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

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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.

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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]

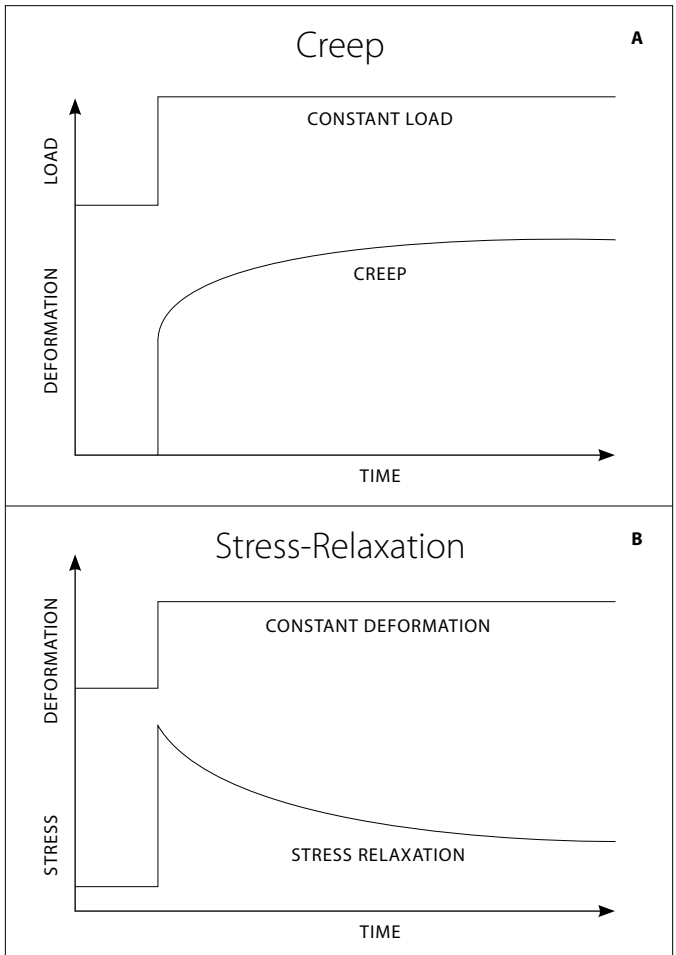

Figure 1. Ligaments, when subjected to a constant stress, display Creep (A) behavior—a time-dependent increase in strain. When ligaments are subjected to a long constant strain they exhibit a decrease in the stresses within the material known as stress-relaxation (B).

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.*)

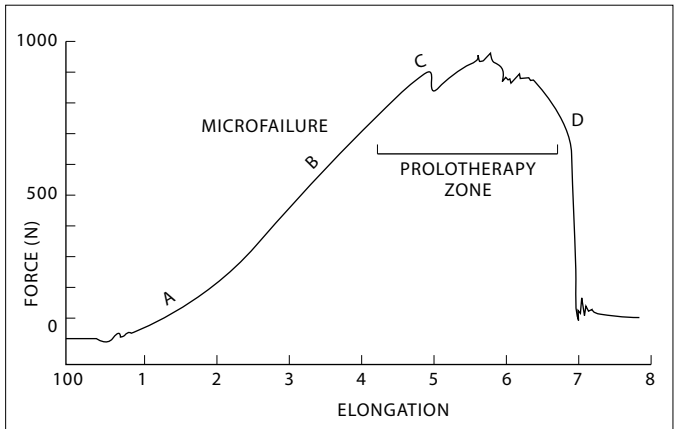

Figure 2. Stress-strain curve for ligaments and tendons. As additional force is applied to the ligaments up until point C, the ligament reverts back to its normal length, once the force is removed. If the force is continued past point C, the ligament is permanently elongated or stressed unless the athlete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

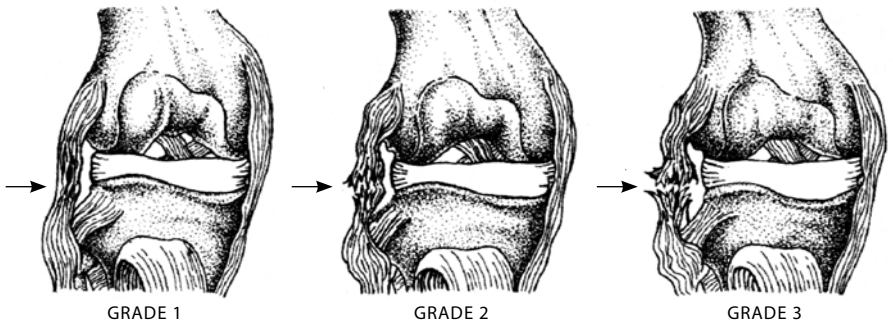

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Figure 3. Grading of ligament injury severity. Grade 1 and 2 ligament injuries are successfully treated with Prolotherapy. Grade 3 injuries, however, often need surgery.
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but enough are intact so 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.
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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]

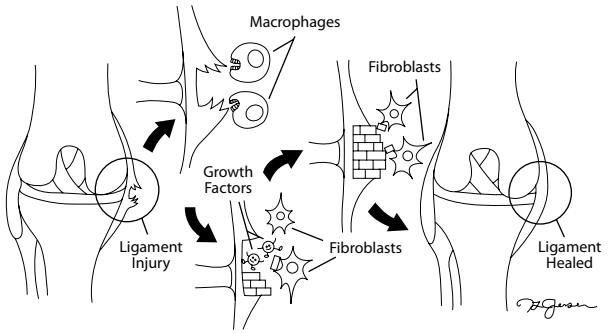
An ACL rupture increases anterior translation and rotational instability and leads to progressively worsening damage to the internal knee structures, including the meniscus and MCL. The most common treatment for an ACL tear is surgery. Conservative treatment can be successful in some patients, but most 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.

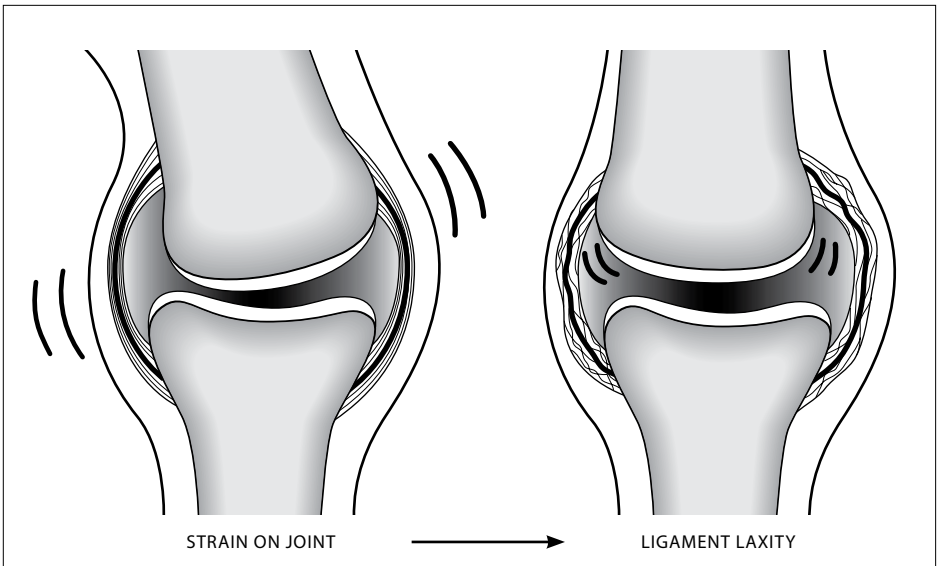


Figure 6. Ligament laxity can cause instability of the joint. The result is stretched ligaments and misaligned joints.

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

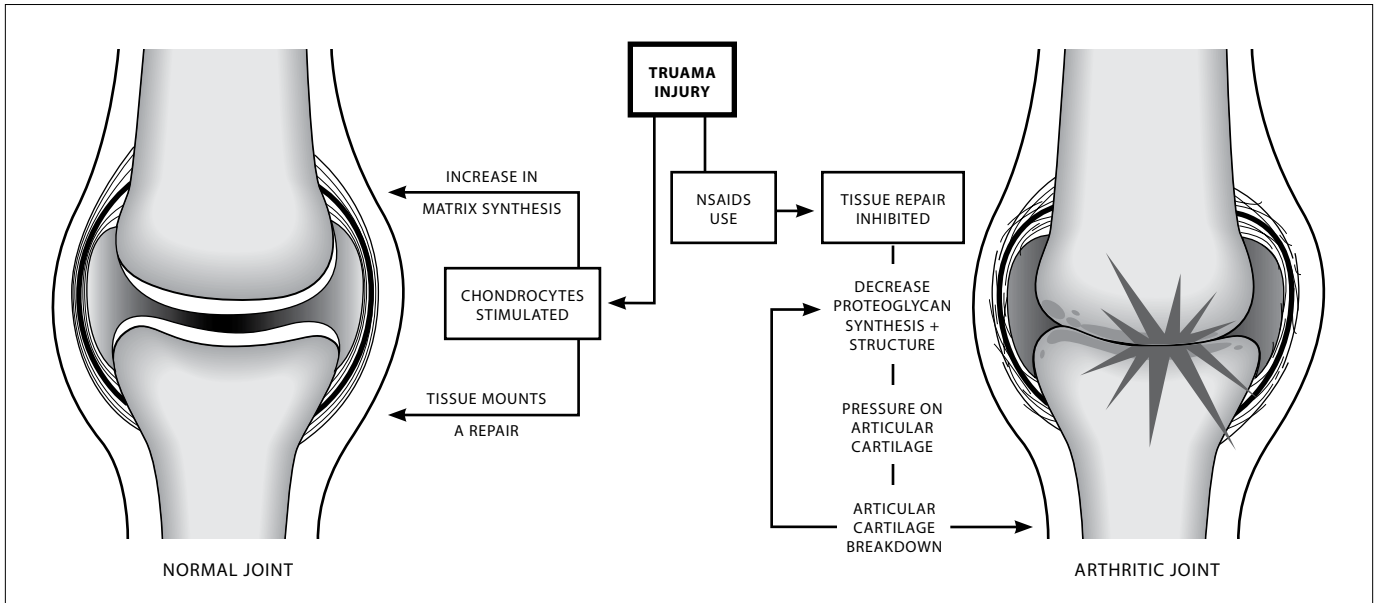


Figure 8. The pathogenesis of osteoarthritis accelerated by NSAIDs. NSAID use inhibits the body's repair processes, leading to decreased proteoglycan and extracellular matrix content and function, which ultimately leads to articular cartilage breakdown.

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]

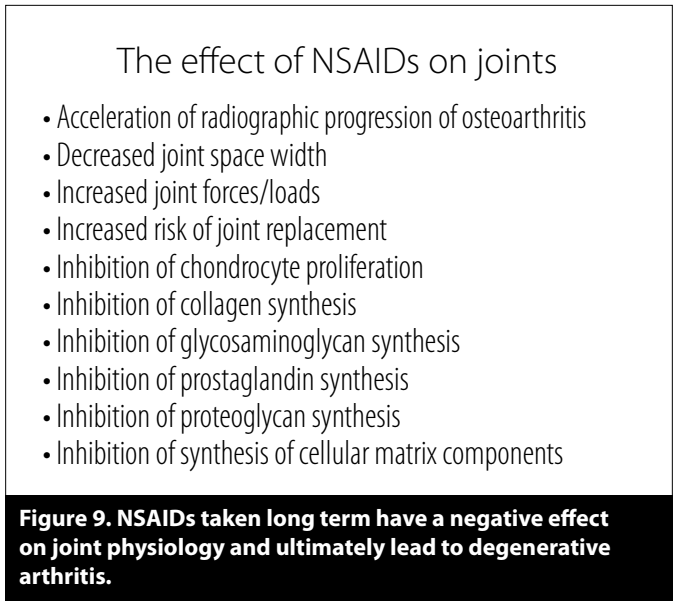


Figure 9. NSAIDs taken long term have a negative effect on joint physiology and ultimately lead to degenerative arthritis.

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.

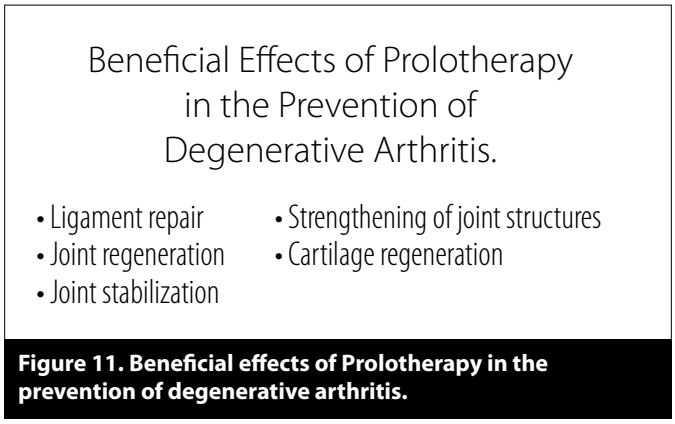


Figure 11. Beneficial effects of Prolotherapy in the prevention of degenerative arthritis.

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. ■

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