Ligament Injury and Healing: An Overview of Current Clinical Concepts

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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.

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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.

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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]

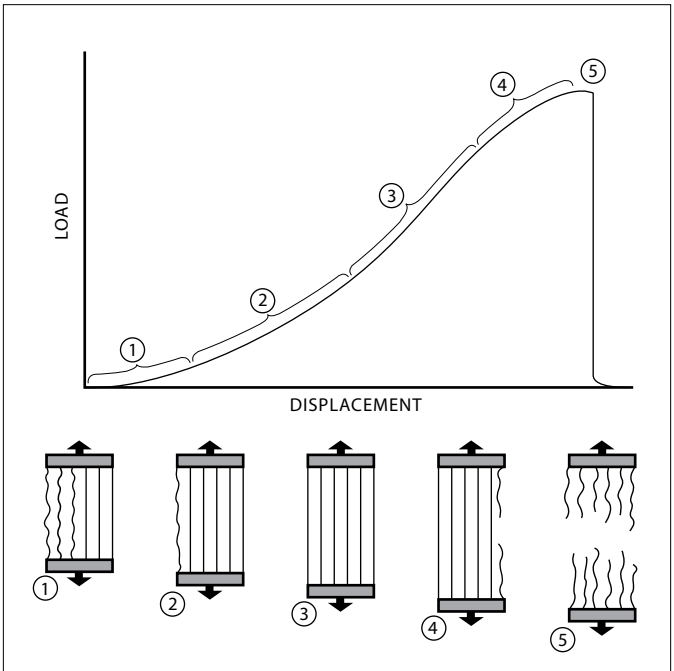

Figure 1. Ligament structural strength graph. As the load is increased, more ligament fibers are recruited (straight lines), and the slack or creep in the fibers is removed until the entire ligament tears. The load at complete failure of the ligament represents its maximum structural strength.

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]

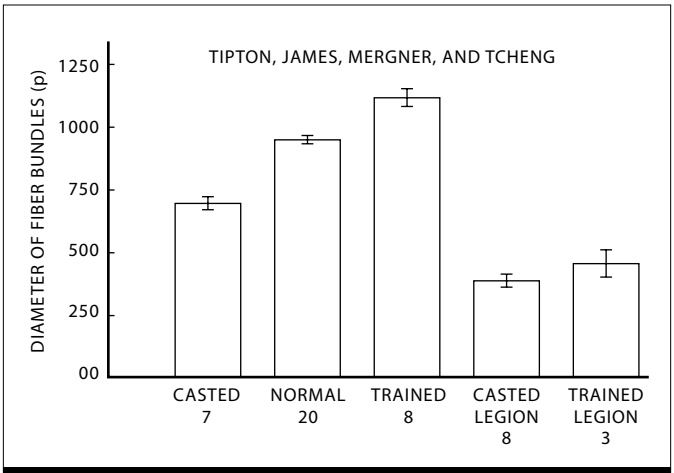

Figure 3. Ligament fiber bundle diameters. Ligament collagen fiber diameters are increased with exercise and diminished significantly when limbs are immobilized.

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. ■

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