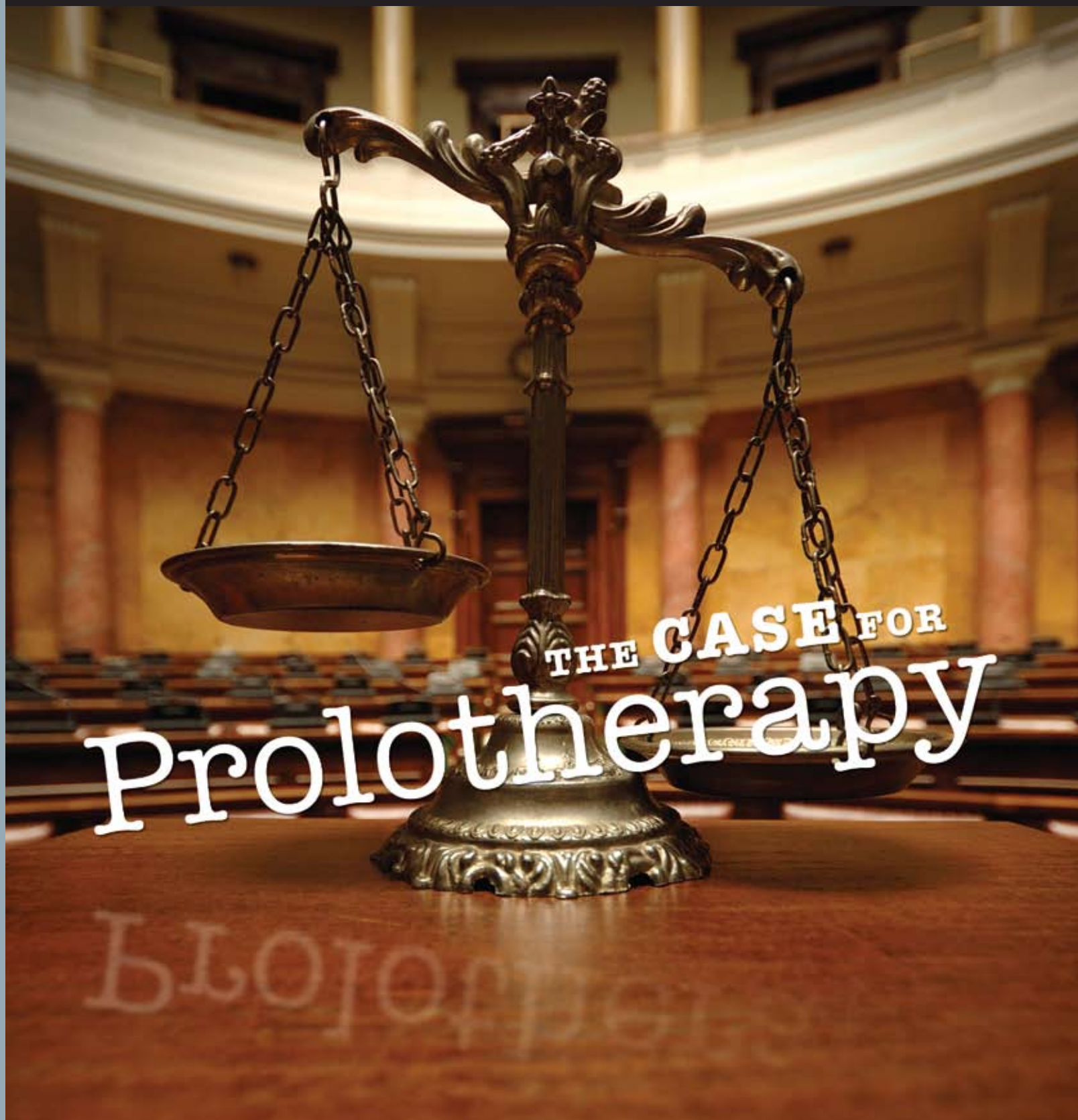
BEULAH LAND PRESS
ISSN 1944-0421 (print)
ISSN 1944-043X (online)

JOURNAL *of* PROLOTHERAPY [*for Doctors & Patients*]

VOLUME THREE | ISSUE FOUR | DECEMBER 2011 www.journal*of*prolotherapy.com



THE CASE FOR Prolotherapy

JOURNAL *of* PROLOTHERAPY
VOLUME THREE | ISSUE FOUR | DECEMBER 2011 | PAGES 737-848
BEULAH LAND PRESS

PROLOTHERAPISTS...

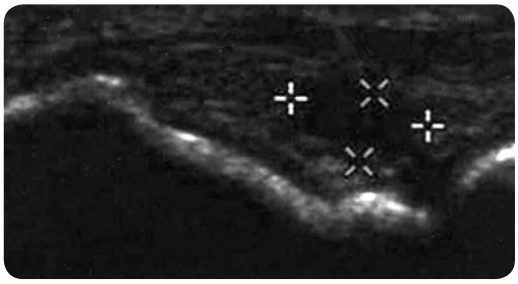
HELPING RELIEVE PAIN
ONE PATIENT AT A TIME

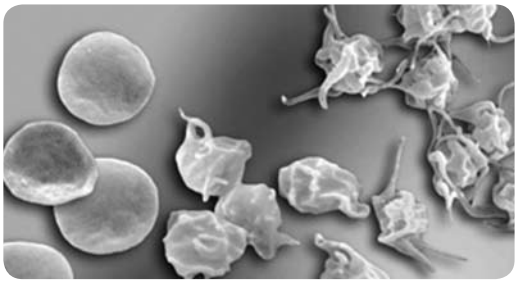
www.getprolo.com

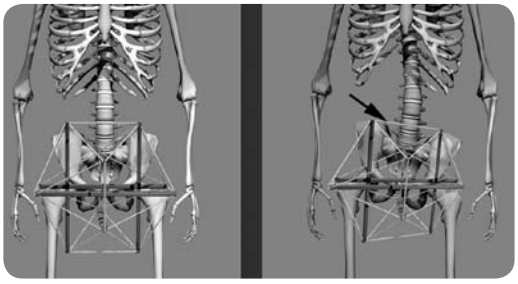
To find a Prolotherapist in your part of the world visit www.getprolo.com

IF YOU ARE A PROLOTHERAPIST & WOULD LIKE YOUR PRACTICE LISTED ON THIS WEBSITE PLEASE VISIT HTTP://GETPROLO.COM/APPLICATION.HTM

Table of Contents







JOP Team

Subscriber Information

ISSN 1944-0421 (print)
ISSN 1944-043X (online)

The *Journal of Prolotherapy*® is unique in that it has a target audience of both physicians and patients. The purpose of this journal is to provide the readers with new cutting-edge information on Prolotherapy, as well as provide a forum for physicians and patients alike to tell their stories.

The *Journal of Prolotherapy*® is published quarterly – in February, May, August, and November by Beulah Land Press, 715 Lake Street, Suite 600, Oak Park, Illinois, 60301. Beginning 2012, *JOP* will become an open access online medical journal.

All subscription inquiries, orders, back issues, claims, and renewals should be addressed to Beulah Land Press, 715 Lake St. Suite 600, Oak Park, IL 60301; phone: 708.848.5011; fax: 708.848.0978. Email: bairdn@journalofProlotherapy.com; http://beulahlandpress.com.

CLAIMS

Claims for undelivered copies must be made no later than one month following the month of publication. The publisher will supply missing copies when losses have been sustained in transit and when the reserve stock will permit.

CHANGE OF ADDRESS

Change of address notices should be sent to *JOP,* 30 days in advance to: JOP 715 Lake St. Suite 600, Oak Park, IL 60301; phone: 708.848.5011; fax: 708.848.0978.

COPYRIGHT PERMISSION

Permission requests to photocopy or otherwise reproduce copyrighted material owned by Beulah Land Press should be requested by contacting Beulah Land Press at 708.848.5011 or by emailing info@benuts.com.

DISCLAIMER

This publication does not constitute medical or other professional advice and should not be taken as such. To the extent the articles published herein may be used to assist in the care of patients, this is the result of the sole professional judgment of the health professional. The health care professional's judgment is the primary component of quality health care. The information presented in this journal is not a substitute for the exercise of such judgment by the health professional. The opinions expressed in the *Journal of Prolotherapy*® are the opinions of the authors of their respective articles and not necessarily that of the publisher. The decisions on what to do for a specific medical condition or symptom should be based on the analysis by the person's private health care professional.

Authors

NICOLE M. BAIRD, CHFP

Nicole M. Baird is a Certified Holistic Fitness Practitioner and is the Administrative Supervisor and Publications Manager for Caring Medical & Rehabilitation Services, as well as Beulah Land Corporation, in Oak Park, Illinois. Her passion for writing, nutrition, and food lead her down the path of co-authoring *The Hauser Diet: A Fresh Look at Healthy Living!* Nicole has an avid interest in nutrition, alternative medicine, exercise, and medical research and has used her knowledge to become an instrumental writer for many of the publications associated with Caring Medical/Beulah Land Corporation's printed materials, including patient brochures, website content, case studies, books, e-newsletters, and *JOP*. Nicole can be reached at Caring Medical & Rehabilitation Services, 715 Lake St. Suite 600, Oak Park, IL 60301; Tel: 708.848.7789; www.caringmedical.com and www.journalofprolotherapy.com.

ERIN E. DOLAN, RN

Erin E. Dolan, RN received her nursing degree from the University of St. Francis in May of 2009 and is a full-time nurse at Caring Medical & Rehabilitation Services in Oak Park, Illinois. Prior to nursing school, she spent eight years in the social service field working with individuals who had developmental disabilities and psychological disorders. Erin has written and researched for numerous health and Prolotherapy articles and blogs. She is passionate about patient care, health and fitness, and is an avid triathlete. Erin may be reached at 715 Lake St., Suite 600, Oak Park, IL 60301; Tel: 708.848.7789; www.caringmedical.com.

KARINA GORDIN, BA, MS

Karina Gordin graduated from Tufts University in 2007 with a bachelor's degree in English, emphasizing creative writing. In 2009 she received a Masters of Natural Products from Massachusetts College of Pharmacy and Health Sciences. Karina has officially combined both degrees to pursue medical journalism, and has since written for publications including *Townsend Letter*, *Healthcare Ledger*, *Lilipoh*, *Natural Standard database*, and *RN Journal*, among others. She is currently developing her own seasonal publication, as well as blogging on the theme of health freedom and wellness. Writing for *Journal of Prolotherapy* has undoubtedly been an unparalleled opportunity and privilege, and Karina always looks forward to collaborating with the publication to provide the kind of ground-breaking reports that can change the world. To contact Karina, email her at write@healthwright.org.

JULIE R. GUNNIGLE, JD

Julie R. Gunnigle, JD is an attorney specializing in litigation and intellectual property. She received her Bachelor of Science in Chemistry from Northern Arizona University, and her Juris Doctorate from the University of Notre Dame Law School. She recently left her position as a Cook County Assistant State's Attorney to open a solo practice in Scottsdale, Arizona. She is licensed to practice in Indiana, Illinois, and before the United States Patent and Trademark Office. Her interests include hiking and trail running. To contact Julie, you may email her at juliegunnigle@gmail.com.

MARION A. HAUSER, MS, RD

Marion A. Hauser, MS, RD received her Bachelor of Science in Nutrition from University of Illinois and her Master of Science in Nutrition and dietetic internship from Eastern Illinois University. Marion is the CEO of Caring Medical and Rehabilitation Services in Oak Park, Illinois and owner of Beulah Land Nutritionals. Marion is one of the primary writers for and manager over the material published by Caring Medical/Beulah Land Corp, including web content, blogs, newsletters, case studies, books, patient materials, and *JOP*. Marion has co-authored *"The Hauser Diet: A Fresh Look at Healthy Living"* and the national best seller entitled *"Prolo Your Pain Away! Curing Chronic Pain with Prolotherapy"* along with a four-book mini series of Prolotherapy books, as well as a comprehensive sports book discussing the use of Prolotherapy for sports injuries. Marion Hauser may be reached at 715 Lake St. Suite 600, Oak Park, IL 60301; Tel: 708.848.7789; www.caringmedical.com.

ROSS A. HAUSER, MD

Ross A. Hauser, MD is board certified in Physical Medicine and Rehabilitation. He received his undergraduate degree from University of Illinois, graduated from the University of Illinois College of Medicine in Chicago, and did his residency at Loyola/Hines VA in Physical Medicine and Rehabilitation. Dr. Hauser is the Medical Director of Caring Medical and Rehabilitation Services in Oak Park, Illinois and is passionate about Prolotherapy and natural medicine. Dr. Hauser and his wife Marion, have written seven books on Prolotherapy, including the national best seller *"Prolo Your Pain Away! Curing Chronic Pain with Prolotherapy,"* now in its third edition, a four-book mini series of Prolotherapy books, and a 900-page epic sports book on the use of Prolotherapy for sports injuries. Dr. Hauser is the current editor-in-chief of the *Journal of Prolotherapy*® and has published a number of outcome studies on the use of dextrose Prolotherapy for a wide array of conditions. Dr. Hauser may be reached at 715 Lake St., Suite 600, Oak Park, IL 60301; Tel: 708.848.7789; www.caringmedical.com.

NICHOLE JENSEN, BS

Nichole Jensen is a 2010 graduate from the University of Minnesota – Twin Cities with a degree in Kinesiology, BS, and minor in biology. She is currently applying to medical school and for an Air Force scholarship with plans of pursuing a career in either Sports Medicine or Emergency Medicine. Nichole works as a receptionist/assistant for Dr. Mark Wheaton at Lakeside Sports and Pain Clinic in Excelsior, Minnesota. She also works part time as a scribe in the emergency room. Nichole enjoys running, as well as cooking and hanging out with friends in her free time.

HAVIL S. MADDELA, BS

Havil S. Maddela has a BS in biology from Loyola University, Chicago. He has a passion for patient care and medical missionary work. Havil is currently a medical student at St. George's University in Grenada, West Indies. Prior to medical school, he worked as a clinical member at Caring Medical and Rehabilitation Services in Oak Park, Illinois, and has been instrumental in the publication of previous Prolotherapy articles.

THOMAS RAVIN, MD

Thomas Ravin, MD attended Colorado College and spent a year abroad at the University of Glasgow in Scotland. After graduating from the University of Colorado Medical School, Dr. Ravin completed an internship at Madigan Army Hospital in Tacoma, Washington. He was in the Special Forces for two years, which included one year in Southeast Asia. He completed both a radiology residency at Fitzsimmons Army Hospital in Denver and a nuclear medicine fellowship at the University of Missouri in Columbia. In addition to promoting Prolotherapy around the world, Dr. Ravin continues to ski race and train in the USSA Masters program. He bicycles between 2,000 and 3,000 miles annually and is a passionate devotee of Pilates. The injuries he has sustained during these activities have spurred his interest particularly in the aches and pains of the active adult athlete. Dr. Ravin feels that Prolotherapy is an underused treatment tool and can keep adult athletes doing the activities they love as Dr. Ravin, in his late sixties, can attest to. Dr. Ravin may be reached at 45 S. Dahlia, St., Denver, CO, 80246; Tel: 303.331.9339; www.tomravinmd.com.

MARK T. WHEATON, MD

Mark T. Wheaton, MD is board-certified in Physical Medicine and Rehabilitation, with fellowship training in Sports Medicine, and has performed Prolotherapy since 1996 in his private practice, Lakeside Sports and Pain Clinic, in Excelsior, Minnesota. Dr. Wheaton was a contributing author to the Hausers' *Prolo Your Pain Away!* and *Prolo Your Sports Injuries Away!* books and was privileged to be a volunteer at their medical missionary clinic for almost 10 years. He also enjoys his role as a Prolotherapy instructor and lecturer, stating, "I owe a great debt to Dr. Gustav Hemwall, who graciously taught the technique of Prolotherapy to me and many other current Prolotherapists through his books and seminars." Dr. Wheaton also uses other complementary methods such as Neural Therapy, Neurotransmitter Therapy, Electrotherapy, Physical Therapy, and Manual Muscle Therapy in his practice. Dr. Wheaton can be reached at Lakeside Sports and Pain Clinic, 21920 Minnetonka Blvd., Excelsior, MN 55331; Tel: 952.593.0500; www.drmarkwheaton.com.

The Case for Prolotherapy – The Opening Argument

Julie R. Gunnigle, JD

AN OPENING ARGUMENT

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

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

PROLOTHERAPY IS EVIDENCE-BASED MEDICINE

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

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

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

PATIENTS DESERVE MORE THAN PAIN MANAGEMENT

In 2001, I caught the front edge of my snowboard during a ski trip in Arizona. My nose caught the snowboard, but my shoulder absorbed most of the impact as I tumbled down the slopes. What seemed like a minor injury at the time (perhaps minor compared to a very gruesome looking nose), never healed correctly and caused pain for years. In what is all too common a story, doctors treated my injury by managing the pain. After multiple consultations and other treatments, I was told that my only option was pain management.

Patients deserve better than having their pain "managed." Patients need and deserve to have their pain resolved. In this issue you will read about how Prolotherapy not only diminishes pain, but is able to strengthen and stabilize painful ligaments. Prolotherapy addresses the underlying problem, not just the symptom of pain.

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

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

Prolotherapy is not merely pain management; it is pain resolution.

PROLOTHERAPY SHOULD BE OFFERED AS A FIRST TREATMENT AND NOT A LAST RESORT

By the time I found Prolotherapy, I had already experienced countless treatments that were not effective. Many patients find Prolotherapy after another doctor has told them that there are no more options or that surgery is the only option.

When a treatment is supported by level A or B evidence it is the recommendation that the clinician provide this service to eligible patients. If patients were to receive Prolotherapy before more invasive services, perhaps many surgeries could be forgone, netting a huge savings in health costs. Further, by promptly treating injuries before they develop into more serious degenerative illnesses, patients would experience fewer disabilities and a higher quality of life.

PROLOTHERAPY IS WELL ESTABLISHED

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

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

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

Not only is the efficacy of Prolotherapy supported by the literature, but Prolotherapy has its own specialty college within the American Osteopathic Association, is performed

and taught at the University of Wisconsin School of Medicine, and has even been cited by the Mayo Clinic as a treatment for ligament pain. Furthermore, Prolotherapy training is a requirement in the neuromuscular residency training for Osteopathic doctors, and is common in Osteopathic medical schools and universities.

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

THE VERDICT FOR PROLOTHERAPY

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

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

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

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 joint[9]; 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 Sylnasol (sodium psylliate), a five percent solution of fatty acid, to stabilize temporomandibular joints after he found that the solution could induce fibrogenesis of the injured tissues without causing adverse effects on non-involved tissues.[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 Sylnasol injections. He was the first to coin the term Prolotherapy. He eventually published a medical book entitled *Ligament and Tendon Relaxation Treated by Prolotherapy* in which he noted, "The treatment consists of the injection of a solution within the relaxed ligament and tendon which will stimulate the production of new fibrous tissue and bone cells that will strengthen the 'weld' of fibrous tissue and bone to stabilize the articulation and permanently eliminate the disability. To the treatment of proliferating new cells, I have applied the name *Prolotherapy* from the word 'proli-' (Latin) meaning offspring; 'proliferate'-to produce new cells in rapid succession."[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-HEMWALL 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 fingers[188-203]
- Degenerative spinal disease including spondylosis, spondylolisthesis and degenerative disc disease[204-209]
- Osteochondral defects[210-215]

Joint Instability

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

- Ligament tears and injury[216-220]
- Labral tears and degeneration[221]
- Meniscus tears and degeneration[222, 223]
- Congenital conditions such as joint hypermobility syndrome and Ehlers-Danlos syndrome[224]

Tendinopathy

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

- Tendinopathy[225-231]
- Tendinosis[232-235]
- Tendinitis[236-240]
- Grade one and two tears (partial tears)[241-242]
- Enthesopathies including osteitis pubis and medial tibial stress syndrome[243-245]
- Muscle origin pain and tears[246-248]

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 syndrome[253-256]

- Fibromyalgia[257]
- Complex Regional Pain syndrome[258]
- Chronic headaches[259-262]
- Radiculopathy[263, 264]
- Autonomic symptoms, including Barré-Lieou syndrome[265-268]
- Apophyseal growth plate injuries, including Osgood-Schlatter disease[87, 394]
- Other[269-278]

PROLOTHERAPY AS AN ALTERNATIVE TREATMENT

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

- Tendinitis or bursitis[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 repairs[290-292]
- 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 arthrocopic 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 then 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. ■

BIBLIOGRPAHY

1. Babcok, 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.hackettthemwall.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. *Mobility 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 cruicate 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: Hanleey 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 Phyiology 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 Biophysic 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 Paloa 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 pathophysiologic 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. Escarpanter J, et al. Resultados terapeuticos en la osteoarthritis de la rodilla con infiltraciones de ozona. *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. Washuttl 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 Biotechol.* 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, umbelicial 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 Biotechol.* 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;1:1:23-32.

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. Ebrahimian 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. Connoly 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 atulogous 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 Orthopedics 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. Muscler 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. Connoly 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. Muscler G, et al. Selective retention of bone marrow-derived cells to enhance spinal fusion. *Clinical Orthopedics 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. Diekman 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;8:203-212.

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 epicondylosis: 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/bjsm.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-Lieou 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 casing 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 autlogous bone marrow grafting. *Clincal 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 autogous 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. Autlogous 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 autlogous 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 Rheumatologic 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 Rheumtologic 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 microscopial study of the effects of crystalloid and water-soluble glucocorticoids on articular cartilage. *Scandanavian 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 hylauronic acid in treatmen 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 Assessement 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 osteoarthtis 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 osteoarthtritic 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. Johsnon 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 transaction 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.

ABSTRACT

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

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

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

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

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

Journal of Prolotherapy. 2011;3(4):765-789.
KEYWORDS: chronic musculoskeletal pain, clinical evidence, degenerative joint disease, dextrose Prolotherapy, level of evidence, ligament laxity, Osgood-Schlatter disease, osteoarthritis, scientific literature review, tendinopathy.

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

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

Introduction

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

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

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

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

Prolotherapy has emerged as a cost-effective treatment option for chronic musculoskeletal and arthritic pain. It involves the injection of a small amount of solution into multiple painful ligament and tendon insertions (enthesis), typical trigger points, as well as into the adjacent joint spaces to induce healing of the injured structures. It is presumed to work by stimulating weakened structures such as ligaments and tendons to strengthen, tighten and heal by the induced proliferation of cells. George S. Hackett, MD, a trauma surgeon from Canton, Ohio, who coined the term in the mid 1950s describes it this way, "The treatment consists of the injection of a solution within the relaxed ligament and tendon which will stimulate the production of new fibrous tissue and bone cells that will strengthen the 'weld' of fibrous tissue and bone to stabilize the articulation and permanently eliminate the disability…My definition of Prolotherapy as applied medically in the treatment of skeletal disability is 'the rehabilitation of an incompetent structure by the generation of new cellular tissue.'"[10, 11] Though the exact process by which Prolotherapy decreases pain and reduces skeletal disability is debated, Prolotherapy has been found historically to induce ligament and tendon hypertrophy[12, 13] and strengthening,[14,15] stabilize unstable joints such as the sacroiliac joint, cervical spine and temporomandibular joint[16-18]; as well as eliminate musculoskeletal pain in all joints of the body including the knees, shoulders, and ankles,[19, 20] and induce musculoskeletal repair via the stimulation of growth factors via the inflammatory healing cascade,[21-25] as well as reduce neurogenic inflammation.[26, 27] While there are many solutions that can be used in Prolotherapy, including pumice, P2G (dextrose, phenol, glycerin), sodium morrhuate and more recently, platelet rich plasma, stem cell, and lipoaspirate, the most common solution used is dextrose.[28-33] Gustav A. Hemwall, MD, is credited as the first doctor to use just dextrose by itself as the proliferant for Prolotherapy, when Sylnasol (fatty acid derivative) was no longer available.[34] This is why dextrose Prolotherapy case studies do not start appearing in the medical literature until the early 1980s, whereas other Prolotherapy articles and case reports using other proliferants appear much earlier.[35, 36] Typical concentrations of dextrose used in Prolotherapy are from five to twenty-five percent.[37, 38]

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

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

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

Dextrose Prolotherapy, if widely used, could have a tremendous impact on reducing musculoskeletal pain, disability and cost because of the following: nine to twenty percent of adults in the United States experience chronic pain[65, 66]; of these 89% have some degree of long-term or short-term disability[67]; nearly all chronic pain patients have substantially reduced health-related quality of life[68]; ligament injuries often fail to heal completely[69]; unresolved ligament tears and sprains can completely alter joint mechanics[70, 71]; ligament and tendon injuries account for 45% of all musculoskeletal injuries in the United States[72]; ligament laxity and its associated joint instability is a leading cause of spinal and joint degeneration[73-75]; and when hypermobility is sought it is the most common finding among patients presenting to a rheumatologist.[76] To help determine the efficacy for dextrose Prolotherapy to treat these and other musculoskeletal conditions, we undertook this scientific literature review.

OBJECTIVE

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

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

METHODS

All research articles, case series and case reports, nonrandomized and randomized controlled studies involving at least five human subjects that involved dextrose Prolotherapy injections were included. Only those that used exclusively dextrose as the proliferant and/or an anesthetic were included. Dextrose Prolotherapy articles that used P2G, which includes phenol, glycerin and dextrose and sodium morrhuate were excluded, as were those in which patients also received high velocity manipulation. All other forms of Prolotherapy, including those using pumice, platelet rich plasma, bone marrow, lipoaspirate, and stem cells were also excluded. When patients were educated on specific types of exercises to perform, this information is provided in the analysis. All data was obtained by a thorough search of electronic databases including the most common medical search engines including PUBMED, OMNIMEDICALHEALTHLINE, MEDLINE, EMBASE, AMED, CINAHL and MEDSCAPE. To be included, at least one outcome measure related to pain intensity, such as the visual analog scale (VAS) or numerical rating scale (NRS) had to be measured. The primary outcome for this review was relief of musculoskeletal pain with dextrose Prolotherapy injections. The search found references in both the English and Korean languages. Research articles and case studies were found in American, Korean, British and Australian medical journals.

RESULTS

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

Case Reports and Case Studies of Dextrose Prolotherapy

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

CHRONIC MUSCULOSKELETAL PAIN

Kim, Shin and Seo[78] report on treating 67 patients with chronic musculoskeletal pain (average of 5.48 years) with two monthly sessions of 15% dextrose Prolotherapy. The VAS showed a statistically significant reduction of pain from 7.0 to 4.31 after the first set of injections and went down to 2.55 after the second series of injections. (*See Table 1.*) Kim et al.[79] did a similar report on 20 patients with chronic musculoskeletal pain treated once with a 12.5% dextrose solution. This study showed that one dextrose Prolotherapy treatment reduced VAS by 80% (ratio of pre/post VAS of 0.36).

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

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

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

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

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

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

NONSPECIFIC LOW BACK AND PELVIC PAIN

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

LOW BACK AND PELVIC PAIN DUE TO SPECIFIC CAUSES

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

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

Topol et al. studied the efficacy of 12.5% dextrose Prolotherapy in 24 elite kicking-sport athletes (soccer and rugby) with chronic groin pain on average for 15 months from osteitis pubis and/or adductor tendinopathy.[97] Monthly injections were given into the enthesis around the symphysis pubis. On average 2.8 treatments were given. Final data collection was on average 17.2 months after the last Prolotherapy session. The mean reduction in pain during sports as measured by the VAS improved from 6.3 to 1.0 and the mean reduction in Nirschl Pain Phase Scale (NPPS) score improved from 5.3 to 0.8 (both $p<0.001$). Twenty of the 24 patients had no pain and 22 of 24 were unrestricted with sports at final data collection. Naeim et al. used a 25% dextrose/1% lidocaine solution to perform a pilot study on seven patients with iliolumbar syndrome.[98] The dextrose Prolotherapy injection therapy resolved the pain in six out of the seven patients (rated six good results and one poor result). This was compared with nine patients who received a 1% lidocaine solution injected in the same location with only four out of nine having good results. Khan studied 37 patients with chronic non-responding coccygodynia treated with dextrose Prolotherapy.[99] A VAS was recorded for all patients before and after injection of a 20% dextrose/0.4% lidocaine solution into the coccyx. Depending on pain relief, patients were given a second injection at two weeks and a third one at the six week mark. The mean VAS before Prolotherapy was 8.5. It was 3.4 after the first injection and 2.5 after the second injection. Miller et al. performed a prospective consecutive patient series using bi-weekly disc space injections of dextrose Prolotherapy (25% dextrose/0.25T bupivicaine, 3cc total solution used) for patients experiencing chronic advanced degenerative discogenic leg pain, with or without low back pain on average for 39 months.[100] Seventy-six patients with moderate to severe degenerative disc disease without herniation and with concordant pain reproduction with CT discography were included. All had failed physical therapy and fluoroscopically guided epidural steroid injection treatment. Each patient was injected on average 3.5 times. In the responder group (33/76) the mean numeric (0-10) pain scale ratings were 8.9 at study entry and 2.5 at two months and 2.6 at 18 months (average) after the last Prolotherapy session. Forty-three out of 76 patients experienced less than 20% pain relief and were considered non-responders. Overall, 48.4% of patients fell into the sustained improvement group with an average improvement in numeric pain scores of 71%, comparing pre-treatment and 18 month measurements.

NONSPECIFIC KNEE PAIN

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

KNEE PAIN DUE TO SPECIFIC CAUSES

Jo et al. treated 40 patients with ligament injury of the knee with 15% dextrose Prolotherapy.[102] VAS pain scores were recorded before, one, two, four, and eight weeks after one Prolotherapy treatment. VAS scores dropped from 8.0 to 1.3, eight weeks after the dextrose Prolotherapy treatment. Hauser[103] performed a retrospective study utilizing dextrose Prolotherapy as first-line treatment for 28 knees in 24 patients with MRI-documented meniscal pathology including 18 with tears. The average number of Prolotherapy visits per patient was six, using 12.5% dextrose, given every four to six weeks. Dextrose Prolotherapy caused a statistically significant decline in patients' knee pain and stiffness, decreasing from 7.2 to 1.6 and 6.0 to 1.8, respectively. Only

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

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

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

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

Ryan et al. prospectively evaluated the treatment of overuse patellar tendinopathy in 47 patients (mean duration 21.8 months).[106] Under ultrasound guidance, 25% dextrose was injected into abnormal hypoechoic areas and anechoic clefts/foci in the thickened portion of the patellar tendon. Patients received a median of 4 injections an average of 6.4 weeks apart. At 45 week follow-up, mean baseline and follow-up pain scores (VAS) were: pain at rest, 38.4 and 18.7 ($P<0.01$); pain with ADLs, 51.1 and 25.8 ($P<0.01$); and pain with sport activity, 78.1 and 38.8 ($P<0.01$). (*See Table 4.*) Pain scores improved by 51% at rest, 49.5% during ADLs, and 50% during sport activity (all $P<0.01$), and 53% of patients reported ≥50% pain reduction. Pre-post (n) ultrasound evaluation of intratendinous tearing revealed that VAS pain scores at rest, during ADLs and during sport activity correlated with changes to echotexture severity (r values 0.306, 0.379 and 0.428, respectively; $P<0.05$); as pain scores decreased, echotexture improved.

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

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

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

NONSPECIFIC HEADACHE, NECK AND TMJ PAIN

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

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

SPECIFIC NECK PAIN

Hooper et al. did a case series on 15 patients (18 sides) with chronic whiplash related neck pain (14 patients had motor vehicle accidents) treated with intraarticular zygapophysial joint dextrose Prolotherapy injection therapy.[112] Intraarticular Prolotherapy was given by placing 0.5 to 1cc of 20% dextrose solution into each zygapophysial joint, after confirmation of location with radiographic contrast. The mean Neck Disability Index (NDI) was 24.7 and decreased post treatment to 14.2 (2 months), 13.5 (6 months) and 10.9 (12 months). The average change over 12 months reached statistical significance ($p<0.0001$). Centeno et al. documented that fluoroscopically guided cervical 12.5% dextrose Prolotherapy for instability could resolve the neck instability and the pain.[113] Six patients who had documented cervical instability at 11 cervical levels from a motor vehicle accident, were treated with fluoroscopically guided cervical dextrose Prolotherapy at the sites of the instability. Patients with more than 2.7 mm of absolute cervical translation and at least 50% reduction of cervical and referred pain with a two day rigid cervical immobilization test were admitted into the study. Participants underwent three dextrose Prolotherapy injections at all sites where the cervical instability was demonstrated. The mean post-test VAS score of 3.8 was significantly less than the mean pre-test VAS score of 5.8. Radiographic analysis by blinded radiologists after dextrose Prolotherapy also showed significant reductions in extension and flexion translation of cervical vertebrae in the areas that, prior to Prolotherapy, showed instability. (*See Figure 1.*)

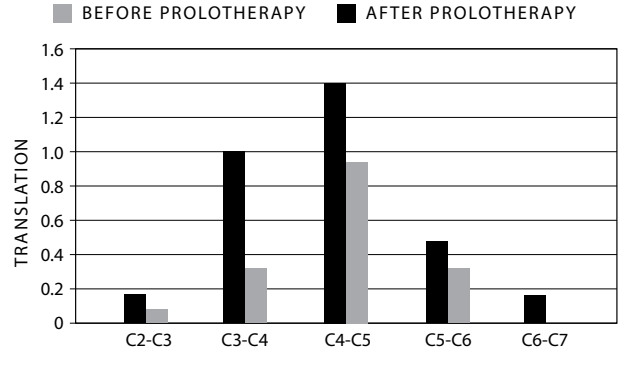


Figure 1. Translation in cervical flexion after three Prolotherapy injections.
Adapted from: Centeno CJ, Elliott J, Elkins WL. Fluoroscopically guided cervical Prolotherapy for instability with blinded pre and post radiographic reading. *Pain Physician*. 2005;8:67-72. Figure 1.

NONSPECIFIC ELBOW PAIN

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

LATERAL EPICONDYLAR PAIN OF THE ELBOW

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

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

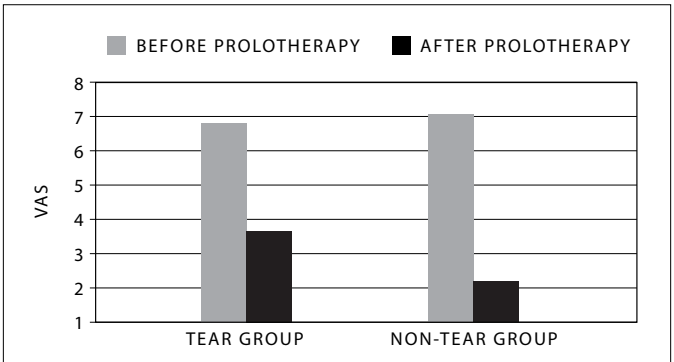


Figure 2. Comparison of treatment effect according to the findings of ultrasonography (Tear vs. Non-tear) (p<0.01).
Adapted from: Shin JY, Seo KM, Kim DK. The effect of Prolotherapy on lateral epicondylitis of elbow. *The Journal of the Korean Academy of Rehabilitation Medicine*. 2002;26:764-768. Figure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

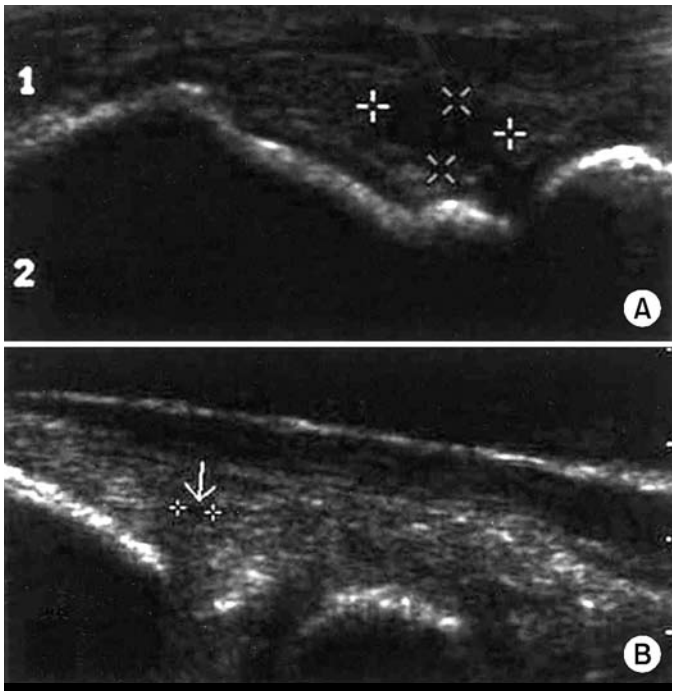


Figure 3. Ultrasound of lateral elbow before and after Prolotherapy. Initial anechoic focus (A) was filled with fibrillar pattern except small anechoic focus after treatment (B).
Used with permission from: Kang SH, Seo KM, Kim DK. Ultrasonographic findings of chronic lateral epicondylitis with partial tear before and after Prolotherapy. *The Journal of the Korean Academy of Rehabilitation Medicine*. 2004;28:88-93. Figure 6.

ACHILLES TENDINOPATHY

Lyftogt treated 169 Achilles tendons over a four year period with chronic Achilles tendinopathy (average length of symptoms two years) with subcutaneous dextrose Prolotherapy.[117] Initial VAS of the group went from 6.5 to 0.5 after six treatments, with a follow-up period of two years. Ninety percent of patients were satisfied with the treatments.[118] Maxwell published a study on the use of hyperosmolar dextrose (25%) to treat 32 patients representing 33 tendons with chronic tendinosis of the Achilles with the use of ultrasound.[119] The patients were treated every six weeks until symptoms resolved or no improvement was shown. The mean number of treatment sessions was 4.0. A mean percentage reduction for VAS1 (pain at rest) of 88.2% (p<0.0001), for VAS2 (pain during normal daily activity) of 84.0% (p<0.0001), and for VAS3 (pain during or after sporting activities) of 78.1% (p<0.0001) was observed. (*See Table 5.*) They also documented that the dextrose Prolotherapy caused the mean tendon thickness to decrease from 11.7 to 11.1 mm (p<0.007). At a mean of 12 months after treatment, 20 patients remained asymptomatic, nine experienced only mild symptoms, and one patient reported moderate symptoms.

Ryan, Wong and Taunton[120] administered a 25% dextrose-lidocaine solution intratendinously on 108 Achilles tendons in 99 patients experiencing pain for greater than six months at either the Achilles tendon insertion or midportion. Eighty-six of the cases were at the Achilles midportion, and 22 reported pain and pathology at the insertion. The chronic Achilles tendinoses were documented by ultrasound and the injections were sonographically guided. VAS items were recorded at baseline, post-treatment and at a 28.6 month follow-up. A median of five injection sessions was needed for each patient, spaced on average 5.6 weeks

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

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

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

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

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

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

Hauser et al. published six other observational (pilot) studies on the use of dextrose Prolotherapy for chronic pain of the ankle, foot, wrist, hand, shoulder, and hip.[121-126] Hauser reported on 19 patients with chronic ankle pain (average 3.3 years) treated with 15% dextrose Prolotherapy.[121] The mean number of treatments was 4.4. Starting NRS and stiffness levels were 7.9 and 5.4, respectively, and decreased to 1.6 and 1.5, respectively, at mean 21 month follow-up, reaching statistical significance. All but one patient achieved greater than 50% pain relief. Hauser performed a similar observational study on 19 patients with chronic foot and toe pain.[122] All 100% improved in their pain and stiffness with 15% dextrose Prolotherapy. NRS scores decreased from 7.1 to 2.3, with 18 month follow-up. The results of his study on 31 patients with chronic wrist pain showed that dextrose Prolotherapy decreased VAS from 5.5 to 1.4 after 3.6 treatments.[123] For the 40 patients who suffered from chronic hand and finger pain, dextrose Prolotherapy caused NRS to decrease from 5.9 to 2.6 after an average of 4.5 treatments.[124] Hauser performed a retrospective study on 61 patients representing 94 hips who had been in pain on average for 63 months, and were treated quarterly with Hackett-Hemwall dextrose Prolotherapy. Pain levels decreased from 7.0 to 2.4 (NRS) after Prolotherapy; 89% experienced more than 50% of pain relief and more than 94% showed improvements in walking and exercise ability.[125] Another retrospective study on 94 shoulders in 90 patients with an average of 53 months of unresolved shoulder pain showed that pain levels decreased with 15% dextrose Prolotherapy from 7.1 to 2.3 (NRS) after an average of 3.8 treatments with an average follow-up time of 20 months.[126] All of the Hauser studies reached statistical significance using the paired t-test for pain relief to at least the $p<0.01$ level. Jo et al. of Korea performed a dextrose Prolotherapy study on 29 patients suffering from shoulder pain.[127] The 15% dextrose Prolotherapy decreased pain levels from 7.2 to 2.0 (NRS), eight weeks after the last treatment, which was statistically significant at the $p<0.05$ level.

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

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

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

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

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

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

CHRONIC SPINAL PAIN: LITIGANTS AND NON-LITIGANTS

Researchers from several international universities collaborated to compare outcomes for litigants and non-litigants with chronic spinal pain treated with dextrose Prolotherapy.[132] A total of 147 consecutive patients with chronic spinal pain were treated with 20% dextrose and 0.75% lidocaine into facet capsules of the cervical, thoracic, or lumbar spine, as well as the iliolumbar and dorsal sacroiliac ligaments. Injections were given on a weekly basis for up to three weeks. A set of three injections was repeated in one month if symptoms persisted and ongoing laxity was identified. Seventy-one litigants (had retained a lawyer for an unresolved claim at the start of treatment) and 76 non-litigants were treated. They were given the Neck Disability Index, Patient Specific Functional Scale, and Roland-Morris Disability Questionnaire before treatment and approximately one year after treatment. At the 1-year follow-up, patients were also asked to rate their change in symptoms, function, and ability to work. Both litigants and non-litigants showed significant improvement from baseline on all disability scales ($p<0.001$). There were no differences in the percentage of litigants/non-litigants reporting improvement on impression of change scales or symptoms (91%/92%), function (90%/90%), improved ability to work (76%/75%), and willingness to repeat treatment (91%/93%).

DEXTROSE PROLOTHERAPY IN LIEU OF SURGERY

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

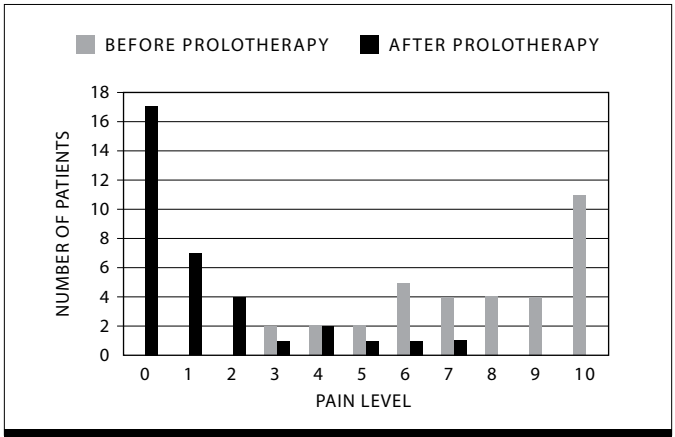


Figure 4. Before and after pain levels in 34 patients who received Hackett-Hemwall dextrose Prolotherapy in lieu of surgery.

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

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

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

CONTROLLED, NONRANDOMIZED DEXTROSE PROLOTHERAPY STUDIES

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

Randomized Controlled Studies on Dextrose Prolotherapy

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

DEXTROSE PROLOTHERAPY COMPARED TO STEROID FOR SACROILIAC JOINT PAIN

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

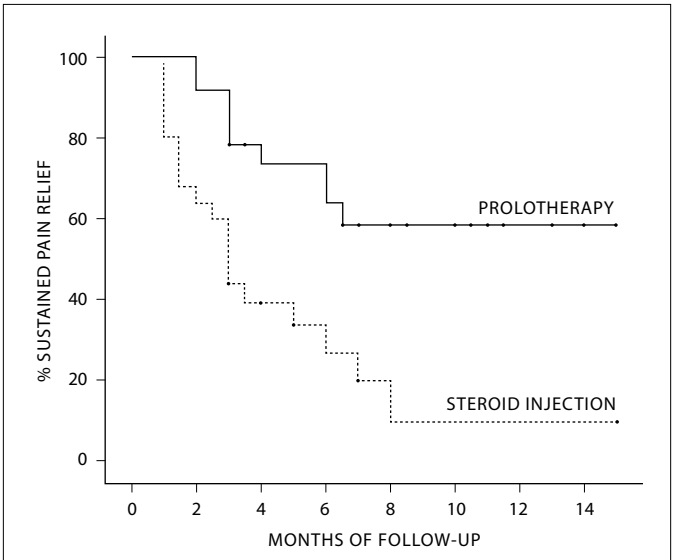


Figure 5. Kaplan-Meier plot showing cumulative incidence of sustained 50% or greater pain relief, higher in the Prolotherapy group compared to the steroid group.

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

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

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

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

Kim, Na and Moon from Yonsei University College of Medicine in Korea did a prospective, randomized controlled study comparing 5% dextrose Prolotherapy with saline and lidocaine trigger point injections for myofascial pain syndrome.[137] Sixty-four typical myofascial pain patients were injected with either 5% dextrose (23), normal saline (20) or 0.5% lidocaine (21) into their tender trigger points. VAS and pressure threshold algometer (kg/cm^2) were used as measuring tools before, immediately after, and seven days after the injection therapies. The Mean VAS was 6.8 before treatment. Mean VAS was not significantly different in the three groups before and immediately after injections. But after seven days, only the dextrose group showed significantly

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

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

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

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

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

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

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

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

Reeves and Hassanein published two randomized, prospective, placebo-controlled double-blind studies on dextrose Prolotherapy for osteoarthritis of the thumb, fingers and knees.[138, 139] In the first study, osteoarthritic thumbs and fingers were treated either with a 10% dextrose/0.075% xylocaine solution or a 0.075% xylocaine solution alone.[138] Seventy-four symptomatic osteoarthritis joints received dextrose Prolotherapy and seventy-six osteoarthritic joints received xylocaine injections. The injections into the joints was done at 0, 2, and 4 months with assessment at six months after the first injections. Pain at rest, grip and pain with movement improved more in the dextrose group than the xylocaine group. (*See Figure 6.*) Pain with movement improved 42% in the dextrose group compared to 15% in the xylocaine group to reach statistical significance ($p<0.027$). Flexion range of motion improved more in the dextrose group ($p=.003$). In a similar study on knee osteoarthritis, Reeves and Hassanein completed three bimonthly injections of 9cc of either 10% dextrose and .075% lidocaine versus .075% lidocaine solution in patients with knee osteoarthritis (grade 2) with or without ACL laxity.[139] In total, 111 knees involving 68 patients with OA participated in this double-blind randomized placebo-controlled study. The Hotelling multivariate analysis of paired observations between 0 and 6 months for pain, swelling, buckling episodes and knee flexion revealed significantly more benefit from the dextrose injection group. By 12 months (six injections) the dextrose-treated knees improved in pain (44% decrease), swelling complaints (63% decrease), knee buckling frequency (85% decrease), and in flexion range (14 degrees increase). Analysis of blinded radiographic readings of zero- and 12-month films revealed stability of all radiographic variables except for two variables which improved with statistical significance (lateral patellofemoral cartilage thickness ($p=.019$) and distal femur width in mm ($p=.021$). In knees with ACL laxity the Hotelling multivariate analysis of paired values at 0 and 12 months for pain, swelling, joint flexion and joint laxity in the dextrose-treated knees, revealed a statistically significant improvement ($p=.021$). Individual paired *t*-tests indicated that blinded measurements of goniometric knee flexion

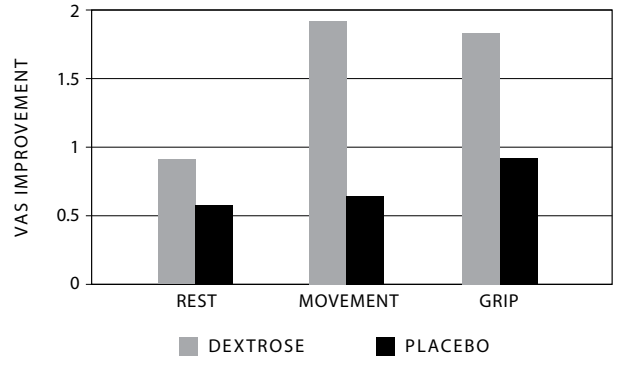


Figure 6. Improvement of Visual Analogue Scale (VAS) for rest pain, movement pain, and grip pain between 0 and 6 months in osteoarthritic joints comparing dextrose Prolotherapy versus placebo.
Adapted from: Reeves KD, Hassanein K. Randomized, prospective, placebo-controlled double-blind study of dextrose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

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

DEXTROSE PROLOTHERAPY VERSUS LIDOCAINE INJECTIONS VERSUS USUAL CARE

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

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

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

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

DEXTROSE PROLOTHERAPY VERSUS SALINE INJECTIONS AND EXERCISE FOR KNEE OSTEOARTHRITIS

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

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

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

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

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

DEXTROSE PROLOTHERAPY COMPARED TO ECCENTRIC LOADING EXERCISES FOR ACHILLES TENDINOSIS

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

DEXTROSE PROLOTHERAPY VERSUS SALINE INJECTIONS FOR TEMPOROMANDIBULAR JOINT HYPERMOBILITY

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

Discussion

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

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

Level of Evidence for Dextrose Prolotherapy

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

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

TENDINOPATHY AND MYOFASCIAL PAIN SYNDROME

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

LIGAMENT AND MENISCUS INJURY

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

OSTEOARTHRITIS AND DEGENERATIVE CONDITIONS

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

SPINAL PAIN

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

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

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

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

* No VAS or NRS.

Table 12. Levels of clinical evidence and study design.
Adapted from: Oxford Centre for evidence-based medicine. http://www.cebm.net.

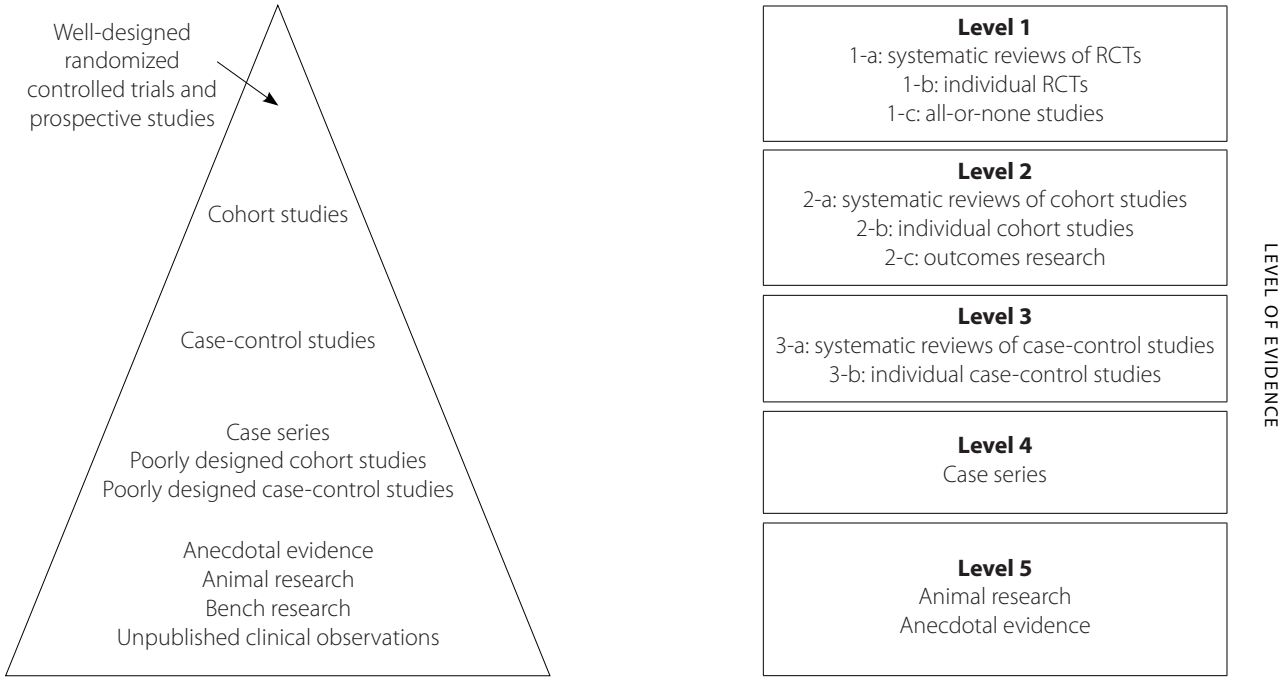


Table 13. U.S. Preventative Services Task Force quality of evidence grades. The USPSTF grades the quality of the overall evidence for a service on a 3-point scale (good, fair, poor).

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

Prolotherapy produces short-term improvement in pain and disability comparable to corticosteroid injection in patients with iliac crest pain syndrome.[134] There is level 3 evidence of good clinical outcome in patients with chronic iliolumbar syndrome,[98] significant and comparable improvement in pain and disability between patients with chronic cervical, thoracic or lumbar pain actively involved versus not involved in litigation,[132] and significant and comparable pain reduction in patients with lumbar herniated nucleus pulposus whether or not they received epidural block prior to Prolotherapy.[135] Level 3 and 4 evidence shows significant pain reduction and significant correlation between changes in pain level and radiographic findings in patients with post-MVA neck pain and disability,[113] significant reduction in pain and disability in patients with low back and pelvic pain,[95] chronic spinal pain,[92] and sacroiliac pain[95, 96] significant pain reduction in patients with coccygodynia,[99] and significant reduction in neck pain disability in patients with chronic whiplash pain.[112]

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

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

CHRONIC MUSCULOSKELETAL PAIN

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

THE EFFECTIVENESS OF DEXTROSE PROLOTHERAPY FOR MUSCULOSKELETAL PAIN

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

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

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

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

ADVERSE EFFECTS

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

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

STRENGTHS AND LIMITATIONS

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

IMPLICATIONS FOR RESEARCH

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

IMPLICATIONS FOR PRACTICE

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

OPEN ACCESS

BIBLIOGRAPHY

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

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

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

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

118. Lyftogt J. Subcutaneous Prolotherapy for Achilles tendinopathy: the best solution? *Australasian Musculoskeletal Medicine Journal.* 2007;November:107-109.

119. Maxwell N, et al. Sonographically guided intratendinous injection of hyperosmolar dextrose to treat chronic tendinosis of the Achilles tendon: a pilot study. *American Journal of Radiology.* 2007;October:w215-w220.

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

121. Hauser R, et al. Dextrose Prolotherapy injections for chronic ankle pain. *Practical Pain Management.* 2010;January/February:70-76.

122. Hauser R, et al. A retrospective observational study on Hackett-Hemwall dextrose Prolotherapy for unresolved foot and toe pain at an outpatient charity clinic in rural Illinois. *Journal of Prolotherapy.* 2011;3(1):543-551.

123. Hauser R, et al. Dextrose Prolotherapy for unresolved wrist pain. *Practical Pain Management.* 2009;November/December:72-79.

124. Hauser R, et al. A retrospective observational study on Hackett-Hemwall dextrose Prolotherapy for unresolved hand and finger pain at an outpatient charity clinic in rural Illinois. *Journal of Prolotherapy.* 2010;2(4):480-486.

125. Hauser R, et al. A retrospective study on Hackett-Hemwall dextrose Prolotherapy for chronic hip pain at an outpatient charity clinic in rural Illinois. *Journal of Prolotherapy.* 2009;1(2):76-88.

126. Hauser R, et al. A retrospective study on Hackett-Hemwall dextrose Prolotherapy for chronic shoulder pain at an outpatient charity clinic in rural Illinois. *Journal of Prolotherapy.* 2009;1(4):205-216.

127. Jo D, et al. The effects of Prolotherapy on shoulder pain. *Korean Journal of Anesthesiology.* 2004;46:589-592.

128. Ryan M, et al. Sonographically guided intratendinous injections of hyperosmolar dextrose/lidocaine: a pilot study for the treatment of chronic plantar fasciitis. *British Journal of Sports Medicine.* 2009;43:303-306.

129. Curtin M, et al. The effectiveness of Prolotherapy in the management of recalcitrant medial tibial stress syndrome: a pilot study. *British Journal of Sports Medicine.* 2011;45:e1.

130. Lyftogt J. Chronic exertional compartment syndrome and Prolotherapy. *Australasian Musculoskeletal Medicine Journal.* 2006;11:83-85.

131. Reeves K. Treatment of consecutive severe fibromyalgia patients with Prolotherapy. *Journal of Orthopedic Medicine.* 1994;16:84-89.

132. Hooper R, et al. Prospective case series of litigants and non-litigants with chronic spinal pain treated with dextrose Prolotherapy. *International Musculoskeletal Medicine Journal.* 2011;33:15-20.

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

134. Kim H, et al. Comparison between the effect of local steroid injection and Prolotherapy on iliac crest pain syndrome. *The Journal of the Korean Academy of Rehabilitation Medicine.* 2007;31:20-24.

135. Jo D, et al. The effects of Prolotherapy on the lumbar nucleus pulposus. *The Journal of the Korean Pain Society.* 2003;16:68-72.

136. Kim W, et al. A randomized controlled trial of intra-articular Prolotherapy versus steroid injection for sacroiliac joint pain. *Journal of Alternative and Complementary Medicine.* 2010;16:1285-1290.

137. Kim M, et al. Comparison on treatment effects of dextrose water, saline, and lidocaine for trigger point injections. *Journal of the Korean Academy of Rehabilitation Medicine.* 1997;21:967-973.

138. Reeves K, et al. Randomized, prospective, placebo-controlled double-blind study of dextrose Prolotherapy for osteoarthritic thumb and finger (DIP, PIP, and trapeziometacarpal) joints: evidence of clinical efficacy. *The Journal of Alternative and Complementary Medicine.* 2000;6:311-320.

139. Reeves K, et al. Randomized prospective double-blind placebo-controlled study of dextrose Prolotherapy for knee osteoarthritis with or without ACL laxity. *Alternative Therapies.* 2000;6:68-79.

140. Topol G, et al. Hyperosmolar dextrose injection for recalcitrant Osgood-Schlatter disease. Pediatrics. 2011;128(5):e1-e8.

141. Rabago D, et al. *Dextrose Prolotherapy for knee osteoarthritis: Results of a randomized controlled trial* (Poster presentation); Osteoarthritis Research Society International (OARSI) World Congress on Osteoarthritis; San Diego California, September 15-17, 2011.

142. Yelland M, et al. Prolotherapy injections, saline injections, and exercises for chornic low-back pain: a randomized trial. *Spine.* 2003;29:9-16.

143. Yelland M, et al. Prolotherapy injections and eccentric loading exercises for painful Achilles tendinosis: a randomized trial. *British Journal of Sports Medicine.* 2011;45:421-428.

144. Refai H, et al. The efficacy of dextrose Prolotherapy for temporomandibular joint hypermobility: a preliminary prspective, randomized, double-blind, placebo-controlled clinical trial. *Journal of Oral and Maxillofacial Surgery.* 2011. Doi:10.1016j.joms.2011.02.128. Published online July 15, 2011.

145. Emshoff R, et al. Estimation of clinically important change for visual analog scales measuring chronic temporomandibular disorder pain. *Journal of Orofacial Pain.* 2010;Summer;24:262-269.

146. Lee J, et al. Clinically important change in the visual analog scale after adequate pain control. *Academic Emergency Medicine.* 2003;10:1128-1130.

147. Farrar J, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain.* 2001;94:149-158.

148. Salaffi F, et al. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. *European Journal of Pain.* 2004;8:283-291.

149. Wells G, et al. Minimally clinically important difference module: summary, recommendations and research agenda. *Journal of Rheumatology.* 2001;28:452-454.

150. Bird S, et al. Clinically significant changes in pain along with the visual analog scale. *Annals of Emergency Medicine.* 2001;38:639-643.

151. Ostelo R, et al. Interpreting change scores for pain and functional status in low back pain: towards international consensus regarding minimal important change. *Spine.* 2008;33:90-94.

152. Medina J, et al. Rating the levels of evidence in sports-medicine research. *Athletic Therapy Today.* 2006;July:45-48.

153. OCEBM Levels of Evidence Work Group. "The Oxford 2011 levels of Evidence". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653.

154. Guyatt G, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendation. *British Medical Journal.* 2008;336:924-926.

155. Grade Working Group. Grading quality of evidence and strength of recommendations. *British Medical Journal.* 2004;328:1-8.

156. U.S. Preventative Services Task Force Ratings: Grade Definitions. *Guide to Clinical Preventative Services.* Third Edition: Periodic Updates. 2000-2003. http://www.uspreventiveservicestaskforce.org/3rduspstf/ratings.htm.

157. Atkins D, et al. Grading quality of evidence and strength of recommendations. *British Medical Journal.* 2004;328:1490. doi: 10.1136/bmj.328.7454.1490 (published 17, June 2004).

158. Lohr K. Rating the strength of scientific evidence: relevance for quality improvement programs. *International Journal of Health Care.* 2004;16:9-18.

159. Evans D. Hierarchy of evidence: a framework for ranking evidence evaluating healthcare interventions. *Journal of Clinical Nursing.* 2003;12:77-84.

160. Benson K, et al. A comparison of observational studies and randomized controlled trials. *New England Journal of Medicine.* 2000;342:1878-1886.

161. Black N. Why we need observational studies to evaluate the effective of healthcare. *British Medical Journal.* 1996;312:1215-1218.

162. Mckee M, et al. Interpreting the evidence: choosing between randomised and non-randomised studies. *British Medical Journal.* 1999;319:312-315.

163. U.S. Preventative Services Task Force Procedure Manual. AHRQ Publication No. 08-05118-EF, July 2008. http://www.uspreventiveservicestaskforce.org/uspstf08/methods/procman.

164. Rabago D, et al. Prolotherapy in primary care practice. *Primary Care.* 2010;37:65-80.

165. Dorman T. Prolotherapy: a survey. *The Journal of Orthopaedic Medicine.* 1993;15:49-50.

166. Dagenais S, et al. Side effects and adverse events related to intraligamentous injection of sclerosing solutions (Prolotherapy) for back and neck pain: a survey of practitioners. *Archives of Physical Medicine and Rehabilitation.* 2006;87:90-913.

167. Hauser R, et al. *Prolo Your Pain Away!* Second Edition. Beulah Land Press, Oak Park, IL. 2004; p. 21.

168. Fullerton B, et al. Ultrasounography in regenerative injection (Prolotherapy) using dextrose, platelet-rich plasma and other injectants. *Physical Medicine and Rehabilitation Clinics of North America.* 2010;21:585-605.

169. Fullerton B. High-resolution ultrasound and magnetic resonance imaging to document tissue repair after Prolotherapy: A report of 3 cases. *Archives of Physical Medicine and Rehabilitation.* 2008;89:377-385.

170. Topol G, et al. Biological response of severe degenerative arthrosis of the knee to serial 12.5% dextrose injections A radiographic and pathological assessment. AAOM presentation, Las Vegas, April 29, 2011.

171. Oxman A, et al. Summarizing the evidence. In: *The users' guides to the medical literature: a manual for evidence-based clinical practice.* Guyatt G, Drummond R (Eds). AMA Publications, IL, USA (2002).

172. Guyatt G, et al. Moving from evidence to action. In: *The users' guides to the medical literature: a manual for evidence-based clinical practice.* Guyatt G, Drummond R (Eds). AMA Publications, IL, USA (2002).

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

Mark T. Wheaton, MD & Nichole Jensen, BS

ABSTRACT

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

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

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

Journal of Prolotherapy. 2011;3(4):790-812.
KEYWORDS: collagen, degeneration, fibroblasts, growth factors, healing, inflammation, injury, instability, ligaments, osteoarthritis, Prolotherapy, repair, sprain/strain.

INTRODUCTION

Ligamentous injuries can occur at almost every joint in the body. Ankle sprains are the most common ligamentous injury, constituting 30% of all injuries seen in sports medicine clinics and the primary musculoskeletal injury seen by primary care.[1] Knee pain from ligament injury is also a common complaint, affecting an estimated 20% of the general adult population. The medial collateral ligament (MCL) is the most frequently injured ligament in the knee. In many cases, through a 3-stage inflammatory and healing process, the body is able to repair the injury on its own, with a full clinical recovery of the strength and stability of the joint. However, if the injury is severe or if multiple injuries have taken place at a joint, the damage to the surrounding ligamentous and cartilaginous tissues and other structures of the joint can reach a state that is beyond the body's ability to fully repair and restore. Damage to the anterior cruciate ligament (ACL) causes the highest incidence of pathologic joint instability.[2] This begins the downward spiral of degeneration of the joint surfaces and the development of osteoarthritis and chronic pain.

Osteoarthritis is the most common form of arthritis and is typically found in the older population, but there has been a rise in the number of cases reported in the younger adult population, frequently related to joint injuries occurring in athletics, work, or other daily activities. Osteoarthritis can be caused by intrinsic factors (primary OA), which have a genetic and/or biomechanical etiology, as well as extrinsic causes (secondary OA), which are caused by external factors, such as direct trauma, overuse or repetitive motion injuries, corticosteroids, obesity, and/or ligamentous injuries, leading to joint hypermobility and instability. Patients have come to rely on surgical procedures when the pain, disability and imaging studies are determined to be sufficient to warrant such a procedure. Many surgeries

performed are based primarily on the findings of imaging studies, most commonly magnetic resonance imaging (MRI), which is unable to identify the most common pain generator(s), including ligaments, joint capsules, muscles and tendons, nor is it able to assess dynamic instability.

There are many treatments used to treat the pain and instability symptoms due to ligamentous injuries and osteoarthritis. Conservative treatments include pain medications, chiropractic, physical therapy, manual therapies, acupuncture, and intra-articular injections of cortisone or hyaluronate (viscosupplementation). The use of medications, including NSAIDs, narcotics (opioids), sedatives, muscle relaxers, anti-depressants, and anti-seizure drugs, have acute and chronic effects on the user and impact the healing process in many cases. Common adverse effects experienced with use of these medications are well-documented. Narcotics not only alter the neuropsychological and pathophysiological responses of the body, but also affect both innate and adaptive immune function. Opioids can act either directly on the target cells or indirectly on centrally mediated pathways. Chronic use has demonstrated decreased proliferation of antibodies, macrophage progenitor cells and lymphocytes, inhibition of natural killer cells and phagocytic activity, cytokine expression and leukocyte migration, as well as have significant affects on immune cell differentiation.[3, 4] In animal studies, two hours after a subcutaneous injection of morphine, a 70% depression of blood lymphocyte proliferation was noticed, as well as a 30-40% inhibition of natural killer cell activity.[5]

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

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

THE PROPERTIES AND PHYSIOLOGY OF LIGAMENTS

Ligaments are dense bands of collagenous tissue which span joints, linking bone to bone. They are comprised of a more vascular outer layer called the epiligament, which is indistinguishable from the actual ligament itself, and merges into the periosteum of the bone around the ligament attachment site. Biochemically, ligaments are approximately two-thirds water and one-third solid with the water likely responsible for contributing to cellular function and viscoelastic behavior. The solid components of ligaments are principally collagen (type I collagen accounting for 85% of the collagen and the rest made up of types III, V, VI, XI and XIV) which account for approximately 75% of the dry weight with the balance being made up by proteoglycans (<1%), elastin and other proteins and glycoproteins such as actin, laminin and the integrins.[6, 7, 8] During formation and development of ligaments, triple helical collagen molecules are aligned to form fibrils that are organized in a parallel fashion and folded in a crimped state into fibers, which are interconnected by crosslinks giving collagen fibers incredible strength. Early in growth and developmental processes the crosslinks are immature and weak, but increase in strength with development and age. The crosslinked collagen forms the extracellular matrix (ECM) and the structure of the ligament. The main function of ligaments is to maintain smooth joint motion, restrain excessive joint displacement and provide stability across the joint. For example, ligaments of the knee provide passive stability, guide the motion of the femur and tibia, define contact mechanics between the femur and tibia, and restrain excessive motion to prevent dislocation.[8, 9]

Ligaments, over time, respond to loads with overall increase in mass, stiffness (ability to resist strain) and load failure, as well as increases in ultimate stress (the force per unit area) and strain failure (the change in length relative to the original length). Biological factors including age, maturation, mobilization/immobilization of a joint, tension and exercise affect the biomechanical properties of ligaments. Ligaments display viscoelastic behavior, meaning they have the ability to resist shear stress, but also have the ability when stressed to return to their

original state. The structural properties of ligaments are tested using Stress-Relaxation, stretching the specimen to a constant length and measuring the change in stress over time, the Creep Test, a constant force with a gradual increase in length over time, as well as tensile strength via Load-Elongation Curve where stiffness (N/mm) is the slope, ultimate load (N) is the highest load placed before failure, ultimate elongation (mm) is the maximum elongation at failure, and energy absorbed at failure (N-mm) is the area under the curve and the maximum energy stored by the complex. (*See Figure 1.*) The mechanical properties of ligaments are observed via a Stress-Strain Curve where tensile strength (N/mm2) is the maximum stress achieved, ultimate strain (in %) is the strain at failure, and strain energy density (MPa) is the area under the curve. The stress-strain curve is dependent on a ligament's substance, molecular bonds and composition.[8]

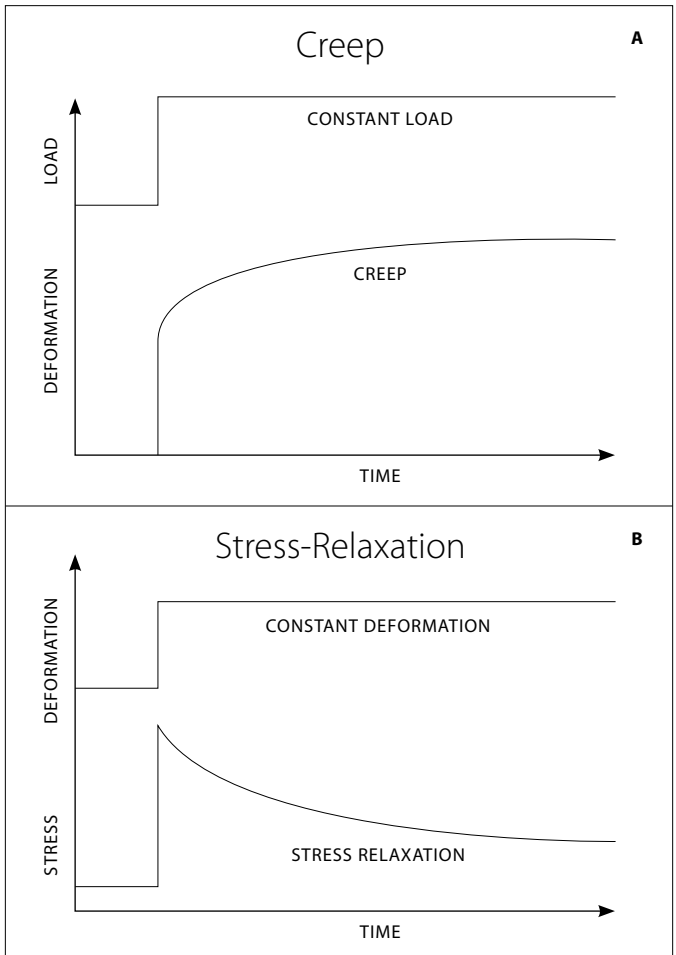


Figure 1. Ligaments, when subjected to a constant stress, display Creep (A) behavior—a time-dependent increase in strain. When ligaments are subjected to a long constant strain they exhibit a decrease in the stresses within the material known as stress-relaxation (B).

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

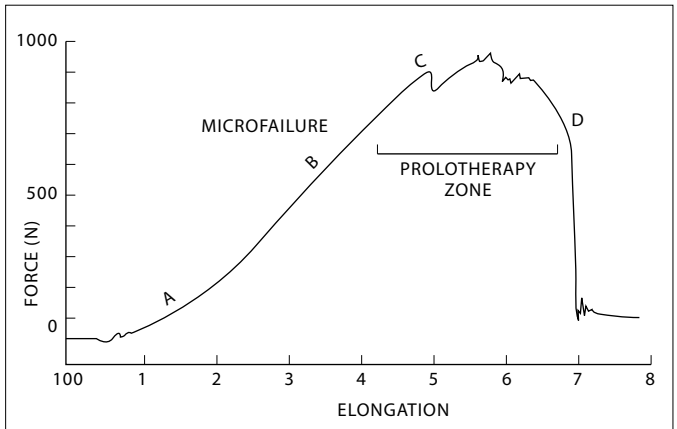
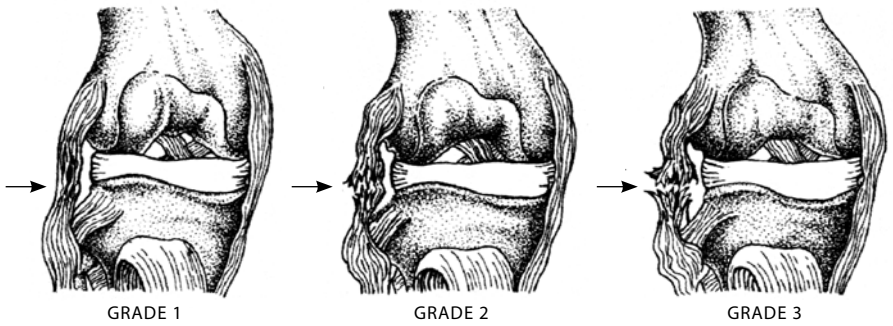


Figure 2. Stress-strain curve for ligaments and tendons. As additional force is applied to the ligaments up until point C, the ligament reverts back to its normal length, once the force is removed. If the force is continued past point C, the ligament is permanently elongated or stressed unless the athlete receives Prolotherapy.

Used with permission from: Hauser RA, et al. *Prolo Your Sports Injuries Away!* Oak Park, IL: Beulah Land Press; 2001. Figure 17-10.

THE BIOMECHANICAL CONSEQUENCES TO LIGAMENT INJURY

When the forces subjected to a ligament are too great, failure occurs, resulting in drastic changes in the structure and physiology of the joint. Ligament injuries, also called sprains, can occur due to direct trauma, indirect trauma or indirect intrasubstance (intrinsic or extrinsic) factors and are evaluated on a scale from Grade I to Grade III. (*See Figure 3.*) Grade I sprains consist of mild stretching of ligamentous tissue with no discontinuity of the ligament or clinical signs of excess laxity. Grade II sprains have moderate stretching of the ligament with some torn fibers,



Used with permission from: P. Brukner, K. Khan. Fundamental Principles. Clinical Sports Medicine. McGraw-Hill.

Figure 3. Grading of ligament injury severity. Grade 1 and 2 ligament injuries are successfully treated with Prolotherapy. Grade 3 injuries, however, often need surgery.
Used with permission from: Hauser RA, et al. *Prolo Your Sports Injuries Away!* Oak Park, IL: Beulah Land Press; 2001. Figure 5-16.

but enough are intact so that the damaged ligament has not failed. However, joints with Grade II sprains have an abnormal laxity compared to the uninjured side. Grade III sprains consist of severe tearing and nearly complete or complete ligament disruption with significant joint laxity.[11] The term "joint laxity" can be defined clinically and biomechanically. Clinically, joint laxity refers to the subjective impression of abnormal movement of one bone relative to the other when a joint is manipulated or displaced by intrinsic muscle forces and is typically compared to the contralateral joint or normal external control. Biomechanically, it relates to the quantitative measure of the six independent degrees of freedom for a given joint and the specific forces or movements that are causing the displacement.[12] Disruption of the ligamentous tissue results in instability of the joint, increasing the sliding of joint surfaces, decreasing the efficiency of the muscles, and altering the joint mechanics. Cartilage within a joint is the thickest where contact pressure is the greatest; however, with an injured or loose joint, joint motion is larger. When joint stability is compromised, the kinematics between the bones changes, disrupting the load distribution on the cartilage and bone in magnitude, direction and location of contact, causing wear and increased shear forces, ultimately leading to osteochondral degeneration and increasing the risk for development of osteoarthritis. For example, disruption of ligamentous structures in the knee produces tibiofemoral offset, transferring contact stresses to regions of thinner cartilage with less support, which puts added stress on already weakened ligaments, causing greater ligament injury and increasing the pressure on the cartilage.

As soon as a ligament injury is sustained, the body initiates the healing process, which takes place in three overlapping stages. The first stage takes place within the first 48-72 hours following an injury and is associated with hemorrhaging and inflammation. The disrupted ligament ends retract and a hypertrophic vascular response, including increases in both the vascularity and blood flow to the area, takes place forming granulation tissue. This promotes the formation of a platelet-rich blood clot in the gap which forms a lattice structure for cellular events to take place. This response decreases over time. The second stage encourages matrix and cellular proliferation and begins 48 hours after the injury and continues over the next 6 weeks. During the second stage, inflammatory cells, including neutrophils, monocytes and macrophages, are directed to the injury site to begin phagocytosis of debris, lysis, and removal of damaged cells. An influx of fibroblasts to the site by chemotactic agents begins synthesis of "scar tissue," a dense cellular collagenous connective tissue matrix, to bridge the torn ligament ends. Initially the new collagen matrix is very disorganized with multiple structural defects, but after a few weeks of healing the inflammatory cells decrease in number, the capillaries become less prominent and the granulation tissue matures into mature collagen with the aggregation of fibrils into mature fibers aligned with the long axis of the ligament. In days to weeks following the injury, the third stage of healing, remodeling and maturation, begins. During this stage, the fibroblasts continue to remodel the matrix, filling in defects of the scar, resulting in a matrix similar in appearance to uninjured tissue, but physiological variations in composition and architecture, as well as mechanical deficits, remain. (*See Figure 4.*) The new scar tissue has altered proteoglycan and collagen composition with increased percentages of type III collagen tissue, as well as decreased size of the diameters of the new collagen fibrils. Also, the new scar collagen fibers are not packed as closely as a normal ligament, lack mature collagen crosslinks, and have altered cell connections resulting in incomplete resolution of matrix flaws, which leave "weak spots" in the scar matrix. The overall healing and recovery depends on the

	Inflammatory	Proliferative	Remodeling
Effect on blood	Increased blood flow	Formation of new blood vessels	New blood vessels mature
Symptoms	Swelling and pain increase	Swelling and pain subside	If tissue is strong, pain subsides
Physiology	Immune cells, called macrophages, remove damaged tissue	Immune cells, called fibroblasts, form new collagen	Increased density and diameter of collagen fibers occur if healing is not hindered
Length of time	Immediate response occurs for a week	Begins at day 2 or 3 after injury and continues for 6 weeks	Continues from day 42 until 18 months after injury

Figure 4. Three stages of healing after soft tissue injury.
Used with permission from: Hauser RA, et al. *Prolo Your Sports Injuries Away!* Oak Park, IL: Beulah Land Press; 2001. Figure 9-3.

size of the initial gap, the contact between torn ligament ends, and the degree of joint movement.[7, 8, 13-15] Review of the literature suggests that minimizing the gap between ligament ends appears to alter the healing process, both structurally and mechanically. Studies using adult rabbit medial collateral ligaments (MCL) found some structural and mechanical advantages to having the cut ends in contact during the healing process, opposed to gap healing, and demonstrated improvements in structural strength and stiffness. The structural differences were hypothesized to be due to larger and/or more frequent "defects" in the scars of the gap healing ligaments compared to those with contacted ends and contralateral structures as well.[12]

Not all ligaments have equal healing potential. For example, the MCL is able to heal and restore adequate knee joint stability if it is an isolated injury. On the other hand, the anterior cruciate ligament (ACL) has a poor prognosis for healing, predisposing the knee to recurrent injury, progressive intra-articular meniscal and hyaline cartilage damage, decreased joint stability, and can increase the risk for development of osteoarthritis. The increased damage to intra-articular tissue and progressive degenerative changes of an ACL tear is thought to be due to the knee's ability to better tolerate valgus instability, as with an MCL tear, compared to rotary instability observed post-ACL tears.[12]

The MCL resists valgus forces which push the knee medially. It has the ability to heal spontaneously with conservative treatment and in studies actually produced better results than surgical repair when varus-valgus knee stability and biomechanical properties were compared. Immobilization following MCL injury has been shown to lead to greater disorganization of collagen fibers, decreased structural properties, decreased mechanical properties and slower recovery to the resorbed insertion sites.[9] In studies by Frank, et al, rabbit MCLs were tested to be structurally healed to 70-80% of normal strength and stiffness and mechanically healed to 30% of normal strength based on cross-sectional size, while the laxity and load-relaxation improved to 80-90% of the normal within six to 14 weeks following injury. However, the creep behaviors demonstrated elongation greater than twice that of a normal MCL for many months following an injury, with no recovery in length, creating the potential for permanent elongation.[14] Another study compared patients with medial knee laxity to those with normal knees to determine if any differences existed in knee structure and biomechanics. They found that the prevalence of osteoarthritis was greater in those with significantly more medial knee instability; they also noted these subjects had more muscle contractions on the medial side of the knee compared to those without osteoarthritis. Lewek, Ramsey, and Mackler believed the high muscle contractions can lead to high joint compressive forces which accelerate the progression of osteoarthritis.[16]

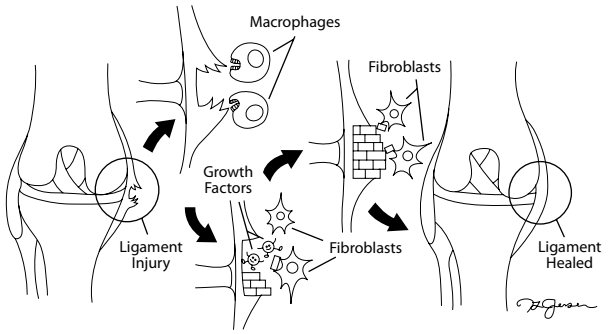
An ACL rupture increases anterior translation and rotational instability and leads to progressively worsening damage to the internal knee structures, including the meniscus and MCL. The most common treatment for an ACL tear is surgery. Conservative treatment can be successful in some patients, but most commonly produces poor results when compared to only 20-25% less-than-satisfactory results with ACL reconstruction. Grafts for ACL reconstruction include autografts from bone-patellar tendon-bone (BPTB) and quadruple strand semitendinosis and gracilis (QSTG) or allografts from a cadaver. The BPTB is harvested from the central 1/3 of the patellar tendon, at 8-10 mm in width, and is chosen for its relatively high stiffness and strength, as well as opportunity for bone-to-bone fixation. The QSTG is chosen because it has similar properties to the patellar graft, requires less morbidity during harvesting and does not cause anterior knee pain. In clinical trials, no conclusive evidence suggested superiority of one graft over the other.

Both grafts were effective when the knee was subjected to anterior tibial loads. It was noted that the QSTG was slightly more effective when the knee was at higher flexion angles, although neither of the grafts were effective when the knee was subjected to loads simulating the pivot shift test. Also, the type of fixation devices have been analyzed to try to determine what would provide the best anchoring and stability, including the use of interference screws, soft tissue washers, suture-post constructs, simple staples and cross-pins, but no clear consensus was found as the best anchoring device. Studies have shown that the most stable knee was constructed when the interference screws were placed close to the articular surface (proximal to the drill hole in the top of the tibia) compared to central fixation (deeper within the hole) or distal fixation (on the distal tibial tuberosity).[8]

CELLULAR RESPONSE TO LIGAMENT INJURY

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

Mesenchymal cells are multi-potent stem cells with the ability to differentiate into many different types of cells. They are embryonic undifferentiated connective tissue derived from the mesoderm of an embryo. Their composition is a prominent ground substance matrix



Ligament Injury	Stage 1	Stage 2	Stage 3
	Inflammation 48 - 72 Hours	Proliferation 48 hrs - 6 weeks	Remodeling & Maturation 6 weeks - 6+ months

Figure 5. After ligament injury, the healing process takes place in three overlapping stages, lasting from six weeks to six or more months. During this time the body utilizes many cells, growth factors and proteins to aid in the removal of damaged tissue, synthesis of new "scar tissue" to fill in the gaps, and remodeling of the ligament structure to a mature state, which closely resembles the uninjured ligament.

with a loose aggregate of reticular fibrils (i.e., type III collagen) and unspecified cells. They have the ability to migrate easily, such as to an injured site. Macrophages are a type of white blood cell, which aids in the process of cleaning up and digesting damaged, dying or dead cells. They respond in "2 waves" at the onset of damage. The wave first occurs with muscle membrane lysis and inflammation and begins by degrading the contents of injured fibers. The second wave occurs with the release of various substances, including basic fibroblastic growth factor (BFGF), transforming growth factor-beta (TGF-β) and transforming growth factor alpha (TGF-α) to trigger a cascade of pathways to help with the healing process.[8] The release of the growth factors signals fibroblast and inflammatory cells to the injured tissue, stimulates fibroblast proliferation, and promotes the synthesis of collagenous proteins, as well as non-collagenous proteins, for the repair and regeneration of new connective tissue. Growth factors are small polypeptides synthesized by a variety of cells in the immune and musculoskeletal systems. They work in conjunction with proteoglycans by binding to cell surface receptors, triggering transduction pathways which stimulate production of proteins involved in wound healing, as well as affecting the concentrations of other growth factors via numerous feedback loops.[8] Platelet-derived growth factor (PDGF) is a potent chemotactic agent which drives the proliferation of cells of mesenchymal

origin, as well progenitor cell populations, directing the migration, differentiation and function of specialized mesenchymal and migratory cells.[17] It is required for cellular division of fibroblasts and aids in the tissue repair, regeneration and remodeling processes. Transforming growth factor-beta (TGF-β) is a protein which controls proliferation and cell differentiation, as well as apoptosis, of various cells throughout the body. It plays a large role in the SMAD pathway, activating transcription factors and regulating T-cell development.[18] It also works to block the activation of lymphocytes and monocyte-derived phagocytes. Both PDGF and TFG-β play key roles in stimulating the processes of ECM deposition and the repair and regeneration of connective tissue. Fibroblast growth factors (FGF) are either protein- or steroid-derived hormones that interact with proteoglycans within the ECM, stimulating proliferation and differentiation of cells. They are sometimes described as "promiscuous" in nature due to the variety of molecules they are able to bind and elicit responses from at a single cell receptor. The interaction of the FGF with the proteoglycans in the ECM affects the activity and stability of signaling molecules within the extracellular matrix.[19] Basic fibroblast growth factor (BFGF) is present in the basement membranes and ECM of blood vessels and mediates angiogenesis, the formation of new blood vessels, after a wound is sustained and promotes the healing process.[20] Epidermal growth factor (EGF) is a protein that regulates cell growth, proliferation and differentiation. It initiates signaling cascades by binding to specific cell surface receptors, which increases the calcium allowed to flow into the cell. This causes increases in both glycolysis and protein synthesis, which support increased expression of genes promoting DNA synthesis and cell proliferation.[21]

ETIOLOGY OF THE DEVELOPMENT OF OSTEOARTHRITIS

The etiology of osteoarthritis (OA) has not been fully elucidated. It is clear, however, that the breakdown of joint cartilage occurs when the repair and replacement of cartilage cells does not keep pace with the destruction of cartilage. There are many causes of joint injury, as well as associated risk factors which increase the likelihood of joint degeneration. It may be caused by a systemic (genetic) predisposition or by local (mechanical) factors. For some the cause is known (secondary), but for others the cause is unknown (primary). For example, a person may have an inherited predisposition to develop the disease, but it may only materialize when a biomechanical insult (such as a knee injury) has occurred.[22] It should be emphasized that osteoarthritis is primarily a degenerative process, not an inflammatory one as the name implies. A more appropriate term would be osteoarthrosis or degenerative joint disease.

Ligament damage or weakness is one cause of joint degeneration. Joint subluxations, dysplasia, and incongruity disrupt the normal distribution of weight and stresses on the articular surfaces of the joint leading to cartilage injury and joint degeneration. The disruption of ligaments and joint capsules, causing increased joint laxity, increases the risk of articular cartilage injury because the joint motion is no longer stabilized by the ligament structure.[23] These mechanical abnormalities cause changes in the areas of contact on opposing surfaces and increase the magnitude of impact loading and shear and compression forces on some regions of cartilage. (*See Figure 6.*) The mechanical properties of articular cartilage depend on the macromolecular framework consisting of collagens and aggregating proteoglycans, as well as the water content within the macromolecular framework. The collagens give the tissue its strength, while the interaction of the proteoglycans with water gives the tissue its stiffness (resistance) to compression, resilience, and durability.[24, 25] The cartilage is the thickest in areas where contact pressure is greatest. After a ligament injury, joint motion becomes greater and may offset the contact surfaces to regions where the cartilage may be thinner and less able to support the applied stresses.[26] The loss of sensory innervation of the joint and surrounding muscles also increases the susceptibility of joint degeneration because of an increase in the instability of the joint.[24] When the load is applied slowly, the muscles are able to contract and absorb much of the energy and stabilize the joint. However, if the load is sudden, the muscles do not have time to respond to stabilize the joint and decrease the forces applied to the cartilage surfaces. Even normal levels of joint use may cause articular surface injury and degeneration in unstable, subluxed, or malaligned joints and in joints that do not have normal innervation.[27] Genetic hypermobility syndromes, such as Ehlers-Danlos Syndrome, as well as non-genetic hypermobility (Benign Hypermobility Syndrome) where trauma or injury is absent, increase the likelihood of OA development. Further prospective studies are needed to study the effects of non-traumatic hypermobility as it relates to OA.

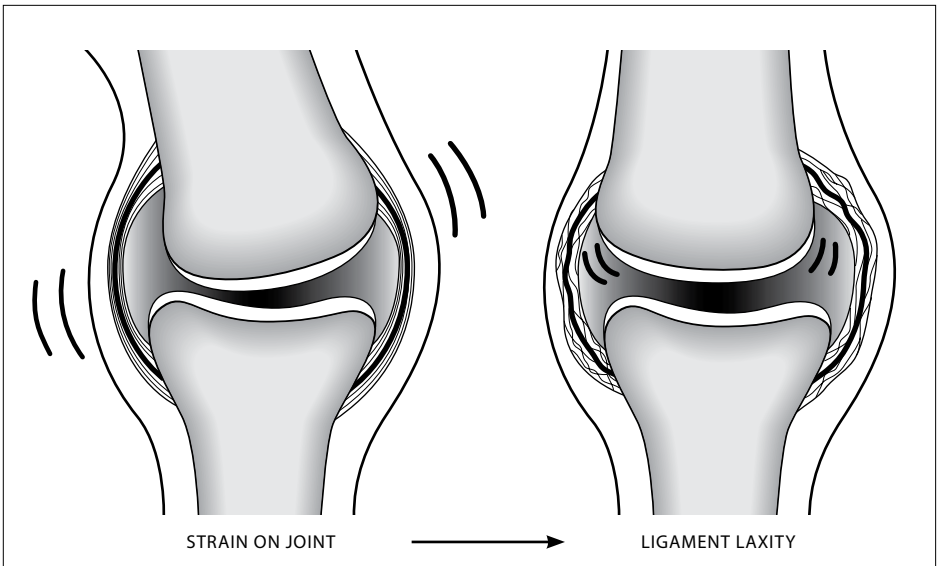


Figure 6. Ligament laxity can cause instability of the joint. The result is stretched ligaments and misaligned joints.

Direct trauma is a second cause of joint degeneration and is typically associated with athletic participation. The articular surface can be damaged by single or repetitive impact from a direct blow to the joint or bones that form the joint. It can also be damaged by torsional loading resulting from twisting or turning of joint surfaces that are relative to each other. The rate of loading also affects the type of damage that may be caused by sudden impact axial compression or torsional strain. During slow impact loading, the movement of fluid within the cartilage allows it to deform and decrease the forces applied to the matrix macromolecular framework. In sudden or high impact loading, the matrix macromolecular framework suffers a greater level of stress because the loading occurs too fast to allow for adequate fluid movement and tissue deformation.[27] One study performed a 36 year follow-up of 141 participants who had sustained a hip or knee injury after 22 years of age and found that, due to the deleterious effects of trauma that had compromised the structural integrity of the joint, 96 (68%) of the participants had developed osteoarthritis in the injured joint.[28] Another study showed that 80% of American football players with a history of knee injury showed signs of osteoarthritis 10 to 30 years after retiring.[29] Soccer players also have an increased incidence rate of osteoarthritis in the lower extremity joints, mainly the knee, when compared to a control group of the same age. The most common types of injuries are sprains and strains, which are usually caused by excessive forces applied to a joint in an abnormal direction. This leads to a high number of meniscal and ligamentous injuries that ultimately translate to an increased instability within the joint.[30, 31] While direct trauma or compression to the cartilage surfaces alone can cause OA over time, it is unquestionably the concomitant ligament injury in the majority of these cases which sets the joint up for OA development. When cartilage wear and degradation outpace cartilage repair, the wheels are set in motion for joint degeneration.

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

Another risk factor for joint degeneration is above-average body weight, supported by the fact that for every one pound increase in weight, the overall force across the knee in a single-leg stance increases two to three pounds.[22, 24] Other risk factors considered in association with development of OA include: poor posture, age, abnormal joint anatomy and alignment, associated diseases, genetics, failure to accurately realign fractures,

Risk Factors for Development of Osteoarthritis	
Major Factors	**Ligament Damage** - joint subluxations, dysplasia and incongruity disrupt normal distribution of weight. **Direct Trauma** – damage to articular surface from single or repetitive impact. **Overuse** – Excessive joint loading wears down articular surface tissues.
Others	Above-average body weight, failure to accurately realign fractures, car accidents, poor posture, age, gender, abnormal joint anatomy or alignment, bone deformities, associated joint diseases, genetic factors, occupation, hormones, diet, race, physical activity.

Figure 7. Risk factors for development of osteoarthritis.

leaving room for abnormal movement and deviation; and car accidents, which subject the body to sudden impacts that may cause injury to ligaments and muscles and lead to pain and weakness in the spine and extremities.[24] Genetic factors account for 50% of cases of osteoarthritis in the hand and hip and a smaller percentage in the knees.[22]

PREVALENCE AND COSTS OF TREATMENT OF OSTEOARTHRITIS

The number of reported cases of osteoarthritis have been on the rise in the past quarter century. In 1995 it was projected that approximately 21 million Americans suffered from osteoarthritis. As of 2005, based on data collected from The National Health and Nutrition Examination Survey I (NHANES I), osteoarthritis affected 27 million of the 46 million people in the United States that suffer from arthritis. Also, recent data shows that one out of two Americans are at risk for knee osteoarthritis over their lifetime.[36] Hip osteoarthritis occurs in 0.7 to 4.4% of adults and knee osteoarthritis occurs in approximately 5 percent of the American population between the ages of 35 to 54.[37-40] It is estimated that 15 percent of the world's population also experiences pain and joint degeneration due to the presence of osteoarthritis.[41] The number of hospitalizations as a result of OA has doubled in the last 15 years. In 1993, there were 322,000 hospitalizations, and in 2006 the number rose to 735,000.[42]

Any movable joint in the human body is vulnerable to development of osteoarthritis. Knee joints, due to their location between the long lever arms of the tibia and femur, as well as repetitive exposure to high-impact loads and vulnerability in different planes and joint angles, are especially susceptible to direct trauma and ligament injury and more likely to develop osteoarthritis after an injury.[43] Meniscal tears and cartilage damage, as well as ACL tears, alter the contact surfaces within the joint, limiting the contact forces to a smaller area leading to more rapid wearing down and degeneration of the articular surfaces.[44-46] Other factors that play a role in the development of osteoarthritis in the knee are medial joint laxity, higher BMI (Body Mass Index) values, lesser quadriceps femoris strength, lesser knee flexion, greater knee adduction, and greater co-contraction of the quadriceps femoris and gastrocnemius muscles.[47, 48] The hip is more stable than the knee due to its ball-and-socket configuration and surround musculature, but research has shown individuals involved in high load-bearing activities, including heavy manual labor, frequent stair climbing, and high-intensity sports such as soccer and football, have higher rates of osteoarthritis than their counterparts without such exposure.[32, 49-55] The shoulder, due to its shallow glenoid socket and great range of motion, is very susceptible to connective tissue injury, including those due to repetitive high-stress activities and dislocations, and subsequent development of OA. Anterior instability has also been associated with development of OA.[56-58] The ankles, wrists and hands are at increased risk for osteoarthritis after traumatic injuries, including sprains of supporting ligaments and fractures of adjacent bones. Injuries with narrowing of the joint space and extra-articular malunion disrupt articular contact surfaces, leading to poor biomechanics and increased wearing of the contact surfaces. Weakness and instability may also be present and permit excessive motion.[54, 59-66] The spine is also at risk for degeneration and osteoarthritis, especially with repetitive strains, overuse, injuries, accidents, surgery, excessive weight, poor posture, sedentary life style, and even genetic predisposition, producing weakness and instability. The loss of stability of spinal ligaments can lead to changes in the lordotic curves, disc herniations, degeneration of discs, spondylolisthesis, development of bone spurs, spinal stenosis, foraminal narrowing, and degeneration of facet joints, as well as many other pain generating syndromes.[67, 68]

The cost of treatment for OA can put a large burden on both the patient and the health care system alike. Medications, even if effective in reducing pain, exact a great cost over the long-term, both in the costs of the medications themselves, but also relative to the side effects, complications, and secondary medical problems

(morbidity and mortality). The financial burden associated with OA requires consideration of both medical-surgical (direct) costs and work-loss (indirect) costs. One report estimated the total cost of bilateral knee joint replacements at over $85,000. This included the hospital stay, surgeon fees, anesthesiologist fees, a 5-day stay in an inpatient rehabilitation center, and a pathologist visit. However, this did not include outpatient physical therapy because the length of treatment is unknown. Luckily for this patient, much of the expenses were covered by insurance.[23] The cost of hip and knee replacements have risen from about $7,000 in 1997 to an average of $32,000 for the knee and $37,000 for the hip in 2003.[69] The average out-of-pocket expense as a direct result of osteoarthritis was approximately $2,600 per person per year with a total annual disease cost of $5,700.[70, 71] Job-related osteoarthritis costs were estimated to be between $3.4 and $13.2 billion per year. Other studies reported average annual direct medical, drug, and indirect work loss costs were $8601, $2941, and $4603, respectively.[72]

TREATMENT OPTIONS

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

STANDARD NON-SURGICAL TREATMENT OPTIONS

Medications are the most common option used to treat the pain and disability commonly experienced with ligament injuries and OA. Medications fall into two categories: over-the-counter (OTC) medications and prescription medications.

Analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) are two commonly used OTC medications and both have their pros and cons. Analgesics, like acetaminophen, are used as a short-term treatment for mild to moderate pain associated with ligament injuries and osteoarthritis. However, it can cause acetaminophen-induced toxicity, which includes hepatotoxicity and potential renal damage.[73] NSAIDs are also used to reduce pain, but also aid in the reduction of inflammation associated with ligament injuries and OA. Aspirin has been used as an OTC treatment for symptoms related to soft tissue injuries and OA for decades but platelet inhibition and GI bleeding risk have made it unacceptably risky to use on a regular basis.

The pharmaceutical industry manufactured NSAIDs many years ago to improve short-term functioning for patients by inhibiting COX enzyme pathways. Drug companies then developed COX-2 NSAIDs which were felt to have the same pain-relieving effects as nonselective NSAIDs, but without the inherent risk of gastroduodenal mucosal damage or cardiac and renal complications.[74, 75] The COX-2 NSAIDs celecoxib (Celebrex®) and refocoxib (Vioxx®) entered the market with great acclaim. Both were touted as more convenient with twice-a-day (Celebrex) or once-a-day (Vioxx) dosing to relieve arthritis pain, stiffness and inflammation without as many GI effects.

However, a significant number of cases causing indigestion, abdominal pain, and nausea occurred after consumption. With time and a preponderance of evidence, it became clear that the purported GI-protective effects were being reported more frequently than had been originally thought. Because of these risks, the manufacturers of COX-NSAIDs have had to revise their literature to recommend the lowest effective dose for the shortest time period possible.[75] So while the NSAIDs are routinely prescribed for joint and muscle pain, the risks can far outweigh the benefits in symptom-relief. Furthermore, using these drugs does nothing to correct the previously proposed underlying problem—injured ligaments and damaged cartilage—and, in fact, they interfere with the first stage of healing, even in tissues with excellent blood supply, slowing soft-tissue repair and thus accelerating joint degeneration. In addition, reducing the perception of pain causes more overuse of a damaged joint. It is ample argument as to why many injuries progress more rapidly to osteoarthritis.

One study demonstrated a termination of the entire inflammatory proliferative phase of healing after taking Peroxicam. They found no macrophages present after two days and very little regeneration of soft tissue by day four, when compared to the normal healing process.[76] Another study produced similar results with a delayed regenerative process after muscles were treated with Flurbiprofen. The soft tissues were significantly weaker and under microscope had incomplete healing compared to the control tissue.[77] The results of a study of 180 rats, 60 were given NSAIDs, 60 were given COX-2 inhibitors and 60 were control, showed significantly lower failure loads, poorly organized morphology and consistency within the fibrocartilage zones, and decreased deposition and maturation of tendon during healing in the test subjects compared to the controls. They concluded with the suggestion that early inhibition of the inflammatory cascade has lasting negative effects on ligament- and tendon-to-bone healing.[78] Ibuprofen was also noted to decrease the strength of flexor tendons after four weeks of NSAID therapy. The peak forces before disruption were decreased by 300 percent, from 12 newtons to 2.5 newtons. Extensor tendons showed similar results with control and NSAID-treated tendon breaking strengths of 12 and 3.5 newtons respectively.[79]

NSAIDs can also lead to increased degenerative changes within joints. In the early stage of OA, the chondrocytes attempt to repair the cartilage tissue. However, the use of NSAIDs disrupts this process and degradative enzymes overwhelm the regenerative process, halting any repair. A downward spiral begins leading to compositional, molecular and structural changes affecting the intrinsic mechanical properties of the articular cartilage and produces swelling.[80] (*See Figure 8.*) A trial consisting of 812 patients were split into two groups, one of which was given NSAIDs and the other a placebo, showed that neither group had a reduction in their symptoms and at follow-ups both one and two years later, increased degenerative changes were noted on radiographic films of subjects who were given the NSAID compared to those who had taken the placebo.[81] Also, another study showed acetabular deterioration did not differ in age, sex, pain or walking ability, but was varied based on the amount of NSAIDs taken. Newman and his colleagues found the use of NSAIDs was associated with the progressive formation of multiple small subcortical cysts and subchondral bone thinning and suggested, based on the clinical and experimental findings, regular NSAID use has "powerful and potentially harmful effects on cartilage and bone."[82] Similar results were demonstrated on additional studies of radiographs taken three years after continued NSAID use revealing increased numbers of cysts present, more severe progression of degeneration of articular cartilage, and greater overall destruction of the joint.[83, 84] It is unclear if individuals who regularly use NSAIDs have increased degenerative changes and osteoarthritis joints due to true deleterious effects on the cartilage or increased physical

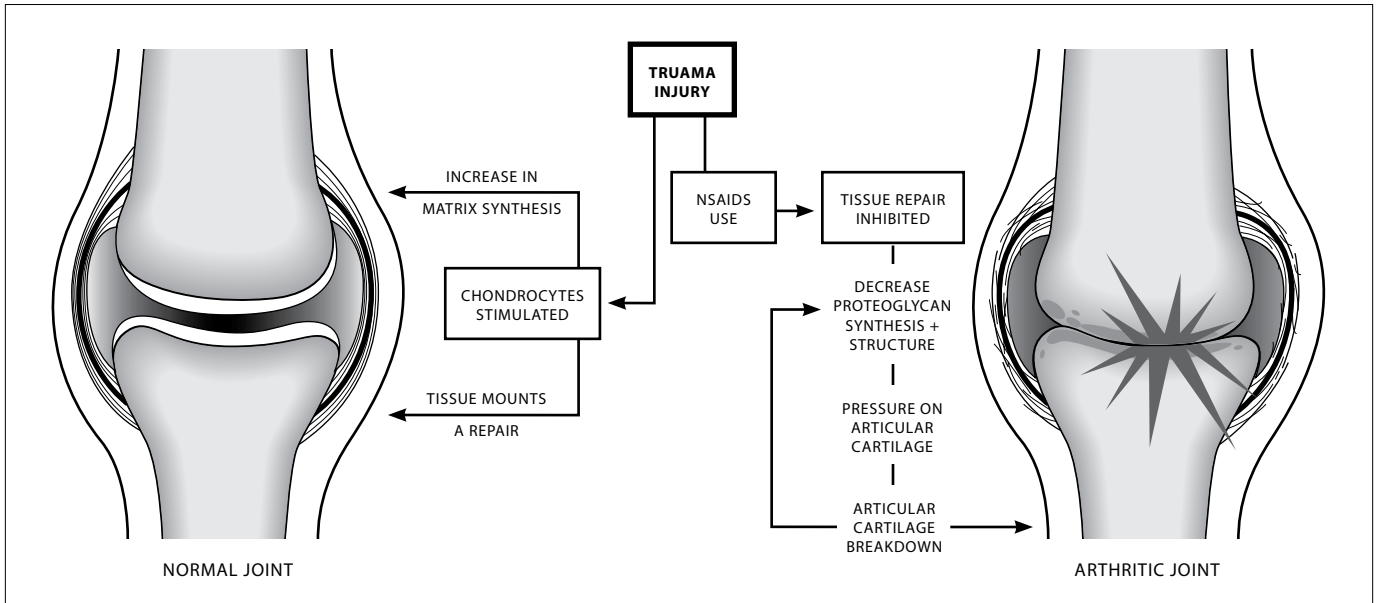


Figure 8. The pathogenesis of osteoarthritis accelerated by NSAIDs. NSAID use inhibits the body's repair processes, leading to decreased proteoglycan and extracellular matrix content and function, which ultimately leads to articular cartilage breakdown.

activity and excessive mechanical loading following pain relief or a combination of both.[85, 86] Canine studies have also showed accelerated degeneration of the articular cartilage after NSAID use, which is suspected to be due to inhibition of the COX enzymes, decreased production of proteoglycans and glycosaminoglycans, and increased degeneration, as well as inhibition of replication of cartilage chondrocytes. NSAIDs also have been shown to effect proliferation, cell cycle kinetics, and cytotoxicity. (*See Figure 9.*) A study by Gossec regarding the use of NSAIDs to treat the symptoms of OA found those who used NSAIDs increased their risk for hip replacement by 50% over a two-year period compared to those who did not take NSAIDs on a regular basis.[87-96]

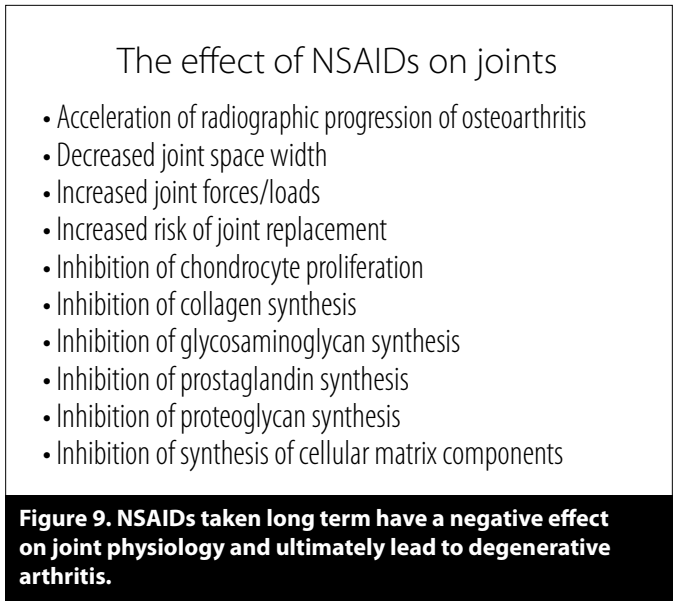


Figure 9. NSAIDs taken long term have a negative effect on joint physiology and ultimately lead to degenerative arthritis.

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

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

Bracing may be used to temporarily treat symptoms of ligamentous tears by providing stability after an injury. It can be a cost-effective and simple alternative to a more complex and expensive intervention and can provide symptomatic relief of the pain resulting from weakness and instability. However, bracing does not fix the problem; it does not strengthen the ligaments or tendons which are causing the problem. The use of a brace may also lead to deconditioning of the musculature surrounding the joint because the muscles become dependent on the additional support provided by the brace and do not fire properly. Immobilization following ligamentous injury decreases the ability of the scar to resist strain, decreases the maximal load to failure and energy a ligament can absorb, and the ligament has less stiffness than before.[13] The same principles are used to treat the symptoms of osteoarthritis, but the results have not been very conclusive. Bracing helps provide support, but does not address the degeneration within the joint. Studies by the American Academy of Orthopaedic Surgeons were not able to support or reject the use of braces with a valgus-directing force for medial osteoarthritis of the knee or a varus-directing force for lateral osteoarthritis of the knee.[100]

Physical therapy, as well as other conservative treatment options, can be beneficial in the management of the symptoms from ligament injuries and osteoarthritis. In animal studies performed by Jung et al., the use of moderate, prolonged exercise was shown to be effective in increasing the cross-sectional area, as well as mechanical properties of swine extensor tendons, indicating improved tissue quality.[9] Ultrasound, laser photostimulation, deep heat, pulsed magnetic and electromagnetic fields, and electrical stimulation are commonly used to treat tendinopathies with the intent to decrease the stiffness of the scar tissue.[9] Another study compared the prognosis of two groups of patients with knee osteoarthritis. One group received treatment involving a combination of manual physical therapy and supervised exercise and the other

group received ultrasound therapy at a sub-therapeutic intensity. Both groups received treatment twice a week for four weeks. After one year, the patients who had received the four weeks of physical therapy had made significant statistical gains compared to the control group based on the results of knee radiographs and additional testing. They also reported that 20% of the patients in the control group had undergone knee arthroplasty, compared to only 5% of the patients in the treatment group.[101] Additionally, a study by Cooper et al. reviewed multiple forms of therapy used to treat symptoms of osteoarthritis. They found that exercise was the most successful treatment method for reducing pain and improving physical function in patients. Patients who received proprioceptive and balance training saw improvements in quadriceps and hamstring muscle strength when compared with a standard rehabilitation program. No conclusions could be made on the effectiveness of the use of proprioceptive and balance exercises in the rehabilitation process after ACL injury.[102] Further research is required to determined whether proprioceptive and balance training with improvements in quadriceps and hamstring muscle strength confer any long-term benefits in pain reduction and slowing of cartilage loss in OA. However, it has been shown that weight loss was highly effective in the reduction of pain and the improvement of function associated with osteoarthritic symptoms in obese patients.[103] The combination of weight loss and exercise was also successful and provided the best results in a second study comparing the physical function, pain, and mobility in older overweight and obese adults with knee osteoarthritis.[104] Reduced weight-bearing exercise such as recumbent biking and pool therapy are better tolerated forms of exercise for patients with advanced osteoarthritis, especially for the obese. While unlikely to reduce OA disease progression, this approach contributes to weight loss, gains in strength, and improvement in cardiovascular function. In those individuals who have undiagnosed and untreated ligamentous injury and joint instability, the effectiveness of physical therapeutics is sub-optimal unless ligament function and joint stability are restored.

Injection therapies using various growth factors and cells for treatment of ligament injuries have been the focus of recent research and have become available as treatment options for patients, though many are not covered by insurance. Platelets play a large role in the release of growth factors, including activation of pathways to release platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β) and epidermal growth factor (EGF).[105] Macrophages produce basic fibroblast growth factor (BFGF), transforming growth factor alpha (TGF-α), as well as TGF-β and PDGF, which attract fibroblasts and inflammatory cells to the wound, stimulate fibroblast proliferation, as well as the synthesis of collagen and non-collagenous proteins.[106, 107] In vitro studies have shown that the presence of TGF-β increases cell proliferation as well as EGF due to its chemotactic and proliferative effects on fibroblasts, stimulating synthesis of non-collagenous proteins and glycosaminoglycans. BFGF was also observed to attract fibroblasts to the wound site and stimulate replication. However, the location of the injury, as well as the age of the subject and skeletal maturity affected the ability of growth factors to stimulate fibroblasts. In a more vascular ligament, such as the MCL, the response to growth factors was much greater compared to the response elicited by damage to the less-vascular ACL. Overall it was suggested that the effects of growth factors on cell proliferation and protein synthesis was tissue dependent and therapeutic interventions must account for differences in response to injuries of different ligament tissues. In vivo studies demonstrated accelerated and improved quality of healing with the use of growth factors, however detrimental effects were observed at higher concentrations.[8] TGF-β was also shown to increase the size of ligament scars, but did not improve their material strength and did not alter matrix deficiencies. Gene therapy uses transfer techniques to deliver growth factors for longer periods of time at the sites of ligament and tendon healing. It is a fairly new technique that has recently begun to evolve. Prior to gene therapy, collagen and cellulose sponges were used to produce detectable levels of growth factors, but the effects only lasted for a few days. Several obstacles impede practical implementation including adenovirus infectivity and possible immune reactions against the antigen that would decrease expression of the introduced gene.[8] Cell therapy is the newest intervention, which incorporates the use of progenitor cells in combination with growth factors to improve wound healing. Mesenchymal stem cells (MSCs) or mesenchymal progenitor cells (MPCs) are implanted into the injured tendon or ligamentous structure and have been observed to significantly improve the structural properties of the connective tissue.[8] The use of growth factors causes direct recruitment and activation of local fibroblasts.[15] Platelet-rich plasma (PRP) is one example of a growth factor injection therapy and is considered a form of Prolotherapy. PRP consists of the

collection of autologous blood, which is subjected to two states of centrifugation to separate the PRP from platelet-poor plasma and red blood cells, and then is injected into ligaments, tendons and other soft tissue such as muscles to stimulate healing of soft tissue, as well as bone.[108] PRP has gained a lot of traction in recent years among many physicians who diagnose and treat joint pain due to the healing properties of platelets and their ability to initiate and amplify healing cascades and recruit reparative cells as well as other healing factors associated with soft tissue repair. PRP has been shown to stimulate repair of chronic tendinopathies, including lateral epicondylitis, plantar fasciitis and cartilage degeneration, in a similar manor to standard Prolotherapy treatments.[109] It has been described fully in prior issues of *The Journal of Prolotherapy*.

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

JOINT SURGERY: THE OTHER SIDE OF THE STORY

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

All of these procedures have risk factors inherent with surgery and are overall very costly compared to other treatment options, including lost income from time off work and lengthy rehabilitation. They also do not address the ligament dysfunction and instability issue. In fact, arthroscopic procedures and surgical repairs increase the weakness and instability in the joint because it involves the cutting of muscles and fascia and removal of discs, cartilage, and ligament tissue.[110] Production of scar tissue is also an inevitable consequence of surgery, both in the skin and in the deeper tissues, even with arthroscopic procedures.

Surgery involves the use of sedation, anesthesia, and/or an epidural during the procedure with potential complications. Some major complications from anesthesia include respiratory depression, brain anoxia from depressed breathing, heart arrhythmia, and malignant hyperthermia.[111, 112] Minor complications from anesthesia can range from chipped teeth to throat irritation and sores to post-injection headaches and even pneumonia.[110] Other risks associated with surgery include embolism, excess hemorrhaging, infection, nerve injury, and device issues. Thrombus formation (blood clots) and embolism can occur because of several factors, including fat emboli as well as decreased mobility which causes sluggish movement of blood through the leg veins. The risk can be reduced through the use of blood thinning medications (anticoagulants), elastic stockings, exercises to increase blood flow in the leg muscles, or plastic boots that inflate with air to compress the muscles in the legs, but blood clots still may occur. Infections can occur in the wound or deep around the prosthesis. Minor infections are treated with antibiotics but major or deep infections may require surgery and/or the removal of the prosthesis. Also, infections in the body can spread to the joint replacement where bacteria can harbor due to a paucity of vascular tissues needed to fight off infections. Nerve injury may also occur as a complication of surgery. This is more common when the surgery involves the correction of a major joint deformity or lengthening of a shorter limb because of arthritic deformity.[113]

Because surgery involves the removal of tissue from the affected joint, the patient's original anatomy is altered. This usually means a change in the joint biomechanics, which may create secondary problems. Surgery also may increase the required rehabilitation time because it often necessitates an extended period of immobilization or limited motion due to pain, wound healing, or to allow for reduction of swelling, all of which increase deconditioning and disability. Rehabilitation can last for weeks, months, or years and returning to one's previous functional or athletic level may not occur.[110] Surgical interventions for ligament injury may invigorate the inflammatory response, increasing the risk of early cartilage degeneration.[43] Ligament-injured joints are

at increased risk for osteoarthritis. Neither conservative treatments (i.e., physical rehabilitation), nor surgical procedures appear to reduce the prevalence of secondary osteoarthritis. The mechanical instability in a ligament-injured joint likely initiates the degenerative cascade due to changes in the area of contact of the joint surface, disrupting the load distribution on the cartilage and bone. It is even suggested that a "stable" prolonged inflammatory responses can accelerate the progression of OA.[8] Joint replacement due to severe end-stage OA has improved the pain and function of many people so that it will, for the foreseeable future, continue to benefit a certain sub-set of patients who receive it. But it has been the premature use of surgery, driven by patients feeling that they have exhausted all other avenues and surgeons who see surgery as the definitive solution in even marginal cases or who lack the understanding of the predisposing factors, especially ligamentous disruption, which, if properly diagnosed and treated before the occurrence of disabling end-stage OA, would lead to successful outcomes and prevention of many unnecessary joint replacements and other surgical procedures.

PROLOTHERAPY: THE NATURAL SOLUTION FOR LIGAMENT INJURY AND OSTEOARTHRITIS

Prolotherapy is an alternative to the accepted treatment norms for osteoarthritis and joint degeneration, especially as it relates to ligament injury. The term "Prolotherapy" was coined by George S. Hackett, MD in 1956, and he defined the treatment as "the injection of a solution within the relaxed ligament and tendon which will stimulate the production of new fibrous tissue and bone cells that will strengthen the weld of fibrous tissue and bone to stabilize the articulation and permanently eliminate the disability."[114] It addresses the main issue that is the root of the problem: ligament weakness and/or injury. As demonstrated in early animal studies by Hackett, ligaments injected with a natural dextrose-based solution triggers cellular proliferation. A mild inflammatory response initiates the three-stage wound healing process, as described earlier, and produces the growth of new ligament and tendon tissue. The new tissues are very similar to normal ligament and tendon tissue, except they are much thicker, stronger, and contain fibers of varying thickness that testify to the ongoing creation of collagen in the tissue.[114-117] (*See Figure 10.*)

Effects of Five Prolotherapy Treatments

	Prolotherapy Injected Ligaments	Saline Injected Ligaments (control)	% Change
Ligament Mass (mg)	132.2	89.7	44
Ligament Thickness (mm)	1.01	0.79	27
Ligament Mass Length (mg/mm)	6.45	4.39	47
Junction Strength (N)	119.1	93.5	28

Figure 10. The effects of five Prolotherapy treatments to the medial collateral ligament. Prolotherapy causes a statistically significant increase in ligament mass and strength as well as bone-ligament junction strength.
Used with permission from: Hauser RA, et al. *Prolo Your Sports Injuries Away!* Oak Park, IL: Beulah Land Press; 2001. Figure 6-7.

There are three categories of proliferants that have been used; irritants, osmotic shock agents, and chemotactic agents. Irritants (e.g., phenol, tannic acid, quinine) create a local tissue reaction which causes granulocyte infiltration. Osmotic shock agents (e.g., glucose, zinc sulfate) create a local tissue reaction to stimulate granulocyte infiltration by dehydration. Chemotactic agents (e.g., sodium morrhuate) cause direct activation of local inflammatory cells.[15] The most commonly used solution contains dextrose mixed with an anesthetic and diluted with sterile water or saline. Many substances can be used as proliferating agents, separate from or added to the standard dextrose solution including zinc sulfate, P2G (phenol, glycerin, and glucose), sodium morrhuate (derived from cod oil), calcium gluconate, pumice and others. Other substances and nutrients can be added to the solution, depending on the Prolotherapy physician's experience and training, as well as the condition being treated.

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

pain six weeks after three Prolotherapy treatments of 1cc of 5% sodium morrhuate and 1cc of 1% xylocaine to the SI (sacroiliac) joints every two weeks; only three patients had no improvement.[15] A study by Drs. Klein, Dorman, Ongley and Eek regarding knee ligament instability reported that all five patients who completed the study reported marked decrease in knee pain with a significant decrease in joint laxity in all axes measured following Prolotherapy treatment. Dorman and Klein also studied the effects of Prolotherapy on the posterior sacroiliac ligaments and found after six weekly injections there was an increase in the average ligament diameter from 0.055 micrometers to 0.087 micrometers, measured by electron microscopy. They also found increased numbers of collagen-producing fibroblasts, as well as linear ligament orientation similar to what is found in normal ligaments.[115, 118, 119] Auburn et al. also examined the effects of Prolotherapy on the cross-sectional area of the iliolumbar ligaments and found, by ultrasound, that six weeks after one injection of a 4cc procaine, 1cc 50% dextrose and 0.5cc of PQU (2.34ml Phenol liquefied, 5.73 GM Quinine HCL, 1.26 GM Urea USP) to designated medial and lateral injections sites, the ligament thickness increased in the medial portion from 0.91cm at baseline to 1.2cm, 27% growth, and in the lateral portion from 1.35cm to 1.7cm, 21% growth.[120] Another study documented changes in pelvic alignment secondary to suspected loosening of the SI ligaments. They reported changes in the measurements of pelvic inclination (angles each side of the pelvic bones makes with the ground) on both the right and left sides when comparing the angles from before and after Prolotherapy. This was attributed to a definite tightening of the ligaments as there was a decrease in the difference between the two sides, as well as a reduction in pain and an increase in function.[121] Hauser performed a study of 34 patients who had been told by doctors they would need surgery, including joint replacements, arthroscopic procedures, fusions and ligament and tendon repairs, to repair their chronic pain problems. After an average of 4.5 treatments using 15% dextrose Prolotherapy, the pain levels reported by the patients decreased from 7.6 to 3.1 and 91% of the patients felt Prolotherapy provided 50% or greater relief in their pain.[122] Reeves tested the effects of Prolotherapy solutions containing different concentrations of dextrose, comparing a 10% solution against a 25% solution, on patients with ACL laxity. The subjects reported improvements in ACL laxity, pain, swelling and knee range of motion in both groups, with comparable results when comparing the two solutions.[123] A study using a solution containing 5% sodium morrhuate showed not only an increase in the number of cells at the injured ligament site, but also a wider variety of cell types, including fibroblasts, neutrophils, lymphocytes and plasma cells, as well as many unidentifiable cells.[117] Additionally, Dr. Liu found that after a series of five injections of 5% sodium morrhuate into the MCL of rabbits, the ligament mass increased by 44%, the ligament thickness increased by 27%, and the strength of the ligament bone junction increased by 28%, demonstrating that Prolotherapy causes tissue growth and strengthening.[116]

A unique syndrome reported in the literature which is rarely recognized that warrants mention for its responsiveness to Prolotherapy is called Barré-Lieou Syndrome. It was first described in 1925 by Jean Alexandre Barré, MD, a French neurologist, and in 1928 by Yong-Choen Lieou, a Chinese physician, each studying it independently.[124] It consists of a constellation of symptoms stemming from dysfunction of the posterior cervical sympathetic nerves along the cervical spine vertebrae caused by weakened, stretched, or damaged cervical spine ligaments. The symptoms which characterize Barré-Lieou Syndrome include some or all of the following: headache, vertigo, tinnitus, neck pain, sinus congestion, blurred vision, hoarseness, and other symptoms related to abnormal tension on the sympathetic nervous system in the neck. While none of these symptoms confirm a diagnosis of Barré-Lieou Syndrome, the clinical case for it becomes more compelling when many of these symptoms are grouped together. The usual studies do little to diagnose this syndrome. Clinical recognition of Barré-Lieou Syndrome and its definitive resolution by Prolotherapy eliminates the need for costly investigational assessment and unnecessary and inappropriate interventions targeting the various symptoms that are part of Barré-Lieou Syndrome.

It proves useful to compare the safety of Prolotherapy to the surgical risks described earlier. One study surveyed 494,845 patients treated for chronic pain with Prolotherapy and found only eighty (0.00016 percent) complications. Sixty-six of the cases were considered minor complications and included allergic reactions and pneumothoraces, while 14 were defined as major complications and required hospitalization.[125] Prolotherapy does not require anesthesia or the removal of tissue from the body or addition of foreign objects into the body, only takes a few minutes, does not require rehabilitation, and has a

minimal risk of complications.[110] Furthermore, there is negligible down-time following treatment, no damage or destruction of nerves or blood vessels, and scar tissue is not produced.

The Florida Academy of Pain Medicine (FAPM) reviewed literature for Regenerative Injection Therapy (RIT) to inform and familiarize readers with RIT, to outline indications and conditions treated with RIT as well as contraindications, and encourage the use of RIT in pain pathology related to connective tissue. FAPM uses regenerative injection therapy as another term for Prolotherapy. They found, in over 530,000 patients treated, 48% to 82% of patients reported improvements related to return to work and previous function, while resolution of pain ranged from zero to 100%, and reported complications that included 28 pneumothoraces, 24 allergic reactions, one grand mal seizure and one aseptic meningitis. They also concluded RIT's effectiveness in treatment of chronic musculoskeletal pain due to post-traumatic and degenerative changes in connective tissue such as ligaments, tendons, fascia and intervertebral discs. The FAPM suggests the use of RIT to treat ligaments (intra-articular, periarticular, capsular), tendons, fascia, entheses, and intervertebral discs which have sustained sprain, strain, enthesopathy, tendinosis/ligamentosis, or pathological laxity and experience chronic pain, pain from overuse, hypermobility/subluxations, thoracic and lumbar vertebral compression fractures, osteoarthritis, spinal instability secondary to ligament laxity, and intolerance to NSAIDs, steroids, or opiates. In conclusion, they feel that RIT is safe in treating a number of pain syndromes arising from ligament and tendon diatheses as well as other pain problems and also state that reviews of the current literature suggests the use of NSAIDs and steroid preparation for chronic pain as well as degenerative conditions is limited in treating the condition and only is helpful in "curbing a significant inflammatory reaction."[126]

The American Association of Orthopaedic Medicine (AAOM) also supports the use of Prolotherapy for the treatment of selected cases of low back pain and other chronic myofascial pain syndromes because the process stimulates the proliferation of collagen to promote non-surgical soft tissue repair that strengthens ligaments and relieves pain.[127] One study of volunteers demonstrated an average increase of 65% in the cross-sectional diameter of posterior sacroiliac ligaments three months post-treatment; improvements in lumbar range of motion when comparing measurements before and after treatment were also documented. These findings are suggestive of ligament proliferation and soft tissue healing.[115, 118] A study by Yelland et al. reported improvements after injections of both plain dextrose and a placebo of saline, with statistically significant decreases in pain and disability scores after both 12 and 24 months. The authors suggested that the bleeding and tissue disruption associated with needle and saline injections also has a mild proliferant effect. They concluded by stating Prolotherapy was a safe and valid treatment option for a selected group of chronic low back pain patients, adding that if insurers were to adopt a universal policy for denying payment for chronic low back pain treatments based on lack of definitive evidence, no one with chronic low back pain would be able to obtain treatment and, furthermore, that coverage should be provided for treatments that are biologically plausible and supported by literature through clinical trials.[128] Vert Mooney, MD, an orthopedic surgeon and former chairman of orthopedics at the University of California, San Diego, was quoted "that this fringe treatment (Prolotherapy) is no longer at the periphery and seems to be at the frontier of a justifiable, rational treatment with a significant potential to avoid destructive procedures."[129]

Reeves has performed many randomized studies on the injection of dextrose Prolotherapy into osteoarthritic thumbs, fingers and knees. After a series of three injections to the medial and lateral ligaments of the distal interphalangeal (DIP), proximal interphalangeal (PIP) and trapeziometacarpal (thumb CMC) of one half milliliter of either 10% dextrose and 0.075% xylocaine (active) or 0.075% xylocaine (control), it was reported that pain at rest and with gripping improved in the dextrose group, including reported improvements in pain with movements of the fingers, especially with flexion. Similar results were produced in a second study after three bimonthly injections of 9cc 10% dextrose and 0.075% lidocaine (active) when compared to the injections of 0.075% lidocaine (control). He also found that a 10% dextrose solution resulted in clinically and statistically significant improvements in symptoms associated with knee osteoarthritis with decreased pain, swelling and knee buckling frequency, as well as improved range of motion. Also at the end of one year, eight of 13 of the patients with ACL laxity were noted to have ACLs that were no longer lax.[130, 131] Radiographic comparison of

the knees at zero and 12 months revealed stability of all radiographic variables with improvements in lateral patellofemoral cartilage thickness as well as distal femur width. Hauser also has conducted radiographic studies of osteoarthritic knees by measuring the joint spaces before Prolotherapy and after a series of injections. He treated five knees of three adult patients with a standard solution of 15% dextrose, 10% Sarapin and added 2IU of Human Growth Hormone to each intra-articular joint injection, with each patient receiving six to14 injections per knee. X-rays taken one year after starting Prolotherapy showed increases in the joint space width of all knees, in both the femorotibial joint and the patellofemoral joint. Patients reported decreased pain in their knees with reduced need for pain medication. They also noticed improved range of motion and function and did not feel limited in regard to their knees.[132] Similar results using 15% dextrose solution demonstrated cartilage repair within the hip with decreased pain and improved function. Eighty-nine percent of the patients experienced at least 50% reduction of their pain with over 70% reporting reduced crunching and stiffness. Eighty-five percent were able to cut their pain medication usage by at least 50% and more than 82% reported improved function and daily living. Also, some patients had before and after X-rays which revealed increases in the joint space widths consistent with cartilage repair and the patient's subjective reporting of their symptoms.[133]

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

In addition to a favorable safety profile, Prolotherapy produces positive results in 75 to 90% of patients by resolving chronic pain issues.[110] It is the treatment of choice for ligament injuries (sprains, tears, instability, and benign hypermobility syndrome) and the resultant cartilage degeneration that these injuries cause. The loss of articular cartilage and the osteophytes (bone spurs) located at the entheses where ligaments attach to bone at the margins of joints and in the spine can be prevented or reversed after one of the main causes of joint degeneration (i.e., instability) is eliminated by the stabilizing effects produced by Prolotherapy. (*See Figure 11.*) The process of stimulated ligament repair is joint reconstruction at its core. The vastly different risk-benefit profile of Prolotherapy versus joint replacement surgery or drugs makes Prolotherapy the treatment of choice in all but the most extreme cases of ligament injury and joint degeneration.

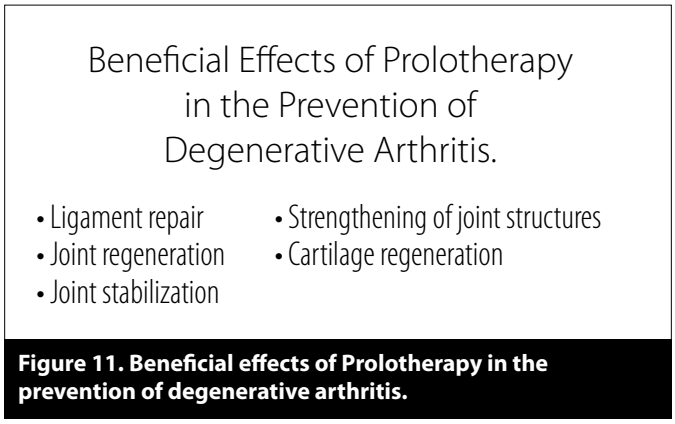


Figure 11. Beneficial effects of Prolotherapy in the prevention of degenerative arthritis.

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

CONCLUSION: SUMMARY COMMENTS

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

REFERENCES

1. Mahaffey D, et al. Ankle and foot injuries in sports. *Clinical Family Practice*. 1999;1(1):233-250.
2. Levy D, et al. (2011). Soft Tissue Knee Injury. Retrieved from: http://emedicine.medscape.com/article/826792-overview#a0199.
3. Roy S, et al. Effects of Opioids on the immune system. *Neurochemical Research*. 1996;21(11):11375-1386.
4. Vallejo R, et al. Opioid therapy and immunosuppression: a review. *American Journal of Therapeutics*. 2004;11(5):354-365.
5. Bayer B, et al. Morphine inhibition of lymphocyte activity is mediated by an opioid dependent mechanism. *Neuropharmacology*. 1990;29(4):369-374.
6. Frank C. Ligament structure, physiology and function. *Journal of Musculoskeletal and Neuronal Interactions*. 2004;4(2):199-201.
7. Van Der Esch M, et al. Joint laxity and the relationship between muscle strength and functional ability in patients with knee osteoarthritis. *Arthritis Care and Research*. 2006;55(6):953-959.
8. Woo S, et al. Injury and repair of ligaments and tendons. *Annuals Reviews of Biomedical Engineering*. 2000;2:83-118.
9. Jung H, et al. Role of biomechanics in the understanding of normal, injured and healing ligaments and tendons. *Sports Medicine, Arthroscopy, Rehabilitation, Therapy & Technology*. 2009;1(1):9.
10. Hollister S. *Structure and function of ligaments and tendons* [Online Lecture Notes]. Retrieved from: http://www.engin.umich.edu/class/bme456/ligten/ligten.htm.
11. Provenzano P, et al. Subfailure damage in ligament: a structural and cellular evaluation. *Journal of Applied Physiology*. 2002;92(1):362-371.
12. Frank C, et al. Ligament healing: a review of some current clinical and experimental concepts. *The Iowa Orthopaedic Journal*. 1992;12:21-28.
13. Vereeke West R, et al. Soft-tissue physiology and repair. In A. Vaccaro (8). *Orthopaedic Knowledge Update 8*. 2005; (15-27). American Academy of Orthopaedic Surgeons: Rosemount, IL.
14. Frank C, et al. Optimisation of the biology of soft tissue repair. *Journal of Science and Medicine in Sport*. 1999;2(3):190-210.
15. Schwartz R. Prolotherapy: a literature review and retrospective study. *Journal of Neurology, Orthopaedic Medicine, and Surgery*. 1991;12(3):220-223.
16. Lewek M, et al. Knee stabilization in patients with medial compartment knee osteoarthritis. *Arthritis and Rheumatism*. 2005;52(9):2845-2853.
17. Heldin C. Structural and functional studies on platelet-derived growth factor. *EMBO Journal*. 1992;11(12):4251-4259.
18. Massagué J. TGF-beta signal transduction. *Annual Review of Biochemistry*. 1998;67:753–91.
19. Green P, et al. Promiscuity of fibroblast growth factor receptors. *Bioessays*. 1996;18(8):639-46.
20. Ornitz D, et al. Fibroblast growth factors. *Genome Biology*. 2001;2(3). Available at: http://www.biomedcentral.com/content/pdf/gb-2001-2-3-reviews3005.pdf. Accessed on October 12, 2011.
21. Carpenter G, et al. Epidermal growth factor. *The Journal of Biological Chemistry*. May 1990;265(14):7709-12.
22. Felson D, et al. Osteoarthritis: new insights part 1: the disease and its risk factors. *Annals of Internal Medicine*. 2000;133(8):635-46.
23. Brody J. Personal health; a new set of knees comes at a price: a whole lot of pain. *New York Times*, published February 8, 2005.
24. Buckwalter J, et al. Athletics and Osteoarthritis. *The American Journal of Sports Medicine*. 1997;25(6):873-881.

25. Buckwalter J, et al. Joint injury, repair, and remodeling: roles in post-traumatic osteoarthritis. *Clinical Orthopaedics and Related Research*. 2004;(423):7-16.
26. Andriacchi T, et al. A framework for the in vivo pathomechanics of osteoarthritis at the knee. *Annals of Biomedical Engineering*. 2004;32(3):447-457.
27. Buckwalter J. Sports, joint injury, and posttraumatic osteoarthritis. *The Journal of Orthopaedic and Sports Physical Therapy*. 2003;33(10):578-588.
28. Gelber A, et al. Joint injury in young adults and risk for subsequent knee and hip osteoarthritis. *Annals of Internal Medicine*. 2000;133(5):321-328.
29. Rall K, et al. A study of long term effects of football injury to the knee. *Missouri Medicine*. Jun 1984;61:435-438.
30. Kujala U, et al. Osteoarthritis of weight bearing joints of lower limbs in former elite male athletes. *BMJ (Clinical Research Ed.)*. 1994;308(6923):231-234.
31. Kujala U, et al. Knee osteoarthritis in former runners, soccer players, weight lifters, and shooters. *Arthritis and Rheumatism*. 1995;38(4):539-546.
32. Juhakoski R, et al. Risk factors for the development of hip osteoarthritis: a population-based prospective study. *Rheumatology (Oxford, England)*. 2009;48(1):83-87.
33. Adams J. Injury to the throwing arm. A study of traumatic changes in the elbow joints of boy baseball players. *California Medicine*. 1965;102:127-132.
34. Bennett G. Shoulder and elbow lesions of professional baseball pitcher. *JAMA*. 1941;117:510-514.
35. Forward D, et al. Do young patients with malunited fractures of the distal radius inevitable develop symptomatic post-traumatic osteoarthritis? *The Journal of Bone and Joint Surgery, British Volume*. 2008;90(5):629-637.
36. Lawrence R, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States, part II. *Arthritis and Rheumatism*. 2008;58(1):26-35.
37. Lawrence R, et al. Estimates of the prevalence of selected arthritis and musculoskeletal diseases in the United States. *Arthritis and Rheumatism*. 1998;41(5):778-799.
38. Lawrence R, et al Estimates of the prevalence of selected arthritis and musculoskeletal diseases in the United States. *Journal of Rheumatology*. 1989;16(4):427-441.
39. Felson D, et al. Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Annals of Internal Medicine*. 2000;133(8):635-646.
40. Petersson I, et al. Radiographic osteoarthritis of the knee classified by the Ahlback and Kellgren & Lawrence systems for the tibiofemoral joint in people aged 35-54 years with chronic knee pain. *Annals of the Rheumatic Diseases*. 1997;56(8):493-496.
41. Felson D, et al. The incidence and natural history of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. *Arthritis and Rheumatism*. 1995;38(10):1500-1505.
42. HCUP Facts and Figures, 2006: AHRQ analysis of arthritis hospitalizations, retrieved from *Hospitalizations for Osteoarthritis Rising Sharply*. Available at: http://www.ahrq.gov/news/nn/nn090308.htm. Accessed on: October 12, 2011.
43. Fleming B, et al. Ligament injury, reconstruction, and osteoarthritis. *Current Opinion in Orthopaedics*. 2005;16(5):354-362.
44. Hart A, et al. Assessment of osteoarthritis after reconstruction of the anterior cruciate ligament: a study using single-photon emission computed tomography at ten years. *The Journal of Bone and Joint Surgery, British Volume*. 2005;87(11):1483-1487.
45. Liden M, et al. Osteoarthritic changes after anterior cruciate ligament reconstruction using bone-patellar tendon-bone or hamstring tendon autografts: a retrospective, 7 year radiographic and clinical follow-up study. *Arthroscopy*. 2008;24(8):899-908.
46. Neuman P, et al. 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(9):1717-1725.
47. Rudolph K, et al. Age-related changes in strength, joint laxity, and walking patterns: are they related to knee osteoarthritis? *Physical Therapy*. 2007;87(11):1422-1432.
48. Schmitt L, et al. Instability, Laxity, and physical Function in patients with medial knee osteoarthritis. *Physical Therapy*. 2008:88(12):1506-1516.
49. Bierma-Zeinstra S, et al. Risk factors and prognostic factors of hip and knee osteoarthritis. *Nature Clinical Practice, Rheumatology*. 2007;3(2):78-85.
50. Hoaglund F, et al. Primary osteoarthritis of the hip: etiology and epidemiology. *The Journal of the American Academy of Orthopaedic Surgeons*. 2001;(5):320-327.
51. Jensen L, et al. Hip osteoarthritis: influence of work with heavy lifting, climbing stairs or ladders, or combining kneeling/squatting with heavy lifting. *Occupational and Environmental Medicine*. 2008;61(1):6-19.
52. Vingard E, et al. Osteoarthritis of the hip in women and its relation to physical load at work and in the home. *Annals of the Rheumatic Diseases*. 1997;56(5):293-298.
53. Shepard G, et al. Ex-professional association footballers have an increased prevalence of osteoarthritis of the hip compared with age matched controls despite not having sustained notable hip injuries. *British Journal of Sports Medicine*. 2003;37(1):80-81.
54. Koh J, et al. Osteoarthritis in other joints (hip, elbow, foot, ankle, toes, wrist) after sports injuries. *Clinics in Sports Medicine*. 2005;24(1):57-70.
55. Callahan L, et al. Osteoarthritis in retired National Football League players: The role of injuries and playing position. *Arthritis and Rheumatism*. 2002;(46):S415.
56. Neer C, et al. Recent experience in total shoulder replacement. *Journal of Bone and Joint Surgery*. 1982;64(3):319-337.
57. Ogawa K, et al. Osteoarthritis in shoulders with traumatic anterior instability: preoperative survey using radiography and computed tomography. *Journal of Shoulder and Elbow Surgery*. 2006;15(1):23-29.
58. Woodward T, et al. The painful shoulder: part II. Acute and chronic disorders. *American Family Physician*. 2000;1(11):3291-3300.
59. Dvorak J, et al. Football injuries and physical symptoms. *The American Journal of Sports Medicine*. 2000;28:S-3-S-9.

60. Hintermann B, et al. Medial ankle instability: an exploratory, prospective study of fifty-two cases. *American Journal of Sports Medicine*. 2004;32(1):183-190.

61. Karlsson J, et al. Chronic lateral instability of the ankle in athletes. *Sports Medicine (Aukland, N.Z.)*. 1993;16(5):355-365.

62. Valderrabano V, et al. Ligamentous posttraumatic ankle osteoarthritis. *The American Journal of Sports Medicine*. 2006;34(4):612-620.

63. Hashimoto T, et al. A kinematic study of ankle joint instability due to rupture of the lateral ligaments. *Foot and Ankle International*. 1997;18(11):729-734.

64. Jones W, et al. Beware the sprained wrist. The incidence and diagnosis of scapholunate instability. *The Journal of Bone and Joint Surgery, British Volume*. 1988;70(2):293-297.

65. Rettig A, et al. Epidemiology of hand and wrist injuries in sports. *Clinics in Sports Medicine*. 1998;17(3):401-406.

66. Knirk J, et al. Intraarticular fractures of the distal end of the radius in young adults. *The Journal of Bone and Joint Surgery, American Volume*. 1986;68(5):647-59.

67. Ray C, et al. Understanding Osteoarthritis of the Spine. *Spine Health: Trusted Information for Pain Relief*. Available at: http://www.spine-health.com/conditions/arthritis/understanding-osteoarthritis-spine. Accessed on October 12, 2011.

68. Vogt M, et al. Lumbar olisthesis and lower back symptoms in elderly white women. The study of osteoporotic fractures. *Spine*. 1998;23(23):2640-2647.

69. Revolution Health Group: How to cover – and cut – the rising cost of osteoarthritis care. Available at: http://www.revolutionhealth.com/conditions/arthritis/osteoarthritis/what-you-can-do/arthritis-costs?id=article.2007-07-13.0406371040&section=section_02. Accessed on October 12, 2011.

70. Gabriel S, et al. Direct medical costs unique to people with arthritis. *Journal of Rheumatology*. 1997;24(4):719-725.

71. Maetzel A, et al. Community hypertension and arthritis project study team. The economic burden associated with osteoarthritis, rheumatoid arthritis, and hypertension: a comparative study. *Annals of Rheumatic Diseases*. 2004;63(4):395-401.

72. White A, et al. Direct and indirect costs of pain therapy for osteoarthritis in an insured population in the United States, 2008.

73. Hylek E, et al. Acetaminophen and other risk factors for excessive warfarin anticoagulation. *JAMA*. 1998;279(9):657-662.

74. Camu F, et al. Pharmacology of systemic analgesics. *Best Practice and Research Clinical Anesthesiology*. 2002;12(4):475-488.

75. Solomon G. The use of cox-2-specific inhibitors with specific attention to use in patients requiring orthopedic surgical interventions. *Orthopedic Special Edition*. 2002;8:11-13.

76. Greene J. Cost-conscious prescribing of nonsteroidal anti-inflammatory drugs for adults with arthritis. *Archives of Internal Medicine*. 1992;152:1995-2002.

77. Almekinders L. An in vitro investigation into the effects of repetitive motion and nonsteroidal anti-inflammatory medication on human tendon fibroblasts. *American Journal of Sports Medicine*. 1995;23:119-123.

78. Waknine Y. NSAIDs inhibit tendon-to-bone healing in rotator cuff repair. Presented at the American Orthopedic Society for Sports Medicine. June 28, 2004. Available at: http://www.medscape.com/viewarticle/481998. Accessed October 12, 2011.

79. Kulick M. Oral ibuprofen: evaluation of its effect on peritendinous adhesions and the breaking strength of a tenorrhaphy. *The Journal of Hand Surgery*. 1986;11A:100-119.

80. Hauser R. The acceleration of articular cartilage degeneration in osteoarthritis by nonsteroidal anti-inflammatory drugs. *Journal of Prolotherapy*. 2010;2(1):305-322.

81. Wright J. The double-edges sword of COX-2 selective NSAIDs. *Canadian Medical Association Journal*. 2002;167(10):1131-1137.

82. Newman N, et al. Acetabular bone destruction related to non-steroidal anti-inflammatory drugs. *The Lancet*. 1985;2(8445):11-13.

83. Ronningen H, et al. Indomethacin treatment in osteoarthritis of the hip joint. *Acta Orthopaedica Scandinavica*. 1979;50(2):169-174.

84. Huskisson E, et al. Effects of anti-inflammatory drugs on the progression of osteoarthritis of the knee. *Journal of Rheumatology*. 1995;22(10):1941-1946.

85. Reijman M, et al. Is there an association between the use of different types of nonsteroidal anti-inflammatory drugs and radiologic progression of osteoarthritis? The Rotterdam Study. *Arthritis and Rheumatism*. 2005;52(10):3137-3142.

86. Buckland-Wright J, et al. Quantitative microfocal radiography detects changes in OA knee joint space width in patients in placebo-controlled trial of NSAID therapy. *Journal of Rheumatology*. 1995;22(5):937-943.

87. Palmoski M, et al. Aspirin aggravates the degeneration of canine joint cartilage caused by immobilization. *Arthritis and Rheumatism*. 1982;25(11):1333-1342.

88. Palmoski M, et al. Effect of salicylate and indomethacin on glycosaminoglycan and prostaglandin E2 synthesis in intact canine cartilage ex vivo. *Arthritis and Rheumatism*. 1984;27(4):398-403.

89. Palmoski M, et al. Marked suppression by salicylate of the augmented proteoglycan synthesis in osteoarthritis cartilage. *Arthritis and Rheumatism*. 1980;23(1):83-91.

90. Palmoski M, et al. Effects of some nonsteroidal antiinflammatory drugs on proteoglycan metabolism and organization in canine articular cartilage. *Arthritis and Rheumatism*. 1980;23(9):1010-1020.

91. Brandt K, et al. Nonsteroidal anti-inflammatory drugs in treatment of osteoarthritis. *Clinical Orthopedics and Related Research*. 1986;(213):84-91.

92. Palmoski M, et al. Relationship between matrix proteoglycan content and the effects of salicylate and indomethacin on articular cartilage. *Arthritis and Rheumatism*. 1983;26(4):528-531.

93. Serni U, et al. Is there preliminary in-vivo evidence for an influence of nonsteroidal anti-inflammatory drugs on progression in osteoarthritis? Part II-evidence from animal models. *Osteoarthritis and Cartilage*. 1999;7(3):351-352.

94. Chang J, et al. Effects of non-steroidal anti-inflammatory drugs on cell proliferation and death in cultured epiphysealarticular chondrocytes of fetal rats. *Toxicology*. 2006;228(2-3):111-123.

95. Brochhausen C, et al. Cyclooxygenases and prostaglandin E2 in growth plate chondrocytes in vitro and in situ – Prostaglandin E2 dependent proliferation of growth plate chondrocytes. *Arthritis Research and Therapy*. 2006;8(3):R78.

96. Gossec L, et al. Predictive factors of total hip replacement due to primary osteoarthritis: a prospective 2 year study of 505 patients. *Annals of Rheumatic Diseases*. 2005;64(7):1028-1032.

97. Caldwell J, et al. Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. *The Journal of Pain and Symptom Management*. 2002;23(4):278-291.

98. Woo S, et al. Injury and repair of musculoskeletal soft tissues. *AJ Orth Res*. 1988;6:907-931.

99. Mankin H. Localization of tritiated thymidine in articular cartilage of rabbits inhibits growth in immature cartilage. *Journal of Bone and Joint Surgery*. 1962;44A:682.

100. American Academy of Orthopaedic Surgeons (2008). Treatment of osteoarthritis of the knee (non-arthroplasty): Full Guideline. Adopted by the American Academy of Orthopaedic Surgeons Board of Directors, December 6, 2008.

101. Deyle G, et al. Effectiveness of manual physical therapy and exercise in osteoarthritis of the knee. A randomized, controlled trial. *Annals of Internal Medicine*. 2000;132(3):173-181.

102. Cooper R, et al. A systematic review of the effect of propriocetive and balance exercises on people with an injured or reconstructed anterior cruciate ligament. *Research in Sports Medicine*. 2005;3(2):163-178.

103. Jamtvedt G, et al. Physical therapy interventions for patients with osteoarthritis of the knee: an overview of systematic reviews. *Physical Therapy*. 2008;88(1):123-136.

104. Messier S, et al. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trials. *Arthritis and Rheumatism*. 2004;50(5):1501-1510.

105. Midwood K, et al. Tissue repair and the dynamics of the extracellular matrix. *The International Journal of Biochemistry & Cell Biology*. 2004;36(6):1031–1037.

106. Tidball J, et al. Macrophage invasion does not contribute to muscle membrane injury during inflammation. *Journal of Leukocyte Biology*. 1999;65(4):492–498.

107. Schiaffino S, et al. *Skeletal muscle repair and regeneration. Advances in muscle research (3rd ed.)*. Dordrecht, The Netherlands: Springer; 2008.

108. Foster T, et al. Platelet-rich plasma: from basic science to clinical applications. *The American Journal of Sports Medicine*. 2009;37(11):2259-2272.

109. Sampson S, et al. Platelet rich plasma injection grafts for musculoskeltal injuries: a review. *Current Reviews in Musculoskeletal Medicine*. 2008;1(1):165-174.

110. Hauser R, et al. *Prolo Your Sports Injuries Away*. Oak Park, IL: Beulah Land Press; 2001.

111. Chevron V, et al. Respiratory impact of new anesthetic agents. *Revue des Maladies Respiratoires*. 1998;15(2):123-128.

112. Snoeck M, et al. Malignant hyperthermia as a complication of anesthesia: predisposition is hereditary. *Nederlands Tijdschrift Voor Geneeskunde*. 1997;141(13):616-619.

113. American Academy of Orthopaedic Surgeons (2007). Joint Replacement. Retrieved from: http://orthoinfo.aaos.org/topic.cfm?topic=A00233.

114. Hackett G. *Ligament and Tendon Relaxation Treated by Prolotherapy*. 3rd ed. Springfield, IL: Charles S. Thomas; 1958.

115. Klein R, et al. Proliferant injections for low back pain: histologic changes of injected ligaments and objective measurements of lumbar spinal mobility before and after treatment. *Journal of Neurologic and Orthopedic Medicine and Surgery*. 1989;10:123-126.

116. Liu Y, et al. An in situ study of the influence of a sclerosing solution in rabbit medial collateral ligaments and its junction strength. *Connective Tissue Research*. 1983;11:95-102.

117. Maynard J. Morphological and Biomechanical effects of sodium morrhuate on tendons. *Journal of Orthopaedic Research*. 1985;3:236-248.

118. Klein R, et al. Prolotherapy: an alternative way of managing low back pain. *Journal of Musculoskeletal Medicine*. 1997;45-49.

119. Ongly M, et al. Ligament instability of knees: a new approach to treatment. *Manual medicine*. 1988;3:152-154.

120. Auburn A, et al. Increase in cross sectional area of the iliolumbar ligament using Prolotherapy agents: an ultrasonic case study. *Journal of Prolotherapy*. 1999;1(3):156-162.

121. LaCourse M, et al. A report on the asymmetry of iliac inclination. *Journal of Orthopaedic Medicine*. 1990;12.

122. 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.

123. Reeves K, et al. Long-term effects of dextrose Prolotherapy for anterior cruciate ligament laxity. *Alternative Therapies in Healthy and Medicine*. 2003;9(3):58-62.

124. Barré J. Sur un syndrome sympathique cervical posterieur et sa cause frequente l'arthrite cervical. *Revue Neurologique, Paris*. 1926;1246-1254.

125. Dorman T. Prolotherapy, a Survey. *Journal of Orthopaedic Medicine*. 1993;15(2);49-50.

126. Linetsky F, et al. Regenerative injection therapy (RIT): effectiveness and appropriate usage. Position paper by *The Florida Academy of Pain Medicine (FAPM)*. 2001;1-12.

127. Klein R, et al. Prolotherapy for the treatment of back pain. *American Association of Orthpaedic Medicine Position Statement*. 2006;1-5.

128. Yelland M, et al. Prolotherapy injections saline injections and exercises for chronic low back pain: a randomized trial. *Spine*. 2004;29(1):9-16.

129. Mooney V. Prolotherapy at the fringe of medical care, or is it at the frontier? *Spine*. 2003;3(4):253-4.

130. Reeves K, et al. Randomized, prospective placebo-controlled double-blind study of dextrose Prolotherapy for osteoarthritic thumb and finger joints: evidence of clinical efficacy. *Journal of Alternative and Complementary Medicine*. 2000;6(4):311–320.

131. Reeves K, et al. Randomized, prospective placebo-controlled double-blind study of dextrose Prolotherapy for osteoarthritic thumb and finger joints: evidence of clinical efficacy. *Journal of Alternative and Complementary Medicine*. 2000;6(4):77-80.

132. Hauser R, et al. Standard clinical x-ray studies document cartilage regeneration in five degenerated knees after Prolotherapy. *Journal of Prolotherapy*. 2009;1(1):22-28.

133. Hauser R, et al. A retrospective study on Hackett-Hemwall dextrose Prolotherapy for chronic hip pain at an outpatient charity clinic in rural Illinois. *Journal of Prolotherapy*. 2009;1(2):76-88.

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

Karina Gordin, BA, MS

ABSTRACT

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

Journal of Prolotherapy. 2011;3(4):813-825.
KEYWORDS: autologous blood, cartilage, collagen, growth factors, inflammation, injection, musculoskeletal injuries, platelets, Prolotherapy, tendonitis.

A NEW PARADIGM

As the 2000-2010 *Bone and Joint Decade* elapsed, its global initiative to advance research of joint injuries[2] ushered in therapeutic interventions that aimed to enhance tissue regeneration and reduce degenerative mechanisms. The current research trend in the arena of joint injury launched breakthroughs in scientific investigations and technology, providing important new insights into musculoskeletal injury, which, according to a study conducted by the World Health Organization, is the most frequent cause of intensive long-term pain and disability, affecting millions of people worldwide.[3] Musculoskeletal diseases, ranging from back pain and bodily injuries to arthritis and osteoporosis, are reported more often than any other health complaint by U.S. patients. In 2004, lost wages and treatment expenses related to musculoskeletal diseases was estimated to cost a total of $849 billion, equal to 7.7% of the gross domestic product (GDP).[4] In 2005, the majority of both lost work and bed days were attributed to health conditions associated with musculoskeletal diseases.[5] The social impact of bone and cartilage pathologies imposes high costs and ultimate loss of income: in the United States alone, osteoarthritic medicines cost $5.31 billion in 2007,[6] and musculoskeletal conditions cost nearly $128 billion per year in direct medical expenses.[7] Such as, one report approximated the total cost of bilateral knee joint replacements at over $85,000, which included a hospital stay, surgeon and anesthesiologist fees, a 5-day inpatient rehabilitation center stay, and a pathologist visit.[8]

Without a doubt, the need to spotlight musculoskeletal conditions and functional, cost-effective treatments is urgent, considering factors such as increased popularity of sporting activities and related tissue injuries, including tendon and ligament trauma accounting for 45% of all musculoskeletal injuries in the U.S.A.[9] Broadly speaking, insufficient understanding of these escalating musculoskeletal disorders, including osteoarthritis development, has generated a wide array of symptom based treatment options, including narcotics, anti-inflammatories, corticosteroid injections, surgery, ice, heat, analgesics, rest, braces and wraps, and physical therapy.[10] Considering such protocols, it is apparent that basic human physiology is misapplied; namely, common tendon therapies aim at handicapping inflammation, while false assumptions attribute inflammation to osteoarthritis whereas the etiology primarily involves degeneration. In fact, the term *osteoarthritis*, relating to the most common form of arthritis, is a bit of a misnomer, and may be better identified as osteoarthrosis, since inflammation plays an insignificant role compared to corroding of cartilage and loss of sensory innervations of the joint and surrounding muscles. What initially starts off as a sprain or strain, commonly attributable to excessive forces applied to a joint in an abnormal direction, eventually translates into meniscal and ligamentous injury, ultimately leading

to increased instability within a joint.[11] Progression of such degeneration eventually indicates arthroscopy, joint replacement, or in some cases spinal fusion as last resort care when pain, disability and imaging studies warrant it. If imaging studies focused beyond common sources of pain like degenerative joint cartilage and spinal disc disability, and considered pain generators like ligaments, joint capsules, muscles and tendons, then would surgery still be warranted as the last resort? According to large randomized trials examining such interventions, it was concluded that surgery like arthroscopy has a limited role as a treatment of osteoarthritis.[12] The fact that soft tissues (connective tissues) and alternative interventions are rarely considered in diagnosis, avoidable and expensive protocols are performed, generating annual direct medical, drug and indirect work loss costs at $8,601, $2,941, and $4,603, respectively.[13] Accordingly, reliable preventative interventions and regenerative solutions pose promising new alternatives to traditional long-term palliative care,[14] improving clinical outcomes, and providing a new perspective on understanding the wound healing process.

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

RATIONALE FOR PRPP

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

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

The significant feature of platelets is the alpha granules, which organically promote healing of soft tissue by facilitating the release of one's own growth factors; the process is simple and efficient since growth factors are readily available in significant amounts upon PRP activation. Normally at resting state thrombin is required

to trigger platelet activation, in turn prompting platelets to morph into strategic shapes,[23] develop branches, extend over injured tissue, and ultimately release growth factors that stimulate the inflammatory cascade and healing. (*See Figure 1.*) The main growth factors contained in the granules are transforming growth factor beta (TFG-β), which stimulates cell replication and fibronectin binding, vascular endothelial growth factor (VEGF), which is a potent stimulator of angiogenesis, platelet-derived growth factor (PDGF), which stimulates tissue remodeling, and epithelial growth factor (EGF), which induces cell migration and replication, amongst others. (*See Table 1.*) Combined, the growth factors play a critical role in the healing process and tissue regeneration, forming a cascade of diverse pathways, initiating activation of gene expression, and protein production. This specific feature of PRP directly addresses chronic non-healing tendon injuries, which traditional therapies approach with corticosteroid injections, medications like NSAIDs, and surgery; all of which, studies suggest, exhibit adverse side effects, ranging from atrophy, bleeding ulcers, and kidney damage, respectively.[24] In fact, it appears that the longer a musculoskeletal condition persists, the more resistant it becomes to traditional therapies; more over, it has been documented that protracted symptoms and relapses are regularly observed post conservative treatments.[25] So unlike traditional therapies, which ultimately treat tissue injuries without amending the inherent poorly healing properties or underlying pathology,[26] Platelet Rich Plasma Prolotherapy has been shown to enhance the early cascade of tissue repair processes both in vitro[27] and in vivo.[28, 29] Recent reports have accounted a more rapid epithelialization (coating of epithelial tissue), more dense and mature bone with better organized trabeculae (supporting strands of connective tissue), and greater bone regeneration occurring when PRPP is utilized in the treatment.[30]

The potent cocktail of growth factors containing a variety of biologic mediators can be applied directly to the healing site via Prolotherapy, an injection technique that has steadily gained widespread exposure as a form of pain management in both complementary and allopathic medicine. George S. Hackett, MD, who coined the term Prolotherapy[31] described it as "The treatment [which] consists of the injection of a solution within the relaxed ligament and tendon which will stimulate the production of new fibrous tissue and bone cells that will strengthen the 'weld' of fibrous tissue and bone to stabilize the articulation and permanently eliminate the disability."[32] Physiologically speaking, this mode of treatment is particularly considerable since, as a result of mechanical factors, tendons and ligaments are vulnerable to injury and quite stubborn to heal. Expressly, tendons are composed of tenocytes, water, a variety of minor specialized cells, and millions of tightly woven fibrous collagen proteins, which form a durable strand of tissue, and naturally anchor to the bone to form a resilient mineralized connection. Ligaments are bands of tough, fibrous dense regular connective tissue comprising attenuated collagenous fibers connecting two bones, and are involved in the stability of the joint. The greatest amount of stress to ligaments and tendons is where they attach to bone: the fibro-osseous junction. Following

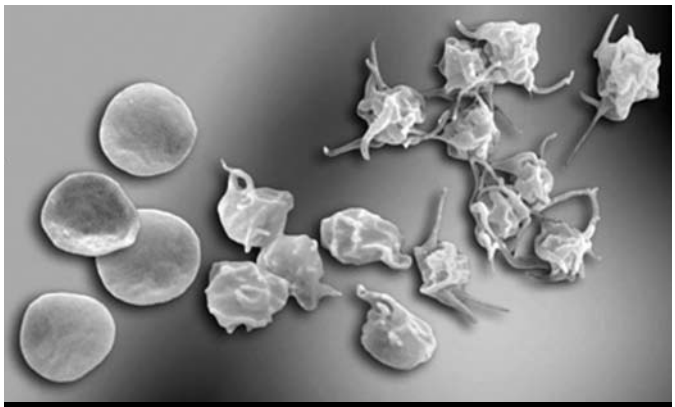


Figure 1. Active (right) and inactive (left) platelets.
Photo used with permission from University of Pennsylvania School of Medicine.

Table 1. Growth factor chart.
Used with permission from: Eppley BL, et al. Platelet quantification and growth factor analysis from platelet-rich plasma: implications for wound healing. *Plast Reconstr Surg.* 2004 November;114(6):1502–8.

Platelet-derived growth factor (PDGF)	• Stimulates cell replication • Promotes angiogenesis • Promotes epithelialization • Promotes granulation tissue formation
Transforming growth factor (TGF)	• Promotes formation of extracellular matrix • Regulates bone cell metabolism
Vascular endothelial growth factor (VEGF)	• Promotes angiogenesis
Epidermal growth factor (EGF)	• Promotes cell differentiation & stimulates re-epithelialization, angiogenesis & collagenase activity
Fibroblast growth factor (FGF)	• Promotes proliferation of endothelial cells & fibroblasts • Stimulates angiogenesis

a ligament injury, resulting damage such as laxity may cause joint motion to become greater and offset the contact surface to regions where the cartilage may be thinner and less capable of supporting applied stresses, causing tremendous pain.[33] According to Daniel Kayfetz, MD, the most sensitive structures that cause pain are the periosteum (covering of bone) and ligaments. Dr. Kayfetz remarks that in the scale of pain sensitivity, the periosteum ranks first, followed by ligaments, tendons fascia, and finally muscle.[34]

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

Tendinitis: *The suffix "itis" signifies inflammation, and applies to extensive, acute tendon injuries with accompanying inflammation.*[35]
Tendinosis: *The suffix "osis" signifies chronic degeneration without accompanying inflammation. Specifically, non-healing condition resultant from accumulation of microscopic injuries as the basis of pain and disability in chronically injured tendon tissue.*[36] *Tendinosis was first considered by German researchers in the 1940s; however, the term's more modern application relates to Puddu et al.*[37] *and Nirschl et al.*[38]
Tendinopathy: *The suffix "opathy" signifies no particular pathology, and may be applied to tendon injuries in general.*

Ligaments and tendons generally have a poor blood supply and heal at a comparatively slow rate, culminating in tissue scarring, which adversely affects function and increases risk of re-injury.[39, 40] Histologic samples from chronic cases indicate that an inflammatory response is not activated, but rather a limitation of the normal tendon repair system with a fibroblastic and a vascular response called angiofibroblastic degeneration.[41, 42] In the interest of embracing rather than suppressing the inflammation, PRPP injection prompts a local inflammation, triggering a wound healing cascade, and results in the deposition of new collagen, of which tendons and ligaments are composed. The new collagen contracts as it matures, in turn tightening and subsequently reinforcing the injected painful area. That is all the body requires, the remaining healing stages take care of themselves. They include: inflammation, proliferation and remodeling.[43]

Figure 2 depicts the cellular components involved in the three phases of healing.

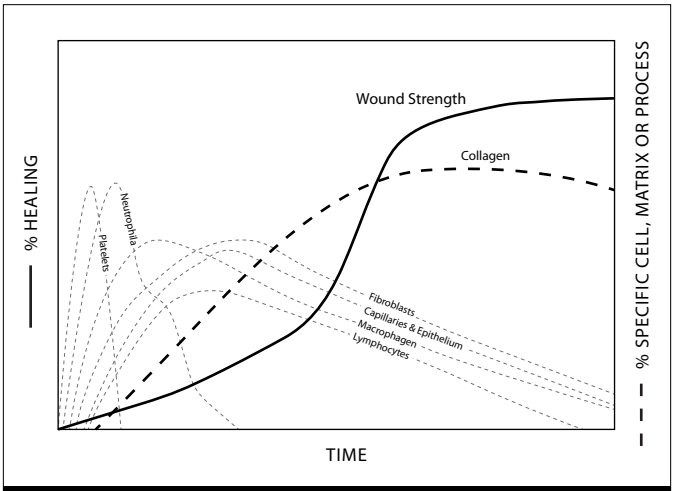


Figure 2. The physiology of healing of the chronic wound.
From emedicine.com. Image reprinted with permission from eMedicine.com, 2009.

During the primary inflammatory phase, the functions of activated platelets involve:

- Adhesion
- Aggregation
- Clot retraction
- Pro-coagulation
- Cytokine signaling
- Chemokine release
- Growth factor release
- Anti-microbial

Presently there is evidence to suggest that PRP grafts may be either anti-inflammatory or pro-inflammatory in specific tissue at certain concentrations, or dose-response curves.[44]

At the site of tissue injury, the latter exists to as yet an unknown PRP concentration and succeeding migration and proliferation of progenitor stem cells at the tissue injury site.[45]

Following the preliminary inflammatory phase, which generally lasts for two to three days, fibroblasts enter the site and commence the proliferative phase, which lasts from two to four weeks.[46] Fundamentally speaking, low pH and low oxygen levels encourage fibroblast proliferation in the injury site,[47] leading to the deposition of collagen and ground substances. Ultimately, the wound narrows

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

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

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

PLATELET RICH PLASMA PROCESSING

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

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

Figure 3. SmartPReP2 centrifuge from Harvest Technologies where the patient's blood is centrifuged to extract platelet rich plasma to be used for Prolotherapy injections.

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

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

Weibrich et al. observed an advantageous effect with platelet concentrations of approximately 106/μL. Further they state that higher concentrations might have a paradoxically inhibitory effect.[58] A study by Lui et al. demonstrated that type I collagen production and fibroblast were enhanced by just the right concentration of platelets, ultimately emphasizing the importance of qualified devices.[59] Once the PRP is expertly yielded, it may remain sterile and the concentrated platelets viable for up to 8 hours, ready for injection. Considering the data from imaging studies such as MRI and radiographs, as well as clinical exams and the highly recommended dynamic musculoskeletal ultrasound with a transducer of 6 to 13 Hz, the area of injury is marked and directly injected with or without an appropriate anesthetic, such as lidocaine or marcaine. In addition to the local anesthetics, physicians may further assist patients, who find Prolotherapy painful, by prescribing Tylenol® or Vicodin® to be taken prior to Prolotherapy treatments. Some physicians may use an anesthetic cream that is rubbed on the specific area, thereby decreasing pain of needle injection. Some spray an anesthetic like lidocaine on the skin, or inject some anesthetic into the skin to abate pain associated with a needle piercing skin, which some patients complain is the most painful part of the procedure. Of course the pain intensity varies from patient to patient during the Prolotherapy treatment. However, the consensus remains that it's minimal compared to untreated chronic pain endured by patients on a daily basis.

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

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

healing tendon injuries including lateral epicondylosis, plantar fasciitis[63, 64] as well as knee ligaments, rotator cuff tears, wound healing, Achilles tendon tears, anterior cruciate ligaments (ACL), amongst others. There is also a range of publications in other fields including ENT, cardiology and plastic surgery. The following is a review of some of the more recent studies of PRPP.

ELBOW

Medically classified as lateral epicondylitis, tennis elbow is characterized by tissue degeneration of the wrist and forearm extensor tendons at the elbow. Commonly, injuries are caused by mechanical overloading[65] of the forearm muscles, constant repeated actions associated with racquet sports, manual work in which twisting hand movements are involved, weight training, a variety of other traumatic movement of the elbow or wrist, and abnormal micro-vascular responses.[66] Histologic specimens from chronic cases confirm that tendinosis is not an acute inflammatory condition but rather a failure of the normal tendon repair mechanism associated with angiofibroblastic degeneration.[67] An estimated four in 1,000 individuals are affected with this condition at some time,[68] and is a frequent cause of missed work.[69, 70]

Numerous methods have been advocated for treating elbow tendinosis, including rest, non-steroidal anti-inflammatory medication, bracing, physical therapy, iontrophoresis,[71] extracorporeal shock wave therapy, and botulism toxin.[72] Corticosteroid injections have been used extensively in this case, but studies show that there is conflicting evidence about their efficacy.[73, 74] In February 2011, *Orthopedics* published a study[75] demonstrating the efficacy of a single PRP injection for recalcitrant common extensor or flexor tendons, otherwise unresponsive to nonsurgical treatments like steroid injections. Such promising results were further substantiated in a double-blind, randomized controlled trial published in *The American Journal of Sports Medicine*. One-hundred patients with chronic lateral epicondylitis, randomly assigned to a leukocyte-enriched PRP or corticosteroid group, demonstrated significantly increased function and reduced pain in the PRP group, "exceeding the effect of corticosteroid injection even after a follow-up of 2 years."[76] The next Prospective Cohort study, also documented in the *American Journal of Sports Medicine*, evaluated the use of platelet rich plasma as a treatment for chronic severe epicondylar tendinosis. Mishra et al. examined 140 patients, 20 of whom met the study criteria and were surgical candidates who had previously failed conservative therapies. Of those, five were controls treated with local anesthetic bupivicaine, while the remaining 15 study subjects received one PRP injection. Notably, the study group observed 60% improvement in their visual analog pain scores at 8 weeks, 81% improvement in their visual analog pain scores (P=0.001) at 6 months, and 93% at final follow-up at 12-38 months (mean, 25.6 months; range, 12-38 months). Markedly there were no adverse effects or complications, with a 94% return to sporting activities, and a 99% return to daily activity.[77] Confoundings are limited to 60% attrition rate in the control group as 3/5 of the subjects withdrew from the study or sought outside treatment at eight weeks.

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

FOOT

Plantar fasciitis is a common cause of heel pain, potentially resulting in pathologic degenerative tissue changes, similar to tennis elbow. It has been estimated that in a typical podiatric practice, approximately 40% of patients complain of heel pain. Severe or prolonged cases of plantar fasciitis may result in partial or full thickness tearing of the plantar fascia, which encapsulates the muscles in the sole of the foot. This very important connective tissue is responsible for supporting the arch of the foot and endures tension that is approximately two times body weight. Barett et al. enrolled nine patients in a pilot study to evaluate PRP injections for plantar fasciitis. Patients met the criteria upon willingness to avoid conservative treatments such as NSAIDs, bracing and cortisone injection for 90 days prior. Ultrasound confirmed that all patients demonstrated hypoechoic and thickened plantar

fascia. Following a 3cc of autologous PRP injection under ultrasound guidance, thickness and increased signal intensity of the fascial bands were observed. Six of nine patents achieved complete symptomatic relief following a period of two months. One of three unsuccessful patients eventually found complete relief following an additional PRP injection. At one year, 77.9% patients had complete resolution of symptoms.[79]

ACHILLES

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

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

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

KNEE

Lesions of anterior cruciate ligament (ACL) represents one of the most common traumas in sporting practice, ranging from 75,000 to 100,000 cases per year in the United States.[84] The loss of the knee center rotation following ACL lesions causes a functional overload, leading to cartilage defects, meniscal lesions and early gonarthritis. It is worth recalling that the blood supply is from within the ligament as opposed to around it; therefore, blood supply is commonly disrupted during injury when the ligament is torn.[85] ACL injuries may be attributed to sports including football, soccer and basketball where deceleration and swift cutting movements are common; knee joints are particularly vulnerable to such trauma and subsequent ligament injury on account of their location between the two longest lever arms in the body, tibia and femur, which

experience high repetitive impact loads.[86] ACL and medial collateral ligament (MCL) may both sustain an injury if, say, an athlete is struck by another from behind and outside. Such injury is often accompanied by an audible "pop" usually with, though occasionally without, pain.[87] Untreated, relaxed, or torn ACLs have been shown to precipitate degeneration of the meniscus and eventual degenerative osteoarthritis,[88] given the decreased joint stability and alteration of biomechanical forces.

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

The combination meniscal injury incurred at time of ACL damage is very commonly associated with knee osteoarthritis[89] considering biomolecular damage to type II collagen and an initial increase in proteoglycan content.[90]

> ***Proteoglycan:*** *cementing like glycoproteins occurring in connective tissue, influencing both activity and stability of proteins as well as signaling molecules within the extracellular matrix.*[91]

In other words, stressors change anatomy of a joint creating an unfavorable environment for other structures like meniscus, ligaments and cartilage. In a single-center, uncontrolled, prospective preliminary study, Sampson et al. evaluated the clinical effects of intra-articular PRP injections in a small group of participants with primary and secondary knee osteoarthritis. Outcome measures included the Brittberg-Peterson Visual Pain (Visual Analog Scale [VAS]), Activities, and Expectations score and the Knee Injury and Osteoarthritis Outcome Scores at preinjection visit and at 2-, 5-, 11-, 18-, and 52-week follow-up visits. Scores demonstrated significant and nearly linear improvements in knee pain and symptom relief, with majority of patients expressing a favorable response at 12 months following treatment.[92]

A prospective pilot study conducted by Ventura et al.[93] evaluated the efficacy of using platelet rich plasma growth factors as a potential treatment in anterior cruciate ligament surgery. Twenty patients with laxity caused by torn ACL underwent arthroscopically assisted reconstruction with autologous quadrupled hamstring tendon graft (QHTG). Platelet gel was applied in the femoral and tibial tunnels. The rehabilitation protocol standardized for both randomized growth factor group and control, included: immediate postoperative mobilization without a knee brace, protected weight bearing for three weeks, and return to sporting activities at six months, during which time patients were evaluated both clinically and functionally. CT highlighted a significant difference ($P<0.01$) between ACL density of the two groups. At six months following surgery, the ACL density between the PRP treated group and control was noticeably different, with the treated group exhibiting uniform density and improved structure. In the control, the ligament was less structured and incompletely filled the femoral and tibial tunnels. As this study demonstrates, PRP based growth factors may accelerate the integration of the new ACL in the femoral and tibial tunnels.

Following a PRP injection in rat patellar tendons, Kajikawa et al. demonstrated increased quantity of circulation-derived cells in the early phase of tendon repair after injury, versus controls.[94] With respect to other animal studies, a rabbit patella tendon was ruptured and subsequently sealed with platelet-rich plasma gel; after three weeks, a histological examination showed swift recovery with particular emphasis on angiogenesis earlier in the healing process, more mature and dense vessels and greater fiber elasticity.[95] In a human model, Kon et al.[96] examined the role of PRP in treating jumper's knee, a condition characterized by microscopic ruptures in Patellar tendon commonly in high-impact jumping sports. In this prospective pilot study, participants were all male athletes with a mean age of 25.5 years, for whom both surgery and nonsurgical treatments like steroid injections had little effect. At six month follow-up, functional recovery indicated six participants with complete recovery, eight with marked improvement, and six cases with mild to no improvement. Ultimately, statistically significant recovery from pre-treatment levels to six months was observed, with improved knee function and quality of life, marked satisfaction and return to sport.

ROTATOR CUFF

Rotator cuff injury of one or more of the four shoulder muscles can range from inflammation without any permanent damage, such as tendonitis, to a complete or partial tear of the muscle that might require surgery. Rotator cuff surgery is one of the most common

procedures performed by orthopedic surgeons, with over 250,000 performed annually in the United States alone. The tendons of the rotator cuff, not the muscles, are most commonly torn. Of the four tendons, the supraspinatus is most frequently torn, usually occurring at its point of insertion onto the humeral head at the greater tuberosity.[97] The poor healing capacity of the torn rotator cuff is well known. Once torn, the injury either remains the same size or expands in size with time.[98] In a prospective study conducted by Scarpone et al.,[99] 14 patients had rotator cuff tears with no significant AC joint thickness with impingement and no other significant symptomatic pathology. It must be noted that all 14 patients, strongly considering surgical options, failed non-operative treatments, including NSAIDs, physical therapy, and corticosteroid injections. In the study, skin was anaesthetized with 1% xylocaine and under ultrasound guidance; 3ml of autologous platelet concentrate (APC) was injected directly into the tendon sheath at the injury site. The PRPP effect was measured radiographically with MRI, strength and endurance was tested and patients underwent an analog pain scale. Each measurement was carried out prior to PRP injection, four weeks post-injection, and eight weeks post-injection. Results demonstrated 12 of 14 subjects statistically significant improvements in pain scale and strength, as well as endurance at eight weeks. Of the 12 patients, six had radiographic evidence of healing of their tendinopathy on MRI at eight weeks. Of the four patients who were considering surgery due to persistent pain, two went on to have rotator cuff surgery. No acute complications associated with the procedure occurred.

Reflecting on all the aforementioned conditions that PRP Prolotherapy serves, anecdotal evidence suggests that the procedure emerges as an unparalleled low-risk, natural and highly-effective nonsurgical solution that triggers the body's own healing capacity.

DISCUSSION

The United States *Bone and Joint Decade* has successfully spotlighted musculoskeletal injuries, which, despite being more prevalent than conditions like heart disease, cancer and respiratory problems, still fail to receive the same attention on account of associated death rarity. Nevertheless, awareness of the growing burden of related disorders on society has been raised, focusing close attention on injuries like sprains and strains commonly incurred during sudden movement or excessive use (16.3 million injuries in 2004); fractures (15.3 million); open wounds, cuts and punctures (10.3 million); and contusions and bruises (8.4 million). In 2005, 107.7 million adults, one in two aged 18 and over, reported suffering from a musculoskeletal condition lasting three months or longer during the past year. According to the *Burden of Musculoskeletal Disease in the United States*, "this is nearly twice the number who reported any other medical condition. In addition, nearly 15 million adults reported they were unable to perform at least one common activity, such as self-care, walking, or rising from a chair, on a regular basis due to their musculoskeletal condition."[100]

The conveniently obtainable PRP and the strikingly straightforward, simple to perform Prolotherapy injection procedure holds promise to harness the body's natural healing power by effectively supercharging one's own capacity for tissue regeneration. So while conventional treatments for soft tissue injury like NSAIDs and steroid injections seek to decrease painful symptoms by reducing inflammation, PRPP embraces this process and in turn initiates growth of new tissue and collagen, ultimately correcting injury as opposed to symptoms. This method of treatment repeatedly demonstrates successful outcomes for a variety of conditions. PRPP may come to be considered a logical first step of treatment prior to, or possibly instead of, surgical intervention for some injuries. This treatment is important to alleviate pain and disability particularly at a time when the current trend estimates 61 million persons at risk of musculoskeletal disease by 2020.[101] Approximately 1 in 10 injuries ensues during sports activities, and another one in 10 in automobile or pedestrian accidents.[102] So whether a person is a working professional determined to promptly resume work, a weekend warrior eager to get back in the game, or simply long to recommence daily activities, PRPP offers new hope for natural healing. "It's a better option for problems that don't have a great solution—it's nonsurgical and uses the body's own cells to help it heal," says Dr. Allan Mishra, an assistant professor of orthopedics at Stanford University Medical Center and one of the primary researchers in the field. "I think it's fair to say that PRP has the potential to revolutionize not just sports medicine but all of orthopedics. It needs a lot more study, but we are obligated to pursue this." Scores of studies are currently underway to elucidate questions that still remain unanswered regarding long-term stability of this procedure and the possible modifications that can still be done to achieve even better results. ■

REFERENCES:

1. Lynch S, et al. Role of platelet-derived growth factor in wound healing: synergistic effects with other growth factors. *Proc Natl Acad Sci*. 1987;84:7696-7700.
2. Sampson S, et al. Platelet rich plasma injection grafts for musculoskeletal injuries review. *Curr Rev Musculoskelet Med*. 2008;1:165-174.
3. Woolf A, et al. Burden of major musculoskeletal conditions. *Bull World Health Organ*. 2003;81:646-656.
4. United States Bone and Joint Decade: *The burden of musculoskeletal diseases in the United States*. Rosemont IL: American Academy of Orthopaedic Surgeons; 2008.
5. National Center for Health Statistics, National Health Interview Survey, 2005.
6. Arnold M, et al. The pharma report: top 20 pharma companies. *Medical Marketing & Media*. 2008;45-55.
7. Arthritis Foundation Web site. Available at http://arthritis.org/cost-arthritis.php. Accessed on Oct 4, 2011.
8. Brody J. Personal Health; A new set of knees comes at a price: a whole lot of pain. *New York Times*. 2008. published February 8, 2005.
9. Praemer A. Musculoskeletal conditions in the United States. 2nd ed. *Rosemont: American Academy of Orthopaedic Surgeons*; 1999.
10. Wheaton M, et al. The ligament injury connection to osteoarthritis. *Journal of Prolotherapy*. 2010;2(1):294-304.
11. Kujala U, et al. Knee osteoarthritis in former runners, soccer players, weight lifters and shooters. *Arthritis and Rheumatism*. 1995;38(4):539-546.
12. Felson D. Athroscopy as treatment for knee osteoarthritis. *Best Pract Res Clin Rheumatol*. 2010;24(1):47-50.
13. White A, et al. Direct and indirect costs of pain therapy for osteoarthritis in an insured population in the United States. *Journal of Occupational and Environmental Medicine*. 2008;50(9): 998-1005.
14. Kader D, et al. Achilles tendinopathy: some aspects of basic science and clinical management. *Br J Sports Med*. 2002;36:239-49.
15. Anitua E, et al. The potential impact of the preparation rich in growth factors (PRFG) in different medical fields. *Biomaterials*. 2007;28:4551-4560.
16. Ferrari M, et al. A new technique for hemodilution, preparation of autologous platelet-rich plasma and intra-operative blood salvage in cardiac surgery. *Int J Artif Organs*. 1987;10:47-50.
17. Vacanti J, et al. Tissue engineering: the design and fabrication of living replacement devices for surgical reconstruction and transplantation. *Lancet*. 1999;354:32-34.
18. Weibrich G, et al. Growth factor levels in platelet-rich plasma and correlations with donor age, sex, and platelet count. *J Craniomaxillofacial Surg*. 2002;30:97-102.
19. Sylvia S. Mader. *Biology Seventh Edition*. New York, NY; McGraw Hill Companies, Inc.; 2001.
20. Ignatavicius D, et al. *Medical-Surgical Nursing: A Nursing Process Approach*. Philadelphia, PA: W. B. Saunders Company; 1991.
21. Marx R, et al. *Dental and craniofacial applications of platelet rich plasma.* Carol Stream: Quintessen Publishing Co, Inc.; 2005.
22. Pietrzak W, et al. Scientific foundations platelet rich plasma: biology and new technology. *J Craniofac Surg*. 2005;16(6):1043-54.
23. Canalis E, et al. Effects of platelet-derived growth factor on bone formation in vitro. *J Cell Physiol*. 1989;140:530-537.
24. Jobe F, et al. Lateral and medial epicondylitis of the elbow. *J Am Acad Orthop Surg*. 1994;2:1-8.
25. Alternative treatments: dealing with chronic pain. *Mayo Clinic Health Letter*. April 2005;23(4).
26. Antiua E, et al. Autologous fibrin matrices potential source of biological mediators that modulate tendon cell activities. *J Biomed Mater Res Pt A*. 2006;(2):285-93.
27. Stephen E, et al. Platelet-derived growth factor enhancement of a mineral-collagen bone substitute. *J Periodontol*. 2000;71:1887-1892.
28. Lynch S, et al. The effects of short-term application of a combination of platelet-derived and insulin-like growth factors on periodontal wound healing. *J Periodontol*. 1991;62:458-467.
29. Stefani C, et al. Platelet-derived growth factor/insulin-like growth factor-1 around implants placed into extraction sockets: a histometric study in dogs. *Implant Dent*. 2000;9:126-132.
30. Marx R, et al. Platelet-rich plasma: growth factor enhancement for bone grafts. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1998;85:638-646.
31. Hackett G. Referral pain and sciatica in diagnosis of low back disability. *JAMA*. 1957;163:183-185.
32. Hackett G, et al. *Ligament and Tendon Relaxation Treated by Prolotherapy. Third Edition*. Springfield, IL. 1958.
33. Andriacchi T, et al. A framework for the in vivo pathomechanics of osteoarthritis at the knee. *Annals of Biomedical Engineering*. 2004;32(3):447-457.
34. Kayfetz D. Occipital-cervical (whiplash) injuries treated by Prolotherapy. *Medical Trial Technique Quarterly*. 1963;9-29.
35. Khan K, et. al. Overuse tendinosis, not tendonitis. *The Physician and Sports medicine*. 2000;28(5):38-48.
36. Khan K, et al. Histopathology of common tendinopathies: update and implications for clinical management. *Sports Medicine*. 1999;27:393-408.
37. Puddu G, et al. A classification of Achilles tendon disease. *American Journal of Sports Medicine*. 1976;4:145-150.
38. Nirschl R, et al. Tennis elbow: the surgical treatment of lateral epicondylitis. *Journal of Bone and Joint Surgery (Am)*. 1979;61:832-839.
39. Fenwick S, et al. The vasculature and its role in the damaged and healing tendon. *Arthritis Res*. 2002;4:252-60.
40. Browner, B. et al. *Skeletal Trauma.* Philadelphia, PA: W.B. Saunders Company, 1992;1:87-88.
41. Mishra A, et al. Treatment of chronic elbow tendinosis with buffered platelet rich plasma. *Am J Sports Med*. 2006;10(10):1-5.
42. Edwards S, et al. Autologous blood injections for refractory lateral epicondylitis. *Am J Hand Surg*. 2003;28(2):272-8.
43. Kumar V, et al. Chapter 2- Acute and chronic inflammation. In: Robbins and Cotran *Pathologic Basis of Disease*. 7th ed. 2005 Saunders.

44. El-Sharkawy H, et al. Platelet-rich plasma: growth factors and pro-and-anti-inflammatory properties. *J Periodontol*. 2007;78:661-669.
45. Haynesworth S, et al. Mitogenic stimulation of human mesenchymal stem cells by platelet releasate. Poster Presentation, *American Academy of Orthopedic Surgery*. March 2001.
46. Quinn J. (1998). *Tissue Adhesives in Wound Care*. Hamilton, Ont. B.C. Decker, Inc. Electronic book.
47. Liu Y, et al. Fibroblast proliferation due to exposure to a platelet concentrate in vitro is pH dependent. *Wound Rep Reg*. 2002;10:336-340.
48. Barnett M, et al. Use of platelet rich plasma and bone marrow derived mesenchymal stem cells in foot and ankle surgery. *Techniques in Foot and Ankle Surgery*. 2007;6(2):89-94.
49. Komarcevic A. The modern approach to wound treatment. *Med Pregl*. Jul-Aug 2000;53:363-8.
50. Everts P, et al. Platelet-rich plasma and platelet gel: a review. *JECT*. 2006;38:174-187.
51. Crane D, et al. Platelet rich plasma (PRP) matrix grafts. *Practical Pain Management*. January/February 2008;1-10.
52. Kumar V, et al. Acute and chronic inflammation. In: Robbins and Cotran, eds. *Pathologic Basis of Disease*. 7th ed. Saunders; 2005.
53. Kevy S, et al. Preparation of growth factors enriched autologous platelet gel. Proceedings of the 27th Annual Meeting of Service Biomaterials, April 2001.
54. Froum S, et al. Effect of platelet rich plasma on bone growth and osseointegration in human maxillary sinus grafts: three bilateral case reports. *Int J Periodont Restor Dent*. 2002;22:45.
55. Weibrich G, et al. Curasan PRP kit vs. PCCS PRP system: collection efficiency and platelet counts of two different methods for the preparation of platelet rich plasma. *Clin. Oral Implant Res*. 2002;13:437.
56. Marx R, et al. Platelet rich plasma: a primer. *Practical Pain Management*. March 2008.
57. Haynesworth S, et al. Mitogenic stimulation of human mesenchymal stem cells by platelet release suggest a mechanism for enhancement of bone repair by platelet concentrates. Presented at the 48th Meeting of the Orthopedic Research Society. Boston, MA, 2002.
58. Weibrich G, et al. Effect of platelet concentration in platelet rich plasma on peri-implant bone regeneration. *Bone*. 2004;34:665-671.
59. Tiossi R, et al. PRP: A possibility in regenerative therapy. *Int Journal of Morphology*. 2007.
60. Hauser R. Caring Medical website. Available at: http://www.caringmedical.com/therapies/Prolotherapy-info/soreness.asp. Accessed on May 25, 2010.
61. Manchikanti L, et al. Therapeutic opioids: a 10 year perspective on complexities and complications of the escalating use, abuse, and non-medical use of opioids. *Pain Physician*. 2008;11(2 Suppl):S63-88.
62. Eisenstein T. Opioid modulation of immune responses: effects of phagocyte and lymphoid cell populations. *Journal of Neuroimmunology*. 1998;83:36-44.
63. Mishra A, et al. Treatment of chronic elbow tendinosis with buffered platelet-rich plasma. *Am J Sports Med*. 2006;10(10):1-5.
64. Barrett S, et al. Growth factors for chronic plantar fasciitis. *Podiatry Today*. 2004;17:37-42.
65. Wang J, et al. Biomechanical basis for tendinopathy. *Clin Orthop Relat Res*. 2006;443:320-332.
66. Smith R, et al. Abnormal microvascular responses in lateral epicondylitis. *Br J Rheum*. 1994;33:1166-1168.
67. Jobe F, et al. Lateral and medial epicondylitis of the elbow. *J Am Acad Orthop Surg*. 1994;2:1-8.
68. Hamilton P. The prevalence of humeral epicondylitis: a survey in general practice. *J R Coll Gen Pract*. 1986;36:464-465.
69. Labelle H, et al. Lack of scientific evidence for the treatment of lateral epicondylitis of the elbow. *J Bone Joint Surg Br*. 1992;74:646-651.
70. Dimberg L. The prevalence and causation of tennis elbow in a population of workers in an engineering industy. *Ergonomics*. 1987;30:573-579.
71. Nirschl R, et al. Iontrophoretic administration of dexamethasone sodium phosphate for acute epicondylitis: a randomized, double-blinded placebo-controlled study. *Am J Sports Med*. 2003;31:189-198.
72. Keizer S, et al. Botulinum toxin injection versus surgical treatment for tennis elbow. *Clin Orthop relat Res*. 2002;401:125-131.
73. Altay T, et al. Local injection treatment for lateral epicondylitis. *Clin Orthop Relat Res*. 2002;398:127-130.
74. Newcomer K, et al. Corticosteroid injection in early treatment of lateral epicondylitis. *Clin J Sports Med*. 2001;11:214-222.
75. Hechtman K, et al. Platelet-rich plasma injection reduces pain in patients with recalcitrant epicondylitis. *Orthopaedics*. 2011;34(2):92.
76. Gosens T, et al. Ongoing positive effect of platelet rich plasma versus corticosteroid injection in lateral epicondylitis: a double-blind randomized controlled trial with a 2 year follow-up. *The American Journal of Sports Medicine*. 2011;39(6):1200-8.
77. Mishra A, et al. Treatment of chronic elbow tendinosis with buffered platelet-rich plasma. *Am J Sports Med*. 2006;10(11):1774–1778.
78. Edwards S, et al. Autologous blood injections for refractory lateral epicondylitis. *Am J Hand Surg*. 2003;28(2):272-8.
79. Barrett S, et al. Growth factors for chronic plantar fasciitis. *Podiatry Today*. 2004;17:37–42.
80. Aspenberg P, et al. Platelet concentrate injection improves Achilles tendon repair in rats. *Acta Orthop Scand*. 2004;75(1):93-99.
81. Sanchez M, et al. Comparison of surgically repaired Achilles tendon tears using platelet rich fibrin matrices. *Am J Sports Med*. 2007;35(2):245-251.
82. Vos Robert J, et al. Platelet rich plasma injection for chronic Achilles tendinopathy. *JAMA*. 2010;303(2):144-149.
83. Yelland M, et al. Prolotherapy injections and eccentric loading exercises for painful Achilles tendinosis: a randomised trial. *Br J Sports Med*. 2009;June. doi:10.1136/bjsm.2009.057968.

84. Aichroth P. Osteochondritis dissecans of the knee: a clinical survey. *J Bone Joint Surg*. 1971;53:440-447.

85. Rowley D. *The Musculoskeletal System*. New York, NY: Chapman & Hall Medical; 1997;246.

86. Fleming B, et al. Ligament injury, reconstruction, and osteoarthritis. *Current Opinion in Orthopaedics*. 2005;16(5):354-362.

87. Hartnett N, et al. Delay in diagnosis of anterior cruciate ligament injury in sport. *N Z Med J*. 2001 Jan 26;114(1124):11-3.

88. Feretti A. Osteoarthritis of the knee after ACL reconstruction. *Int Orthop*. 1991;15:367-371.

89. Oiestad B, et al. Knee osteoarthritis after anterior cruciate ligament injury. *The American Journal of Sports Medicine*. 2009;37(7):1434-43.

90. Nelson F, et al. Early post-traumatic osteoarthritis like changes in human articular cartilage following rupture of the anterior cruciate ligament. *Osteoarthritis and Cartilage/OARS, Osteoarthritis Research Society*. 2006;14(2):114-119.

91. Iozzo R. Matrix proteoglycans: from molecular design to cellular function. *Annu. Rev. Biochem*. 1998;67:609–652.

92. Sampson S, et al. Injection of platelet-rich plasma in patients with primary and secondary knee osteoarthritis: a pilot study. *Am J Phys Med Rehabil*. 2010;89:961-969.

93. Ventura A, et al. Use of growth factors in ACL surgery-preliminary study. *Journal of Orthopaedic Traumatology*. 2008;6:76-79.

94. Kajikawa Y, et al. Platelet-rich plasma enhances the initial mobilization of circulation-derived cells for tendon healing. *J cell Physiol*. 2008;215(3):837-45.

95. Lyras D, et al. Immunohistochemical study of angiogenesis after local administration of platelet rich plasma in a patellar tendon defect. *International Orthopaedics*. 2010;34(1):143-148.

96. Kon E. et al. Platelet rich plasma: new clinical application. A pilot study for treatment of jumper's knee. *Injury, Int J. Care Injured*. 2009;40:598-603.

97. Yadav H, et al. Rotator cuff tears: pathology and repair. *Knee Surg Sports Traumatol Arthrosc*. 2009;17(4):409-21.

98. Carpenter J, et al. Rotator cuff defect healing: a biomechanical and histologic analysis in animal model. *J Shoulder Elbow Surg*. 1998;7(6):599-605.

99. Gamradt S, et al. PRP as a treatment alternative for symptomatic rotator cuff tendinopathy for patients failing conservative treatments. *Techniques in Orthopaedics*. 2007;22(1):26-33.

100. United States Bone and Joint Decade: *The burden of musculoskeletal diseases in the United States*. Rosemont IL: American Academy of Orthopaedic Surgeons; 2008.

101. Centers for Disease Control and Prevention. Arthritis prevalence and activity limitations, United States, 1990. *MMWR Morbid Mortal Wkly Rep*. 1994;43:433–8.

102. American Academy of Orthopaedic Surgeons. (2009, April). Half of all musculoskeletal injuries occur in home. Retrieved October 4 2011 from http://www.aaos.org.

Tensegrity to Tendinosis

Thomas Ravin, MD

ABSTRACT

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

Journal of Prolotherapy. 2011;3(4):826-835.
KEYWORDS: biotensegrity, collagen, ECM, extracellular matrix, Prolotherapy, tendinosis, tensegrity.

INTRODUCTION

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

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

TENSEGRITY

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

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

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

Donald Ingber, MD, a Harvard researcher in the biological sciences working at about the same time, wrote about the concept of mechanotransduction or biotensegrity in 1993.[1] The idea of using *hierarchical tensegrity structures* as a means of explaining how the animal model of tensegrity works was in the biochemical and biophysical literature, but a recent article by Dr. Ingber discusses many biological

Figure 1. This is an example of sculpture tensegrity by Kenneth Snelson at the First Bank Building in downtown Denver. Ref: Ravin T. AAMM. 2003

Figure 2. This is an example of mechanical tensegrity by the Wright brothers. Ref: Ravin T. AAMM. 2006

applications of this idea.[2] Knowledge gleaned from study of hierarchical tensegrity structures explains how large land animals can be mechanically strong, flexible and lightweight and yet respond by changing the shape of the body to accommodate specific tasks, such as altering the bony architecture because of gravity or guiding the bony growth from fetus to adulthood. Tensegrity enables the immediate response to changes in force by altering the stiffness in direct proportion to the applied mechanical stress.[3]

Hierarchical tensegrity structures have all the features of architectural models but also have prestressed elements of different size scales.[2] (*See Figure 3.*) One element can be as large as the bones, ligaments, muscles and tendons of the legs and within it can be an element that might

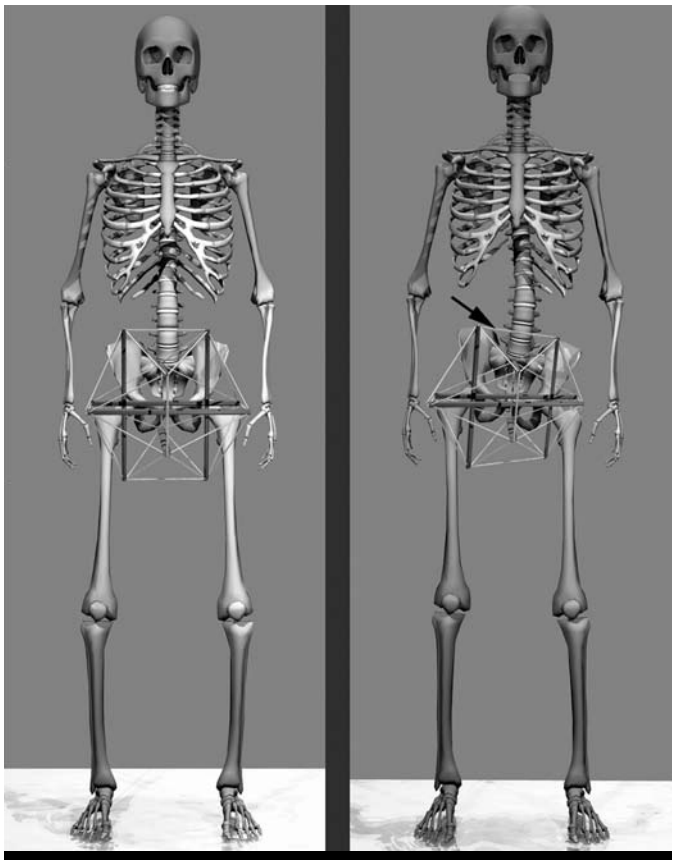


Figure 3. This is one example of biotensegrity by Tom Ravin, MD. Ref: Ravin T. AAMM. 2004

include a single muscle bundle and its tendon attachment to the bone. (*See Figure 4.*) Smaller still is a collagen fiber of the tendon attaching to the cell wall of a fibroblast in the ECM.[4] Hierarchical tensegrity at the cellular level affects cell wall function that alters the cytoplasm, including the actin and α-actin that give the cell its shape and mobility. The tensegrity continues even further to the intracellular proteins that change shape and function depending on stresses to the cytoskeleton and this explains how our tissues respond to growth, work, play and injuries. The whole cell itself is the final sensor because it integrates multiple local signals with other environmental inputs before reacting to the stress. (*See Figure 5.*)

EXTRACELLULAR MATRIX

The ECM is the principal extracellular component of all tissues and organs. Its main components—collagen, elastin, proteoglycan, fibronectin and laminin—allow it to play a pivotal role in hierarchical tensegrity. As a structural material, it controls the spatial organization in the tissue, from nanometer, micrometer, millimeter, and centimeter

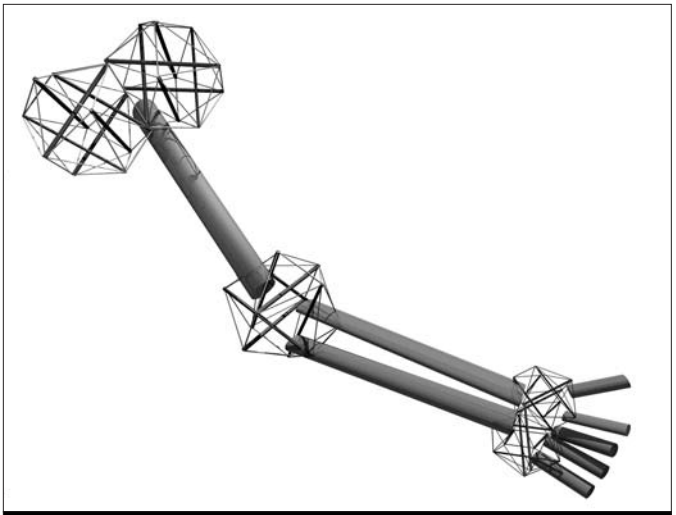


Figure 4. This example of biotensegrity by Tom Ravin M.D. conveys the idea of progressively smaller units that extend to the smallest joints. There are prestressed elements beyond the joints down to the extracellular matrix and into the cell walls. Ref: Ravin T. AAMM. 2004

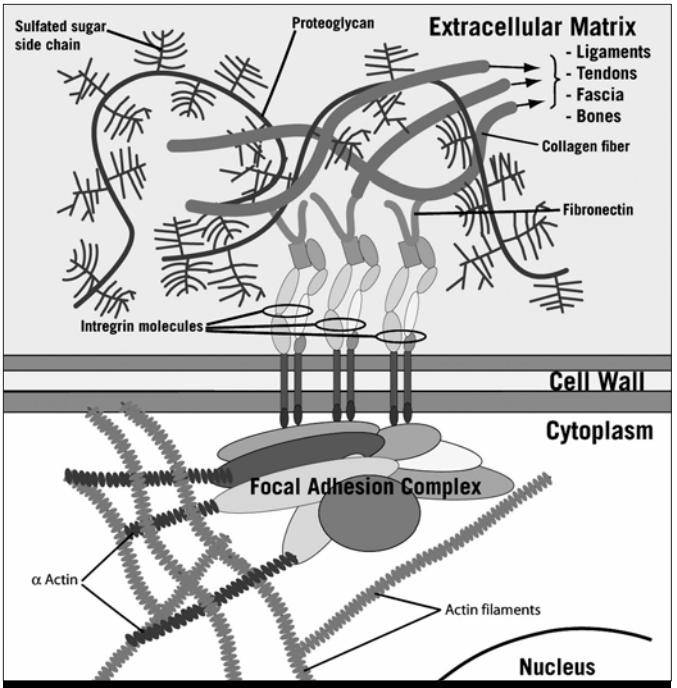


Figure 5. The smallest collagen fibers of the ligaments, tendons, fascia and bones in the ECM attach to the proteoglycans and to fibronectin. Proteoglycans are long sugar molecules (10,000 to 25,000 units) combined with long protein molecules and have many sulfated sugars as side chains. These molecules are rigid and resist compression and the sulfated sugars allow the ECM to change the turgor. There are two molecules that connect the ECM with the cytoplasm of the cell—these are the integrin molecules and the focal adhesion complexes. The integrin molecule spans the cell wall and attaches to the focal adhesion complex in the cytoplasm. The α-actin molecule, which has some contractile elements, attaches to the focal adhesion complex and the actin filaments. The actin filaments then transmit the forces throughout the cell to the nucleus and to other signaling organelles. This arrangement allows the biotensegrity of whole body to almost instantly transmit information from the outside world to the inside of a cell and visa versa. Ref: Ravin T. AAMM. 2011

to meter length scales. It is the connection between the nanometer features and the larger-scale organization that controls the motility and positions of cells, their geometry and mechanical connectivity. This ability to alter the composition and organization lends itself to a wide range of forms and functions ranging from solid in bone to pliable in tendons and cartilage.[5] The major components of the ECM are incredibly stable and over time may develop covalent bonds in response to stress that can change their functional properties. An illustrative example is provided by collagen, the most abundant molecule in the ECM. The half-life for collagen before turnover through degradation by the matrix metalloproteinases is 2–4 years in bone, 10–15 years in skin and ~100 years in tendon.[6]

Strains of the ECM of only a few percent translate into very small alterations in the cytoskeleton and these tiny mechanical stimuli can be transduced into chemical and electrical signals, causing a number of cellular responses.[3] The most common are the chemical ones, such as stretch-sensitive ion channels and G-protein coupled receptors. Despite the prevalence of these receptors, only a relatively small set, the integrins and cadherins, appears to be capable of responding to mechanical cues. (*See Figure 5.*) Integrins have elements that connect to the fibronectin in the ECM and molecular components that transverse the cell walls and attach to the intracellular focal adhesion complexes.[7] These dynamic protein complexes consisting of multiple integrins linked to a focal adhesion complex, as an integrated unit, provide the mechanical link between the cytoskeleton and the ECM.[5] This bridging between cellular components and the ECM enables the this complex to serve as the conduit through which signal mechanotransduction occurs in response to physical force. The extent and degree of the stress can alter the configuration of the focal adhesion complex such that in one situation it might cause unraveling of a protein molecule and reveal a hidden binding site or in another alter the nuclear membrane. These simple and other more complex reactions enable the focal adhesion complex to act as a strain gauge and allow for varying degrees of response.

In another situation the strain might stabilize the integrin-ECM connection and provide a way to concentrate intracellular stresses on some molecules while shielding most of the other cellular components.[5] This gives the ECM and focal adhesion complex the ability to organize and modify their structures instantaneously at the cellular level and still respond to long-term low-level stresses that create physiological changes, such as alterations in the shape of a bone, at the tissue level. All of these features cause the ECM to also be a source of "tissue memory" by binding, integrating and controlling the presentation of growth factors and other ligands to cell wall receptor sites. This allows the ECM to act in some ways like DNA.[8, 9]

Entheses, Ligaments and Tendons

ENTHESES

Both ligaments and tendons share the enthesis organ's biology and biomechanics.[10] The entheses also include structures adjacent to the entheses themselves to help reduce stress concentration at the attachments sites. The ligaments and tendons (LTs) are similar in the way they link the soft to the solid structures. The entheses provide strong and stable anchorage for these structures but also protect them from damage and injury by aiding in the smooth transfer of force between the soft and hard tissue. The gross structure of the enthesis reveals a flaring in order to increase the surface area of the attachment. Individual entheses also combine to form a larger and stronger attachment site called a *conjoined enthesis*, just as the sartorius, gracilis and semitendinosus combine on the tibia at the *pes anserinus*.[11] In the last ten years there has been an increasing interest in the concept of "*conjoined LTs enthesis,*" or where the tendons and ligaments blend together as they attach to bone. This is demonstrated at the lateral epicondyle where the common extensor tendon merges imperceptibly with the lateral collateral ligament and the annular ligament. Another example is the conjoined LT enthesis in the shoulder where the distal glenohumeral ligaments meld with the rotator cuff tendons on the humerus. The plantar aspects of the foot have multiple layers of conjoined tendons and LT combinations, such as where the long and short plantar ligaments, tibialis posterior and the peroneus longus share entheses to all the tarsal bones except the talus.[12]

Benjamin, Shaw and others have studied the enthesis in detail and have found that it is more than just the LT attachment site. It includes the bony prominences such as the superior tuberosity adjacent to the Achilles tendon that acts like a pulley, reducing stress on the tendon in dorsiflexion. The Achilles tendon also has Kager's fat pad, the tip of which presses into the retrocalcaneal bursa. These particular structures are adapted to resist compression or shear when the foot is dorsiflexed and reduce friction and the build up of heat. LTs often attach to bone near tuberosities or are sunken into pits, which also act like pulleys to dissipate stress away from the attachment site itself. It is interesting that the Achilles tendon fat pad is the only part of the normal Achilles tendon enthesis organ that is innervated. This makes it the probable source of pain from the normal tendon.[13]

LTs are designed to bear and transmit high tensile loads along their longitudinal axes so they have structural characteristics that confer a greater stiffness and resistance in the axial dimension. The highly nonlinear response of the LT tissues is due to the hierarchical tensegrity structure of the collagen network. The structural integrity and the viscoelastic characteristics of LTs result mainly from the interaction between collagenous proteins and non-collagenous proteins-proteoglycans in the ECM. This interaction allows both reversible (slip-links) and irreversible (rupture) detachment of the glycosaminoglycans (GAG) from the proteins.[14] There also are other cellular and molecular tensile stress absorbers that are discussed in the tendon and tendinosis sections.

LIGAMENTS

Recent ligament research supports the idea that ligaments have two functions and anatomies. One function is that they are the static stabilizers of joints and the second function is sensory or proprioceptive. The presence of mechanosensors implies a sensory role for some ligaments and that this afferent information could regulate the stiffness of the muscles surrounding the joint and improve its stability.[15]

The anatomic vision of ligament anatomy—that ligaments are static structures that fail by fracturing like pieces of soft iron (as illustrated in Strollers' book) and that they are avascular—is being replaced as their microanatomy is unraveled.[16] Immunohistologic chemisty and newer microimaging techniques available in the last fifteen to

twenty years are showing them to be dynamic structures closely connected to the tensegrity transduction system and the ECM.

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

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

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

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

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

TENDONS

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

A quick review of tendon anatomy will help reveal where the new research and some old ideas can aid in our understanding of the structure and function of these complex entities. Tendons have many hierarchical tensegrity scales beginning with individual collagen fibers, which attach to the cell walls of tenocytes and tenoblasts by way of the focal adhesion complex. In the ECM three collagen molecules arrange in helices that are held together by hydrogen bonds in a coiled shape and are called tropocollagen. Five tropocollagen molecules constitute a microfibril and multiple microfibrils aggregate and form fibrils. The fibril is defined as a collection of fibers that is surrounded by an endotendon.[10] Fibrils are grouped into fibres; collections of fibres form bundles and bundles

form fascicles. The endotendon is mostly ECM with most of the tenocytes (TC), tenoblasts (TB), blood vessels and nerves. Some tendons have little or no endotendon and are thought to be involved in transferring stress.[18] There is a helical organization of the whole tendon, from the shiny white tendon to the collagen molecules. This allows the collagen molecules to behave like cables or ropes that deform under tensile stress and improve the handling of their loads.[23] These loads are defined as tensile stress, which is a measure of the internal forces acting within a deformable body. (Wikipedia)

Many of the tendons that are of particular interest to a musculoskeletal physician have to do with joints used in throwing and walking. These muscles do not transmit their load just to bone but also to adjacent muscles and "non-muscular tissue" or the fascia. Wood Jones first explored this idea in the 1940s. A good example of this is where the gluteus maximus attaches to the tendon of the tensor fascia lata and the iliotibial band and not to the greater trochanter.[24] This anatomic arrangement links muscles together to form "mechanical chains" and most muscles in the legs have some direct attachment to the fascia.[25] These muscle and tissue arrangements allow the muscles to distribute tensile stress to the fascicles, then to the fibrils and eventually to the microfibrils and the tropocollagen and finally to the collagen molecules in the ECM that attach to the integrin complex on the cell wall.

Another feature of tendons is the ability of the fascicles to slide independently, which allows them to transmit tensile stress while changing direction, such as going around the medial malleolus. This feature also allows them to change shape as the muscle contracts and also creates a space for the blood vessels.[26] The fibrils also can slide relative to adjacent fibrils and this may account for up to 50% of a tendon's ability to absorb tensile strain.[27]

As tensile stress is further distributed down the tensegrity scale another feature of tendons comes into play—the crimp in the collagen. At rest, LTs' collagen fibrils are in a wavy or crimped configuration. The crimp acts like a shock absorber or a buffer, permitting slight elongation to occur without fibrous damage. The crimp performs like a shock absorber that stores the stretch energy and when the stress is released the elastic recoil returns up to 90% of this stored energy.[28] As the tendon is stretched, the crimps begin to disappear progressively or individually rather than simultaneously from the ends toward the centre of the collagen fascicle. The collagen crimp allows for a graded response to acute stretching and works with increasing stress up to about 4% of the LTs' length.[29]

As the length of the tendon exceeds 4% the tensile stress shifts to the collagen fibril, which is the primary force-transmitting unit of the tendon.[30] The stress at this level leads to some slippage of the ECM's protein and GAG molecules relative to each other as their crosslinks break.[31] This level of tensile stress also causes the tenocytes and fibroblasts that are in the fibrils and inter-fascicular spaces to be deformed. The collagen molecules of the ECM that attach to the integrin molecules on the cell surface sense the collagen stress and signal the cells to produce more collagen and ECM. This induces a two- or three-fold increase in collagen formation that peaks around 24 hours after exercise and remains elevated for up to 80 hours. The degradation of collagen proteins also increases in response to exercise and is a physiological response to healing. This illustrates that to increase tendon collagen some period of rest (from 36 to 72 hours) is required. This time frame may be compressed with training and conditioning. In any case, without sufficient rest a continuous loss of collagen is likely to occur.[32] (*See Figure 6.*)

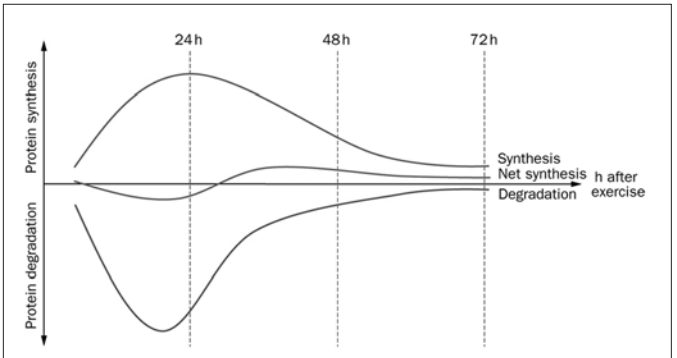


Figure 6. Acute exercise in humans is followed by an increase in both the synthesis and degradation of collagen in tendons. Notice that there is more degeneration than synthesis until 36-72 hours after the stress. If the rest periods are too short degradation will prevail and lead to tendinosis.
Ref: Magnusson PS. The pathogenesis of tendinopathy; balancing the response to loading. *Nature Reviews Rheumatology*. 2010.

The tenocytes also have mechanisms for continuing to dissipate the stress on the tendons. Tenocytes are like myofibroblasts and respond to rapid length increases with a rapid force increase associated with elastic resistance. This is followed by rapid loss of tissue tension associated with both viscoelastic relaxation and actin cytoskeleton disruption. The recovery of the tension is biphasic,

described as rapid active response (RAR) and gradual active response (GAR), restoring the tissue tension and rebuilding the actin cytoskeleton. The RAR occurs within seconds of a sudden stretch and is completed in less than a minute, and GAR begins a few minutes post-stretch and lasts more than 20 minutes. Both of these responses are mediated by Ca++ channels and reflect the distortion of the cell walls. Both result in cytoskeletal structural changes that include increased actin molecules in the direction of the force and are proportional to the applied stress.[33]

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

TENDINOSIS

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

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

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

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

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

Tendinosis creates a wide variation in cell density, ranging from areas of near zero cells to areas with many cells that are metabolically active. These areas also have collagen fascicules with unequal crimping, loss of transverse bands, ruptured fibers and increased type III collagen with decreased crosslinks. The abnormal microenvironments

and altered tensegrity of tendinosis induce differentiation of some tenoblasts into adipocytes, others to chondroblasts and even to osteoblasts, which explains the existence of lipid accumulation, mucoid formation and tissue calcification in areas of tendinosis.[44] In these areas of tendinosis there is a considerable increase in both nerves and vessels.[45]

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

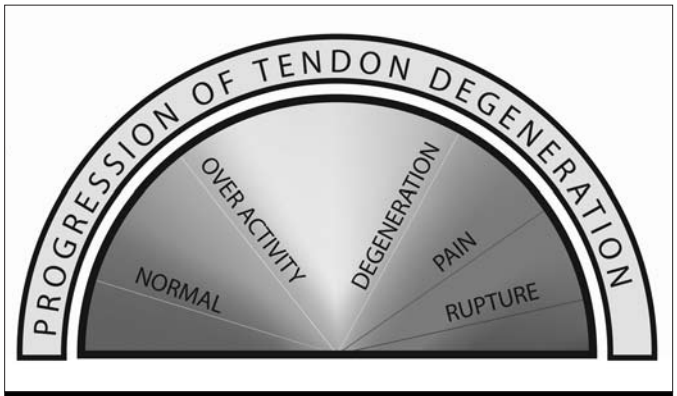


Figure 7. This image portrays the progression of tendinosis from (on the left) a normal response to stress by a progressively weaker and painful tendon to a structure that ruptures with the slightest additional stress. The image should give one an idea of the time for progression and recovery. It may be possible to go from normal to very painful or even rupture in one day but recovery is slower.
Ref: Ravin T. AAMM. 2011

A CASE FOR PROLOTHERAPY

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

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

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

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

The current therapy for tendinosis once tendons are degenerated may best be described as regenerative. Rest now seems essential to healing. The question is how we balance stress and rest. Beyond rest, the treatment options for tendinosis seem to be equal to the number of doctors treating. This emphasizes the need for a better and more complete diagnosis of tendinosis. Understanding of

tensegrity can shed light as physicians seek to understand how ligaments repair, why tendinosis occurs and how cells respond to the stresses of living, working and playing. ■

REFERENCES

Please note comments the author has added as guides to some of the references.

1. Wong J, et al. Cell attachment and protein adsorption to polypyrrole thin films. *Mat Res Soc Proc.* 1993;293:179-184.
2. Ingber D. Cellular mechanotransduction: putting all the pieces together again. *J FASEB.* 2006;20:811-827. *(This is a must read article but hard to read. It puts together some of the most important building blocks for musculoskeletal medicine of the future.)*
3. Ciquet M, et al. From mechanotransduction to extracellular matrix gene expression in fibroblasts. *Biochimica et Biophysica Acta*. 2009;1793:911-920.
4. Ingber D. Tensegrity I. Cell structure and hierarchical systems biology. *J Cell Sci*. 2003;116:1157–1173.
5. Dufort C, et al. Balancing forces: architectural control of mechanotransduction. *Nature*. 2011;12:310-319. *(This article has several illustrative images summarizing the intracellular components of intracellular biotensegrity and its relationship to mechanotransduction.)*
6. Avery N, et al. Enzymic and non-enzymic cross-linking mechanisms in relation to turnover of collagen: relevance to aging and exercise. *Scand J Med. Sci Sports*. 2005;15:231–240.
7. Geiger B, et al. Environmental sensing through focal adhesions. *Nature Rev Mol Cell Biol*. 2009;10:21–33.
8. Hynes R. The extracellular matrix: not just pretty fibrils. *Science*. 2009;326:1216–1219.
9. Wozniak M, et al. Mechanotransduction in development: a growing role for contractility. *Nature Rev Mol Cell Biol*. 2009;10:34-43.
10. Shaw H, et al. Structure–function relationships of entheses in relation to mechanical load and exercise. *Scand J Med Sci Sports*. 2007;17:303–315.
11. Benjamin M, et al. Structure-function relationships in tendons: a review. *J. Anat*. 2008;212:211-228. *(This article and the one above by Shaw HM unify the gross anatomy down to the cellular components of the enthesis. The anatomy images are worth looking at.)*
12. Milz S, et al. Molecular composition and pathology of entheses on the medial and lateral epicondyles of the humerus: a structural basis for epicondylitis. *Ann Rheum Dis*. 2004;63:1015-1021.
13. Shaw H, et al. The innervation of the enthesis organ of the rat Achilles tendon. *J Anat*. 2005;208:402-408.
14. Ciarletta P, et al. A finite dissipative theory of temporary interfibrillar bridges in the extracellular matrix of ligaments and tendons. *J R Soc Interface*. 2009;6:909-924.
15. Barrack R, et al. The sensory function of knee ligaments. In Daniel BM, Akeson WH, O'Connor (ed). *Knee Ligaments: Structure, Function, Injury and Repair.* New York: Raven; 1990;95-114.
16. Stoller D. *Stoller's Atlas of Orthopaedics and Sports Medicine*. New York, NY: Lippincott Williams & Wilkins; 2008.
17. Hagert E, et al. General innervation pattern and sensory corpuscles in the scapholunate interosseous ligament. *Cells Tissues Organs*. 2004;177:47-54.
18. Hagert E, et al. Immunohistochemical analysis of wrist ligament innervation in relation to their structural composition. *J Hand Surg*. 2007;32A:30-36. *(This is a major contribution to our understanding of ligaments and how they function and changes the way we should think about our treatment of ligaments.)*
19. Mataliotakis G, et al. Sensory innervation of the subregions of the scapholunate interosseous ligament in relation to their structural composition. *J Hand Surg Am*. 2009;34(8):1413-1421.
20. Del Valle M, et al. Immunohistochemical analysis of mechanoreceptors in the human posterior cruciate ligament. *J Arthroplasty*. 2009;13(8):916-922.
21. Schutte M, et al. Neural anatomy of the human anterior cruciate ligament. *JBJS*. 1987;69(A)(2):243-247.
22. Thomopoulos S, et al. The effect of muscle loading on flexor tendon-to-bone healing in a canine model. *J Orthop Res*. 2008 December; 26(12):1611–1617.
23. Bozec L, et al. Collagen fibrils; nanoscale ropes. *Biophys J*. 2007;92:70-75.
24. Wood Jones F. *The Principles of Anatomy as Seen in the Hand*. London, England: Balliere, Tindall and Cox; 1944.
25. Myers T. *Anatomy Trains: Myofascial Meridians for Manual and Movement Therapist*. Edinburgh, Scotland: Churchill Livingstone; 1987.
26. Ravin T, et al. *Principles of Prolotherapy*. Denver, CO: American Academy of Musculoskeletal Medicine; 2008.
27. Screen H, et al. An investigation into the effects of the hierarchical structure of tendon fascicles on micromechanical properties. *Proc Inst Mech EngH*. 2004;218:109-119.
28. Franchi M, et al. Crimp morphology in relaxed and stretched rat Achilles tendon. *J Anat*. 2007;210(1):1–7. *(The images in the article are very effective; I regret that I was unable to get permission to use them.)*
29. Hansen K, et al. Recruitment of tendon crimp with applied tensile strain. *J Biomech Eng*. 2002;124:72-77.
30. Perry D, et al. A comparison of the size distribution of collagen fibrils in connective tissues as a function of age and possible relation between fibril size distribution and mechanical properties. *Proc R Soc Lond B Biol Sci*. 1978;203:305-321.
31. Bailey A. Molecular mechanisms of ageing in connective tissues. *Mech Ageing Dev*. 2001;122:735-755.
32. Magnusson S, et al. The pathogenesis of tendinopathy: balancing the response to loading. *Nat Rev Rheumatol*. 2010;6:262-268. *(This is a very useful review article. It is going to influence how we think about treating tendinosis and already is doing so in Europe. The key graph from this article is in this paper as Figure 5.)*
33. Nekouzadeh A, et al. Stretch-activated force shedding, force recovery and cytoskeletal remodeling in contractile fibroblasts. *J Biomech*. 2008;41(14):2964-2971.
34. Hinz D, et al. Mechanisms of force generation and transmission by myofibroblasts. *Curr Opin Biotechnol*. 2003;14(5):538-546.
35. Tomasek J, et al. Myofibroblasts and mechano-regulation of connective tissue remodeling. *Nat Rev Mol Cell Biol*. 2002;3(5):349-363.

36. Mehta S, et al. Etiologic and pathogenetic factors for rotator cuff tendinopathy. *Clin Sports Med*. 2003;22:791-812.

37. Holmes G, et al. Etiologic factors associated with symptomatic Achilles tendinopathy. *Foot ankle Int*. 2006;27:952-959.

38. Magra M, et al. Genetic aspects of tendinopathy. *J Sci Med Sport*. 2008;11:243-247.

39. Inkovic A, et al. Overuse injuries in female athletes. *Croat Med J*. 2007;48:767-778.

40. Batista F, et al. Achilles tendinopathy in diabetes mellitus. *Foot Ankle Int*. 2008;29:498-501.

41. Li Z, et al. Inflammatory response of human tendon fibroblasts to cyclic mechanical stretching. *Am J Sports Med*. 2004;32:435-440.

42. van der Linden P, et al. Increased risk of Achilles tendon rupture with quinolone antibacterial use, especially in elderly patients taking oral corticosteroids. *Arch Intern Med*. 2003;163:1801-1807.

43. Abate M, et al. Pathogenesis of tendinopathies: inflammation or degeneration? *Arthritis Research & Therapy*. 2009;11:235-250.

44. Zhang J, et al. Mechanobiological response of tendon stem cells: implications of tendon homeostasis and pathogenesis of tendinopathy. *J Ortho Res*. 2010;28:639-643.

45. Magnusson S, et al. The pathogenesis of tendinopathy: balancing the response to loading. *Nat Rev Rheumatol*. 2010;6:262-268.

Ligament Injury and Healing: An Overview of Current Clinical Concepts

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

ABSTRACT

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

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

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

Journal of Prolotherapy. 2011;3(4):836-846.
KEYWORDS: corticosteroids, exercise, immobility, ligament healing, ligament injury, NSAIDs, Prolotherapy.

INTRODUCTION

Ligaments are dense bands of fibrous connective tissue that serve to join two or more bones of the musculoskeletal system. Ligaments cross joints with wide ranges of motion as well as joints with little motion and may appear as long sheets of opaque tissue or short thickened strips in joint capsules. Although they vary in size, shape, orientation, and location, ligaments primarily function to provide stabilization of joints both at rest and during normal range of motion. While ligaments were once thought to be inactive structures, they are, in fact, complex tissues that respond to many local and systemic influences.[1] Ligament injuries are among the most common causes of musculoskeletal joint pain and disability encountered in primary practice today. **Ligament injuries create disruptions in the balance between joint mobility and joint stability, which can lead to abnormal transmission of forces throughout the joint, resulting in damage to other structures in and around the joint.** Knees, hips, shoulders, ankles, elbows, and wrists are among some of the joints most commonly affected by ligament injuries. While there is a vast body of knowledge available regarding the structure and function of normal ligaments, understanding the structure and function of injured ligaments becomes more complicated due to the variability and unpredictable nature of ligament healing. This may be due to the dramatic physiological and structural changes that ligaments sustain as a result of injury, as well as the complex and dynamic cellular processes that occur during healing. These processes create alterations in the biology and biomechanics of the injured ligament, leading to inadequate healing and tissue formation that is inferior to the tissue it replaces. The incomplete healing and persisting differences in the new ligament tissue result in ligament laxity, which predisposes the joint to further injury. Ligament injury and subsequent laxity cause joint instability, which leads to chronic pain, diminished function, and ultimately

osteoarthritis of the affected joint.[2-5] Despite the numerous strategies that have been employed over the years attempting to improve ligament healing after injury, osteoarthritis, the long-term consequence of ligament injury, continues to be the most common joint disorder in the world.[6] Therefore, understanding the complex cellular processes that occur as a result of ligament injury, along with determining and implementing strategies that optimize ligament restoration are necessary to reduce the enormous individual and public health impacts of osteoarthritis.

Understanding the complex cellular processes that occur as a result of ligament injury, along with determining and implementing strategies that optimize ligament restoration are necessary to reduce the enormous individual and public health impacts of osteoarthritis.

LIGAMENT STRUCTURE AND FUNCTION

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

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

Ligaments prevent excessive motion of joints by providing passive stabilization and guiding joints through normal range of motion under tensile load. In doing so, ligaments transfer force to and from the skeleton while dynamically distributing the loads applied to them in order to perform specific movement patterns.[13] Ligaments also function to provide joint homeostasis through their viscoelastic properties that reflect the complex interactions between collagens, proteoglycans, water, and other proteins.[1, 14] The viscoelastic properties, along with the recruitment of crimped collagen, contribute to the mechanical behavior of the structure under loading conditions. When tension is applied, ligaments deform, or elongate, in a non-linear fashion through the recruitment of crimped collagen fibers. As the tension placed on the ligament increases, the collagen fibers progressively un-crimp, or elongate, until all fibers are nearly linear. (*See Figure 1.*) As the

fibers become increasingly linear, the ligament structure becomes increasingly stiff. Varying degrees of ligament stiffness are necessary for various loads and various ranges of joint motion. Ligaments can lose their ability to retain their original shape when stretched or elongated past a certain point for a prolonged period of time. When this occurs, the ligament becomes lax and unable to properly support the joint, leading to instability, pain, and eventual osteoarthritis of the joint. When an applied load causes all fibers to become nearly linear, the ligament continues to absorb energy until tensile failure or disruption of the tissue. Just as overstretched ligaments cause joint instability, ligament disruptions, or tears, will also create joint instability. In attempt to prevent overstretching and disruption, ligaments utilize their viscoelastic properties to exhibit both creep and relaxation behaviors. Creep and load relaxation behaviors help to prevent fatigue failure of the tissue when ligaments are loaded in tension. Creep is defined as the deformation, or elongation, of a ligament over time under a constant load or stress. Load relaxation refers to a decrease in stress of the tissue over time when the ligament is subjected to a constant elongation.[15-17]

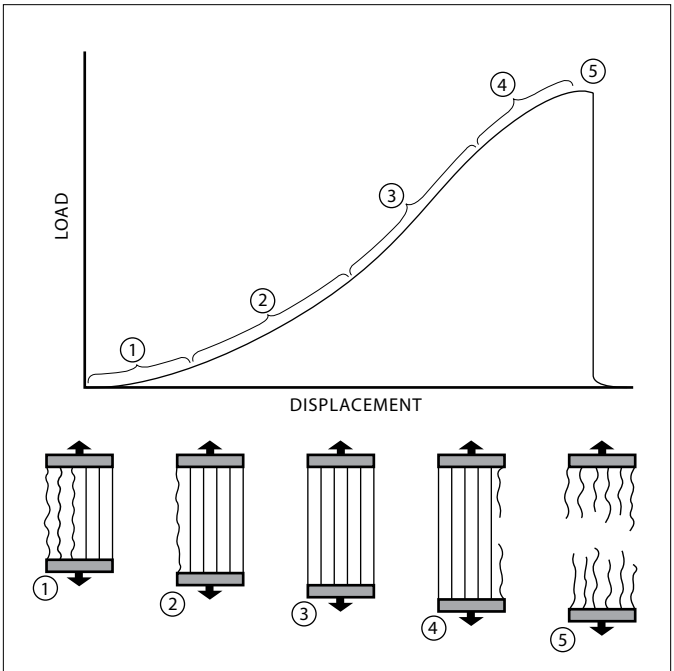


Figure 1. Ligament structural strength graph. As the load is increased, more ligament fibers are recruited (straight lines), and the slack or creep in the fibers is removed until the entire ligament tears. The load at complete failure of the ligament represents its maximum structural strength.

LIGAMENT RESPONSE TO INJURY

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

Several growth factors have been identified, each playing a specific role in the inflammatory process. Some of the numerous growth factors which have been identified include Platelet-Derived Growth Factor, Transforming Growth Factor-β, Vascular Endothelial Growth Factor, and Fibroblast Growth Factor. Platelet-Derived Growth Factor and Transforming Growth Factor-β attract immune system cells to the area and stimulate them to proliferate. Vascular Endothelial Growth Factor aids in new blood vessel formation, which increases vascularity in injured areas. Fibroblast Growth Factor promotes the growth of the cells involved in collagen and cartilage formation. When stimulated by growth factors, neutrophils, monocytes, and other immune cells migrate to the injured tissue to initiate matrix turnover by ingesting and removing debris and damaged cells during the inflammatory phase. The proliferative/repair phase begins when immune cells release various growth factors and cytokines, which initiate fibroblast proliferation to rebuild the ligament tissue matrix. The tissue formed initially appears as disorganized scar tissue with more blood vessels, fat cells, fibroblastic and inflammatory cells than normal ligament tissue.[1, 18] Over the next several weeks, fibroblast cells deposit various types of collagen,

proteoglycans, other proteins and glycoproteins to the matrix. The collagen becomes aligned with the long axis of the ligament during this time, however, the newly formed type of collagen fibrils are abnormal and smaller in diameter than normal ligament tissue. After a few weeks, the proliferative phase merges into the remodeling phase in which collagen maturation occurs for months to years after the initial injury. With time, the tissue matrix starts to resemble normal ligament tissue, however, critical differences in matrix structure and function persist. (*See Figure 2.*) In fact, evidence suggests that the injured ligament structure is replaced with tissue that is grossly, histologically, biochemically, and biomechanically similar to scar tissue.[15, 19-21] As Frank et al. note, even fully remodeled scar tissue remains grossly, microscopically, and functionally different from normal tissues.[22]

Normal Ligaments	Ligament Scars
• Bimodal (large) collagen fibrils	• Smaller collagen fibrils
• Cell and matrix turnover low	• Cell and matrix turnover high
• Collagen aligned	• Collagen disorganized
• Collagen densely packed	• Flaws between fibers
• High matrix-cell ratio	• Lower matrix-cell ratio
• Low cell density	• Higher cell density
• Mature collagen cross-links	• Immature collagen cross-links
• Primarily collagen Type I	• More collagen III
• Primarily small proteoglycans	• Larger proteoglycans
• Rare cell division	• More cell division

Figure 2. Differences between normal ligaments and scars.

The remodeling phase of ligament repair can continue for months to years, during which time collagen and ligament matrix are continually overturned by processes of tissue synthesis and degradation. This provides ongoing opportunities for the ligament to adapt with functional improvement, or degrade and fail with applied loads. The persisting abnormalities present in the remodeled ligament matrix can have profound implications on joint biomechanics depending on the functional demands placed on the tissue. Because remodeled ligament tissue is morphologically and biomechanically inferior to normal ligament tissue, ligament laxity results, causing functional disability of the affected joint and predisposing other soft tissues in and around the joint to further damage. Some of the identifiable differences in remodeled matrix verses normal ligament matrix include altered proteoglycan and collagen types,[23, 24] failure of collagen crosslinks to mature,[7, 25] persistence of small collagen fibril diameters,[22, 26] altered cell connections,[28] increased vascularity,[22, 25] abnormal innervation, increased cellularity and the incomplete resolution of matrix flaws.[1, 22] Research suggests that persisting collagen abnormalities may be the most critical to ligament tissue function, however, virtually all tissue components other than collagen likely play equally important direct and indirect roles in tissue function.[22, 29-31] Normal ligament tissue is primarily composed of type I collagen, which is responsible for the stiffness and strength of the tissue. After injury, fibroblasts primarily synthesize type III collagen and to a much lesser extent Type I collagen.[32, 33] The densely packed cross-linked formation of type I collagen fibrils in normal ligaments accounts for stability, strength, and stiffness of the ligament. The abnormal collagen cross-linking and smaller collagen fibril sizes of the repaired ligament create weaknesses in tissue strength and stiffness which remain for months to years after initial injury.[22, 25, 29, 30, 34-36] In addition, evidence suggest that remodeled collagen fibrils are not packed as densely as in normal ligaments and the remodeled tissue contains materials other than collagen, such as blood vessels, fat cells, and inflammatory cell pockets which contribute to weakness.[1, 18, 22]

In order to understand ligament healing, many studies use the medial collateral ligaments (MCLs) of rabbits as experimental models. Studies on rabbit MCLs have shown that healing or remodeled MCLs are ultimately weaker, less stiff, and absorb less energy before failure than normal MCLs.[34, 37, 38] Several studies have documented that conservatively treated injured MCLs typically regain only 40% to 80% of their structural stiffness and strength compared to normal MCLs.[15, 17, 22] On the other hand, the viscoelastic characteristics of the injured MCL have a somewhat better recovery, as these properties return to within 10-20% of normal MCL behavior.[22] This results in greater stress relaxation, which indicates that the ligament which sustained the injury maintains loads less efficiently than the normal ligament. Remodeled MCLs also exhibit inferior creep properties, elongating more than twice as much as normal MCLs, even at low tensions.[1, 22, 39, 40] In addition, remodeled MCLs are at risk for permanent elongation because after loading they do not appear to return to their original length as quickly or as completely as normal MCLs.[22] The laxity of the healing MCL leads to mechanical instability of the knee joint, which alters the contact mechanics of the joint. When the knee or any joint is unstable, sliding between joint surfaces increases, and the efficiency of muscles surrounding the joint decreases.

This creates alterations in the load distribution of the joint, which disrupts the underlying cartilage and bone, causing wear and increasing shear, eventually leading to osteochondral degeneration or osteoarthritis.[41]

Animal studies have shown that different ligaments heal at different rates[15, 42-47] and combined ligament injuries heal with inferior rate and quality than isolated injures.[15, 42, 43, 48-52] Most animal studies focus on the ACL and MCL of the knee joint and while these structures may heal at varying rates comparatively and among different animal species, the quality of the remodeled tissue remains inferior to that of normal ligaments.[26, 30, 32, 35, 42, 54, 55-57] In fact, studies of healing ligaments have consistently revealed that following rupture, certain ligaments do not heal independently, while others do heal, but with inferior compositional properties compared to normal tissue.[37, 48, 58, 59] It is not uncommon for individuals to experience more than one ligament injury during a single traumatic event. Rabbit models have demonstrated that combined ACL/MCL injuries result in inferior structural and material properties of the healing MCL compared with those of the isolated MCL model.[42, 43, 49-52] Some researchers believe that this may be related to the immobility of animals with painfully unstable knees or the excessive forces placed on the healing MCL tissue when there is damage to the ACL.[15] As previously mentioned, while some ligaments heal spontaneously, be it with inadequate tissue configuration, other ligaments exhibit very poor intrinsic healing ability. This may be related to the specific properties of the particular ligament that was injured, the type of ligament injury (partial or full disruption), or interventions employed after ligament injury.

CURRENT STRATEGIES FOR OPTIMIZING LIGAMENT REPAIR

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

IMMOBILIZATION AND REST

Injured limbs are traditionally rested by splinting or casting. While immobilization of the affected joint has long been prescribed following ligament injury, it has since been discovered that healing ligaments are dramatically affected by the presence or absence of joint motion. The theory is that rest or immobilization will prevent further tissue damage in the joint by limiting movement, thereby decreasing pain and swelling. It is also thought that rest may improve recovery time, decrease functional problems, and reduce long-term pain. However, immobilizing a joint with a ligament injury can cause detrimental side effects, such as synovial adhesions,[62] increasing collagen degradation with decreasing collagen synthesis,[7] and a greater percentage of disorganized collagen fibrils.[34, 38] Despite this evidence, rest and the RICE (Rest, Ice, Compression, Elevation) protocol continue to be commonly prescribed as the first line treatment for ligament, tendon, and other soft tissue injuries. Immobilization causes ligament physiology to progressively switch from an anabolic to a more catabolic state. One study that measured collagen fiber bundle diameters in the normal and repaired ligaments of dogs, clearly documented that increased or decreased levels of exercise will greatly influence the strength of ligaments. The study showed that the amount of exercise performed by the animal was directly correlated with the number of collagen fibrils, their arrangement, and their average thickness within the ligament.[63] Decreased loading of ligament tissue alters matrix turnover so that with time, matrix degradation exceeds formation and the newly synthesized matrix is less well organized, and the tissue stiffness and strength declines. Prolonged limb immobilization decreases the glycosaminoglycan and water content and the degree of orientation of the matrix collagen fibrils within the ligaments. Ultimately this causes

the ligaments to have less mass and strength. (*See Figure 3.*) Decreased ligament loading has a profound effect on decreasing the strength of the ligament-bone junction (fibro-osseous junction) because immobilization causes subperiosteal osteoclasts to resorb much of the bony inserts of the ligaments. This causes a substantial decline in the tensile strength at the bone-ligament interface.[64] According to the most recent systematic reviews of research on soft tissue injuries in humans, there appears to be no controlled study that favors immobilization for the treatment of ligament injuries.[65, 66]

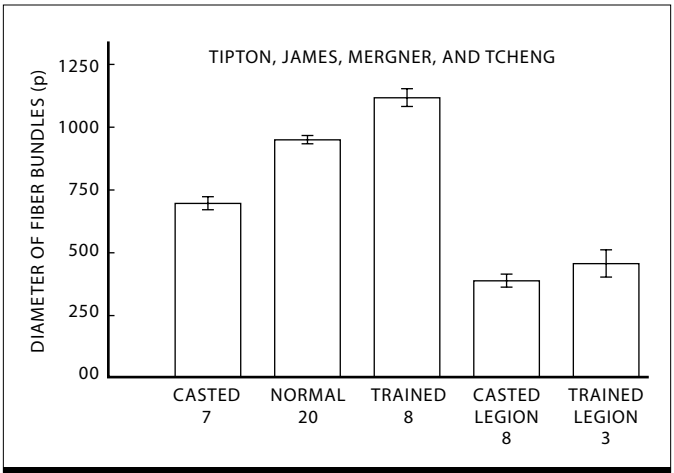


Figure 3. Ligament fiber bundle diameters. Ligament collagen fiber diameters are increased with exercise and diminished significantly when limbs are immobilized.

MOBILIZATION AND EXERCISE

Early controlled resumption of activity after injury, including repetitive loading on injured soft tissue structures such as ligaments and tendons has profoundly beneficial effects including enhanced cellular synthetic and proliferative effects, increased strength, size, matrix organization and collagen content of ligaments and tendons.[67] Mobilization has been shown to benefit the injured ligament by causing it to form more connective tissue, resulting in tissue that is stronger and stiffer than an immobilized counterpart.[15, 42-44, 68] Motion causes an increase of blood flow to the affected joint, providing the damaged ligament tissue with nutrients and metabolites necessary for tissue repair and healing. Under loading conditions, cells within the ligament detect tissue strains and respond by modifying the tissue. Results of numerous animal studies have shown that the strength of repaired ligaments is greater in animals which were allowed to continue to exercise, rather than to rest.[69-72] According to Kerkhoff et al., in a systematic review of research on ankle ligament injuries in 2,184 adults, functional treatment involving motion of the affected joint was a statistically significant strategy for healing the injured ligament, compared with immobilization. Patients who treated their ligament injuries with motion, versus immobilization, were able to return to work quicker, return to sport quicker, and demonstrated less objective instability as tested by stress X-ray.[65] In another systematic review, early mobilization was found to decrease pain, swelling and stiffness, and allowed a greater preservation of range of motion and return to work.[66] Mobilization for the treatment of soft tissue damage has also been found to decrease muscle atrophy, disuse osteoporosis, adhesions, and joint stiffness following injury.[73-79] Overall, carefully controlled exercise plans promote healing of injured ligaments.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

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

CORTICOSTEROID INJECTIONS

Corticosteroid injections have long been used to treat musculoskeletal disorders including ligament injuries. Although steroid injections have been shown to be effective in decreasing inflammation and pain of ligament injuries for up to six to eight weeks, the histological, biochemical, and biomechanical properties of ligament healing are inhibited.[90, 91] Their anti-inflammatory actions stem from their ability to prevent lysosomal enzyme release and to inhibit the accumulation of neutrophils and other inflammatory cells and the synthesis of inflammatory mediators, including cytokines, at the injury site.[92]

Corticosteroid injections into injured ligaments have an adverse effect on healing. Corticosteroid injections into ligaments and tendons have been known to inhibit fibroblast function and thus collagen synthesis[93-95] even causing collagen necrosis at the injection site.[96, 97] The steroid-injected ligaments have smaller cross sectional areas[91, 98, 100] and are weaker with decreased peak tensile strength[99, 100] and decreased load (energy) to ligament failure.[99, 100] Because of these inhibitory effects on ligament healing, several extensive reviews have cautioned against their use to treat ligament injuries especially in athletes.[101-103]

PROLOTHERAPY

Prolotherapy has emerged as an injection therapy treatment option for musculoskeletal and arthritic pain. It involves the injection of a small amount of various proliferant solutions (such as hypertonic dextrose, sodium morrhuate, platelet rich plasma) at the painful entheses of ligaments and tendons, as well as trigger points and adjacent joint spaces to induce healing of the injured structures.[104] Histologic studies of ligaments and tendons following Prolotherapy injections have shown an enhanced inflammatory healing reaction involving fibroblastic and capillary proliferation, along with growth factor stimulation.[105-107] Growth factors, including basic fibroblast growth factor and platelet-derived growth factor, mediate the biological processes necessary for soft tissue repair in muscles, tendons, and ligaments after acute, traumatic or overuse injury.[108, 109] Prolotherapy injection therapy is known by various names including proliferative therapy, regenerative injection therapy and platelet rich plasma.[110] Animal research has documented that Prolotherapy-injected ligaments have an increased ligament mass, extracellular matrix, thickness and junction strength with bone.[111-115]

Prolotherapy is given to the articular ligaments of the entire spine, pelvis and peripheral joints to tighten unstable joints. Case series have documented the efficacy of Prolotherapy for ligament injuries of the sacroiliac joint,[116-118] low back,[119, 120] neck,[121, 122] shoulder,[123] elbow,[124] knee,[125, 126] temporomandibular joint,[127, 128] and other articulations.[129, 130]

CONCLUSION

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

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

Numerous strategies have been employed over the year attempting to improve ligament healing after injury or surgery. One of the most important advances in the treatment of ligament injuries has come from the understanding that controlled early resumption of activity can stimulate repair and restoration of function, and that treatment of ligament injuries with prolonged rest may delay recovery and adversely affect the tissue to repair. Likewise, although steroid injections and nonsteroidal anti-inflammatory medications have been shown to be effective in decreasing inflammation and pain of ligament injuries for up to six to eight weeks, the histological, biochemical, and biomechanical properties of ligament healing are inhibited. For this reason their use is cautioned in athletes who have ligament injuries. As

such, NSAIDs are no longer recommended for chronic soft tissue (ligament) injuries, and for acute ligament injuries should be used for the shortest period of time, if used at all. Regenerative medicine techniques, such as Prolotherapy, have shown success in case series involving ligament injuries of the spine and peripheral joints, but studies in more controlled settings and with large numbers are needed in the future. ■

REFERENCES

1. Frank C. Ligament structure, physiology and function. *Journal of Musculoskeletal and Neuronal Interactions.* 2004;4(2):199-201.
2. Fleming B, et al. Ligament injury, reconstruction, and osteoarthritis. *Current Opinion in Orthopedics.* 2005;16(5):354-362.
3. Koh J, et al. Osteoarthritis in other joints (hip, elbow, foot, toes, wrist) after sports injuries. *Clinical Sports Medicine.* 2005;24:57-70.
4. Connell D, et al. MR imaging of thumb carpometacarpal joint ligament injuries. *Journal of Hand Surgery.* 2004;29:46-54.
5. Martou G, et al. Surgical treatment of osteoarthritis of the carpometacarpal joint of the thumb: a systematic review. *Plastic and Reconstructive Surgery.* 2004;114:1-32.
6. Arden N, et al. Osteoarthritis: epidemiology. *Best Practice & Research Clinical Rheumatology*. 2006;20(1):3-25.
7. Vereeke, et al. Soft-tissue physiology and repair. In: Vaccaro A, ed. *Orthopaedic Knowledge Update 8.* Rosemont, IL: American Academy of Orthopaedic Surgeons; 2005:15-27.
8. Amiel D, et al. Repetitive motion disorders of the upper extremity: effect of loading on metabolism and repair of tendons and ligaments. *American Academy of Orthopaedic Surgery.* 1995;217-213.
9. Benjamin M, et al. The cell and developmental biology of tendons and ligaments. *International Review of Cytology.* 2000;196:85-130.
10. Lo I, et al. The cellular matrix: a feature of tensile bearing dense soft connective tissues. *Histology and Histopathology.* 2002;17:523-537.
11. Chowdhury P, et al, The "epiligament" of the rabbit medial collateral ligament: a quantitative morphological study. *Connective Tissue Research.* 1991;27:33-50.
12. Bray R. Blood supply of ligaments: a brief overview. *Orthopaedics.* 1995;3:39-48.
13. Benjamin,M, et al. Where tendons and ligaments meet bone: attachment sites ('entheses') in relation to exercise and/or mechanical load. *Journal of Anatomy*. 2006;208:471-490.
14. Jung H, et al. Understanding normal, injured and healing ligaments and tendons: the role of biomechanics. Available at: http://www.gustrength.com/injury:understanding-ligaments-and-tendons. Accessed December 30, 2011.
15. Frank C, et al. Ligament healing a review of some current clinical and experimental concepts. *The Iowa Orthopaedic Journal.* 1992;12:21-28.
16. Akeson W, et al. Ligament biology and biomechanics. In: Finerman G, ed. American Academy of Orthopaedic Surgeons Symposium on Sports Medicine: The Knee. St. Louis, MO: CV Mosby Co; 1985:111.
17. Andriacchi T, et al. Ligament injury and repair. In: Woo SL-Y Buckwalter JA, eds. *Injury and Repair of the Musculoskeletal Soft Tissues.* Park Ridge, IL: Am Acad Orthop Surg; 1988:103.
18. Shrive N, et al. Soft-tissue "flaws" are associated with material properties of the healing rabbit medial collateral ligament. *Journal of Orthopaedic Research*. 1995;13:923-929.
19. Jack E. Experimental rupture of the medial collateral ligament of the knee. *Journal of Bone and Joint Surgery*. 1950;32(B):306.
20. Miltner J, et al. Experimental reproduction of joint sprains. *Proceedings of the Society for Experimental Biology and Medicine.* 1933;30:883.
21. Miltner J, et al. Experimental joint sprain pathologic study. *Archives of Surgery.* 1937;35:234.
22. Frank C, et al. Optimization of the biology of soft tissue repair. *Journal of Science and Medicine in Sport.* 1999;2(3):190-210.
23. Plaas A, et al. Proteoglycan metabolism during repair of the ruptured medial collateral ligament in skeletally mature rabbits. *Archives of Biochemistry and Biophysics.* 2000;374:35-41.
24. Amiel D, et al. Collagen alteration in medial collateral ligament healing in a rabbit model. *Connective Tissue Research.* 1987;16:357-366.
25. Frank C, et al. Rabbit medial collateral ligament scar weakness is associated with decreased collagen pyridinoline crosslink density. *Journal of Orthopedic Research.* 1995;13:157-165.
26. Frank C, et al. Collagen fibril diameters in the healing adult rabbit medial collateral ligament. *Connective Tissue Research.* 1992;27:251-263.
27. Lo I, et al. The cellular networks of normal ovine medial collateral and anterior cruciate ligaments are not accurately recapitulated in scar tissue. *Journal of Anatomy.* 2002;200:283-296.
28. Bray R, et al. Normal and healing ligament vascularity: a quantitative histological assessment in the adult rabbit medial collateral ligament. *Journal of Anatomy.* 1996;188:87-95.
29. Shrive N, et al. Soft tissue "flaws" are associated with the material properties of the healing rabbit medial collateral ligament. *Journal of Orthopedic Research.* 1995;13:923-929.
30. Frank C, et al. Collagen fibril diameters in the rabbit medial collateral ligament scar: a longer term assessment. *Connective Tissue Research.* 1997;36:261-269.
31. Hildebrand K, et al. Scar formation and ligament healing. *Canadian Journal of Surgery.* 1998;41:425-429.
32. Hsu S, et al. Functional tissue engineering of ligament healing. *Sports Medicine, Arthroscopy, Rehabilitation, Therapy & Technology.* 2010;2:2-10.
33. Liu S, et al. Collagen in tendon, ligament, and bone healing: A current review. *Clinical Orthopedics and Related Research.* 1995;318:265-278.
34. Woo S, et al. Biomechanics of knee ligaments: injury, healing, and repair. *Journal of Biomechanics.* 2006;39:1-20.

35. Niyibizi C, et al. Type V collagen is increased during rabbit medial collateral ligament healing. *Knee Surgery and Sports Traumatology Arthroscopy.* 2000;8(5):281-285.
36. Plaas A, et al. Proteoglycan metabolism during repair of the ruptured medial collateral ligament in skeletally mature rabbits. *Archives of Biochemistry and Biophysics.* 2000;374(1):35-41.
37. Weiss J, et al. Evaluation of a new injury model to study medial collateral ligament healing: primary repair versus nonoperative treatment. *Journal of Orthopaedic Research.* 1991;9(4):516-528.
38. Woo S, et al. The biomechanical and morphological changes in the medial collateral ligament of the rabbit after immobilization and remobilization. *Journal of Bone and Joint Surgery—American Volume.* 1987;69(8):1200-1211.
39. Thornton G, et al. Early medial collateral ligament scars have inferior creep behavior. *Journal of Orthopedic Research.* 2000;18:238-246.
40. Newton P, et al. Ultrastructural changes in knee ligaments following immobilization. *Matrix.* 1990;10(5):314-319.
41. Fleming B, et al. Ligament injury, reconstruction and osteoarthritis. *Current Opinion in Orthopedics.* 2005;16(5):354-362.
42. Bray R, et al. Joint instability alters scar quantity and quality and quality in healing a rabbit ligament. *Orthopedic Transactions.* 1990;14:322.
43. Bray R, et al. The early effects of joint immobilization on medial collateral ligament healing in an ACL-deficient knee: a gross anatomic and biomechanical investigation in the adult rabbit model. *Journal of Orthopedic Research.* 1991.
44. Hart D, et al. Healing of the medial collateral ligament in rats. The effects of repair, motion and secondary stabilizing ligaments. *Journal of Bone and Joint Surgery.* 1987;69(A):1194.
45. Inoue M, et al. Treatment of the medial collateral ligament injury. The importance of anterior cruciate ligament on the varus-valgus knee laxity. *American Journal of Sports Medicine.* 1987;15:15.
46. Ogata K, et al. The intra-articular effect of various post-operative managements following knee ligament repair. An experimental study in dogs. *Clinical Orthopedics.* 1980;150:271.
47. Piper T, et al. Early mobilization after knee ligament repair in dogs: an experimental study. *Clinical Orthopedics.* 1980;150:277.
48. Woo S, et al. Injury and repair of ligaments and tendons. *Annual Review of Biomedical Engineering.* 2000;2:83-118.
49. Fetto J, et al. Medial collateral ligament injuries of the knee: a rationale for treatment. *Clinical Orhtopedics.* 1978;132:206-218.
50. Warren R, et al. Injuries of the anterior cruciate and medial collateral ligaments of the knee. A long term follow-up of 86 cases. Part II. *Clinical Orthopedics.* 1978;136:198-211.
51. Yamaji T, et al. Medial collateral ligament healing one year after a concurrent medial collateral ligament and anterior cruciate ligament injury: an interdisciplinary study in rabbits. *Journal of Orthopedic Research.* 1996;14:223-227.
52. Ohno K, et al. Healing of the medial collateral ligament after a combined medial collateral and anterior cruciate ligament: comparison of repair and non-repair of medial collateral ligament tears in rabbits. *Journal of Orthopedic Research.* 1995;13:442-449.
53. Scheffler S, et al. Structure and function of the healing medial collateral ligament in a goat model. *Annals of Biomedical Engineering.* 2001;29(2):173-180.
54. Frank C, et al. Medial collateral ligament healing. A multidisciplinary assessment in rabbits. *American Journal of Sports Medicine.* 1983;11(6):379-389.
55. Abramowitch S, et al. A biomechanical and histological evaluation of the structure and function of the healing medial collateral ligament in a goat model. *Knee Surgery, Sports Traumatology, Arthroscopy.* 2003;11(3):155-162.
56. Marshall J, et al. Instability of the knee. A long-term experimental study in dogs. *Journal of Bone and Joint Surgery.* 1971;53(A):1561.
57. O'Donoghue D, et al. Repair and reconstruction of the anterior cruciate ligament in dogs. Factors influencing long-term results. *Journal of Bone and Joint Surgery.* 1971;53(A):710.
58. Woo S, et al. Treatment of the medial collateral ligament injury. II: Structure and function of canine knees in response to differing treatment regimens. *American Journal of Sports Medicine.* 1987;15:22-29.
59. Frank C, et al. Molecular biology and biomechanics of normal and healing ligaments: a review. *Osteoarthritis and Cartilage.* 1999;7:130-140.
60. Hintermann B. Biomechanics of the ligaments of the unstable ankle joint. *Sportverletz Sportschaden.* 1996;10(3):48-54.
61. Hubbard T. Ankle ligament healing after an acute ankle sprain: an evidence-based approach. *Journal of Athletic Training.* 2008;43(5):523-529.
62. Woo S, et al. Connective tissue response to immobility. Correlative study of biomechanical and biochemical measurements of normal and immobilized rabbit knees. *Arthritis & Rheumatism.* 1975;18:257-264.
63. Tipton C, et al. Influence of exercise on strength of medial collateral knee ligaments of dogs. *American Journal of Physiology.* 1970;216(3):894-902.
64. Buckwalter J. Activity vs. rest in the treatment of bone, soft tissue and joint injuries. *Iowa Orthopedic Journal.* 1995;15:29-42.
65. Kerkhoffs G, et al. Immobilisation and functional treatment for acute lateral ankle ligament injuries in adults. *Cochrane Database Systematic Review.* 2002;(3). Retrieved online on 12/23/11 from http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003762/abstract.
66. Nash C. Resting injured limbs delays recovery: a systematic review. *The Journal of Family Practice.* 2004;53(9). Retrieved online on 12/23/11 from http://www.jfponline.com/Pages.asp?AID=1772.
67. Buckwalter J. Activity vs. rest in the treatment of bone, soft tissue and joint injuries. *Iowa Orthopedic Journal.* 1995;15:29-42.
68. Vailas A. Physical activity and its influence on the repair process of medial collateral ligaments. *Connective Tissue Research.* 1981;9:25.
69. Goldstein W, et al. Early mobilization of rabbit medial collateral ligament repairs: biomechanic and histologic study. *Archives of Physical Medicine and Rehabilitation.* 1984;65(5):239-242.

70. Walsh S, et al. Knee immobilization inhibits biomechanical maturation of the rabbit medial collateral ligament. *Clinical Orthopedics and Related Research.* 1993;297:253-261.
71. Thornton G, et al. Strength of medial structures of the knee joint are decreased by isolated injury to the medial collateral ligament and subsequent joint immobilization. *Journal of Orthopedic Research.* 2005;23(5):1191-8.
72. Thornton G, et al. Healing ligaments have decreased cyclic modulus compared to normal ligaments and immobilization further compromises healing ligament response to cyclic loading. *Journal of Orthopedic Research.* 2003;21(4):716-722.
73. Pneumaticos S, et al. The effects of early mobilization in the healing of Achilles tendon repair. *Foot & Ankle International.* 2000;21:551-557.
74. Gelberman R, et al. The effects of mobilization on the vascularization of healing flexor tendons in dogs. *Clinical Orthopedics.* 1980;153:283-289.
75. Kannus P. Immobilisation or early mobilization after an acute soft tissue injury. *The Physician and Sportsmedicine.* 2000;28:58-63.
76. Halikis M, et al. Effect of immobilization, immediate mobilization and delayed mobilization of the resistance to digital flexion using a tendon injury model. *American Journal of Hand Surgery.* 1997;22(A):464-472.
77. Romanelli D, et al. Achilles rupture in the athlete: current science and treatment. *Sports Medicine and Arthroscopy Review.* 2000;8:377-386.
78. Viidik A, et al. The effect of training on the tensile strength of isolated rabbit tendons. *Scandinavian Journal of Plastic and Reconstructive Surgery.* 1967;1:141-147.
79. Peacock E, et al. Biological principles in the healing of long tendons. *Surgical Clinics of North America.* 1965;45:461-476.
80. Mehallo C, et al. Practical management: Nonsteroidal anti-inflammatory drug use in athletic injuries. *Clinical Journal of Sports Medicine.* 2006;16:170-174.
81. Dhners L, et al. Effects of nonsteroidal anti-inflammatory drugs on bone formation and soft-tissue healing. *Journal of the American Academy of Orthopedic Surgery.* 2004;12:139-143.
82. Radi Z, et al. Effects of cyclooxygenase inhibition on bone, tendon, and ligament healing. *Inflammation Research.* 2005;54:358-366.
83. Slatyer M. A randomized controlled trial of Piroxicam in the management of acute ankle sprain in Australian regular army recruits. *American Journal of Sports Medicine.* 1997;25:544-553.
84. Elder C, et al. A cyclooxygenase-2 inhibit impairs ligament healing in the rat. *American Journal of Sports Medicine.* 2001;29:801-810.
85. Warden S, et al. Low-intensity pulsed ultrasound accelerates and a nonsteroidal anti-inflammatory drug delays knee ligament healing. *American Journal of Sports Medicine.* 2006;34:1094-1102.
86. Warden S. Cyclo-oxygenase-2 inhibitors: beneficial or detrimental for athletes with acute musculoskeletal injuries? *Sports Medicine.* 2005;35:271-283.
87. Ziltener J, et al. Non-steroidal anti-inflammatory drugs for athletes: an update. *Annals of Physical Medicine and Rehabilitation.* 2010;53:278-282.
88. Fournier P, et al. Sports injuries and NSAID. *Rev Med Suisse.* 2008;6:1702-1705.
89. Paoloni J, et al. Non-steroidal anti-inflammatory drugs in sports medicine: guidelines for practical but sensible use. *British Journal of Sports Medicine.* 2009;43:863-865.
90. Mackie J, et al. Mechanical properties of rabbit tendons after repeated anti-inflammatory steroid injections. *Medicine and Science in Sports.* 1974;6:198-202.
91. Walsh W, et al. Effects of a delayed steroid injection on ligament healing using a rabbit medial collateral ligament model. *Biomaterials.* 1995;16:905-910.
92. Shapiro P, et al. The effect of local corticosteroid or Ketorolac exposure on hilogoic and biomechanical properties of rabbit tendon and cartilage. *Hand.* 2007;2:165-172.
93. Berliner D, et al. Effects of corticosteroids on fibroblast functions. *Research Journal of the Reticuloendothelial Society.* 1967;4:284-313.
94. Kapetanos G. The effect of the local corticosteroids on the healing and biomechanical properties of the partially injured tendon. *Clinical Orthopedics.* 1982;163:170-179.
95. Oxlund H. The influence of a local injection of cortisol on the mechanical properties of tendons and ligaments and the indirect effect on skin. *Acta Orthopedics Scandinavica.* 1980;51:231-238.
96. Balasubramaniam P, et al. The effect of injection of hydrocortisone into rabbit calcaneal tendons. *The Journal of Bone and Joint Surgery.* 1972;54B: 729-734.
97. Scutt N, et al. Glucocorticoids inhibit tenocyte proliferation and tendon progenitor cell recruitment. *Journal of Orthopedic Research.* 2006;24:173-182.
98. Wiggins M, et al. Effects of local injection of corticosteroids on the healing of ligaments. A follow-up report. *Journal of Bone and Joint Surgery.* 1995;77A:1682-1691.
99. Noyes F, et al. Effect of intra-articular corticosteroids on ligament properties. A biomechanical and histological study in rhesus knees. *Clinical Orthopedics.* 1977;123:197-209.
100. Wiggins M. Healing characteristics of a type-1 collagenous structure treated with corticosteroids. *American Journal of Sports Medicine.* 1994;22:279-288.
101. Nichols A. Complications associated with the use of corticosteroids in the treatment of athletic injuries. *Clinical Journal of Sports Medicine.* 2005;15:370-375.
102. Fredberg U. Local corticosteroid injection in sport: review of literature and guidelines for treatment. *Scandanavian Journal of Medical Science and Sports.* 1997;7:131-139.
103. Fadale P, et al. Corticosteroid injections: Their use and abuse. *Journal of the American Academy of Orthopedic Surgery.* 1994;2:133-140.
104. Kim S, et al. Critical review of Prolotherapy for osteoarthritis, low back pain and other musculoskeletal conditions: A physiatric perspective. *American Journal of Physical Medicine and Rehabilitation.* 2004;83:379-389.
105. Maynard J. Morphological and biomechanical effects of sodium morrhuate on tendons. *Journal of Orthopaedic Research.* 1985;3:236-248.

106. 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.

107. 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.

108. 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.

109. Creaney L, et al. Growth factor delivery methods of sports injuries: the state of play. *British Journal of Sports Medicine.* 2008;42:314-320.

110. Sanchez M, et al. Platelet-rich therapies in treatment of orthopaedic sport injuries. *Sports Medicine.* 2009;39:345-354.

111. Liu Y. An in situ of the influence of a sclerosing solution in rabbit medial collateral ligaments and its junction strength. *Connective Tissue Research.* 1983;2:95-102.

112. Jensen K, et al. Response of knee ligaments to Prolotherapy in a rat injury model. *American Journal of Sports Medicine.* 2008;36:1347-1357.

113. Klein R. Proliferant injections for low back pain: histologic changes of injected ligaments and objective measures of lumbar spine mobility before and after treatment. *Journal of Neurology, Orthopedic Medicine and Surgery.* 1989;10:141-144.

114. Harman R, et al. A retrospective review of 62 cases of suspensory ligament injury in sport horses treated with adipose-derived stem and regenerative cell therapy. *Proceedings of the Veterinarian Orthopedic Society*, 2006.

115. Dahlgren L. Use of adipose derived stem cells in tendon and ligament injuries. *American College of Veterinarian Surgery Symposium on Equine Small Animal Proceedings.* 2006;150-151.

116. Hackett G. Shearing injury to the sacroiliac joint. *Journal of the International College of Surgeons.* 1954;22:631-642.

117. Lee J, et al. Effects of intraarticular Prolotherapy on sacroiliac joint pain. *Korean Journal of Pain.* 2009;229-233.

118. Cusi M, et al. The use of Prolotherapy in the sacro-iliac joint. *British Journal of Sports Medicine.* 2010;44:100-104.

119. Hackett G. Back pain following trauma and disease-Prolotherapy. *Military Medicine.* 1961;July:517-525.

120. Hackett, G. Low back pain. *The British Journal of Physical Medicine.* 1956;19:25-35.

121. 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.

122. Centeno C, et al. Fluoroscopically guided cervical Prolotherapy for instability with blinded pre and post radiographic reading. *Pain Physician.* 2005;8:67-72.

123. Jo D, et al. The effects of Prolotherapy on shoulder pain. *Korean Journal of Anesthesiology.* 2004;46:589-592.

124. Hauser R, et al. Hackett-Hemwall dextrose Prolotherapy for unresolved elbow pain. *Practical Pain Management.* 2009;October:14-26.

125. Kim J. The effect of Prolotherapy for osteoarthritis of the knee. *Journal of the Korean Academy of Rehabilitation Medicine*. 2002;26:445-448.

126. Reeves K, et al. Randomized prospective double-blind placebo-controlled study of dextrose Prolotherapy for knee osteoarthritis with or without ACL laxity. *Alternative Therapies*. 2000;6:68-79.

127. Hakala R. Prolotherapy in the treatment of TMD. *The Journal of Craniomandibular Practice*. 2005;23:1-6.

128. Schultz L. A treatment of subluxation of the temporomandibular joint. *Journal of the American Medical Association*. September 25, 1937.

129. 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.

130. Hauser R, et al. *Prolo Your Sports Injuries Away!* Oak Park, Il: Beulah Land Press; 2001.

The Case for Prolotherapy – The Closing Argument

Julie R. Gunnigle, JD

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

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

PROLOTHERAPY AS A FIRST RESORT

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

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

THE VERDICT FOR PROLOTHERAPY

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

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

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

Organizations Who Support, Teach, and Promote Prolotherapy

American Association of Orthopedic Medicine (AAOM)
600 Pembrook Drive,
Woodland Park, CO 80863
Phone: 888.687.1920
Fax: 719.687.5184
www.aaomed.org

GetProlo.com
Beulah Land Corporation
715 Lake St. Suite 600
Oak Park, IL 60301
Phone: 708.848.5011
Fax: 708.848.8053
www.getprolo.com

The American Academy of Osteopathy
3500 DePauw Blvd, Suite 1080
Indianapolis, IN 46268
Phone: 317.879.1881
Fax: 317.879.0563
www.academyofosteopathy.org

American Academy of Musculo-Skeletal Medicine (AAMSM)
45 S. Dahlia St.
Denver, CO 80246
Phone: 303.270.9191
www.aamsm.com

Canadian Association of Orthopaedic Medicine
www.caom.ca/Prolo_page.html

The Hackett Hemwall Foundation
2532 Balden Street,
Madison, WI 53713 USA
www.HackettHemwall.org

The American Osteopathic Association of Prolotherapy Integrative Pain Management
(formerly College of Sclerotheraputic Pain Management)
303 S. Ingram Ct.
Middletown, DE 19709
Phone: 302.376.8080
Toll Free: 800.471.6114
Fax: 302.376.8081
www.acopms.com

American Osteopathic Academy of Sports Medicine (AOASM)
2810 Crossroads Drive, Suite 3800
Madison, WI 53718
Phone: 608.443.2477
Fax: 608.443.2474
www.aoasm.org

Florida Academy of Pain Management
PO Box 13489
St. Petersburg, FL 33733
Phone: 727.581.4319
Fax: 727.581.8537
www.fapmmed.net

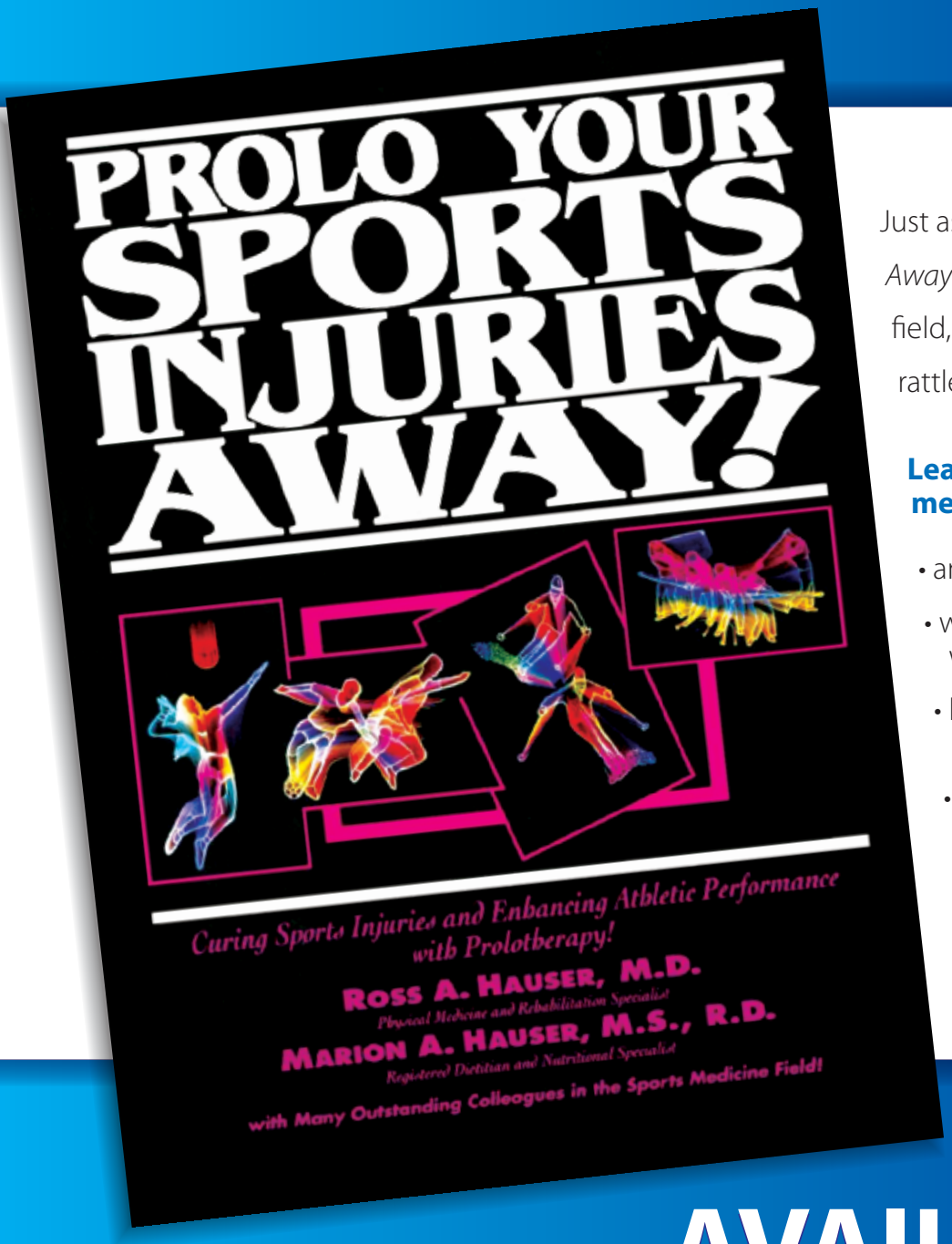
American Holistic Veterinary Medical Association
2218 Old Emmorton Road
Bel Air, MD 21015
Phone: 410.569.0795
Fax: 410.569.2346
www.ahvma.org

The International Veterinary Acupuncture Society
2625 Redwing Rd. Suite 160
Fort Collins, CO 80526
Phone: 970.266.0666
Fax: 970.266.0777
www.ivas.org

British Institute of Musculoskeletal Medicine
PO Box 1116
Bushey, WD23 9BY
Phone: 0208.421.9910
Fax: 0208.386.4183
www.bimm.org.uk

Australian Association of Musculoskeletal Medicine
Assoc Prof Michael Yelland
School of Medicine
Logan Campus, Griffith University
University Drive
Meadowbrook QLD 4131
AUSTRALIA
www.musmed.com/about.html

CURING SPORTS INJURIES
and Enhancing Athletic Performance
WITH PROLOTHERAPY



Just as the original book *Prolo Your Pain Away!* affected the pain management field, *Prolo Your Sports Injuries Away!* has rattled the sports world.

Learn the twenty myths of sports medicine including the myths of:

- anti-inflammatory medications
- why cortisone shots actually weaken tissue
- how ice, rest, & immobilization may actually hurt the athlete
- why the common practice of taping and bracing does not stabilize injured areas
- & why the arthroscope is one of athletes' worst nightmares!

AVAILABLE AT
www.amazon.com
www.beulahlandpress.com &

Doctors

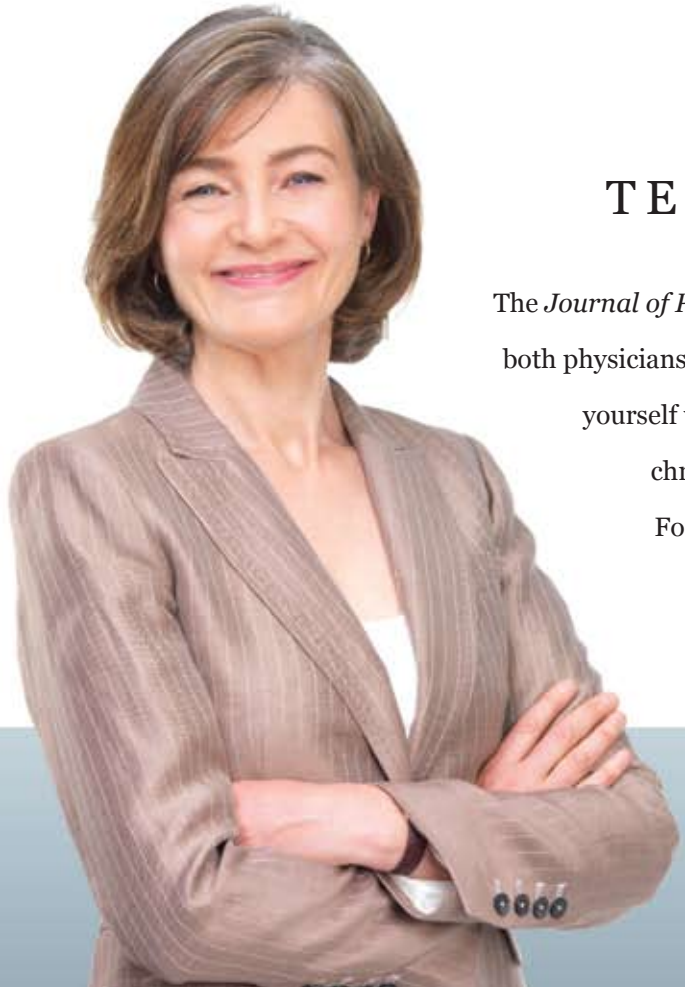
SHARE YOUR EXPERIENCE

Calling all Prolotherapists! Do you have a Prolotherapy article you would like published in the *Journal of Prolotherapy*? We would love to review it and help you share it with the world! For information, including submission guidelines, please log on to the authors' section of www.journalofprolotherapy.com.

[JOURNAL *of* PROLOTHERAPY.COM]
[708-848-5011]

Patients

TELL US YOUR STORIES



The *Journal of Prolotherapy* is unique in that it has a target audience of both physicians and patients. Help spread the word to other people like yourself who may benefit from learning about your struggle with chronic pain, and first-hand experience with Prolotherapy. For information on how to tell your story in the *Journal of Prolotherapy*, please log on to the contact section of www.journalofprolotherapy.com.

JOP
JOURNAL *of* PROLOTHERAPY

[*for Doctors & Patients*]