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- & why the arthroscope is one of athletes’ worst nightmares!
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The Case for Prolotherapy –  
The Opening Argument  

Julie R. Gunnigle, JD

Most attorneys begin a case with the simple words “Ladies and Gentlemen of the Jury.” The case for Prolotherapy can and must begin a little differently. This journal is not intended for the eyes of jury, because it is not a jury that needs convincing. Instead, this issue is intended for the interested practitioner who wants to learn more, the healed patient who is fighting his insurance company for coverage, or the long-suffering friend who receiving endless cortisone shots that do not end his joint pain. In this issue, the practitioners and researchers on the front lines of the fight against chronic pain will outline the evidence for Prolotherapy.

Any case lives or dies by the evidence that supports it. Medicine should be no different. The recent push for evidence-based medicine underscores the idea that treatments should be supported by systematic reviews of clinical research and cost effective compared to its benefits. Evidence based medicine seeks to move beyond conventional wisdom and traditional remedies, and bring the results of research to clinical settings. In the case for Prolotherapy, the strength and weight of the evidence shows that it is effective at reducing pain, affordable, and low risk.

Prolotherapy is evidence-based medicine

The prevalence of musculoskeletal conditions is staggering. According to the U.S. Bone and Joint Initiative, the cost of dealing with musculoskeletal conditions is an estimated $849 billion dollars a year. This seems staggering until one considers that one out of every two Americans will require medical care for a bone or joint issue in their lifetime. With an aging population and a populace that has become accustomed to an increasingly sedentary lifestyle, these numbers are only expected to grow in the coming years. If a lasting, cost effective treatment is available for even a portion of those suffering from arthritis and other joint ailments, it could improve the quality of life for millions while containing health care costs.

This issue explores the evidence in the case for Prolotherapy as a treatment for musculoskeletal conditions. When considering a treatment, the U.S. Preventative Services Task Force (USPSTF) ranks evidence on a three-point scale as good, fair, or poor, and weighs the benefits against the risks posed. For example, good evidence includes well-designed, well-conducted studies that directly assess effects on health outcomes, while fair evidence would include evidence sufficient to determine effects on health outcomes, but perhaps lacking in the size, scope, or consistency of individual studies. When there is good or fair evidence for a procedure, and the benefits of the service outweigh its harms, the USPSTF issues an A or B recommendation respectively.

This issue presents the evidence to support an A and B recommendation for the use of dextrose Prolotherapy. This is because studies show not only that Prolotherapy is effective, but perhaps as important, it is a low risk, inexpensive outpatient procedure that allows for quick recovery and near instantaneous return to normal activities.

Patients deserve more than pain management

In 2001, I caught the front edge of my snowboard during a ski trip in Arizona. My nose caught the snowboard, but my shoulder absorbed most of the impact as I tumbled down the slopes. What seemed like a minor injury at the time (perhaps minor compared to a very gruesome looking nose), never healed correctly and caused pain for years. In what is all too common a story, doctors treated my injury by managing the pain. After multiple consultations and other treatments, I was told that my only option was pain management.
Patients deserve better than having their pain “managed.” Patients need and deserve to have their pain resolved. In this issue you will read about how Prolotherapy not only diminishes pain, but is able to strengthen and stabilize painful ligaments. Prolotherapy addresses the underlying problem, not just the symptom of pain.

In this issue, you will find a scientific literature review limited solely to dextrose Prolotherapy. This review pooled data from over 2,400 patients treated with dextrose Prolotherapy and found that, in studies using comparable scales, patients experience an average 4.4 point reduction in pain on the Visual Analogue Scale or Numeric Rating Scale after treatment. In plain English, when patients were asked to rank their pain on a zero to 10 scale, they ranked their pain an average 4.4 points lower at the end of Prolotherapy treatment than at the beginning. Not only is this statistic a huge quality of life improvement for an individual, it is over 150% the pain relief required for treatment to be considered clinically significant.

The evidence shows Prolotherapy lowers pain, but also decreases ligament laxity, helping restore and heal the joint. Left unchecked, a ligament-injured joint is a risk for osteoarthritis, causing further pain and disability. This issue shows how Prolotherapy is different than cortisone treatments or ibuprofen, in that it helps restore the compromised structure and prevent further degeneration. It is not merely pain management; it is pain resolution.

**Prolotherapy is well established**

If you have ever sought reimbursement for Prolotherapy, you have probably heard these words before: “[Your insurance company] considers Prolotherapy (also known as proliferant therapy or proliferation therapy) experimental and investigational for any indications.” Prolotherapy was first used in the fifth Century B.C., and while the methods have changed, the science behind Prolotherapy has not. By inducing inflammation in injured ligaments, Prolotherapy stimulates the body’s healing mechanisms and self-repair. Nevertheless, insurance companies across the board regard Prolotherapy as experimental even for patients who have experienced a complete resolution of their pain.

There are multiple reasons why Prolotherapy should not be considered an “experimental” procedure, but first consider what the term “experimental” means. There is no uniform definition for the term. “Experimental” means whatever an insurance company says it means in the insurance contract. Typically, these definitions look to whether a procedure is generally recognized in the medical community as effective and appropriate for the specific diagnosis being treated. Occasionally the language may merely rely on the judgment of the Plan Administrator, leaving the patient unable to determine on his own what will be covered. Rarely, a plan or jurisdiction may rely on a more specific definition of “experimental.”

Consider, for example, a more specific definition adopted by the Kansas Board of Healing Arts, albeit for purposes other than insurance. Under their definition, a procedure is not experimental if it is “taught as an acceptable method or procedure as part of the core curriculum of an approved professional school,” “taught as an acceptable method or procedure by an academic training institution in an approved post graduate program in the healing arts” or “based upon sufficient learned publications supporting [its] safety and efficacy.”

Not only is the efficacy of Prolotherapy supported by the literature, but Prolotherapy has its own specialty college within the American Osteopathic Association, is performed...
and taught at the University of Wisconsin School of Medicine, and has even been cited by the Mayo Clinic as a treatment for ligament pain. Furthermore, Prolotherapy training is a requirement in the neuromuscular residency training for Osteopathic doctors, and is common in Osteopathic medical schools and universities.

While Prolotherapy is routinely not covered, many insurance companies continue to cover treatments that are not supported by evidence. There is not evidence for example, that cortisone has any benefit beyond three weeks, and some studies have suggested that cortisone may accelerate the arthritic process. More extreme examples include certain types of arthroscopy for knee osteoarthritis that have been shown to have no benefit, compared to sham operations, or placebo. Before we ask one more patient to undergo an expensive and painful surgery and rehabilitation, we should examine the evidence whether the procedure is effective. By creating a culture of evidence-based medicine, patients will receive better care and health care cost could be kept in check.

THE VERDICT FOR PROLOTHERAPY

This issue lays out in detail the case for Prolotherapy. The evidence shows that Prolotherapy is effective for a wide range of injuries caused by injured ligaments and other soft tissue structures. The evidence shows Prolotherapy has a role in preventing arthritis, restoring joints, and even healing our pets. The evidence shows that it is effective at reducing pain, affordable, and low risk. Moreover, the case for Prolotherapy asks us to reexamine the way we treat injuries. Over half of the people reading this will seek medical attention for a joint or bone injury in their lifetime. They deserve nothing less than the best care, and the best care is that which is supported by evidence.
Journal of Prolotherapy International Medical Editorial Board Consensus Statement on the Use of Prolotherapy for Musculoskeletal Pain

Ross A. Hauser, MD; Havil S. Maddela, BS; Donna Alderman, DO; Gunter Baehnisch, MD; Robert Banner, MD; Peter J. Blakemore, DO; José Eleazar Calderón, MD; Gary B. Clark, MD; Mark DeLaurentis, MD, FACS; George H. Kramer, MD; John Neustadt, ND; Joan Resk, DO, JD; José Hector Salazar, MD; Garrett Swetlikoff, ND; Rodney S. Van Pelt, MD; Mark T. Wheaton, MD

Tendinosis; as well as other conditions such as enthesopathies and degenerative osteoarthritis involving the peripheral and spinal joints.

History of Prolotherapy

The theory of Prolotherapy was investigated and practiced as early as the fifth century B.C. by Hippocrates himself. Hippocrates would treat unstable joints by cauterizing the ligaments with a hot metal rod. Although the procedure was rudimentary and experimental, the hypothesis proposed by Hippocrates was that induced inflammation of injured ligaments will lead to self-repair and that was the one of the first steps towards utilizing the body's own healing mechanism to heal connective tissues. Later in the first century B.C., Celsus, who was a Roman encyclopedist, described the treatment of hydrocele around the testicle via the injections of a Potassium nitrate solution. This provided a prototype of successful treatment of hernias centuries later by Dr. George Heaton in 1832. Dr. Heaton realized that he could tighten the connective tissues around the inguinal ring by injecting them with Quercus Alba (white oak) solution. This provided a prototype of successful treatment of hernias centuries later by Dr. George Heaton in 1832. Dr. Heaton realized that he could tighten the connective tissues around the inguinal ring by injecting them with Quercus Alba (white oak) solution. The injection of hernias, varicose veins, and hemorrhoids eventually became known as Sclerotherapy, because the injection “sclerosed,” or fibrosed, the area.

In 1936, Earl Gedney, DO, an osteopathic surgeon, expanded the technique of sclerotherapy by injecting medial and lateral collateral ligaments of unstable knees.

While pre- and post- ultrasounds and pre- and post- X-rays and biopsy studies in animals have shown that Prolotherapy regenerates damaged musculoskeletal tissues, the mechanism of action of the various types of Prolotherapy is not completely understood. For further information, see the Histology of Prolotherapy section.
with a solution known as Neoplasmoid. Dr. Gedney found these treatments successful and soon began to treat posterior sacroiliac ligaments with the same solution, also yielding good results. Dr. Gedney published results of this injection therapy to treat the ligamentous pathology involving the knee and lower back including the sacroiliac joint; the annular ligaments of vertebral discs for degenerative disc disease, as well as papers on the use of this type of injection therapy for any hypermobile joint in the body.

In 1953 the formation of the first medical organization dedicated to Prolotherapy, then known as sclerotherapy, was the American Osteopathic Association of Sclerotherapy, an affiliate of the American Osteopathic Association. That organization has changed names several times over the years, with its current name the American Osteopathic Association of Prolotherapy Integrative Pain Management and pending name change to the American Osteopathic Association of Prolotherapy Regenerative Medicine.

In 1937, a dentist and facial surgeon at the University of Illinois, Louis Schultz, MD started using Sylnasol (sodium psylliate), a five percent solution of fatty acid, to stabilize temporomandibular joints after he found that the solution could induce fibrogenesis of the injured tissues without causing adverse effects on non-involved tissues. In 1939, a trauma surgeon in Canton, Ohio, George S. Hackett, MD, expanded the concept of tendon pathology and ligament laxity to chronic musculoskeletal pain. He successfully treated various types of spinal conditions in the low back and neck with Sylnasol injections. He was the first to coin the term Prolotherapy. He eventually published a medical book entitled Ligament and Tendon Relaxation Treated by Prolotherapy in which he noted, “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. To the treatment of proliferating new cells, I have applied the name Prolotherapy from the word ‘proli’—(Latin) meaning offspring; ‘proliferate’—to produce new cells in rapid succession.” He published numerous papers over the next twenty-five years documenting the success rate of Prolotherapy in the elimination of chronic musculoskeletal pain including results on 1,800 patients with chronic low back and noted an 82% cure rate at 12 years after treatment of Prolotherapy. Dr. Hackett was also the first to describe in detail the pain referral patterns down the extremities from injured ligaments in the back and neck.

Dr. Hackett’s main student and proponent of Prolotherapy was a Chicago surgeon by the name of Gustav A. Hemwall, MD, whom he met in 1955, at an American Medical Association meeting. Dr. Hemwall and Hackett promoted Prolotherapy at various medical meetings and this eventually led to the second medical society devoted to Prolotherapy called The Prolotherapy Association. Upon Dr. Hackett’s death in 1969, Dr. Hemwall was the main proponent and teacher of Prolotherapy for the next 30 years, until his death in 1998 at the age of 90. The technique of Prolotherapy that they practiced and taught became known as the Hackett-Hemwall technique of Prolotherapy. The Hackett Hemwall Foundation was set up in their honor to provide high-quality medical treatment to people around the world who would otherwise be unable to afford medical care. The Foundation also promotes research and training to health care professionals in Prolotherapy. Dr. Hemwall eventually found that a simple solution of hypertonic dextrose could be effectively used as the proliferant in the Prolotherapy injections.

While Hackett-Hemwall Prolotherapy is given every three to six weeks to simulate the proliferative phase of healing in the inflammatory cascade, other techniques of Prolotherapy—including the west coast and Lyfotgk technique of Prolotherapy—give treatments up to every week. In more recent years, the solutions for Prolotherapy have expanded to autologous blood products including platelet rich plasma (PRP), and most recently, stem/stromal cells from either bone marrow or adipose (fat). Experimentally cultured stem cells of both bone marrow and adipose have been used successfully to repair various defects including cartilage. However FDA regulations prohibit the culture expansion or manipulation of cells in clinical use.

Recent protocols have been developed for the use of direct bone marrow and adipose (fat) derived Stem Cell Prolotherapy which do not violate FDA guidelines. Typically, autologous stem cell solutions utilized for Prolotherapy are given monthly to every few months, as needed.*

*The aforementioned are just a few of the great names in Prolotherapy. To read more on these and other physicians including Thomas Dorman, MD, David Shuman, DO, Thomas Ravin, MD, K. Dean Reeves, MD, Paul Goodley, MD, Jeffrey Patterson, MD and others and their role in the history of Prolotherapy please see The History of Prolotherapy by Felix Linetsky, MD in Prolo Your Sports Injuries Away! [Oak Park, IL: Beulah Land Press; 2001:25-37.] and A History of the American College of Osteopathic Sclerotherapeutic Pain Management by Donna Alderman, DO in the Journal of Prolotherapy [2009;1(4):200-204.]
Epidemiology of Pain

The incidence of musculoskeletal pain is rising in epidemic proportions all across the globe. In the United States, nine to twenty percent of adults suffer from chronic musculoskeletal pain at any one time. There are currently 15 million individuals who are limited from one daily activity by musculoskeletal pain, and that number is estimated to reach 67 million people by 2030. Additional studies have shown that nearly all chronic pain patients have a substantially reduced health-related quality of life, with 42% unable to work due to pain and 63% unable to engage in routine activities of daily living. The number of knee/hip replacements due to musculoskeletal injuries increased from 290,700 to 383,500 from 1997 to 2005, and by 2030, the number of these surgical procedures is estimated to increase annually to 572,000 and 3.48 million respectively. The cost of medical care in treating musculoskeletal pain is astounding, costing Americans in 2004, $849 billion or 7.7% of the gross national product. The anticipated medical costs are expected to double over the next fifteen years.

Musculoskeletal pain can be caused by any type of trauma to the musculoskeletal system, including damage to bones, joints, muscles, tendons, ligaments, bursae, labrum, menisci or nerves. Damage to any of these musculoskeletal components can occur from an acute injury, gradual wear and tear of the tissue, or a combination of both of these factors. The most common cause for musculoskeletal pain, however, is ligament and tendon pathology. The American Academy of Orthopedic Surgeons calculated that ligament and tendon injuries account for 45% of all musculoskeletal injuries in the United States. Due to the difficulty in detecting and diagnosing injuries caused by ligament and tendon pathology via MRI and X-ray, the percentage of musculoskeletal pain caused by ligament/tendon pathology is most likely much higher, especially in chronic pain cases. Ligaments and tendons are soft, collagenous tissues consisting of functional complexes of interdependent aggregations of collagen, elastin, glycoproteins, protein polysaccharides, water, and cells, with the major component of ligaments and tendons being collagen, water, and proteoglycans. Ligaments and tendons are the main connective tissue structures which stabilize and move joints. They often fail to heal completely, because they constantly absorb the brunt force of physical activity, they have a poor blood supply, and the compression, resilience, and durability of articular cartilage decreases with age in correlation to the decrease in water content of the human body, allowing more force to be transmitted to the joint soft tissue structures. Studies have shown that unresolved ligament tears and sprains can completely alter joint mechanics, while ligament laxity and its associated joint instability has been indicated to be the leading cause of spinal and joint degeneration. As stated by Dr. George Hackett, “A joint is only as strong as its weakest ligament.”

Histology of Prolotherapy

Prolotherapy resolves painful injuries by several mechanisms. Through animal and human research, including biopsy and ultrasound analysis, Prolotherapy injections have been found to induce the repair of soft tissue structures, such as ligament and tendons. Prolotherapy strengthens ligaments and tendons by inducing repair via the stimulation of growth factors via the inflammatory healing cascade. An increase of glucose concentration (dextrose) causes an increase in cell protein synthesis, DNA synthesis, cell volume, and proliferation. Prolotherapy utilizes the effects of dextrose concentration, as well as other proliferants to stimulate inflammation, which in turn, stimulates ligament size and mass, and tendon hypertrophy, extracellular matrix, fibroblastic proliferation, increased ligament-bone junction strength and repair of articular cartilage defects. The increase of extra-cellular glucose concentration from Prolotherapy injections causes cells to proliferate and produce platelet-derived growth factor, transforming growth factor B, epidermal growth factor, fibroblast growth factor, insulin-like growth factor, and connective tissue growth factor. These growth factors are pertinent to the repair, health, and growth of tendons, ligaments, and other soft tissue. The injected dextrose has been shown to induce healing over a wide range of percent concentrations, protect injured cartilage, and cause biological effects by inflammatory and non-inflammatory mechanisms. Newer theories and techniques of Prolotherapy have provided additional explanations as to the mechanisms of healing by Prolotherapy, including the resolution of neurogenic inflammation.

Types of Prolotherapy

All the various types of Prolotherapy seek to normalize the physiology in injured tissues toward regeneration and renewal. There are many types of Prolotherapy including...
Hackett-Hemwall, Subcutaneous, Platelet Rich Plasma, Prolozone™ and Stem Cell Prolotherapy using either bone marrow or adipose (fat) tissue.

**HACKETT-HEMWALL PROLO THERAPY (DEXTROSE)**

Hackett-Hemwall Prolotherapy is a type of Prolotherapy that incorporates the teaching and techniques of George S. Hackett, MD and Gustav A. Hemwall, MD. This technique typically utilizes an inflammatory concentration of hypertonic dextrose of 12.5 to 25%. The injections are given into and around the entire painful or injured area. The emphasis is on treating all tender areas and resolving joint instability by treating ligaments and other joint stabilizing structures. Most treatments are given every four to six weeks to allow time for growth of the new connective tissues. The average person requires three to six visits total.

**SUBCUTANEOUS PROLO THERAPY**

Subcutaneous Prolotherapy (also called Neurofascial or Neural Prolotherapy) involves the injection of 5% dextrose into the subcutaneous tissues to induce healing. Research into the healing effects of this type of Prolotherapy originated by a family physician from New Zealand named John Lyftogt, MD. The injections are given just underneath the skin at the location of sensitized peptidergic nerves. These nerves contain transient receptor potential vaniloid receptors (or capsaicin receptors) and are known as TRPV1 nerves. These nerves are sensitized because of trauma, injury or constriction and represent sites of neurogenic inflammation. Neurogenic inflammation was first termed “inflammatory neuritis” by Dr. George Hackett in the 1950s. Peptidergic sensory nerves are important because they maintain the health and renewal of joint structures, such as ligament and tendons. Injections of 5% dextrose at the sites of sensitized nerves can completely eliminate pain from neurogenic inflammation. The injections are typically given weekly for five to ten visits.

**PROLOZONE™**

Prolozone is a Prolotherapy technique that utilizes ozone gas, along with other therapeutic substances to stimulate healing and reduce pain in injured soft tissues and joints. The ozone gas is produced when oxygen is exposed to an electric spark via a corona discharge ozone generator. The concentration of ozone in the final gas mixture is between 1-3%. Therapeutic injections of ozone into soft tissue structures, such as muscles, tendons and ligaments as well as arthritic joints for the relief of pain has been utilized for decades in medical clinics around the world. Various case series have been published documenting the analgesic effect of ozone in osteoarthritis. Double-blind randomized-controlled studies have also documented the therapeutic effects of Prolozone in the treatment of low back pain with and without sciatica. As a powerful oxidizing agent, ozone has been found to have a pro-inflammatory as well as an anti-inflammatory effect, depending on the concentration utilized. Its proposed mechanisms for tissue repair and regeneration include the stimulating of growth factor production and release. Prolozone treatments are typically given weekly for three to 12 treatments, and can be utilized alongside traditional dextrose Prolotherapy.

**PLATELET RICH PLASMA (PRP)**

PRP involves the injection of concentrated platelets, which release growth factors to stimulate recovery in non-healing soft tissue injuries. PRP contains platelets, wherein reside growth factors that are necessary for healing soft tissues, including platelet-derived growth factor, transforming growth factor and others, which exert their effects on fibroblasts and other immune cells causing their proliferation and thereby accelerating the regeneration of injured tissues. Activated platelets also secrete stromal cell derived factor 1 alpha (SDF-1a) which supports primary adhesion and migration of mesenchymal stem/stromal cells. The preparation consists of an autologous blood collection (blood from the patient), plasma separation (blood is centrifuged), and application of the plasma rich in growth factors (injecting the plasma into the area). PRP Prolotherapy is typically given every one to two months for one to six visits. High-density platelet rich plasma (HD-PRP) is defined as autologous blood with concentrations of platelets at equal or greater than four (4) times circulating baseline levels, and which increases the important bioactive protein load (growth factors) in a direct correlative fashion. Cell ratios in average circulating whole blood contain only 6% platelets. In true high-density PRP preparations, the concentration achieved is 94%. An average patient platelet count is 250,000 platelets/dl. Four times this is 1 million platelets/dl, which is considered the desired benchmark for “therapeutic PRP.”

**STEM CELL PROLO THERAPY**

This term describes using autologous adult pluripotent mesenchymal stem cells (MSCs) from an individual’s bone marrow or adipose (fat) tissue, as the “proliferating” solution.
An interesting observation made about MSCs is the ability to “home in” and help repair areas of tissue injury. Stem cell Prolotherapy is typically done for more advanced cases of joint degeneration, including osteochondral defects, or where dextrose Prolotherapy and/or PRP Prolotherapy have not resolved a problem. Sources for these cells are a person’s own bone marrow or adipose (fat) tissue. With stem cell Prolotherapy a stem cell niche (microenvironment which favors healing) is moved from one tissue in which these niches are abundant (adipose or bone marrow) into one where they are scarce (a non-repairing connective tissue). Stem cells are activated by specific cues within this localized environment to either self-replicate or differentiate. From these niches, the tissues, and ultimately the body, can maintain function and replace cells that have been damaged or have died. The niche is a physiologically segregated area of the tissue wherein stem cells are restrained from commitment to extensive proliferation and differentiation and where the stem cells are housed throughout life. Of particular interest is the observation in degenerative diseases, such as osteoarthritis, that an individual’s adult stem cell frequency and potency may be depleted, with reduced proliferative capacity and ability to differentiate. It has been suggested that addition of these missing stem/stromal cell elements might help these degenerative conditions. Studies have demonstrated such improvement with adult stem cell therapy by the successful regeneration of osteoarthritic damage and articular cartilage defects. In 2003, Murphy et al. reported significant improvement in medial meniscus and cartilage regeneration with autologous stem cell therapy in an animal model. Not only was there evidence of marked regeneration of meniscal tissue, but the usual progressive destruction of articular cartilage, osteophytic remodeling and subchondral sclerosis commonly seen in osteoarthritic disease was reduced in MSC-treated joints compared with controls. In 2008, Centeno et al. reported significant knee cartilage growth and symptomatic improvement in a human case report using culture expanded autologous MSCs from bone marrow. In 2011, Albano and Alexander used autologous adipose cells as a living bioscaffold and stem cell source to repair a torn patellar tendon. The number of treatments varies depending on condition and prior treatment regime, with clinical protocols in the recent medical literature. Stem cell Prolotherapy is typically given every month to few months.*

Lipoaspirate Prolotherapy (ADSC)
While bone marrow has historically been used as a source of MSCs, adipose (fat)-derived stem/stromal cells (ADSCs) have been shown to have nearly identical fibroblast-like morphology and colonization (GFU-F), immune phenotype, successful rate of isolation, and differentiation capabilities. Autologous bone marrow stem cell volume is limited, but adipose tissue represents a large reservoir of stem cells. Research also supports as much as 500 to 1000 times as many mesenchymal and stromal vascular stem-like cells in adipose as compared to bone marrow. ADSCs have been shown, in multiple studies, to improve wound healing and stimulate fibroblast proliferation, migration and collagen secretion, thereby increasing connective tissue tensile strength and healing. Multiple human and animal investigations have clearly demonstrated the in vitro ability of AD-SCs to differentiate into, and repair, musculoskeletal connective tissues including ligament, tendon, cartilage, disc, muscle, nerve tissue, bone, hematopoietic-supporting stroma, to actively participate in tissue homeostasis, regeneration, and wound healing. Lipoaspirate Prolotherapy is typically given every four to six weeks.

Bone Marrow Prolotherapy
The primary current use of adult stem cells in orthopaedic therapies are those derived from the bone marrow. In orthopaedic therapies, bone repair and regeneration is driven by the implanted bone marrow MSCs (BMSCs) that either engraft directly into the bone or are recruited from the marrow to the bone. Human studies have documented enhanced treatment outcomes for nonunion fractures, avascular necrosis (osteonecrosis) and spinal fusions with the utilization of BMSCs. The FDA has already approved the use of bone marrow stem cells for use in orthopaedics and many companies have products that help separate and thus concentrate the BMSCs from plasma and red blood cells. Centrifugation can concentrate BMSCs up to seven times the normal levels seen in whole marrow without losing cell viability, functionality and ability to osteogenically differentiate. Initial research found that using whole bone marrow increased fusion rates in nonunion fractures 28%, but with centrifuged marrow, healing increased to 70%. Others have documented the facilitation of healing with increased BMSC’s counts. Cell counts in the literature for concentrated marrow have ranged for 16.4 x 10^6 cells/ml to as high as 2.2 x 10^9 cells/ml in successful fusions or healings in orthopedic procedures. Numerous publications have demonstrated the benefits of...

*The various nomenclature for the specific types of heterogeneous cells in these injections includes stromal or undifferentiated stromal cells.
concentrated bone marrow for the regeneration of various structures of the skeletal system including bone, cartilage, and connective tissues. With the exception of a few studies, bone marrow derived mesenchymal stem cells have an enhanced potential for chondrogenic differentiation as compared to adipose stem cells. Proponents of bone marrow-derived stem cells note the large number of human studies and the fact that bone marrow contains the necessary MSCs and growth factors that are needed for use in orthopedic medicine. Typically bone marrow Prolotherapy is given every four to eight weeks.

**COMMON SIGNS AND SYMPTOMS AS POSSIBLE INDICATIONS FOR PROLOTHERA:**

- Laxity of a tested joint, especially compared to the non-painful side
- Distinct tender points at the entheses where tendons or ligaments attach to the bones
- Chronic muscle spasms
- Recurrent swelling or fullness in a joint
- Popping, clicking, grinding, or catching sensations in joints
- Temporary benefit from chiropractic, osteopathic, or self-manipulation that fails to resolve
- Recurrent joint subluxations or dislocations
- Aching, burning or tingling pain or sensation that is referred into an upper or lower extremity

**MUSCULOSKELETAL INDICATIONS FOR PROLOTHERA:**

Prolotherapy is indicated for the following groups of conditions: degenerative arthritis including degenerative joint disease and spondylosis; enthesopathies; ligament injury, including ligament laxity and grade one and two tears; tendinopathy, including tendinosis and tendinitis, and grade one and two tears; joint instability from ligament, labrum or meniscus injury, including congenital conditions including joint hypermobility syndrome and Ehlers-Danlos syndrome; apophysitis and other apophyseal and growth plate injuries, including Osgood-Schlatter disease; other conditions including the pain from complex regional pain syndrome, myofascial pain syndrome, fibromyalgia, post-surgery pain syndrome, and patellofemoral pain syndrome; as well as to augment surgical procedures including ligament and tendon repair (typically grade 3 or complete tears) and fusions.

**CONDITIONS SUCCESSFULLY TREATED BY PROLOTHERA:**

**Degenerative Arthritis**

Prolotherapy is indicated for the following degenerative arthritis (osteoarthritis or osteoarthrosis) conditions:

- Degenerative joint disease involving all peripheral joints including the knees, hips and fingers
- Degenerative spinal disease including spondylosis, spondylolisthesis and degenerative disc disease
- Osteochondral defects

**Joint Instability**

Prolotherapy is indicated for these ligamentous injuries and other conditions that can cause joint instability and pain:

- Ligament tears and injury
- Labral tears and degeneration
- Meniscus tears and degeneration
- Congenital conditions such as joint hypermobility syndrome and Ehlers-Danlos syndrome

**Tendinopathy**

Prolotherapy is indicated for the following conditions involving tendons and the entheses:

- Tendinopathy
- Tendinosis
- Tendinitis
- Grade one and two tears (partial tears)
- Enthesopathies including osteitis pubis and medial tibial stress syndrome
- Muscle origin pain and tears

Prolotherapy in rare situations can be used for complete tendon tears such as when a patient is not a surgical candidate or has strong desires/reasons not to get surgery. Two case reports show repair of a complete tear/rupture, an Achilles tendon and anterior cruciate ligament tear.

**OTHER MUSCULOSKELETAL CONDITIONS**

Prolotherapy can be successfully used, along with other therapies for the following musculoskeletal conditions:

- Post-surgical Pain syndrome
- Myofascial Pain syndrome
- Fibromyalgia\textsuperscript{257}
- Complex Regional Pain syndrome\textsuperscript{258}
- Chronic headaches\textsuperscript{259-262}
- Radiculopathy\textsuperscript{263, 264}
- Autonomic symptoms, including Barre-Lieou syndrome\textsuperscript{265-268}
- Apophyseal growth plate injuries, including Osgood-Schlatter disease\textsuperscript{37, 394}
- Other\textsuperscript{269-278}

**Prolotherapy as an alternative treatment**

Prolotherapy is a viable alternative to pain medications including NSAIDs, physiotherapy, and/or cortisone (steroid) injection for the following conditions:

- Tendinitis or bursitis\textsuperscript{56, 64, 227}
- Epicondylitis (epicondylosis)\textsuperscript{24, 234, 237}
- Plantar fasciitis (fasciosis)\textsuperscript{64, 225, 233, 279}
- Tendinopathy (tendinosis or other enthesopathy)\textsuperscript{52, 77, 83, 162, 163, 166}
- Ligament injury (tear or laxity)\textsuperscript{9, 55, 116, 200, 202, 217}
- Degenerative arthritis (degenerative joint and spinal disease)\textsuperscript{57, 93, 205, 206, 209, 277}
- Neuritis\textsuperscript{85, 86, 89, 92}
- Temporomandibular Joint syndrome\textsuperscript{14, 15, 197, 280}
- Myofascial Pain syndrome\textsuperscript{64, 83-85, 230, 255, 281}
- Fracture pain\textsuperscript{274, 278}

Prolotherapy can be used as an alternative to surgery for the following conditions:

- Degenerative arthritis (degenerative joint disease)\textsuperscript{93, 109, 188, 189, 194, 211, 221, 222}
- Degenerative spinal arthritis (spondylosis and degenerative disc disease)\textsuperscript{10, 11, 17, 277, 282, 283}
- Tendon or ligament tear\textsuperscript{114, 241, 242, 284}

**Prolotherapy to enhance surgical outcomes**

Prolotherapy can be used to potentially enhance outcomes in the following surgical procedures:

- Fusion\textsuperscript{288, 289}
- Ligament repairs\textsuperscript{290-292}
- Bone fractures and other lesions\textsuperscript{27, 28, 293, 294, 295}
- Osteochondral defects\textsuperscript{25, 26, 28, 296-299}

**Prolotherapy compared to traditional therapies – The example of knee osteoarthritis**

Musculoskeletal diseases are extremely common and have important consequences to the individual and society. Musculoskeletal diseases according to the World Health Organization are one of the most significant causes of disability around the world. In regard to the burden due to musculoskeletal diseases, osteoarthritis (OA) represents over 50% of the absolute disability-adjusted-life years and this burden is rapidly growing in both the developed and developing world.\textsuperscript{300, 301}

OA is the most common form of arthritis in the world.\textsuperscript{302} It is characterized pathologically by both focal loss of articular cartilage and marginal and central new bone formation. OA of the knee, the principal large joint affected, results in disabling knee symptoms in an estimated 10% of people older than 55 years, a quarter of whom are severely disabled.\textsuperscript{303} The risk of disability attributable to knee OA alone is as great as that due to cardiac disease and greater than that due to any other medical disorder in the elderly.\textsuperscript{304} A recent World Health Organization report on the global burden of disease indicates that knee OA is likely to become the fourth most important global cause of disability in women and the eighth most important in men.\textsuperscript{305} The annual costs attributable to knee OA are immense.

Knee OA is associated with symptoms of pain and functional disability. Physical disability arising from pain and loss of functional capacity reduces quality of life and increases the risk of further morbidity. When attempts to reduce symptoms by exercise, lifestyle change, and non-steroidal anti-inflammatory drugs fail, more invasive therapies are sought. The current standard of care for unresponsive knee OA by the above methods includes injection of corticosteroids or hyaluronic acid (or its derivatives) into the joint. If these fail, then often arthroscopic or joint replacement procedures are recommended.
INTRAARTICULAR CORTICOSTEROID TREATMENT FOR KNEE OSTEOARTHRITIS GIVES ONLY SHORT TERM PAIN RELIEF (<3 WEEKS)

The effects of intraarticular steroids in knee OA have been assessed in numerous studies. A recent Cochrane Database Systemic Review concluded that the short-term benefit of pain reduction with intraarticular corticosteroids in the treatment of knee OA is well established, however there is a lack of evidence that any benefit occurs after three weeks. Others have confirmed that there is no evidence that intraarticular corticosteroids have any long lasting beneficial effects, while some authors note that intraarticular corticosteroids actually accelerate the arthritic process.

HYALURONIC ACID CAN GIVE PAIN RELIEF FOR SEVERAL MONTHS, BUT NOT LONG TERM

The role of hyaluronic acid (HA and its derivatives) in pain reduction, functional improvement, and in disease modification has been assessed in over one hundred clinical trials. The overall consensus by various systematic reviews is that although pain relief from HA may be obtained for several months, rather than several weeks as with steroid, this benefit may be offset by a course of three to five weekly injections with the logistical and cost issues that entails. Another concern is that the amount of pain relief on a visual analogue scale (VAS) when overall results are tallied is actually quite small (less than 1 on a 0-10 scale).

There is minimal to no evidence that HA injections have any disease modifying effects. There is little evidence that one HA preparation has any distinct pain-relieving effect over another. The U.S. government agency for healthcare research and quality in 2009 published a clinician’s guide for effective health care noting that “viscosupplementation resulted in no meaningful improvement when used as a treatment for osteoarthritis of the knee.”

ARTHROSCOPIC CHONDROPLASTY HAS NO LONG TERM EVIDENCE FOR MECHANICAL KNEE SYMPTOMS

Arthroscopic chondroplasty with or without meniscectomy is a common treatment for mechanical knee symptoms including locking, giving way or catching. The term chondroplasty is used for mechanical or thermal reshaping of uneven articular cartilage. The aim is to debride loose chondral flaps and fibrillated articular cartilage to a smoother surface. Meniscectomy is the surgical removal of all or part of a torn meniscus. Both chondroplasty and meniscectomy involve the removal of knee cartilage or fibrocartilage (menisci) in an attempt to decrease the symptoms caused from impinging osteophytes, articular cartilage and meniscal tears and flaps. Patients who have early-stage degenerative disease and mechanical symptoms of relatively short duration do better with arthroscopic chondroplasty than those who have undergone previous arthroscopy, advanced disease, and chronic, persistent pain. However, no evidence indicates that arthroscopic procedures can predictably serve as a long-term option in the management of the arthritic knee with mechanical symptoms.

Multiple articles have confirmed that significant rates of cartilage loss are seen in patients post-partial or complete meniscectomy compared to healthy controls. Long-term results following these procedures reveal a high incidence of poor
results, degenerative arthritis and ligament laxity.\textsuperscript{342, 343} Multiple studies have confirmed that the removal of meniscal tissue from the knee increases joint pressure and instability, leading to an acceleration of the degeneration process.\textsuperscript{344-350}

**KNEE REPLACEMENT SURGERY (ARTHROPLASTY) IMPROVES LONG TERM QUALITY OF LIFE**

Total joint replacement is the most common treatment for advanced osteoarthritis of the knee, with the primary goal of the procedure to improve the patient’s quality of life. Many scientific studies and systematic reviews have found that total knee arthroplasties, including minimally invasive techniques, were found to be quite effective in terms of long-term improvement in health-related quality-of-life dimensions including pain relief and activities of daily living.\textsuperscript{351-357}

**PROLOTHERAPY IN THE TREATMENT AND PREVENTION OF KNEE OSTEOARTHRITIS**

Scientific evidence is available that Prolotherapy should be utilized in the treatment of knee osteoarthritis. Currently there are no standard treatment options which have been able to arrest the development of osteoarthritis. Progression of joint degeneration often eventually leads to joint replacement. While there are many risk factors for joint degeneration, it is well accepted that the major cause of knee osteoarthritis is ligament dysfunction, especially to the anterior cruciate ligament.\textsuperscript{358-364} Being that ligament injury, excess laxity, joint hypermobility, and clinical instability are known to be major causes of osteoarthritis, any treatment which can address restoration of ligament function would help reduce the incidence, pain, and dysfunction of osteoarthritis, as well as the need for total joint replacements.

Prolotherapy promotes ligament repair by causing a thickening and tightening of ligaments, as well as the ligament-bone interface (fibro-osseous junction).\textsuperscript{365-369} This includes stimulating the repair of the anterior cruciate ligament resulting in increased knee stability.\textsuperscript{370-372} Two randomized, prospective, placebo-controlled, double-blind clinical trials of dextrose Prolotherapy revealed a statistically significant benefit from the Prolotherapy injections over control. Prolotherapy improved patients’ quality of life including statistically significant improvement of pain, as well as other quality of life measures including ability to walk and knee instability complaints.\textsuperscript{373, 374} Case series in animals and humans have documented improved radiographs and articular cartilage regeneration with Prolotherapy.\textsuperscript{375-380} Other studies using Prolotherapy have confirmed that Prolotherapy reduces the need for knee surgeries including meniscectomy and total joint replacement.\textsuperscript{381-383}

**SUMMARY OF PROLOTHERAPY VERSUS OTHER COMMON INVASIVE PROCEDURES FOR KNEE OSTEOARTHRITIS**

Scientific evidence is available that Prolotherapy should be utilized in the treatment of knee osteoarthritis. Osteoarthritis outnumbers all other forms of arthritis combined; the knee being the most commonly involved joint. Knee OA is associated with symptoms of pain and functional disability. Physical disability arising from pain and loss of functional capacity reduces quality of life and increases the risk of further morbidity. When attempts to reduce symptoms by exercise, lifestyle change, and non-steroidal anti-inflammatory drugs fail, more invasive therapies are sought. The current standard of care for unresponsive knee OA by the above methods includes injection of corticosteroids or hyaluronic acid (viscosupplementation) into the joint. If these fail, then often arthroscopic procedures or total joint replacements are recommended.

No common standard therapies used arrest or reverse knee degenerative arthritis. Intraarticular corticosteroids and/or hyaluronic acid (viscosupplementation) have been shown to provide only temporary (less than three months or shorter) pain relief. Long-term benefit with these therapies has not been shown. Only total joint replacement has been found to provide long-term pain relief. Arthroscopic knee surgery with or without joint lavage has been found to be no better than sham (placebo) procedures and is no longer recommended for routine knee osteoarthritis. Arthroscopy with chondroplasty or meniscectomy can reduce symptoms such as knee locking and instability, but long-term, accelerates the degenerative process in the knee.

By promoting ligament repair, Prolotherapy addresses the major causes of osteoarthritis including ligament injury, excess laxity, joint hypermobility and clinical instability. Studies in Prolotherapy have documented anterior cruciate ligament repair, knee joint stabilization, improvement of radiographic studies, and improved quality of life for patients with knee osteoarthritis. Two randomized, prospective, placebo-controlled, double-blind clinical trials of dextrose Prolotherapy revealed a statistically significant benefit from the Prolotherapy injections over control. Prolotherapy improved patients’ quality of life including
statistically significant improvement of pain, as well as other quality of life measures, including ability to walk and knee instability complaints. Case series in animals and humans have documented improved radiographs and articular cartilage regeneration with Prolotherapy. Other studies using Prolotherapy have confirmed that Prolotherapy reduces the need for knee surgeries including meniscectomy and total joint replacement.

SIDE EFFECTS AND ADVERSE EVENTS WITH PROLOTHERAPY

Prolotherapy, as in all invasive medical procedures, carries risks. While these risks are real, Prolotherapy compared to even anti-inflammatory medications (NSAIDs) or acetaminophen is magnitudes safer, as these medications are responsible for tens of thousands of people dying each year.\(^{384-307}\) There is scientific data proving that NSAIDs have the propensity to accelerate articular cartilage deterioration in osteoarthritis.\(^{308}\) The main risks related to Prolotherapy are a result of needle trauma and inadvertent needle placement. Common side effects at the treatment site include pain, stiffness, bleeding, bruising and swelling. Potential, less common adverse events include nerve, ligament or tendon injury, spinal headache, pneumothorax, nerve damage, spinal cord injury, disc injury, and infection.\(^{389, 390}\) Prolotherapy spinal injections, as with all spinal injections, carry serious risks, including injury to the spinal cord and event death, although these are extremely rare.\(^{391-393}\) Potential allergic and anaphylactic reactions to the agents injected can also occur.

IMPLICATIONS FOR PRACTICE

The practice of Prolotherapy involves years of scientific and clinical research, case studies involving thousands of patients, and treated patients comprising tens of thousands, who attribute to the efficacy of the treatment. The mechanism and application of the treatment have been proven to be sound and safe, producing medically positive results, both short and long-term. The theory of Prolotherapy complies with the current medical standards and understanding of human physiology that is involved with the healing of injured musculoskeletal tissues. Positive results have been reported in the scientific medical literature in case series, nonrandomized and randomized for many musculoskeletal conditions, in both osteopathic and allopathic professions.

Clinicians make their recommendations to patients on the basis of their knowledge of human physiology in both health and disease. Since most chronic pain results from the degeneration and injury of musculoskeletal structures such as ligaments, tendons, other soft tissues and joints, and the nerves that support them, then regenerative injection therapy (Prolotherapy) makes physiological sense. Prolotherapy should be one of the preferred therapies when clinicians, including doctors, nurses, and other allied health care professionals, discuss treatment options with patients who suffer from musculoskeletal pain.

BIBLIOGRAPHY


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.

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. 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. 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. 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. 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. 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. By 2030, it is estimated to nearly 600,000 hip replacements and 1.4 million knee replacements by the year 2015. By 2030, it is estimated to nearly 600,000 hip replacements and 1.4 million knee replacements will escalate.

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. 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. By 2030, it is estimated to nearly 600,000 hip replacements and 1.4 million knee replacements 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 (enthesis), 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.’” 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 and strengthening, stabilize unstable joints such as the sacroiliac joint, cervical spine and temporomandibular joint, 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, as well as reduce neurogenic inflammation. 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. Gustav A. Hemwall, MD, is credited as the first doctor to use just dextrose by itself as the proliferant for Prolotherapy, when Synasol (fatty acid derivative) was no longer available. 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. Typical concentrations of dextrose used in Prolotherapy are from five to twenty-five percent.

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. 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. Increased glucose concentration (dextrose) causes an increase in cell protein synthesis, DNA synthesis, cell volume and proliferation. 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, transforming growth factor-beta (TGF-β), epidermal growth factor, basic fibroblast growth factor, insulin-like growth factor, and connective tissue growth factor. These are some of the growth factors that are pertinent to the repair, health and growth of tendons, ligaments and other soft tissues. Dextrose injected into tissues has been found in animal and human studies to stimulate inflammation, ligament size, tendon hypertrophy, extracellular matrix, fibroblastic proliferation, and repair of articular cartilage defects. It has also been shown to...
induce healing over a wide range of percent concentrations, protect injured cartilage, and cause biological effects by inflammatory and noninflammatory mechanisms.

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, of these 89% have some degree of long-term or short-term disability; nearly all chronic pain patients have substantially reduced health-related quality of life; ligament injuries often fail to heal completely; unresolved ligament tears and sprains can completely alter joint mechanics; ligament laxity and its associated joint instability is a leading cause of spinal and joint degeneration, and when hypermobility is sought it is the most common finding among patients presenting to a rheumatologist.

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

**OBJECTIVE**

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

**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, liposapirate, 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 Seo 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. 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).
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.\textsuperscript{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.

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.\textsuperscript{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.\textsuperscript{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.

\textbf{Low Back and Pelvic Pain Due to Specific Causes}

Lee treated 20 patients with an 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

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### Table 1. VAS before and after Prolotherapy by body part.


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

### Table 2. Use of Prolotherapy for pain in individual joints.

Prolotherapy caused a statistically significant decline in pain.\textsuperscript{80-90}
every other week for three weeks.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 3.3 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.\textsuperscript{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.\textsuperscript{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/0.25T bupivicaine, 3cc total solution used) for patients experiencing chronic advanced degenerative discogenic leg pain, with or without low back pain on average for 39 months.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. Hauser\textsuperscript{103} 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 patients with knee osteoarthritis who suffered with pain from 4.2 to 2.5 after treatment. The dextrose Prolotherapy caused statistically significant improvements in VAS score, pain rating score and the Western Ontario Macmaster Universities Osteoarthritis Index (WOMAC) (p<0.05). (See Table 3.)

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>
<thead>
<tr>
<th>Mean Baseline VAS (mm)</th>
<th>Mean 45 week follow-up VAS (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain at rest (VAS1)*</td>
<td>38.4</td>
</tr>
<tr>
<td>Pain with daily living (VAS2)*</td>
<td>51.1</td>
</tr>
<tr>
<td>Pain with sport (VAS3)*</td>
<td>78.1</td>
</tr>
</tbody>
</table>

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

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 enthesis of the maseter 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.)

**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.\textsuperscript{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.\textsuperscript{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. 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.

**Figure 3. Ultrasound of lateral elbow before and after Prolotherapy.** Initial anechoic focus (A) was filled with fibrillar pattern except small anechoic focus after treatment (B).

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

<table>
<thead>
<tr>
<th>Score</th>
<th>Before Therapy</th>
<th>After Therapy</th>
<th>Mean % Change in VAS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Midportion</td>
<td>Insertional</td>
<td>Combined</td>
</tr>
<tr>
<td>VAS1</td>
<td>41.7</td>
<td>30.3</td>
<td>38.2</td>
</tr>
<tr>
<td>VAS2</td>
<td>55.5</td>
<td>45.3</td>
<td>52.4</td>
</tr>
<tr>
<td>VAS3</td>
<td>73.9</td>
<td>66.4</td>
<td>71.6</td>
</tr>
</tbody>
</table>

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.

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

<table>
<thead>
<tr>
<th>Midportion</th>
<th>Before Prolotherapy</th>
<th>After Prolotherapy</th>
<th>At 28 month Follow-up</th>
<th>Mean change in ES Pretest to Post-test</th>
<th>Mean change in ES Pretest to Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS1</td>
<td>34.1</td>
<td>12.6</td>
<td>3.3</td>
<td>21.3*</td>
<td>30.8*</td>
</tr>
<tr>
<td>VAS2</td>
<td>50.2</td>
<td>21.8</td>
<td>9.5</td>
<td>28.2*</td>
<td>40.7*</td>
</tr>
<tr>
<td>VAS3</td>
<td>70.7</td>
<td>36.7</td>
<td>16.7</td>
<td>34.0*</td>
<td>54.0*</td>
</tr>
</tbody>
</table>

Note—ES is a measure of the effect size on the difference represented as Cohen’s d. VAS1 = pain at rest, VAS2 = pain with activities of daily living, VAS3 = pain during or immediately after sports participation. \* indicates a significant difference between time interval to 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.130 The patients' mean duration with weekly subcutaneous dextrose (20%) Prolotherapy and all patients reported a marked improvement in 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 Hauser80, 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.)
The Case for Prolotherapy: Evidence-Based Use of Dextrose Prolotherapy for Musculoskeletal Pain

Two controlled, nonrandomized dextrose Prolotherapy studies have been reported on in the medical literature. Kim et al.\textsuperscript{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 triamcinolone 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.\textsuperscript{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.

### CONTROLLED, NONRANDOMIZED DEXTROSE PROLOThERAPY STUDIES

<table>
<thead>
<tr>
<th>Area treated</th>
<th>Average pain level prior to Prolotherapy</th>
<th>Average pain level after Prolotherapy</th>
<th>Percent of patients who reported &gt; 50% pain relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee</td>
<td>6.8</td>
<td>3.0</td>
<td>100%</td>
</tr>
<tr>
<td>Back</td>
<td>6.0</td>
<td>2.1</td>
<td>96%</td>
</tr>
<tr>
<td>Neck</td>
<td>6.6</td>
<td>2.1</td>
<td>90%</td>
</tr>
<tr>
<td>Shoulder</td>
<td>7.0</td>
<td>2.6</td>
<td>90%</td>
</tr>
<tr>
<td>Hip</td>
<td>7.1</td>
<td>2.4</td>
<td>100%</td>
</tr>
</tbody>
</table>

### DEXTROSE PROLOThERAPY COMPAREd TO STERoid FOR SACROIliAC JI NT 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.\textsuperscript{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.

### 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.)

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|}
\hline
Area treated & Average pain level prior to Prolotherapy & Average pain level after Prolotherapy & Percent of patients who reported > 50% pain relief \\
\hline
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% \\
\hline
\end{tabular}
\caption{Pre and post Prolotherapy results for patients told that surgery was the only option to resolve their chronic pain.\textsuperscript{80,81,82,84,89}}
\end{table}

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.

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. 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

<table>
<thead>
<tr>
<th>Primary Authors</th>
<th>Condition/Treatments</th>
<th># of Patients/Joints</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim136</td>
<td>Sacroiliac pain Prolotherapy vs. Steroids</td>
<td>23 - dextrose 25 - steroid injection</td>
<td>The cumulative incidence of &gt; 50% pain relief at 15 months: 58.7% - Prolotherapy group, 10.2% - steroid group (p&lt;0.005).</td>
</tr>
<tr>
<td>Kim137</td>
<td>Myofascial pain syndrome dextrose vs. saline vs. lidocaine Prolotherapy</td>
<td>23 - dextrose 20 - saline 21 - lidocaine</td>
<td>VAS decrease - dextrose = 4.48, lidocaine = 2.65, saline = 2.90 (p&lt;0.01).</td>
</tr>
<tr>
<td>Reeves138</td>
<td>Finger &amp; thumb osteoarthritis dextrose vs. lidocaine Prolotherapy</td>
<td>27 total patients 74 - dextrose 76 - xilocaine</td>
<td>Pain with movement improved 42% in the dextrose group compared to 15% in the xilocaine group (p&lt;0.027).</td>
</tr>
<tr>
<td>Reeves139</td>
<td>Knee osteoarthritis dextrose vs. lidocaine Prolotherapy</td>
<td>68 total patients 58 - dextrose 53 - lidocaine</td>
<td>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&lt;0.015)</td>
</tr>
<tr>
<td>Topal140</td>
<td>Osgood-Schlatter disease dextrose Prolotherapy vs. lidocaine injection vs. supervised usual care to reduce sport alteration and sport-related symptoms</td>
<td>54 total patients 38 - dextrose 13 - lidocaine 14 - usual care</td>
<td>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&lt;0.0001).</td>
</tr>
<tr>
<td>Rabago41</td>
<td>Knee osteoarthritis</td>
<td>89 total patients 30 - dextrose 28 - saline 31 - exercise</td>
<td>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&lt;0.01) and controls (p&lt;0.01).</td>
</tr>
<tr>
<td>Yelland142</td>
<td>Chronic low back pain dextrose Prolotherapy vs. saline injections &amp; exercise vs. normal activity</td>
<td>110 total patients 54 - dextrose vs. 56 - saline 55 - exercise vs. 55 - normal activity</td>
<td>Achieved &gt; 50% reduction in pain - glucose/lignocaine VAS: 0.46 versus saline VAS: 0.36 (p&lt;0.05).</td>
</tr>
<tr>
<td>Yelland143</td>
<td>Achilles tendinosis dextrose Prolotherapy vs. eccentric loading exercises</td>
<td>14 - dextrose 15 - loading exercises 14 - combined</td>
<td>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.</td>
</tr>
<tr>
<td>Refai144</td>
<td>Temporomandibular joint hypermobility dextrose Prolotherapy vs. saline injections</td>
<td>12 total patients 6 - dextrose 6 - saline</td>
<td>Significantly less pain intensity in both groups. The active group showed a significant reduction in MMO (maximal mouth opening) at the 12th week postoperatively.</td>
</tr>
</tbody>
</table>
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.


<table>
<thead>
<tr>
<th>Solution</th>
<th>Before</th>
<th>Immediately after</th>
<th>7 days after</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% D/W**</td>
<td>6.87</td>
<td>4.83</td>
<td>2.39*</td>
</tr>
<tr>
<td>Saline</td>
<td>6.50</td>
<td>5.65</td>
<td>3.85</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>6.95</td>
<td>5.14</td>
<td>4.05</td>
</tr>
</tbody>
</table>

* 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).


<table>
<thead>
<tr>
<th>Solution</th>
<th>Before</th>
<th>Immediately after</th>
<th>7 days after</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% D/W**</td>
<td>1.79</td>
<td>2.07</td>
<td>2.49*</td>
</tr>
<tr>
<td>Saline</td>
<td>1.70</td>
<td>2.02</td>
<td>1.91</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>1.75</td>
<td>2.27</td>
<td>2.07</td>
</tr>
</tbody>
</table>

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

Reeves and Hassanein published two randomized, prospective, placebo-controlled double-blind studies on dextrose Prolotherapy for osteoarthritis of the thumb, fingers and knees. 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. 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=0.03). 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. 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...
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. 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 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, 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.

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. 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 subjections 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. 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. 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. 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. 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. 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.100 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, 138 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 function111; pain and swelling139, 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.

<table>
<thead>
<tr>
<th>Primary Authors</th>
<th>Condition</th>
<th># of Patients/Treated areas</th>
<th>Before</th>
<th>After</th>
<th>VAS or NRS (0-10)</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim\textsuperscript{78}</td>
<td>Chronic MLS pain</td>
<td>67</td>
<td>7.0</td>
<td>2.55</td>
<td></td>
<td>4.5</td>
</tr>
<tr>
<td>Kim\textsuperscript{79}</td>
<td>Chronic MLS pain</td>
<td>20</td>
<td>–</td>
<td>–</td>
<td>Reduced by 80%</td>
<td></td>
</tr>
<tr>
<td>Hauser\textsuperscript{80-81} (11 Studies)</td>
<td>Chronic MLS pain</td>
<td>709</td>
<td>6.3</td>
<td>2.2</td>
<td></td>
<td>4.1</td>
</tr>
<tr>
<td>Lytgo\textsuperscript{9}</td>
<td>Chronic MLS pain</td>
<td>127</td>
<td>6.7</td>
<td>0.76</td>
<td></td>
<td>5.9</td>
</tr>
<tr>
<td>Hooper\textsuperscript{92}</td>
<td>Chronic MLS pain</td>
<td>177</td>
<td>–</td>
<td>–</td>
<td>91% of patients had a decreased level of pain*</td>
<td></td>
</tr>
<tr>
<td>Lytgo\textsuperscript{94}</td>
<td>Chronic MLS pain</td>
<td>41</td>
<td>7.6</td>
<td>1.4</td>
<td></td>
<td>6.2</td>
</tr>
<tr>
<td>Lee\textsuperscript{85}</td>
<td>Sacroiliac pain</td>
<td>20</td>
<td>6.0</td>
<td>1.0</td>
<td>NRS 5.0, Oswestry Disability Index 34.1-12.6*</td>
<td></td>
</tr>
<tr>
<td>Cusi\textsuperscript{96}</td>
<td>Sacroiliac pain</td>
<td>25</td>
<td>–</td>
<td>–</td>
<td>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)*</td>
<td></td>
</tr>
<tr>
<td>Topol\textsuperscript{97}</td>
<td>Osteitis pubis</td>
<td>24</td>
<td>6.3</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naeim\textsuperscript{98}</td>
<td>Illiolumbar syndrome</td>
<td>7</td>
<td>–</td>
<td>–</td>
<td>86% reported good results*</td>
<td></td>
</tr>
<tr>
<td>Khan\textsuperscript{99}</td>
<td>Coccygodynia</td>
<td>37</td>
<td>8.5</td>
<td>2.5</td>
<td></td>
<td>5.8</td>
</tr>
<tr>
<td>Miller\textsuperscript{100}</td>
<td>Lumbar disc pain</td>
<td>33</td>
<td>–</td>
<td>–</td>
<td>6.3 (responder group)</td>
<td></td>
</tr>
<tr>
<td>Miller\textsuperscript{101}</td>
<td>Lumbar disc pain</td>
<td>43</td>
<td>–</td>
<td>–</td>
<td>&lt; 20% pain relief (non responder group)</td>
<td></td>
</tr>
<tr>
<td>Jo\textsuperscript{102}</td>
<td>Knee ligament injury</td>
<td>40</td>
<td>8.0</td>
<td>1.3</td>
<td></td>
<td>6.7</td>
</tr>
<tr>
<td>Hauser\textsuperscript{103}</td>
<td>Meniscus injury</td>
<td>28</td>
<td>7.2</td>
<td>1.6</td>
<td></td>
<td>5.6</td>
</tr>
<tr>
<td>Reeves\textsuperscript{104}</td>
<td>ACL injury</td>
<td>16</td>
<td>–</td>
<td>–</td>
<td>VAS1-45%, VAS2-43%, VAS3-35%</td>
<td></td>
</tr>
<tr>
<td>Kim\textsuperscript{105}</td>
<td>Knee osteoarthritis</td>
<td>20</td>
<td>6.5</td>
<td>2.65</td>
<td>VAS-3.8, Total WOMAC 38.53-13.47</td>
<td></td>
</tr>
<tr>
<td>Ryan\textsuperscript{106}</td>
<td>Patellar tendinopathy</td>
<td>47</td>
<td>–</td>
<td>–</td>
<td>VAS1-19.7, VAS2-25.3, VAS3-39.3</td>
<td></td>
</tr>
<tr>
<td>Hakala\textsuperscript{107}</td>
<td>TMJ dysfunction</td>
<td>26</td>
<td>–</td>
<td>–</td>
<td>Clicking improved in 73%; Pain improved in 81%</td>
<td></td>
</tr>
<tr>
<td>Hakala\textsuperscript{108}</td>
<td>TMJ dysfunction</td>
<td>55</td>
<td>–</td>
<td>–</td>
<td>42% of pain cured (0), 71% &lt; 1 (0-5 pain scale)*</td>
<td></td>
</tr>
<tr>
<td>Hauser\textsuperscript{109}</td>
<td>Headache pain</td>
<td>15</td>
<td>–</td>
<td>–</td>
<td>39% reported 100% improvement; 100% received relief in frequency &amp; intensity*</td>
<td></td>
</tr>
<tr>
<td>Hooper\textsuperscript{110}</td>
<td>Whiplash neck pain</td>
<td>15</td>
<td>24.7</td>
<td>10.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Centeno\textsuperscript{111}</td>
<td>Cervical instability</td>
<td>6</td>
<td>5.8</td>
<td>3.8</td>
<td></td>
<td>2.0</td>
</tr>
<tr>
<td>Shin\textsuperscript{112}</td>
<td>Lateral epicondylitis</td>
<td>84</td>
<td>6.79</td>
<td>2.95</td>
<td></td>
<td>3.8</td>
</tr>
<tr>
<td>Kang\textsuperscript{113}</td>
<td>Lateral epicondylitis</td>
<td>12</td>
<td>7.12</td>
<td>2.5</td>
<td></td>
<td>4.6</td>
</tr>
<tr>
<td>Lytgo\textsuperscript{114}</td>
<td>Achilles tendinopathy</td>
<td>169</td>
<td>6.5</td>
<td>0.5</td>
<td></td>
<td>6.0</td>
</tr>
<tr>
<td>Maxwell\textsuperscript{115}</td>
<td>Achilles tendinosis</td>
<td>33</td>
<td>–</td>
<td>–</td>
<td>VAS1-88%, VAS2-84%, VAS3-78% (p&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td>Ryan\textsuperscript{116}</td>
<td>Achilles tendinopathy</td>
<td>108</td>
<td>–</td>
<td>–</td>
<td>Midportion: VAS1-30.8, VAS2-40.7, VAS3-50.4 Insertional: VAS1-30.2, VAS2-41.3, VAS3-51.9</td>
<td></td>
</tr>
<tr>
<td>Jo\textsuperscript{117}</td>
<td>Shoulder pain</td>
<td>29</td>
<td>7.2</td>
<td>2.0</td>
<td></td>
<td>5.2</td>
</tr>
<tr>
<td>Ryan\textsuperscript{118}</td>
<td>Plantar fasciitis</td>
<td>20</td>
<td>–</td>
<td>–</td>
<td>VAS1-26.5, VAS2-49.7, VAS3-52.9, (p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Curtin\textsuperscript{119}</td>
<td>Medial tibial stress syndrome</td>
<td>7</td>
<td>–</td>
<td>–</td>
<td></td>
<td>4.0</td>
</tr>
<tr>
<td>Lytgo\textsuperscript{120}</td>
<td>Chronic exertional compartment syndrome</td>
<td>24</td>
<td>–</td>
<td>–</td>
<td>21 patients were satisfied with results at 6 month follow-up</td>
<td></td>
</tr>
<tr>
<td>Reeves\textsuperscript{121}</td>
<td>Fibromyalgia</td>
<td>31</td>
<td>4.86</td>
<td>3.30</td>
<td></td>
<td>32% average overall pain reduction</td>
</tr>
<tr>
<td>Hooper\textsuperscript{122}</td>
<td>Chronic lumbar pain</td>
<td>35/62</td>
<td>12.3/8.9</td>
<td>7.1/4.3</td>
<td>Litigants/Non-litigants. RMDQ (0-24). Before: p=0.001. After: p=0.02*</td>
<td></td>
</tr>
<tr>
<td>Hooper\textsuperscript{123}</td>
<td>Chronic thoracic pain</td>
<td>50/20</td>
<td>3.0/4.7</td>
<td>5.9/6.7</td>
<td>Litigants/Non-litigants. Patient specific functional (0-10). Before: p=0.0003. After: p=0.27*</td>
<td></td>
</tr>
<tr>
<td>Hooper\textsuperscript{124}</td>
<td>Chronic cervical pain</td>
<td>23/3</td>
<td>22.3/20.3</td>
<td>14.3/10.7</td>
<td>Litigants/Non-litigants. NDI scores (0-50). Before: p=0.63. After: p=0.49*</td>
<td></td>
</tr>
<tr>
<td>Hauser\textsuperscript{125}</td>
<td>In lieu of surgery</td>
<td>34</td>
<td>7.6</td>
<td>1.3</td>
<td></td>
<td>6.3</td>
</tr>
</tbody>
</table>

* No VAS or NRS.
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 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.\(^ {112}\)

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 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.\(^ {112}\)
CHRONIC MUSCULOSKELETAL PAIN

Level 3 and 4 evidence supports the use of dextrose Prolotherapy for significant relief of chronic musculoskeletal pain, as well as diffuse musculoskeletal pain involving the ankle, elbow, foot, hand, hip, knee, shoulder, back, neck, temporomandibular joint, temporomandibular joint, temporomandibular joint, and wrist. Fair to high quality evidence supports the use of dextrose Prolotherapy for chronic and/or diffuse musculoskeletal pain involving the spine and peripheral joints. 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. 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." 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. "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.

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. 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. 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.\textsuperscript{165, 166}

\textbf{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.\textsuperscript{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.

\textbf{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.\textsuperscript{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,\textsuperscript{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.

\textbf{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.\textsuperscript{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,\textsuperscript{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.

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The Ligament Injury-Osteoarthritis Connection: The Role of Prolotherapy in Ligament Repair and the Prevention of Osteoarthritis

Mark T. Wheaton, MD & Nichole Jensen, BS

ABSTRACT

Ligaments are specialized bands of fibrous connective tissue which hold bones in approximation, providing mechanical support and stability across a joint to allow for fluid joint motion and prevent excessive joint displacement. When ligaments are injured, structural, mechanical and physiologic changes occur and joint stability is compromised. A healing response is initiated in an attempt to repair the damage. The degree of healing and repair is dependent on the ligament's location and the amount of damage that has occurred. Ligaments with greater vascularity (e.g., medial collateral ligament) have the ability to undergo substantial repair, whereas other ligaments (e.g., anterior cruciate ligament) are limited in their ability to restore joint strength and stability. When a full recovery does not occur, the joint is subjected to changes in joint motion resulting in instability leading to biomechanical changes across joint surfaces which increases the risk for degenerative changes and the development of osteoarthritis. It is well-established that high-force or repetitive injury to a joint increases the chances that the joint will develop osteoarthritis over time.

There are many options to treat the symptoms of ligament injury and osteoarthritis including rest, ice, heat, non-steroidal anti-inflammatory drugs (NSAIDs), narcotics, physical therapy and exercise, corticosteroid injections, and surgery, but none of these treatments helps restore ligament stability nor prevents or reverses articular cartilage breakdown. There is one treatment available that is able to address ligament function directly, improve stability, and reduce the pain, incidence and dysfunction associated with ligament injuries and osteoarthritis: Proliferation Injection Therapy, also known as Prolotherapy.

Prolotherapy is a decades-old, little-used, but well-documented procedure that stimulates the body's naturally-occurring healing processes to produce more collagen within injured joint ligaments, providing increased stability, decreased pain and improved function. This article reviews the physiology of ligaments and damage sustained due to injury, the body's response to injury, and the process of ligament repair, as well as degenerative changes and dysfunction that occur when full restoration of ligament function is not achieved. A review of the scientific Prolotherapy literature is summarized, making the case in support of its use for treatment of joint injury and unresolved pain.


KEYWORDS: collagen, degeneration, fibroblasts, growth factors, healing, inflammation, injury, instability, ligaments, osteoarthritis, Prolotherapy, repair, sprain/strain.

INTRODUCTION

Ligamentous injuries can occur at almost every joint in the body. Ankle sprains are the most common ligamentous injury, constituting 30% of all injuries seen in sports medicine clinics and the primary musculoskeletal injury seen by primary care. Knee pain from ligament injury is also a common complaint, affecting an estimated 20% of the general adult population. The medial collateral ligament (MCL) is the most frequently injured ligament in the knee. In many cases, through a 3-stage inflammatory and healing process, the body is able to repair the injury on its own, with a full clinical recovery of the strength and stability of the joint. However, if the injury is severe or if multiple injuries have taken place at a joint, the damage to the surrounding ligamentous and cartilaginous tissues and other structures of the joint can reach a state that is beyond the body's ability to fully repair and restore. Damage to the anterior cruciate ligament (ACL) causes the highest incidence of pathologic joint instability. This begins the downward spiral of degeneration of the joint surfaces and the development of osteoarthritis and chronic pain.

Osteoarthritis is the most common form of arthritis and is typically found in the older population, but there has been a rise in the number of cases reported in the younger adult population, frequently related to joint injuries occurring in athletics, work, or other daily activities. Osteoarthritis can be caused by intrinsic factors (primary OA), which have a genetic and/or biomechanical etiology, as well as extrinsic causes (secondary OA), which are caused by external factors, such as direct trauma, overuse or repetitive motion injuries, corticosteroids, obesity, and/or ligamentous injuries, leading to joint hypermobility and instability. Patients have come to rely on surgical procedures when the pain, disability and imaging studies are determined to be sufficient to warrant such a procedure. Many surgeries
performed are based primarily on the findings of imaging studies, most commonly magnetic resonance imaging (MRI), which is unable to identify the most common pain generator(s), including ligaments, joint capsules, muscles and tendons, nor is it able to assess dynamic instability.

There are many treatments used to treat the pain and instability symptoms due to ligamentous injuries and osteoarthritis. Conservative treatments include pain medications, chiropractic, physical therapy, manual therapies, acupuncture, and intra-articular injections of cortisone or hyaluronate (viscosupplementation). The use of medications, including NSAIDs, narcotics (opioids), sedatives, muscle relaxers, anti-depressants, and anti-seizure drugs, have acute and chronic effects on the user and impact the healing process in many cases. Common adverse effects experienced with use of these medications are well-documented. Narcotics not only alter the neuropsychological and pathophysiological responses of the body, but also affect both innate and adaptive immune function. Opioids can act either directly on the target cells in the body, but also affect both innate and adaptive immune function. Chronic use has demonstrated decreased proliferation of antibodies, macrophage progenitor cells and lymphocytes, inhibition of natural killer cells and phagocytic activity, cytokine expression and leukocyte migration, as well as have significant affects on immune cell differentiation. In animal studies, two hours after a subcutaneous injection of morphine, a 70% depression of blood lymphocyte proliferation was noticed, as well as a 30-40% inhibition of natural killer cell activity.

Surgical options include arthroscopies, ligament reconstruction, fusions and total joint replacements. This often leads to further joint degeneration and additional surgery. Joint replacement surgery is the accepted treatment for advanced joint degeneration/osteoarthritis but it is clear that surgery is employed far too early and far too often. None of these interventions, conservative or surgical, address the damage to the ligaments or the resultant instability of the joint.

There is, however, evidence that the Prolotherapy injection method has the ability to stimulate repair of degenerative cartilage (Wheaton M. JOP 2010) and treat the most common and under-recognized source of osteoarthritis: ligament injury. It has been clearly demonstrated for decades that ligaments are a common and certain source of pain and dysfunction. Though the primary focus of this article is the connection between ligament injuries and the development of osteoarthritis, the article also presents Prolotherapy as a valid treatment to repair existing ligament damage and slow or prevent the degenerative progression of the injured joint.

Ligaments are dense bands of collagenous tissue which span joints, linking bone to bone. They are comprised of a more vascular outer layer called the epiligament, which is indistinguishable from the actual ligament itself, and merges into the periosseum of the bone around the ligament attachment site. Biochemically, ligaments are approximately two-thirds water and one-third solid with the water likely responsible for contributing to cellular function and viscoelastic behavior. The solid components of ligaments are principally collagen (type I collagen accounting for 85% of the collagen and the rest made up of types III, V, VI, XI and XIV) which account for approximately 75% of the dry weight with the balance being made up by proteoglycans (<1%), elastin and other proteins and glycoproteins such as actin, laminin and the integrins. During formation and development of ligaments, triple helical collagen molecules are aligned to form fibrils that are organized in a parallel fashion and folded in a crimped state into fibers, which are interconnected by crosslinks giving collagen fibers incredible strength. Early in growth and developmental processes the crosslinks are immature and weak, but increase in strength with development and age. The crosslinked collagen forms the extracellular matrix (ECM) and the structure of the ligament. The main function of ligaments is to maintain smooth joint motion, restrain excessive joint displacement and provide stability across the joint. For example, ligaments of the knee provide passive stability, guide the motion of the femur and tibia, define contact mechanics between the femur and tibia, and restrain excessive motion to prevent dislocation.

Ligaments, over time, respond to loads with overall increase in mass, stiffness (ability to resist strain) and load failure, as well as increases in ultimate stress (the force per unit area) and strain failure (the change in length relative to the original length). Biological factors including age, maturation, mobilization/immobilization of a joint, tension and exercise affect the biomechanical properties of ligaments. Ligaments display viscoelastic behavior, meaning they have the ability to resist shear stress, but also have the ability when stressed to return to their
original state. The structural properties of ligaments are tested using Stress-Relaxation, stretching the specimen to a constant length and measuring the change in stress over time, the Creep Test, a constant force with a gradual increase in length over time, as well as tensile strength via Load-Elongation Curve where stiffness (N/mm) is the slope, ultimate load (N) is the highest load placed before failure, ultimate elongation (mm) is the maximum elongation at failure, and energy absorbed at failure (N-mm) is the area under the curve and the maximum energy stored by the complex. (See Figure 1.) The mechanical properties of ligaments are observed via a Stress-Strain Curve where tensile strength (N/mm²) is the maximum stress achieved, ultimate strain (in %) is the strain at failure, and strain energy density (MPa) is the area under the curve. The stress-strain curve is dependent on a ligament’s substance, molecular bonds and composition.⁸

As a joint is ranged, some fibers tighten while others loosen depending on the positions of the adjacent bones and the forces that are applied across the joint. As a ligament is stretched, an “uncrimping” of the crimp in the collagen fibrils takes place. There is very little resistance in the crimp, making it easy to stretch out, and it has a relatively low stiffness. As the fibrils become uncrimped the collagen fibril backbone begins to be stretched, giving rise to a stiffer material. When maximal loads are reached and fibrils begin to fail, damage accumulates, stiffness is reduced, and the ligament begins to fail.¹⁰ The greatest stresses are applied at the attachment sites of the ligaments and tendons to the bone at the fibro-osseous junction. (See Figure 2.)

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When the forces subjected to a ligament are too great, failure occurs, resulting in drastic changes in the structure and physiology of the joint. Ligament injuries, also called sprains, can occur due to direct trauma, indirect trauma or indirect intrasubstance (intrinsic or extrinsic) factors and are evaluated on a scale from Grade I to Grade III. (See Figure 3.) Grade I sprains consist of mild stretching of ligamentous tissue with no discontinuity of the ligament or clinical signs of excess laxity. Grade II sprains have moderate stretching of the ligament with some torn fibers,
but enough are intact so that the damaged ligament has not failed. However, joints with Grade II sprains have an abnormal laxity compared to the uninjured side. Grade III sprains consist of severe tearing and nearly complete or complete ligament disruption with significant joint laxity. The term “joint laxity” can be defined clinically and biomechanically. Clinically, joint laxity refers to the subjective impression of abnormal movement of one bone relative to the other when a joint is manipulated or displaced by intrinsic muscle forces and is typically compared to the contralateral joint or normal external control. Biomechanically, it relates to the quantitative measure of the six independent degrees of freedom for a given joint and the specific forces or movements that are causing the displacement. Disruption of the ligamentous tissue results in instability of the joint, increasing the sliding of joint surfaces, decreasing the efficiency of the muscles, and altering the joint mechanics. Cartilage within a joint is the thickest where contact pressure is the greatest; however, with an injured or loose joint, joint motion is larger. When joint stability is compromised, the kinematics between the bones changes, disrupting the load distribution on the cartilage and bone in magnitude, direction and location of contact, causing wear and increased shear forces, ultimately leading to osteochondral degeneration and increasing the risk for development of osteoarthritis. For example, disruption of ligamentous structures in the knee produces tibiofemoral offset, transferring contact stresses to regions of thinner cartilage with less support, which puts added stress on already weakened ligaments, causing greater ligament injury and increasing the pressure on the cartilage.

As soon as a ligament injury is sustained, the body initiates the healing process, which takes place in three overlapping stages. The first stage takes place within the first 48-72 hours following an injury and is associated with hemorrhaging and inflammation. The disrupted ligament ends retract and a hypertrophic vascular response, including increases in both the vascularity and blood flow to the area, takes place forming granulation tissue. This promotes the formation of a platelet-rich blood clot in the gap which forms a lattice structure for cellular events to take place. This response decreases over time. The second stage encourages matrix and cellular proliferation and begins 48 hours after the injury and continues over the next 6 weeks. During the second stage, inflammatory cells, including neutrophils, monocytes and macrophages, are directed to the injury site to begin phagocytosis of debris, lysis, and removal of damaged cells. An influx of fibroblasts to the site by chemotactic agents begins synthesis of “scar tissue,” a dense cellular collagenous connective tissue matrix, to bridge the torn ligament ends. Initially the new collagen matrix is very disorganized with multiple structural defects, but after a few weeks of healing the inflammatory cells decrease in number, the capillaries become less prominent and the granulation tissue matures into mature collagen with the aggregation of fibrils into mature fibers aligned with the long axis of the ligament. In days to weeks following the injury, the third stage of healing, remodeling and maturation, begins. During this stage, the fibroblasts continue to remodel the matrix, filling in defects of the scar, resulting in a matrix similar in appearance to uninjured tissue, but physiological variations in composition and architecture, as well as mechanical deficits, remain. (See Figure 4.) The new scar tissue has altered proteoglycan and collagen composition with increased percentages of type III collagen tissue, as well as decreased size of the diameters of the new collagen fibrils. Also, the new scar collagen fibers are not packed as closely as a normal ligament, lack mature collagen crosslinks, and have altered cell connections resulting in incomplete resolution of matrix flaws, which leave “weak spots” in the scar matrix. The overall healing and recovery depends on the...
The MCL resists valgus forces which push the knee medially. It has the ability to heal spontaneously with conservative treatment and in studies actually produced better results than surgical repair when varus-valgus knee stability and biomechanical properties were compared. Immobilization following MCL injury has been shown to lead to greater disorganization of collagen fibers, decreased structural properties, decreased mechanical properties and slower recovery to the resurbed insertion sites.9 In studies by Frank, et al, rabbit MCLs were tested to be structurally healed to 70-80% of normal strength and stiffness and mechanically healed to 30% of normal strength based on cross-sectional size, while the laxity and load-relaxation improved to 80-90% of the normal within six to 14 weeks following injury. However, the creep behaviors demonstrated elongation greater than twice that of a normal MCL for many months following an injury, with no recovery in length, creating the potential for permanent elongation.14 Another study compared patients with medial knee laxity to those with normal knees to determine if any differences existed in knee structure and biomechanics. They found that the prevalence of osteoarthritis was greater in those with significantly more medial knee instability; they also noted these subjects had more muscle contractions on the medial side of the knee compared to those without osteoarthritis. Lewek, Ramsey, and Mackler believed the high muscle contractions can lead to high joint compressive forces which accelerate the progression of osteoarthritis.16

An ACL rupture increases anterior translation and rotational instability and leads to progressively worsening damage to the internal knee structures, including the meniscus and MCL. The most common treatment for an ACL tear is surgery. Conservative treatment can be successful in some patients, but most commonly produces poor results when compared to only 20-25% less-than-satisfactory results with ACL reconstruction. Grafts for ACL reconstruction include autografts from bone-patellar tendon-bone (BPTB) and quadruple strand semitendinosis and gracilis (QSTG) or allografts from a cadaver. The BPTB is harvested from the central 1/3 of the patellar tendon, at 8-10 mm in width, and is chosen for its relatively high stiffness and strength, as well as opportunity for bone-to-bone fixation. The QSTG is chosen because it has similar properties to the patellar graft, requires less morbidity during harvesting and does not cause anterior knee pain. In clinical trials, no conclusive evidence suggested superiority of one graft over the other.
Both grafts were effective when the knee was subjected to anterior tibial loads. It was noted that the QSTG was slightly more effective when the knee was at higher flexion angles, although neither of the grafts were effective when the knee was subjected to loads simulating the pivot shift test. Also, the type of fixation devices have been analyzed to try to determine what would provide the best anchoring and stability; including the use of interference screws, soft tissue washers, suture-post constructs, simple staples and cross-pins, but no clear consensus was found as the best anchoring device. Studies have shown that the most stable knee was constructed when the interference screws were placed close to the articular surface (proximal to the drill hole in the top of the tibia) compared to central fixation (deeper within the hole) or distal fixation (on the distal tibial tuberosity).8

**Cellular Response to Ligament Injury**

There are many cells, growth factors, and proteins associated with the onset of a ligamentous injury and healing, each playing a key role at various stages during the repair process. Platelets are small, regularly shaped, clear cell fragments that are involved in hemostasis and blood clot formation, both needed for ligament healing and proliferation. They also are a natural source of growth factors and play a key role in the activation of multiple pathways and the release of growth factors.8 Fibroblasts are cells that are located between rows of crimped fibers and synthesize and maintain collagen, the ECM, and overall ligamentous structure. They also play a large role in the healing process. Active fibroblasts can be recognized by their branched cytoplasm and abundant rough endoplasmic reticulum (ER), whereas inactive fibroblasts, called fibrocytes, are smaller, spindle shaped, and have a reduced rough ER. Active fibroblasts are in charge of making collagen, glycosaminoglycans, reticular and elastic fibers, glycoproteins, and cytokine thymic stromal lymphopoietin (TSLP). In growing individuals, fibroblasts are also actively dividing and synthesizing ground substance. When tissue damage occurs, fibrocytes are stimulated and induce the proliferation of fibroblasts. (See Figure 5.)

Mesenchymal cells are multi-potent stem cells with the ability to differentiate into many different types of cells. They are embryonic undifferentiated connective tissue derived from the mesoderm of an embryo. Their composition is a prominent ground substance matrix with a loose aggregate of reticular fibrils (i.e., type III collagen) and unspecified cells. They have the ability to migrate easily, such as to an injured site. Macrophages are a type of white blood cell, which aids in the process of cleaning up and digesting damaged, dying or dead cells. They respond in “2 waves” at the onset of damage. The wave first occurs with muscle membrane lysis and inflammation and begins by degrading the contents of injured fibers. The second wave occurs with the release of various substances, including basic fibroblastic growth factor (BFGF), transforming growth factor-beta (TGF-β) and transforming growth factor alpha (TGF-α) to trigger a cascade of pathways to help with the healing process.8 The release of the growth factors signals fibroblast and inflammatory cells to the injured tissue, stimulates fibroblast proliferation, and promotes the synthesis of collagenous proteins, as well as non-collagenous proteins, for the repair and regeneration of new connective tissue. Growth factors are small polypeptides synthesized by a variety of cells in the immune and musculoskeletal systems. They work in conjunction with proteoglycans by binding to cell surface receptors, triggering transduction pathways which stimulate production of proteins involved in wound healing, as well as affecting the concentrations of other growth factors via numerous feedback loops.8 Platelet-derived growth factor (PDGF) is a potent chemotactic agent which drives the proliferation of cells of mesenchymal
origin, as well progenitor cell populations, directing the migration, differentiation and function of specialized mesenchymal and migratory cells. It is required for cellular division of fibroblasts and aids in the tissue repair, regeneration and remodeling processes. Transforming growth factor-beta (TGF-β) is a protein which controls proliferation and cell differentiation, as well as apoptosis, of various cells throughout the body. It plays a large role in the SMAD pathway, activating transcription factors and regulating T-cell development. It also works to block the activation of lymphocytes and monocyte-derived phagocytes. Both PDGF and TFG-β play key roles in stimulating the processes of ECM deposition and the repair and regeneration of connective tissue. Fibroblast growth factors (FGF) are either protein- or steroid-derived hormones that interact with proteoglycans within the ECM, stimulating proliferation and differentiation of cells. They are sometimes described as “promiscuous” in nature due to the variety of molecules they are able to bind and elicit responses from at a single cell receptor. The interaction of the FGF with the proteoglycans in the ECM affects the activity and stability of signaling molecules within the extracellular matrix. Basic fibroblast growth factor (BFGF) is present in the basement membranes and ECM of blood vessels and mediates angiogenesis, the formation of new blood vessels, after a wound is sustained and promotes the healing process. Epidermal growth factor (EGF) is a protein that regulates cell growth, proliferation and differentiation. It initiates signaling cascades by binding to specific cell surface receptors, which increases the calcium allowed to flow into the cell. This causes increases in both glycolysis and protein synthesis, which support increased expression of genes promoting DNA synthesis and cell proliferation.

**ETIOLOGY OF THE DEVELOPMENT OF OSTEOARTHRITIS**

The etiology of osteoarthritis (OA) has not been fully elucidated. It is clear, however, that the breakdown of joint cartilage occurs when the repair and replacement of cartilage cells does not keep pace with the destruction of cartilage. There are many causes of joint injury, as well as associated risk factors which increase the likelihood of joint degeneration. It may be caused by a systemic (genetic) predisposition or by local (mechanical) factors. For some the cause is known (secondary), but for others the cause is unknown (primary). For example, a person may have an inherited predisposition to develop the disease, but it may only materialize when a biomechanical insult (such as a knee injury) has occurred. It should be emphasized that osteoarthritis is primarily a degenerative process, not an inflammatory one as the name implies. A more appropriate term would be osteoarthrosis or degenerative joint disease.

Ligament damage or weakness is one cause of joint degeneration. Joint subluxations, dysplasia, and incongruity disrupt the normal distribution of weight and stresses on the articular surfaces of the joint leading to cartilage injury and joint degeneration. The disruption of ligaments and joint capsules, causing increased joint laxity, increases the risk of articular cartilage injury because the joint motion is no longer stabilized by the ligament structure. These mechanical abnormalities cause changes in the areas of contact on opposing surfaces and increase the magnitude of impact loading and shear and compression forces on some regions of cartilage. (See Figure 6.) The mechanical properties of articular cartilage depend on the macromolecular framework consisting of collagens and aggregating proteoglycans, as well as the water content within the macromolecular framework. The collagens give the tissue its strength, while the interaction of the proteoglycans with water gives the tissue its stiffness (resistance) to compression, resilience, and durability. The cartilage is the thickest in areas where contact pressure is greatest. After a ligament injury, joint motion becomes greater and may offset the contact surfaces to regions where the cartilage may be thinner and less able to support the applied stresses. The loss of sensory innervation of the joint and surrounding muscles also increases the susceptibility of joint degeneration because of an increase in the instability of the joint. When the load is applied slowly, the muscles are able to contract and absorb much of the energy and stabilize the joint. However, if the load is sudden, the muscles do not have time to respond to stabilize the joint and decrease the forces applied to the cartilage surfaces. Even normal levels of joint use may cause articular surface injury and degeneration in unstable, subluxed, or malaligned joints and in joints that do not have normal innervation. Genetic hypermobility syndromes, such as Ehlers-Danlos Syndrome, as well as non-genetic hypermobility (Benign Hypermobility Syndrome) where trauma or injury is absent, increase the likelihood of OA development. Further prospective studies are needed to study the effects of non-traumatic hypermobility as it relates to OA.
Direct trauma is a second cause of joint degeneration and is typically associated with athletic participation. The articular surface can be damaged by single or repetitive impact from a direct blow to the joint or bones that form the joint. It can also be damaged by torsional loading resulting from twisting or turning of joint surfaces that are relative to each other. The rate of loading also affects the type of damage that may be caused by sudden impact axial compression or torsional strain. During slow impact loading, the movement of fluid within the cartilage allows it to deform and decrease the forces applied to the matrix macromolecular framework. In sudden or high impact loading, the matrix macromolecular framework suffers a greater level of stress because the loading occurs too fast to allow for adequate fluid movement and tissue deformation.27 One study performed a 36 year follow-up of 141 participants who had sustained a hip or knee injury after 22 years of age and found that, due to the deleterious effects of trauma that had compromised the structural integrity of the joint, 96 (68%) of the participants had developed osteoarthritis in the injured joint.28 Another study showed that 80% of American football players with a history of knee injury showed signs of osteoarthritis 10 to 30 years after retiring.29 Soccer players also have an increased incidence rate of osteoarthritis in the lower extremity joints, mainly the knee, when compared to a control group of the same age. The most common types of injuries are sprains and strains, which are usually caused by excessive forces applied to a joint in an abnormal direction. This leads to a high number of meniscal and ligamentous injuries that ultimately translate to an increased instability within the joint.30, 31 While direct trauma or compression to the cartilage surfaces alone can cause OA over time, it is unquestionably the concomitant ligament injury in the majority of these cases which sets the joint up for OA development. When cartilage wear and degradation outpace cartilage repair, the wheels are set in motion for joint degeneration.

A third cause of joint degeneration is overuse. This can be associated with jobs involving manual labor with repetitive motions such as farming, construction work, and lifting heavy loads. Heavy manual labor and stresses in the work environment are major predictors in development of hip osteoarthritis.32 Hip osteoarthritis was diagnosed in 41 subjects (4.9%) after a 22-year follow-up study of 840 participants. Baseball players also have an increased risk of developing osteoarthritis in their shoulders and elbows due to the repetitive motion of pitching and throwing.33, 34 The average Major League Baseball pitcher throws over 3,000 pitches per season with little rest between games. Excess joint loading forces at the extremes of motion repeated many times over contribute to joint and connective tissue wear and degeneration. A biomechanically sound shoulder and elbow joint, strong and well-conditioned muscles, excellent pitching technique and mechanics, and adequate rest afford the athlete the best-case scenario for avoiding overuse injuries leading to degeneration. When all of these things are in place and injury still occurs, could it be that subtle, unrecognized ligament deficiency is responsible for overuse injuries? (See Figure 7.)

Another risk factor for joint degeneration is above-average body weight, supported by the fact that for every one pound increase in weight, the overall force across the knee in a single-leg stance increases two to three pounds.22, 24 Other risk factors considered in association with development of OA include: poor posture, age, abnormal joint anatomy and alignment, associated diseases, genetics, failure to accurately realign fractures,
leaving room for abnormal movement and deviation; and car accidents, which subject the body to sudden impacts that may cause injury to ligaments and muscles and lead to pain and weakness in the spine and extremities. Genetic factors account for 50% of cases of osteoarthritis in the hand and hip and a smaller percentage in the knees.

**Prevalence and Costs of Treatment of Osteoarthritis**

The number of reported cases of osteoarthritis have been on the rise in the past quarter century. In 1995 it was projected that approximately 21 million Americans suffered from osteoarthritis. As of 2005, based on data collected from The National Health and Nutrition Examination Survey I (NHANES I), osteoarthritis affected 27 million of the 46 million people in the United States that suffer from arthritis. Also, recent data shows that one out of two Americans are at risk for knee osteoarthritis over their lifetime. Hip osteoarthritis occurs in 0.7 to 4.4% of adults and knee osteoarthritis occurs in approximately 5 percent of the American population between the ages of 35 to 54. It is estimated that 15 percent of the world’s population also experiences pain and joint degeneration due to the presence of osteoarthritis. The number of hospitalizations as a result of OA has doubled in the last 15 years. In 1993, there were 322,000 hospitalizations, and in 2006 the number rose to 735,000.

Any movable joint in the human body is vulnerable to development of osteoarthritis. Knee joints, due to their location between the long lever arms of the tibia and femur, as well as repetitive exposure to high-impact loads and vulnerability in different planes and joint angles, are especially susceptible to direct trauma and ligament injury and more likely to develop osteoarthritis after an injury. Meniscal tears and cartilage damage, as well as ACL tears, alter the contact surfaces within the joint, limiting the contact forces to a smaller area leading to more rapid wearing down and degeneration of the articular surfaces. Other factors that play a role in the development of osteoarthritis in the knee are medial joint laxity, higher BMI (Body Mass Index) values, lesser quadriceps femoris strength, lesser knee flexion, greater knee adduction, and greater co-contraction of the quadriceps femoris and gastrocnemius muscles. The hip is more stable than the knee due to its ball-and-socket configuration and surround musculature, but research has shown individuals involved in high load-bearing activities, including heavy manual labor, frequent stair climbing, and high-intensity sports such as soccer and football, have higher rates of osteoarthritis than their counterparts without such exposure. The shoulder, due to its shallow glenoid socket and great range of motion, is very susceptible to connective tissue injury, including those due to repetitive high-stress activities and dislocations, and subsequent development of OA. Anterior instability has also been associated with development of OA. The ankles, wrists and hands are at increased risk for osteoarthritis after traumatic injuries, including sprains of supporting ligaments and fractures of adjacent bones. Injuries with narrowing of the joint space and extra-articular malunion disrupt articular contact surfaces, leading to poor biomechanics and increased wearing of the contact surfaces. Weakness and instability may also be present and permit excessive motion. The spine is also at risk for degeneration and osteoarthritis, especially with repetitive strains, overuse, injuries, accidents, surgery, excessive weight, poor posture, sedentary life style, and even genetic predisposition, producing weakness and instability. The loss of stability of spinal ligaments can lead to changes in the lordotic curves, disc herniations, degeneration of discs, spondylolisthesis, development of bone spurs, spinal stenosis, foraminal narrowing, and degeneration of facet joints, as well as many other pain generating syndromes.

The cost of treatment for OA can put a large burden on both the patient and the health care system alike. Medications, even if effective in reducing pain, exact a great cost over the long-term, both in the costs of the medications themselves, but also relative to the side effects, complications, and secondary medical problems.
(morbidity and mortality). The financial burden associated
with OA requires consideration of both medical-
surgical (direct) costs and work-loss (indirect) costs. One
report estimated the total cost of bilateral knee joint
replacements at over $85,000. This included the hospital
stay, surgeon fees, anesthesiologist fees, a 5-day stay in
an inpatient rehabilitation center, and a pathologist visit.
However, this did not include outpatient physical therapy
because the length of treatment is unknown. Luckily
for this patient, much of the expenses were covered by
insurance. The cost of hip and knee replacements have risen from about $7,000 in 1997 to an average of
$32,000 for the knee and $37,000 for the hip in 2003. The
average out-of-pocket expense as a direct result of
osteoarthritis was approximately $2,600 per person per
year with a total annual disease cost of $5,700. Job-
related osteoarthritis costs were estimated to be between
$3.4 and $13.2 billion per year. Other studies reported
average annual direct medical, drug, and indirect work
loss costs were $8601, $2941, and $4603, respectively.

TREATMENT OPTIONS

There are many options for the treatment of the symptoms
of ligament injury and osteoarthritis. Treatment of
ligament injuries can take two approaches: conservative
management or surgical intervention. Current conservative
management options include rest, immobilization,
exercises and physical therapy, growth factor injections,
cortisone injections, gene transfer technology, collagen
scaffold/cell therapy, ultrasound, laser photostimulation,
deep heat, pulsed magnetic and electromagnetic
fields, electrical stimulation and Prolotherapy. Surgical
interventions for ligamentous injuries can include
arthroscopic investigation, debridement, ligament
tightening, and ligament reconstruction. Surgical
interventions for osteoarthritis include arthroscopy,
arthrodesis, arthroplasty, and total joint replacement.
When OA involves the spine, laminectomy, laminotomy,
discectomy, disc replacement and various types of fusion
are the surgical choices.

STANDARD NON-SURGICAL TREATMENT OPTIONS

Medications are the most common option used to treat the
pain and disability commonly experienced with ligament
injuries and OA. Medications fall into two categories:
over-the-counter (OTC) medications and prescription
medications. Analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) are two commonly used OTC medications
and both have their pros and cons. Analgesics, like acetaminophen, are used as a short-term treatment for mild to moderate pain associated with ligament injuries
and osteoarthritis. However, it can cause acetaminophen-
induced toxicity, which includes hepatotoxicity and
potential renal damage. NSAIDs are also used to reduce
pain, but also aid in the reduction of inflammation associated with ligament injuries and OA. Aspirin has been
used as an OTC treatment for symptoms related to soft
tissue injuries and OA for decades but platelet inhibition
and GI bleeding risk have made it unacceptably risky to
use on a regular basis.

The pharmaceutical industry manufactured NSAIDs
many years ago to improve short-term functioning for
patients by inhibiting COX enzyme pathways. Drug
companies then developed COX-2 NSAIDs which were
felt to have the same pain-relieving effects as nonselective
NSAIDs, but without the inherent risk of gastrointestinal mucosal damage or cardiac and renal complications. The
COX-2 NSAIDs celecoxib (Celebrex®) and refecoxib
(Vioxx®) entered the market with great acclaim. Both were
touted as more convenient with twice-a-day (Celebrex) or
once-a-day (Vioxx) dosing to relieve arthritis pain, stiffness
and inflammation without as many GI effects.

However, a significant number of cases causing indigestion,
abdominal pain, and nausea occurred after consumption.
With time and a preponderance of evidence, it became clear that the purported GI-protective effects were being
reported more frequently than had been originally thought. Because of these risks, the manufacturers of
COX-NSAIDs have had to revise their literature to
recommend the lowest effective dose for the shortest time
period possible. So while the NSAIDs are routinely
prescribed for joint and muscle pain, the risks can far
outweigh the benefits in symptom-relief. Furthermore,
using these drugs does nothing to correct the previously
proposed underlying problem—injured ligaments and
damaged cartilage—and, in fact, they interfere with the
first stage of healing, even in tissues with excellent blood
supply, slowing soft-tissue repair and thus accelerating
joint degeneration. In addition, reducing the perception
of pain causes more overuse of a damaged joint. It is
ample argument as to why many injuries progress more
rapidly to osteoarthritis.
One study demonstrated a termination of the entire inflammatory proliferative phase of healing after taking Peroxicam. They found no macrophages present after two days and very little regeneration of soft tissue by day four, when compared to the normal healing process. Another study produced similar results with a delayed regenerative process after muscles were treated with Flurbiprofen. The soft tissues were significantly weaker and under microscope had incomplete healing compared to the control tissue. The results of a study of 180 rats, 60 were given NSAIDs, 60 were given COX-2 inhibitors and 60 were control, showed significantly lower failure loads, poorly organized morphology and consistency within the fibrocartilage zones, and decreased deposition and maturation of tendon during healing in the test subjects compared to the controls. They concluded with the suggestion that early inhibition of the inflammatory cascade has lasting negative effects on ligament- and tendon-to-bone healing. Ibuprofen was also noted to decrease the strength of flexor tendons after four weeks of NSAID therapy. The peak forces before disruption were decreased by 300 percent, from 12 newtons to 2.5 newtons. Extensor tendons showed similar results with control and NSAID-treated tendon breaking strengths of 12 and 3.5 newtons respectively.

NSAIDs can also lead to increased degenerative changes within joints. In the early stage of OA, the chondrocytes attempt to repair the cartilage tissue. However, the use of NSAIDs disrupts this process and degradative enzymes overwhelm the regenerative process, halting any repair. A downward spiral begins leading to compositional, molecular and structural changes affecting the intrinsic mechanical properties of the articular cartilage and produces swelling. A trial consisting of 812 patients were split into two groups, one of which was given NSAIDs and the other a placebo, showed that neither group had a reduction in their symptoms and at follow-ups both one and two years later, increased degenerative changes were noted on radiographic films of subjects who were given the NSAID compared to those who had taken the placebo. Also, another study showed acetabular deterioration did not differ in age, sex, pain or walking ability, but was varied based on the amount of NSAIDs taken. Newman and his colleagues found the use of NSAIDs was associated with the progressive formation of multiple small subcortical cysts and subchondral bone thinning and suggested, based on the clinical and experimental findings, regular NSAID use has “powerful and potentially harmful effects on cartilage and bone.”

Similar results were demonstrated on additional studies of radiographs taken three years after continued NSAID use revealing increased numbers of cysts present, more severe progression of degeneration of articular cartilage, and greater overall destruction of the joint. It is unclear if individuals who regularly use NSAIDs have increased degenerative changes and osteoarthritis joints due to true deleterious effects on the cartilage or increased physical

Figure 8. The pathogenesis of osteoarthritis accelerated by NSAIDs. NSAID use inhibits the body’s repair processes, leading to decreased proteoglycan and extracellular matrix content and function, which ultimately leads to articular cartilage breakdown.
activity and excessive mechanical loading following pain relief or a combination of both.\textsuperscript{85,86} Canine studies have also showed accelerated degeneration of the articular cartilage after NSAID use, which is suspected to be due to inhibition of the COX enzymes, decreased production of proteoglycans and glycosaminoglycans, and increased degeneration, as well as inhibition of replication of cartilage chondrocytes. NSAIDs also have been shown to effect proliferation, cell cycle kinetics, and cytotoxicity. (See Figure 9.) A study by Gossec regarding the use of NSAIDs to treat the symptoms of OA found those who used NSAIDs increased their risk for hip replacement by 50\% over a two-year period compared to those who did not take NSAIDs on a regular basis.\textsuperscript{87-96}

There are other conservative (non-surgical) options for treating ligament injuries and osteoarthritis and its associated symptoms. Among these are the use of braces, physical therapy, chiropractic care, acupuncture, transcutaneous electrical nerve stimulation (TENS), low-level laser therapy, ultrasound, electrical muscle stimulation, thermotherapy, massage, traction, and taping.

Bracing may be used to temporarily treat symptoms of ligamentous tears by providing stability after an injury. It can be a cost-effective and simple alternative to a more complex and expensive intervention and can provide symptomatic relief of the pain resulting from weakness and instability. However, bracing does not fix the problem; it does not strengthen the ligaments or tendons which are causing the problem. The use of a brace may also lead to deconditioning of the musculature surrounding the joint because the muscles become dependent on the additional support provided by the brace and do not fire properly. Immobilization following ligamentous injury decreases the ability of the scar to resist strain, decreases the maximal load to failure and energy a ligament can absorb, and the ligament has less stiffness than before.\textsuperscript{13}

The same principles are used to treat the symptoms of osteoarthritis, but the results have not been very conclusive. Bracing helps provide support, but does not address the degeneration within the joint. Studies by the American Academy of Orthopaedic Surgeons were not able to support or reject the use of braces with a valgus-directing force for medial osteoarthritis of the knee or a varus-directing force for lateral osteoarthritis of the knee.\textsuperscript{100}

Opioid (narcotic) medications are another category of prescription drugs used to treat ligament injuries and OA. Opiates are prescribed for patients with soft tissue and osteoarthritis pain when NSAIDs and analgesics are ineffective. However, their use is usually limited because of the high rate of development for tolerance, dependence, constipation, and other adverse effects that may occur.\textsuperscript{97} Because osteoarthritis and chronic soft tissue pain predominates in the older populations, central nervous system side effects are regularly encountered with narcotics resulting in cognitive impairment and increasing the risk for falls and the likelihood of the development of intolerable constipation as well. In addition, studies have shown opioids to have a negative effect on immune function such as B-cells and T-cells as well as the spleen and thymus.\textsuperscript{98,99}

Physical therapy, as well as other conservative treatment options, can be beneficial in the management of the symptoms from ligament injuries and osteoarthritis. In animal studies performed by Jung et al., the use of moderate, prolonged exercise was shown to be effective in increasing the cross-sectional area, as well as mechanical properties of swine extensor tendons, indicating improved tissue quality.\textsuperscript{9} Ultrasound, laser photostimulation, deep heat, pulsed magnetic and electromagnetic fields, and electrical stimulation are commonly used to treat tendinopathies with the intent to decrease the stiffness of the scar tissue.\textsuperscript{9} Another study compared the prognosis of two groups of patients with knee osteoarthritis. One group received treatment involving a combination of manual physical therapy and supervised exercise and the other
group received ultrasound therapy at a sub-therapeutic intensity. Both groups received treatment twice a week for four weeks. After one year, the patients who had received the four weeks of physical therapy had made significant statistical gains compared to the control group based on the results of knee radiographs and additional testing. They also reported that 20% of the patients in the control group had undergone knee arthroplasty, compared to only 5% of the patients in the treatment group. Additionally, a study by Cooper et al. reviewed multiple forms of therapy used to treat symptoms of osteoarthritis. They found that exercise was the most successful treatment method for reducing pain and improving physical function in patients. Patients who received proprioceptive and balance training saw improvements in quadriceps and hamstring muscle strength when compared with a standard rehabilitation program. No conclusions could be made on the effectiveness of the use of proprioceptive and balance exercises in the rehabilitation process after ACL injury. Further research is required to determine whether proprioceptive and balance training with improvements in quadriceps and hamstring muscle strength confer any long-term benefits in pain reduction and slowing of cartilage loss in OA. However, it has been shown that weight loss was highly effective in the reduction of pain and the improvement of function associated with osteoarthritic symptoms in obese patients. The combination of weight loss and exercise was also successful and provided the best results in a second study comparing the physical function, pain, and mobility in older overweight and obese adults with knee osteoarthritis. Reduced weight-bearing exercise such as recumbent biking and pool therapy are better tolerated forms of exercise for patients with advanced osteoarthritis, especially for the obese. While unlikely to reduce OA disease progression, this approach contributes to weight loss, gains in strength, and improvement in cardiovascular function. In those individuals who have undiagnosed and untreated ligamentous injury and joint instability, the effectiveness of physical therapeutics is sub-optimal unless ligament function and joint stability are restored.

Injection therapies using various growth factors and cells for treatment of ligament injuries have been the focus of recent research and have become available as treatment options for patients, though many are not covered by insurance. Platelets play a large role in the release of growth factors, including activation of pathways to release platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β) and epidermal growth factor (EGF). Macrophages produce basic fibroblast growth factor (BFGF), transforming growth factor alpha (TGF-α), as well as TGF-β and PDGF, which attract fibroblasts and inflammatory cells to the wound, stimulate fibroblast proliferation, as well as the synthesis of collagen and non-collagenous proteins. In vitro studies have shown that the presence of TGF-β increases cell proliferation as well as EGF due to its chemotactic and proliferative effects on fibroblasts, stimulating synthesis of non-collagenous proteins and glycosaminoglycans. BFGF was also observed to attract fibroblasts to the wound site and stimulate replication. However, the location of the injury, as well as the age of the subject and skeletal maturity affected the ability of growth factors to stimulate fibroblasts. In a more vascular ligament, such as the MCL, the response to growth factors was much greater compared to the response elicited by damage to the less-vascular ACL. Overall it was suggested that the effects of growth factors on cell proliferation and protein synthesis was tissue dependent and therapeutic interventions must account for differences in response to injuries of different ligament tissues. In vivo studies demonstrated accelerated and improved quality of healing with the use of growth factors, however detrimental effects were observed at higher concentrations. TGF-β was also shown to increase the size of ligament scars, but did not improve their material strength and did not alter matrix deficiencies. Gene therapy uses transfer techniques to deliver growth factors for longer periods of time at the sites of ligament and tendon healing. It is a fairly new technique that has recently begun to evolve. Prior to gene therapy, collagen and cellulose sponges were used to produce detectable levels of growth factors, but the effects only lasted for a few days. Several obstacles impede practical implementation including adenovirus infectivity and possible immune reactions against the antigen that would decrease expression of the introduced gene. Cell therapy is the newest intervention, which incorporates the use of progenitor cells in combination with growth factors to improve wound healing. Mesenchymal stem cells (MSCs) or mesenchymal progenitor cells (MPCs) are implanted into the injured tendon or ligamentous structure and have been observed to significantly improve their material strength and did not alter matrix deficiencies. The use of growth factors causes direct recruitment and activation of local fibroblasts. Platelet-rich plasma (PRP) is one example of a growth factor injection therapy and is considered a form of Prolotherapy. PRP consists of the
collection of autologous blood, which is subjected to two states of centrifugation to separate the PRP from platelet-poor plasma and red blood cells, and then is injected into ligaments, tendons and other soft tissue such as muscles to stimulate healing of soft tissue, as well as bone. PRP has gained a lot of traction in recent years among many physicians who diagnose and treat joint pain due to the healing properties of platelets and their ability to initiate and amplify healing cascades and recruit reparative cells as well as other healing factors associated with soft tissue repair. PRP has been shown to stimulate repair of chronic tendinopathies, including lateral epicondylitis, plantar fasciitis and cartilage degeneration, in a similar manor to standard Prolotherapy treatments. It has been described fully in prior issues of The Journal of Prolotherapy.

**Platelet-rich plasma (PRP) is one example of a growth factor injection therapy and is considered a form of Prolotherapy.**

**Joint Surgery: The Other Side of the Story**

Surgery is the end-stage option for the treatment of osteoarthritis pain. It can be in the form of arthroscopy, arthrodesis, arthroplasty, and total joint replacement. When it involves the spine, laminectomy, laminotomy, discectomy, disc replacement, and various types of fusion are the surgical choices. Many of these surgical procedures produce successful outcomes, such as a total hip replacement for an otherwise healthy older individual who has no joint space left and cannot bear weight due to pain. But far too often surgery is recommended prematurely or offered as the only treatment option left. Additionally, there is a lack of definitive studies prospectively showing the treatment (surgery) group significantly improved over the control group. This could, in large part, be due to the difficulty in randomizing the treatment group based on the independent assessment variable of pain level, functional status, and imaging studies, as well as the impossibility of double-blinding the study properly.

All of these procedures have risk factors inherent with surgery and are overall very costly compared to other treatment options, including lost income from time off work and lengthy rehabilitation. They also do not address the ligament dysfunction and instability issue. In fact, arthroscopic procedures and surgical repairs increase the weakness and instability in the joint because it involves the cutting of muscles and fascia and removal of discs, cartilage, and ligament tissue. Production of scar tissue is also an inevitable consequence of surgery, both in the skin and in the deeper tissues, even with arthroscopic procedures.

Surgery involves the use of sedation, anesthesia, and/or an epidural during the procedure with potential complications. Some major complications from anesthesia include respiratory depression, brain anoxia from depressed breathing, heart arrhythmia, and malignant hyperthermia. Minor complications from anesthesia can range from chipped teeth to throat irritation and sores to post-injection headaches and even pneumonia. Other risks associated with surgery include embolism, excess hemorrhaging, infection, nerve injury, and device issues. Thrombus formation (blood clots) and embolism can occur because of several factors, including fat emboli as well as decreased mobility which causes sluggish movement of blood through the leg veins. The risk can be reduced through the use of blood thinning medications (anticoagulants), elastic stockings, exercises to increase blood flow in the leg muscles, or plastic boots that inflate with air to compress the muscles in the legs, but blood clots still may occur. Infections can occur in the wound or deep around the prosthesis. Minor infections are treated with antibiotics but major or deep infections may require surgery and/or the removal of the prosthesis. Also, infections in the body can spread to the joint replacement where bacteria can harbor due to a paucity of vascular tissues needed to fight off infections. Nerve injury may also occur as a complication of surgery. This is more common when the surgery involves the correction of a major joint deformity or lengthening of a shorter limb because of arthritic deformity.

Because surgery involves the removal of tissue from the affected joint, the patient’s original anatomy is altered. This usually means a change in the joint biomechanics, which may create secondary problems. Surgery also may increase the required rehabilitation time because it often necessitates an extended period of immobilization or limited motion due to pain, wound healing, or to allow for reduction of swelling, all of which increase deconditioning and disability. Rehabilitation can last for weeks, months, or years and returning to one’s previous functional or athletic level may not occur. Surgical interventions for ligament injury may invigorate the inflammatory response, increasing the risk of early cartilage degeneration. Ligament-injured joints are
at increased risk for osteoarthritis. Neither conservative treatments (i.e., physical rehabilitation), nor surgical procedures appear to reduce the prevalence of secondary osteoarthritis. The mechanical instability in a ligament-injured joint likely initiates the degenerative cascade due to changes in the area of contact of the joint surface, disrupting the load distribution on the cartilage and bone. It is even suggested that a “stable” prolonged inflammatory responses can accelerate the progression of OA. Joint replacement due to severe end-stage OA has improved the pain and function of many people so that it will, for the foreseeable future, continue to benefit a certain sub-set of patients who receive it. But it has been the premature use of surgery, driven by patients feeling that they have exhausted all other avenues and surgeons who see surgery as the definitive solution in even marginal cases or who lack the understanding of the predisposing factors, especially ligamentous disruption, which, if properly diagnosed and treated before the occurrence of disabling end-stage OA, would lead to successful outcomes and prevention of many unnecessary joint replacements and other surgical procedures.

### Prolotherapy: The Natural Solution for Ligament Injury and Osteoarthritis

Prolotherapy is an alternative to the accepted treatment norms for osteoarthritis and joint degeneration, especially as it relates to ligament injury. The term “Prolotherapy” was coined by George S. Hackett, MD in 1956, and he defined the treatment as “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.”

Prolotherapy causes a statistically significant increase in ligament mass and strength as well as bone-ligament junction strength. Used with permission from: Hauser RA, et al. Prolo Your Sports Injuries Away! Oak Park, IL: Beulah Land Press; 2001. Figure 6-7.

There are three categories of proliferants that have been used; irritants, osmotic shock agents, and chemotactic agents. Irritants (e.g., phenol, tannic acid, quinine) create a local tissue reaction which causes granulocyte infiltration. Osmotic shock agents (e.g., glucose, zinc sulfate) create a local tissue reaction to stimulate granulocyte infiltration by dehydration. Chemotactic agents (e.g., sodium morrhuate) cause direct activation of local inflammatory cells.

The most commonly used solution contains dextrose mixed with an anesthetic and diluted with sterile water or saline. Many substances can be used as proliferating agents, separate from or added to the standard dextrose solution including zinc sulfate, P2G (phenol, glycerin, and glucose), sodium morrhuate (derived from cod oil), calcium gluconate, pumice and others. Other substances and nutrients can be added to the solution, depending on the Prolotherapy physician’s experience and training, as well as the condition being treated.

Numerous studies have demonstrated the development and growth of new ligamentous tissue in joints throughout the body using any of the commonly used proliferants and have produced similar results to those of Dr. Hackett and Dr. Hemwall. A retrospective study by Dr. Robert Schwartz of 43 patients with chronic low back pain, all of whom had been unresponsive to surgery, showed 93% of those patients reporting significant improvement in their

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**Effects of Five Prolotherapy Treatments**

<table>
<thead>
<tr>
<th></th>
<th>Prolotherapy Injected Ligaments</th>
<th>Saline Injected Ligaments (control)</th>
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<tr>
<td>Ligament Mass (mg)</td>
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<td>89.7</td>
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<td>Ligament Mass Length (mg/mm)</td>
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<td>47</td>
</tr>
<tr>
<td>Junction Strength (N)</td>
<td>119.1</td>
<td>93.5</td>
<td>28</td>
</tr>
</tbody>
</table>

Figure 10. The effects of five Prolotherapy treatments to the medial collateral ligament. Prolotherapy causes a statistically significant increase in ligament mass and strength as well as bone-ligament junction strength.
pain six weeks after three Prolotherapy treatments of 1cc of 5% sodium morrhuate and 1cc of 1% xylocaine to the SI (sacroiliac) joints every two weeks; only three patients had no improvement. A study by Drs. Klein, Dorman, Ongley and Eek regarding knee ligament instability reported that all five patients who completed the study reported marked decrease in knee pain with a significant decrease in joint laxity in all axes measured following Prolotherapy treatment. Dorman and Klein also studied the effects of Prolotherapy on the posterior sacroiliac ligaments and found after six weekly injections there was an increase in the average ligament diameter from 0.055 micrometers to 0.087 micrometers, measured by electron microscopy. They also found increased numbers of collagen-producing fibroblasts, as well as linear ligament orientation similar to what is found in normal ligaments. Auburn et al. also examined the effects of Prolotherapy on the cross-sectional area of the iliolumbar ligaments and found, by ultrasound, that six weeks after one injection of a 4cc procaine, 1cc 50% dextrose and 0.5cc of PQU (2.34ml Urea USP) to designated medial and lateral injections sites, the ligament thickness increased in the medial portion from 0.91cm at baseline to 1.2cm, 27% growth, and in the lateral portion from 1.35cm to 1.7cm, 21% growth. Another study documented changes in pelvic alignment secondary to suspected loosening of the SI ligaments. They reported changes in the measurements of pelvic inclination (angles each side of the pelvic bones makes with the ground) on both the right and left sides when comparing the angles from before and after Prolotherapy. This was attributed to a definite tightening of the ligaments as there was a decrease in the difference between the two sides, as well as a reduction in pain and an increase in function. Hauser performed a study of 34 patients who had been told by doctors they would need surgery, including joint replacements, arthroscopic procedures, fusions and ligament and tendon repairs, to repair their chronic pain problems. After an average of 4.5 treatments using 15% dextrose Prolotherapy, the pain levels reported by the patients decreased from 7.6 to 3.1 and 91% of the patients felt Prolotherapy provided 50% or greater relief in their pain. Reeves tested the effects of Prolotherapy solutions containing different concentrations of dextrose, comparing a 10% solution against a 25% solution, on patients with ACL laxity. The subjects reported improvements in ACL laxity, pain, swelling and knee range of motion in both groups, with comparable results when comparing the two solutions. A study using a solution containing 5% sodium morrhuate showed not only an increase in the number of cells at the injured ligament site, but also a wider variety of cell types, including fibroblasts, neutrophils, lymphocytes and plasma cells, as well as many unidentifiable cells. Additionally, Dr. Liu found that after a series of five injections of 5% sodium morrhuate into the MCL of rabbits, the ligament mass increased by 44%, the ligament thickness increased by 27%, and the strength of the ligament bone junction increased by 28%, demonstrating that Prolotherapy causes tissue growth and strengthening.

A unique syndrome reported in the literature which is rarely recognized that warrants mention for its responsiveness to Prolotherapy is called Barré-Lieou Syndrome. It was first described in 1925 by Jean Alexandre Barré, MD, a French neurologist, and in 1928 by Yong-Choen Lieou, a Chinese physician, each studying it independently. It consists of a constellation of symptoms stemming from dysfunction of the posterior cervical sympathetic nerves along the cervical spine vertebrae caused by weakened, stretched, or damaged cervical spine ligaments. The symptoms which characterize Barré-Lieou Syndrome include some or all of the following: headache, vertigo, tinnitus, neck pain, sinus congestion, blurred vision, hoarseness, and other symptoms related to abnormal tension on the sympathetic nervous system in the neck. While none of these symptoms confirm a diagnosis of Barré-Lieou Syndrome, the clinical case for it becomes more compelling when many of these symptoms are grouped together. The usual studies do little to diagnose this syndrome. Clinical recognition of Barré-Lieou Syndrome and its definitive resolution by Prolotherapy eliminates the need for costly investigational assessment and unnecessary and inappropriate interventions targeting the various symptoms that are part of Barré-Lieou Syndrome.

It proves useful to compare the safety of Prolotherapy to the surgical risks described earlier. One study surveyed 494,845 patients treated for chronic pain with Prolotherapy and found only eighty (0.00016 percent) complications. Sixty-six of the cases were considered minor complications and included allergic reactions and pneumothoraces, while 14 were defined as major complications and required hospitalization. Prolotherapy does not require anesthesia or the removal of tissue from the body or addition of foreign objects into the body, only takes a few minutes, does not require rehabilitation, and has a
minimal risk of complications. Furthermore, there is negligible down-time following treatment, no damage or destruction of nerves or blood vessels, and scar tissue is not produced.

The Florida Academy of Pain Medicine (FAPM) reviewed literature for Regenerative Injection Therapy (RIT) to inform and familiarize readers with RIT, to outline indications and conditions treated with RIT as well as contraindications, and encourage the use of RIT in pain pathology related to connective tissue. FAPM uses regenerative injection therapy as another term for Prolotherapy. They found, in over 530,000 patients treated, 48% to 82% of patients reported improvements related to return to work and previous function, while treated, 48% to 82% of patients reported improvements for Prolotherapy. They found, in over 530,000 patients uses regenerative injection therapy as another term in pain pathology related to connective tissue. FAPM as well as contraindications, and encourage the use of RIT in pain pathology related to connective tissue. FAPM uses regenerative injection therapy as another term for Prolotherapy. They found, in over 530,000 patients treated, 48% to 82% of patients reported improvements related to return to work and previous function, while resolution of pain ranged from zero to 100%, and reported complications that included 28 pneumothoraces, 24 allergic reactions, one grand mal seizure and one aseptic meningitis. They also concluded RIT’s effectiveness in treatment of chronic musculoskeletal pain due to post-traumatic and degenerative changes in connective tissue such as ligaments, tendons, fascia and intervertebral discs.

The FAPM suggests the use of RIT to treat ligaments (intra-articular, periarticular, capsular), tendons, fascia, entheses, and intervertebral discs which have sustained sprain, strain, enthesopathy, tendinosis/ligamentosis, or pathological laxity and experience chronic pain, pain from overuse, hypermobility/subluxations, thoracic and lumbar vertebral compression fractures, osteoarthritis, spinal instability secondary to ligament laxity, and intolerance to NSAIDs, steroids, or opiates. In conclusion, they feel that RIT is safe in treating a number of pain syndromes arising from ligament and tendon diatheses as well as other pain problems and also state that reviews of the current literature suggests the use of NSAIDs and steroid preparation for chronic pain as well as degenerative conditions is limited in treating the condition and only is helpful in “curbing a significant inflammatory reaction.”

Additional studies have found that treatment of chronic low back pain and other chronic myofascial pain syndromes because the process stimulates the proliferation of collagen to promote non-surgical soft tissue repair that strengthens ligaments and relieves pain. One study of volunteers demonstrated an average increase of 65% in the cross-sectional diameter of posterior sacroiliac ligaments three months post-treatment; improvements in lumbar range of motion when comparing measurements before and after treatment were also documented. These findings are suggestive of ligament proliferation and soft tissue healing. A study by Yelland et al. reported improvements after injections of both plain dextrose and a placebo of saline, with statistically significant decreases in pain and disability scores after both 12 and 24 months. The authors suggested that the bleeding and tissue disruption associated with needle and saline injections also has a mild proliferant effect. They concluded by stating Prolotherapy was a safe and valid treatment option for a selected group of chronic low back pain patients, adding that if insurers were to adopt a universal policy for denying payment for chronic low back pain treatments based on lack of definitive evidence, no one with chronic low back pain would be able to obtain treatment and, furthermore, that coverage should be provided for treatments that are biologically plausible and supported by literature through clinical trials. Vert Mooney, MD, an orthopedic surgeon and former chairman of orthopedics at the University of California, San Diego, was quoted “that this fringe treatment (Prolotherapy) is no longer at the periphery and seems to be at the frontier of a justifiable, rational treatment with a significant potential to avoid destructive procedures.”

Reeves has performed many randomized studies on the injection of dextrose Prolotherapy into osteoarthritic thumbs, fingers and knees. After a series of three injections to the medial and lateral ligaments of the distal interphalangeal (DIP), proximal interphalangeal (PIP) and trapeziometacarpal (thumb CMC) of one half milliliter of either 10% dextrose and 0.075% xylocaine (active) or 0.075% xylocaine (control), it was reported that pain at rest and with gripping improved in the dextrose group, including reported improvements in pain with movements of the fingers, especially with flexion. Similar results were produced in a second study after three bimonthly injections of 9cc 10% dextrose and 0.075% lidocaine (active) when compared to the injections of 0.075% lidocaine (control). He also found that a 10% dextrose solution resulted in clinically and statistically significant improvements in symptoms associated with knee osteoarthritis with decreased pain, swelling and knee buckling frequency, as well as improved range of motion. Also at the end of one year, eight of 13 of the patients with ACL laxity were noted to have ACLs that were no longer lax. Radiographic comparison of
the knees at zero and 12 months revealed stability of all radiographic variables with improvements in lateral patellofemoral cartilage thickness as well as distal femur width. Hauser also has conducted radiographic studies of osteoarthritic knees by measuring the joint spaces before Prolotherapy and after a series of injections. He treated five knees of three adult patients with a standard solution of 15% dextrose, 10% Sarapin and added 2IU of Human Growth Hormone to each intra-articular joint injection, with each patient receiving six to 14 injections per knee. X-rays taken one year after starting Prolotherapy showed increases in the joint space width of all knees, in both the femorotibial joint and the patellofemoral joint. Patients reported decreased pain in their knees with reduced need for pain medication. They also noticed improved range of motion and function and did not feel limited in regard to their knees. Similar results using 15% dextrose solution demonstrated cartilage repair within the hip with decreased pain and improved function. Eighty-nine percent of the patients experienced at least 50% reduction of their pain with over 70% reporting reduced crunching and stiffness. Eighty-five percent were able to cut their pain medication usage by at least 50% and more than 82% reported improved function and daily living. Also, some patients had before and after X-rays which revealed increases in the joint space widths consistent with cartilage repair and the patient’s subjective reporting of their symptoms.

The degenerative process associated with weak and unstable joints can be slowed and potentially prevented by treatment with Prolotherapy. If treated in the early stages, the proliferation of new ligament tissue strengthens the joint and helps restore proper joint mechanics and fluid joint motion. By decreasing laxity of the ligaments and instability of the joint, contact forces can be redistributed back onto the areas of thickest cartilage that are designed to handle high loads and reduce the stress at thinner, weaker points, allowing for healing to take place and preventing degeneration. Even in later stages of degeneration and OA, improvements in pain, instability and function are possible as described in the above studies. By adding stability to the joint, along with the proliferative inflammatory process provided by Prolotherapy, the body is able to repair damages incurred to the articular surfaces and restore the joint space width.

In addition to a favorable safety profile, Prolotherapy produces positive results in 75 to 90% of patients by resolving chronic pain issues. It is the treatment of choice for ligament injuries (sprains, tears, instability, and benign hypermobility syndrome) and the resultant cartilage degeneration that these injuries cause. The loss of articular cartilage and the osteophytes (bone spurs) located at the entheses where ligaments attach to bone at the margins of joints and in the spine can be prevented or reversed after one of the main causes of joint degeneration (i.e., instability) is eliminated by the stabilizing effects produced by Prolotherapy. (See Figure 11.) The process of stimulated ligament repair is joint reconstruction at its core. The vastly different risk-benefit profile of Prolotherapy versus joint replacement surgery or drugs makes Prolotherapy the treatment of choice in all but the most extreme cases of ligament injury and joint degeneration.

Gustav Hemwall, MD, built on Dr. Hackett’s definitive work and the discovery of the link between ligaments and joint pain by emphasizing the recognition of ligaments as the key source of chronic pain. He accomplished this through his many years in clinical practice and by teaching other physicians about the use of Prolotherapy. He taught that Prolotherapy is an extremely safe and effective procedure when thorough study of anatomy is combined with the proper physician training. To continue the advancement of the original research and the proper use of Prolotherapy first described by Drs. Hackett and Hemwall, the Hackett-Hemwall Foundation provides training to physicians in the technique of Prolotherapy. A full discussion of Dr. Hackett’s research and the technique of Prolotherapy is found in the book he co-authored with Dr. Hemwall, *Ligament and Tendon Relaxation Treated by Prolotherapy*.  

**Figure 11. Beneficial effects of Prolotherapy in the prevention of degenerative arthritis.**

- Ligament repair
- Joint regeneration
- Joint stabilization
- Strengthening of joint structures
- Cartilage regeneration
A review of past and current literature has provided ample evidence to definitively support the connection between ligament injury and joint instability and the development of degenerative osteoarthritis of peripheral joints and the spine. At best, standard treatment protocols temporarily modify patients’ symptoms and, at worst, they may result in unexpected side effects (e.g., drugs) or morbidity with more aggressive intervention (e.g., surgery). The Prolotherapy approach is the most reasonable and effective treatment method for joint-related problems because it addresses the most common cause of joint pain and disability, relies on the body’s natural repair and healing processes, results in long-term improvement, can treat virtually every accessible joint in the body, obviates the need for higher risk and/or destructive interventions, has an extremely favorable safety profile, is compatible with an active lifestyle with little down-time involved, and ultimately saves both direct and indirect health care costs. The relative shortcomings of Prolotherapy are: the need for adequate time and treatment to receive full benefit, the use of needles which carries some degree of discomfort and apprehension, the lack of well-trained Prolotherapists throughout the country, general non-acceptance of the method from the health care industry, and costs that are usually borne by the patient. Prolotherapy is not a panacea, in that it cannot completely resolve every joint problem, but when used in a timely fashion and performed by a skilled practitioner of the technique, it overcomes nearly all the objections to its regular use. As more research into joint disability and healing is gathered and well-designed clinical studies are performed confirming current understanding, Prolotherapy will likely become a part of the medical school curriculum and be more available to vast numbers of people across the nation who suffer from the disabling effects of chronic pain. ■

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Comprehensive Scientific Overview on the Use of Platelet Rich Plasma Prolotherapy (PRPP)

Karina Gordin, BA, MS

ABSTRACT
As noted in this review, over the past decade substantial advancements have been made in optimizing musculoskeletal diagnoses and repair. As a result, the research trend has evolved to recognize preventative measures and innovative treatments, which ultimately aim to improve patient quality of life and reduce the costly social impact of soft tissue and joint pathologies. One such treatment, which stands out for its cost-effectiveness and regenerative capabilities, is Platelet Rich Plasma Prolotherapy (PRPP). Now used with increased frequency for conditions such as tendinopathy, sprains, strains and laxities, PRPP is an effective alternative to conventional treatments (NSAIDs, surgery, corticosteroids) on account of its supra-physiologic concentration of platelets rich in the seven fundamental protein growth factors, which play a central role in the healing process.1

KEYWORDS: autologous blood, cartilage, collagen, growth factors, inflammation, injection, musculoskeletal injuries, platelets, Prolotherapy, tendonitis.

A NEW PARADIGM

As the 2000-2010 Bone and Joint Decade elapsed, its global initiative to advance research of joint injuries2 ushered in therapeutic interventions that aimed to enhance tissue regeneration and reduce degenerative mechanisms. The current research trend in the arena of joint injury launched breakthroughs in scientific investigations and technology, providing important new insights into musculoskeletal injury, which, according to a study conducted by the World Health Organization, is the most frequent cause of intensive long-term pain and disability, affecting millions of people worldwide.3 Musculoskeletal diseases, ranging from back pain and bodily injuries to arthritis and osteoporosis, are reported more often than any other health complaint by U.S. patients. In 2004, lost wages and treatment expenses related to musculoskeletal diseases was estimated to cost a total of $849 billion, equal to 7.7% of the gross domestic product (GDP).4 In 2005, the majority of both lost work and bed days were attributed to health conditions associated with musculoskeletal diseases.5 The social impact of bone and cartilage pathologies imposes high costs and ultimate loss of income: in the United States alone, osteoarthritic medicines cost $5.31 billion in 2007,6 and musculoskeletal conditions cost nearly $128 billion per year in direct medical expenses.7 Such as, one report approximated the total cost of bilateral knee joint replacements at over $85,000, which included a hospital stay, surgeon and anesthesiologist fees, a 5-day inpatient rehabilitation center stay, and a pathologist visit.8

Without a doubt, the need to spotlight musculoskeletal conditions and functional, cost-effective treatments is urgent, considering factors such as increased popularity of sporting activities and related tissue injuries, including tendon and ligament trauma accounting for 45% of all musculoskeletal injuries in the U.S.A.9 Broadly speaking, insufficient understanding of these escalating musculoskeletal disorders, including osteoarthritis development, has generated a wide array of symptom based treatment options, including narcotics, anti-inflammatories, corticosteroid injections, surgery, ice, heat, analgesics, rest, braces and wraps, and physical therapy.10 Considering such protocols, it is apparent that basic human physiology is misapplied; namely, common tendon therapies aim at handicapping inflammation, while false assumptions attribute inflammation to osteoarthritis whereas the etiology primarily involves degeneration. In fact, the term osteoarthritis, relating to the most common form of arthritis, is a bit of a misnomer, and may be better identified as osteoarthrosis, since inflammation plays an insignificant role compared to corroding of cartilage and loss of sensory innervations of the joint and surrounding muscles. What initially starts off as a sprain or strain, commonly attributable to excessive forces applied to a joint in an abnormal direction, eventually translates into meniscal and ligamentous injury, ultimately leading...
to increased instability within a joint.\textsuperscript{11} Progression of such degeneration eventually indicates arthroscopy, joint replacement, or in some cases spinal fusion as last resort care when pain, disability and imaging studies warrant it. If imaging studies focused beyond common sources of pain like degenerative joint cartilage and spinal disc disability, and considered pain generators like ligaments, joint capsules, muscles and tendons, then would surgery still be warranted as the last resort? According to large randomized trials examining such interventions, it was concluded that surgery like arthroscopy has a limited role as a treatment of osteoarthritis.\textsuperscript{12} The fact that soft tissues (connective tissues) and alternative interventions are rarely considered in diagnosis, avoidable and expensive protocols are performed, generating annual direct medical, drug and indirect work loss costs at $8,601, $2,941, and $4,603, respectively.\textsuperscript{13} Accordingly, reliable preventative interventions and regenerative solutions pose promising new alternatives to traditional long-term palliative care,\textsuperscript{14} improving clinical outcomes, and providing a new perspective on understanding the wound healing process.

Amongst a variety of breakthroughs addressing musculoskeletal conditions, Platelet Rich Plasma Prolotherapy (PRPP) stands out as a minimally invasive procedure that both safely and effectively accelerates natural healing, prompting the sequela of reduced treatments frequency and morbidity, while reinforcing functional recovery.\textsuperscript{15} Since first being introduced by Ferrari et al.\textsuperscript{16} in 1987 following an open heart surgery, platelet rich plasma has swiftly gained recognition as a versatile, biocompatible and cost-effective “tissue engineering”\textsuperscript{17} modality, stimulating therapeutic uses in a variety of medical fields, including orthopedics, dentistry, ENT, neurosurgery, ophthalmology, urology, wound healing, as well as cosmetic, cardiothoracic and maxillofacial surgery.\textsuperscript{18} Most recently, PRPP has found popular and effective applications in sports medicine, offering relief to two of the Pittsburgh Steelers’ biggest stars, Hines Ward and Troy Polamalu, as well as the golfer Tiger Woods, several major league pitchers, roughly 20 professional soccer players, and scores of recreational athletes. Of course the continued prevalence of sporting activities has generated an epidemic of musculoskeletal disorders, considering the fact that sports and athletics involve tremendous force: tennis players may serve continuously up to 140 miles per hour; pitchers throw a baseball 100 miles per hour, while marathon competitors run five minute miles for 26 miles, and so on. It is therefore no wonder the body begins to break down, and attention must be focused on tendons, ligaments and joints, potentially establishing platelet rich plasma grafting techniques (PRPP) as one of the mainstay of tissue regeneration.

\textbf{Rationale for PRPP}

The PRPP benefit lies simply in supra-physiologic concentrations of platelets. To be precise, platelets compose less than 1\% of blood, as their job is typically reserved for restoring hemostasis (stoppage of bleeding), construction of new connective tissue, and revascularization. Red blood cells (RBC), which primarily aid in delivering oxygen from lungs to other body cells, and white blood cells (WBC), which fight infections, kill germs and carry off dead blood cells, constitute 44\% and 0.7\% by volume of whole blood, respectively.\textsuperscript{19} Namely, there are about one billion red blood cells in two to three drops of blood, and, for every 600 red blood cells, there are about 40 platelets and one white cell.\textsuperscript{20} Plasma, the liquid component of blood made mostly of water and functions as a transporter for cells, composes the remaining 54.3\% by volume of whole blood. The rationale for PRP benefits lies in reversing the blood ratio by decreasing RBC to 5\%, which are less useful in the healing process, and increasing platelets to 94\% to initiate recovery.\textsuperscript{21} Naturally, platelet concentration is subject to slight variability due to manufacturer’s equipment.

To put it into perspective, 200,000 platelets/ul is the normal concentration, and as studies have demonstrated, clinical efficacy may be indicated with a minimum of 4x the baseline, which is the benchmark for “therapeutic PRP,” a count of 1 million/\(\mu\)L as measured in the standard 6-mL aliquot. Thus, platelet rich plasma is defined as a volume of plasma fraction of autologous (patient is both donor and receiver) blood, containing platelet concentration above baseline.\textsuperscript{22} The autologous quality of PRP preparation eliminates any concerns of disease transmission or immunogenic reactions, which exist with allograft or xenograft preparations, given that the patient is both donor and recipient of the graft material.

The significant feature of platelets is the alpha granules, which organically promote healing of soft tissue by facilitating the release of one’s own growth factors; the process is simple and efficient since growth factors are readily available in significant amounts upon PRP activation. Normally at resting state thrombin is required
to trigger platelet activation, in turn prompting platelets to morph into strategic shapes, develop branches, extend over injured tissue, and ultimately release growth factors that stimulate the inflammatory cascade and healing. (See Figure 1.) The main growth factors contained in the granules are transforming growth factor beta (TGF-β), which stimulates cell replication and fibronectin binding, vascular endothelial growth factor (VEGF), which is a potent stimulator of angiogenesis, platelet-derived growth factor (PDGF), which stimulates tissue remodeling, and epithelial growth factor (EGF), which induces cell migration and replication, amongst others. (See Table 1.)

Combined, the growth factors play a critical role in the healing process and tissue regeneration, forming a cascade of diverse pathways, initiating activation of gene expression, and protein production. This specific feature of PRP directly addresses chronic non-healing tendon injuries, which traditional therapies approach with corticosteroid injections, medications like NSAIDs, and surgery; all of which, studies suggest, exhibit adverse side effects, ranging from atrophy, bleeding ulcers, and kidney damage, respectively. In fact, it appears that the longer a musculoskeletal condition persists, the more resistant it becomes to traditional therapies; more over, it has been documented that protracted symptoms and relapses are regularly observed post conservative treatments. So unlike traditional therapies, which ultimately treat tissue injuries without amending the inherent poorly healing properties or underlying pathology, Platelet Rich Plasma Prolotherapy has been shown to enhance the early cascade of tissue repair processes both in vitro and in vivo. Recent reports have accounted a more rapid epithelialization (coating of epithelial tissue), more dense and mature bone with better organized trabeculae (supporting strands of connective tissue), and greater bone regeneration occurring when PRPP is utilized in the treatment.

The potent cocktail of growth factors containing a variety of biologic mediators can be applied directly to the healing site via Prolotherapy, an injection technique that has steadily gained widespread exposure as a form of pain management in both complementary and allopathic medicine. George S. Hackett, MD, who coined the term Prolotherapy described it as “The treatment [which] 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.” Physiologically speaking, this mode of treatment is particularly considerable since, as a result of mechanical factors, tendons and ligaments are vulnerable to injury and quite stubborn to heal. Expressly, tendons are composed of tenocytes, water, a variety of minor specialized cells, and millions of tightly woven fibrous collagen proteins, which form a durable strand of tissue, and naturally anchor to the bone to form a resilient mineralized connection. Ligaments are bands of tough, fibrous dense regular connective tissue comprising attenuated collagenous fibers connecting two bones, and are involved in the stability of the joint. The greatest amount of stress to ligaments and tendons is where they attach to bone: the fibro-osseous junction. Following
a ligament injury, resulting damage such as laxity may cause joint motion to become greater and offset the contact surface to regions where the cartilage may be thinner and less capable of supporting applied stresses, causing tremendous pain. According to Daniel Kayfetz, MD, the most sensitive structures that cause pain are the periosteum (covering of bone) and ligaments. Dr. Kayfetz remarks that in the scale of pain sensitivity, the periosteum ranks first, followed by ligaments, tendons fascia, and finally muscle.

Tendons and ligaments are particularly susceptible to injury when overwhelmed with the responsibility of transferring a great deal of force, repeatedly. Consequently, collagen fibers in the connective tissue may form micro tears and inflammation instigating conditions including tendinitis, or more appropriately, tendinosis, or tendinopathy.

**Tendinitis:** The suffix "itis" signifies inflammation, and applies to extensive, acute tendon injuries with accompanying inflammation.

**Tendinosis:** The suffix "osis" signifies chronic degeneration without accompanying inflammation. Specifically, non-healing condition resultant from accumulation of microscopic injuries as the basis of pain and disability in chronically injured tendon tissue. Tendinosis was first considered by German researchers in the 1940s; however, the term’s more modern application relates to Puddu et al. and Nirschl et al.

**Tendinopathy:** The suffix “opathy” signifies no particular pathology, and may be applied to tendon injuries in general.

Ligaments and tendons generally have a poor blood supply and heal at a comparatively slow rate, culminating in tissue scarring, which adversely affects function and increases risk of re-injury. Histologic samples from chronic cases indicate that an inflammatory response is not activated, but rather a limitation of the normal tendon repair system with a fibroblastic and a vascular response called angiofibroblastic degeneration. In the interest of embracing rather than suppressing the inflammation, PRPP injection prompts a local inflammation, triggering a wound healing cascade, and results in the deposition of new collagen, of which tendons and ligaments are composed. The new collagen contracts as it matures, in turn tightening and subsequently reinforcing the injected painful area. That is all the body requires, the remaining healing stages take care of themselves. They include: inflammation, proliferation and remodeling.

Presently there is evidence to suggest that PRP grafts may be either anti-inflammatory or pro-inflammatory in specific tissue at certain concentrations, or dose-response curves.

At the site of tissue injury, the latter exists to as yet an unknown PRP concentration and succeeding migration and proliferation of progenitor stem cells at the tissue injury site.

Following the preliminary inflammatory phase, which generally lasts for two to three days, fibroblasts enter the site and commence the proliferative phase, which lasts from two to four weeks. Fundamentally speaking, low pH and low oxygen levels encourage fibroblast proliferation in the injury site, leading to the deposition of collagen and ground substances. Ultimately, the wound narrows...
as actin contracts and fibroblasts differentiate into myofibroblasts. Given that fibroblasts are the primarily deficient cells with chronic injury, the proliferative phase is vital for musculoskeletal renewal. Appropriately, the PRPP grafts function via a triad of interactions, known as the cell proliferation triangle. 48 The last phase of this triangle involves the maturing and strengthening of collagen; essentially, tissue repair begins when the production and break down of collagen equalizes, a process which can last over one year. This remodeling period is characterized by type III collagen being replaced by type I collagen, reorganization, and disappearance of blood neovessels. 49 A competent Prolotherapy specialist ensures that each element of this triangle is present for effective tissue renewal and pain relief; otherwise, an incomplete or unabated stage results in loss of tissue homeostasis as well as pain and loss of function. Most reviews published on this matter tend to focus on growth factors contained within the platelet’s alpha granules, but it is equally important to acknowledge that if platelets are not suspended with biologic levels of additional constituents of plasma, including cytokines, fibrin and leukocytes, then the graft may be either ineffective or less effective. 50

On the other hand, if say fibrin levels are too high, or platelet activation occurs prior to collagen binding, the graft is likewise inhibited. Further functions of platelet activation and the subsequent cascade of events that develop include cytokine signaling, chemokine release and mitogenesis 52 (cell mitosis production). The active secretion of the growth factors typically begins within 10 minutes of being initiated by the clotting process of blood. Within one hour, approximately 95% of the presynthesized growth factors are secreted. 53

Matrix Graft: A tissue graft incorporating autologous growth factors and/or autologous undifferentiated cells in a cellular matrix whose design depends on the receptor site and tissue of regeneration. 51

PLATELET RICH PLASMA PROCESSING

While the standard proliferant utilized in Prolotherapy is typically dextrose-based, platelet rich plasma is growing in popularity and with it the various PRP preparation techniques. Gradient density cell separation and concentration of platelets from autologous whole blood varies from the use of test tube collection and laboratory centrifuges to the more sophisticated device employing a floating shelf technology.

Though in essence the end goal of platelet sequestering devices is akin, parameters such as viability, functionality, quantity of platelets, as well as concentration of growth factors should be confirmed by a scholarly, peer-reviewed journal. Studies asserting lack of PRP benefits can often be traced to poor-quality PRP produced by inadequate devices. Moreover, studies presenting little benefit from PRP often use damaged or inactivated platelets, and have statistically insufficient data to draw a valid conclusion. For example, an article by Froum et al. 54 included only three patients and introduced multiple independent variables to confound their results; in addition, the study did not test the platelet concentrations as other studies. Weibrich and Klies 55 documented the inadequacies of various devices that may contribute to poor trial results, finding them to be deficient in developing therapeutic levels of platelets compared to quality devices like the Harvest SmartPReP2 platelet concentrate system as well as Biomet Biologics GPS III system, described here for simplicity. (See Figure 3.) Approximately 30 to 60ml of venous blood is drawn from the anteceubital (bend of arm) vein using the aseptic technique; an 18 or 19G butterfly needle is advised in efforts to prevent trauma to the platelets, which are at resting state. Subsequently, blood is placed in an FDA approved, sterile centrifuge and spun for 15 minutes at 3,200 rpm, separating blood into platelet poor plasma (PPP), RBC and PRP. (See Figure 4.) While the PPP is discarded through a special port, the PRP is shaken in a vacuumed space for 30 seconds to re-suspend the platelets. Clinical studies established that an increase of three to four fold above

![Figure 3. SmartPReP2 centrifuge from Harvest Technologies where the patient’s blood is centrifuged to extract platelet rich plasma to be used for Prolotherapy injections.](image-url)
may further assist patients, who find Prolotherapy painful, by prescribing Tylenol® or Vicodin® to be taken prior to Prolotherapy treatments. Some physicians may use an anesthetic cream that is rubbed on the specific area, thereby decreasing pain of needle injection. Some spray an anesthetic like lidocaine on the skin, or inject some anesthetic into the skin to abate pain associated with a needle piercing skin, which some patients complain is the most painful part of the procedure. Of course the pain intensity varies from patient to patient during the Prolotherapy treatment. However, the consensus remains that it’s minimal compared to untreated chronic pain endured by patients on a daily basis.

Soreness following PPRP is commonly experienced since the injections must travel through some muscles to access ligaments and tendons. Between the second and fourth weeks, called the “window period” of healing, initial stabilization induced by PPRP subsides and because the initial growth of tissue is incomplete, some of the original pain may return. To ensure an accurate evaluation of results, follow-up is typically recommended four to six weeks after each treatment, thus avoiding patient evaluation within the “window period” of healing. To facilitate swift sore muscle resolution, massage therapy and moist heat applied to the area is recommended. Nutritional products to encourage soft tissue healing, such as bromelain, MSM, and high potency enzymes, are sometimes recommended. Gentle manipulation techniques, such as myofascial release, strain-counter-strain, or activator gun treatments, may be helpful as well. Other modalities that improve circulation and assist the healing from PPRP include acupuncture, Rolfing, electrical stimulation, magnets, infrared heat, and ultrasound.60 It is important to note that for PRPP to be most effective, patients should avoid anti-inflammatory medications to ease pain, as they may be counter-productive to the underlying PRPP recovery process. Narcotic medications, such as Vicodin, Tylenol with Codeine, and Darvocet, should be avoided on account of their immune-suppressive properties, which too is counter-productive since the immune system is critical for healing following PRPP.61,62

There is extensive documentation of both animal and human studies, with widespread applications, demonstrating the safety and efficacy of properly managed PRPP. Though most studies to date are pilot designs with small sample sizes, recently emerging literature demonstrates beneficial effects of PRPP for chronic non-

Figure 4. Blood after being centrifuged allows the clinician to extract the platelet rich plasma to be used for injection.

baseline as an acceptable standard.56 Haynesworth et al.57 demonstrated that the proliferation of adult mesenchymal stem cells and their differentiation were directly related to the platelet concentration, particularly showing a dose-response curve, which indicated that an adequate cellular response to platelet concentrations first began when a four to five fold increase over baseline platelet numbers was achieved.

Weibrich et al. observed an advantageous effect with platelet concentrations of approximately 106/µL. Further they state that higher concentrations might have a paradoxically inhibitory effect.58 A study by Lui et al. demonstrated that type I collagen production and fibroblast were enhanced by just the right concentration of platelets, ultimately emphasizing the importance of qualified devices.59 Once the PRP is expertly yielded, it may remain sterile and the concentrated platelets viable for up to 8 hours, ready for injection. Considering the data from imaging studies such as MRI and radiographs, as well as clinical exams and the highly recommended dynamic musculoskeletal ultrasound with a transducer of 6 to 13 Hz, the area of injury is marked and directly injected with or without an appropriate anesthetic, such as lidocaine or marcaine. In addition to the local anesthetics, physicians
healing tendon injuries including lateral epicondylitis, plantar fasciitis,63, 64 as well as knee ligaments, rotator cuff tears, wound healing, Achilles tendon tears, anterior cruciate ligaments (ACL), amongst others. There is also a range of publications in other fields including ENT, cardiology and plastic surgery. The following is a review of some of the more recent studies of PRPP.

**Elbow**

Medically classified as lateral epicondylitis, tennis elbow is characterized by tissue degeneration of the wrist and forearm extensor tendons at the elbow. Commonly, injuries are caused by mechanical overloading of the forearm muscles, constant repeated actions associated with racquet sports, manual work in which twisting hand movements are involved, weight training, a variety of other traumatic movement of the elbow or wrist, and abnormal micro-vascular responses.66 Histologic specimens from chronic cases confirm that tendinosis is not an acute inflammatory condition but rather a failure of the normal tendon repair mechanism associated with angiofibroblastic degeneration.67 An estimated four in 1,000 individuals are affected with this condition at some time and is a frequent cause of missed work.69, 70

Numerous methods have been advocated for treating elbow tendinosis, including rest, non-steroidal anti-inflammatory medication, bracing, physical therapy, iontrophoresis, extracorporeal shock wave therapy, and botulism toxin.72 Corticosteroid injections have been used extensively in this case, but studies show conflicting evidence regarding their efficacy.68 In February 2011, *Orthopedics* published a study demonstrating the efficacy of a single PRP injection for recalcitrant common extensor or flexor tendons, otherwise unresponsive to nonsurgical treatments like steroid injections. Such promising results were further substantiated in a double-blind, randomized controlled trial published in *The American Journal of Sports Medicine*. One-hundred patients with chronic lateral epicondylitis, randomly assigned to a leukocyte-enriched PRP or corticosteroid group, demonstrated significantly increased function and reduced pain in the PRP group, “exceeding the effect of corticosteroid injection even after a follow-up of 2 years.”76 The next Prospective Cohort study, also documented in the *American Journal of Sports Medicine*, evaluated the use of platelet rich plasma as a treatment for chronic severe epicondylar tendinosis. Mishra et al. examined 140 patients, 20 of whom met the study criteria and were surgical candidates who had previously failed conservative therapies. Of those, five were controls treated with local anesthetic bupivacaine, while the remaining 15 study subjects received one PRP injection. Notably, the study group observed 60% improvement in their visual analog pain scores at 8 weeks, 81% improvement in their visual analog pain scores (P=0.001) at 6 months, and 93% at final follow-up at 12-38 months (mean, 25.6 months; range, 12-38 months). Markedly there were no adverse effects or complications, with a 94% return to sporting activities, and a 99% return to daily activity.77 Confoundings are limited to 60% attrition rate in the control group as 3/5 of the subjects withdrew from the study or sought outside treatment at eight weeks.

In 2003, Edwards and Calandruccio demonstrated that 22 of 28 (79%) subjects with refractory chronic epicondylitis were entirely pain free following autologous blood injection therapy.78 The 28 patients were followed-up for an average of 9.5 months (range 6-24 mo.). Before autologous blood injections, the average pain score was 7.8 (range 4-10). The average Nirschl stage was 6.5 (range 5-7). Following autologous blood injections the average pain score decreased from 7.8 to 2.3 while the average Nirschl stage decreased from 6.5 to 2.0. Of note, there was no reported worsening or recurrence of pain and no other adverse events. Pain following buffered PRP injection was variable, but comparable to prior steroid injections subjects received before the study. Lack of control group and small sample size limits this study.

**Foot**

Plantar fasciitis is a common cause of heel pain, potentially resulting in pathologic degenerative tissue changes, similar to tennis elbow. It has been estimated that in a typical podiatric practice, approximately 40% of patients complain of heel pain. Severe or prolonged cases of plantar fasciitis may result in partial or full thickness tearing of the plantar fascia, which encapsulates the muscles in the sole of the foot. This very important connective tissue is responsible for supporting the arch of the foot and endures tension that is approximately two times body weight. Barett et al. enrolled nine patients in a pilot study to evaluate PRP injections for plantar fasciitis. Patients met the criteria upon willingness to avoid conservative treatments such as NSAIDs, bracing and cortisone injection for 90 days prior. Ultrasound confirmed that all patients demonstrated hypoechoic and thickened plantar...
fascia. Following a 3cc of autologous PRP injection under ultrasound guidance, thickness and increased signal intensity of the fascial bands were observed. Six of nine patients achieved complete symptomatic relief following a period of two months. One of three unsuccessful patients eventually found complete relief following an additional PRP injection. At one year, 77.9% patients had complete resolution of symptoms.79

ACHILLES

The Achilles tendon is located in the back of the leg and attaches to the heel bone (calcaneus). It is the largest and strongest tendon in the body, enabling elevating on the toes and jumping. Achilles tendinitis may occur from wearing inappropriate footwear, or from repetitive jumping especially on poor surfaces, eventually causing either acute or chronic injury. The former is characterized by inflammation while in chronic cases there is degeneration of the tendon fibers that may progress to a partial or complete tear.

In a study conducted by Per Aspenberg and Olena Virchenko,80 platelet concentrate injection was shown to improve Achilles tendon repair in an established model of 296 Sprague-Dawley rats. The Achilles tendon was transected (cut across) and a 3mm segment removed. Following six hours, a platelet concentrate was injected percutaneously (needle puncture of skin) into the hematoma (clotted blood caused by break in blood vessel). This increased tendon callus strength as well as stiffness by roughly 30% following a one week period, persisting for as long as three weeks post injection. At this time, the mechanical testing indicated an improvement in material features, i.e., greater maturation of the tendon callus. Ultimately, it may be interpreted that platelet concentrate may prove useful for the treatment of Achilles tendon ruptures.

Sanchez et al. reported on a case control study of 12 athletes with complete Achilles rupture.81 The athletes similarly had open Achilles repair; specifically, six had PRGF, while the treatment group showed no wound complications and experienced earlier functional restoration: ROM (seven vs. 11 wks.), jogging (11 vs. 18 wks.) and training (14 vs. 21 wks.). The authors measured IGF-I, TGF-β1, PDGF-AB, EDF, VEGF and HGE, and noted that the number of platelets were directly correlated to the level of growth factors, and improved collagen organization. More data demonstrating positive outcomes following PRP injections for Achilles tendinopathy is presented by Robert J. de Vos et al. in a stratified, block-randomized, double-blind, placebo-controlled trial.82 Fifty-four patients, aged 18 to 70 years, with chronic tendinopathy 2 to 7 cm above the Achilles tendon insertion were randomized into a PRP group (control) or saline injection group (placebo), accompanied by eccentric exercises. Treatment outcomes were measured using a Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire, which specifically evaluated pain score and activity level at baseline as well as 6, 12 and 24 weeks, with higher scores corresponding to less pain and increased activity. Following 24 weeks, the mean VISA-A score improved considerably in the PRP group by 21.7 points and in the placebo group by 20.5 points. While the increase was not significantly different between control and placebo groups, improvement in pain and activity following PRP injection was significant in its own right. Yelland et al. conducted a similar randomized study, comparing the effectiveness of single or combined use of eccentric exercise with Prolotherapy to treat painful mid-portion Achilles tendinosis. Over a 12 month period, the main outcome of the 43 patients was prospectively measured using the VISA-A questionnaire, focusing on pain, stiffness and limitation of activity; at 12 months, the percentage of participants achieving the minimum clinically important change (MCIC) was 73% for eccentric load exercise, 79% for Prolotherapy, and 86% for combined treatment. The study concluded that compared with eccentric load exercise alone, reduction in stiffness and limitation of activity occurred earlier with Prolotherapy, while pain was additionally reduced earlier with combined treatment.83

KNEE

Lesions of anterior cruciate ligament (ACL) represents one of the most common traumas in sporting practice, ranging from 75,000 to 100,000 cases per year in the United States.84 The loss of the knee center rotation following ACL lesions causes a functional overload, leading to cartilage defects, meniscal lesions and early gonarthritis. It is worth recalling that the blood supply is from within the ligament as opposed to around it; therefore, blood supply is commonly disrupted during injury when the ligament is torn.85 ACL injuries may be attributed to sports including football, soccer and basketball where deceleration and swift cutting movements are common; knee joints are particularly vulnerable to such trauma and subsequent ligament injury on account of the location between the two longest lever arms in the body, tibia and femur, which
experience high repetitive impact loads. ACL and medial collateral ligament (MCL) may both sustain an injury if, say, an athlete is struck by another from behind and outside. Such injury is often accompanied by an audible “pop” usually with, though occasionally without, pain. Untreated, relaxed, or torn ACLs have been shown to precipitate degenerative osteoarthritis, given the decreased joint stability and alteration of biomechanical forces.

**Meniscus:** The meniscus primarily distributes stresses and forces evenly across the knee joint, though in a compromised state, contact forces increase over a smaller area of cartilage causing abrasion, and ultimately joint degeneration.

The combination meniscal injury incurred at time of ACL damage is very commonly associated with knee osteoarthritis, considering biomolecular damage to type II collagen and an initial increase in proteoglycan content.

**Proteoglycan:** cementing like glycoproteins occurring in connective tissue, influencing both activity and stability of proteins as well as signaling molecules within the extracellular matrix.

In other words, stressors change anatomy of a joint creating an unfavorable environment for other structures like meniscus, ligaments and cartilage. In a single-center, uncontrolled, prospective preliminary study, Sampson et al. evaluated the clinical effects of intra-articular PRP injections in a small group of participants with primary and secondary knee osteoarthritis. Outcome measures included the Brittberg-Peterson Visual Pain (Visual Analog Scale [VAS]), Activities, and Expectations score and the Knee Injury and Osteoarthritis Outcome Scores at preinjection visit and at 2-, 5-, 11-, 18-, and 52-week follow-up visits. Scores demonstrated significant and nearly linear improvements in knee pain and symptom relief, with majority of patients expressing a favorable response at 12 months following treatment.

A prospective pilot study conducted by Ventura et al. evaluated the efficacy of using platelet rich plasma growth factors as a potential treatment in anterior cruciate ligament surgery. Twenty patients with laxity caused by torn ACL underwent arthroscopically assisted reconstruction with autologous quadrupled hamstring tendon graft (QHTG). Platelet gel was applied in the femoral and tibial tunnels. The rehabilitation protocol standardized for both randomized growth factor group and control, included: immediate postoperative mobilization without a knee brace, protected weight bearing for three weeks, and return to sporting activities at six months, during which time patients were evaluated both clinically and functionally. CT highlighted a significant difference (P<0.01) between ACL density of the two groups. At six months following surgery, the ACL density between the PRP treated group and control was noticeably different, with the treated group exhibiting uniform density and improved structure. In the control, the ligament was less structured and incompletely filled the femoral and tibial tunnels. As this study demonstrates, PRP based growth factors may accelerate the integration of the new ACL in the femoral and tibial tunnels.

Following a PRP injection in rat patellar tendons, Kajikawa et al. demonstrated increased quantity of circulation-derived cells in the early phase of tendon repair after injury, versus controls. With respect to other animal studies, a rabbit patella tendon was ruptured and subsequently sealed with platelet-rich plasma gel; after three weeks, a histological examination showed swift recovery with particular emphasis on angiogenesis earlier in the healing process, more mature and dense vessels and greater fiber elasticity. In a human model, Kon et al. examined the role of PRP in treating jumper’s knee, a condition characterized by microscopic ruptures in Patellar tendon commonly in high-impact jumping sports. In this prospective pilot study, participants were all male athletes with a mean age of 25.5 years, for whom both surgery and nonsurgical treatments like steroid injections had little effect. At six month follow-up, functional recovery indicated six participants with complete recovery, eight with marked improvement, and six cases with mild to no improvement. Ultimately, statistically significant recovery from pre-treatment levels to six months was observed, with improved knee function and quality of life, marked satisfaction and return to sport.

**Rotator Cuff**

Rotator cuff injury of one or more of the four shoulder muscles can range from inflammation without any permanent damage, such as tendonitis, to a complete or partial tear of the muscle that might require surgery. Rotator cuff surgery is one of the most common
procedures performed by orthopedic surgeons, with over 250,000 performed annually in the United States alone. The tendons of the rotator cuff, not the muscles, are most commonly torn. Of the four tendons, the supraspinatus is most frequently torn, usually occurring at its point of insertion onto the humeral head at the greater tuberosity. The poor healing capacity of the torn rotator cuff is well known. Once torn, the injury either remains the same size or expands in size with time. In a prospective study conducted by Scarpone et al., 14 patients had rotator cuff tears with no significant AC joint thickness with impingement and no other significant symptomatic pathology. It must be noted that all 14 patients, strongly considering surgical options, failed non-operative treatments, including NSAIDs, physical therapy, and corticosteroid injections. In the study, skin was anaesthetized with 1% xylocaine and under ultrasound guidance; 3ml of autologous platelet concentrate (APC) was injected directly into the tendon sheath at the injury site. The PRPP effect was measured radiographically with MRI, strength and endurance was tested and patients underwent an analog pain scale. Each measurement was carried out prior to PRP injection, four weeks post-injection, and eight weeks post-injection. Results demonstrated 12 of 14 subjects statistically significant improvements in pain scale and strength, as well as endurance at eight weeks. Of the 12 patients, six had radiographic evidence of healing of their tendinopathy on MRI at eight weeks. Of the four patients who were considering surgery due to persistent pain, two went on to have rotator cuff surgery. No acute complications associated with the procedure occurred.

Reflecting on all the aforementioned conditions that PRP Prolotherapy serves, anecdotal evidence suggests that the procedure emerges as an unparalleled low-risk, natural and highly-effective nonsurgical solution that triggers the body’s own healing capacity. The conveniently obtainable PRP and the strikingly straightforward, simple to perform Prolotherapy injection procedure holds promise to harness the body’s natural healing power by effectively supercharging one’s own capacity for tissue regeneration. So while conventional treatments for soft tissue injury like NSAIDs and steroid injections seek to decrease painful symptoms by reducing inflammation, PRPP embraces this process and in turn initiates growth of new tissue and collagen, ultimately correcting injury as opposed to symptoms. This method of treatment repeatedly demonstrates successful outcomes for a variety of conditions. PRPP may come to be considered a logical first step of treatment prior to, or possibly instead of, surgical intervention for some injuries. This treatment is important to alleviate pain and disability particularly at a time when the current trend estimates 61 million persons at risk of musculoskeletal disease by 2020. Approximately 1 in 10 injuries ensue during sports activities, and another one in 10 in automobile or pedestrian accidents. So whether a person is a working professional determined to promptly resume work, a weekend warrior eager to get back in the game, or simply long to recommence daily activities, PRPP offers new hope for natural healing. “It’s a better option for problems that don’t have a great solution—it’s nonsurgical and uses the body’s own cells to help it heal,” says Dr. Allan Mishra, an assistant professor of orthopedics at Stanford University Medical Center and one of the primary researchers in the field. “I think it’s fair to say that PRP has the potential to revolutionize not just sports medicine but all of orthopedics. It needs a lot more study, but we are obligated to pursue this.” Scores of studies are currently underway to elucidate questions that still remain unanswered regarding long-term stability of this procedure and the possible modifications that can still be done to achieve even better results.
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Tensegrity to Tendinosis

Thomas Ravin, MD

ABSTRACT

Biotensegrity or hierarchical tensegrity can explain how prestressed structures function in animals to transfer the stresses created by gravity, movement, digestion and emotional factors to the extracellular matrix (ECM). Tensegrity’s connection to the ECM is explored, and the mechanotransduction of signals that prompt cellular changes in entheses, ligaments and tendons is discussed. The relationship between stress to the ECM and its effects on development of tendinosis at the cellular level is introduced. Recent findings demonstrating that tendinosis begins long before the patient experiences pain are examined, and the importance of balance between stress and rest in recovery is explored.

KEYWORDS: biotensegrity, collagen, ECM, extracellular matrix, Prolotherapy, tendinosis, tensegrity.

INTRODUCTION

I first started my “case for Prolotherapy” wanting to further examine several areas of interest to me, such as the method by which fibroblasts morph into myofibroblasts, new developments in understanding tendinosis, and the differences between ligaments and tendons. In the five to seven years since I looked into these areas for the book I co-authored, *Principles of Prolotherapy*, I have read numerous articles and research papers that have helped me in treating my patients and I wanted to share this information. As my research progressed in each of these areas of musculoskeletal medicine a common thread emerged—tensegrity. Tensegrity explains how altering the extracellular matrix (ECM) with a needle leads to wound healing, why excessive tendon stress leads to tendinosis and how the mecananochemistry of tendons and ligaments defines their function. It also explains why fibroblasts change to myofibroblasts and shorten ligaments and how tenocytes repair overuse injuries in tendons.

This paper will superficially explore some of the major new research about tensegrity as it applies to the ECM, the entheses, ligaments, tendons and tendinosis.

TENSEGRITY

The word tensegrity can be used to describe many ideas employed in architectural design, bicycle wheels, spider webs and toys and even Carlos Castaneda’s “warrior’s path with heart.” In architecture and animals tensegrity is associated with a type of structure in which the integrity is based on a balance between tension and compression components. Buckminster Fuller in 1948 coined the term tensegrity after he saw a sculpture created by Kenneth Snelson for Black Mountain College. (Wikipedia)

Steve Levin, MD, first presented it to the orthopedic medical community at a meeting of the North American Academy of Manipulative Medicine in 1980. It often is illustrated using Snelson sculptures (*See Figure 1.*) or architectural models such as the Wright flyer. (*See Figure 2.*) These models have some distinct relationships:

- Loading members only in pure compression or pure tension, which means the structures will fail only if the cables yield or the rods buckle.
- The structure has mechanical stability, which means the members remain in tension/compression as the stress on the structure increases.
- The cables are prestressed, which means the cables are rigid in tension. Tensional forces naturally transmit themselves over the shortest distance between two points. This makes them precisely positioned to withstand stress.
- These features of tensegrity mean that no structural member experiences bending.

Donald Ingber, MD, a Harvard researcher in the biological sciences working at about the same time, wrote about the concept of mechanotransduction or biotensegrity in 1993.1 The idea of using hierarchical tensegrity structures as a means of explaining how the animal model of tensegrity works was in the biochemical and biophysical literature, but a recent article by Dr. Ingber discusses many biological
applications of this idea. Knowledge gleaned from study of hierarchical tensegrity structures explains how large land animals can be mechanically strong, flexible and lightweight and yet respond by changing the shape of the body to accommodate specific tasks, such as altering the bony architecture because of gravity or guiding the bony growth from fetus to adulthood. Tensegrity enables the immediate response to changes in force by altering the stiffness in direct proportion to the applied mechanical stress.

Hierarchical tensegrity structures have all the features of architectural models but also have prestressed elements of different size scales. One element can be as large as the bones, ligaments, muscles and tendons of the legs and within it can be an element that might include a single muscle bundle and its tendon attachment to the bone. Smaller still is a collagen fiber of the tendon attaching to the cell wall of a fibroblast in the ECM. Hierarchical tensegrity at the cellular level affects cell wall function that alters the cytoplasm, including the actin and α-actin that give the cell its shape and mobility. The tensegrity continues even further to the intracellular proteins that change shape and function depending on stresses to the cytoskeleton and this explains how our tissues respond to growth, work, play and injuries. The whole cell itself is the final sensor because it integrates multiple local signals with other environmental inputs before reacting to the stress.

**EXTRACELLULAR MATRIX**

The ECM is the principal extracellular component of all tissues and organs. Its main components—collagen, elastin, proteoglycan, fibronectin and laminin—allow it to play a pivotal role in hierarchical tensegrity. As a structural material, it controls the spatial organization in the tissue, from nanometer, micrometer, millimeter, and centimeter...
to meter length scales. It is the connection between the nanometer features and the larger-scale organization that controls the motility and positions of cells, their geometry and mechanical connectivity. This ability to alter the composition and organization lends itself to a wide range of forms and functions ranging from solid in bone to pliable in tendons and cartilage. The major components of the ECM are incredibly stable and over time may develop covalent bonds in response to stress that can change their functional properties. An illustrative example is provided by collagen, the most abundant molecule in the ECM. The half-life for collagen before turnover through degradation by the matrix metalloproteinases is 2–4 years in bone, 10–15 years in skin and ~100 years in tendon.

Strains of the ECM of only a few percent translate into very small alterations in the cytoskeleton and these tiny mechanical stimuli can be transduced into chemical and electrical signals, causing a number of cellular responses. The most common are the chemical ones, such as stretch-sensitive ion channels and G-protein coupled receptors. Despite the prevalence of these receptors, only a relatively small set, the integrins and cadherins, appears to be capable of responding to mechanical cues. (See Figure 5.) Integrins have elements that connect to the fibronectin in the ECM and molecular components that transverse the cell walls and attach to the intracellular focal adhesion complexes. These dynamic protein complexes consisting of multiple integrins linked to a focal adhesion complex, as an integrated unit, provide the mechanical link between the cytoskeleton and the ECM. This bridging between cellular components and the ECM enables the complex to serve as the conduit through which signal mechanotransduction occurs in response to physical force. The extent and degree of the stress can alter the configuration of the focal adhesion complex such that in one situation it might cause unraveling of a protein molecule and reveal a hidden binding site or in another alter the nuclear membrane. These simple and other more complex reactions enable the focal adhesion complex to act as a strain gauge and allow for varying degrees of response.
In another situation the strain might stabilize the integrin-ECM connection and provide a way to concentrate intracellular stresses on some molecules while shielding most of the other cellular components. This gives the ECM and focal adhesion complex the ability to organize and modify their structures instantaneously at the cellular level and still respond to long-term low-level stresses that create physiological changes, such as alterations in the shape of a bone, at the tissue level. All of these features cause the ECM to also be a source of “tissue memory” by binding, integrating and controlling the presentation of growth factors and other ligands to cell wall receptor sites. This allows the ECM to act in some ways like DNA.

Benjamin, Shaw and others have studied the enthesis in detail and have found that it is more than just the LT attachment site. It includes the bony prominences such as the superior tuberosity adjacent to the Achilles tendon that acts like a pulley, reducing stress on the tendon in dorsiflexion. The Achilles tendon also has Kager’s fat pad, the tip of which presses into the retrocalcaneal bursa. These particular structures are adapted to resist compression or shear when the foot is dorsiflexed and reduce friction and the build up of heat. LTs often attach to bone near tuberosities or are sunken into pits, which also act like pulleys to dissipate stress away from the attachment site itself. It is interesting that the Achilles tendon fat pad is the only part of the normal Achilles tendon enthesis organ that is innervated. This makes it the probable source of pain from the normal tendon.

LTs are designed to bear and transmit high tensile loads along their longitudinal axes so they have structural characteristics that confer a greater stiffness and resistance in the axial dimension. The highly nonlinear response of the LT tissues is due to the hierarchical tensegrity structure of the collagen network. The structural integrity and the viscoelastic characteristics of LTs result mainly from the interaction between collagenous proteins and non-collagenous proteins-proteoglycans in the ECM. This interaction allows both reversible (slip-links) and irreversible (rupture) detachment of the glycosaminoglycans (GAG) from the proteins. There also are other cellular and molecular tensile stress absorbers that are discussed in the tendon and tendinosis sections.

Recent ligament research supports the idea that ligaments have two functions and anatomies. One function is that they are the static stabilizers of joints and the second function is sensory or proprioceptive. The presence of mechanosensors implies a sensory role for some ligaments and that this afferent information could regulate the stiffness of the muscles surrounding the joint and improve its stability.

The anatomic vision of ligament anatomy—that ligaments are static structures that fail by fracturing like pieces of soft iron (as illustrated in Stroller’s book) and that they are avascular—is being replaced as their microanatomy is unraveled. Immunohistologic chemistry and newer microimaging techniques available in the last fifteen to
twenty years are showing them to be dynamic structures closely connected to the tensegrity transduction system and the ECM.

It now is clear that there are two types of ligaments: those that consist of densely packed collagen fibres and fascicles and those with the fascicles surrounded by an area of loose connective tissue called the epifascicular region. The ratio of epifascicular to fascicular regions varies greatly in ligaments and when individual ligaments are subjected to scrutiny it can be observed that some ligaments have a lot of epifascicular space and others very little. The ligaments that are predominantly densely packed collagen fibers have only a minimal epifascicular region and almost no innervation. In the other type of ligaments the fascicular bundles and the epifascicular spaces are nearly equal in size. The ligaments with more epifascicular space contain the innervation and blood supplies. The majority of fascicles at the entheses have a high percentage of epifascicular space.\textsuperscript{17, 18}

The ligaments with a high percentage of fascicles are the static stabilizers or, in tensegrity terms, the tension elements. The ligaments with a high percentage of epifascicular space are involved in gathering afferent information such as tension, position and speed of movement. The sensory elements in the ligament are similar to those in the skin. A brief review of these sensors is helpful in understanding how ligaments function:

- Free nerve endings are pain fibers and are mostly in the epifascicular region with just a few in the fascicles.
- The Ruffini corpuscles function as pressure sensors and low vibration sensors and have a low threshold in relation to pressure. They are slow adapting and respond to static conditions of position and stretch.
- The Pacini corpuscles sense pressure and higher vibrations. They sense dynamic changes such as changes in velocity or acceleration and deceleration.
- Golgi apparatuses sense tension. These are slow adaptors and give information about passive stretch and active contraction and they inhibit muscle contraction.

In the wrist there are many ligaments and these have been studied extensively in research correlating their anatomy with their function. In particular the epifascicular anatomy of wrist ligaments was correlated with their known functions. The dorsal ligaments of the wrist have densely placed collagen fibers and limited innervation and function mainly to constrain the scapholunate relative motion. The volar ligaments, which work together to support the wrist throughout its entire range of wrist motion, have a high percentage of epifascicular space and are among the most innervated ligaments in the wrist.\textsuperscript{18, 19}

The wrist ligaments have been the subjects of the most extensive studies comparing form to function, but similar research currently exists for the posterior cruciate ligament (PCL).\textsuperscript{20} In the anterior cruciate ligament (ACL) almost 1% of the total area is nerve.\textsuperscript{21} These studies also have demonstrated the presence of blood vessels throughout the ligaments, particularly in the epifascicular space. So the idea that ligaments have limited blood supplies only applies to the densest regions of the fascicular portions of the ligaments. Immediately following injury the blood supply is derived from the epifascicular and epiligamentous tissues. The injured, frayed or disrupted area is pink or even red from the blood clots and increased blood supply. As the wound heals and the energy demands of the wound decrease, the hypervascular region disappears.\textsuperscript{22}

**TENDONS**

The basic functions of tendons are simple enough. They just connect muscles to bones and transmit forces so that they create movement. The musculoskeletal physician, however, needs to know more about how these complex and elegant structures actually go about these tasks. It seems that at almost every level of this tensegrity structure something important to know has been learned in the last two to eight years. Understanding more about tendons in general might be helpful in making decisions about how best to treat tendinosis.

A quick review of tendon anatomy will help reveal where the new research and some old ideas can aid in our understanding of the structure and function of these complex entities. Tendons have many hierarchical tensity scales beginning with individual collagen fibers, which attach to the cell walls of tenocytes and tenoblasts by way of the focal adhesion complex. In the ECM three collagen molecules arrange in helices that are held together by hydrogen bonds in a coiled shape and are called tropocollagen. Five tropocollagen molecules constitute a microfibril and multiple microfibrils aggregate and form fibrils. The fibril is defined as a collection of fibers that is surrounded by an endotendon.\textsuperscript{19} Fibrils are grouped into fibres; collections of fibres form bundles and bundles...
form fascicles. The endotendon is mostly ECM with most of the tenocytes (TC), tenoblasts (TB), blood vessels and nerves. Some tendons have little or no endotendon and are thought to be involved in transferring stress. There is a helical organization of the whole tendon, from the shiny white tendon to the collagen molecules. This allows the collagen molecules to behave like cables or ropes that deform under tensile stress and improve the handling of their loads. These loads are defined as tensile stress, which is a measure of the internal forces acting within a deformable body. (Wikipedia)

Many of the tendons that are of particular interest to a musculoskeletal physician have to do with joints used in throwing and walking. These muscles do not transmit their load just to bone but also to adjacent muscles and “non-muscular tissue” or the fascia. Wood Jones first explored this idea in the 1940s. A good example of this is where the gluteus maximus attaches to the tendon of the tensor fascia lata and the iliotibial band and not to the greater trochanter. This anatomic arrangement links muscles together to form “mechanical chains” and most muscles in the legs have some direct attachment to the fascia. These muscle and tissue arrangements allow the muscles to distribute tensile stress to the fascicles, then to the fibrils and eventually to the microfibrils and the tropocollagen and finally to the collagen molecules in the ECM that attach to the integrin complex on the cell wall.

Another feature of tendons is the ability of the fascicles to slide independently, which allows them to transmit tensile stress while changing direction, such as going around the medial malleolus. This feature also allows them to change shape as the muscle contracts and also creates a space for the blood vessels. The fibrils also can slide relative to adjacent fibrils and this may account for up to 50% of a tendon’s ability to absorb tensile strain.

As tensile stress is further distributed down the tensegrity scale another feature of tendons comes into play—the crimp in the collagen. At rest, LTs’ collagen fibrils are in a wavy or crimped configuration. The crimp acts like a shock absorber or a buffer, permitting slight elongation to occur without fibrous damage. The crimp performs like a shock absorber that stores the stretch energy and when the stress is released the elastic recoil returns up to 90% of this stored energy. As the tendon is stretched, the crimps begin to disappear progressively or individually rather than simultaneously from the ends toward the centre of the collagen fascicle. The collagen crimp allows for a graded response to acute stretching and works with increasing stress up to about 4% of the LTs’ length.

As the length of the tendon exceeds 4% the tensile stress shifts to the collagen fibril, which is the primary force-transmitting unit of the tendon. The stress at this level leads to some slippage of the ECM’s protein and GAG molecules relative to each other as their crosslinks break. This level of tensile stress also causes the tenocytes and fibroblasts that are in the fibrils and inter-fascicular spaces to be deformed. The collagen molecules of the ECM that attach to the integrin molecules on the cell surface sense the collagen stress and signal the cells to produce more collagen and ECM. This induces a two- or three-fold increase in collagen formation that peaks around 24 hours after exercise and remains elevated for up to 80 hours. The degradation of collagen proteins also increases in response to exercise and is a physiological response to healing. This illustrates that to increase tendon collagen some period of rest (from 36 to 72 hours) is required. This time frame may be compressed with training and conditioning. In any case, without sufficient rest a continuous loss of collagen is likely to occur. (See Figure 6.)

The tenocytes also have mechanisms for continuing to dissipate the stress on the tendons. Tenocytes are like myofibroblasts and respond to rapid length increases with a rapid force increase associated with elastic resistance. This is followed by rapid loss of tissue tension associated with both viscoelastic relaxation and actin cytoskeleton disruption. The recovery of the tension is biphasic,
described as rapid active response (RAR) and gradual active response (GAR), restoring the tissue tension and rebuilding the actin cytoskeleton. The RAR occurs within seconds of a sudden stretch and is completed in less than a minute, and GAR begins a few minutes post-stretch and lasts more than 20 minutes. Both of these responses are mediated by Ca++ channels and reflect the distortion of the cell walls. Both result in cytoskeletal structural changes that include increased actin molecules in the direction of the force and are proportional to the applied stress.33

Cytoskeletal disruption may shield cell-cell adhesions, cell-matrix adhesions and internal cellular components connected to the actin cytoskeleton from large stresses. This suggests that the structure, mechanics and biochemistry of myofibroblasts combine in an intricate choreography to enable stress release for protection of internal structures followed by rapid tissue tension recovery as the cell rebuilds and remodels its cytoskeleton.34, 35

TENDINOSIS

Painful tendon “tendinosis” was considered not too long ago to be an inflammation that could be treated with rest, stretching, NSAIDs or cortisone. In the last five years, however, there has been an explosion of research and ideas on the nature and treatment of tendinosis. The observation today is that tendinosis is present in 35% of adults over the age of 35 years and that 50% of the shoulders of 65-year-olds have evidence of tendinosis even though they are asymptomatic.36

The factors that lead to tendinosis can be divided into two major groups: intrinsic and extrinsic. The intrinsic ones seem obvious but often are overlooked. These issues may be major causes of asymptomatic tendinosis that is present in the older population.37 These include:

- Genetic variation sequence of amino acids in Type I collagen as well as the ratios of Type I to other types of collagen.38
- Endocrine issues such as estrogen in younger women and older men.39
- Metabolic issues such as obesity, diabetes mellitus, lipid disorders and hypertension that alter microvascularity.40

The extrinsic factors are also familiar to most of us in the musculoskeletal medicine community. These include:

- Using tendons too much, too hard and for too long, all at one time.
- Training errors that may be the result of a bad habit, which for many individuals can be hard to identify. In the adult athlete who has been doing a sport for many years these bad habits often are the result of compensation for another old injury. To find these training errors coaching and video often are the best answers.
- Training in either very hot or cold conditions. There is developing evidence that heat injury to tendons is a real problem. The heat generation is the result of friction in the tendinous structures and increased metabolic activity. The heat inside the tendon can easily achieve a temperature of greater than 42.5°C with continuous hard exercise. It is above this temperature that the tendon proteins begin to denature.37, 41
- Training or competing while on fluoroquinolone drugs and possibly on statins in the older populations.42
- The understanding of the pain in tendons has undergone a major shift in the last ten years. The working theory that the pain is the result of inflammation has shifted to a new theory that it is the result of degeneration. Research to explain the nature of the chronic arthroidides that involve the entheses resulted in the paradigm shift. The nature of tendon pain and dysfunction was evaluated anatomically and pathologically and it was clear that normal tendons under stress showed evidence of restructuring. It also was evident that healthy exercise led to both synthesis and degradation of collagen but synthesis prevailed. Figure 6 shows the overall picture and illustrates the fine line between progressive growth and degeneration. The balance between synthesis and degradation is taking place at the cellular level and if the balance is tipped to degeneration by any of the factors discussed above, the process becomes progressive. The disruption of one adhesion complex causes the adjacent elements to take up the load and then they fail. This begins a cascade that becomes self-sustaining and eventually leads to tendinosis. The degenerative changes progress until pain develops and finally the tendon ruptures.43

Tendinosis creates a wide variation in cell density, ranging from areas of near zero cells to areas with many cells that are metabolically active. These areas also have collagen fascicules with unequal crimping, loss of transverse bands, ruptured fibers and increased type III collagen with decreased crosslinks. The abnormal microenvironments
and altered tensegrity of tendinosis induce differentiation of some tenoblasts into adipocytes, others to chondroblasts and even to osteoblasts, which explains the existence of lipid accumulation, mucoid formation and tissue calcification in areas of tendinosis. In these areas of tendinosis there is a considerable increase in both nerves and vessels.

Rest alone is not the solution to tendinosis. Figure 7 illustrates that some stress is necessary for the tendon to regenerate. The challenge for the patient and clinician is to find the right balance between stress and rest in all activities.

Figure 7. This image portrays the progression of tendinosis from (on the left) a normal response to stress by a progressively weaker and painful tendon to a structure that ruptures with the slightest additional stress. The image should give one an idea of the time for progression and recovery. It may be possible to go from normal to very painful or even rupture in one day but recovery is slower.

Ref: Ravin T. AAMM. 2011

A CASE FOR PROLOTHERAPY

Hierarchical tensegrity explains why it makes more sense to treat lax ligaments or compression elements before fixing tendons. If the ligaments are lax, there will be more stress on the tendons. This is particularly true in the case of conjoined LTs, where the injury or degeneration of one component directly affects the other. Prolotherapy allows the physician to repair the compression elements when they are stretched or torn.

In all the musculoskeletal system problems that we diagnose and treat, the ECM plays a critical role that is just beginning to be unraveled. Understanding how the tissues relate to the ECM and the ECM relates to the cells opens up whole new avenues for understanding the musculoskeletal system. The ECM allows the smallest movements of our body to be transmitted almost instantly to every cell by way of tensegrity and prestressed elements. It is clear that altered movement patterns not only waste energy but also change how our whole body works. It is possible to imagine how postural decompensation can affect every cell in the body and how this could be critical in both health and disease. The developing awareness of the ECM as a key part in the mechanotransduction of stress from the tissue level to the cell opens up new avenues to explain how tissues heal their wounds and repair themselves.

Understanding the different functions of ligaments and their innervations should begin to influence how we treat them and with what. The idea that there are two different ligament types in at least three joints means that probably all joints have similar arrangements. Do we treat them all the same with our cocktail of choice or should we consider the function of the ligament before we start the injection? The ligament examination now takes on a whole new meaning. It will be interesting to see if the newer ultrasound and MRI machines and techniques will be useful defining the ligament function or functions and aid us in treatment decisions. “Proliferative therapy” seems the right phrase to explain what we are doing here by stimulating the growth of new ligament, and in 99% of the treatments the response to therapy is consistent with the well-established understanding of tissue repair and wound healing.

Tendons provide clear examples of hierarchical tensegrity in both health and disease. The new information on tendons, from the enthesis to the tenocyte cytoskeleton, challenges all of us to integrate these ideas into our practices. This newer information should begin to help us reconcile the clear differences among the clinical history, physical examination, MRI, ultrasound and surgical findings. The wide discrepancies among these methodologies need to be reconciled to improve the diagnosis of tendinosis.

The current therapy for tendinosis once tendons are degenerated may best be described as regenerative. Rest now seems essential to healing. The question is how we balance stress and rest. Beyond rest, the treatment options for tendinosis seem to be equal to the number of doctors treating. This emphasizes the need for a better and more complete diagnosis of tendinosis. Understanding of
tensegrity can shed light as physicians seek to understand how ligaments repair, why tendinosis occurs and how cells respond to the stresses of living, working and playing.

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Ligament Injury and Healing: An Overview of Current Clinical Concepts

Ross A. Hauser, MD & Erin E. Dolan, RN

**Abstract**

Ligament injuries are among the most common causes of musculoskeletal joint pain and disability encountered in primary practice today. Ligament injuries create disruptions in the balance between joint mobility and joint stability, causing abnormal force transmission throughout the joint resulting in damage to other structures in and around the joint. Osteoarthritis, the long-term consequence of non-healed ligament injury, continues to be the most common joint disorder in the world.

Ligaments heal through a distinct sequence of cellular events that occur through three consecutive phases: the acute inflammatory phase, the proliferative or regenerative phase, and the tissue remodeling phase. The whole process can occur over months, and despite advances in therapeutics, many ligaments do not regain their normal tensile strength.

Numerous strategies have been employed over the years attempting to improve ligament healing after injury or surgery. One of the most important advances in the treatment of ligament injuries has come from the understanding that controlled early resumption of activity can stimulate repair and restoration of function, and that treatment of ligament injuries with prolonged rest may delay recovery and adversely affect the tissue repair. Likewise, although steroid injections and nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to be effective in decreasing inflammation and pain of ligament injuries for up to six to eight weeks, the histological, biochemical, and biomechanical properties of ligament healing are inhibited. For this reason their use is cautioned in athletes who have ligament injuries. As such, NSAIDs are no longer recommended for chronic soft tissue (ligament) injuries, and for acute ligament injuries should be used for the shortest period of time, if used at all. Regenerative medicine techniques, such as Prolotherapy, have been shown in case series and clinical studies, to resolve ligament injuries of the spine and peripheral joints. More Prolotherapy studies in more controlled settings with larger numbers would further prove the effectiveness of this therapy.


**Keywords:** corticosteroids, exercise, immobility, ligament healing, ligament injury, NSAIDs, Prolotherapy.

**Introduction**

Ligaments are dense bands of fibrous connective tissue that serve to join two or more bones of the musculoskeletal system. Ligaments cross joints with wide ranges of motion as well as joints with little motion and may appear as long sheets of opaque tissue or short thickened strips in joint capsules. Although they vary in size, shape, orientation, and location, ligaments primarily function to provide stabilization of joints both at rest and during normal range of motion. While ligaments were once thought to be inactive structures, they are, in fact, complex tissues that respond to many local and systemic influences.

Ligament injuries are among the most common causes of musculoskeletal joint pain and disability encountered in primary practice today. Ligament injuries create disruptions in the balance between joint mobility and joint stability, which can lead to abnormal transmission of forces throughout the joint, resulting in damage to other structures in and around the joint. Knees, hips, shoulders, ankles, elbows, and wrists are among some of the joints most commonly affected by ligament injuries. While there is a vast body of knowledge available regarding the structure and function of normal ligaments, understanding the structure and function of injured ligaments becomes more complicated due to the variability and unpredictable nature of ligament healing. This may be due to the dramatic physiological and structural changes that ligaments sustain as a result of injury, as well as the complex and dynamic cellular processes that occur during healing. These processes create alterations in the biology and biomechanics of the injured ligament, leading to inadequate healing and tissue formation that is inferior to the tissue it replaces. The incomplete healing and persisting differences in the new ligament tissue result in ligament laxity, which predisposes the joint to further injury. Ligament injury and subsequent laxity cause joint instability, which leads to chronic pain, diminished function, and ultimately
osteoarthritis of the affected joint.\textsuperscript{3-5} Despite the numerous strategies that have been employed over the years attempting to improve ligament healing after injury, osteoarthritis, the long-term consequence of ligament injury, continues to be the most common joint disorder in the world.\textsuperscript{6} Therefore, understanding the complex cellular processes that occur as a result of ligament injury, along with determining and implementing strategies that optimize ligament restoration are necessary to reduce the enormous individual and public health impacts of osteoarthritis.

**Ligament Structure and Function**

Ligaments are primarily composed of water, collagen, and various amino acids. Approximately two thirds of total ligament mass can be attributed to water and one third can be attributed to solids.\textsuperscript{1} Collagen represents approximately 75\% of the dry weight of ligaments, while the remaining 25\% contains proteoglycans, elastin, and other proteins and glycoproteins. Type I collagen accounts for nearly 85\% of the total collagen within ligaments and the remaining balance consists of types III, V, VI, XI, and XIV collagen.\textsuperscript{1,7} Microscopic studies of ligament tissues have shown that bundles of collagen fibers are composed of smaller fibrils arranged in a parallel fashion along the long axis of the ligament. The collagen fibers appear to have a characteristic, specially designed cross-linked formation, which contributes to the incredible strength of ligaments. Under microscope, the collagen bundles appear undulated or crimped along their length and it is believed that the crimping is present in relation to the loading capacity or tension applied to ligaments. With load-bearing, certain areas of the ligament uncrimp, which allows the ligament to elongate without sustaining structural damage.\textsuperscript{1,8} It appears that some fibers tighten or loosen depending on musculoskeletal positioning and applied forces, which supports the joint through various tensions and ranges of motion.

Fibroblasts, which produce and maintain the extracellular matrix, are located between the rows of collagen fibers. Recent studies suggest that fibroblast cells in normal ligaments may be capable of cell-to-cell communication allowing the coordination of cellular and metabolic processes throughout the tissue.\textsuperscript{1,9,10} Proteoglycans, also found in the extracellular matrix, store water and contribute to the viscoelastic properties of ligaments. These viscoelastic features allow ligaments to progressively lengthen when under tension and return to their original shape when the tension is removed. Ligaments attach to bones at specific sites on the bone called “insertions.” Both ligaments and their insertion sites can vary in configuration and their geometric shape appears to relate to the manner in which the fibers within the ligament are engaged as the joint moves. The direction of joint movement determines which fibers within a particular ligament are recruited for the performance of the specific movement. Ligaments are covered by a more vascular and cellular overlying layer called the epiligament, which is often indistinguishable from the actual ligament. The epiligament contains sensory and proprioceptive nerves with more nerves located closer to the boney ligament insertion sites.\textsuperscript{1,11,12} When ligaments are strained, the proprioceptive nerves initiate neurological feedback signals that activate muscle contraction around the joint, which allows the body to protect and stabilize the joint after injury.

Ligaments prevent excessive motion of joints by providing passive stabilization and guiding joints through normal range of motion under tensile load. In doing so, ligaments transfer force to and from the skeleton while dynamically distributing the loads applied to them in order to perform specific movement patterns.\textsuperscript{13} Ligaments also function to provide joint homeostasis through their viscoelastic properties that reflect the complex interactions between collagens, proteoglycans, water, and other proteins.\textsuperscript{1,14} The viscoelastic properties, along with the recruitment of crimped collagen, contribute to the mechanical behavior of the structure under loading conditions. When tension is applied, ligaments deform, or elongate, in a non-linear fashion through the recruitment of crimped collagen fibers. As the tension placed on the ligament increases, the collagen fibers progressively un-crimp, or elongate, until all fibers are nearly linear. (See Figure 1.) As the
fibers become increasingly linear, the ligament structure becomes increasingly stiff. Varying degrees of ligament stiffness are necessary for various loads and various ranges of joint motion. Ligaments can lose their ability to retain their original shape when stretched or elongated past a certain point for a prolonged period of time. When this occurs, the ligament becomes lax and unable to properly support the joint, leading to instability, pain, and eventual osteoarthritis of the joint. When an applied load causes all fibers to become nearly linear, the ligament continues to absorb energy until tensile failure or disruption of the tissue. Just as overstretched ligaments cause joint instability, ligament disruptions, or tears, will also create joint instability. In attempt to prevent overstretching and disruption, ligaments utilize their viscoelastic properties to exhibit both creep and relaxation behaviors. Creep and load relaxation behaviors help to prevent fatigue failure of the tissue when ligaments are loaded in tension. Creep is defined as the deformation, or elongation, of a ligament over time under a constant load or stress. Load relaxation refers to a decrease in stress of the tissue over time when the ligament is subjected to a constant elongation.15-17

**Figure 1. Ligament structural strength graph.** As the load is increased, more ligament fibers are recruited (straight lines), and the slack or creep in the fibers is removed until the entire ligament tears. The load at complete failure of the ligament represents its maximum structural strength.

**Ligament Response to Injury**

When ligaments are exposed to loading over an extended period of time, they increase in mass, stiffness, and load to failure.7 However, when ligaments are overloaded, or exposed to tensions greater than the structures can sustain, the tissue fails resulting in partial or complete ligament discontinuities. When these discontinuities, also known as disruptions or tears, occur, the body responds by attempting to heal the injury through a specialized sequence of overlapping, but distinct cellular events. These events are the same that occur as part of the body’s response to any soft tissue injury and can be categorized by three consecutive phases that occur over time: the acute inflammatory phase, the proliferative or regenerative/repair phase, and the tissue remodeling phase. The acute inflammatory phase begins within minutes of injury and continues over the next 48-72 hours. During this phase, blood collects at the site of injury and platelet cells interact with certain matrix components to change their shape and initiate clot formation. The platelet-rich fibrin clot releases growth factors that are necessary for healing and provides a platform on which many cellular events occur.

Several growth factors have been identified, each playing a specific role in the inflammatory process. Some of the numerous growth factors which have been identified include Platelet-Derived Growth Factor, Transforming Growth Factor-β, Vascular Endothelial Growth Factor, and Fibroblast Growth Factor. Platelet-Derived Growth Factor and Transforming Growth Factor-β attract immune system cells to the area and stimulate them to proliferate. Vascular Endothelial Growth Factor aids in new blood vessel formation, which increases vascularity in injured areas. Fibroblast Growth Factor promotes the growth of the cells involved in collagen and cartilage formation. When stimulated by growth factors, neutrophils, monocytes, and other immune cells migrate to the injured tissue to initiate matrix turnover by ingesting and removing debris and damaged cells during the inflammatory phase. The proliferative/repair phase begins when immune cells release various growth factors and cytokines, which initiate fibroblast proliferation to rebuild the ligament tissue matrix. The tissue formed initially appears as disorganized scar tissue with more blood vessels, fat cells, fibroblastic and inflammatory cells than normal ligament tissue.1, 18 Over the next several weeks, fibroblast cells deposit various types of collagen,
proteoglycans, other proteins and glycoproteins to the matrix. The collagen becomes aligned with the long axis of the ligament during this time, however, the newly formed type of collagen fibrils are abnormal and smaller in diameter than normal ligament tissue. After a few weeks, the proliferative phase merges into the remodeling phase in which collagen maturation occurs for months to years after the initial injury. With time, the tissue matrix starts to resemble normal ligament tissue, however, critical differences in matrix structure and function persist. (See Figure 2.) In fact, evidence suggests that the injured ligament structure is replaced with tissue that is grossly, histologically, biochemically, and biomechanically similar to scar tissue. As Frank et al. note, even fully remodeled scar tissue remains grossly, microscopically, and functionally different from normal tissues.

The remodeling phase of ligament repair can continue for months to years, during which time collagen and ligament matrix are continually overturned by processes of tissue synthesis and degradation. This provides ongoing opportunities for the ligament to adapt with functional improvement, or degrade and fail with applied loads. The persisting abnormalities present in the remodeled ligament matrix can have profound implications on joint biomechanics depending on the functional demands placed on the tissue. Because remodeled ligament tissue is morphologically and biomechanically inferior to normal ligament tissue, ligament laxity results, causing functional disability of the affected joint and predisposing other soft tissues in and around the joint to further damage. Some of the identifiable differences in remodeled matrix verses normal ligament matrix include altered proteoglycan and collagen types, failure of collagen crosslinks to mature, persistence of small collagen fibril diameters, altered cell connections, increased vascularity, abnormal innervation, increased cellularity and the incomplete resolution of matrix flaws. Research suggests that persisting collagen abnormalities may be the most critical to ligament tissue function, however, virtually all tissue components other than collagen likely play equally important direct and indirect roles in tissue function. Normal ligament tissue is primarily composed of type I collagen, which is responsible for the stiffness and strength of the tissue. After injury, fibroblasts primarily synthesize type III collagen and to a much lesser extent Type I collagen. The densely packed cross-linked formation of type I collagen fibrils in normal ligaments accounts for stability, strength, and stiffness of the ligament. The abnormal collagen cross-linking and smaller collagen fibril sizes of the repaired ligament create weaknesses in tissue strength and stiffness which remain for months to years after initial injury.

In addition, evidence suggest that remodeled collagen fibrils are not packed as densely as in normal ligaments and the remodeled tissue contains materials other than collagen, such as blood vessels, fat cells, and inflammatory cell pockets which contribute to weakness.

In order to understand ligament healing, many studies use the medial collateral ligaments (MCLs) of rabbits as experimental models. Studies on rabbit MCLs have shown that healing or remodeled MCLs are ultimately weaker, less stiff, and absorb less energy before failure than normal MCLs. Several studies have documented that conservatively treated injured MCLs typically regain only 40% to 80% of their structural stiffness and strength compared to normal MCLs. On the other hand, the viscoelastic characteristics of the injured MCL have a somewhat better recovery, as these properties return to within 10-20% of normal MCL behavior. This results in greater stress relaxation, which indicates that the ligament which sustained the injury maintains loads less efficiently than the normal ligament. Remodeled MCLs also exhibit inferior creep properties, elongating more than twice as much as normal MCLs, even at low tensions. The laxity of the healing MCL leads to mechanical instability of the knee joint, which alters the contact mechanics of the joint. When the knee or any joint is unstable, sliding between joint surfaces increases, and the efficiency of muscles surrounding the joint decreases.
This creates alterations in the load distribution of the joint, which disrupts the underlying cartilage and bone, causing wear and increasing shear, eventually leading to osteochondral degeneration or osteoarthritis.41

Animal studies have shown that different ligaments heal at different rates15, 42-47 and combined ligament injuries heal with inferior rate and quality than isolated injuries.15, 42, 43, 48-52 Most animal studies focus on the ACL and MCL of the knee joint and while these structures may heal at varying rates comparatively and among different animal species, the quality of the remodeled tissue remains inferior to that of normal ligaments.26, 30, 32, 35, 42, 54, 55-57 In fact, studies of healing ligaments have consistently revealed that following rupture, certain ligaments do not heal independently, while others do heal, but with inferior compositional properties compared to normal tissue.37, 48, 58, 59

It is not uncommon for individuals to experience more than one ligament injury during a single traumatic event. Rabbit models have demonstrated that combined ACL/ MCL injuries result in inferior structural and material properties of the healing MCL compared with those of the isolated MCL model.42, 43, 49-52 Some researchers believe that this may be related to the immobility of animals with painfully unstable knees or the excessive forces placed on the healing MCL tissue when there is damage to the ACL.15 As previously mentioned, while some ligaments heal spontaneously, be it with inadequate tissue configuration, other ligaments exhibit very poor intrinsic healing ability. This may be related to the specific properties of the particular ligament that was injured, the type of ligament injury (partial or full disruption), or interventions employed after ligament injury.

CURRENT STRATEGIES FOR OPTIMIZING LIGAMENT REPAIR

As discussed earlier, ligament healing is slow and often incomplete. Joint laxity caused by ligament injury improves slowly over a period of six weeks to a year. However, at six weeks to one year after injury, a large percentage of patients still have objective mechanical laxity and subjective joint instability.60, 61 In ligament injuries to the ankle, up to 31% exhibit a positive anterior drawer sign six months after injury. Additionally, feelings of instability affected 7% to 42% of participants up to one year after injury.61 Several strategies have been implemented over the years attempting to restore the properties of the injured ligament to pre-injury status including rest, mobilization, non-steroidal anti-inflammatory drugs, corticosteroid injections, and Prolotherapy, among others. While each of these therapies can help with the subjective symptom of pain following ligament injury, they do not all contribute to the cellular repair and healing of ligament tissue. In fact, some of these therapies have been shown to be detrimental to the ligament healing process by suppressing and inhibiting certain cellular processes that are required for ligament tissue repair. Other therapies have been shown to contribute to healing through their stimulation of certain cellular processes involved in the regeneration of ligament tissue.

IMMobilization and Rest

Injured limbs are traditionally rested by splinting or casting. While immobilization of the affected joint has long been prescribed following ligament injury, it has since been discovered that healing ligaments are dramatically affected by the presence or absence of joint motion. The theory is that rest or immobilization will prevent further tissue damage in the joint by limiting movement, thereby decreasing pain and swelling. It is also thought that rest may improve recovery time, decrease functional problems, and reduce long-term pain. However, immobilizing a joint with a ligament injury can cause detrimental side effects, such as synovial adhesions,62 increasing collagen degradation with decreasing collagen synthesis,2 and a greater percentage of disorganized collagen fibrils.34, 38 Despite this evidence, rest and the RICE (Rest, Ice, Compression, Elevation) protocol continue to be commonly prescribed as the first line treatment for ligament, tendon, and other soft tissue injuries. Immobilization causes ligament physiology to progressively switch from an anabolic to a more catabolic state. One study that measured collagen fiber bundle diameters in the normal and repaired ligaments of dogs, clearly documented that increased or decreased levels of exercise will greatly influence the strength of ligaments. The study showed that the amount of exercise performed by the animal was directly correlated with the number of collagen fibrils, their arrangement, and their average thickness within the ligament.63 Decreased loading of ligament tissue alters matrix turnover so that with time, matrix degradation exceeds formation and the newly synthesized matrix is less well organized, and the tissue stiffness and strength declines. Prolonged limb immobilization decreases the glycosaminoglycan and water content and the degree of orientation of the matrix collagen fibrils within the ligaments. Ultimately this causes...
the ligaments to have less mass and strength. (See Figure 3.) Decreased ligament loading has a profound effect on decreasing the strength of the ligament-bone junction (fibro-osseous junction) because immobilization causes subperiosteal osteoclasts to resorb much of the bony inserts of the ligaments. This causes a substantial decline in the tensile strength at the bone-ligament interface.\textsuperscript{64} According to the most recent systematic reviews of research on soft tissue injuries in humans, there appears to be no controlled study that favors immobilization for the treatment of ligament injuries.\textsuperscript{65, 66} Kerkhoff et al., in a systematic review of research on ankle ligament injuries in 2,184 adults, functional treatment involving motion of the affected joint was a statistically significant strategy for healing the injured ligament, compared with immobilization. Patients who treated their ligament injuries with motion, versus immobilization, were able to return to work quicker, return to sport quicker, and demonstrated less objective instability as tested by stress X-ray.\textsuperscript{65} In another systematic review, early mobilization was found to decrease pain, swelling and stiffness, and allowed a greater preservation of range of motion and return to work.\textsuperscript{66} Mobilization for the treatment of soft tissue damage has also been found to decrease muscle atrophy, disuse osteoporosis, adhesions, and joint stiffness following injury.\textsuperscript{73-79} Overall, carefully controlled exercise plans promote healing of injured ligaments.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs have been a mainstay treatment of ligament injuries for many years, especially for acute sports injuries, but new research has shown that NSAIDs are only mildly effective in relieving the symptoms of most muscle, ligament, and tendon injuries and are potentially deleterious to soft tissue healing.\textsuperscript{80, 81} There are reasons to expect that NSAIDs might have an adverse effect on healing as prostaglandin-induced inflammation is an early sequel of injury and results in the recruitment of cells into the area of injury for the removal of necrotic debris and the initiation of the healing process. NSAIDs specifically block the cyclooxygenase enzymes which catalyze the conversion of arachidonic acid to prostaglandins which play a significant role in ligament healing.\textsuperscript{82} Furthermore, the analgesic effect of NSAIDs may permit patients to ignore early symptoms of ligament injury, further damaging ligaments, and thus, delay definitive healing. One study looked at the use of Piroxicam in the treatment of acute ankle sprains in the Australian military. While the recruits were able to resume training more rapidly, in the long-term, an increase in ankle instability was evidenced by a positive anterior drawer sign in the Piroxicam group.\textsuperscript{83} Multiple studies on the use of NSAIDs of the cyclooxygenase-2 (COX-2) inhibitor class have shown these medications inhibit ligament healing, leading to impaired mechanical strength.\textsuperscript{84-86} Their use is cautioned in athletes who have ligament injuries. As such, NSAIDs are no longer recommended for chronic soft tissue (ligament) injuries, and for acute ligament injuries should be used for the shortest period of time, if used at all.\textsuperscript{87-89}

Mobilization and Exercise

Early controlled resumption of activity after injury, including repetitive loading on injured soft tissue structures such as ligaments and tendons has profoundly beneficial effects including enhanced cellular synthetic and proliferative effects, increased strength, size, matrix organization and collagen content of ligaments and tendons.\textsuperscript{15, 42-44, 68} Mobilization has been shown to benefit the injured ligament by causing it to form more connective tissue, resulting in tissue that is stronger and stiffer than an immobilized counterpart.\textsuperscript{15, 42-44, 68} Motion causes an increase of blood flow to the affected joint, providing the damaged ligament tissue with nutrients and metabolites necessary for tissue repair and healing. Under loading conditions, cells within the ligament detect tissue strains and respond by modifying the tissue. Results of numerous animal studies have shown that the strength of repaired ligaments is greater in animals which were allowed to continue to exercise, rather than to rest.\textsuperscript{69-72} According to...
Corticosteroid injections have long been used to treat musculoskeletal disorders including ligament injuries. Although steroid injections have been shown to be effective in decreasing inflammation and pain of ligament injuries for up to six to eight weeks, the histological, biochemical, and biomechanical properties of ligament healing are inhibited. Their anti-inflammatory actions stem from their ability to prevent lysosomal enzyme release and to inhibit the accumulation of neutrophils and other inflammatory cells and the synthesis of inflammatory mediators, including cytokines, at the injury site.

Corticosteroid injections into injured ligaments have an adverse effect on healing. Corticosteroid injections into ligaments and tendons have been known to inhibit fibroblast function and thus collagen synthesis even causing collagen necrosis at the injection site. The steroid-injected ligaments have smaller cross sectional areas and are weaker with decreased peak tensile strength and decreased load (energy) to ligament failure. Because of these inhibitory effects on ligament healing, several extensive reviews have cautioned against their use to treat ligament injuries especially in athletes.

Prolotherapy has emerged as an injection therapy treatment option for musculoskeletal and arthritic pain. It involves the injection of a small amount of various proliferant solutions (such as hypertonic dextrose, sodium morrhuate, platelet rich plasma) at the painful entheses of ligaments and tendons, as well as trigger points and adjacent joint spaces to induce healing of the injured structures. Histologic studies of ligaments and tendons following Prolotherapy injections have shown an enhanced inflammatory healing reaction involving fibroblastic and capillary proliferation, along with growth factor stimulation. Growth factors, including basic fibroblast growth factor and platelet-derived growth factor, mediate the biological processes necessary for soft tissue repair in muscles, tendons, and ligaments after acute, traumatic or overuse injury. Prolotherapy injection therapy is known by various names including proliferative therapy, regenerative injection therapy and platelet rich plasma. Animal research has documented that Prolotherapy-injected ligaments have an increased ligament mass, extracellular matrix, thickness and junction strength with bone.

Prolotherapy is given to the articular ligaments of the entire spine, pelvis and peripheral joints to tighten unstable joints. Case series have documented the efficacy of Prolotherapy for ligament injuries of the sacroiliac joint, low back, neck, shoulder, elbow, knee, temporomandibular joint, and other articulations.

Ligament injuries are among the most common causes of musculoskeletal joint pain and disability encountered in primary practice today. Ligament injuries create disruptions in the balance between joint mobility and joint stability, causing abnormal force transmission throughout the joint resulting in damage to other structures in and around the joint. Osteoarthritis, the long-term consequence of non-healed ligament injury, continues to be the most common joint disorder in the world.

Ligaments heal through a distinct sequence of cellular events that occur through three consecutive phases: the acute inflammatory phase, the proliferative or regenerative phase, and the tissue remodeling phase. Ligament healing is often slow and incomplete. Joint laxity caused by ligament injury improves slowly over a period of six week to a year. However, at six weeks to one year after injury, a large percentage of patients still possess objective mechanical laxity and subjective joint instability. In ligament injuries to the ankle, up to 31% who experience positive anterior drawer signs six months after surgery. Additionally, feelings of instability affected 7% to 42% of participants up to one year after injury.

Numerous strategies have been employed over the year attempting to improve ligament healing after injury or surgery. One of the most important advances in the treatment of ligament injuries has come from the understanding that controlled early resumption of activity can stimulate repair and restoration of function, and that treatment of ligament injuries with prolonged rest may delay recovery and adversely affect the tissue to repair. Likewise, although steroid injections and nonsteroidal anti-inflammatory medications have been shown to be effective in decreasing inflammation and pain of ligament injuries for up to six to eight weeks, the histological, biochemical, and biomechanical properties of ligament healing are inhibited. For this reason their use is cautioned in athletes who have ligament injuries. As
such, NSAIDs are no longer recommended for chronic soft tissue (ligament) injuries, and for acute ligament injuries should be used for the shortest period of time, if used at all. Regenerative medicine techniques, such as Prolotherapy, have shown success in case series involving ligament injuries of the spine and peripheral joints, but studies in more controlled settings and with large numbers are needed in the future.

REFERENCES

LIGAMENT INJURY AND HEALING: AN OVERVIEW OF CURRENT CLINICAL CONCEPTS


LIGAMENT INJURY AND HEALING: AN OVERVIEW OF CURRENT CLINICAL CONCEPTS


The Case for Prolotherapy – The Closing Argument

Julie R. Gunnigle, JD

Chronic pain can dominate a patient’s life. From the physiological disability of being unable to perform daily activities, to the financial cost of missed work and expensive procedures, the pain can quickly spread from the body to the pocketbook. Left unresolved, pain can dominate every aspect of life, robbing patients of their ability to care for themselves or provide a decent life for their family. When it comes to pain, modern medicine is sometimes more concerned with pain management than the treatment of the pain’s underlying causes.

In this issue, the practitioners and researchers on the front lines of the fight against chronic pain outlined the evidence for Prolotherapy. In this issue, you read the evidence that shows that Prolotherapy is an effective tool to not only manage pain, but to resolve it. The case for Prolotherapy is supported by the idea that medicine should be evidence-based. Put simply, a procedure should be supported by literature, and it should be cost effective compared to its benefits. In the case for Prolotherapy, the verdict is that it is effective at reducing pain, affordable, and low risk. In short: Prolotherapy is evidence-based medicine.

PROLOTHERAPY AS A FIRST RESORT

Many patients discover Prolotherapy after experiencing untold numbers of costly and ineffective treatments, eventually being told that there are no other options for treating their joint pain. Imagine for just a moment, if all of that time, energy, and money could be saved by making Prolotherapy a treatment of first resort. Imagine a world where skilled doctors perform Prolotherapy in lieu of other costly, invasive, and ineffective procedures. This is not to say that Prolotherapy is a cure-all, but if even a portion of joint replacements and other surgeries could be prevented, the cost savings would be staggering. More importantly, the patient’s quality of life would be dramatically improved.

The U.S. Preventative Services Task Force (USPSTF) ranks a procedure based on the quality of the evidence to support it, and the benefit of the procedure weighed against its risks. The evidence presented in this issue qualifies as both A and B level evidence, that is, gold standard evidence in support of Prolotherapy. Moreover, when a procedure is supported by A and B level evidence, USPSTF guidelines provide that the treatment be offered to eligible patients. This means that patients should be offered Prolotherapy as a primary treatment option, and not merely as a last-ditch effort when all other procedures have failed. By postponing healing, we are wasting time and money and failing the patient.

THE VERDICT FOR PROLOTHERAPY

In this issue you have read just some of the evidence that Prolotherapy is an effective treatment for a wide range of injuries caused by injured ligaments and other soft tissue structures. The evidence shows that Prolotherapy has a role in preventing arthritis and restoring joints. It is an outpatient, low-risk procedure that allows the patient to resume normal activities nearly instantaneously. It is well-established, non-experimental, evidence-based medicine. So why is Prolotherapy not the most practiced treatment for musculoskeletal injuries?

The irony is very real. Insurance companies routinely cover procedures that are not supported by evidence and, in fact, have been shown to be destructive. Cortisone, for example, has been shown to not only have no pain relieving effects three weeks after treatment, some research notes that cortisone accelerates the development of degenerative arthritis in the treated joint. Nevertheless, if research leads, insurance companies will hopefully follow. If doctors offer Prolotherapy appropriately, patients will see the value in this treatment. As patients experience the benefits and these results continue to be published, they will demand the treatment even more.

A patient’s path to recovery is beset with obstacles. From choosing which procedures to undergo, to arguing with the insurance company, navigating modern medicine is no easy task, particularly while coping with pain and attempting to heal. Prolotherapy is evidence-based therapy. Not only should it be covered by insurance companies as one of many other pain-reducing therapies, evidence validates its use early, rather than late, as a pain-reducing therapy. By offering evidence-based medicine, patients are assured that they are receiving the best care possible. Patients deserve nothing less.
Organizations Who Support, Teach, and Promote Prolotherapy

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