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The Use of Dextrose Prolotherapy for myofascial Pain Dysfunction syndrome: a double-blind placebo-controlled study

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Abstract: Musculoskeletal diseases including TMJ myofascial pain dysfunction syndrome accounted for the majority of both lost work and bad days due to health conditions. Dextrose prolotherapy has emerged as a cost-effective treatment option for chronic musculoskeletal and arthritic pain and function. It involves the injection of a small amount of solution (5 – 25 %) into multiple painful ligament and tendon insertions (enthesis), typical trigger points, as well as into the adjacent joint spaces to induce healing of the injured structures. The objective of this study is to evaluate the use of dextrose 5% Prolotherapy for musculoskeletal pain in patients suffering from TMJ myofascial pain dysfunction syndrome with or without hypermobility. Dextrose Prolotherapy, if widely used, could have a tremendous impact on reducing musculoskeletal pain and disability, that improves population life-style and ability to work.

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Introduction

Chronic musculoskeletal disease is a major cause of pain and reduced quality of life. Recently, about 107.7 million adults, aged 18 years and over, reported suffering from a musculoskeletal conditions all over the world. In addition, nearly 15 million adults were reported 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 in USA was $ 849 billion or 7.7 percent of the gross national American product and perhaps in other countries too.

Furthermore, musculoskeletal diseases including TMJ myofascial pain syndrome accounted for the majority of both lost work and bad days due to health conditions (2). 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 and function. It involves the injection of a small amount of solution into multiple painful ligament and tendon insertions (enthesis), typical trigger points, as well as into the adjacent joint spaces to induce healing of the injured structures (3). 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 (3).

There is evidence supporting the use of dextrose Prolotherapy for diffuse muscusloskeletal pain involving the spine, pelvis and peripheral joints (3). Dextrose Prolotherapy was recommended for such musculoskeletal conditions as tendinopathy, ligament sprains, Osgood - Schlatter disease and degenerative joint disease, including osteoarthritis (3).

Prolotherapy has been found to induce ligament and tendon hypertrophy and strengthening (4), stabilize unstable joints such as the sacroiliac joint, cervical spine and temporomandibular joint (5-7); as well as eliminate musculoskeletal pain in all joints of the body including the knees, shoulders, and ankles and induce musculoskeletal repair via the stimulation of growth factors via the inflammatory healing cascade (8-10). Gustav A. Hemwall, before the year 1980, is credited as the first investigator to use just dextrose by itself as a proliferant for Prolotherapy, when Sylnasol (fatty acid derivative) was no longer available (11). Concentrations of dextrose used in Prolotherapy are from 5 – 25 % (12,13). Ligament laxity and its associated joint instability is a leading cause of spinal and joint degeneration (14); and when hypermobility is sought it is the most common finding among patients presenting to a rheumatologist (15).

Refai et al (16), 2011, completed a double-blind, placebo-controlled randomized clinical trial on 12 patients with painful subluxation or dislocation of the temporomandibular joint. Patients were given four injections into and around their temporomandibular

joint with 3 ml of 10% dextrose solution and mepivacaine or with saline and mepivacaine. Each person was given two series of injections six weeks apart. They showed, with the exception of maximal mouth opening *MMO, that there were no statistically significant differences between the active and placebo groups throughout the study. On the other hand, they concluded that prolotherapy with 10% dextrose appears promising for the treatment of symptomatic TMJ hypermobility, as evidenced by the therapeutic benefits, simplicity, safety, patient`s acceptance of the injection technique, and lack of significant side effects. Despite the overwhelming evidence of its effectiveness, prolotherapy has yet to achieve full acceptance by the medical community.

Aim of the study

The objective of this study is to evaluate the efficacy of the use of dextrose 5% Prolotherapy for musculoskeletal pain in patients suffering from TMJ myofascial pain syndrome with or without hypermobility.

Patients and methods

Patients who suffered from TMJ pain for several years and had seen for many medical doctors—including some who were told that no other treatment options were available, were chosen for this study. Thirty patients suffering from TMJ myofascial pain syndrome were included. They involved both sexes and any age. All joints should have clicking and pain, or painful subluxation or dislocation upon palpation. Patients previously managed with other types of solutions including pumice, P2G (dextrose, phenol, glycerin), sodium morrhuate and more recently, platelet rich plasma, stem cell, and lipoaspirate were excluded from the study.

Then subjects were classified into two groups; 15 patients each: -

Group I: was given 5 ml 5% dextrose injected into trigger points of myofascial muscles and tendons and in the TMJ region, immediately after palpation, one week postoperative, 3 weeks and 3 months.

Group II: was given placebo saline solution injected also in the same points, and in the same schedule (immediately after palpation, one week postoperative, 3 weeks and 3 months).

On each injection visit, patients were examined and palpated with regard to TMJ pain on palpation, maximal mouth opening MMO, clicking sound, and frequency of subluxations (number of locking episodes per day or month). These findings were checked up just before injection, immediately after, one week postoperative, 3 weeks and 3 months.

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 (3).

Dextrose Prolotherapy is presumed to work by several mechanisms including a direct osmotic and inflammatory growth effect. Its injections below a 10% solution directly stimulate proliferation of cells and tissue without causing a histological inflammatory reaction (17, 18). However, when it is injected in greater than 10 % solution it is presumed to produce a (concentrated) osmotic gradient outside 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.

A normal human cell contains only 0.1% dextrose (19). Increased glucose concentration (dextrose) causes an increase in cell protein synthesis, DNA synthesis, cell volume and proliferation (20, 21).

Dextrose Prolotherapy, if widely used, could have a tremendous impact on reducing musculoskeletal pain and disability.

Pain intensity were measured using the visual analog scale, VAS, (Fig 1) in monitoring the response to treatment (0 – 10 scale).

Patients were followed up for at least 3 months. Results were studied analyzed and tabulated.

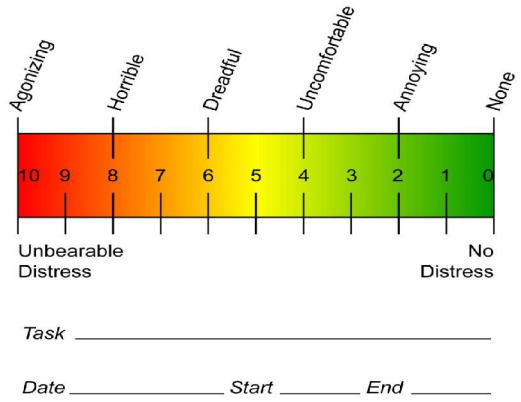

Fig 1: Visual analog scale VAS for pain assessment.

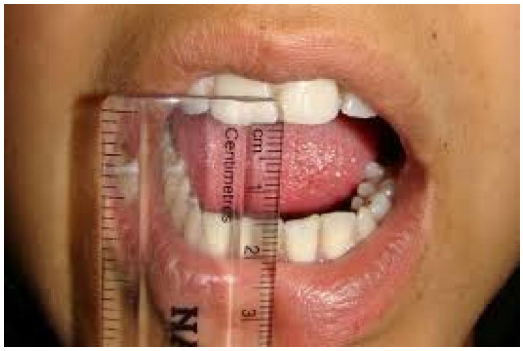

Fig 2: Mouth opening calibration.

Results

Thirty patients; 26 females and 4 males were included in this study. Their ages ranges from 30 – 40 years. In this study, many of the subjective symptoms of pain, stiffness, and crunching sensation in patients with TMJ dysfunction were reduced in 92% of the prolotherapy patients by greater than 50% of pain present at the beginning of the study (Table 1). Clicking was also disappeared and subluxation or hypermobility was reduced (Table 2). Moreover, the mouth range of movement and maximal mouth opening were improved (Table 2).

Overall, substantial improvements were reported in range of motion, pain medication utilization, disability, depression/anxiety, quality of life, and patient satisfaction. These improvements persisted through the follow up period at 3 months after the conclusion of prolotherapy treatments.

The visual analog scale VAS showed a statistically significant reduction of pain from 7.5 to 3.20 after the first set of dextrose injections and went down to 2.40 after the second series of injections and became 1.5 at 3 months (Table 1). Whereas, immediately after placebo saline injection, pain decreases from 6.5 to 5.5 and went down to 4 after the second injection and became 3 at 3 months (Table 1). The Mean VAS was not significantly different in the two groups before and immediately after injections. But after seven days, only the dextrose group showed significantly lower scores of 3.20, compared to 5.5 in the normal saline group ($p<0.01$). The increase in pressure threshold with 5% dextrose compared to the other group also reached statistical significance.

Comparing the effects of local saline injection with that of dextrose Prolotherapy on TMJ pain syndrome (Table 2) showed improvements in both groups compared to the pre-injection levels and a big significant difference was observed between the groups, particularly 3 months after injection.

Table 1: VAS before and after prolotherapy.

N=15	Immediate	After 1 week	After 3 weeks	After 3 months
Dextrose 5%	7.50	3.20	2.40	1.5
Placebo	6.5	5.5	4	3

Table 2: Clinical findings before and after injections. W = Week, M = Month, D = Dextrose, S = Saline, MMO = Maximum mouth opening.

Symptom / Visit	TMJ Pain		MMO		Clicking		Hypermobility	
	D	S	D	S	D	S	D	S
Before injection	8	8	One finger	One finger	present	present	All	All
Immediate after injection	7.50	6.5	One finger	One finger	present	present	All	All
1st W	3.20	5.5	Two fingers	One finger	Present in 4 patients	present	All	All
3rd w	2.40	4	2.5 fingers	One finger	Disappeared	Present in 10 patients	Present in 9 patients	Present in 9 patients
3rd M	1.5	3	3 fingers	Two fingers	Disappeared	Present in 6 patients	Present in 6 patients	Present in 9 patients

Discussion

More than 15% of adults suffer from chronic facial pain (22), and one of the most common causes is Temporomandibular Joint Disease TMD (23). It occurs predominantly in women, with the female to male ratio ranging from 2:1 to 6:1, with 90% of those seeking treatment being women in their childbearing years (24,25). These findings coincides with our data in the present study. In our study, many of the subjective symptoms of pain, stiffness, and crunching sensation in patients with TMJ dysfunction were reduced by greater than 50% in the majority of the prolotherapy patients (Table 1). Clicking was also disappeared and subluxation was reduced (Table 2). Moreover, the mouth range of movement and maximal mouth opening were improved (Table 2).

Several years before, the first-line approach to managing TMD typically includes resting the jaw, relaxing the jaw muscles, and doing jaw exercises as recommended by a physical therapist (29). Recommendations may also include eating a soft diet that minimizes hard repetitive chewing of crunchy or chewy foods, such as bagels and steak. All chewing gum must be stopped, talking minimized, and teeth clenching discouraged. Relaxation exercises that emphasize gentle range of motion of the joint are

recommended. Application of warm compresses to the affected area twice daily, for 10 minutes, to decrease pain and increase joint movement are done. If this fails, then typically a short course of an anti-inflammatory medication such as ibuprofen is prescribed and often a dental consultation is given. The dentist then evaluates the patient for malocclusion and bruxism. Many times, a mouth splint used at night can completely resolve or control the problem.

Prolotherapy, as defined by Webster's Third New International Dictionary, is "the rehabilitation of an incompetent structure, such as a ligament or tendon, by the induced proliferation of cells." "Prolo" comes from the word proliferate. Prolotherapy injections proliferate or stimulate the growth of new, normal ligament and tendon tissue (30). In human studies on prolotherapy, biopsies performed after the completion of treatment showed statistically significant increases in collagen fiber and ligament diameter of up to 60% (31).

Prolotherapy is based on the concept that the cause of most chronic musculoskeletal pain is ligament and/or tendon weakness (or laxity). Prolotherapy has been shown in one double-blinded animal study (32) over a six-week period to increase ligament mass by 44%, ligament thickness by 27%, and the ligament-bone junction strength by 28%. Another animal study (33) confirmed that prolotherapy induced the normal healing reaction that occurs when an injured tissue is healing itself. In this study, the prolotherapy caused the circumference of tendons to increase by approximately 25% after six weeks of time.

Prolotherapists have a long history treating TMD since the time of Louis W. Schultz, MD, DDS (17) in the 1930's. Dr. Schultz was unique in that he was both a dentist and a physician. He was an Associate Professor in the Department of Surgery at the University of Illinois and Rush College of Medicine. He published several papers on the treatment of subluxation of the temporomandibular joint, including one in 1937 in the Journal of the American Medical Association (34). In this paper he described just how common TMJ syndrome was and that the traditional treatments of rest, appliances in the mouth, physical therapy, and surgery were only partially successful. He described a simple method of shortening and strengthening the TMJ capsule by injection (later termed prolotherapy). He tested various solutions in animals until he found one that caused a strengthening of the ligaments that support the TMJ but caused no injury to other structures (35). In regard to prolotherapy into the TMJ he found that:

- There was no alteration of the normal joint cavity; the proliferation occurred in the ligaments.
- There were no gross changes in the ligaments other than their thickening.
- Lymphocytes infiltrate the area injected within 30 minutes.
- Proliferation of tissue can be seen in four to six days.

We found in our study that clicking was disappeared after 3 weeks. This finding agrees with the results of Schultz (35) who found that a series of three to five injections were required to often permanently stop the clicking, pain, and hypermobility of the TMJ. Dr. Schultz noted also that over the course of his twenty years of doing prolotherapy for TMD, not only was it effective, but also the treatment lacked significant side effects, and this is the situation in our study too.

Comparing the pre-and post- therapy pain scores (Table 1,2) in our study indicates that there is a significant change from dextrose therapy as compared to saline group. These results coincide with what is generally accepted in the pain literature (35) that a change (0 to 10 scales) on the Visual Analogue Scale (VAS) or Numeric Rating Scale (NRS) of 3 or a percentage change of 40% or more 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 (39-45). In 93% of the case series in this review (25 out of 27) that used these pain scales, dextrose Prolotherapy met this criteria. 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.

Despite the overwhelming evidence of its effectiveness, prolotherapy has yet to achieve full acceptance by the medical community. Perhaps it is due to, the huge profits that pharmaceutical field of Prolotherapy, points out, " the substances used in Prolotherapy are not therapies receive." Nevertheless, several years ago the big companies have nothing patented in the field of trigger point therapy or acupuncture, both of which are accepted today. Furthermore, there is a resistance to Prolotherapy perhaps because it would substantially reduce the number of surgeries.

In order to fully appreciate how Prolotherapy works, it is essential to understand the natural healing process that it mimics, known in the world of medicine as "the natural healing cascade." This process is complex, but has been extensively studied by the medical community and is readily understood (48).

When an injury occurs to a muscle, joint, tendon or ligament, or loss of fluid in the body through aging

or illness causes a weakening of these tissues, it becomes inflamed, or irritated. This irritation provokes a defensive immune response and sequestering of fibroblasts into the damaged area. These cells produce the miraculous healing compound collagen (48). Absorbed into and around the damaged tissue, the collagen builds up and fortifies these structures. It then shrinks and stabilizes. After proliferative therapy, a ligament can become 50% thicker and 200-400% stronger (48).

It is interesting to consider that inflammation is the inciting factor that actually stimulates the entire healing process.

In his massive and scholarly tome, "Prolo Your Sports Injury Away," Dr. Ross Hauser (3), further, suggests a very intriguing theory about Prolotherapy, inflammation and sports injuries.

Sports injuries are commonly "treated" with an injection of steroids—which are administered specifically for their anti-inflammatory effect. Hauser wonders if recurring sports injuries aren't in fact caused by this routine use of steroid injections—which by their very nature would interfere with the body's ability to produce fibroblasts and therefore to produce the collagen it sorely needs to repair and strengthen its damaged tissue.

If this indeed proves to be true, then the decision to choose Prolotherapy over corticosteroid injections could mean the difference between a record-breaking career and / or a career-breaking decision.

The TMJ is often predisposed to similar degenerative changes and pathologies seen in other synovial joints as a consequence of the frequent and repetitive stresses that the TMJ undergoes (26). Symptoms commonly associated with TMD include pain at the TMJ, generalized orofacial pain, chronic headaches and ear aches, jaw dysfunction including hyper- and hypo-mobility and limited movement or locking of the jaw, painful clicking or popping sounds with opening or closing of the mouth, and difficulty chewing or speaking (27). While pain is the most common symptom, some people report no pain, but still have problems using their jaws. Sometimes the bite just feels "off." Additional symptoms may include ringing in the ears, ear pain, decreased hearing, dizziness, and vision problems (28).

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Dextrose Prolotherapy is presumed to work by several mechanisms including a direct osmotic and inflammatory growth effect. Its injections below a 10% solution directly stimulate proliferation of cells and tissue without causing a histological inflammatory reaction (17, 18). However, when it is injected in greater than 10% solution it is presumed to produce a (concentrated) osmotic 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.

A normal human cell contains only 0.1% dextrose (19). Increased glucose concentration (dextrose) causes an increase in cell protein synthesis, DNA synthesis, cell volume and proliferation (20, 21).

Two controlled, nonrandomized dextrose Prolotherapy studies have been reported on in the medical literature (36,37). Kim et al. (36) 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 Osqwestry questionnaire improved in both groups compared to the pre-injection levels and no significant difference was observed between the groups. 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. (37) 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 (Numeric Rating Scale) 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. This is also what was exactly happened with our results in the present study (Table 1). The Mean VAS was not significantly different in the two 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 ($p<0.01$). The increase in pressure threshold with 5% dextrose compared to the other two groups also reached statistical significance.

Kim, Na and Moon (38) 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. Sixty-four typical myofascial pain patients were injected with either 5% dextrose (23 patients), normal

saline (20 patients) or 0.5% lidocaine (21 patients) 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. These findings were nearly similar to our results (Table 1), in which we find lower score of 3.20 with dextrose group compared to 5.5 in the normal saline group. The authors (36 – 38) agree with our opinion in the conclusion that 5% dextrose should be the solution of choice for trigger point injections, which is the dose we used it in this study.

Conclusion

Dextrose Prolotherapy, if widely used, could have a tremendous impact on reducing musculoskeletal pain and disability arising from myofascial pain dysfunction syndrome, that improves population life-style and ability to work. We also concluded that 5% dextrose should be the solution of choice for trigger point injections.

Recommendations

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 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 (46,47). Dextrose Prolotherapy, if widely used, could have a tremendous impact on reducing musculoskeletal pain and disability.

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References

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. *Ross A. Hauser, Marion A. Hauser, Nicole M. Baird,* evidence-based use of dextrose prolotherapy for musculoskeletal pain**:** a Scientific literature review. *Journal of Prolotherapy*. 2011;3(4):765-789.
4. 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.
5. Hackett G. Shearing injury to the sacroiliac joint. *Journal of the International College of Surgeons.* 1954;22:631-642.
6. Schultz L. A treatment of subluxation of the temporomandibular joint. *Journal of the American Medical Association.* September 25, 1937.
7. 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.
8. Reeves K. Sweet relief: Prolotherapy targets sprains and strains. *Biomechanics*. 2004;9:24-35.
9. Reeves K. Prolotherapy for patients with musculoskeletaldisorders. *Journal of Musculoskeletal Medicine.* 2002;390-301.
10. Reeves K. Prolotherapy: basic science, clinical studies, and technique. In Lennard TA (ED). *Pain Procedures in Clinical Practice.* (2nd Edition). Philadelphia; Hanleey and Belfus; 2000:172-190.
11. Hauser R, et al. *Prolo Your Pain Away!* Second Edition. Beulah Land Press, Oak Park IL. 2004, p.21.
12. Lyftogt J. Subcutaneous Prolotherapy treatment of refractory knee, shoulder and lateral elbow pain. *Australias Musculoskeletal Medicine Journal.* 2007;12:110-112.
13. 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.
14. Wheaton M, et al. The ligament injury connection to osteoarthritis. *Journal of Prolotherapy*. 2010;2:294-304.
15. 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.
16. Refai H, et al. The efficacy of dextrose Prolotherapy for temporomandibular joint hypermobility: a preliminary prspective, randomized, double-blind, placebo-controlled clinical trial. *Journal of Oral and Maxillofacial Surgery*. 2011. Doi:10.1016j.joms.2011.02.128. Published online July 15, 2011.
17. Jensen K, et al. Response of knee ligaments to Prolotherapy in a rat injury model. *American Journal of Sports Medicine*. 2008;36:1347-1357.
18. Jensen K, et al. Early inflammatory response of knee ligaments to Prolotherapy in a rat model. *Journal of Orthopedic Research*. 2008;26:816-823.
19. 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.
20. 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.
21. McGinn S, et al. High glucose and endothelial cell growth: novel effects independent of autocrine TGF-beta 1 and hyperosmolality. *American Journal of Phyiology and Cell Physiology*. 2003;234:C1374-C1386.
22. American Dental Association. Available at http://www.ada.org/public/topics/tmd_tmj.asp Accessed 11/9/07.
23. National Institute of Dental and Craniofacial Research. Available at: http://www.nidcr.nih.gov. Accessed 11/9/07.
24. Van Korff M, Dworkin, SF, Le Resche L, and Kruger A. An epidemiologic comparison of pain complaints. Pain. 1988. 32: 173-183.
25. Ta LE and Dionne RA. Treatment of painful temporomandibular joints with a cyclooxygenase-2 inhibitor: a randomized comparison of celecoxib to naprosyn. Pain. 2004. 111: 13-21.
26. Helland MM. Anatomy and function of the temporomandibular joint. JOSPT. 1980. 1(3): 145-52.
27. Mayo Clinic. Available at: http://www.mayoclinic.com/health/tmj-disorders/DS00355/DSECTION=6 Accessed 11/9/07.
28. The TMJ Association. Available at: http://www.tmj.org/basics.asp Accessed 11/9/07.
34 . Eriksson PO and Zafar H. Musculoskeletal disorders in the jaw, face and neck. In Rakel RE, Bope ET, eds., Conn's Current Therapy in TMJ. WB Saunders. Philadelphia, PA. 2005. pp 1128-1133.
29. Dorman T. Treatment for spinal pain arising in ligaments using Prolotherapy: A retrospective study. Journal of Orthopaedic Medicine. 1991. 13(1): 13-19.
30. Klein R. Proliferant injections for low back pain: histologic changes of injected ligaments and objective measures of lumbar spine mobility before and after treatment. Journal of Neurology, Orthopedic Medicine and Surgery. 1989. 10: 141-144.
31. Liu Y. An in situ study of the influence of a sclerosing solution in rabbit medical collateral ligaments and its junction strength. Connective Tissue Research. 1983. 2: 95-102.
32. Maynard J. Morphological and biomechanical effects of sodium morrhuate on tendons. Journal of Orthopaedic Research. 1985. 3: 236-248.
33. Schultz L. A treatment of subluxation of the temporomandibular joint. JAMA. September 25, 1937.
34. Schultz L. Twenty years' experience in treating hypermobility of the temporomandibular joints. American Journal of Surgery. Vol. 92. December 1956.
35. 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.
36. Jo D, et al. The effects of Prolotherapy on the lumbar nucleus pulposus. *The Journal of the Korean Pain Society*. 2003;16:68-72.
37. Kim MY, et al. *J Korean Acad Rehabil Med*. 1997 Oct;21(5):967-973. Korean.
38. 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.
39. Lee J, et al. Clinically important change in the visual analog scale after adequate pain control. *Academic Emergency Medicine*. 2003;10:1128-1130.
40. 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.
41. 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.
42. Wells G, et al. Minimally clinically important difference module: summary, recommendations

and research agenda. *Journal of Rheumatology*. 2001;28:452-454.
43. Bird S, et al. Clinically significant changes in pain along with the visual analog scale. *Annals of Emergency Medicine*. 2001;38:639-643.
44. 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.
45. 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.
46. 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.
47. Marc Darrow, M.D., William Faber, The Natural Healing Cascade: March 18, 2012, https//: Jointrehab.com.

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