ml of a 20% dextrose/0.1% lidocaine solution. The mean length of symptoms was 24 months and the mean length of treatment was seven weeks. The VAS score decreased from 6.7 to 0.76 at 21 month follow-up. Hooper and Ding followed 177 consecutive patients during a two year period with a history of chronic spinal pain who completed Prolotherapy treatment.⁹² The treatment regime involved injection of a 20% dextrose and 0.75% xylocaine solution injected weekly into the involved facet capsules as well as the iliolumbar and dorsal sacroiliac ligaments in patients with low back pain. Cervical, thoracic and low back spinal pain was treated weekly for up to three weeks. If needed, that same sequence was repeated in one month. Level of pain and improvement in activities of daily living were measured on a five-point scale. Ninety-one percent of patients reported reduction in pain level, 85% of patients reported an improvement in ADLs, and 84% had an improvement in ability to work.

NONSPECIFIC LOW BACK AND PELVIC PAIN

Hauser reported on 145 patients who experienced low back pain an average of 58 months, who were treated on average with four sessions of dextrose (12.5%) Prolotherapy, quarterly, at a charity clinic.⁹³ The patients were contacted on average 12 months after their last Prolotherapy session. In these patients, pain levels decreased from 5.6 to 2.7 (NRS, 1-10 scale); 89% experienced more than 50% pain relief, reaching statistical significance at $p < 0.000001$ using a matched sample paired *t*-test. Results were similar in the patients who were told by at least one medical doctor that there was no other treatment option (N=55) or that surgery was the only option (N=26). Lyftogt treated 41 consecutive patients with a mean duration of 5.5 years of recalcitrant lumbago with a series of subcutaneous dextrose Prolotherapy treatments.⁹⁴ Ninety percent improved by more than 50% from an initial mean VAS of 7.6 with 29% reaching VAS of 0 at a mean treatment length of 8.3 weeks. The mean end VAS was 1.4 after an average of 7.2 treatment sessions.

LOW BACK AND PELVIC PAIN DUE TO SPECIFIC CAUSES

Lee treated 20 patients with on average 40 months of sacroiliac pain confirmed by 50% or more improvement in response to local anesthetic block. Patients underwent intraarticular Prolotherapy to the sacroiliac joint with 25% dextrose

every other week for three weeks.⁹⁵ The Numeric Rating Scale (NRS) and Oswestry Disability Index (ODI) were significantly improved from 6 and 34.1 to 1 and 12.6 ($p<0.01$), respectively, at one month after Prolotherapy. The mean duration of pain relief of 50% or more was 12.2 months as determined by Kaplan-Meier survival analysis. Cusi and associates also treated 25 patients suffering from sacroiliac pain with dextrose Prolotherapy.⁹⁶ All the patients had persistent suboptimal stability of the sacroiliac joint following a three month specific exercise program. All patients were treated with three injections of an 18% dextrose Prolotherapy into the dorsal interosseous ligament of the affected sacroiliac joint under CT guidance, six weeks apart. The patients were asked questions involving the Quebec Back Pain Disability Scale, and Roland-Morris Back Pain and Multi-Form Questionnaire at 3, 12 and 24 months. The average follow-up on the patients was 26 months. All the pain and functional questionnaires demonstrated significant improvements at all time intervals ($p<0.001$). Clinical examination scores for sacroiliac instability (including the sacroiliac glide test and posterior pelvic pain provocation test) also showed statistically significant improvement at the $p<0.001$ level.

Topol et al. studied the efficacy of 12.5% dextrose Prolotherapy in 24 elite kicking-sport athletes (soccer and rugby) with chronic groin pain on average for 15 months from osteitis pubis and/or adductor tendinopathy.⁹⁷ Monthly injections were given into the enthesis around the symphysis pubis. On average 2.8 treatments were given. Final data collection was on average 17.2 months after the last Prolotherapy session. The mean reduction in pain during sports as measured by the VAS improved from 6.3 to 1.0 and the mean reduction in Nirschl Pain Phase Scale (NPPS) score improved from 5.3 to 0.8 (both $p<0.001$). Twenty of the 24 patients had no pain and 22 of 24 were unrestricted with sports at final data collection. Naeim et al. used a 25% dextrose/1% lidocaine solution to perform a pilot study on seven patients with iliolumbar syndrome.⁹⁸ The dextrose Prolotherapy injection therapy resolved the pain in six out of the seven patients (rated six good results and one poor result). This was compared with nine patients who received a 1% lidocaine solution injected in the same location with only four out of nine having good results. Khan studied 37 patients with chronic non-responding coccygodynia treated with dextrose Prolotherapy.⁹⁹ A VAS was recorded for all patients before and after injection of a 20% dextrose/0.4% lidocaine solution into the coccyx. Depending on pain relief, patients were given a second injection at two weeks

and a third one at the six week mark. The mean VAS before Prolotherapy was 8.5. It was 3.4 after the first injection and 2.5 after the second injection. Miller et al. performed a prospective consecutive patient series using bi-weekly disc space injections of dextrose Prolotherapy (25% dextrose/0.25% bupivacaine, 3cc total solution used) for patients experiencing chronic advanced degenerative discogenic leg pain, with or without low back pain on average for 39 months.¹⁰⁰ Seventy-six patients with moderate to severe degenerative disc disease without herniation and with concordant pain reproduction with CT discography were included. All had failed physical therapy and fluoroscopically guided epidural steroid injection treatment. Each patient was injected on average 3.5 times. In the responder group (33/76) the mean numeric (0-10) pain scale ratings were 8.9 at study entry and 2.5 at two months and 2.6 at 18 months (average) after the last Prolotherapy session. Forty-three out of 76 patients experienced less than 20% pain relief and were considered non-responders. Overall, 48.4% of patients fell into the sustained improvement group with an average improvement in numeric pain scores of 71%, comparing pre-treatment and 18 month measurements.

NONSPECIFIC KNEE PAIN

Hauser et al. reported on 119 knees that received dextrose Prolotherapy for unresolved knee pain.¹⁰¹ Patients had suffered with knee pain on average for five years and were treated with four sessions of 12.5% dextrose Prolotherapy, quarterly at a charity clinic. On average, 15 months after their last Prolotherapy sessions, a statistically significant decline of pain was observed from a 6.5 to 2.3 (NRS), as well as stiffness and crepitation.

KNEE PAIN DUE TO SPECIFIC CAUSES

Jo et al. treated 40 patients with ligament injury of the knee with 15% dextrose Prolotherapy.¹⁰² VAS pain scores were recorded before, one, two, four, and eight weeks after one Prolotherapy treatment. VAS scores dropped from 8.0 to 1.3, eight weeks after the dextrose Prolotherapy treatment. Hauser¹⁰³ performed a retrospective study utilizing dextrose Prolotherapy as first-line treatment for 28 knees in 24 patients with MRI-documented meniscal pathology including 18 with tears. The average number of Prolotherapy visits per patient was six, using 12.5% dextrose, given every four to six weeks. Dextrose Prolotherapy caused a statistically significant decline in patients' knee pain and stiffness, decreasing from 7.2 to 1.6 and 6.0 to 1.8, respectively. Only

one of the patients stated that Prolotherapy did not meet their expectations and ended up having surgery. Reeves and Hassanein used intraarticular dextrose Prolotherapy, with either 10 or 25% dextrose, for patients with knee pain and anterior cruciate ligament laxity as documented by KT1000 anterior displacement difference (ADD) of 2mm or more.¹⁰⁴ Sixteen patients were treated at zero, two, four, six and 10 months with 6-9cc of dextrose proliferant. Then, depending on patient preference, injection of either 10% or 25% dextrose was given every two to four months through 36 months. Ten of the 16 knees measured by KT 1000 ADD were normal at the three year follow-up. VAS pain scores improved overall from 5.9 to 4.1 with stair use, and from 4.2 to 2.5 with walking at the 12 month mark and to 3.8 and 2.4, respectively at 36 months. Clinically and statistically significant improvements were observed in ACL laxity, pain with walking, pain with stair use, swelling, and knee range of motion. Kim evaluated the effect of dextrose Prolotherapy on knee osteoarthritis.¹⁰⁵ Twenty individuals with knee osteoarthritis who suffered with pain for six months or greater and had Kellgren's grade 2 by X-ray were injected monthly with 15% to 25% dextrose for four months. VAS pain score went from 6.5 to 2.65 after treatment. The dextrose Prolotherapy caused statistically significant reductions in VAS score, pain rating score and the Western Ontario Macmaster Universities Osteoarthritis Index (WOMAC) (p<0.05). (See Table 3.)

Table 3. Before and after Prolotherapy pain scores in 20 patients with osteoarthritis of the knee.
Adapted from: Kim JM. The effect of Prolotherapy for osteoarthritis of the knee. *Journal of the Korean Academy of Rehabilitation Medicine*. 2002;26:445-448. Table 3.

	Before treatment	After treatment
VAS ¹	6.53	2.65*
Pain rating score WOMAC ²	65.94	19.47*
Pain	42.94	15.59*
Stiffness	35.29	13.24*
Physical function	39.86	13.66*
Total score	38.53	13.47*

1. VAS: Visual Analogue Scale
2. WOMAC: Western Ontario Mac-Master Universities Osteoarthritis Index
* p <0.05

Ryan et al. prospectively evaluated the treatment of overuse patellar tendinopathy in 47 patients (mean duration 21.8 months).¹⁰⁶ Under ultrasound guidance, 25% dextrose was injected into abnormal hypoechoic areas and anechoic clefts/foci in the thickened portion of the patellar tendon.

Patients received a median of 4 injections an average of 6.4 weeks apart. At 45 week follow-up, mean baseline and follow-up pain scores (VAS) were: pain at rest, 38.4 and 18.7 (P<0.01); pain with ADLs, 51.1 and 25.8 (P<0.01); and pain with sport activity, 78.1 and 38.8 (P<0.01). (See Table 4.) Pain scores improved by 51% at rest, 49.5% during ADLs, and 50% during sport activity (all P<0.01), and 53% of patients reported ≥50% pain reduction. Pre-post (n) ultrasound evaluation of intratendinous tearing revealed that VAS pain scores at rest, during ADLs and during sport activity correlated with changes to echotexture severity (r values 0.306, 0.379 and 0.428, respectively; P<0.05); as pain scores decreased, echotexture improved.

Table 4. A summary of VAS for pain at baseline and at 45 week follow-up.
Adapted from: Ryan M, et al. Ultrasound-guided injections of hyperosmolar dextrose for overuse patellar tendinopathy: a pilot study. *Br J Sports Med*. 2011;45:972-977.

	Mean Baseline VAS (mm)	Mean 45 week follow-up VAS (mm)
Pain at rest (VAS1)*	38.4	18.7
Pain with daily living (VAS2)*	51.1	25.8
Pain with sport (VAS3)*	78.1	38.8

* Indicates a significant difference in pain score across all time points at p<0.001. VAS (Visual Analog Scale).

NONSPECIFIC HEADACHE, NECK AND TMJ PAIN

Hakala published two reports on the use of dextrose Prolotherapy for temporomandibular dysfunction.^{107,108} In total, he reported on 81 joints involving 56 patients. In the first study, of the 26 patients studied, TMJ clicking improved in 19 (73%) and disappeared in 12 (46%); TMJ pain improved in 21 (81%) and disappeared in 11 (42%). In the second study, all joints had clicking and pain upon palpation. The pain upon palpation was a 2.8 on a 0 to 5 scale and the signs and symptoms persisted despite at least five months of treatment with an intraoral orthosis and home exercises. The patients received 12.5% dextrose Prolotherapy into the affected joint and tender entheses of the masseter muscle. Four treatments were given over an average of 14 week period. At 12 week recall, 32 joints stopped clicking altogether and in 43 joints no clicking could be detected by palpation (only reported by the patient). The palpation pain report improved to a level 1 or less in 39 joints (71%) and had reached a 0 level in 23 joints (42%). Hauser with a similar technique using a 15%

dextrose Prolotherapy solution for TMJ, giving an average of 4.6 treatments, noted the NRS pain levels went from 5.9 to 2.5 in 14 patients with chronic TMJ pain.¹⁰⁹ Hauser et al. reported on the use of dextrose Prolotherapy for recurring headache and migraine pain if patients reported neck pain before or during the headache. The treatments were given into the neck and suboccipital Hackett-Hemwall trigger points.¹¹⁰ Fifteen patients were treated for either tension headaches (8) or migraine headaches (7) with a 15% dextrose Prolotherapy solution done quarterly. All study participants had at least monthly headaches prior to Prolotherapy and 67% reported headache intensity of 10 out of 10 (NRS) prior to Prolotherapy and the other 33% reported at least an 8 out of 10. After Prolotherapy, 47% had no headaches and all 100% experienced some relief from the Prolotherapy in regard to headache intensity and frequency. None reported headache intensity greater than 8 after Prolotherapy. Hauser also reported on the efficacy of 15% dextrose Prolotherapy on relieving neck pain in 98 patients treated quarterly.¹¹¹ The average length of pain prior to Prolotherapy was 4.9 years. Pain and stiffness levels prior to Prolotherapy were 5.6 and 6.7 and these decreased to 2.3 and 2.4, respectively, after an average of 4.2 Prolotherapy treatments. In a subgroup of 43 patients who were told by at least one medical doctor that there were no other treatment options available, their pain levels declined from 7.5 to 2.7.

SPECIFIC NECK PAIN

Hooper et al. did a case series on 15 patients (18 sides) with chronic whiplash related neck pain (14 patients had motor vehicle accidents) treated with intraarticular zygapophysial joint dextrose Prolotherapy injection therapy.¹¹² Intraarticular Prolotherapy was given by placing 0.5 to 1cc of 20% dextrose solution into each zygapophysial joint, after confirmation of location with radiographic contrast. The mean Neck Disability Index (NDI) was 24.7 and decreased post treatment to 14.2 (2 months), 13.5 (6 months) and 10.9 (12 months). The average change over 12 months reached statistical significance ($p < 0.0001$). Centeno et al. documented that fluoroscopically guided cervical 12.5% dextrose Prolotherapy for instability could resolve the neck instability and the pain.¹¹³ Six patients who had documented cervical instability at 11 cervical levels from a motor vehicle accident, were treated with fluoroscopically guided cervical dextrose Prolotherapy at the sites of the instability. Patients with more than 2.7 mm of absolute cervical translation and at least 50% reduction of cervical and referred pain with a two day rigid cervical

immobilization test were admitted into the study. Participants underwent three dextrose Prolotherapy injections at all sites where the cervical instability was demonstrated. The mean post-test VAS score of 3.8 was significantly less than the mean pre-test VAS score of 5.8. Radiographic analysis by blinded radiologists after dextrose Prolotherapy also showed significant reductions in extension and flexion translation of cervical vertebrae in the areas that, prior to Prolotherapy, showed instability. (See Figure 1.)

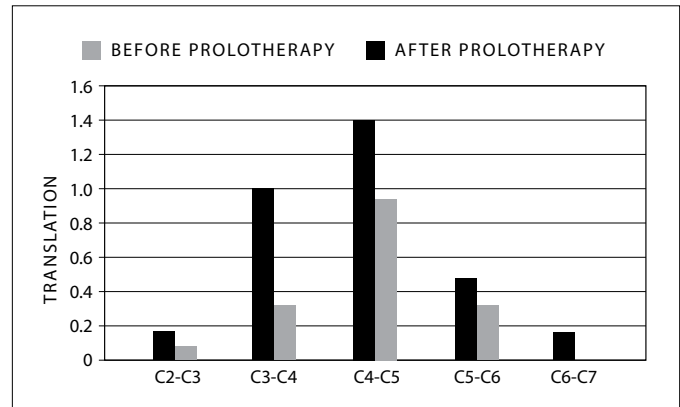


Figure 1. Translation in cervical flexion after three Prolotherapy injections.
Adapted from: Centeno CJ, Elliott J, Elkins WL. Fluoroscopically guided cervical Prolotherapy for instability with blinded pre and post radiographic reading. *Pain Physician*. 2005;8:67-72. Figure 1.

NONSPECIFIC ELBOW PAIN

A case series by Hauser involving 36 patients who suffered with elbow pain for over four years treated by using the Hackett-Hemwall technique with 15% dextrose Prolotherapy decreased elbow pain from 5.1 to 1.6, reaching statistical significance at the $p < 0.000001$ level.¹¹⁴ The patients received on average 4.3 Prolotherapy treatments and the average follow-up period was 31 months. Ninety-four percent of the patients obtained greater than 50% or more pain relief with the treatment.

LATERAL EPICONDYLAR PAIN OF THE ELBOW

Shin et al. studied 84 patients with lateral epicondylitis who were treated with dextrose Prolotherapy.¹¹⁵ The pain score was evaluated by using VAS before treatment and one month and six months after the third treatment. Ultrasonography was performed on 49 patients who were suspicious of a tendinous tear. Dextrose Prolotherapy decreased VAS from 6.79 to 2.95 which reached statistical significance ($p < 0.01$). The VAS scores decreased more in

subjects without tendinous tear (7.08 to 2.16) than those with partial tendinous tear (6.9 to 3.67) but both reached statistical significance at the $p < 0.01$ level. (See Figure 2.) Kang confirmed these results in the analysis of 12 patients with lateral epicondylitis who were treated with 15% dextrose Prolotherapy.¹¹⁶ Each patient was treated five times at monthly intervals and the results were monitored with VAS and ultrasonography before and one month after the last Prolotherapy session. VAS scores dropped from 7.12 to 2.5 after Prolotherapy which reached statistical significance ($p < 0.05$). Before Prolotherapy every case had anechoic focus without normal fibrillar pattern, which represented partial tear of the extensor tendons. Seven of the cases showed focal or diffuse hypoechoic foci with loss of normal fibrillar pattern of the tendon, indicative of tendinosis. After dextrose Prolotherapy, all of the ultrasounds showed improvements in pattern including smaller anechoic foci and a filling in of the anechoic foci with fibrillar pattern, indicative of repair of the degenerated or torn tendons. (See Figure 3.)

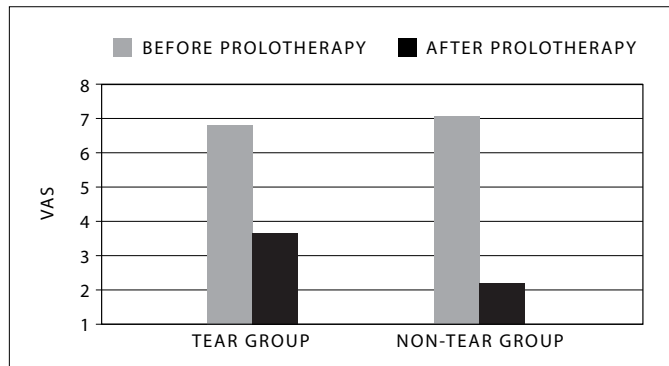
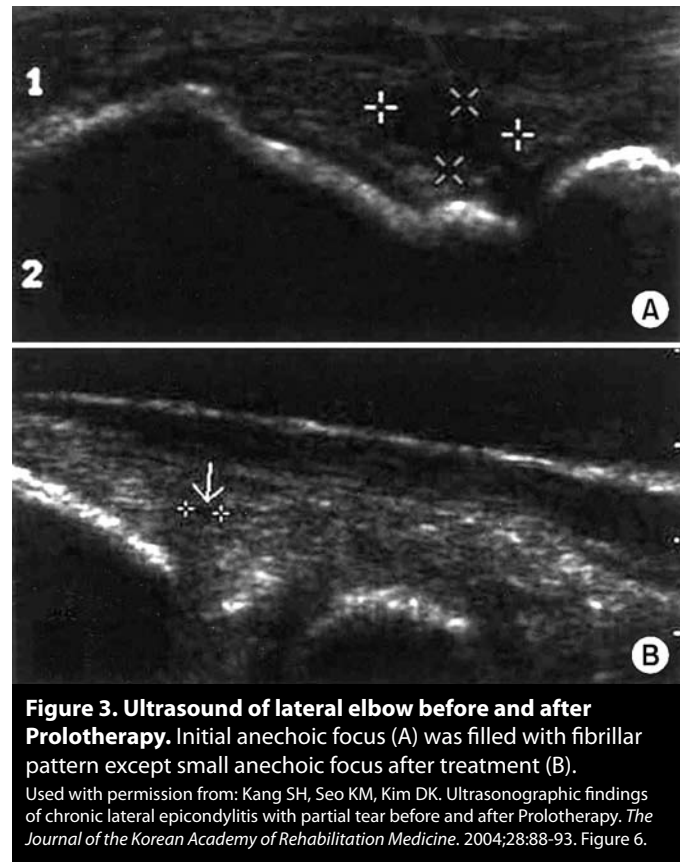


Figure 2. Comparison of treatment effect according to the findings of ultrasonography (Tear vs. Non-tear) (p < 0.01).
Adapted from: Shin JY, Seo KM, Kim DK. The effect of Prolotherapy on lateral epicondylitis of elbow. *The Journal of the Korean Academy of Rehabilitation Medicine.* 2002;26:764-768. Figure 2.

ACHILLES TENDINOPATHY

Lyftogt treated 169 Achilles tendons over a four year period with chronic Achilles tendinopathy (average length of symptoms two years) with subcutaneous dextrose Prolotherapy.¹¹⁷ Initial VAS of the group went from 6.5 to 0.5 after six treatments, with a follow-up period of two years. Ninety percent of patients were satisfied with the treatments.¹¹⁸ Maxwell published a study on the use of hyperosmolar dextrose (25%) to treat 32 patients representing 33 tendons with chronic tendinosis of the Achilles with the use of ultrasound.¹¹⁹ The patients were treated every six weeks until symptoms resolved or no improvement was



shown. The mean number of treatment sessions was 4.0. A mean percentage reduction for VAS1 (pain at rest) of 88.2% ($p < 0.0001$), for VAS2 (pain during normal daily activity) of 84.0% ($p < 0.0001$), and for VAS3 (pain during or after sporting activities) of 78.1% ($p < 0.0001$) was observed. (See Table 5.) They also documented that the dextrose Prolotherapy caused the mean tendon thickness to decrease from 11.7 to 11.1 mm ($p < 0.007$). At a mean of 12 months after treatment, 20 patients remained asymptomatic, nine experienced only mild symptoms, and one patient reported moderate symptoms.

Ryan, Wong and Taunton¹²⁰ administered a 25% dextrose-lidocaine solution intratendinously on 108 Achilles tendons in 99 patients experiencing pain for greater than six months at either the Achilles tendon insertion or midportion. Eighty-six of the cases were at the Achilles midportion, and 22 reported pain and pathology at the insertion. The chronic Achilles tendinosis were documented by ultrasound and the injections were sonographically guided. VAS items were recorded at baseline, post-treatment and at a 28.6 month follow-up. A median of five injection sessions was needed for each patient, spaced on average 5.6 weeks

Table 5. Visual Analog Scale (VAS) scores for study group before and after dextrose injection therapy treatment of chronic Achilles tendinosis.

Adapted from: Maxwell NJ, Ryan MB, Taunton JE. Sonographically guided intratendinous injection of hyperosmolar dextrose to treat chronic tendinosis of the Achilles tendon: a pilot study. *American Journal of Radiology*. 2007; October:w215-w220. Table 1.

Score	Mean VAS Score						Mean % Change in VAS Score		
	Before Therapy			After Therapy			Midportion	Insertional	Combined
	Midportion	Insertional	Combined	Midportion	Insertional	Combined			
VAS1	41.7	30.3	38.2	4.7	4.1	4.5	88.7	86.5	88.2
VAS2	55.5	45.3	52.4	7.8	9.6	8.4	85.9	78.8	84.0
VAS3	73.9	66.4	71.6	12.4	23.4	15.7	83.2	64.7	78.1

Note: Combined = both groups combined, VAS1 = pain at rest, VAS2 = pain during normal daily activity, VAS3 = pain during or after sports or other physical activity. p<0.001.

apart. A statistically significant improvement in pain scores was observed for both midportion and insertional in mean percent reduction in pain at 28 month follow-up. Midportion improvement was reported as VAS1 (pain at rest) of 30.8%, VAS2 (pain with activities of daily living) of 40.7% and VAS3 (pain with sports) of 50.4%. (See Table 6.) Pain reduction at insertional achilles reported as VAS1 of 30.2%, VAS2 of 41.3%, and VAS3 of 51.9%. Reductions in the size and severity of hypoechoic regions and intratendinous tears and improvements in neovascularity were observed.

NONSPECIFIC ANKLE, FOOT, WRIST, HAND, SHOULDER AND HIP PAIN

Hauser et al. published six other observational (pilot) studies on the use of dextrose Prolotherapy for chronic pain of the ankle, foot, wrist, hand, shoulder, and hip.¹²¹⁻¹²⁶ Hauser reported on 19 patients with chronic ankle pain (average 3.3 years) treated with 15% dextrose Prolotherapy.¹²¹ The mean number of treatments was 4.4. Starting NRS and stiffness levels were 7.9 and 5.4, respectively, and decreased to 1.6 and 1.5, respectively, at mean 21 month follow-up, reaching statistical significance. All but one patient achieved greater than 50% pain relief. Hauser performed a similar

observational study on 19 patients with chronic foot and toe pain.¹²² All 100% improved in their pain and stiffness with 15% dextrose Prolotherapy. NRS scores decreased from 7.1 to 2.3, with 18 month follow-up. The results of his study on 31 patients with chronic wrist pain showed that dextrose Prolotherapy decreased VAS from 5.5 to 1.4 after 3.6 treatments.¹²³ For the 40 patients who suffered from chronic hand and finger pain, dextrose Prolotherapy caused NRS to decrease from 5.9 to 2.6 after an average of 4.5 treatments.¹²⁴ Hauser performed a retrospective study on 61 patients representing 94 hips who had been in pain on average for 63 months, and were treated quarterly with Hackett-Hemwall dextrose Prolotherapy. Pain levels decreased from 7.0 to 2.4 (NRS) after Prolotherapy; 89% experienced more than 50% of pain relief and more than 94% showed improvements in walking and exercise ability.¹²⁵ Another retrospective study on 94 shoulders in 90 patients with an average of 53 months of unresolved shoulder pain showed that pain levels decreased with 15% dextrose Prolotherapy from 7.1 to 2.3 (NRS) after an average of 3.8 treatments with an average follow-up time of 20 months.¹²⁶ All of the Hauser studies reached statistical significance using the paired t-test for pain relief to at least the p<0.01 level. Jo et al. of Korea performed a dextrose Prolotherapy

study on 29 patients suffering from shoulder pain.¹²⁷ The 15% dextrose Prolotherapy decreased pain levels from 7.2 to 2.0 (NRS), eight weeks after the last treatment, which was statistically significant at the p<0.05 level.

Table 6. Summary of Visual Analog Scale items for patients experiencing midportion Achilles tendinosis.

Adapted from: Ryan M, et al. Favorable outcomes after sonographically guided intratendinous injection of hyperosmolar dextrose for chronic insertional midportion Achilles tendinosis. *AJR*. 2010;194:1047-1053.

Midportion Achilles	Before Prolotherapy	After Prolotherapy	At 28 month Follow-up	Mean change in ES Pretest to Post-test	Mean change in ES Pretest to Follow-up
VAS1	34.1	12.6	3.3	21.3 ^a	30.8 ^a
VAS2	50.2	21.8	9.5	28.2 ^a	40.7 ^a
VAS3	70.7	36.7	16.7	34.0 ^a	54.0 ^a

Note—ES is a measure of the effect size on the difference represented as Cohen's difference. VAS1 = pain at rest. VAS2 = pain with activities of daily living. VAS3 = pain during or immediately after sports participation. ^a Indicates a significant difference between time interval to a p value of 0.001. ES is a measure of the effect size of the difference represented as Cohen's d.

PLANTAR FASCIITIS, MEDIAL TIBIAL STRESS SYNDROME, COMPARTMENT SYNDROME AND FIBROMYALGIA

Ryan reported on the effectiveness of sonographically guided injections of hyperosmolar dextrose (25%) at reducing pain associated with chronic plantar fasciitis.¹²⁸ Twenty patients were treated at six week intervals for a median of three visits. A significant decrease ($p < 0.001$) in all mean VAS items was observed from pre-test to post-test: VAS 1 (at rest) 36.8 to 10.3; VAS 2 (ADLs) 74.7 to 25.0; and VAS 3 (sports activity) 91.6 to 38.7, and no change in their pain levels was reported at 11.8 month follow-up. Curtin also published a study using dextrose Prolotherapy under ultrasound guidance, but this involved seven patients with recalcitrant medial tibial stress syndrome.¹²⁹ Patients were treated with a 15% dextrose solution and all patients reported a marked improvement in their symptoms. A significant decrease in mean average pain was reported measured by VAS scores at four weeks and 18 weeks (both $p < 0.05$) compared to baseline. The median VAS average pain score improvement per subject was 4/10. Lyftogt treated 24 patients with the diagnosis of chronic exertional compartment syndrome of the lower extremity with weekly subcutaneous dextrose (20%) Prolotherapy and followed them prospectively.¹³⁰ The patients' mean duration of symptoms was 4.8 years. Twenty-one patients were satisfied with the results at six month follow-up. Nineteen patients had a VAS score upon follow-up of < 1 . Reeves treated 31 consecutive severe fibromyalgia patients with 12.5% dextrose Prolotherapy an average of 3.5 times.¹³¹ The patients reported an overall decrease of 32.1% of pain levels over 16 regions of their body. All regions of the body were noted to have less average pain after injection.

CHRONIC SPINAL PAIN: LITIGANTS AND NON-LITIGANTS

Researchers from several international universities collaborated to compare outcomes for litigants and non-litigants with chronic spinal pain treated with dextrose Prolotherapy.¹³² A total of 147 consecutive patients with chronic spinal pain were treated with 20% dextrose and 0.75% lidocaine into facet capsules of the cervical, thoracic, or lumbar spine, as well as the iliolumbar and dorsal sacroiliac ligaments. Injections were given on a weekly basis for up to three weeks. A set of three injections was repeated in one month if symptoms persisted and ongoing laxity was identified. Seventy-one litigants (had retained a lawyer for an unresolved claim at the start of treatment) and 76 non-litigants were treated. They were given the Neck

Disability Index, Patient Specific Functional Scale, and Roland-Morris Disability Questionnaire before treatment and approximately one year after treatment. At the 1-year follow-up, patients were also asked to rate their change in symptoms, function, and ability to work. Both litigants and non-litigants showed significant improvement from baseline on all disability scales ($p < 0.001$). There were no differences in the percentage of litigants/non-litigants reporting improvement on impression of change scales or symptoms (91%/92%), function (90%/90%), improved ability to work (76%/75%), and willingness to repeat treatment (91%/93%).

DEXTROSE PROLOTHERAPY IN LIEU OF SURGERY

Hauser followed 34 consecutive patients prospectively who were told by another medical doctor that surgery was needed to resolve their particular chronic pain problem.¹³³ Surgeries the patients were told they needed included 20 joint replacements, nine arthroscopic procedures, three fusions and four tendon/ligament repairs. Patients received on average 4.5 treatments with 15% dextrose Prolotherapy. Pain levels decreased from 7.6 to 1.3. (See Figure 4.) Ninety-one percent of patients felt Prolotherapy gave them 50% or greater pain relief. In this study, Prolotherapy was able to eliminate the need for surgery in 31 out of the 34 patients. In other studies by Hauser^{80, 81, 82, 84, 89} a similar statistically significant decrease in pain was seen after dextrose Prolotherapy (in lieu of surgery) in patients who were told by a medical doctor that surgery was their only option. (See Table 7.)

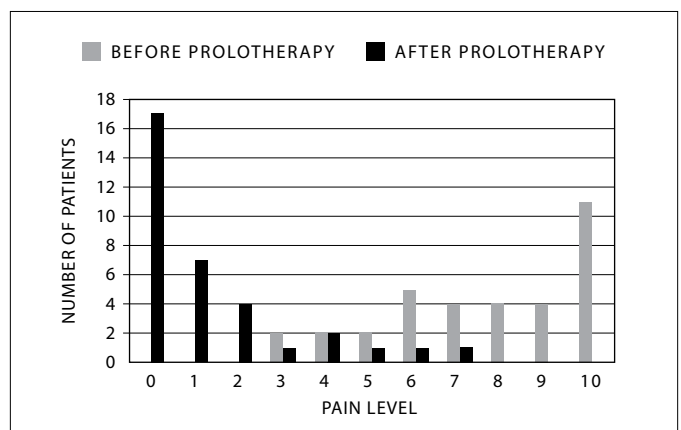


Figure 4. Before and after pain levels in 34 patients who received Hackett-Hemwall dextrose Prolotherapy in lieu of surgery.

Adapted from: Hauser R, et al. Prolotherapy as an alternative to surgery. A prospective pilot study of 34 patients from a private medical practice. *Journal of Prolotherapy*. 2010;2(1):272-281.

Table 7. Pre and post Prolotherapy results for patients told that surgery was the only option to resolve their chronic pain. ^{80, 81, 82, 84, 89}

Area treated	Average pain level prior to Prolotherapy	Average pain level after Prolotherapy	Percent of patients who reported > 50% pain relief
Knee	6.8	3.0	100%
Back	6.0	2.1	96%
Neck	6.6	2.1	90%
Shoulder	7.0	2.6	90%
Hip	7.1	2.4	100%

CONTROLLED, NONRANDOMIZED DEXTROSE PROLOTHERAPY STUDIES

Two controlled, nonrandomized dextrose Prolotherapy studies have been reported on in the medical literature. Kim et al.¹³⁴ compared the effects of local steroid injection with that of dextrose Prolotherapy on iliac crest pain syndrome. Twenty-two patients in each group were treated with either a mixture of lidocaine and triamcinalone or of dextrose and lidocaine. The effectiveness of treatment was evaluated by VAS and modified Oswestry questionnaire before injection, 30 minutes, one week, four weeks and three months after injection respectively. Both the VAS and Oswestry questionnaire improved in both groups compared to the pre-injection levels and no significant difference was observed between the group. With one treatment of dextrose Prolotherapy, the VAS improved from 8.04 to 5.74 and the steroid group from 8.13 to 5.96. Jo et al.¹³⁵ compared dextrose Prolotherapy alone and with an epidural steroid injection in the treatment of lumbar radiculopathy from a herniated nucleus pulposus, confirmed by MRI. Eighteen patients received Prolotherapy after an epidural block and five patients received just 15% dextrose Prolotherapy. The NRS score improved from 7.6 to 3.1 (eight weeks after the intervention) in the epidural/Prolotherapy group and 7.0 to 2.4 in the five patients just receiving Prolotherapy. There were no statistical differences between the two groups.

Randomized Controlled Studies on Dextrose Prolotherapy

Nine randomized controlled trials have been performed evaluating the effectiveness of dextrose Prolotherapy versus other injection and standard therapies. (See Table 8.)

DEXTROSE PROLOTHERAPY COMPARED TO STEROID FOR SACROILIAC JOINT PAIN

Kim, Less and Won from Chonnam National University Hospital in Korea performed a prospective randomized controlled trial of intraarticular 25% dextrose Prolotherapy versus steroid injection for sacroiliac joint pain.¹³⁶ The sacroiliac joint pain was confirmed by greater than 50% pain relief with a local anesthetic block in patients who experienced pain for greater than three months and had failed medical treatment. The patients' injections were all given under fluoroscopic guidance with a biweekly schedule and a maximum of three injections. Pain and disability scores were assessed at baseline, two weeks, and monthly after completion of treatment. Twenty-three patients were in the Prolotherapy group and 25 in the steroid group. The cumulative incidence of greater than 50% pain relief at 15 months was 58.7% in the Prolotherapy group and 10.2% in the steroid group, as determined by Kaplan-Meier analysis. A statistically significant difference between the two groups was observed ($p < 0.005$). (See Figure 5.) The authors concluded that intraarticular Prolotherapy provided statistically significant relief of sacroiliac joint pain, and its effects lasted longer than those of steroid injections.

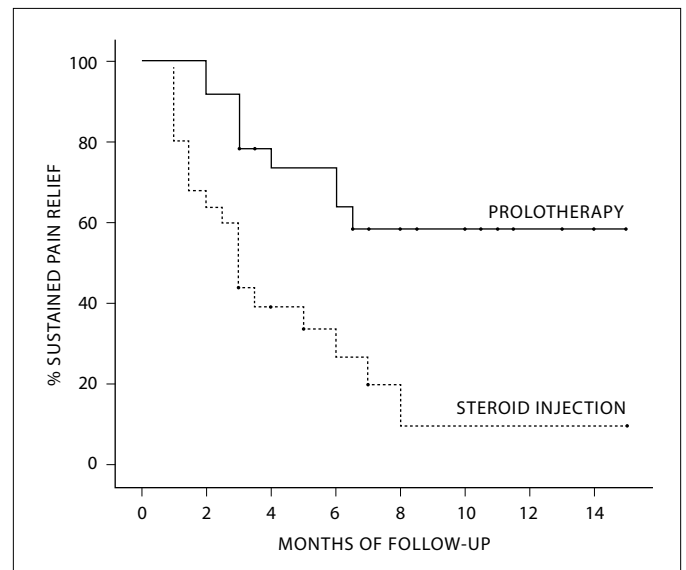


Figure 5. Kaplan-Meier plot showing cumulative incidence of sustained 50% or greater pain relief, higher in the Prolotherapy group compared to the steroid group.

Adapted from: Kim WM, Lee HG, Won CJ. A randomized controlled trial of intra-articular Prolotherapy versus steroid injection for sacroiliac joint pain. *Journal of Alternative and Complementary Medicine*. 2010;16:1285-1290. Figure 3.

Table 8. Randomized controlled trials evaluating the effectiveness of dextrose Prolotherapy versus other injection and standard therapies.

Primary Authors	Condition/Treatments	# of Patients/Joints	Results
Kim ¹³⁶	Sacroiliac pain Prolotherapy vs. Steroids	23 - dextrose 25 - steroid injection	The cumulative incidence of > 50% pain relief at 15 months: 58.7% - Prolotherapy group, 10.2% - steroid group (p<0.005).
Kim ¹³⁷	Myofascial pain syndrome dextrose vs. saline vs. lidocaine Prolotherapy	23 - dextrose 20 - saline 21 - lidocaine	VAS decrease - dextrose = 4.48, lidocaine = 2.65, saline = 2.90 (p<0.01).
Reeves ¹³⁸	Finger & thumb osteoarthritis dextrose vs. lidocaine Prolotherapy	27 total patients 74 - dextrose 76 - xylocaine	Pain with movement improved 42% in the dextrose group compared to 15% in the xylocaine group (p<0.027).
Reeves ¹³⁹	Knee osteoarthritis dextrose vs. lidocaine Prolotherapy	68 total patients 58 - dextrose 53 - lidocaine	Using the Hotelling multivariate analysis of paired observations between 0 and 6 months for pain, swelling, buckling episodes and knee flexion revealed significantly more benefit from the dextrose injection group. (p<0.015)
Total ¹⁴⁰	Osgood-Schlatter disease dextrose Prolotherapy vs. lidocaine injection vs. supervised usual care to reduce sport alteration and sport-related symptoms	54 total patients 38 - dextrose 13 - lidocaine 14 - usual care	At 1 year, asymptomatic sport (NPPS=0) was more common in dextrose-treated knees than knees treated with only lidocaine (32 of 38 vs 6 of 13; p=.024) or only usual care (32 of 38 vs 2 of 14; p<0.0001).
Rabago ¹⁴¹	Knee osteoarthritis	89 total patients 30 - dextrose 28 - saline 31 - exercise	WOMAC scores for Prolotherapy subjects showed significantly greater improvement at 52 weeks; 15.32 for Prolotherapy compared to 7.68 for saline injection and 8.25 for exercise. KPS showed similar improvement compared to baseline status (p<0.01) and controls (p<0.01).
Yelland ¹⁴²	Chronic low back pain dextrose Prolotherapy vs. saline injections & exercise vs. normal activity	110 total patients 54 - dextrose vs. 56 - saline 55 - exercise vs. 55 - normal activity	Achieved > 50% reduction in pain - glucose/lignocaine VAS: 0.46 versus saline VAS: 0.36 (p<0.05).
Yelland ¹⁴³	Achilles tendinosis dextrose Prolotherapy vs. eccentric loading exercises	14 - dextrose 15 - loading exercises 14 - combined	At 12 months, proportions achieving the minimum clinical important change for VISA-A Questionnaire (20 points) were 73% for ELE, 79% for dextrose Prolotherapy and 86% for combined treatment. Mean increases in VISA-A scores at 12 months were 23.7 for ELE, 27.5 for Prolotherapy and 41.1 for combined treatment. At six weeks and 12 months, these increases were significantly less for ELE than for combined treatment with dextrose Prolotherapy.
Refai ¹⁴⁴	Temporomandibular joint hypermobility dextrose Prolotherapy vs. saline injections	12 total patients 6 - dextrose 6 - saline	Significantly less pain intensity in both groups. The active group showed a significant reduction in MMO (maximal mouth opening) at the 12th week postoperatively.

DEXTROSE PROLOTHERAPY TRIGGER POINT INJECTIONS VERSUS SALINE AND LIDOCAINE FOR MYOFASCIAL PAIN SYNDROME

Kim, Na and Moon from Yonsei University College of Medicine in Korea did a prospective, randomized controlled study comparing 5% dextrose Prolotherapy with saline and lidocaine trigger point injections for myofascial pain syndrome.¹³⁷ Sixty-four typical myofascial pain patients

were injected with either 5% dextrose (23), normal saline (20) or 0.5% lidocaine (21) into their tender trigger points. VAS and pressure threshold algometer (kg/cm²) were used as measuring tools before, immediately after, and seven days after the injection therapies. The Mean VAS was 6.8 before treatment. Mean VAS was not significantly different in the three groups before and immediately after injections. But after seven days, only the dextrose group showed significantly

lower scores of 2.4, compared to 3.85 in the normal saline group and 4.0 in the lidocaine group ($p < 0.01$). The increase in pressure threshold with 5% dextrose compared to the other two groups also reached statistical significance. (See Tables 9 & 10.) The authors concluded that 5% dextrose should be the solution of choice for trigger point injections.

Table 9. Comparison of Visual Analog Scale (VAS) score according to solution in patients with myofascial pain syndrome.
Adapted from: Kim MY, Na YM, Moon JH. Comparison on treatment effects of dextrose water, saline, and lidocaine for trigger point injections. *Journal of the Korean Academy of Rehabilitation Medicine*. 1997;21:967-973. Table 7.

Solution	Mean		
	Before	Immediately after	7 days after
5% D/W**	6.87	4.83	2.39*
Saline	6.50	5.65	3.85
Lidocaine	6.95	5.14	4.05

* $p < 0.01$ (Kruskal-Wallis 1-way ANOVA)
** 5% Dextrose water

Table 10. Comparison of pressure threshold according to solution in patients with myofascial pain syndrome. (kg/cm²).
Adapted from: Kim MY, Na YM, Moon JH. Comparison on treatment effects of dextrose water, saline, and lidocaine for trigger point injections. *Journal of the Korean Academy of Rehabilitation Medicine*. 1997;21:967-973. Table 8.

Solution	Mean		
	Before	Immediately after	7 days after
5% D/W**	1.79	2.07	2.49*
Saline	1.70	2.02	1.91
Lidocaine	1.75	2.27	2.07

* $p < 0.05$ (Kruskal-Wallis 1-way ANOVA)
** 5% Dextrose water

DEXTROSE PROLOTHERAPY COMPARED TO LIDOCAINE FOR OSTEOARTHRITIS OF FINGERS, THUMBS AND KNEES

Reeves and Hassanein published two randomized, prospective, placebo-controlled double-blind studies on dextrose Prolotherapy for osteoarthritis of the thumb, fingers and knees.^{138, 139} In the first study, osteoarthritic thumbs and fingers were treated either with a 10% dextrose/0.075% xylocaine solution or a 0.075% xylocaine solution alone.¹³⁸ Seventy-four symptomatic osteoarthritis joints received dextrose Prolotherapy and seventy-six osteoarthritic joints received xylocaine injections. The injections into the joints was done at 0, 2, and 4 months with assessment at six months

after the first injections. Pain at rest, grip and pain with movement improved more in the dextrose group than the xylocaine group. (See Figure 6.) Pain with movement improved 42% in the dextrose group compared to 15% in the xylocaine group to reach statistical significance ($p < 0.027$). Flexion range of motion improved more in the dextrose group ($p = .003$). In a similar study on knee osteoarthritis, Reeves and Hassanein completed three bimonthly injections of 9cc of either 10% dextrose and .075% lidocaine versus .075% lidocaine solution in patients with knee osteoarthritis (grade 2) with or without ACL laxity.¹³⁹ In total, 111 knees involving 68 patients with OA participated in this double-blind randomized placebo-controlled study. The Hotelling multivariate analysis of paired observations between 0 and 6 months for pain, swelling, buckling episodes and knee flexion revealed significantly more benefit from the dextrose injection group. By 12 months (six injections) the dextrose-treated knees improved in pain (44% decrease), swelling complaints (63% decrease), knee buckling frequency (85% decrease), and in flexion range (14 degrees increase). Analysis of blinded radiographic readings of zero- and 12-month films revealed stability of all radiographic variables except for two variables which improved with statistical significance (lateral patellofemoral cartilage thickness ($p = .019$) and distal femur width in mm ($p = .021$)). In knees with ACL laxity the Hotelling multivariate analysis of paired values at 0 and 12 months for pain, swelling, joint flexion and joint laxity in the dextrose-treated knees, revealed a statistically significant improvement ($p = .021$). Individual paired *t*-tests indicated that blinded measurements of goniometric knee flexion

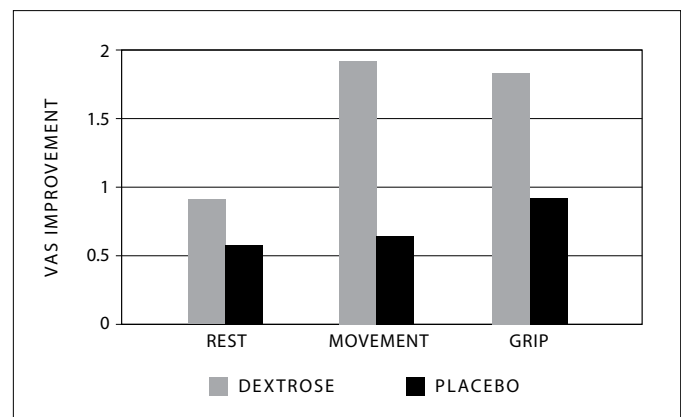


Figure 6. Improvement of Visual Analogue Scale (VAS) for rest pain, movement pain, and grip pain between 0 and 6 months in osteoarthritic joints comparing dextrose Prolotherapy versus placebo.
Adapted from: Reeves KD, Hassanein K. Randomized, prospective, placebo-controlled double-blind study of dextrose Prolotherapy for osteoarthritic thumb and finger (DIP, PIP, and trapeziometacarpal) joints: evidence of clinical efficacy. *The Journal of Alternative and Complementary Medicine*. 2000;6:311-320. Figure 1.

range improved by 12.8 degrees ($p=.005$) and anterior displacement difference improved by 57% ($p=.025$). Eight out of 13 dextrose-treated knees with ACL laxity were no longer lax at the conclusion of one year.

DEXTROSE PROLOTHERAPY VERSUS LIDOCAINE INJECTIONS VERSUS USUAL CARE

Topol et al.¹⁴⁰ performed a double-blind randomized placebo-controlled trial to evaluate dextrose Prolotherapy in the treatment of Osgood-Schlatter disease. Patients with recalcitrant Osgood-Schlatter disease greater than three months duration were enrolled if they demonstrated anterior knee pain in the absence of either patellofemoral crepitus or patellar origin of tenderness, were able to replicate the exact severity and locality of pain to the tibial tuberosity during a single leg squat, and who had not benefited from two months of progressive strength training and physical therapy. Upon enrollment, patients (girls aged nine to 15 and boys aged 10 to 17) were randomized to injections of either dextrose 12.5% with lidocaine 1% ($n=21$) or lidocaine 1% ($n=22$), or usual care, i.e., supervised exercise ($n=22$). Patients received injections at zero, one, and two months under double-blind conditions; at three months, subjects not achieving an Nirschl Pain Phase Scale (NPSS) score of 0 were offered monthly dextrose injection as needed under open-label conditions. The mean age (range) of patients was 13.3 (9-17).

In the dextrose group, the mean (SD) NPSS scores at baseline and six months, and the mean (SD) difference between zero and six months were 4.6 (1.0) and 0.7 (1.2), 3.9 (0.3), $p<0.0001$; for the lidocaine group, 4.2 (1.0) and 1.8 (1.4), 2.4 (0.3), $p<0.0001$; and for the usual care group, 4.3 (1.0) and 3.1 (1.6), 1.2 (0.4), $p<0.0001$. Between-groups analysis found significantly greater reductions in mean NPSS score in the dextrose group than in the lidocaine ($p=0.004$) and usual care groups ($p<0.0001$), and significantly greater reduction in the lidocaine versus usual care group ($p=0.024$).

After three months, nine lidocaine-treated and eight usual care-treated patients switched to dextrose for a total of 38 recipients (plus the original 21 dextrose patients); the remainder of patients continued their assigned treatment. At one year, patients with NPSS score <4 by treatment in previous nine months were dextrose, 38/38; lidocaine, 12/13; and usual care, 10/14. Between-group differences were dextrose vs. lidocaine, $p=0.518$; dextrose vs. usual care, $p=0.008$; and lidocaine vs. usual care, $p=0.139$.

At one year, patients with an NPSS score of 0 by treatment in previous nine months were dextrose, 32/38; lidocaine, 6/13; and usual care, 2/14. Between-group differences were dextrose vs. lidocaine, $p=0.024$; dextrose vs. usual care, $p<0.0001$; and lidocaine vs. usual care, $p=0.005$.

DEXTROSE PROLOTHERAPY VERSUS SALINE INJECTIONS AND EXERCISE FOR KNEE OSTEOARTHRITIS

Rabago and associates at the University of Wisconsin performed a double-blind, three armed randomized placebo-controlled trial to evaluate dextrose Prolotherapy for chronic knee osteoarthritis.¹⁴¹ The injector, all assessors and injection group subjects were blinded to the group allocations of either Prolotherapy, saline injections, or at-home exercises. Blinded injections were performed at one, five, and nine weeks with as-needed injection session at weeks 13 and 17. A single intraarticular injection was given along with extra-articular injections done at peri-articular tendon and ligament insertion points. Exercise subjects received an exercise manual and in-person instruction on home exercises to perform. The primary outcome measure was a composite score on the Western Ontario McMaster University Osteoarthritis Index (WOMAC; 100 points); the secondary outcome measure was the Knee Pain Scale (KPS); both done at baseline, 5, 9, 12, 26 and 52 weeks.

Eighty-nine subjects with moderate to severe knee osteoarthritis received an average of 4.3 Prolotherapy injection sessions over a 17-week treatment period. All groups reported improved composite WOMAC scores compared to baseline status ($p<0.01$) at 52 weeks. However, WOMAC scores for Prolotherapy subjects, adjusted for gender, age and body mass index showed significantly greater improvement on WOMAC score at 52 weeks; 15.32 for Prolotherapy compared to 7.68 for saline injection and 8.25 for exercise. KPS scores of Prolotherapy subjects showed similar improvement per injected knee compared to baseline status ($p<0.001$) and controls ($p<0.01$). There were no adverse events reported.

DEXTROSE PROLOTHERAPY VERSUS SALINE INJECTIONS AND EXERCISE FOR CHRONIC LOW BACK PAIN

Yelland, Galsziou and Bogduk conducted a randomized controlled trial with two-by-two factorial design, triple-blinded for injection status, and single-blinded for exercise status comparing dextrose Prolotherapy and saline injections

for chronic low back pain.¹⁴² One-hundred-ten participants with nonspecific low back pain of average 14 years duration were randomized to receive repeated dextrose Prolotherapy (n=54) (20% glucose/0.2% lignocaine) or normal saline injections (n=56) into tender lumbopelvic ligaments and randomized to perform either flexion/extension exercises (n=55) or normal activity (n=55) over six months. Pain intensity (VAS) scores at 2.5, 4, 6, 12, and 24 months were taken. Ligament injections, with exercises and with normal activity, resulted in significant and sustained reductions in pain and disability throughout the trial. At 12 months, the proportions achieving more than 50% reduction in pain from baseline by injection group were glucose/lignocaine: 0.46 versus saline 0.36. The authors noted that participants exhibited marked and sustained improvements in their chronic low back pain and disability with the glucose/lignocaine injections for two years, but this also occurred in the saline group. In this study, both the dextrose Prolotherapy and saline group reached statistical significance at the $p < 0.05$ level for improvements in VAS pain intensity and disability score.

DEXTROSE PROLOTHERAPY COMPARED TO ECCENTRIC LOADING EXERCISES FOR ACHILLES TENDINOSIS

Yelland and associates at Griffith University in Queensland Australia completed a single-blinded randomized clinical trial comparing the cost-effectiveness of eccentric loading exercises (ELE) with dextrose Prolotherapy injections used singly and in combination for painful Achilles tendinosis.¹⁴³ Participants were randomized to a 12 week program of eccentric loading exercises (n=15) or Prolotherapy injections of hypertonic glucose with lignocaine alongside the affected tendon (n=14) or combined treated (n=14). At 12 months, proportions achieving the minimum clinical important change for VISA-A Questionnaire (20 points) were 73% for ELE, 79% for dextrose Prolotherapy and 86% for combined treatment. Mean increases in VISA-A scores at 12 months were 23.7 for ELE, 27.5 for Prolotherapy and 41.1 for combined treatment. At six weeks and 12 months, these increases were significantly less for ELE than for combined treatment with dextrose Prolotherapy. Combined treatment with dextrose Prolotherapy had the lowest incremental cost per additional responder compared with ELE.

DEXTROSE PROLOTHERAPY VERSUS SALINE INJECTIONS FOR TEMPOROMANDIBULAR JOINT HYPERMOBILITY

Colleagues at the University of Cairo, all faculty of Oral and Dental Medicine, completed a randomized, double-blind, placebo-controlled clinical trial on 12 patients with painful subluxation or dislocation of the temporomandibular joint.¹⁴⁴ Patients were treated with four injections into and around their temporomandibular joint with 3cc solution of 10% dextrose and mepivacaine or with saline and mepivacaine. Each person was given two series of injections six weeks apart. A numeric score scale (0 to 10) expressing TMJ pain on palpation, maximal mouth opening, clicking sound, and frequency of subluxations (number of locking episodes per month) were assessed at each injection appointment just before the injection procedure and three months after the last injection. By the end of the study, each group showed significant improvement in TMJ pain on palpation and number of locking episodes and insignificant improvement in clicking sound. With the exception of MMO, there were no statistically significant differences throughout the study intervals between the active and placebo groups. The dextrose Prolotherapy group showed a significant reduction in MMO compared to the saline group at the 12th week post injection. The authors concluded, "Prolotherapy with 10% dextrose appears promising for the treatment of symptomatic TMJ hypermobility, as evidenced by the therapeutic benefits, simplicity, safety, patients' acceptance of the injection technique, and lack of significant side effects."

Discussion

In this scientific literature review, data from 44 case series, two nonrandomized controlled trials and nine randomized controlled trials were evaluated for the effectiveness of dextrose Prolotherapy for musculoskeletal pain. This is the first scientific literature review to focus solely on *dextrose* Prolotherapy. It is generally accepted in the pain literature that a change on the Visual Analogue Scale (VAS) or Numeric Rating Scale (NRS) (0 to 10 scales) of 3 or a percentage change of 40% or more comparing the pre- and post- therapy pain levels designates a clinically significant change from the therapy tested, though one international consensus regarding low back pain proposed a change of 1.5 on the VAS and 2 for the NRS.¹⁴⁵⁻¹⁵¹ In 93% of the case series in this review (25 out of 27) that used these pain

scales, dextrose Prolotherapy met this criteria. (See Table 11.) These 27 case series represent 1,398 patients having 1,478 treated areas, whose data when pooled showed a decline of 4.41 on the VAS and NRS for pain relief. This amount of pain relief is clinically significant based on the standards used to judge other pain therapies.

Level of Evidence for Dextrose Prolotherapy

Two of the most commonly used methods to determine quality of evidence in medicine are the Oxford Centre of Evidence-Based Medicine (CEBM) and the U.S. Preventative Services Task Force (USPSTF) quality of evidence grades. Strengths of therapeutic recommendations are subsequently made from this information.

The Oxford Centre of Evidence-Based Medicine has separated the types of studies into five categories or levels of evidence to help clinicians determine the value of the results reported.^{152, 153} (See Table 12.) Level 1 evidence represents the best and most unbiased information and represents randomized controlled clinical trials. Level 2 evidence arises from nonrandomized cohort studies, while level 3* evidence is attained from retrospective case-control studies whereas Level 4 evidence is from case series. Anecdotal or animal evidence is considered level 5. The U.S. Preventative Services Task Force grades the quality of the overall scientific evidence for a therapy on a 3-point scale.¹⁵⁴⁻¹⁵⁶ (See Table 13.) The good evidence grade includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes. Fair evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies. The USPSTF then grades its recommendations according to one of five classifications (A,B,C,D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms). (See Table 14.) According to the U.S. Preventative Services Task Force (USPSTF) level A evidence means the USPSTF strongly recommends that clinicians provide the service to eligible patients. The USPSTF, at this level of evidence, found good evidence that the service improves important health outcomes and concludes that benefits outweigh harms. In level B evidence, the USPSTF recommends that clinicians provide this service to eligible patients. The USPSTF found with level B evidence, at least

fair evidence that the service improves important health outcomes and concludes that benefits outweigh harms.

TENDINOPATHY AND MYOFASCIAL PAIN SYNDROME

Strong level 1 evidence demonstrates that dextrose Prolotherapy results in substantially reduced pain levels and pain-free resumption of sport activities in Osgood-Schlatter disease.¹⁴⁰ There is level 3 and 4 evidence of statistically and clinically significant reduction in pain from baseline to last follow-up in Achilles tendinosis,^{117, 119, 120} lateral epicondylitis,^{115, 116} overuse patellar tendinopathy,¹⁰⁶ plantar fasciitis,¹²⁸ and chronic groin pain.⁹⁷ There is level 2 evidence that dextrose Prolotherapy significantly improves pain and trigger point sensitivity to pressure in myofascial pain syndrome.¹³⁷

LIGAMENT AND MENISCUS INJURY

Level 1, 3 and 4 evidence confirms that dextrose Prolotherapy results in statistically significant pain relief and return of function from ligament injury of the sacroiliac joint,^{95, 96, 136} knee,^{102, 104} and neck.^{112, 113} There is also level 3 evidence that dextrose Prolotherapy provides pain relief and improvement in exercise ability and activities of daily living from meniscus degeneration and tears.¹⁰³

OSTEOARTHRITIS AND DEGENERATIVE CONDITIONS

Strong level 1 evidence exists showing that dextrose Prolotherapy results in significant improvement in osteoarthritis-related function¹⁴¹; pain and swelling^{139, 141}; and buckling episodes, knee flexion range, lateral patellofemoral cartilage thickness, distal femur width, ADD and laxity in patients with knee osteoarthritis.¹³⁹ Level 1 evidence shows significant improvement in pain with movement, flexion range, and joint narrowing in patients with osteoarthritic finger and thumb joints.¹³⁸

SPINAL PAIN

There is level 1 evidence that dextrose Prolotherapy results in significantly greater long-term pain reduction than corticosteroid injection in patients with sacroiliac joint pain.¹³⁶ Level 2 evidence supports the fact that dextrose

* Opinions differ as to what truly represents a level 3 versus a level 4 study. As a group, the case series in this literature review comprise unresolved chronic pain patients who did not respond to previous traditional treatments. The cohort groups are the untreated patients before dextrose Prolotherapy.

Table 11. Effectiveness of Prolotherapy for musculoskeletal (MLS) pain. Description of case studies on dextrose Prolotherapy.

Primary Authors	Condition	# of Patients/ Treated areas	VAS or NRS (0-10)		
			Before	After	Decrease
Kim ⁷⁸	Chronic MLS pain	67	7.0	2.55	4.5
Kim ⁷⁹	Chronic MLS pain	20	–	–	Reduced by 80%
Hauser ⁸⁰⁻⁹⁰ (11 Studies)	Chronic MLS pain	709	6.3	2.2	4.1
Lyftogt ⁹¹	Chronic MLS pain	127	6.7	0.76	5.9
Hooper ⁹²	Chronic MLS pain	177	–	–	91% of patients had a decreased level of pain*
Lyftogt ⁹⁴	Low back pain	41	7.6	1.4	6.2
Lee ⁹⁵	Sacroiliac pain	20	6.0	1.0	NRS 5.0, Oswerty Disability Index 34.1-12.6*
Cusi ⁹⁶	Sacroiliac pain	25	–	–	Positive clinical outcomes for 76% at the 3 month, 76% at 12 month, and 32% at 24 month follow up on all clinical measures (QBPDS, RMQ, RM Multi)*
Topol ⁹⁷	Osteitis pubis	24	6.3	1.0	VAS 5.3, Nirschl Pain Phase Scale 5.3-0.8
Naeim ⁹⁸	lilolumbar syndrome	7	–	–	86% reported good results*
Khan ⁹⁹	Coccygodynia	37	8.5	2.5	5.8
Miller ¹⁰⁰	Lumbar disc pain	33	–	–	6.3 (responder group)
Miller ¹⁰⁰	Lumbar disc pain	43	–	–	< 20% pain relief (non responder group)
Jo ¹⁰²	Knee ligament injury	40	8.0	1.3	6.7
Hauser ¹⁰³	Meniscus injury	28	7.2	1.6	5.6
Reeves ¹⁰⁴	ACL injury	16	–	–	VAS1-45%, VAS2-43%, VAS3-35%
Kim ¹⁰⁵	Knee osteoarthritis	20	6.5	2.65	VAS-3.8, Total WOMAC 38.53-13.47
Ryan ¹⁰⁶	Patellar tendinopathy	47	–	–	VAS1-19.7, VAS2-25.3, VAS3-39.3
Hakala ¹⁰⁷	TMJ dysfunction	26	–	–	Clicking improved in 73%; Pain improved in 81%
Hakala ¹⁰⁸	TMJ dysfunction	55	–	–	42% of pain cured (0), 71% < 1 (0-5 pain scale)*
Hauser ¹⁰⁹	Headache pain	15	–	–	39% reported 100% improvement, 100% received relief in frequency & intensity*
Hooper ¹¹²	Whiplash neck pain	15	24.7	10.9	Neck Disability Index (p<0.0001)*
Centeno ¹¹³	Cervical instability	6	5.8	3.8	2.0
Shin ¹¹⁵	Lateral epicondylitis	84	6.79	2.95	3.8
Kang ¹¹⁶	Lateral epicondylitis	12	7.12	2.5	4.6
Lyftogt ¹¹⁷	Achilles tendinopathy	169	6.5	0.5	6.0
Maxwell ¹¹⁹	Achilles tendinosis	33	–	–	VAS1-88%, VAS2-84%, VAS3-78% (p<0.0001)
Ryan ¹²⁰	Achilles tendinopathy	108	–	–	Midportion: VAS1-30.8, VAS2-40.7, VAS3-50.4 Insertional: VAS1-30.2, VAS2-41.3, VAS3-51.9
Jo ¹²⁷	Shoulder pain	29	7.2	2.0	5.2
Ryan ¹²⁸	Plantar fasciitis	20	–	–	VAS1-26.5, VAS2-49.7, VAS3-52.9, (p<0.001)
Curtin ¹²⁹	Medial tibial stress syndrome	7	–	–	4.0
Lyftogt ¹³⁰	Chronic exertional compartment syndrome	24	–	–	21 patients were satisfied with results at 6 month follow-up
Reeves ¹³¹	Fibromyalgia	31	4.86	3.30	32% average overall pain reduction
Hooper ¹³²	Chronic lumbar pain	35/62	12.3/8.9	7.1/4.3	Litigants/Non-litigants. RMDQ (0-24). Before: p=0.001. After: p=0.02*
Hooper ¹³²	Chronic thoracic pain	50/20	3.0/4.7	5.9/6.7	Litigants/Non-litigants. Patient specific functional (0-10). Before: p=0.0003. After: p=0.27*
Hooper ¹³²	Chronic cervical pain	23/3	22.3/20.3	14.3/10.7	Litigants/Non-litigants. NDI scores (0-50). Before: p=0.63. After: p=0.49*
Hauser ¹³³	In lieu of surgery	34	7.6	1.3	6.3

* No VAS or NRS.

Table 12. Levels of clinical evidence and study design.

Adapted from: Oxford Centre for evidence-based medicine. <http://www.cebm.net>.

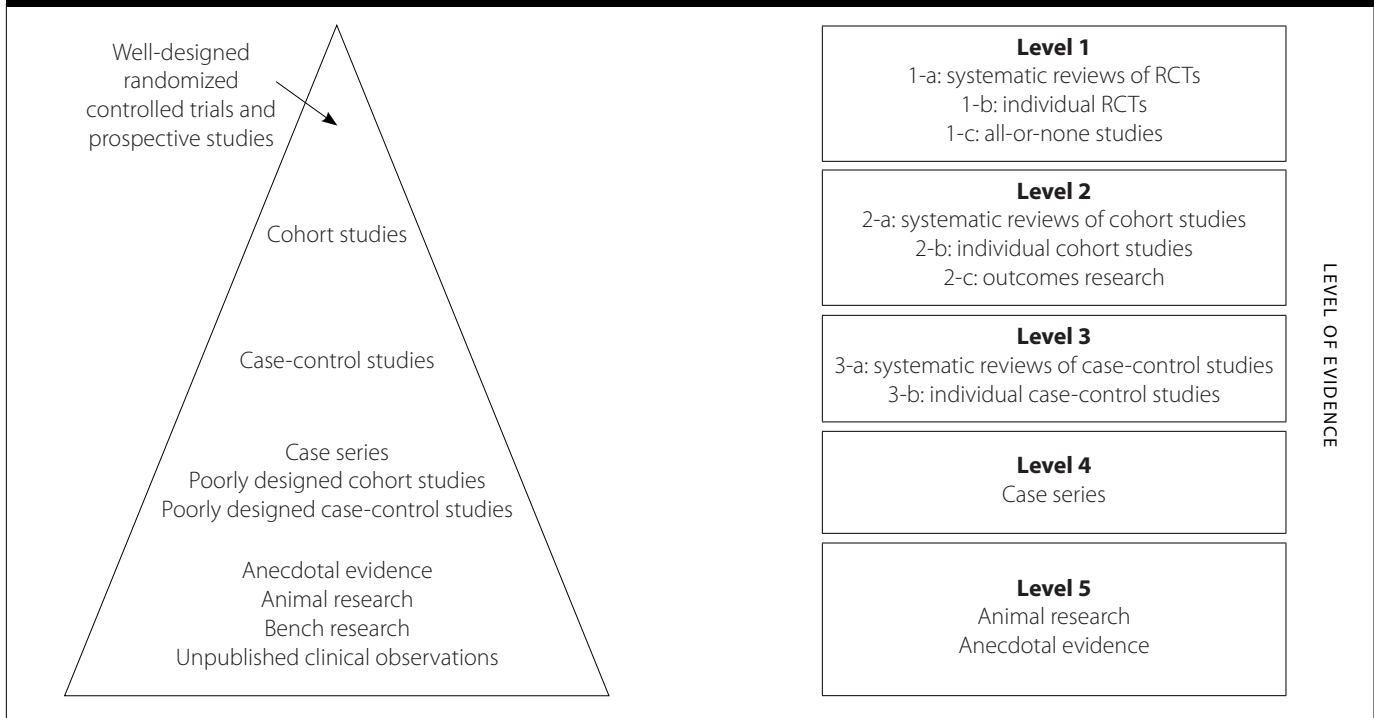


Table 13. U.S. Preventative Services Task Force quality of evidence grades. The USPSTF grades the quality of the overall evidence for a service on a 3-point scale (good, fair, poor).

Good	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.
Fair	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.
Poor	Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

post-MVA neck pain and disability,¹¹³ significant reduction in pain and disability in patients with low back and pelvic pain,⁹⁵ chronic spinal pain,⁹² and sacroiliac pain^{95, 96} significant pain reduction in patients with coccygodynia,⁹⁹ and significant reduction in neck pain disability in patients with chronic whiplash pain.¹¹²

Table 14. U.S. Preventative Services Task Force strength of recommendations. The USPSTF grades its recommendations according to one of five classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms).

A.	Good scientific evidence suggests that the benefits of the clinical service substantially outweigh the potential risks. Clinicians should discuss the service with eligible patients.
B.	At least fair scientific evidence suggests that the benefits of the clinical service outweighs the potential risks. Clinicians should discuss the service with eligible patients.
C.	At least fair scientific evidence suggests that there are benefits provided by the clinical service, but the balance between benefits and risks are too close for making general recommendations. Clinicians need not offer it unless there are individual considerations.
D.	At least fair scientific evidence suggests that the risks of the clinical service outweighs potential benefits. Clinicians should not routinely offer the service to asymptomatic patients.
I.	Scientific evidence is lacking, of poor quality, or conflicting, such that the risk versus benefit balance cannot be assessed. Clinicians should help patients understand the uncertainty surrounding the clinical service.

Prolotherapy produces short-term improvement in pain and disability comparable to corticosteroid injection in patients with iliac crest pain syndrome.¹³⁴ There is level 3 evidence of good clinical outcome in patients with chronic iliolumbar syndrome,⁹⁸ significant and comparable improvement in pain and disability between patients with chronic cervical, thoracic or lumbar pain actively involved versus not involved in litigation,¹³² and significant and comparable pain reduction in patients with lumbar herniated nucleus pulposus whether or not they received epidural block prior to Prolotherapy.¹³⁵ Level 3 and 4 evidence shows significant pain reduction and significant correlation between changes in pain level and radiographic findings in patients with

CHRONIC MUSCULOSKELETAL PAIN

Level 3 and 4 evidence supports the use of dextrose Prolotherapy for significant relief of chronic musculoskeletal pain,^{78, 79, 92, 132} as well as diffuse musculoskeletal pain involving the ankle,⁸³ elbow,^{90, 91} foot,⁸⁶ hand,⁸⁵ hip,⁸⁴ knee,^{82, 91} shoulder,^{81, 91, 127} back,^{80, 94} neck,⁸⁹ temporomandibular joint,^{88, 107, 108} and wrist.⁸⁷

THE EFFECTIVENESS OF DEXTROSE PROLOTHERAPY FOR MUSCULOSKELETAL PAIN

In this review, we found fair to high quality evidence to support the use of dextrose Prolotherapy for musculoskeletal pain. (See Table 15.) There is level 1 and grade A evidence to support the use of dextrose Prolotherapy in the treatment of Osgood-Schlatter disease, myofascial pain syndrome, knee osteoarthritis, tendinopathy and pain involving the sacroiliac joint. Level 3 and grade B evidence exist to support the use of dextrose Prolotherapy for chronic and/or diffuse musculoskeletal pain involving the spine and peripheral joints. Of the nine randomized double-blind controlled clinical trials, seven found dextrose Prolotherapy significantly more effective than saline injections and standard therapies for musculoskeletal pain. The two other double-blind controlled clinical trials showed statistically significant reduction of pain in the pre- and post-dextrose Prolotherapy patients. The 44 case series, comprised of 2,296 areas treated, consistently showed a statistically significant decline in pain levels when before and after dextrose Prolotherapy pain levels were compared using statistical analyses including a matched paired *t*-test. While these case studies are not comparing dextrose Prolotherapy to another manner of treatment, they have the advantage of assessing the effectiveness of dextrose Prolotherapy that patients and doctors encounter in clinical practice. Though they lack the methodological strengths of randomization

and control, the case studies documented in this review show overwhelming positive outcomes for clearly long-term, documented chronic musculoskeletal pain. Most of the patients treated in these case studies clearly had failed standard traditional care and had chronic *progressive* musculoskeletal conditions that typically cause debilitating pain as time goes on.

While the gold standard in scientific research is randomized, controlled trials, the USPSTF and others have acknowledged the valid contribution of evidence generated by a wide range of different types of research and that the ultimate goal for broad-ranging recommendations is what would be the expected outcome in actual practice circumstances.¹⁵⁹⁻¹⁶² The USPSTF’s own procedure manual notes, “The USPSTF seeks to make recommendations based on projections of what would be expected from widespread implementation of the preventive service with the actual world of U.S. medical practice. For this reason, the Task Force considers carefully the applicability to medical practice of ‘efficacy’ studies, which measure the effects of the preventive care service under ideal circumstances. However, the USPSTF ultimately seeks to base its recommendations on ‘effectiveness’ which is what results could be expected with widespread implementation under usual practice circumstances.”¹⁶³ While dextrose Prolotherapy meets the standard for effectiveness, which is typically the focus on medical therapeutics, dextrose Prolotherapy exhibits a myriad of other benefits that make it appropriate for widespread use including appropriateness, feasibility and affordability.^{159, 160} That is, evidence demonstrates that the intervention works, but also that it can be implemented and fulfills the needs of its consumers. Dextrose Prolotherapy, being a simple cost-effective procedure, can be utilized in any physician office and allows patients to resume normal activities almost immediately. These dimensions provide the evidence that dextrose Prolotherapy meets the gold standard in the use for musculoskeletal pain.

Table 15. Oxford level of evidence and USPSTF evidence grade backing the use of Prolotherapy in various conditions.

Condition	Oxford level of evidence	USPSTF evidence grade
Low back pain	1, 2	A, B
Myofascial pain	1	A
Osgood-Schlatter	1	A
Osteoarthritis (knee)	1	A
Tendinopathy	1, 3	A, B
Chronic Musculoskeletal Pain	3	B
Ligament Injury	1, 3, 4	A, B

ADVERSE EFFECTS

In the vast majority of studies presented in this review, no adverse events or side effects associated with dextrose Prolotherapy were reported. When there were side effects they were minor including pain after the injection, dizziness during the injection, or hematoma.⁷⁹ Dextrose itself is extremely safe even if given intravenously. As of 1998, FDA records for intravenous 25% dextrose solution reported no adverse events to Abbott Labs in 60 years.¹⁶⁴ Previous authors have documented the safety of Prolotherapy and

that adverse effects such as pneumothoraces typically relate to needle placement and not the solutions used.^{165, 166}

STRENGTHS AND LIMITATIONS

It is probable that the currently available literature search on dextrose Prolotherapy was covered during this scientific literature review because dextrose as the sole proliferant for Prolotherapy was first used in the United States by Gustav Hemwall, MD and thus taught to doctors primarily in the United States and English-speaking countries.¹⁶⁷ Dextrose Prolotherapy is not widely available in non-English speaking countries except Korea, so it is doubtful that dextrose Prolotherapy scientific literature was missed because it occurred in another language. The available literature in Korea was translated and available for this review. Screening references of identified case series and trials may result in an over representation of positive studies in this review, because trials with a positive result are more likely to be referred to in other publications, leading to reference bias. It is possible that relevant literature on this topic was inadvertently missed.

IMPLICATIONS FOR RESEARCH

While some studies have been performed to delineate the biological effects of dextrose Prolotherapy, more objective evidence is needed to document tissue response in patients receiving the therapy. Recent advances in ultrasound technology are helping pain clinicians document injuries and improvements with soft tissue interventions. Musculoskeletal ultrasound has been used to document several case series on ligament and tendon tears and injuries repaired with dextrose Prolotherapy.^{168, 169} Larger and controlled studies with ultrasound and/or MRI documentation comparing the regenerative effects of dextrose Prolotherapy to more standard therapies is warranted. Histologic and arthroscopic evaluation of degenerated soft tissues and joints before and after dextrose Prolotherapy, as is being done in one international study,¹⁷⁰ on treated patients would provide the best objective data on dextrose Prolotherapy. Future studies that compare dextrose Prolotherapy to traditional non-injection therapies such as exercise and physical therapy will help clarify the independent role dextrose Prolotherapy could have in the treatment of musculoskeletal pain.

IMPLICATIONS FOR PRACTICE

Clinicians should make their recommendations to patients on the basis of unbiased summaries of the best available

evidence, which are typically represented through systematic reviews and meta-analyses.^{171, 172} In patients with chronic musculoskeletal pain, fair to good quality evidence exists to support the use of dextrose Prolotherapy for pain relief and improvement of function. Potential benefits greatly outweigh the possible adverse side effects. According to the U.S. Preventative Services Task Force grade definitions for strength of recommendations,¹⁵⁶ there is level A and B evidence to support the use of dextrose Prolotherapy for musculoskeletal pain. Level 1 evidence supports the use of dextrose Prolotherapy for knee osteoarthritis, myofascial pain syndrome, sacroiliac pain, Osgood-Schlatter disease, and tendinopathy. Given this body of evidence, clinicians should discuss or provide this service to eligible patients. Dextrose Prolotherapy is one therapy that should be utilized to promote healing of chronically injured soft tissues that cause musculoskeletal pain. If future studies confirm that simple dextrose Prolotherapy stimulates healing for ligament, tendon, cartilage and other musculoskeletal tissues, then dextrose Prolotherapy would be an inexpensive and effective method of repair stimulation that would prove cost-effective for many chronic musculoskeletal conditions.

OPEN ACCESS

The article is distributed under the terms of Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited. ■

BIBLIOGRAPHY

1. Woolf A. Burden of major musculoskeletal conditions. *Bulletin of the World Health Organization*. 2003;81:646-656.
2. United States Bone and Joint Decade: *The Burden of Musculoskeletal Disease in the United States*. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2006.
3. Hottman J. Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation-United States, 2003-2005. *Morbidity and Mortality Weekly Report*. 2006;55:1089-1092.
4. Yelin E. National and state medical expenditures and lost earnings attributable to arthritis and other rheumatic conditions-United States, 2003. *Morbidity and Mortality Weekly Report*. 2007;56:4-7.
5. Kim S. Changes in surgical loads and economic burden of hip and knee replacements in the US: 1997-2004. *Arthritis and Rheumatism*. 2008;59:481-488.
6. Musculoskeletal procedures account for over ten percent of all hospital care in the United States. *U.S. Department of Health and Human Services Agency for Healthcare Research and Quality*. Available at <http://www.ahrq.gov/research/aug07/0907RA32.htm>. Accessed August 2007.

7. Hauser R. The deterioration of articular cartilage in osteoarthritis by corticosteroid injections. *Journal of Prolotherapy*. 2009;1:107-123.
8. American Academy of Orthopaedic Surgeons 2006 Annual Meeting. Chicago, March 22 - 26, 2006. Available at: <http://www.medscape.com/viewcollection/5217>. Accessed on August 17, 2011.
9. Weinstein JN, et al. United States trends and regional variations in lumbar spine surgery: 1992-2003. *Spine*. 2006;31:2707-2714.
10. Hackett G. *Ligament and Tendon Relaxation Treated by Prolotherapy*. Third Edition. Springfield, IL: Charles C. Thomas, 1958.
11. Hackett G. Joint stabilization: an experimental, histologic study with comments on the clinical application in ligament proliferation. *American Journal of Surgery*. 1955;89:968-973.
12. Hackett G. Back pain following trauma and disease – Prolotherapy. *Military Medicine*. 1961;July:517-525.
13. Hackett G. Prolotherapy in whiplash and low back pain. *Postgraduate Medicine*. 1960;February:214-219.
14. Liu Y. An in situ study of the influence of a sclerosing solution in rabbit medial and collateral ligaments and its junction strength. *Connective Tissue Research*. 1983;2:95-102.
15. Maynard J. Morphological and biomechanical effects of sodium morrhuate on tendons. *Journal of Orthopaedic Research*. 1985;3:236-248.
16. Hackett G. Shearing injury to the sacroiliac joint. *Journal of the International College of Surgeons*. 1954;22:631-642.
17. Schultz L. A treatment of subluxation of the temporomandibular joint. *Journal of the American Medical Association*. September 25, 1937.
18. Hooper R, et al. Case series on chronic whiplash related neck pain treated with intraarticular zygapophysial joint regeneration injection therapy. *Pain Physician*. 2007;10:313-318.
19. Hauser R, et al. *Prolo Your Pain Away!* Third Edition. Beulah Land Press, Oak Park, IL, 2007.
20. Hauser R, et al. *Prolo Your Sports Injuries Away!* Beulah Land Press, Oak Park, IL, 2001.
21. Reeves K. Sweet relief: Prolotherapy targets sprains and strains. *Biomechanics*. 2004;9:24-35.
22. Reeves K. Prolotherapy for patients with musculoskeletal disorders. *Journal of Musculoskeletal Medicine*. 2002;390-301.
23. Reeves K. Prolotherapy: basic science, clinical studies, and technique. In Lennard TA (ED). *Pain Procedures in Clinical Practice*. (2nd Edition). Philadelphia; Hanley and Belfus; 2000:172-190.
24. Jensen K, et al. Response of knee ligaments to Prolotherapy in a rat injury model. *American Journal of Sports Medicine*. 2008;36:1347-1357.
25. Jensen K, et al. Early inflammatory response of knee ligaments to Prolotherapy in a rat model. *Journal of Orthopedic Research*. 2008;26:816-823.
26. Lyftogt J. Prolotherapy for recalcitrant lumbago. *Australias Musculoskeletal Medicine Journal*. 2008;13:18-20.
27. Lyftogt J. Subcutaneous Prolotherapy for Achilles tendinopathy. *Australias Musculoskeletal Medicine Journal*. 2007;12:107-109.
28. Gedney E. Use of sclerosing solution may change therapy in vertebral disc problems. *Osteopathic Profession*. 1952;April:11-13, 34,38-39.
29. Reeves K. Technique of Prolotherapy. In Lennard TA (ed): *Physiatric Procedures in Clinical Practice*. Philadelphia. Hanley and Belfus, 1995;57-70.
30. Alderman D. Prolotherapy for musculoskeletal pain. *Practical Pain Management*. 2007;Jan/Feb:10-17.
31. Sampson S, et al. Platelet rich plasma injection grafts for musculoskeletal injuries: a review. *Current Review of Musculoskeletal Medicine*. 2008;1:165-174.
32. Alexander R. Autologous fat grafts as mesenchymal stromal stem cell source for use in Prolotherapy: a simple technique to acquire lipoaspirates. *Journal of Prolotherapy*. 2011;3(3):680-688.
33. Haleem A, et al. The clinical use of human culture-expanded autologous bone marrow mesenchymal stem cells transplanted on platelet-rich fibrin glue in the treatment of articular cartilage defects: a pilot study and preliminary results. *Cartilage*. 2010;1:253-261.
34. Hauser R, et al. *Prolo Your Pain Away!* Second Edition. Beulah Land Press, Oak Park IL. 2004, p.21.
35. Gedney E. Special technique hypermobile joint: a preliminary report. *Osteopathic Profession*. June 1937.
36. Shuman D. Techniques for treating instability of the joints by sclerotherapy. *Osteopathic Profession*. May 1953, pp. 20-23, 32-40.
37. Lyftogt J. Subcutaneous Prolotherapy treatment of refractory knee, shoulder and lateral elbow pain. *Australias Musculoskeletal Medicine Journal*. 2007;12:110-112.
38. Reeves K, et al. Evidence-based regenerative injection therapy (Prolotherapy) in sports medicine. In Seidenberg PH, Beutler PI. (Eds). *The Sports Medicine Resource Manual*. Saunders (Elsevier); 2008;611-619.
39. Reeves K, et al. Evidenced-based regenerative injection (Prolotherapy) in sports medicine. In Seidenberg P, Beutler A (eds.) *The Sports Medicine Resource Manual*. 2008; Saunders Publishing, Philadelphia PA, Chapter 50.
40. Natarajan R, et al. Vascular smooth muscle cells exhibit increased growth in response to elevated glucose. *Biochemistry and Biophysic Research and Communication*. 1992;186:552-560.
41. McGinn S, et al. High glucose and endothelial cell growth: novel effects independent of autocrine TGF-beta 1 and hyperosmolality. *American Journal of Physiology and Cell Physiology*. 2003;234:C1374-C1386.
42. Berl T, et al. Multiple mitogen-activated protein kinases are regulated by hyperosmolality in mouse IMCD cells. *American Journal of Physiology*. 1997;272:305-311.
43. Caruccio L, et al. The heat-shock transcription factor HSF1 is rapidly activated by either hyper- or hypo-osmotic stress in mammalian cells. *Journal of Biochemistry*. 1997;327:341-347.
44. Di Palo S, et al. High glucose concentration induces the overexpression of transforming growth factor-beta through the activation of a platelet-derived growth factor loop in human mesangial cells. *American Journal of Pathology*. 1996;149:2095-2106.

45. Oh J, et al. Sequential effects of high glucose on mesangial cell transforming growth factor-beta 1 and fibronectin synthesis. *Kidney International*. 1998;54:1872-1878.
46. Murphy M, et al. Suppression subtractive hybridization identifies high glucose levels as a stimulus for expression of connective tissue growth factor and other genes in human mesangial cells. *Journal of Biology and Chemistry*. 1999;274:5830-5834.
47. Fukuda K, et al. High concentration of glucose increases mitogenic responsiveness to heparin-binding epidermal growth factor-like growth factor in rat vascular smooth muscle cells. *Arteriosclerosis Thombosis and Vasculature Biology*. 1997;17:1962-1968.
48. Ohgi S, et al. Glucose modulates growth of gingival fibroblasts and periodontal ligament cells: correlation with expression of basic fibroblast growth factor. *Journal of Periodontal Research*. 1996;31:579-588.
49. Pugliese G, et al. Increased activity of the insulin-like growth factor system in mesangial cells cultured in high glucose conditions. Relation to glucose-enhanced extracellular matrix production. *Diabetologia*. 1996;39:775-784.
50. Reeves K. Prolotherapy: injection of growth factors or growth factor production stimulants to growth normal cells or tissue. In Waldman SD (ed): *Pain Management*. Philadelphia, Elsevier, 2006; 1106-1127.
51. Martinez-Zapata M, et al. Efficacy and safety of autologous plasma rich in platelets for tissue regeneration: a systematic review. *Transfusion*. 2009;49:44-56.
52. Creaney L, et al. Growth factor delivery methods of sports injuries: the state of play. *British Journal of Sports Medicine*. 2008;42:314-320.
53. Sanchez M, et al. Platelet-rich therapies in treatment of orthopaedic sport injuries. *Sports Medicine*. 2009;39:345-354.
54. Tabata Y. Tissue regeneration based on growth factor release. *Tissue Engineering*. 2003;9:S5-15.
55. Jensen K, et al. Early inflammatory response of knee ligaments to Prolotherapy in a rat model. *Journal of Orthopaedic Research*. 2008;26:816-823.
56. Jensen K, et al. Response of knee ligaments to Prolotherapy in a rat injury model. *American Journal of Sports Medicine*. 2008;36:1347-1357.
57. Kim H, et al. The effects of anti-inflammatory drugs on histologic findings of the experimental Prolotherapy model. *Journal of the Korean Academy of Rehabilitation Medicine*. 2006;30:378-384.
58. Ahn K, et al. The effect of the Prolotherapy on the injured Achilles tendon in a rat model. *Journal of the Korean Academy of Rehabilitation Medicine*. 2002;26:332-336.
59. Oh S, et al. Dextrose-induced subsynovial connective tissue fibrosis in the rabbit carpal tunnel: a potential model to study carpal tunnel syndrome. *Hand*. 2008;3:34-40.
60. Kim H, et al. Comparison of histological changes in accordance with the level of dextrose-concentration in experimental Prolotherapy model. *Journal of Korean Academy of Rehabilitation Medicine*. 2003;27:935-940.
61. Kim S, et al. The effects of hyperosmolar dextrose and autologous serum injection in the experimental articular defect of rabbit. *Journal of the Korean Academy of Rehabilitation Medicine*. 2006;30:173-178.
62. Park Y, et al. Intra-articular injection of a nutritive mixture solution protects articular cartilage from osteoarthritic progression induced by anterior cruciate ligament transection in mature rabbits: a randomized controlled trial. *Arthritis Research and Therapy*. 2007;9:R8.
63. Lee C. Prolotherapy. *The Journal of the Korean Pain Society*. 2004;Dec:17S:94-98.
64. Lee C, et al. Clinical experience of Prolotherapy for chronic musculoskeletal disease. *The Journal of The Korean Pain Society*. 2001;14:114-117.
65. Croft P, et al. The prevalence of chronic widespread pain in the general population. *Journal of Rheumatology*. 1993;20:710-713.
66. Sternbach R. Survey of pain in the United States: the Nuprin pain report. *Clinical Journal of Pain*. 1986;2:49-53.
67. Louis Harris & Associates. 1999 National Pain Survey. On National Pain Foundation website or www.ultram.com/painsurvey/introduction.htm.
68. Turk D, et al. Toward an empirically derived taxonomy of chronic pain patients: integration of psychological assessment data. *Journal of Consulting and Clinical Psychology*. 1988;56:233-238.
69. Frank C, et al. Ligament healing a review of some current clinical and experimental concepts. *The Iowa Orthopedic Journal*. 1992;12:21-28.
70. Frnak C, et al. Current concepts review-the science of reconstruction of the anterior cruate ligament. *The Journal of Bone and Joint Surgery*. 1997;79:1556-1576.
71. Frank C, et al. Normal ligament properties and ligament healing. *Clinical Orthopedics and Related Research*. 1985;196:15-25.
72. Praemer A. *Musculoskeletal conditions in the United States*. Second Edition. Rosemont: American Academy of Orthopaedic Surgeons; 1999.
73. Wheaton M, et al. The ligament injury connection to osteoarthritis. *Journal of Prolotherapy*. 2010;2:294-304.
74. Bierma-Zeinstra S. Risk factors and prognostic factors of hip and knee osteoarthritis. *Nature Reviews Rheumatology*. 2007;3:78-85.
75. Kirk J, et al. The hypermobility syndrome-musculoskeletal complaints associated with generalized joint hypermobility. *Annals of Rheumatic Diseases*. 1967;26:419-425.
76. Grahame R, et al. Joint hypermobility syndrome is a highly prevalent in general rheumatology clinics, its occurrence and clinical presentation being gender, age and race-related. *Annals of Rheumatic Diseases*. 2006;54:515-523.
77. Hirschberg G, et al. Treatment of the chronic iliolumbar syndrome by infiltration of the iliolumbar ligament. *The Western Journal of Medicine*. 1982;136:372-374.
78. Kim B, et al. The effect of Prolotherapy for the chronic pain of musculoskeletal system. *The Journal of the Korean Academy of Rehabilitation Medicine*. 2001;25:128-133.
79. Kim S, et al. Effects of Prolotherapy on chronic musculoskeletal disease. *The Korean Journal of Pain*. 2002;15:121-125.

80. Hauser R, et al. Dextrose Prolotherapy for unresolved low back pain: a retrospective case series study. *Journal of Prolotherapy*. 2009;1(3):145-155.
81. Hauser R, et al. A retrospective study on Hackett-Hemwall dextrose Prolotherapy for chronic shoulder pain at an outpatient charity clinic in rural Illinois. *Journal of Prolotherapy*. 2009;1(4):205-216.
82. Hauser R, et al. A retrospective study on dextrose Prolotherapy for unresolved knee pain at an outpatient charity clinic in rural Illinois. *Journal of Prolotherapy*. 2009;1(1):11-21.
83. Hauser R, et al. Dextrose Prolotherapy injections for chronic ankle pain. *Practical Pain Management*. 2010;70-76.
84. Hauser R, et al. A retrospective study on Hackett-Hemwall dextrose Prolotherapy for chronic hip pain at an outpatient charity in rural Illinois. *Journal of Prolotherapy*. 2009;1(2):76-88.
85. Hauser R, et al. A retrospective observational study on Hackett-Hemwall dextrose Prolotherapy for unresolved hand and finger pain at an outpatient charity clinic in rural Illinois. *Journal of Prolotherapy*. 2010;2(4):480-486.
86. Hauser R, et al. A retrospective observational study on Hackett-Hemwall dextrose Prolotherapy for unresolved foot and toe pain at an outpatient charity clinic in rural Illinois. *Journal of Prolotherapy*. 2011;3(1):543-551.
87. Hauser R, et al. Dextrose Prolotherapy for unresolved wrist pain. *Practical Pain Management*. 2009;November/December:72-89.
88. Hauser R, et al. Dextrose Prolotherapy and pain of chronic TMJ dysfunction. *Practical Pain Management*. 2007;Nov/Dec:49-55.
89. Hauser R, et al. Dextrose Prolotherapy for unresolved neck pain. *Practical Pain Management*. 2007;October:56-69.
90. Hauser R, et al. Hackett-Hemwall dextrose Prolotherapy for unresolved elbow pain. *Practical Pain Management*. 2009;October:14-26.
91. Lyftogt J. Subcutaneous Prolotherapy treatment of refractory knee, shoulder, and lateral elbow pain. *Australasian Musculoskeletal Medicine*. 2007;12:110-112.
92. Hooper R, et al. Retrospective case series on patients with chronic spinal pain treated with dextrose Prolotherapy. *Journal of Alternative and Complementary Medicine*. 2004;10:670-674.
93. Hauser R, et al. Dextrose Prolotherapy for unresolved low back pain: a retrospective case series study. *Journal of Prolotherapy*. 2009;1(3):145-155.
94. Lyftogt J. Prolotherapy for recalcitrant lumbago. *Australasian Musculoskeletal Medicine Journal*. 2008;May:18-20.
95. Lee J, et al. Effects of intraarticular Prolotherapy on sacroiliac joint pain. *Korean Journal of Pain*. 2009;229-233.
96. Cusi M, et al. The use of Prolotherapy in the sacro-iliac joint. *British Journal of Sports Medicine*. 2010;44:100-104.
97. Topol G, et al. Efficacy of dextrose Prolotherapy in elite male kicking-sport athletes with chronic groin pain. *Archives of Physical Medicine and Rehabilitation*. 2005;86:697-702.
98. Nacim F, et al. Treatment of the chronic iliolumbar syndrome by infiltration of the iliolumbar ligament. *The Western Journal of Medicine*. 1982;136:372-374.
99. Khan S, et al. Dextrose Prolotherapy for recalcitrant coccygodynia. *Journal of Orthopaedic Surgery*. 2008;16:27-29.
100. Miller M, et al. Treatment of painful advanced internal lumbar disc derangement with intradiscal injection of hypertonic dextrose. *Pain Physician*. 2006;9:115-121.
101. Hauser R, et al. A retrospective study on dextrose Prolotherapy for unresolved knee pain at an outpatient charity clinic in rural Illinois. *Journal of Prolotherapy*. 2009;1(1):11-21.
102. Jo D, et al. Effects of Prolotherapy on knee joint pain due to ligament laxity. *The Journal of the Korean Pain Society*. 2004;17:47-50.
103. Hauser R, et al. The case for utilizing Prolotherapy as first-line treatment of meniscal pathology: a retrospective study shows Prolotherapy is effective in the treatment of MRI-documented meniscal tears and degeneration. *Journal of Prolotherapy*. 2010;2(3):416-437.
104. Reeves K, et al. Long term effects of dextrose Prolotherapy for anterior cruciate laxity. *Alternative Therapies*. 2003;9:58-62.
105. Kim J. The effect of Prolotherapy for osteoarthritis of the knee. *Journal of the Korean Academy of Rehabilitation Medicine*. 2002;26:445-448.
106. Ryan M, et al. Ultrasound-guided injections of hyperosmolar dextrose for overuse patellar tendinopathy: a pilot study. *Br J Sports Med*. 2011;45:972-977.
107. Hakala R. Prolotherapy in the treatment of TMD. *The Journal of Craniomandibular Practice*. 2005;23:1-6.
108. Hakala R, et al. The use of Prolotherapy for temporomandibular joint dysfunction. *Journal of Prolotherapy*. 2010;2(3):439-446.
109. Hauser R, et al. Dextrose Prolotherapy and pain of chronic TMJ dysfunction. *Practical Pain Management*. 2007; November/December:49-55.
110. Hauser R, et al. Dextrose Prolotherapy for recurring headache and migraine pain. *Practical Pain Management*. 2009;June:58-65.
111. Hauser R, et al. Dextrose Prolotherapy for unresolved neck pain. *Practical Pain Management*. 2007;October:56-69.
112. Hooper R, et al. Case series on chronic whiplash related neck pain treated with intraarticular zygapophysial joint regeneration injection therapy. *Pain Physician*. 2007;10:313-318.
113. Centeno C, et al. Fluoroscopically guided cervical Prolotherapy for instability with blinded pre and post radiographic reading. *Pain Physician*. 2005;8:67-72.
114. Hauser R, et al. Hackett-Hemwall dextrose Prolotherapy for unresolved elbow pain. *Practical Pain Management*. 2009;October:14-26.
115. Shin J, et al. The effect of Prolotherapy on lateral epicondylitis of elbow. *The Journal of the Korean Academy of Rehabilitation Medicine*. 2002;26:764-768.
116. Kang S, et al. Ultrasonographic findings of chronic lateral epicondylitis with partial tear before and after Prolotherapy. *The Journal of the Korean Academy of Rehabilitation Medicine*. 2004;28:88-93.
117. Lyftogt J. Prolotherapy and Achilles tendinopathy: a prospective pilot study of an old treatment. *Australasian Musculoskeletal Medicine Journal*. 2005;10:16-19.

118. Lyftogt J. Subcutaneous Prolotherapy for Achilles tendinopathy: the best solution? *Australasian Musculoskeletal Medicine Journal*. 2007;November:107-109.
119. Maxwell N, et al. Sonographically guided intratendinous injection of hyperosmolar dextrose to treat chronic tendinosis of the Achilles tendon: a pilot study. *American Journal of Radiology*. 2007;October:w215-w220.
120. Ryan M, et al. Favorable outcomes after sonographically guided intratendinous injection of hyperosmolar dextrose for chronic insertional midportion Achilles tendinosis. *AJR*. 2010;194:1047-1053.
121. Hauser R, et al. Dextrose Prolotherapy injections for chronic ankle pain. *Practical Pain Management*. 2010;January/February:70-76.
122. Hauser R, et al. A retrospective observational study on Hackett-Hemwall dextrose Prolotherapy for unresolved foot and toe pain at an outpatient charity clinic in rural Illinois. *Journal of Prolotherapy*. 2011;3(1):543-551.
123. Hauser R, et al. Dextrose Prolotherapy for unresolved wrist pain. *Practical Pain Management*. 2009;November/December:72-79.
124. Hauser R, et al. A retrospective observational study on Hackett-Hemwall dextrose Prolotherapy for unresolved hand and finger pain at an outpatient charity clinic in rural Illinois. *Journal of Prolotherapy*. 2010;2(4):480-486.
125. Hauser R, et al. A retrospective study on Hackett-Hemwall dextrose Prolotherapy for chronic hip pain at an outpatient charity clinic in rural Illinois. *Journal of Prolotherapy*. 2009;1(2):76-88.
126. Hauser R, et al. A retrospective study on Hackett-Hemwall dextrose Prolotherapy for chronic shoulder pain at an outpatient charity clinic in rural Illinois. *Journal of Prolotherapy*. 2009;1(4):205-216.
127. Jo D, et al. The effects of Prolotherapy on shoulder pain. *Korean Journal of Anesthesiology*. 2004;46:589-592.
128. Ryan M, et al. Sonographically guided intratendinous injections of hyperosmolar dextrose/lidocaine: a pilot study for the treatment of chronic plantar fasciitis. *British Journal of Sports Medicine*. 2009;43:303-306.
129. Curtin M, et al. The effectiveness of Prolotherapy in the management of recalcitrant medial tibial stress syndrome: a pilot study. *British Journal of Sports Medicine*. 2011;45:e1.
130. Lyftogt J. Chronic exertional compartment syndrome and Prolotherapy. *Australasian Musculoskeletal Medicine Journal*. 2006;11:83-85.
131. Reeves K. Treatment of consecutive severe fibromyalgia patients with Prolotherapy. *Journal of Orthopedic Medicine*. 1994;16:84-89.
132. Hooper R, et al. Prospective case series of litigants and non-litigants with chronic spinal pain treated with dextrose Prolotherapy. *International Musculoskeletal Medicine Journal*. 2011;33:15-20.
133. Hauser R, et al. Prolotherapy as an alternative to surgery. A prospective pilot study of 34 patients from a private medical practice. *Journal of Prolotherapy*. 2010;2(1):272-281.
134. Kim H, et al. Comparison between the effect of local steroid injection and Prolotherapy on iliac crest pain syndrome. *The Journal of the Korean Academy of Rehabilitation Medicine*. 2007;31:20-24.
135. Jo D, et al. The effects of Prolotherapy on the lumbar nucleus pulposus. *The Journal of the Korean Pain Society*. 2003;16:68-72.
136. Kim W, et al. A randomized controlled trial of intra-articular Prolotherapy versus steroid injection for sacroiliac joint pain. *Journal of Alternative and Complementary Medicine*. 2010;16:1285-1290.
137. Kim M, et al. Comparison on treatment effects of dextrose water, saline, and lidocaine for trigger point injections. *Journal of the Korean Academy of Rehabilitation Medicine*. 1997;21:967-973.
138. Reeves K, et al. Randomized, prospective, placebo-controlled double-blind study of dextrose Prolotherapy for osteoarthritic thumb and finger (DIP, PIP, and trapeziometacarpal) joints: evidence of clinical efficacy. *The Journal of Alternative and Complementary Medicine*. 2000;6:311-320.
139. Reeves K, et al. Randomized prospective double-blind placebo-controlled study of dextrose Prolotherapy for knee osteoarthritis with or without ACL laxity. *Alternative Therapies*. 2000;6:68-79.
140. Topol G, et al. Hyperosmolar dextrose injection for recalcitrant Osgood-Schlatter disease. *Pediatrics*. 2011;128(5):e1-e8.
141. Rabago D, et al. *Dextrose Prolotherapy for knee osteoarthritis: Results of a randomized controlled trial* (Poster presentation); Osteoarthritis Research Society International (OARSI) World Congress on Osteoarthritis; San Diego California, September 15-17, 2011.
142. Yelland M, et al. Prolotherapy injections, saline injections, and exercises for chronic low-back pain: a randomized trial. *Spine*. 2003;29:9-16.
143. Yelland M, et al. Prolotherapy injections and eccentric loading exercises for painful Achilles tendinosis: a randomized trial. *British Journal of Sports Medicine*. 2011;45:421-428.
144. Refai H, et al. The efficacy of dextrose Prolotherapy for temporomandibular joint hypermobility: a preliminary prospective, randomized, double-blind, placebo-controlled clinical trial. *Journal of Oral and Maxillofacial Surgery*. 2011. Doi:10.1016/j.joms.2011.02.128. Published online July 15, 2011.
145. Emshoff R, et al. Estimation of clinically important change for visual analog scales measuring chronic temporomandibular disorder pain. *Journal of Orofacial Pain*. 2010;Summer;24:262-269.
146. Lee J, et al. Clinically important change in the visual analog scale after adequate pain control. *Academic Emergency Medicine*. 2003;10:1128-1130.
147. Farrar J, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;94:149-158.
148. Salaffi F, et al. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. *European Journal of Pain*. 2004;8:283-291.
149. Wells G, et al. Minimally clinically important difference module: summary, recommendations and research agenda. *Journal of Rheumatology*. 2001;28:452-454.
150. Bird S, et al. Clinically significant changes in pain along with the visual analog scale. *Annals of Emergency Medicine*. 2001;38:639-643.
151. Ostelo R, et al. Interpreting change scores for pain and functional status in low back pain: towards international consensus regarding minimal important change. *Spine*. 2008;33:90-94.

152. Medina J, et al. Rating the levels of evidence in sports-medicine research. *Athletic Therapy Today*. 2006;July:45-48.
153. OCEBM Levels of Evidence Work Group. "The Oxford 2011 levels of Evidence". Oxford Centre for Evidence-Based Medicine. <http://www.cebm.net/index.aspx?o=5653>.
154. Guyatt G, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendation. *British Medical Journal*. 2008;336:924-926.
155. Grade Working Group. Grading quality of evidence and strength of recommendations. *British Medical Journal*. 2004;328:1-8.
156. U.S. Preventative Services Task Force Ratings: Grade Definitions. *Guide to Clinical Preventative Services*. Third Edition: Periodic Updates. 2000-2003. <http://www.uspreventiveservicestaskforce.org/3rduspstf/ratings.htm>.
157. Atkins D, et al. Grading quality of evidence and strength of recommendations. *British Medical Journal*. 2004;328:1490. doi: 10.1136/bmj.328.7454.1490 (published 17, June 2004).
158. Lohr K. Rating the strength of scientific evidence: relevance for quality improvement programs. *International Journal of Health Care*. 2004;16:9-18.
159. Evans D. Hierarchy of evidence: a framework for ranking evidence evaluating healthcare interventions. *Journal of Clinical Nursing* 2003;12:77-84.
160. Benson K, et al. A comparison of observational studies and randomized controlled trials. *New England Journal of Medicine*. 2000;342:1878-1886.
161. Black N. Why we need observational studies to evaluate the effective of healthcare. *British Medical Journal*. 1996;312:1215-1218.
162. Mckee M, et al. Interpreting the evidence: choosing between randomised and non-randomised studies. *British Medical Journal*. 1999;319:312-315.
163. U.S. Preventative Services Task Force Procedure Manual. AHRQ Publication No. 08-05118-EF, July 2008. <http://www.uspreventiveservicestaskforce.org/uspstf08/methods/procman>.
164. Rabago D, et al. Prolotherapy in primary care practice. *Primary Care*. 2010;37:65-80.
165. Dorman T. Prolotherapy: a survey. *The Journal of Orthopaedic Medicine*. 1993;15:49-50.
166. Dagenais S, et al. Side effects and adverse events related to intraligamentous injection of sclerosing solutions (Prolotherapy) for back and neck pain: a survey of practitioners. *Archives of Physical Medicine and Rehabilitation*. 2006;87:90-913.
167. Hauser R, et al. *Prolo Your Pain Away!* Second Edition. Beulah Land Press, Oak Park, IL. 2004; p. 21.
168. Fullerton B, et al. Ultrasounography in regenerative injection (Prolotherapy) using dextrose, platelet-rich plasma and other injectants. *Physical Medicine and Rehabilitation Clinics of North America*. 2010;21:585-605.
169. Fullerton B. High-resolution ultrasound and magnetic resonance imaging to document tissue repair after Prolotherapy: A report of 3 cases. *Archives of Physical Medicine and Rehabilitation*. 2008;89:377-385.
170. Topol G, et al. Biological response of severe degenerative arthrosis of the knee to serial 12.5% dextrose injections A radiographic and pathological assessment. AAOM presentation, Las Vegas, April 29, 2011.
171. Oxman A, et al. Summarizing the evidence. In: *The users' guides to the medical literature: a manual for evidence-based clinical practice*. Guyatt G, Drummond R (Eds). AMA Publications, IL, USA (2002).
172. Guyatt G, et al. Moving from evidence to action. In: *The users' guides to the medical literature: a manual for evidence-based clinical practice*. Guyatt G, Drummond R (Eds). AMA Publications, IL, USA (2002).