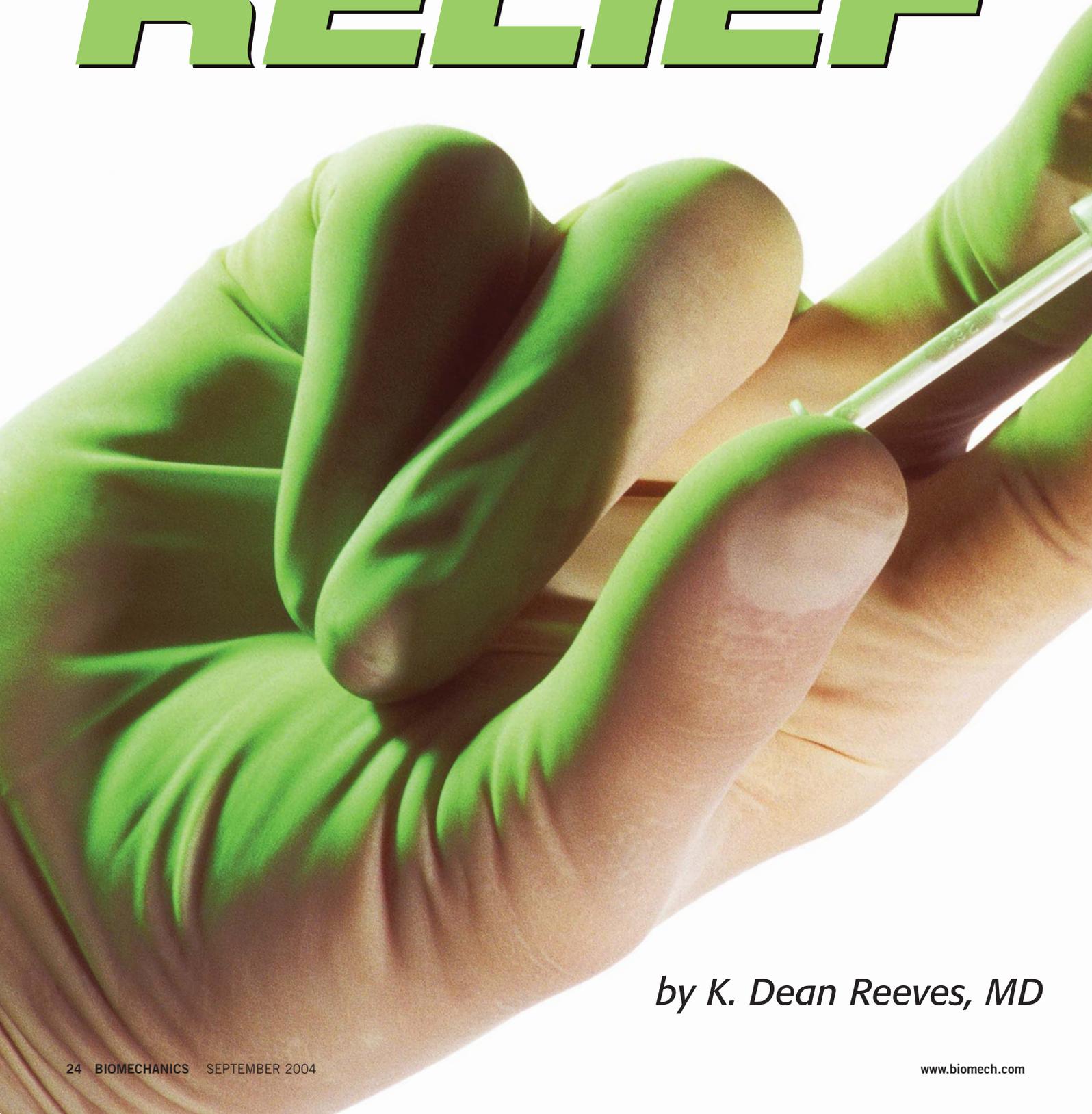
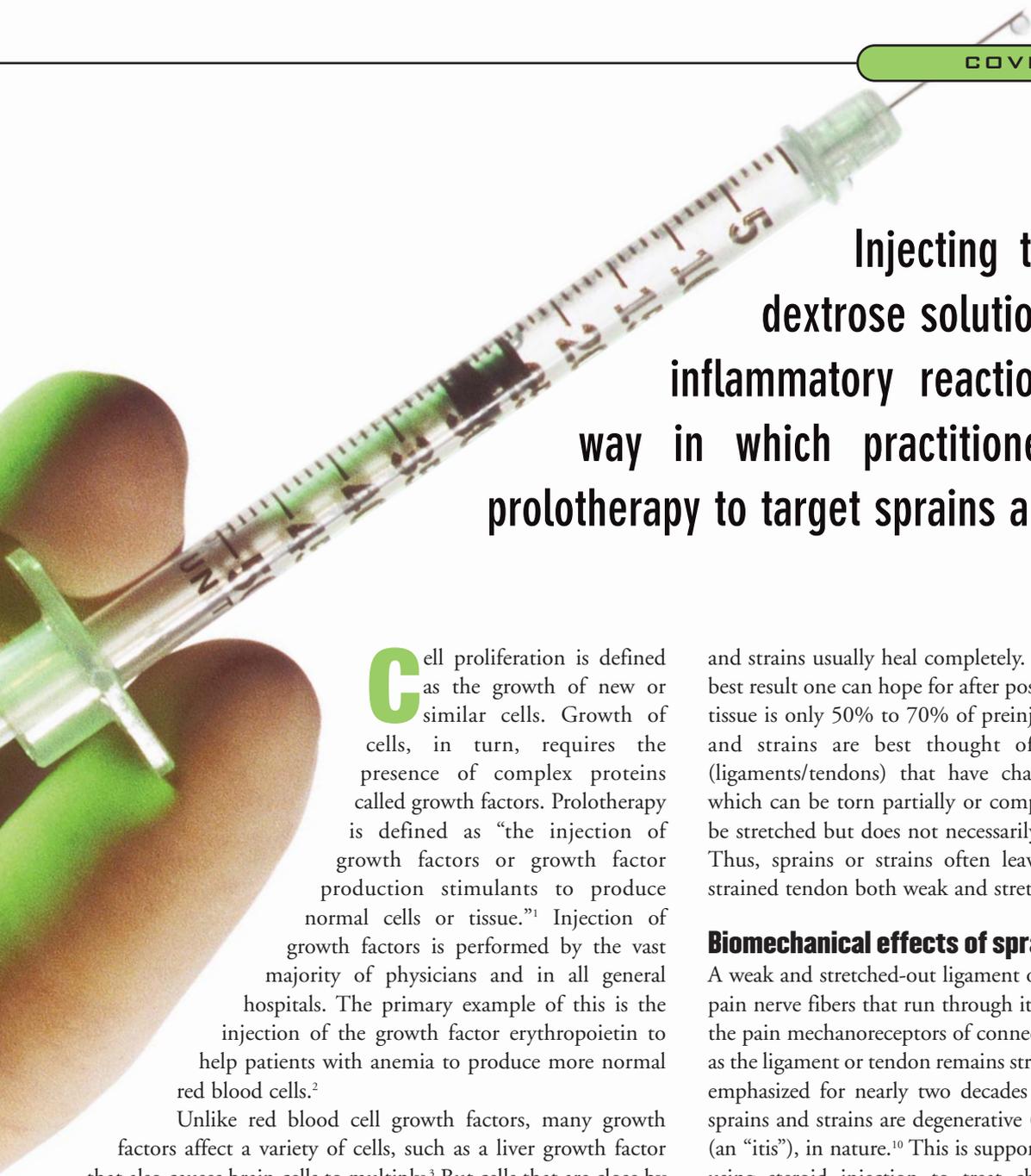


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by K. Dean Reeves, MD



Injecting tendons with a dextrose solution to trigger an inflammatory reaction is just one way in which practitioners are using prolotherapy to target sprains and strains

Cell proliferation is defined as the growth of new or similar cells. Growth of cells, in turn, requires the presence of complex proteins called growth factors. Prolotherapy is defined as “the injection of growth factors or growth factor production stimulants to produce normal cells or tissue.”¹ Injection of growth factors is performed by the vast majority of physicians and in all general hospitals. The primary example of this is the injection of the growth factor erythropoietin to help patients with anemia to produce more normal red blood cells.²

Unlike red blood cell growth factors, many growth factors affect a variety of cells, such as a liver growth factor that also causes brain cells to multiply.³ But cells that are close by and similar, even cells of different ligaments in the knee, respond differently to growth factors.⁴ Therefore, in researching the effects of growth factors, we need to remember that even similar structures can be unique in how they repair (which growth factors they need). In addition, it will be important to try a variety of growth factors in research, regardless of whether their “name” suggests they will be applicable.

Growth factor research is under way in many areas such as injecting growth factors in those with inadequate heart, brain or leg circulation to grow new blood vessels.⁵⁻⁷ However, of particular interest from a biomechanical perspective is the use of prolotherapy for the treatment of sprains, strains, and arthritis.

What is a sprain/strain?

In a sprain the damage is to a ligament, which connects one bone to another bone. In a strain the damage is to a tendon, a similar type of structure but one that connects muscle to bone. A commonly held misconception is that, with enough time, sprains

and strains usually heal completely. It has been reported that the best result one can hope for after postinjury healing of connective tissue is only 50% to 70% of preinjury tensile strength.⁸ Sprains and strains are best thought of as damage to structures (ligaments/tendons) that have characteristics of both a rope, which can be torn partially or completely, and putty, which can be stretched but does not necessarily return to its former length. Thus, sprains or strains often leave the sprained ligament or strained tendon both weak and stretched out.

Biomechanical effects of sprain/strain

A weak and stretched-out ligament or tendon can also stretch the pain nerve fibers that run through it. This type of malfunction in the pain mechanoreceptors of connective tissue can persist as long as the ligament or tendon remains stressed.⁹ Pathology experts have emphasized for nearly two decades that the changes in chronic sprains and strains are degenerative (an “osis”), not inflammatory (an “itis”), in nature.¹⁰ This is supported by reports of poor results using steroid injection to treat chronic sprains/strains, which suggest that the pain is coming not from inflammation¹¹ but rather when pain nerves are stimulated in weak or loose tissue.

Ligaments and tendons, when abnormal, can also cause referred pain and referred numbness.¹² Referred pain from ligaments and tendons can easily be misinterpreted as a disorder of the spinal nerves (radiculopathy). Although referred numbness is very common, the biomechanics of this is not clearly understood.

A metaphor for a failing ligament or tendon is a cartoon character dangling from a rope, with one fiber at a time giving way. When this happens, the part of the muscle connected with that “rope” fiber tightens reflexively, creating a taut band within the muscle. Reflex contractions, also called twitch contractions, occur by reflex in the muscle if the affected ligament or tendon is strummed like a guitar string.⁹ Reflexively taut bands and twitch contractions in muscles are characteristics of myofascial pain. This helps explain why methods of treating myofascial pain that address only muscle changes often lead to recurrent symptoms, since the ligament or tendon changes are not repaired.

In addition, ligaments are responsible for holding disks and bony spinal structures in position. When ligaments in the spine are abnormal or loose, this may cause “segmental dysfunction.” Practitioners who use manipulation to help restore back alignment are treating segmental dysfunction. The need for frequent realignment may suggest that looseness in a ligament or tendon is causing the segmental dysfunction.

The correlation between loose ligaments and arthritis was recognized when knee arthritis developed in humans who had had knee cartilage removed, particularly the medial meniscus. It is interesting to note that to create arthritis in a dog one need only sever the anterior cruciate ligament and three weeks later early changes of arthritis are already seen.¹³ Bone spurs are frequently a reaction of the body to compensate for a loose structure, with the spurs often growing in directions parallel to those of the inadequate ligament/tendon fibers. Typical x-ray findings for arthritis include bone spurs and loss of cartilage. Both are found in joints that are deprived of normal ligament support.

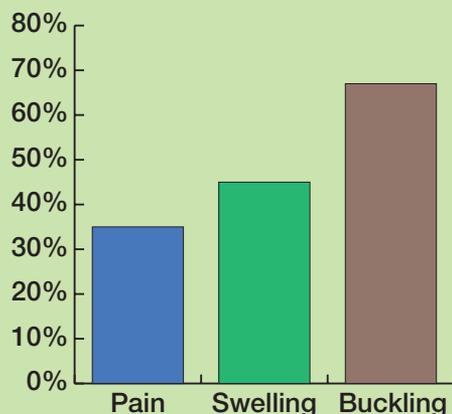
Chronic sprain/strain in the back is suspected of leading to reduced intervertebral disk support, excessive disk movement, and excessive pressure on the disk edges. This excess of disk pressure may be an important contributor to degenerative disk disease and disk herniation.

Chronic sprains and strains result in weak or loose structures that permanently stimulate pain fibers and cause myofascial pain and segmental dysfunction. This pathology predisposes a patient to arthritis and degenerative disk disease. It is clear that pain management approaches that do not correct the original sprain and strain will be limited in benefit.

Stages of healing and types of prolotherapy

After an acute injury, tendons and ligaments go through three stages of healing: inflammatory, proliferative, and remodeling.¹⁰ These stages are a response to the amount of cell damage that has

FIGURE 1. IMPROVEMENT IN KNEES TREATED WITH 10% DEXTROSE, RELATIVE TO PLACEBO GROUP



occurred. In chronic injury states or with microtrauma there is not enough new damage to cells for the body to stimulate its own repair. Thus wear and tear gradually accumulate without any repair until decompensation occurs. To begin proliferation, a practitioner may inject growth factors directly, inject a solution that produces growth factors without inflammation, or inject a solution that produces growth factors by starting a temporary inflammatory process that leads to growth (the way the body normally heals).

Injection of growth factors

To skip the inflammatory phase and begin proliferation, primary growth factors, either singly or in various combinations, may be used for injection. Blood is a source of already produced common growth factors such as insulin-like growth factor 1 (IGF-1), platelet-derived growth factor (PDGF), and transforming growth factor (TGF). Taylor et al demonstrated that even normal ligaments can grow stronger with exposure to injected blood. A single injection of 0.15 ml of blood into the patellar tendon of rabbits resulted in a significantly stronger tendon ($p < 0.014$) with microscopic examination showing completely normal cells.¹⁴ Injection of the patient's own blood has been studied for treatment of tennis elbow in humans by Edwards et al. In that study, average pain levels improved from 7.8 to 2.3 on a 10-point visual analog scale after just one injection of the patients' own blood. Also, 23 of 28 patients with chronic symptoms not responsive to all usual treatments had no pain with vigorous activity after one to three injections.¹⁵

Single or multiple growth factors can also be produced en masse in the laboratory by genetic means and then injected. Forslund demonstrated the potential of a single injection of a growth factor on ligament/tendon tissue when he injected chondrocyte-derived morphogenetic protein-1 (CDMP-1) into rats' Achilles-equivalent tendon within hours of injury. By eight days postinjection, CDMP-1 injected tendons were 39% stronger than noninjected tendons. ($P < 0.0002$).¹⁶ Direct injection of growth factors in human ligaments have not been reported to this point but studies are under way.

Thus far, cartilage repair through the use of growth factor injection has been reported only in animals. Young (maturing) rats developed a thicker knee cartilage when injected just once during knee development with bFGF (basic fibroblast growth factor).¹⁷ Also, full thickness holes (3 to 4 mm) in rabbit knee cartilage have been shown to heal after injection of HGF (hepatocyte growth factor).¹⁸

Injection without inflammation

Dextrose in concentrations greater than 10% causes a reliable temporary inflammatory process, as evidenced by the need to put IV lines into bigger veins for hospital patients receiving concentrated dextrose. However, if dextrose concentration is kept at 10% or less, the osmotic pressure on surrounding cells does not exceed the cells' ability to compensate and inflammation does not occur.

A normal human cell contains only 0.1% dextrose. Upon culturing human cells in glucose concentrations, it has been

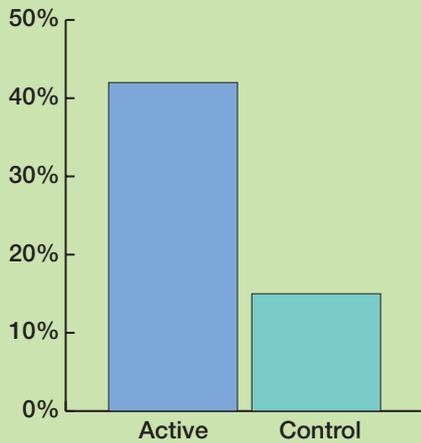
found that an environment with as little as 0.6% glucose causes virtually all the main growth factors for cartilage, ligament, and tendon—not bone—to elevate within minutes to hours.^{19,20} In addition to elevating growth factors for cartilage, some research

indicates that elevating dextrose concentration in a joint reduces cartilage-damaging protein (collagenase) levels.²¹

Why not just take dextrose orally? The stomach is designed to handle high dextrose loads without such growth reactions. Sustained high dextrose loads are not delivered to tissues except in patients with diabetes, for whom control of blood sugar is altered. It has been recognized that patients with diabetes develop extra blood vessels in their eyes, and extra cells in their kidneys and blood vessels. To bypass the stomach and place the dextrose in high concentration where it is therapeutically needed, injection is required.

Two double-blinded placebo-controlled clinical trials of 10% dextrose injection in arthritic joints have been conducted and involved both large and small human joints. One such study demonstrated that in 111 arthritic knees with a pretreatment average of only 2 mm of residual cartilage (35 knees had no residual cartilage in the medial compartment), small-needle injection of only 9 ml of 10% dextrose at zero, two, and four months led to improvements in pain and function significantly better than those achieved in the control group.¹⁹ Improvements in walking pain, swelling, and buckling are shown in Figure 1. In addition, range of motion in the dextrose-treated knees improved by 13.2°. A second double-blinded study involved injecting

FIGURE 2. GRIP PAIN IMPROVEMENT IN HANDS TREATED WITH 10% DEXTROSE VS PLACEBO



PROF PRODUCTS

moderate to severely arthritic fingers (150 joints in 27 patients). With injection of 0.5 ml of 10% dextrose in each joint at zero, two, and four months, subjects injected with dextrose demonstrated significantly better grip pain ($p = 0.027$) and flexion range of motion ($p = 0.003$) than control patients injected with the same bacteriostatic water/dilute lidocaine solution without dextrose (Figure 2).²⁰

Injection of a solution that produces inflammation

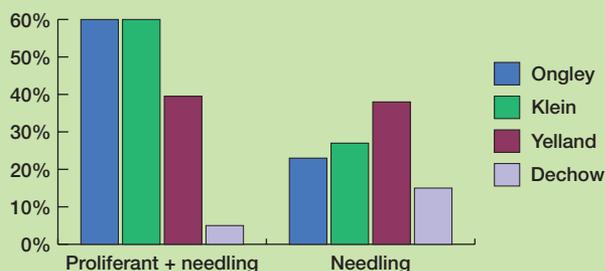
The use of nonsteroidal anti-inflammatory drugs has been popular for decades. However, the potential folly of preventing

natural inflammation after injury was pointed out by Elder, who demonstrated that administering anti-inflammatory medication after an acute injury to the medial collateral ligament of the knee in rats led to a 32% weaker ligament after healing.²² In contrast, nearly 20 years earlier, Liu in 1983 confirmed the ability of an inflammatory solution (sodium morrhuate) to thicken and strengthen normal medial collateral ligament in the rat and measured a 47% increase in medial collateral ligament mass after inflammatory solution injection.²³

Chronic inflammation interferes with healing, but temporary inflammation facilitates healing. Injecting relatively high (greater than 10%) concentrations of dextrose, or any of a variety of other solutions such as dilute phenol, causes temporary inflammation. Nearly 50 years ago Hackett demonstrated that temporary inflammation not only thickens ligaments and tendons, but it also creates a bigger connection to bone.¹² Hackett used an inflammatory solution called Synasol, which is not currently available.

Four double-blinded studies have been conducted to investigate inflammatory injection in chronic low back and leg pain (Figure 3). Unfortunately, the low back has a complicated ligament/tendon structure and proportionally complex referral patterns. These four studies were well blinded, but did not have a true placebo control, since needling itself would be expected to result in microbleeding with release of natural growth factors

FIGURE 3. PAIN REDUCTION IN PATIENTS WITH CHRONIC BACK PAIN



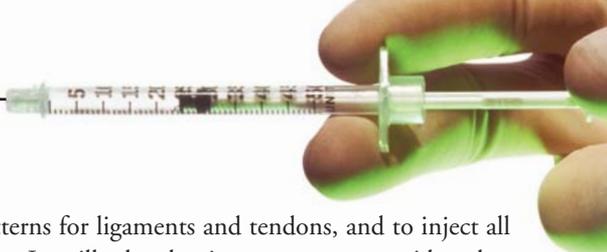
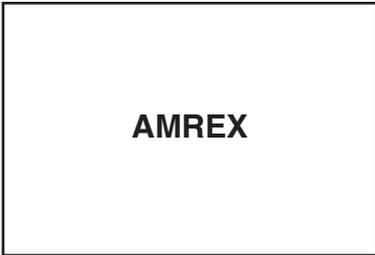
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from blood. Nevertheless, the two researchers who used complete injection for ligaments responsible for both back and leg pain found that including the inflammatory proliferant (phenol 1.25%, dextrose 12.5%, glycerine 12.5%) was significantly ($p < 0.001^{24}$) or nearly significantly ($p = 0.056^{25}$) better than needling alone. In each study, six- to 12-month follow-up revealed an impressive 60% sustained reduction in pain and a comparable reduction in disability ratings. Yelland²⁶ published a study showing sustainable benefit in both dextrose and control (saline) groups consistent with a therapeutic benefit from needling alone. However, his study was hampered by an incomplete injection method that did not introduce proliferant in key areas such as facet ligaments, multifidi, or, for the first four treatments, the deep SI ligament. Dechow²⁷ published strikingly different results, which in retrospect was largely because patients were selected by a rheumatologist who excluded patients with leg pain. Patients were then injected by a different physician who was instructed to inject only certain areas without being allowed to examine the patients. These areas were those that would refer leg pain, not primarily back pain; the treating physician used leg-pain specific injection for patients without leg pain.

These low back pain studies therefore suggest that it is critical for the injecting physician to examine the patient, be familiar

with referral patterns for ligaments and tendons, and to inject all sources of pain. It will also be important to consider that degenerative disks can themselves be sources of low back and leg pain. Indeed, Klein et al²⁵ reported on lumbar intervertebral disk injection with an inflammatory solution (glucosamine + chondroitin sulfate + dextrose + dimethyl sulfoxide) in patients whose pain was reproduced by disk injection (discogram). They found that 57% of patients improved markedly after disk injection, achieving 72% improvement in disability scores and 76% in pain scores. A positive discogram did not perfectly predict who would and would not respond, and further research is indicated. A study on simple dextrose injection for pain from disk origin is nearing completion at this time.

For sprain and strain to heal, tendons or ligaments need to both thicken and tighten, since they are both thinned and stretched when injured. To demonstrate the ability of simple dextrose injection to tighten loose ligament, a study was conducted on 16 consecutive patients with laxity of the ACL ligament as measured by a KT-1000 arthrometer.²⁸ Ten percent to 25% dextrose was used in this study, depending on patient tolerance. Injection of 6 to 9 ml of dextrose solution (depending on comfort level with injection) using an inferomedial approach was performed every two months for a year, and then on an as-

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needed basis for knee pain. Fourteen out of 16 patients had moderate to severe knee osteoarthritis at study onset in addition to measured ACL laxity. At three years post study commencement, patients on average experienced a 44% improvement in pain, a 64% improvement in swelling, and a 72% improvement in looseness (KT1000 side-to-side difference) (Figure 4). Rather than losing range of motion over time, these patients experienced an average improvement in flexion range of motion of 10.5°. For a condition typically associated with declining function, (either moderate to severe osteoarthritis or ACL laxity), these results are encouraging.

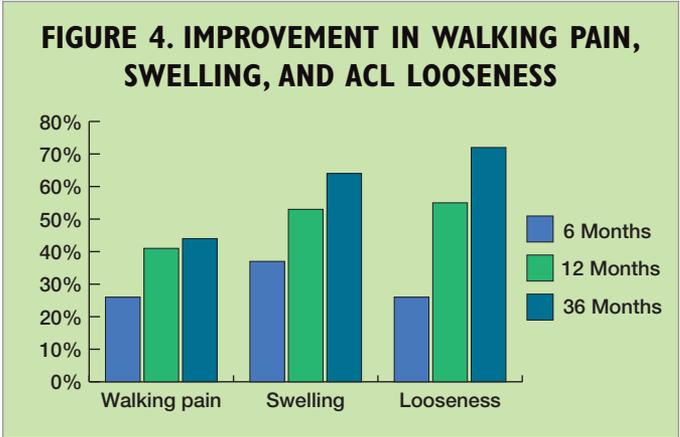
The future of prolotherapy

Applications for prolotherapy are as broad as the diagnosis of “osis” or degenerative change in either connective tissue or cartilage. Common conditions that have responded quite successfully to prolotherapy empirically and merit further study include: temporomandibular joint disorder, shoulder laxity, bicipital tendinosis, medial and lateral epicondylitis, sprained wrist (pseudo-DeQuervain’s), osteoarthritis of the knee and finger, gluteal and trochanteric tendinosis, distal hamstring tendinosis, knee laxity, Achilles tendinosis, chronic ankle sprain, plantar fasciitis, metatarsalgia, costochondritis, osteitis pubis, thigh adductor strain, and pelvic floor sprain/strain. Chronic neck and upper and lower back pain respond as well but are much more difficult to study with consistency between investigators.

Another way to obtain objective and reproducible evidence of healing ligament and tendon is via new-generation ultrasound. These machines provide a detailed view of connective tissue and show defects associated with tendinosis and ligamentosis.

The future of prolotherapy in treating athletes is expected to be in the use of non-inflammatory solutions during the sports season to enhance speed and degree of repair from injuries, and as-needed treatment of injuries off-season with stronger solutions for further repair. The chronic pain that so many athletes expect to endure should be substantially reduced with prolotherapy. A study of elite rugby players that was just accepted for publication is representative of the potential impact of proliferant injection in the athlete.²⁹ The subjects of this consecutive-patient study were

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primarily members of the Rosario, Argentina, rugby team. This is the premiere city team in Argentina and supplies athletes for the Argentinian national rugby team. All subjects had groin and abdominal muscle strain for an average of 15 months that was unresponsive to all usual therapeutic approaches. None of these athletes could play at high level and all had pain even with self-care. After an average of 2.8 sessions of dextrose injection into thigh and abdominal muscle attachments, 20 of the 24 athletes were completely pain-free and 22 had returned to unrestricted high-level play. 

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References are available at www.biomech.com.

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