

Journal of Prolotherapy International Medical Editorial Board Consensus Statement on the Use of Prolotherapy for Musculoskeletal Pain

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PURPOSE

The purpose of this paper is to explicate the theory, scientific evidence, methods, and applications for the procedure of Prolotherapy in the treatment of musculoskeletal pain. The example of knee osteoarthritis is used as an example as to why Prolotherapy should be used compared to other invasive therapies.

GOAL OF PROLOTHERAPY

The goal of Prolotherapy is the resolution of pain and dysfunction and the optimizing of health by the individual regaining the ability to do activities of daily living and exercise. Once this is achieved, the individual will potentially no longer need medical care for pain and disability. When this goal is not possible, Prolotherapy aims to help improve one's quality of life by diminishing pain and improving mobility, activities of daily living, and/or exercise.

INTRODUCTION

Prolotherapy as defined in *Webster's Third New International Dictionary* is "the rehabilitation of an incompetent structure, such as a ligament or tendon, by the induced proliferation of new cells."¹ Most Prolotherapy involves the injection of solutions at the fibro-osseous junctions or entheses, the point at which tendons and ligaments attach to the bone, to induce an inflammatory reaction.² This induction of the inflammatory healing cascade initiates the regeneration and repair of the injured tissues in and around the joint, stabilizing and eliminating the sources of most musculoskeletal pain.* Prolotherapy can be an ideal treatment for chronic musculoskeletal pain caused by sprained, injured or torn tendons and/or ligaments in such conditions as joint instability, ligament laxity and tendinopathy including

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.³ 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.⁴ 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.^{5, 6, 7} 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.⁸ Dr. Gedney published results of this injection therapy to treat the ligamentous pathology involving the knee and lower back including the sacroiliac joint⁹; the annular ligaments of vertebral discs for degenerative disc disease^{10, 11}; as well as papers on the use of this type of injection therapy for any hypermobile joint in the body.^{12, 13} 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 Synlasol (sodium psyllate), 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.^{14, 15} 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 Synlasol 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.”¹⁶ 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.¹⁶⁻¹⁸ 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.^{19, 20}

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.²¹ 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.²² Dr. Hemwall eventually found that a simple solution of hypertonic dextrose could be effectively used as the proliferant in the Prolotherapy injections.^{21, 22}

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 Lyftogt 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).²³ Experimentally cultured stem cells of both bone marrow and adipose have been used successfully to repair various defects including cartilage.²⁴⁻²⁸ However FDA regulations prohibit the culture expansion or manipulation of cells in clinical use.²⁹ 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.^{30, 31} 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.^{32, 33} There are currently 15 million individuals who are limited from one daily activity by musculoskeletal pain,³⁴ and that number is estimated to reach 67 million people by 2030.³⁵ Additional studies have shown that nearly all chronic pain patients have a substantially reduced health-related quality of life,³⁶ with 42% unable to work due to pain and 63% unable to engage in routine activities of daily living.³⁷ The number of knee/hip replacements due to musculoskeletal injuries increased from 290,700 to 383,500 from 1997 to 2005,³⁸ and by 2030, the number of these surgical procedures is estimated to increase annually to 572,000 and 3.48 million respectively.³⁹ 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.⁴⁰ The anticipated medical costs are expected to double over the next fifteen years.⁴¹

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.⁴² 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,⁴³ because they constantly absorb the brunt force of physical activity, they have a poor blood supply,^{44, 45} 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.^{46, 47} Studies have shown that unresolved ligament tears and sprains can completely alter joint mechanics,^{48, 49} while ligament laxity and its associated joint instability has been indicated to be the leading cause of spinal and joint degeneration.⁵⁰⁻⁵² As stated by Dr. George Hackett, "A joint is only as strong as its weakest ligament."¹⁶

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^{53, 54} by inducing repair via the stimulation of growth factors via the inflammatory healing cascade.⁵⁵⁻⁵⁹ An increase of glucose concentration (dextrose) causes an increase in cell protein synthesis, DNA synthesis, cell volume, and proliferation.⁶⁰⁻⁶³ Prolotherapy utilizes the effects of dextrose concentration, as well as other proliferants to stimulate inflammation,⁶⁴ which in turn, stimulates ligament size and mass,⁶⁵ tendon hypertrophy,⁶⁶⁻⁶⁸ extracellular matrix,⁶⁶⁻⁷⁰ fibroblastic proliferation,^{66, 68-70} increased ligament-bone junction strength and repair of articular cartilage defects.^{71, 72} The increase of extra-cellular glucose concentration from Prolotherapy injections causes cells to proliferate and produce platelet-derived growth factor,⁷³ transforming growth factor B,^{74, 75} epidermal growth factor,⁷⁶ fibroblast growth factor,⁷⁷ insulin-like growth factor,⁷⁸ and connective tissue growth factor.⁷⁹ These growth factors are pertinent to the repair, health, and growth of tendons, ligaments, and other soft tissue.⁷⁷⁻⁸¹ The injected dextrose has been shown to induce healing over a wide range of percent concentrations, protect injured cartilage^{71, 72, 82} and cause biological effects by inflammatory and non-inflammatory mechanisms.^{66, 67, 71, 72, 82-84} Newer theories and techniques of Prolotherapy have provided additional explanations as to the mechanisms of healing by Prolotherapy, including the resolution of neurogenic inflammation.^{85, 86}

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-HEM WALL PROLOTHERAPY (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.⁸⁷ This technique typically utilizes an inflammatory concentration of hypertonic dextrose of 12.5 to 25%.^{87, 88} 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 PROLOTHERAPY

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.⁸⁵ The injections are given just underneath the skin at the location of sensitized peptidergic nerves. These nerves contain transient receptor potential vanilloid 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.^{85, 88-90} Neurogenic inflammation was first termed “inflammatory neuritis” by Dr. George Hackett in the 1950s.⁹¹⁻⁹³ 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.^{86, 89} 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%.⁹⁴ 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.^{95, 96} Various case series have been published documenting the analgesic effect of ozone in osteoarthritis.⁹⁷⁻¹⁰⁰ Double-blind randomized-controlled studies have also documented the therapeutic effects of Prolozone in the treatment of low back pain with and without sciatica.^{101, 102} 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.¹⁰³⁻¹⁰⁵ 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.^{106, 107} 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.^{106, 108, 109} Activated platelets also secrete stromal cell derived factor 1 alpha (SDF-1a) which supports primary adhesion and migration of mesenchymal stem/stromal cells.¹¹⁰ 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.)¹¹¹ 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,¹¹² and which increases the important bioactive protein load (growth factors) in a direct correlative fashion.¹¹³ Cell ratios in average circulating whole blood contain only 6% platelets. In true high-density PRP preparations, the concentration achieved is 94%.¹¹⁴ 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.”¹¹⁵

STEM CELL PROLOTHERAPY

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.¹¹⁶ 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).¹¹⁷ 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.^{118, 119} 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.^{120, 121} 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.^{122, 123} 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.¹²⁴ In 2008, Centeno et al. reported significant knee cartilage growth and symptom improvement in a human case report using culture expanded autologous MSCs from bone marrow.¹²⁵ In 2011, Albano and Alexander used autologous adipose cells as a living bioscaffold and stem cell source to repair a torn patellar tendon.¹²⁶ The number of treatments varies depending on condition and prior treatment regime, with clinical protocols in the recent medical literature.^{127, 128} Stem cell Prolotherapy is typically given every month to few months.*

*The various nomenclature for the specific types of heterogeneous cells in these injections includes stromal or undifferentiated stromal cells.

Lipoaspirate Prolotherapy (ADSC)

While bone marrow has historically been used as a source of MSCs, adipose (fat)-derived stem/stromal cells (AD-SCs) have been shown to have nearly identical fibroblast-like morphology and colonization (CFU-F), immune phenotype, successful rate of isolation, and differentiation capabilities.¹²⁹⁻¹³¹ 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.¹³²⁻¹³⁴ AD-SCs 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,¹³⁵ tendon,¹³⁶⁻¹³⁸ cartilage,¹³⁹⁻¹⁴¹ disc,¹⁴² muscle,¹⁴³⁻¹⁴⁵ nerve tissue,¹⁴⁶⁻¹⁴⁸ bone,¹⁴⁹⁻¹⁵¹ hematopoietic-supporting stroma,¹⁵²⁻¹⁵⁴ to actively participate in tissue homeostasis, regeneration, and wound healing.¹⁵⁵⁻¹⁵⁷ 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.¹⁵⁸⁻¹⁶⁰ Human studies have documented enhanced treatment outcomes for nonunion fractures, avascular necrosis (osteonecrosis) and spinal fusions with the utilization of BMSCs.¹⁶¹⁻¹⁶⁴ 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.^{158, 165-167} Initial research found that using whole bone marrow increased fusion rates in nonunion fractures 28%, but with centrifuged marrow, healing increased to 70%.¹⁵⁸ Others have documented the facilitation of healing with increased BMSC’s counts.¹⁶¹⁻¹⁶³ Cell counts in the literature for concentrated marrow have ranged for 16.4×10^6 cells/ml to as high as 2.2×10^9 cells/ml in successful fusions or healings in orthopedic procedures.^{160, 161} Numerous publications have demonstrated the benefits of

concentrated bone marrow for the regeneration of various structures of the skeletal system including bone, cartilage, and connective tissues.¹⁶⁸⁻¹⁷⁶ 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.¹⁷⁷⁻¹⁸² 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.¹⁸³⁻¹⁸⁷ Typically bone marrow Prolotherapy is given every four to eight weeks.

COMMON SIGNS AND SYMPTOMS AS POSSIBLE INDICATIONS FOR PROLOTHERAPY:

- 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 PROLOTHERAPY:

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 PROLOTHERAPY:

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 fingers¹⁸⁸⁻²⁰³
- Degenerative spinal disease including spondylosis, spondylolisthesis and degenerative disc disease²⁰⁴⁻²⁰⁹
- Osteochondral defects²¹⁰⁻²¹⁵

Joint Instability

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

- Ligament tears and injury²¹⁶⁻²²⁰
- Labral tears and degeneration²²¹
- Meniscus tears and degeneration^{222, 223}
- Congenital conditions such as joint hypermobility syndrome and Ehlers-Danlos syndrome²²⁴

Tendinopathy

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

- Tendinopathy²²⁵⁻²³¹
- Tendinosis²³²⁻²³⁵
- Tendinitis²³⁶⁻²⁴⁰
- Grade one and two tears (partial tears)²⁴¹⁻²⁴²
- Enthesopathies including osteitis pubis and medial tibial stress syndrome²⁴³⁻²⁴⁵
- Muscle origin pain and tears²⁴⁶⁻²⁴⁸

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.^{249, 250}

OTHER MUSCULOSKELETAL CONDITIONS

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

- Post-surgical Pain syndrome^{251, 252}
- Myofascial Pain syndrome²⁵³⁻²⁵⁶

- Fibromyalgia²⁵⁷
- Complex Regional Pain syndrome²⁵⁸
- Chronic headaches²⁵⁹⁻²⁶²
- Radiculopathy^{263, 264}
- Autonomic symptoms, including Barré-Lieou syndrome²⁶⁵⁻²⁶⁸
- Apophyseal growth plate injuries, including Osgood-Schlatter disease^{87, 394}
- Other²⁶⁹⁻²⁷⁸

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

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

- Degenerative arthritis (degenerative joint disease)^{93, 109, 188, 189, 194, 211, 212, 221, 222}
- Degenerative spinal arthritis (spondylosis and degenerative disc disease)^{10, 11, 17, 277, 282, 283}
- Tendon or ligament tear^{114, 241, 242, 284}

PROLOTHERAPY TO ENHANCE SURGICAL OUTCOMES

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

- Tendon repairs^{114, 241, 285, 286, 287}

- Fusion^{288, 289}
- Ligament repairs²⁹⁰⁻²⁹²
- Bone fractures and other lesions^{27, 28, 293, 294, 295}
- Osteochondral defects^{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.^{300, 301}

OA is the most common form of arthritis in the world.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.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.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.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.³⁰⁶ Others have confirmed that there is no evidence that intraarticular corticosteroids have any long lasting beneficial effects,³⁰⁷⁻³⁰⁹ while some authors note that intraarticular corticosteroids actually accelerate the arthritic process.³¹⁰⁻³¹³

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.^{314, 315} 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.^{316, 317} 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).^{318, 319}

There is minimal to no evidence that HA injections have any disease modifying effects.³²⁰ There is little evidence that one HA preparation has any distinct pain-relieving effect over another.^{321, 322} 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."³²³

ARTHROSCOPIC DEBRIDEMENT OR JOINT LAVAGE HAVE NO BENEFIT FOR KNEE OSTEOARTHRITIS

Arthroscopy is the most commonly performed type of orthopedic surgery, and the knee is by far the most common joint on which it is performed. Osteoarthritis of the knee being the main indication for the procedure.³²⁴ Numerous clinical trials including multiple randomized controlled trials comparing arthroscopic debridement to sham surgery and

joint lavage, found gold standard evidence that arthroscopic debridement has no benefit for undiscriminated knee osteoarthritis.³²⁵⁻³²⁷ Numerous scientific studies on joint lavage, likewise concluded that joint lavage does not result in a relevant benefit for patients with knee osteoarthritis in terms of pain relief or improvement of function.³²⁸⁻³³⁰ One study published in the prestigious *New England Journal of Medicine* concluded, "This study provides strong evidence that arthroscopic lavage with or without debridement is not better than a placebo procedure in improving knee pain and function. Indeed, at some points during follow-up objective function was significantly worse in the debridement group than in the placebo...the billions of dollars spent on such procedures annually might be put to better use."³²⁶ The U.S. government agency for healthcare research and quality, as well as the American College of Rheumatology and the American Academy of Orthopedic Surgeons have come out against arthroscopic debridement or joint lavage for knee osteoarthritis. All of them noting that there is no evidence that arthroscopic debridement and joint lavage cures or arrests knee osteoarthritis and does not improve joint function or pain.³³¹⁻³³⁴

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.³³⁵⁻³³⁹ Multiple articles have confirmed that significant rates of cartilage loss are seen in patients post-partial or complete meniscectomy compared to healthy controls.^{340, 341} Long-term results following these procedures reveal a high incidence of poor

results, degenerative arthritis and ligament laxity.^{342, 343} Multiple studies have confirmed that the removal of meniscus tissue from the knee increases joint pressure and instability, leading to an acceleration of the degeneration process.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.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.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).³⁶⁵⁻³⁶⁹ This includes stimulating the repair of the anterior cruciate ligament resulting in increased knee stability.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.^{373, 374} Case series in animals

and humans have documented improved radiographs and articular cartilage regeneration with Prolotherapy.³⁷⁵⁻³⁸⁰ Other studies using Prolotherapy have confirmed that Prolotherapy reduces the need for knee surgeries including meniscectomy and total joint replacement.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.³⁸⁴⁻³⁸⁷ There is scientific data proving that NSAIDs have the propensity to accelerate articular cartilage deterioration in osteoarthritis.³⁸⁸ 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

1. Babcock, P. Webster's Third International Dictionary. Springfield, MA: G. & C. Merriam Co; 1971:1815.
2. Hauser R, et al. *Prolo Your Pain Away! Third Edition*. Oak Park, IL: Beulah Land Press; 2007.
3. Chadwick J. *Hippocratic Writings*. 2nd ed. New York, NY: Penguin Book Publishing; 1978.
4. Hoch G. *Injection Treatment of Hydrocele as in Sclerosing Therapy, the Injection Treatment of Hernia, Hydrocele, Varicose Veins and Hemorrhoids*. Yeomens (ed.). London: Bailliere, Tindall & Cox; 1939.
5. Warren J. *Hernia-Strangulated and Reducible with Cure by Subcutaneous Injection*. Boston, MA: Charles N. Thomas; 1881.
6. Van Itallie P. No man invented the hypodermic syringe. *Pulse Pharmacy*. 1965;19:1.
7. Van Itallie P. The rugged beginnings of injection therapy. *Pulse Pharmacy*. 1965;19:1.
8. Gedney E. Special technique hypermobile joint: a preliminary report. *Osteopathic Profession*. June 1937;9:30-31.
9. Gedney E. The hypermobile joint: further reports on the injection method. Read before *Osteopathic Clinical Society of Pennsylvania*, February 13, 1938.
10. Gedney E. Disc Syndrome. *Osteopathic Profession*. September 1951;11-15,38-46.
11. Gedney E. Use of sclerosing solution may change therapy in vertebral disc problems. *Osteopathic Profession*. April 1952; 11-13,34,38-39.
12. Gedney E. Technique for sclerotherapy in the management of hypermobile sacroiliac. *Osteopathic Profession*. August 1952; 16-19,37-38.
13. Gedney E. Progress report on the use of sclerosing solutions in low back syndromes. *Osteopathic Professions*. August 1954; 18-21,40-44.
14. Schultz L. A treatment of subluxation of the temporomandibular joint. *JAMA*. 1937;109:1032-1035.
15. Schultz L. Twenty years' experience in treating hypermobility of the temporomandibular joints. *American Journal of Surgery*. Vol. 92, December 1956.
16. Hackett G. *Joint Ligament Relaxation Treated by Fibro-Osseous Proliferation*. First Edition. Charles C. Thomas, publisher, 1956.
17. Hackett G. Joint stabilization: an experimental, histological study with comments on the clinical application in ligament proliferation. *American Journal of Surgery*. 1955;89:968-973.

18. Hackett G. Back pain following trauma and disease – Prolotherapy. *Military Medicine*. 1961;126:517-525.
19. Hackett G. Referred pain and sciatica in diagnosis of low back disability. *JAMA*. 1957;163:183-185.
20. Hackett G. Referred pain from low back ligament disability. *AMA Archives of Surgery*. 73:878-883, November 1956.
21. Hauser R, et al. *Prolo Your Pain Away! Third Ed.* Oak Park, IL,; Beulah Land Press; 2007;30-42.
22. Hackett Hemwall Foundation. www.hacketthemwall.org.
23. Alderman D, et al. Stem cell Prolotherapy in regenerative medicine: background, theory and protocols. *Journal of Prolotherapy*. 2011;3(3):689-708.
24. Hechtman K. Platelet-rich plasma injection reduces pain in patients with recalcitrant epicondylitis. *Orthopaedics*. 2011;34:92-99.
25. Kuroda R, et al. Treatment of a full-thickness articular cartilage defect in the femoral condyle of an athlete with autologous bone-marrow stromal cells. *Osteoarthritis and Cartilage*. 2006;15:226-231.
26. Chang T, et al. Repair of a large full-thickness articular cartilage defects by transplantation of autologous uncultured bone-marrow-derived mononuclear cells. *Journal of Orthopaedic Research*. 2008;18-26.
27. Weibrich G. Effect of platelet concentration in platelet rich plasma on peri-implant bone regeneration. *Bone*. 2004;34:665-671.
28. Fleming J, et al. Bone cells and matrices in orthopedic tissue engineering. *Orthopaedic Clinics of North America*. 2000;31:357-274.
29. U.S. Food and Drug Administration, Draft Guidance for Industry: Cell Selection Devices for Point of care Production of Minimally Manipulated Autologous Peripheral Blood Stem Cells (PBSCs). Available at: <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm074018.htm>.
30. Alexander R. Autologous fat grafts as mesenchymal stromal stem cell source for use in Prolotherapy: a simple technique to acquire lipoaspirants. *Journal of Prolotherapy*. 2011;3(3):680-688.
31. Alderman D, et al. Advances in regenerative medicine: high-density platelet-rich plasma and stem cell Prolotherapy for musculoskeletal pain. *Practical Pain Management*. October 2011, p.58.
32. Croft P, et al. The prevalence of chronic widespread pain in the general population. *Journal of Rheumatology*. 1993;20:710-713.
33. Sternbach R. Survey of pain in the United States: the Nuprin pain report. *Clinical Journal of Pain*. 1986;2:49-53.
34. Woolf A. Burden of major musculoskeletal conditions. *Bulletin of the World Health Organization*. 2003;81:646-656.
35. Hottman J. Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation-United States, 2003-2005. *Morbidity and Mortality Weekly Report*. 2006;55:1089-1092.
36. Turk D, et al. Toward an empirically derived taxonomy of chronic pain patients: integration of psychological assessment data. *Journal of Consulting and Clinical Psychology*. 1988;56:233-238.
37. Louis Harris & Associates. 1999 National Pain Survey. On National Pain Foundation website. Available at: http://www.nationalpainfoundation.org/pdfs_states/NPF%20Fact%20Sheet.pdf. Accessed September 1, 2011.
38. Musculoskeletal procedures account for over ten percent of all hospital care in the United States. *U.S. Department of Health and Human Services Agency for Healthcare Research and Quality*. Available at <http://www.ahrq.gov/research/aug07/0807RA32.htm>. Accessed September 1, 2011.
39. Kurtz S, et al. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am*. 2007;89:780-785.
40. United States Bone and Joint Decade: The Burden of *Musculoskeletal Disease in the United States*. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2008.
41. The long-term outlook for health care spending. Nov 2007. Congress of the United States. Available at: <http://www.cbo.gov/ftpdocs/87xx/doc8758/11-13-LT-Health.pdf>. Accessed on November 10, 2011.
42. Praemer A. *Musculoskeletal Conditions in the United States*. Second Edition. Rosemont: American Academy of Orthopaedic Surgeons; 1999.
43. Frank C, et al. Ligament healing a review of some current clinical and experimental concepts. *The Iowa Orthopedic Journal*. 1992;12:21-28.
44. Browner B. *Skeletal Trauma*. Philadelphia, PA: W.B. Saunders Company; 1992;1:87-88.
45. Deese J. Compressive neuropathies of the lower extremity. *The Journal of Musculoskeletal Medicine*. November 1988, p. 68-91.
46. Altman P, et al. *Blood and Other Body Fluids*. Washington, DC: Federation of American Societies for Experimental Biology, 1961, p. 349.
47. Buckwater J. Articular cartilage: injuries and potential for healing. *JOSPT*. 1998;28:192-202.
48. Frank C, et al. Current concepts review-the science of reconstruction of the anterior cruciate ligament. *The Journal of Bone and Joint Surgery*. 1997;79:1556-1576.
49. Frank C, et al. Normal ligament properties and ligament healing. *Clinical Orthopedics and Related Research*. 1985;196:15-25.
50. Wheaton M, et al. The ligament injury connection to osteoarthritis. *Journal of Prolotherapy*. 2010;2(1):294-304.
51. Bierma-Zeinstra S. Risk factors and prognostic factors of hip and knee osteoarthritis. *Nature Reviews Rheumatology*. 2007;3:78-85.
52. Kirk J, et al. The hypermobility syndrome-musculoskeletal complaints associated with generalized joint hypermobility. *Annals of Rheumatic Diseases*. 1967;26:419-425.
53. Liu Y. An in situ study of the influence of a sclerosing solution in rabbit medial and collateral ligaments and its junction strength. *Connective Tissue Research*. 1983;2:95-102.
54. Maynard J. Morphological and biomechanical effects of sodium morrhuate on tendons. *Journal of Orthopaedic Research*. 1985;3:236-248.
55. Reeves K. Sweet relief: Prolotherapy targets sprains and strains. *Biomechanics*. 2004;9:24-35.

56. Reeves K. Prolotherapy for patients with musculoskeletal disorders. *Journal of Musculoskeletal Medicine*. 2002;Oct:390-301.
57. Reeves K. Prolotherapy: basic science, clinical studies, and technique. In Lennard TA (ED). *Pain Procedures in Clinical Practice*. (Second Edition). Philadelphia, PA: Hanley and Belfus; 2000;172-190.
58. Jensen K, et al. Response of knee ligaments to Prolotherapy in a rat injury model. *American Journal of Sports Medicine*. 2008;36:1347-1357.
59. Jensen K, et al. Early inflammatory response of knee ligaments to Prolotherapy in a rat model. *Journal of Orthopedic Research*. 2008;26:816-823.
60. Caruccio L, et al. The heat-shock transcription factor HSF1 is rapidly activated by either hyper- or hypo-osmotic stress in mammalian cells. *Journal of Biochemistry*. 1997;327:341-347.
61. Berl T, et al. Multiple mitogen-activated protein kinases are regulated by hyperosmolality in mouse IMCD cells. *American Journal of Physiology*. 1997;272:305-311.
62. McGinn S, et al. High glucose and endothelial cell growth: novel effects independent of autocrine TGF-beta 1 and hyperosmolality. *American Journal of Physiology and Cell Physiology*. 2003;234:C1374-C1386.
63. Natarajan R, et al. Vascular smooth muscle cells exhibit increased growth in response to elevated glucose. *Biochemistry and Biophysical Research and Communication*. 1992;186:552-560.
64. Sanchez M, et al. Platelet-rich therapies in treatment of orthopedic sport injuries. *Sports Medicine*. 2009;39:345-354.
65. Tabata Y. Tissue regeneration based on growth factor release. *Tissue Engineering*. 2003;9:S5-15.
66. Jensen K, et al. Early inflammatory response of knee ligaments to Prolotherapy in a rat model. *Journal of Orthopedic Research*. 2008;26:816-823.
67. Jensen K, et al. Response of knee ligaments to Prolotherapy in a rat injury model. *American Journal of Sports Medicine*. 2008;36:1347-1357.
68. Kim H, et al. The effects of anti-inflammatory drugs on histologic findings of the experimental Prolotherapy model. *Journal of the Korean Academy of Rehabilitation Medicine*. 2006;30:378-384.
69. Ahn K, et al. The effect of the Prolotherapy on the injured Achilles tendon in a rat model. *Journal of the Korean Academy of Rehabilitation Medicine*. 2002;26:332-336.
70. Oh S, et al. Dextrose-induced subsynovial connective tissue fibrosis in the rabbit carpal tunnel: a potential model to study carpal tunnel syndrome. *Hand*. 2008;3:34-40.
71. Kim H, et al. Comparison of histological changes in accordance with the level of dextrose-concentration in experimental Prolotherapy model. *Journal of Korean Academy of Rehabilitation Medicine*. 2003;27:935-940.
72. Kim S, et al. The effects of hyperosmolar dextrose and autologous serum injection in the experimental articular defect of rabbit. *Journal of the Korean Academy of Rehabilitation Medicine*. 2006;30:173-178.
73. Di Palo S, et al. High glucose concentration induces the overexpression of transforming growth factor-beta through the activation of a platelet-derived growth factor loop in human mesangial cells. *American Journal of Pathology*. 1996;149:2095-2106.
74. Oh J, et al. Sequential effects of high glucose on meningeal cell transforming growth factor-beta 1 and fibronectin synthesis. *Kidney International*. 1998;54:1872-1878.
75. Murphy M, et al. Suppression subtractive hybridization identifies high glucose levels as a stimulus for expression of connective tissue growth factor and other genes in human mesangial cells. *Journal of Biology and Chemistry*. 1999;274:5830-5834.
76. Fukuda K, et al. High concentration of glucose increases mitogenic responsiveness to heparin-binding epidermal growth factor-like growth factor in rat vascular smooth muscle cells. *Arteriosclerosis Thrombosis and Vasculature Biology*. 1997;17:1962-1968.
77. Ohgi S, et al. Glucose modulates growth of gingival fibroblasts and periodontal ligament cells: correlation with expression of basic fibroblast growth factor. *Journal of Periodontal Research*. 1996;31:579-588.
78. Pugliese G, et al. Increased activity of the insulin-like growth factor system in mesangial cells cultured in high glucose conditions. Relation to glucose-enhanced extracellular matrix production. *Diabetologia*. 1996;39:775-784.
79. Reeves K. Prolotherapy: injection of growth factors or growth factor production stimulants to growth normal cells or tissue. In Waldman SD (ed): *Pain Management*. Philadelphia, PA: Elsevier; 2006;1106-1127.
80. Martinez-Zapata M, et al. Efficacy and safety of autologous plasma rich in platelets for tissue regeneration: a systematic review. *Transfusion*. 2009;49:44-56.
81. Creaney L, et al. Growth factor delivery methods of sports injuries: the state of play. *British Journal of Sports Medicine*. 2008;42:314-320.
82. Park Y, et al. Intra-articular injection of a nutritive mixture solution protects articular cartilage from osteoarthritic progression induced by anterior cruciate ligament transaction in mature rabbits: a randomized controlled trial. *Arthritis Research and Therapy*. 2007;9:R8.
83. Lee C. Prolotherapy. *The Journal of the Korean Pain Society*. 2004;Dec:17S:94-98.
84. Lee C, et al. Clinical experience of Prolotherapy for chronic musculoskeletal disease. *The Journal of The Korean Pain Society*. 2001;14:114-117.
85. Lyftogt J. Subcutaneous Prolotherapy treatment of refractory knee, shoulder and lateral elbow pain. *Australasian Musculoskeletal Medicine Journal*. 2007;12:110-112.
86. Lyftogt J. Subcutaneous Prolotherapy for Achilles tendinopathy: The best solution? *Australian Musculoskeletal Medicine Journal*. 2007;12:107-109.
87. Hauser R, et al. *Prolo Your Sports Injuries Away!* Oak Park, IL: Beulah Land Press; 2001.
88. Reeves K. Prolotherapy: Basic science, clinical studies, and technique. *Pain Procedures in Clinical Practice*. Second Edition. Edited by Lennard T. Philadelphia PA: Hanley and Belfus, Inc., 2000, pp. 172-189.

89. Lyftogt J. Prolotherapy for recalcitrant lumbago. *Australasian Musculoskeletal Medicine Journal*. 2008;13:18-20.
90. Caterina M, et al. The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature*. 1997;389:816-824.
91. Hackett G. Ligament uninhibited reversible antidromic vasodilation in brochiogenic pathophysiological disease. *Lancet*. 1966;86:398-404.
92. Hackett G, et al. Prolotherapy for headache. Pain in the head and neck and neuritis. *Headache*. 1962;3:11.
93. Hackett G. Ligament relaxation and osteoarthritis, loose jointed versus close jointed. *Rheumatism*. 1959;15:28-33.
94. Shallenberger F. Prolozone – regenerating joints and eliminating pain. *Journal of Prolotherapy*. 2011;630-638.
95. Sanseverino E. Knee joint disorders treated by oxygen-ozone therapy. *Europa Medicophysica*. 1989;3:163-170.
96. Wong R. Ozonoterapia analgesica. *Revista CENIC Ciencias Biologicas*. 1989;20:143-150.
97. Siemsen C. The use of ozone in orthopedics in *Proceedings: Ozone in Medicine, 12th World Congress of the International Ozone Association* (Zurich: International Ozone Association, 1995),125-130.
98. Ceballos A, et al. Tratamiento de la osteoarthritis con ozono. *Revista CENIC Ciencias Biologicas*. 1989;20:15-153.
99. Escarpenter J, et al. Resultados terapeuticos en la osteoarthritis de la rodilla con infiltraciones de ozono. *Rev Cubana Invest Biomed*. 1997;16:124-132.
100. Al-Jaziri A. Pain killing effect of ozone-oxygen injection on spine and joint osteoarthritis. *Saudi Medical Journal*. 2008;29:553-557.
101. Paoloni M. Intramuscular oxygen-ozone therapy in the treatment of acute back pain with lumbar disc herniation—a multicenter, randomized, double-blind, clinical trial of active and simulated lumbar paravertebral injection. *Spine*. 2009;34:1337-1344.
102. Bonetti M. Intraformainal O2-O3 versus periradicular steroidal infiltrations in lower back pain: randomized controlled study. *American Journal of Neuroradiology*. 2005;26:996-1000.
103. Viebahn R. *The Use of Ozone in Medicine*. Second Edition. Heidelberg, Germany: Karl F. Haug Publishers; 1994.
104. Rilling S, et al. *Praxis der Ozon-Sauerstoff-Therapie*. Heidelberg, Germany: Auflage, Verlag Fur Medizin Dr. Ewald Fischer; 1990.
105. Washutl J, et al. *Biochemische Aspekte der Ozon-Sauerstoff-Therapie ArsMedici*. 1986;5:194-199.
106. Creaney L, et al. Growth factor delivery methods in the management of sports injuries: the state of play. *BJSM*. 2008;42:314-320.
107. Marx R, et al. Platelet rich plasma (PRP): a primer. *Pract Pain Manag*. Mar 2008;8(2):46-47.
108. Anitua E, et al. Autologous platelets as a source of proteins for healing and tissue regeneration. *Thromb Haemost*. 2004;91:4-15.
109. Hauser R, et al. The case for utilizing Prolotherapy as first-line treatment of meniscal pathology: a retrospective study shows Prolotherapy is effective in the treatment of MRI-documented meniscal tears and degeneration. *Journal of Prolotherapy*. 2010;2(3):416-437.
110. Marx R, et al. Platelet rich plasma (PRP): a primer. *Practical Pain Management*. March 2008;8(2):46-47.
111. Hall M, et al. Platelet-rich plasma: current concepts and application in sports medicine. *Journal of the American Academy of Orthopedic Surgeons*. 2009;27:602-608.
112. Marx R, et al. Platelet rich plasma (PRP): a primer. *Practical Pain Management*. March 2008;8(2):46-47.
113. Hall M, et al. Platelet-rich plasma: current concepts and application in sports medicine. *Journal of the American Academy of Orthopedic Surgeons*. 2009;27:602-608.
114. Marx R, et al. Platelet rich plasma (PRP): a primer. *Practical Pain Management*. March 2008;8(2):46-47.
115. Marx R. Platelet-rich plasma: evidence to support its use. *J Oral Maxillofac Surg*. 2004;62:489-96.
116. Caplan A, et al. Mesenchymal stem cells and tissue repair. In: *The Anterior Cruciate Ligament: Current and Future Concepts*. Ed. By DW Jackson. New York, Raven press, 1993, p. 405-417.
117. Rigotti G, et al. Adipose-derived mesenchymal stem cells: past, present and future. *Aesth Plast Surg*. 2009;33:271-273.
118. Fraser J, et al. Fat tissue: an underappreciated source of stem cells for biotechnology. *Trends Biotechnol*. 2006;24:150-154.
119. Santiago L, et al. Delivery of adipose-derived precursor cells for peripheral nerve repair. *Cell Transplant*. 2009;18(2):145-58.
120. Murphy J, et al. Reduced chondrogenic and adipogenic activity of mesenchymal stem cells from patients with advanced osteoarthritis. *Arthritis Rheum*. 2002;46:704-13.
121. Luyten F. Mesenchymal stem cells in osteoarthritis. *Curr. Opin. Rheumatol*. 2004;16:559-603.
122. Wakitani S, et al. Mesenchymal cell-based repair of large, full-thickness defects of articular cartilage. *J. Bone Joint Surg (Am)*. 1994;76:579-592.
123. Wakitani S, et al. Human autologous culture expanded bone marrow mesenchymal cell transplantation for repair of cartilage defects in osteoarthritic knees. *Osteoarthritis Cartilage*. 2002;10:199-206.
124. Murphy J, et al. Stem cell therapy in a caprine model of osteoarthritis. *Arthritis Rheum*. 2003;48:3464-3474.
125. Centeno C, et al. Increased knee cartilage volume in degenerative joint disease using percutaneously implanted, autologous mesenchymal stem cells. *Pain Physician*. 2008;11:3:343-353.
126. Albano J, et al. Autologous fat grafting as mesenchymal stem cell source and living bioscaffold in a patellar tendon tear: a case report. *Journal of Sports Medicine*, pending publication 2011.
127. Alderman D, et al. Stem cell Prolotherapy in regenerative medicine: background, theory and protocols. *Journal of Prolotherapy*. 2011;3(3):689-708.
128. Alderman D, et al. Advances in regenerative medicine: high-density platelet rich plasma and stem cell Prolotherapy for musculoskeletal pain. *Practical Pain Management*. Oct 2011;11(8).
129. Izadpanah R, et al. Biologic properties of mesenchymal stem cells derived from bone marrow and adipose tissue. *J Cell Biochem*. 2006;99:1285-1297.

130. Kern S, et al. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood or adipose tissue. *Stem Cells*. 2006;24:1294-1301.
131. Uysal A, et al. Tendon regeneration and repair with adipose derived stem cells. *Curr Stem Cell Res Ther*. Jun 2010;5(2):161-7.
132. Fraser J, et al. Fat tissue: an underappreciated source of stem cells for biotechnology. *Trends Biotechnol*. 2006;24:150-154.
133. Strem B, et al. Multipotential differentiation of adipose tissue-derived stem cells. *Keio J Med*. 2005;54:132-139.
134. Prockop D, et al. *Mesenchymal Stem Cells, Methods and Protocols*. Humana Press, a part of Springer Science, NJ. 2008.
135. Little D, et al. Ligament-derived matrix stimulates a ligamentous phenotype in human adipose-derived stem cells. *Tissue Engineering: Part A*. 2009;16(7):2307-2319.
136. Chen X, et al. Tendon tissue engineering with mesenchymal stem cells and biografts: an option for large tendon defects? *Front Biosci (School Ed)*. 2009 Jun;11:23-32.
137. Uysal A, et al. Tendon regeneration and repair with adipose derived stem cells. *Curr Stem Cell Res Ther*. Jun 2010;5(2):161-7.
138. Uysal A, et al. Differentiation of adipose-derived stem cells for tendon repair. *Methods Mol Biol*. 2011;702:443-51.
139. Jung M, et al. Enhanced early tissue regeneration after matrix-assisted autologous mesenchymal stem cell transplantation in full thickness chondral defects in a minipig model. *Cell Transplantation*. 2009;18(8):923-932.
140. Lee K, et al. Injectable mesenchymal stem cell therapy for large cartilage defects—a porcine model. *Stem Cells*. 2007;25:2965-2971.
141. Dragoo J, et al. Tissue-engineered cartilage and bone using stem cells from human infrapatellar fat pads. *J Bone Joint Surg Br*. 2003;85:740-747.
142. Hsu W, et al. Stem cells from human fat as cellular delivery vehicles in an athymic rat posterolateral spine fusion model. *J Bone Joint Surg Am*. 2008;90:1043-1052.
143. Bacou F, et al. Transplantation of adipose tissue-derived stromal cells increases mass and functional capacity of damaged skeletal muscle. *Cell Transplant*. 2004;13:103-111.
144. Rodriguez L, et al. Clonogenic multipotent stem cells in human adipose tissue differentiate into functional smooth muscle cells. *Proc Natl Acad Sci USA*. 2006;108:12167-12172.
145. Goudenege S, et al. Enhancement of myogenic and muscle repair capacities of human adipose-derived stem cells with forced expression of MyoD. *Mol Ther*. 2009;17:1064-1072.
146. Santiago L, et al. Delivery of adipose-derived precursor cells for peripheral nerve repair. *Cell Transplant*. 2009;18(2):145-58.
147. Di Summa P, et al. Adipose-derived stem cells enhance peripheral nerve regeneration. *J Plast Reconstr Aesthet Surg*. 2010 Sept;63(9):1544-52.
148. Nakada A, et al. Regeneration of central nervous tissue using a collagen scaffold and adipose-derived stromal cells. *Cells Tissues Organs*. 2009;190:326-335.
149. Cowan C, et al. Adipose-derived adult stromal cells heal critical-size mouse calvarial defects. *Nat Biotechnol*. 2004;22:560-567.
150. Dudas J, et al. The osteogenic potential of adipose-derived stem cells for the repair of rabbit calvarial defects. *Ann Plast Surg*. 2006;56:543-548.
151. Yoon E, et al. In vivo osteogenic potential of human adipose-derived stem cells/poly lactide-co-glycolic acid constructs for bone regeneration in a rat critical-sized calvarial defect model. *Tissue Eng*. 2007;13:619-627.
152. Rosenbaum A, et al. The use of mesenchymal stem cells in tissue engineering: a global assessment. *Organogenesis*. 2008 Jan-Mar;4(1):23-37.
153. Cousin B, et al. Reconstitution of lethally irradiated mice by cells isolated from adipose tissue. *Biochem Biophys Res Commun*. 2003;21:1016-1022.
154. Puissant B, et al. Immunomodulatory effect of human adipose tissue-derived adult stem cells: comparison with bone marrow mesenchymal stem cells. *Br J Haematol*. 2005;129:118-129.
155. Kim W, et al. Wound healing effect of adipose-derived stem cells: a critical role of secretory factors on human dermal fibroblasts. *J Dermatol Sci*. 2007 Oct;48(1):15-24.
156. Ebrahimiyan T, et al. Cell therapy based on adipose tissue-derived stromal cells promotes physiological and pathological wound healing. *Arterioscler Thromb Vasc Biol*. 2009;29(4):503-510.
157. Trottier V, et al. IFATS collection: using human adipose-derived stem/stromal cells for the production of new skin substitutes. *Stem Cell*. 2008;26:2713-2723.
158. Connolly J, et al. Development of an osteogenic bone-marrow preparation. *Journal of Bone and Joint Surgery America*. 1989;71:684-691.
159. Gangji V, et al. Treatment of osteonecrosis of the femoral head with implantation of autologous bone-marrow cells. A pilot study. *Journal of Bone and Joint Surgery America*. 2004;86A:1153-1160.
160. Hernigou P, et al. Treatment of osteonecrosis with autologous bone marrow grafting. *Clinical Orthopaedic and Related Research*. 2002;14-23.
161. Hernigou P, et al. Percutaneous autologous bone-marrow grafting for nonunions. Influence of the number and concentration of progenitor cells. *Journal of Bone and Joint Surgery America*. 2005;87:1430-1437.
162. Hernigou P, et al. The use of percutaneous autologous bone marrow transplantation in nonunion and avascular necrosis of bone. *Journal of Bone and Joint Surgery British*. 2005;87:896-902.
163. McLain R, et al. Aspiration of osteoprogenitor cells for augmenting spinal fusion: comparison of progenitor cell concentrations from the vertebral body and iliac crest. *Journal of Bone and Joint Surgery America*. 2005;87:2655-2661.
164. Muschler G, et al. Spine fusion using cell matrix composites enriched in bone marrow-derived cells. *Clinical Orthopaedics and Related Research*. 2003;102-118.
165. Kevy S, et al. Point of care concentration of bone marrow. In: *Orthopedic Research Society*. Chicago Illinois: 2006.
166. Muschler G, et al. Aspiration to obtain osteoblast progenitor cells from human bone marrow: the influence of aspiration volume. *Journal of Bone and Joint Surgery*. 1997;70A:1699-1709.

167. Connolly J. Injectable bone marrow preparations to stimulate osteogenic repair. *Clinical Orthopaedics and Related Research*. 1995;313:8-18.
168. Shenaq D, et al. Mesenchymal progenitor cells and their orthopedic applications: forging a path towards clinical trials. *Stem Cell International*. 2010;519028. doi:10.4061/2010/519028.
169. Chanda D, et al. Therapeutic potential of adult bone marrow-derived mesenchymal stem cells in diseases of the skeleton. *Journal of Cellular Biology*. 2010;111:249-257.
170. Vats A, et al. The stem cell in orthopaedic surgery. *The Journal of Bone and Joint Surgery British*. 2004;86B:159-164.
171. Muschler G, et al. Selective retention of bone marrow-derived cells to enhance spinal fusion. *Clinical Orthopaedics and Related Research*. 2005;432:242-251.
172. Pittenger M, et al. Multilineage potential of adult human mesenchymal stem cells. *Science*. 1999;284(5411):143-147.
173. Caplan A, et al. Mesenchymal stem cells and tissue repair. In: *The Anterior Cruciate Ligament: Current and Future Concepts*. Jackson DW (ed). Raven Press. New York. 1993. pp 405-417.
174. Young R, et al. Use of mesenchymal stem cells in a collagen matrix for Achilles tendon repair. *J. Orthop Res*. 1998;16:406-413.
175. Fortier L, et al. Concentrated bone marrow aspirate improves full-thickness cartilage repair compared with microfracture in the equine model. *Journal of Bone and Joint Surgery America*. 2010;92:1927-1937.
176. Lee K, et al. Injectable mesenchymal stem cell therapy for large cartilage defects—a porcine model. *Stem Cells*. 2007;24:2964-2971.
177. Im G, et al. Do adipose tissue-derived mesenchymal stem cells have the same osteogenic and chondrogenic potential as bone marrow-derived cells? *Osteoarthritis Cartilage/OARS. Osteoarthritis Research Society*. 2005;13:845-853.
178. Afizah H, et al. A comparison between the chondrogenic potential of human bone marrow stem cells and adipose-derived stem cells taken from the same donors. *Tissue Engineering*. 2007;13:659-666.
179. Huang J, et al. Chondrogenic potential of progenitor cells derived from human bone marrow and a patient-matched comparison. *Journal of Orthopedic Research*. 2005;23:1383-1389.
180. Winter A, et al. Cartilage-like gene expression in differentiated human stem cell spheroids: a comparison of bone marrow-derived and adipose tissue-derived stromal cells. *Arthritis and Rheumatism*. 2003;48:418-429.
181. Dickman B, et al. Chondrogenesis of adult stem cells from adipose tissue and bone marrow: induction by growth factors and cartilage-derived matrix. *Tissue Engineering: Part A*. 2010;16:523-533.
182. Bernardo M, et al. Human mesenchymal stem cells derived from bone marrow display a better chondrogenic differentiation compared with other sources. *Connective Tissue Research*. 2007;48:132-140.
183. Khan S, et al. Bone growth factors. *Orthopedic Clinics of North America*. 2000;31:375-388.
184. Muschler G, et al. Practical modeling concepts for connective tissue stem cell and progenitor compartment kinetics. *Journal of Biomedical Biotechnology*. 2003;170-193.
185. Bruder S, et al. Mesenchymal stem cells in osteobiology and applied bone regeneration. *Clinical Orthopaedics and Related Research*. 1998;355S:S247-S256.
186. Granero-Molto F, et al. Role of mesenchymal stem cells in regenerative medicine: application to bone and cartilage repair. *Cell & Tissue-based Therapy*. 2008;255-268.
187. Clark B, et al. Biology of bone marrow stroma. *Annals of New York Academy of Sciences*. 1995;770:70-78.
188. Hauser R, et al. A retrospective study on dextrose Prolotherapy for unresolved knee pain at an outpatient charity clinic in rural Illinois. *Journal of Prolotherapy*. 2009;1(1):11-21.
189. Kim J. The effect of Prolotherapy for osteoarthritis of the knee. *Journal of the Korean Academy of Rehabilitation Medicine*. 2002;26:445-448.
190. Hauser R, et al. A retrospective observational study on Hackett-Hemwall dextrose Prolotherapy for unresolved hand and finger pain at an outpatient charity clinic in rural Illinois. *Journal of Prolotherapy*. 2010;2(4):480-486.
191. Hauser R, et al. Dextrose Prolotherapy for unresolved low back pain: a retrospective case series study. *Journal of Prolotherapy*. 2009;1(3):145-155.
192. Hauser R, et al. A retrospective study on Hackett-Hemwall dextrose Prolotherapy for chronic shoulder pain at an outpatient charity clinic in rural Illinois. *Journal of Prolotherapy*. 2009;1(4):205-216.
193. Hauser R, et al. Dextrose Prolotherapy injections for chronic ankle pain. *Practical Pain Management*. 2010;70-76.
194. Hauser R, et al. A retrospective study on Hackett-Hemwall dextrose Prolotherapy for chronic hip pain at an outpatient charity in rural Illinois. *Journal of Prolotherapy*. 2009;1(2):76-88.
195. Hauser R, et al. A retrospective observational study on Hackett-Hemwall dextrose Prolotherapy for unresolved foot and toe pain at an outpatient charity clinic in rural Illinois. *Journal of Prolotherapy*. 2011;3(1):543-551.
196. Hauser R, et al. Dextrose Prolotherapy for unresolved wrist pain. *Practical Pain Management*. 2009;November/December:72-89.
197. Hauser R, et al. Dextrose Prolotherapy and pain of chronic TMJ dysfunction. *Practical Pain Management*. 2007;November/December:49-55.
198. Hauser R, et al. Dextrose Prolotherapy for unresolved neck pain. *Practical Pain Management*. 2007;October:56-69.
199. Hauser R, et al. Hackett-Hemwall dextrose Prolotherapy for unresolved elbow pain. *Practical Pain Management*. 2009;October:14-26.
200. Kim J. Effects of Prolotherapy on knee joint pain due to ligament laxity. *The Journal of the Korean Pain Society*. 2004;17:47-50.
201. Hauser R, et al. The case for utilizing Prolotherapy as first-line treatment of meniscal pathology: a retrospective study shows Prolotherapy is effective in the treatment of MRI-documented meniscal tears and degeneration. *Journal of Prolotherapy*. 2010;2(3):416-437.

202. Reeves K, et al. Long term effects of dextrose Prolotherapy for anterior cruciate laxity. *Alternative Therapies*. 2003;9:58-62.
203. Kim J. The effect of Prolotherapy for osteoarthritis of the knee. *Journal of the Korean Academy of Rehabilitation Medicine*. 2002;26:445-448.
204. Miller M, et al. Treatment of painful advanced internal lumbar disc derangement with intradiscal injection of hypertonic dextrose. *Pain Physician*. 2006;9:115-121.
205. Hooper R, et al. Prospective case series of litigants and non-litigants with chronic spinal pain treated with dextrose Prolotherapy. *International Musculoskeletal Medicine Journal*. 2011;33:15-20.
206. Klein R, et al. Proliferant injections for low back pain: histologic changes of injected ligaments and objective measurements of lumbar spine mobility before and after treatment. *Journal of Neurology, Orthopedic Medicine and Surgery*. 1989;10:141-144.
207. Dagenais S, et al. Intraligamentous injection of sclerosing solutions (Prolotherapy) for spinal pain: a critical review of literature. *Journal of Spine*. 2005;5:310-3128.
208. Daganais S, et al. Evidence-informed management of chronic low back pain with Prolotherapy. *Journal of Spine*. 2008;3:203-212.
209. Hooper R, et al. Retrospective case series on patients with chronic spinal pain treated with dextrose Prolotherapy. *Journal of Alternative and Complementary Medicine*. 2004;10:670-674.
210. Gabbi A, et al. Biological approaches for cartilage repair. *Journal of Knee Surgery*. 2009;22:36-44.
211. Richter W. Mesenchymal stem cells and cartilage in situ regeneration. *Journal of Internal Medicine*. 2009;266:390-405.
212. Richter W. Cell-based cartilage repair: illusion or solution for osteoarthritis. *Current Opinions in Rheumatology*. 2007;19:451-456.
213. Bruder S, et al. Mesenchymal stem cells in bone development, bone repair, and skeletal regeneration therapy. *Journal of Cell Biochemistry*. 1994;56:283-294.
214. Lee K, et al. Injectable mesenchymal stem cell therapy for large cartilage defects-a porcine model. *Stem Cells*. 2007;25:2964-2971.
215. Wakitani S, et al. Repair of articular cartilage defects in the patella-femoral joint with autologous bone marrow mesenchymal cell transplantations: three case reports involving nine defects in five knees. *Journal of Tissue Engineering & Regenerative Medicine*. 2007;1:74-79.
216. Hooper R, et al. Case series on chronic whiplash related neck pain treated with intraarticular zygapophysial joint regeneration injection therapy. *Pain Physician*. 2007;10:313-318.
217. Centeno C, et al. Fluoroscopically guided cervical Prolotherapy for instability with blinded pre and post radiographic reading. *Pain Physician*. 2005;8:67-72.
218. Kim J. Effects of Prolotherapy on knee joint pain due to ligament laxity. *The Journal of the Korean Pain Society*. 2004;17:47-50.
219. Jo D, et al. The effects of Prolotherapy on shoulder pain. *Korean Journal of Anesthesiology*. 2004;46:589-592.
220. Kim W, et al. A randomized controlled trial of intra-articular Prolotherapy versus steroid injection for sacroiliac joint pain. *Journal of Alternative and Complementary Medicine*. 2010;16:1285-1290.
221. Hauser R. Prolotherapy for hip labral tears: a case series. Paper in the process of submission.
222. Hauser R, et al. The case for utilizing Prolotherapy as first-line treatment of meniscal pathology: a retrospective study shows Prolotherapy is effective in the treatment of MRI-documented meniscal tears and degeneration. *Journal of Prolotherapy*. 2010;2(3):416-437.
223. Hauser R, et al. Platelet rich plasma Prolotherapy as first-line treatment for meniscal pathology. *Practical Pain Management*. 2010;July/August:55-65.
224. Hauser R, et al. Treatment of joint hypermobility syndrome, including Ehlers-Danlos syndrome, with Hackett-Hemwall Prolotherapy. *Journal of Prolotherapy*. 2011;3(2):612-629.
225. Ryan M, et al. Sonographically guided intratendinous injections of hyperosmolar dextrose/lidocaine: a pilot study for the treatment of chronic plantar fasciitis. *British Journal of Sports Medicine*. 2009;43:303-306.
226. Lyftogt J. Subcutaneous Prolotherapy for Achilles tendinopathy. *Australasian Musculoskeletal Medicine Journal*. 2007;12:107-109.
227. Sampson S, et al. Platelet rich plasma injection grafts for musculoskeletal injuries: a review. *Current Review of Musculoskeletal Medicine*. 2008;1:165-174.
228. Reeves K. Prolotherapy: injection of growth factors or growth factor production stimulants to growth normal cells or tissue. In Waldman SD (ed): *Pain Management*. Philadelphia, Elsevier, 2006, pp. 1106-1127.
229. Martinez-Zapata M, et al. Efficacy and safety of autologous plasma rich in platelets for tissue regeneration: a systematic review. *Transfusion*. 2009;49:44-56.
230. Creaney L, et al. Growth factor delivery methods of sports injuries: the state of play. *British Journal of Sports Medicine*. 2008;42:314-320.
231. Sanchez M, et al. Platelet-rich therapies in treatment of orthopaedic sport injuries. *Sports Medicine*. 2009;39:345-354.
232. Mishra A, et al. Treatment of chronic elbow tendinosis with buffered platelet rich plasma. *American Journal of Sports Medicine*. 2006;10(10):1-5.
233. Maxwell N, et al. Sonographically guided intratendinous injection of hyperosmolar dextrose to treatment chronic tendinosis of the Achilles tendon: a pilot study. *American Journal of Roentgenology*. 2007;189:W215-220.
234. Scarpone M, et al. The efficacy of Prolotherapy for lateral epicondylitis: a pilot study. *Clinical Journal of Sports Medicine*. 2008;18:248-254.
235. James S, et al. Ultrasound guided dry needling and autologous blood injection for patellar tendinosis. *British Journal of Sports Medicine*. 2007;8:518-521.
236. Edwards S, et al. Autologous blood injections for refractory lateral epicondylitis. *Am J Hand Surg*. 2003;28(2):272-8.
237. Smith R, et al. Abnormal microvascular responses in lateral epicondylitis. *Br J Rheum*. 1994;33:1166-1168.
238. Jobe F, et al. Lateral and medial epicondylitis of the elbow. *J Am Acad Orthop Surg*. 1994;2:1-8.

239. Hamilton P. The prevalence of humeral epicondylitis: a survey in general practice. *J R Coll Gen Pract.* 1986;36:464-465.
240. Labelle H, et al. Lack of scientific evidence for the treatment of lateral epicondylitis of the elbow. *J Bone Joint Surg Br.* 74:646-651 1992.
241. Karli D, et al. Platelet rich plasma for hamstring tears. *Practical Pain Management.* 2010;June:9-15.
242. Hammond J, et al. Use of autologous platelet-rich plasma to treat muscle strain injuries. *The American Journal of Sports Medicine.* 2009;37:1135-1143.
243. Park J, et al. Ultrasonographic findings of healing of torn tendon in the patients with lateral epicondylitis after Prolotherapy. *Journal of the Korean Society of Medical Ultrasound.* 2003;22:177-183.
244. Linetsky F, et al. Pain management with regenerative injection therapy. In: Boswell MV, Cole BE(eds.) *Weiner's pain management: a practical guide.* 7th ed. Boca Raton, FL: CRC Press; 2006:939-965.
245. Curtin M, et al. The effectiveness of Prolotherapy in the management of recalcitrant medial tibial stress syndrome: a pilot study. *British Journal of Sports Medicine.* 2011;45e1. doi:10.1136/bjism.2010.081554.8.
246. Topol G, et al. Efficacy of dextrose Prolotherapy in elite male kicking-sport athletes with chronic groin pain. *Archives of Physical Medicine and Rehabilitation.* 2005;86:697-702.
247. Hammond J, et al. Use of autologous platelet-rich plasma to treat muscle strain injuries. *The American Journal of Sports Medicine.* 2009;37:1135-1143.
248. Reeves K. Prolotherapy: injection of growth factors or growth factor production stimulants to grow normal cells or tissues. In Waldman SD (ed): *Pain Management.* Philadelphia, PA: Elsevier; 2006;1106-1127.
249. Lazzara M. The non-surgical repair of a complete Achilles tendon rupture by Prolotherapy: biological reconstruction. A case report. *J Orthopaedic Med.* 2005;27:128-132.
250. Grote W, et al. Repair of a complete anterior cruciate tear using Prolotherapy: a case report. *International Musculoskeletal Medicine.* 2009;1:31(4):159-165.
251. Hall M, et al. Platelet-rich plasma: current concepts and application in sports medicine. *Journal of the American Academy of Orthopedic Surgeons.* 2009;17:602-608.
252. Hackett G. Back pain following trauma and disease – Prolotherapy. *Military Medicine.* 1961;July:517-525.
253. Hackett G. Prolotherapy in whiplash and low back pain. *Postgraduate Medicine.* 1960;February:214-219.
254. Reeves K. Sweet Relief: Prolotherapy targets sprains and strains. *Biomechanics.* 2004;9:24-35.
255. Kim M, et al. Comparison on treatment effects of dextrose water, saline, and lidocaine for trigger point injections. *Journal of the Korean Academy of Rehabilitation Medicine.* 1997;21:967-973.
256. Reeves K. Prolotherapy for patients with musculoskeletal disorders. *Journal of Musculoskeletal Medicine.* 2002;390-301.
257. Reeves K. Treatment of consecutive severe fibromyalgia patients with Prolotherapy. *Journal of Orthopedic Medicine.* 1994;16:84-89.
258. Hauser R, et al. The theoretical basis and treatment of complex regional pain syndrome with Prolotherapy. *Journal of Prolotherapy.* 2010;2(2):356-370.
259. Hakala R, et al. The use of Prolotherapy for temporomandibular joint dysfunction. *Journal of Prolotherapy.* 2010;2(3):439-446.
260. Hauser R, et al. Dextrose Prolotherapy and pain of chronic TMJ dysfunction. *Practical Pain Management.* 2007;November/December:49-55.
261. Hauser R, et al. Dextrose Prolotherapy for recurring headache and migraine pain. *Practical Pain Management.* 2009;June:58-65.
262. Kayfetz D, et al. Whiplash injury and other ligamentous headache-its management with Prolotherapy. *Headache.* 1963;3:21-28.
263. Myers A. Prolotherapy treatment of low back pain and sciatica. *Bulletin of the Hospital for Joint Diseases.* 1961;22:1-10.
264. Hackett G. Prolotherapy for sciatica from weak pelvic ligaments and bone dystrophy. *Clinical Medicine.* 1961;8:2301-2316.
265. Kayfetz D, et al. Whiplash injury and other ligamentous headache-its management with Prolotherapy. *Headache.* 1963;3:1-8.
266. Hackett G. Prolotherapy for headache. *Headache.* 1962;1:3-11.
267. Hemwall G. Barré-Licou syndrome. *Journal of Orthopedic Medicine (UK).* 1989;11:79-81.
268. Kayfetz D. Occipito-cervical (whiplash) injuries treated by Prolotherapy. *Medical Trial Technical Quarterly.* 1963;June:9-29.
269. Hackett G, et al. Prolotherapy for headache. Pain in the head and neck, and neuritis. *Headache.* 1962;2:20-28.
270. Creaney L, et al. Growth factor delivery methods of sports injuries: the state of play. *British Journal of Sports Medicine.* 2008;42:314-320.
271. Hirschberg G, et al. Treatment of the chronic iliolumbar syndrome by infiltration of the iliolumbar ligament. *The Western Journal of Medicine.* 1982;136:372-374.
272. Kim B, et al. The effect of Prolotherapy for the chronic pain of musculoskeletal system. *The Journal of the Korean Academy of Rehabilitation Medicine.* 2001;25:128-133.
273. Kim S, et al. Effects of Prolotherapy on chronic musculoskeletal disease. *The Korean Journal of Pain.* 2002;15:121-125.
274. Khan S, et al. Dextrose Prolotherapy for recalcitrant coccygodynia. *Journal of Orthopaedic Surgery.* 2008;16:27-29.
275. Miller M, et al. Treatment of painful advanced internal lumbar disc derangement with intradiscal injection of hypertonic dextrose. *Pain Physician.* 2006;9:115-121.
276. Lyftogt J. Chronic exertional compartment syndrome and Prolotherapy. *Australasian Musculoskeletal Medicine Journal.* 2006;11:83-85.
277. Jo D, et al. The effects of Prolotherapy on the lumbar nucleus pulposus. *Journal of the Korean Pain Society.* 2003;16:68-72.
278. Foye P. Dextrose Prolotherapy for recalcitrant coccygodynia fractures. *Journal of Orthopedic Surgeon (Hong Kong).* 2008;16:27-29.
279. Tsatsos G, et al. Prolotherapy in the treatment of foot problems. *Journal of the Podiatric Medical Association.* 2002;92:36-368.

280. Refai H, et al. The efficacy of dextrose Prolotherapy for temporomandibular joint hypermobility: a preliminary prospective, randomized, double-blind, placebo-controlled clinical trial. *Journal of Oral Maxillofacial Surgery*. 2011;July 12: (Epub ahead of print).
281. Distel L, et al. Prolotherapy: a clinical review of its role in treating chronic musculoskeletal pain. *Physical Medicine and Rehabilitation*. 2011;3(6Suppl):S78-81.
282. Merriman J. Prolotherapy versus operative fusion in the treatment of joint instability of the spine and pelvis. *Journal of the International College of Surgeons*. 1964;42:150-159.
283. Wilkinson H. Injection therapy for enthesopathies causing axial spine pain and the “failed back syndrome”: a single blinded, randomized and cross-over study. *Pain Physician*. 2005;8:167-173.
284. Watson J, et al. Treatment of chronic low-back pain: a 1-year or greater follow-up. *Journal of Alternative and Complementary Medicine*. 2010;16:951-958.
285. Misra A, et al. Treatment of tendon and muscle using platelet-rich plasma. *Clinics in Sports Medicine*. 2009;28:113-125.
286. Sanchez M, et al. Comparison of surgically repaired Achilles tendon tears using platelet-rich fibrin matrices. *American Journal of Sports Medicine*. 2007;35:245-251.
287. de Mos M, et al. Can platelet-rich plasma enhance tendon repair? A cell culture study. *American Journal of Sports Medicine*. 2008;36:1171-1178.
288. Gedney E. Progress report on use of sclerosing solutions in low back syndromes. *The Osteopathic Profession*. 1954;August:18-21,40-44.
289. Gedney E. The application of sclerotherapy in spondylolisthesis and spondylolysis. *The Osteopathic Profession*. 1964;September:66-69,102-105.
290. Hackett G. Joint stabilization through induced ligament sclerosis. *Ohio State Medical Journal*. 1953;49:877-884.
291. Hackett G, et al. Joint stabilization: an experimental, histologic study with comments on the clinical application in ligament proliferation. *American Journal of Surgery*. 1955;89:968-973.
292. Leedy R. Analysis of 50 low back cases 6 years after treatment by joint ligament sclerotherapy. *Osteopathic Medicine*. 1976;6:15-22.
293. Hernigou P, et al. Treatment of osteonecrosis with autologous bone marrow grafting. *Clinical Orthopaedic and Related Research*. 2002;405:14-23.
294. Hauser R. Prolotherapy as an alternative treatment for osteochondritis dissecans. *Journal of Prolotherapy*. 2011;3(1):568-571.
295. Lee E, et al. The potential of stem cells in orthopaedic surgery. *Journal of Bone and Joint Surgery*. 2006;88:841-851.
296. Wakitani W, et al. Human autologous culture expanded bone marrow mesenchymal cell transplantation for repair of cartilage defects in osteoarthritic knees. *Osteoarthritis and Cartilage*. 2002;10:199-206.
297. Hui J, et al. Review article: stem cell therapy in orthopaedic surgery: current status and ethical considerations. *Malaysian Orthopaedic Journal*. 2009;3:4-12.
298. Wakitani W, et al. Autologous bone marrow stroma cell transplantation for repair of full-thickness articular cartilage defects in human patellae: two case reports. *Cell Transplantation*. 2004;13:595-600.
299. Quarto R, et al. Repair of large bone defects with the use of autologous bone marrow stroma cells. *New England Journal of Medicine*. 2001;344:385-386.
300. Brooks P. Musculoskeletal medicine: the challenge of the Bone and Joint Decade. *Journal of Rheumatology*. 2004;7:272-277.
301. Brooks P. The burden of musculoskeletal disease—a global perspective. *Clinical Rheumatology*. 2006;25:778-781.
302. Hazes J, et al. The bone and joint decade 2000-2010. *Journal of Rheumatology*. 2000;27:1-3.
303. Peat G, et al. Knee pain and osteoarthritis in older adults: a review of community burden and current use of health care. *Annals of Rheumatic Diseases*. 2001;60:91-97.
304. Guccione A, et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham study. *American Journal of Public Health*. 1994;84:351-358.
305. Murray C, et al. The global burden of disease. Geneva: World Health Organization. 1997.
306. Bellamy N, et al. Intraarticular corticosteroid for the treatment of osteoarthritis of the knee. *Cochrane Database Systematic Review*. 2006;April 19;2:CD005328.
307. Dieppe P, et al. Intra-articular steroids in osteoarthritis. *Rheumatology and Rehabilitation*. 1980;19:212-217.
308. Ravaud P, et al. Effects of joint lavage and steroid injection in patients with osteoarthritis of the knee. Results of a multicenter, randomized, controlled trial. *Arthritis and Rheumatism*. 1999;42:475-482.
309. Gaffney V, et al. Intra-articular triamcinolone hexacetonide in knee osteoarthritis: factors influencing the clinical response. *Annals of Rheumatologic Diseases*. 1995;54:379-381.
310. Roach J. Comparison of the effects of steroid, aspirin and sodium salicylate on articular cartilage. *Clinical Orthopaedics*. 1975;106:350-356.
311. Rusanen M. Scanning electron microscopical study of the effects of crystalloid and water-soluble glucocorticoids on articular cartilage. *Scandinavian Journal of Rheumatology*. 1986;15:47-51.
312. Wada J. Natural course of osteoarthritis of the knee with and without intra-articular corticosteroid injection. *Bulletin Hospital For Joint Diseases*. 1993;53:43-48.
313. Hauser R. The deterioration of articular cartilage with corticosteroid injections. *Journal of Prolotherapy*. 2009;1(2):107-123.
314. Lo G, et al. Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis. *Journal of the American Medical Association*. 2003;290:3115-3121.
315. Espallargues M, et al. Efficacy and safety of viscosupplementation with Hylan G-F 20 for the treatment of knee osteoarthritis: a systematic review. *International Journal of Technology and Assessment of Health Care*. 2003;19:41-56.

316. Jordan K, et al. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a task force of the standing committee for international clinical studies including therapeutic trials. *Annals of Rheumatic Diseases*. 62:1145-1155.
317. Lohmander L, et al. Intra-articular hylauronan injections in the treatment of osteoarthritis of the knee: a randomized, double blind, placebo-controlled multicentre trial. *Annals of Rheumatic Diseases*. 1996;55:424-431.
318. Wang C, et al. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee. A meta-analysis of randomized controlled trials. *Journal of Bone and Joint Surgery America*. 2004;86-A:538-545.
319. Bellamy N, et al. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Systematic Review*. 2006;2:cd005321.
320. Listrat V, et al. Arthroscopic evaluation of potential structure modifying activity of hyaluronan in osteoarthritis of the knee. *Osteoarthritis and Cartilage*. 1997;5:153-160.
321. Kirchner M, et al. A double-blind randomized controlled trial comparing alternative forms of high molecular weight hyaluronan for the treatment of osteoarthritis of the knee. *Osteoarthritis and Cartilage*. 2006;14:154-162.
322. Reichenbach S, et al. Hylan versus hyaluronic acid for osteoarthritis of the knee: a systematic review and meta-analysis. *Arthritis and Rheumatism*. 2007;57:1410-1418.
323. Agency for Healthcare Research and Quality: three treatments for osteoarthritis of the knee: evidence shows lack of benefit. *Clinicians Guide to Effective Health Care*. Rockville, MD: AHRQ Publication No. 09-EHC001-3; April 2009.
324. Owings M, et al. Ambulatory and inpatient procedures in the United States, 1996. Vital and Health Statistics Series 13, No. 139. Hyattsville Maryland. National Center for Health Statistics, November 1998. DHHS Publication No. PHS 99-1710.
325. Laupattarakasem W, et al. Arthroscopic debridement for knee osteoarthritis. *Cochrane Database of Systematic Reviews*. 2008;issue 1. Art. No.:CD005118. DOI:1002/14651858.pub2.
326. Moseley J, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *New England Journal of Medicine*. 2002;347:81-88.
327. Jackson R, et al. The results of arthroscopic lavage and debridement for osteoarthritis of knees based on severity of degeneration. A 4 to 6 year symptomatic follow-up. *Arthroscopy*. 2003;19:13-20.
328. Reichenbach S, et al. Joint lavage for osteoarthritis of the knee. *Cochrane Database of Systematic Reviews*. 2010;5:CD0073210. DOI:10.1002/14651858.CD007320.pub2.
329. Ike R, et al. Tidal irrigation versus conservative medical management in patients with osteoarthritis of the knee: a prospective randomized study. *Journal of Rheumatology*. 1993;19:772-779.
330. Bazian Ltd. Arthroscopic lavage for osteoarthritis of the knee. *Evidence-based healthcare and public health*. 2005;9:192-199.
331. Agency for Healthcare Research and Quality: Three treatments for osteoarthritis of the knee: Evidence shows lack of benefit. *Clinicians Guide to Effective Health Care*. AHRQ Publication No. 09-EHC001-3. Rockville, MD:AHRQ April 2009.
332. American College of Rheumatology Practice Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee. 2000 update.
333. American Academy of Orthopedic Surgeons. AAOS clinical guidelines on osteoarthritis of the knee (Phase 2). Rosemont, IL. American Academy of Orthopedic Surgeons; 2003, page 15.
334. American Association of Orthopedic Surgeons. Treatment of osteoarthritis of the knee (non-arthroplasty). December 6, 2008. <http://www.aaos.org/Research/guidelines/Guidelinesoaknee.asp>.
335. David T, et al. Arthroscopic debridement of the arthritic knee: indications and results. *Current Opinions in Orthopedics*. 2000;11:9-13.
336. McGinley B, et al. Debridement arthroscopy 10-year followup. *Clinical Orthopaedics & Related Research*. 1999;367:190-194.
337. Stuart M, et al. What, if any, are the indications for arthroscopic debridement of the osteoarthritic knee? *Arthroscopy*. 2006;22:238-239.
338. Siparsky P, et al. Arthroscopic treatment of osteoarthritis of the knee: are there any evidence-based indications? *Clinical Orthopedic Related Research*. 2007;455:107-112.
339. Johnson L. Arthroscopic abrasion arthroplasty: a review. *Clinical Orthopedics*. 2001;391:S306-S317.
340. Flavia M, et al. Rate of knee cartilage loss after partial meniscectomy. *The Journal of Rheumatology*. 2002;29:1954-1956.
341. Englund M, et al. Impact of type of meniscal tear on radiographic symptomatic knee osteoarthritis. A sixteen-year follow-up of meniscectomy with matched controls. *Arthritis and Rheumatism*. 2003;48:2178-2187.
342. Englund M, et al. Patient-relevant outcomes fourteen years after meniscectomy: influence of type of meniscal tear and size of resection. *Rheumatology*. 2001;40:631-639.
343. Johnson R, et al. Factors affecting late results after meniscectomy. *The Journal of Bone and Joint Surgery*. 1974;56A:719-729.
344. MacAusland W. A study of derangement of semilunar cartilages based on 850 cases. *Surgery, Gynecology and Obstetrics*. 1943;77:141-152.
345. Tapper E, et al. Late results after meniscectomy. *Journal of Bone and Joint Surgery*. 1969;517-526.
346. Wynn-Parry C, et al. Meniscectomy. A review of 1,723 cases. *Annals of Physical Medicine and Rehabilitation*. 1958;4:201-215.
347. Woodyard J. A long-term survey after meniscectomy. *Orthopaedics*. 1968;1:29-39.
348. Ahmed A. In vitro measurements of the static pressure distribution in synovial joints. Part one: tibial surface of the knee. *Journal of Biomechanical Engineering*. 1983;105:216-225.
349. Baratz M. Meniscal tears: the effect of meniscectomy and of repair on intra-articular contact areas and stress in the human knee. *American Journal of Sports Medicine*. 1986;14:270-275.
350. Bessette G. The meniscus. *Orthopaedics*. 1992;15:35-42.

351. March L, et al. Outcomes after hip or knee replacement surgery for osteoarthritis. *Musculoskeletal Journal of Australia*. 1999;171:235-238.
352. Ethgen O, et al. Health-related quality of life in total hip and knee arthroplasty. *Journal of Bone and Joint Surgery America*. 2004;86:963-974.
353. Singh J. Epidemiology of knee and hip arthroplasty: a systematic review. *Open Orthopedic Journal*. 2011;5:80-85.
354. Khanna A, et al. Minimally invasive total knee arthroplasty: a systematic review. *Orthopedic Clinics of North America*. 2009;40:479-489.
355. Anderson J, et al. Functional outcome and patient satisfaction in total patients over the age of 75. *Journal of Arthroplasty*. 1996;11:831-840.
356. Berger R, et al. Outpatient total knee arthroplasty with a minimally invasive technique. *Journal of Arthroplasty*. 2005; (7 Supplement 3):33-38.
357. Laskin R. Minimally invasive total knee arthroplasty: the results justify its use. *Clinical Orthopedics and Related Research*. 2004;428:68-73.
358. Wheaton M, et al. The ligament injury connection to osteoarthritis. *Journal of Prolotherapy*. 2010;2(1):294-304.
359. Fleming B. Ligament injury, reconstruction, and osteoarthritis. *Current Opinions in Orthopaedics*. 2005;16:354-362.
360. Neuman P. Prevalence of tibiofemoral osteoarthritis 15 years after non-operative treatment of anterior cruciate ligament injury: a prospective cohort study. *The American Journal of Sports Medicine*. 2008;36:1717-1725.
361. Roos E. Joint injury causes knee osteoarthritis in young adults. *Current Opinions in Rheumatology*. 2005;17:195-200.
362. Oiestad B. Knee osteoarthritis after anterior cruciate ligament injury. *The American Journal of Sports Medicine*. 2009;37:1434-1443.
363. Rudolph K. Age-related changes in strength, joint laxity, and walking patterns: are they related to knee osteoarthritis? *Physical Therapy*. 2007;87:1422-1432.
364. Bierma-Zeinstra S. Risk Factors and prognostic factors of hip and knee osteoarthritis. *Nature clinical Practice Rheumatology*. 2007;3:78-85.
365. Liu Y. An in situ study of the influence of a sclerosing solution in rabbit medial collateral ligaments and its junction strength. *Connective Tissue Research*. 1983;2:95-102.
366. Hackett G. Joint Stabilization: an experimental, histologic study with comments on the clinical application in ligament proliferation. *American Journal of Surgery*. 1955;89:968-973.
367. Reeves K, et al. Evidence-based regenerative injection therapy (Prolotherapy) in sports medicine. In Seidenberg PH, Beutler PI. (Eds). *The Sports Medicine Resource Manual*. Saunders (Elsevier); 2008;611-619.
368. Centeno C, et al. Fluoroscopically guided cervical Prolotherapy for instability with blinded pre and post radiographic reading. *Pain Physician*. 2005;8:67-72.
369. Fullerton B. High-resolution ultrasound and magnetic resonance imaging to document tissue repair after Prolotherapy: a report of 3 cases. *Archives of Physical Medicine and Rehabilitation*. 2008;89:377-385.
370. Kim J. Effects of Prolotherapy on knee joint pain due to ligament laxity. *The Journal of the Korean Pain Society*. 2004;17:47-50.
371. Kim J. The effect of Prolotherapy for osteoarthritis of the knee. *Journal of the Korean Academy of Rehabilitation Medicine*. 2002;26:445-448.
372. Reeves K, et al. Long-term effects of dextrose Prolotherapy injections for anterior cruciate ligament laxity. *Alternative Therapy Health Medicine*. 2003;9:58-62.
373. Rabago D, et al. *Dextrose Prolotherapy for knee osteoarthritis: Results of a randomized controlled trial* (Poster presentation); Osteoarthritis Research Society International (OARSI) World Congress on Osteoarthritis; San Diego California, September 15-17, 2011.
374. Reeves K, et al. Randomized prospective double-blind placebo-controlled study of dextrose Prolotherapy for knee osteoarthritis with or without ACL laxity. *Alternative Therapy Health Medicine*. 2000;6:77-80.
375. Haleem A, et al. The clinical use of human culture-expanded autologous bone marrow mesenchymal stem cells transplanted on platelet-rich fibrin glue in the treatment of articular cartilage defects: a pilot study and preliminary results. *Cartilage*. 2010;1:253-261.
376. Sanchez M, et al. Platelet-rich therapies in treatment of orthopedic sports injuries. *Sports Medicine*. 2009;39:345-354.
377. Kim S, et al. The effects of hyperosmolar dextrose and autologous serum injection in the experimental articular defect of rabbit. *Journal of the Korean Academy of Rehabilitation Medicine*. 2006;30:173-178.
378. Park Y, et al. Intra-articular injection of a nutritive mixture solution protects articular cartilage from osteoarthritic progression induced by anterior cruciate ligament transection in mature rabbits: a randomized controlled trial. *Arthritis Research and Therapy*. 2007;9:R8-R18.
379. Hauser R, et al. Standard clinical X-rays document cartilage regeneration with Prolotherapy. *Journal of Prolotherapy*. 2009;1(1):22-28.
380. Hauser R. The regeneration of articular cartilage with Prolotherapy. *Journal of Prolotherapy*. 2009;1(1):39-44.
381. Hauser R, et al. A retrospective study on dextrose Prolotherapy for unresolved knee pain at an outpatient charity clinic in rural Illinois. *Journal of Prolotherapy*. 2009;1(1):11-21.
382. Hauser R, et al. The case for utilizing Prolotherapy as first-line treatment of meniscal pathology: a retrospective study shows Prolotherapy is effective in treatment of MRI-documented meniscal tears and degeneration. *Journal of Prolotherapy*. 2010;2(3):416-437.
383. Hauser R, et al. Prolotherapy as an alternative to surgery. A prospective pilot study of 34 patients from a private medical practice. *Journal of Prolotherapy*. 2010;2(1):272-281.
384. Lazarou J. Incidence of adverse drug reactions in hospitalized patients. *JAMA*. 1998;279:1200-1205.
385. Centers for Disease Control and Prevention. Unintentional poisoning deaths-United States, 199-2004. *Journal of the American Medical Association*. 2007;297:1309-1311.

386. Wolfe M, Lichtenstein D. Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. *The New England Journal of Medicine*. 1999;340:1888-1899.
387. Bridger S, et al. Deaths from low dose paracetamol poisoning. *British Medical Journal*. 1998;316:1724-1725.
388. Hauser R. The acceleration of articular cartilage degeneration in osteoarthritis by nonsteroidal anti-inflammatory drugs. *Journal of Prolotherapy*. 2010;2(1):305-322.
389. Dorman T. Prolotherapy: A survey. *The Journal of Orthopaedic Medicine*. 1993;15:49-50.
390. Dagenais S, et al. Side effects and adverse events related to intraligamentous injection of sclerosing solutions (Prolotherapy) for back and neck pain: a survey of practitioners. *Archives of Physical Medicine and Rehabilitation*. 2006;87:909-913.
391. Schneider R, et al. Fatality after injection of sclerosing agent to precipitate fibro-osseous proliferation. *Journal of the American Medical Association*. 1959;8:1768-1772.
392. Keplinger J, et al. Paraplegia from treatment with sclerosing agents – report of a case. *Journal of the American Medical Association*. 1960;173:1333-1336.
393. Hunt W, et al. Complications following injection of sclerosing agent to precipitate fibro-osseous proliferation. *Journal of Neurosurgery*. 1961;18:461-465.
394. Topol G, et al. Hyperosmolar dextrose injection for recalcitrant Osgood-Schlatter disease. *Pediatrics*. 2001;128(5):e1-e8.