TREATMENT OF LOW BACK PAIN

WITH REGENERATIVE INJECTION THERAPY (RIT)

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INTRODUCTION

During the last ten years, modulation became a common word among physicians engaged in the practice of chronic pain. Chemomodulation of collagen for treatment of chronic musculoskeletal pain was introduced in 1937 by Drs. Schultz and Gedney. [1,2] Ever since, an enthusiastic group of their followers has been practicing this methodology known as prolotherapy or sclerotherapy and, more recently, as Regenerative Injection Therapy (RIT). [3-49] In reality, Regenerative Injection Therapy is more accurate terminology because it reflects the regenerative/reparative healing process that takes place after injury. The reasoning behind the terminology will be discussed further in this chapter.

Chemomodulation of skin collagen (chemical peels) preceded thermomodulation with lasers for regenerative purposes. Plastic surgeons and dermatologists currently employ both modalities. Thermomodulation of collagen has been known since time of Hippocrates, who employed “hot slender irons” to stabilize the shoulder capsule in recurrent painful dislocations. It is currently recognized that sufficient thermomodulation of collagen can be achieved with lower temperatures to stimulate a proliferative and regenerative/reparative response.

Recently, the orthopaedic community re-invented thermocapsulorrhaphy and the use of thermal treatment in hip arthroscopy, unstable knees, ankles, epicondyles at the elbow, and articular cartilage regeneration. Pain-treating physicians utilize IDET procedures for intradiscal pathology and thermomodulation of collagen whereas radiofrequency procedures are used for neuromodulation.

Case reports, retrospective, prospective, and double blind placebo controlled studies have clearly indicated RIT’s effectiveness in treating chronic musculoskeletal pain arising from post-

traumatic and degenerative changes in connective tissue such as ligaments, tendons, fascia and intervertebral discs. [1-74]

Moreover, animal experiments and human electron microscopic studies have demonstrated that the newly formed connective tissue had structural and biomechanical properties similar to those of normal ligaments and tendons. [1,7-9, 54, 75, 76]

Preliminary results of a clinical prospective trial for chemonucleoannuloplasty with proliferation-causing substances are promising. [66,70-73] We are witnessing the resurgence of annuloplasty performed and promoted in the early 1950s by Gedney. [26, 27, 29] The future is interesting and intriguing if, indeed, we will be able to reverse degenerative changes, abolish pain, and restore functional abilities of chronic pain sufferers.

PURPOSE

The purpose of this chapter is to provide physicians involved in interventional pain treatment with a review of the pertinent literature, clinical and anatomic considerations in relation to regenerative injection therapy for chronic low back pain arising from connective tissue.

Structurally and biomechanically, connective tissues represent a heterogenous group with variations in collagen orientation, cross linking, shape and cell properties. [77-85]

A multitude of dysfunctional and painful syndromes may arise from pathological conditions of connective tissue. Low back pain due to pathology of degenerative or post-traumatic changes in the discs, ligaments, tendons, fasciae, facet joint capsular ligaments or sacroiliac ligaments is often difficult to differentiate based solely on clinical presentation. Left untreated, post-traumatic and overuse injuries of ligaments and tendons can linger indefinitely, eventually leading to degenerative changes, loss of function, deconditioning and chronic pain. The belief that most sprains and strains

are capable of self-repair in 6-8 weeks is belied by the pathological findings. (**56,** 79, 82-85)

Regenerative Injection Therapy (RIT), aka prolotherapy or sclerotherapy, is a less known but long practiced interventional regenerative modality(**3-5**) that was originally described by to treat hydrocele with injections of saltpeter. (86-87) RIT's current technique addresses connective tissues with diagnostic local anesthetic blocks followed by injection of solutions that chemically stimulate regenerative reparative process in injured tissues.

TERMINOLOGY IN LIGHT OF CURRENT SCIENTIFIC UNDERSTANDING

Biegelesen introduced the term "sclerotherapy" in 1936, "sclero," as in Greek "skleros," meaning hard. (45) Thinking sclerotherapy implied scar formation and hardening, Hackett coined the term "prolotherapy" and defined it as "rehabilitation of an incompetent structure by the generation of new cellular tissue."(9) The Latin word 'proli' means offspring. To proliferate is to produce new cells in rapid succession. However, unsuppressed proliferation is an integral factor of malignant growth.

With contemporary understanding of the healing process, RIT is the preferred term because it is recognized that regeneration extends beyond the proliferative stage. On a cellular level RIT is chemomodulation of collagen through repetitive stimulation of inflammatory and proliferative phases in a sophisticated process of tissue regeneration and repair, mediated by numerous growth factors leading to restoration of tensile strength, elasticity, increased mass and load-bearing capacity of connective tissue.(**54-56,** 75, 76, 84) RIT is a type-specific treatment for degenerative, chronic, painful conditions such as enthesopathy, tendinosis, and ligament laxity. (**54-56,** 88, 89)

DIAGNOSIS OF LOCAL AND REFERRAL PAIN WITH INJECTIONS

In the early 30s, Leriche described procaine injections at fibroosseous insertions to diagnose and treat injuries of the ankles.[90] Subsequently, diagnosis of shoulder pain with procaine was described by Haldeman. A few years later, Haldeman and Soto-Hall reported on diagnosis and treatment of painful sacroiliac dysfunctions. Infiltrating posterior sacroiliac, interspinous ligaments at L4-5 and L5-S1, and zygapophyseal joint capsules, they produced marked relaxation of spastic musculature and established routine manipulation of sacroiliac joints under local anesthesia. [91]

In 1938 Steindler and Luck outlined current approaches to diagnosis of low back pain based on local anesthetic injections. They emphasized that posterior divisions of spinal nerves provide sensory supply to musculature, tendons and ligaments (supraspinous, interspinous, iliolumbar, sacroiliac, sacrotuberous and sacrospinous), as well as origins and insertions of aponeurosis of tensor fascia lata, gluteal muscles and thoracolumbar fascia. It was established that no definite diagnosis could be made based on clinical presentation alone and postulated that five criteria should be met to prove a causal relationship between structure and pain. See Table I. [92]

TABLE I. Radiating/referral pain postulates

1. **“Contact with the needle must aggravate the local pain.**
2. **Contact with the needle must aggravate or elicit the radiation of pain**
3. **Procaine infiltration must suppress local tenderness.**
4. **Procaine infiltration must suppress radiation of pain.**
5. **Positive leg signs must disappear."**

In 1939, Kellgren published maps of referral pain from deep somatic structures, including interspinous ligaments. The data was derived from injecting volunteer medical students with hypertonic saline and implicated interspinous ligaments as a significant source of local and referred pain. [93] In 1944, Campbell and Parsons reported on referral pain from upper cervical segments utilizing Kellgren's technique. That same year, Inman and Saunders reported on experimentally induced referred pain from skeletal structures, introducing the concept of "sclerotomes." [94, 95]

Subsequently, in 1948, Hirsh demonstrated that intradiscal injection of procaine provided relief from sciatica. [96]

By 1954, Feinstein and Langton carried out a systematic study of referred pain patterns from midline musculotendinous tissue of the spine obtained by injections of hypertonic saline. They also produced maps of referred pain resembling those published by Kellgren. [93, 97] A few years later, Hackett published maps of referral pain patterns from fibro-osseous attachments of ligaments and tendons of low back, thoracic and cervical areas that corresponded with those of Kellgren and Feinstein but remained largely unknown to the medical community. [8, 9, 11, 15, 22]

(Figures 1 and 2)

Lumbar facet syndrome slowly gained acceptance as a distinct clinical entity after Mooney's publication in 1976. [98]

By 1994, Dussalt and Kaplan produced maps of referral pain from cervical and lumbar zygapophyseal joints obtained with fluoroscopically guided techniques that were similar to Hackett's maps. [99]

Recently, Fortin rediscovered Hackett's sign that pressure over the posterior superior iliac

spine (PSIS) is pathognomonic for sacroiliac joint pain. He produced maps of sacroiliac joint pain referral patterns similar to those of Hackett. [8. 9. 11, 22, 100-102] The size of this publication prohibits reproduction of all these maps for comparison.

Currently, local anesthetic diagnostic blocks are the most reliable and acceptable way to confirm the precise structural source of pain and clinical diagnosis. [103-107]

EVOLUTION OF RIT

The scientific rationale for RIT in chronic pain from ligaments and tendons evolved from injection treatment of hernias. The therapeutic action of injected solutions in hernias was proliferative/regenerative/reparative response that led to fibrotic closure of the defect by newly formed connective tissue.[108-110]

In 1935, Schultz conceived the idea that strengthening the temporomandibular (TMJ) capsule by induced ligament fibrosis may lead to capsular contraction, thus preventing subluxations. *[Photo with caption: "Louis W. Schultz, M.D., D.D.S. (1894-1975)"]* Following animal experiments with Sylnasol (discontinued in the 1960s), he conducted a prospective clinical study of thirty humans with bi-weekly injections of TMJs and reported "entire patient satisfaction." Schultz concluded that the principle of induced hypertrophy of the articular capsule by injecting a fibrosing agent might be applied to other joints capable of subluxations or recurrent dislocations. [1]

In 1937, Gedney reported several successful cases cured with intraligamentous injections of sclerosants for unstable painful sacroiliac and knee joints. [2] *[Photo with caption: "Earl Gedney, D.O. (1901-1976)"]*

In 1945 Bahme published the first retrospective study of one-hundred patients injected an

average of five times with Sylnasol into the posterior sacroiliac ligaments. Eighty percent reported complete resolution of pain. Describing significant co-existence of painful subluxed ribs with hypermobile sacroiliac joints, Bahme explained the phenomenon by concomitant functional scoliosis. [59]

By 1944 Lindblom demonstrated radial annular fissures by cadaveric discography, later describing nucleographic patterns of fifteen discs in thirteen patients.[111] This prompted Gedney and then Shuman to explore therapeutic application of sclerosants for pain related to intervertebral disc (IVD) pathology. Thus, in 1951, Gedney reported Sylnasol injections into the lateral annulus of the lumbar disc for painful degenerative lumbar disc syndromes.[26] By 1954, he reported a 50% pain reduction after treatment of the L4 disc alone.[27] While treating painful hypermobile sacroiliac joints, Gedney emphasized that the amount of solution and the quantity of treatments were highly individual and depended on patient response.[28] In a retrospective study he pointed out the significant statistical coexistence of sacroiliac joint pain and hypermobility with disk pathology at L3, L4 and L5 levels.[29] Also by 1954 Gedney completed a prospective study of one-hundred patients, sixty-five were treated initially with disc injections and thirty-five initially treated with posterior sacroiliac ligament injections. The latter group required fewer intradiscal injections. Therefore he concluded that, in the presence of sacroiliac pain and hypermobility, adequate stabilization of the sacroiliac joint should be achieved in all cases prior to addressing discogenic pain. [29] Gedney stressed the importance of interspinous and iliolumbar ligament injections in treating lumbar spondylolisthesis.**[30]**

Simultaneously in 1954 Shuman evaluated the effectiveness of sclerosant injections for pain from the sacroiliac joints, intervertebral discs, zygapophyseal joint capsules, knees, shoulders and spondylolisthesis in ninety-three respondents to a retrospective survey.

Improvements ranged from 75-98%. [31] He later detailed aspects of treatment integrating manipulative techniques, including manipulation under local anesthesia (introduced earlier by Haldeman and Soto-Hall). Shuman stated that zygapophyseal joint pathology, emphasized by Hackett in 1956, and disc pathology were the more common causes of lower back pain than the sacroiliac joint pathology. [50] [Photo with caption "David Shuman, D.O. (1910 – 1982)]

The largest contribution to the field of prolotherapy was made by George Stuart Hackett. *[Photo with caption: "George S. Hackett, M.D. (1888-1969)"]* who presumed in 1939 that spinal ligaments were responsible for the majority of back pain and by 1956 was able to prove his point.[8] By 1958 he added that tendons at fibro-osseous junctions were another significant source of chronic pain syndromes. [9] Eighty-four patients with sacroiliac ligament pain were treated five to seven times with Sylnasol injections; 82% were symptom-free for six to fourteen years.[6, 8, 9] In initial animal experiments he demonstrated 30-40% increase in tendon size, after Sylnasol injections. [7] **(Figures 3 and 4)** Also, his experimental study indicated hypertrophy induced by proliferation of connective tissue in linear fashion.**[8]** Referred pain maps from ligaments and tendons of lumbar and lumbopelvic regions were derived from carefully recorded observations of 7,000 injections in over 1,000 patients over a period of seventeen years. Pain was reproduced by "needling" and was abolished by local anesthetic infiltration prior to proliferant injections[8.9] **(Figures 1 and 2)** Hackett later pointed out that loose-jointed individuals, i.e. those with congenital ligament laxity, had a positive response to prolotherapy despite the fact that they had a diminished ability to recuperate from sprains and a predisposition to chronic lingering pain. [8-16]

Several of his later publications emphasized the common pathogenesis of impaired local circulation in chronic conditions such as neuritis, headaches, whiplash, osteoporosis, bone

dystrophy, bronchospasm and arteriosclerosis. Excess of antidromic, sympathetic and axon reflex stimulation caused local vasodilatation and edema with a perpetuating vicious cycle, of "tendon relaxation," now understood as degenerative changes such as enthesopathy, tendinosis, and laxity. (14-21)

By 1961 Blasche reported the first prospective study of forty-two patients treated with prolotherapy for lower back pain. Thirty-two were workmans compensation cases; ten had private insurance. Twenty patients observed for three years achieved complete recovery. Thirteen patients reported no change; nine had surgery. Four patients treated with prolotherapy for acute herniated disc had better results than any patients in this study. In three instances during surgery, specimens obtained from injection sites demonstrated "normal fibrous tissue."**(38)**

Hackett's technique was accepted as a standard of care in the legal community when California court ruled in 1967 that a physician is permitted to follow a method or a form of treatment followed by the minority of physicians if he is reputable and of good standing. But if he varies from the minority method, he is in violation as if he deviated from the generally accepted method. The court “concluded as a matter of law that prolotherapy as a method of treatment cannot be said to be an inappropriate mothod of treatment, or to be malpractice even though it has not been accepted as a proper method of treatment by the medical profession generally." (39)

Positive results with Hackett's method were obtained abroad by Ongley, Barbor, Cyriax and Coplans.(40, 41, 46-48) Barbor treated 153 patients who had back pain up to twenty years’ duration. 74% reported satisfactory relief. 11% failed to improve. 16% were lost for follow up. 23% required periodic booster injection for relief. The study utilized a mixture of 2cc Dextrose/Phenol/Glycerine (DPG) and 3cc of local anesthetic. (40)

Cyriax detailed "sclerosant injections" to interspinous and facet joint capsular ligaments of the thoracic and lumbar areas in multiple publications. [46-48]

Leedy reported a 70% improvement following sclerosant injections for low back pain in a 1976 retrospective study. [42] Comparing prolotherapy and acupuncture in the treatment of chronic musculoskeletal pain, Vanderschot concluded that prolotherapy had a faster onset of action and longer lasting pain relief. [112]

By 1978, Chase and Koudele reported up to 70% or better improvement in long-standing cases of painful low back syndromes after sclerosant injections.[43, 44] Koudele also documented findings of Haws and Willman on histologic changes in human connective tissue after sclerotherapy. Biopsies were obtained after patients were treated up to five times with different injectables for low back pain. DPG solution produced early coagulation necrosis, followed by early collagen formation. By six months, a small zone of residual inflammatory cells were observed in an area of dense collagen. In two other specimens treated with DPG, dense collagen with fibrosis, occluded blood vessels and a dense whirl of scar were observed. After injection of pumice suspension, an area of dense collagen and fibrosis surrounding a "lake" of pumice was documented, without a foreign body reaction but with a capsule formation. [44]

Hirshberg published an open prospective trial of sixteen patients with iliolumbar syndrome in 1982. 85% of those treated with 25% Dextrose/Xylocaine solution had complete resolution of pain versus 44% treated with Xylocaine alone. **[60]**

A double blind study of rabbits by Liu in 1983 demonstrated that repeated injections of 5% sodium morrhuate at the fibro-osseous attachments (enthesis) significantly increased bone-ligament-bone junction strength by 28%, ligament mass by 44% and thickness by 27%. [75] By 1985 Maynard reported decreased collagen fibrils and hydroxyproline content and increased

tendon mass in experimental animals injected with sodium morrhuate. The average tendon circumference increased up to 25%. [76]

In a 1987 double-blind randomized study of chronic low back pain, Ongley, Klein and Dorman demonstrated better than 50% improvement in patients injected with a DPG solution versus saline.[53] Bourdeau in 1988 published a five-year retrospective survey of forty-three patients with low back pain treated with prolotherapy. 70% reported "very good" to "excellent" results. [62]

Regeneration and proliferation of human ligaments in response to injections of DPG solution were demonstrated with light and electron microscopy of the pre- and post-injection byopsied tissue. Decreased pain, increased strength and range of motion in the same patients was documented by computerized (Isotechnologies B200) objective testing and published by Klein, Dorman and Johnson in 1989. [54]

By 1991 Schwartz and Sagedy documented a retrospective study of forty-three patients with chronic sacroiliac strain who received three series of proliferant injections at bi-weekly intervals. Improvement was achieved by all but three patients, and ranged from 95% reported by 20 patients to 66% reported by 4 patients. The conclusion was that there is induced proliferation of collagen and dense connective tissue of the ligament is associated with reduction of painful subluxations.[113]

Klein and Eek in 1993 published a double-blind clinical trial of seventy-nine patients with a history of chronic low back pain who did not respond to previous conservative therapy. Subjects were randomly assigned to receive a series of six injections in a double-blind fashion at weekly intervals of either lidocaine/saline or lidocaine/DPG solution into the posterior sacroiliac and interspinous ligaments, fascia, and facet capsules of the low back from L4 to the sacrum. Of

the thirty-nine patients randomly assigned to the proliferant group, thirty had 50% less pain or disability at six months compared to twenty-one of forty in the lidocaine group. Improvements in visual analog, disability, and pain grid scores were greater in the proliferant group. (65)

In 1993 Massie and Mooney informed the medical community that it was possible to stimulate fibroplasia in the intervertebral discs with proliferant injections.(65) Mooney advocated proliferant injections by skilled physicians for chronic painful recurrent sacroiliac sprains. (67, 68)

Matthews reported significant improvement in painful osteoarthritic knees after injection of the ipsilateral sacroiliac ligaments with proliferant solutions in 1995. (69) Also in 1995 Reeves emphasized that enthesopathy may be painful, and that prolotherapy with 12% Dextrose/Xylocaine solution is a type-specific treatment.(55) In 1996 Eek presented preliminary beneficial results of intradiscal proliferant injections for low back pain. (70) In 1997 Klein and Eek published a review article on prolotherapy for low back pain with a technique description. (56)

In 2000, Reeves proved that it is possible to achieve pain reduction and stabilization of the knees with sub-inflammatory concentrations of Dextrose proliferant (74) . The history of RIT from the 1930s to 1950s and from the 1960s to 1980s was reviewed in April of 2000 and 2001 respectively.(4, 5) In February, April and June 2001, Kline and Eek respectively reported on chemomodulation of degenerated chemically sensitive discs. More than forty patients are currently enrolled in their prospective trial. Preliminary results with intradiscal injections are promising. (71-73)

INFLAMMATORY-REGENERATIVE/REPARATIVE RESPONSE

AND DEGENERATIVE PATHWAYS

Inflammatory response is an integral part of the regenerative, reparative process. Inflammatory reaction induced in connective tissue may lead to two distinct repair pathways. The first is regeneration that replaces injured cells with identical cells; the second is fibrosis or replacement of injured cells by fibrous connective tissue. Often a combination of both processes contributes to the repair. Initially in both processes a similar pathway takes place with migration of fibroblasts, proliferation, differentiation and cell-matrix interaction. The latter, together with basement membrane, provides a scaffold for regeneration of pre-existing structures. (78) "...[M]odulation of these cell matrix responses, regardless of the method, provides an intriguing challenge." (83) Cell replication is controlled by chemical and growth factors. Chemical factors may stimulate or inhibit proliferation. Growth factors such as cytokines/chemokines, TGF-ß1 (transforming growth factor ß1), PDGF (platelet derived growth factor), FGF (fibroblast growth factor), VEGF (vascular endothelial growth factor), IGF (insulin-like growth factor), CTF (connective tissue growth factor) and NGF (nerve growth factor) stimulate proliferation. Regenerative potential depends on cell type, genetic information and the size of the defect. Fibrotic healing takes place in the presence of a large, connective tissue defect.(78, 82-84)

Under the best circumstances natural healing may restore connective tissue to its preinjury length but only 50%-75% of its preinjury tensile strength. (55, 82, 83) Connective tissues are bradytropic (i.e., their reparative capability is slower than that of muscle or bone). In the presence of repetitive microtrauma, unjudicious use of NSAIDs and steroid medications, tissue hypoxia, metabolic abnormalities and other less defined causes, connective tissue may divert towards degenerative pathway. (55, 78, 79, 83, 84) ..." A judicious utilization of anti-inflammatory therapy remains useful, albeit adjunctive therapy..." (114) Biopsies from chronic painful locuses

demonstrate disorganized collagen, excessive matrix, insufficient elastin, disorganized mesenchymal cells, vascular buds with incomplete lumen, few or absent white blood cells, neovasculogenesis and neoneurogenesis. [79, 82, 85] Degenerative changes in tendons may be hypoxic, mucoid, mixoid, hyaline, calcific, fibrinoid, fatty, fibrocartilaginous, or any combination of the above. [79, 83, 85]

Degenerative changes found in fibromyalgia syndrome were similar to those described above with dense foci of rough frequently hyalinized fibrillar connective tissue. Vascularization took place at the periphery of these foci where thin nervous fibrils and sometimes small paraganglions were observed with severe degenerative changes of the collagen fibers and marked decrease of fibroblasts. Absence of inflammatory markers was documented. [115]

Repeated eccentric contractions diminish muscle function and increase intramuscular pressure. [82, 83, 116] Edema arising in one muscle compartment secondary to overuse does not spread to the adjacent compartments. Prolonged static muscular efforts predispose to edema that, in turn, leads to decreased perfusion pressure with a subsequent reduction of blood flow, granulocyte plugging of the capillaries, further metabolite accumulation, and vasodilatation. [79. 82, 83, 114, 116]

Repetitive eccentric contractions are a notorious source of microtraumas with microruptures either at the fibroosseous junctions, in the mid substance of the ligaments and tendons, or at the myotendinous interface with insufficient time for recovery. This leads to inadequate regenerative process that turns to a degenerative pathway in tendons, muscles, discs, joint ligaments and cartilage.[82-84, 114, 116]

Impaired circulation at the fibromuscular and fibroosseous interface eventually leads to impaired intraosseous circulation with diminished venous outflow and increase in intraosseous

pressure. This in turn stimulates intraosseous baroreceptors and contributes to nociception transmitted through fine myelinated and nonmyelinated fibers that accompany nutrient vessels into bone and located in perivascular spaces of Haversian canals. Decreased circulation leads to hypoxia, effects calcium metabolism and contributes to progression of osteoarthritis.[11-21, 117-119]

Insertion pathology of the trunk muscles (enthesopathy at the fibroosseous junctions) most commonly affects the following sites: the spinous processes especially at the thoracolumbar region, iliac crests, symphysis pubis, ischial tuberosities, lesser and greater trochanters. **(Figures 5 and 6)** In addition to the above-described pathologic changes, calcium deposits and mineralization of the fibrocartilaginous zone were documented in enthesopathies. [79] A large study examined traumatically ruptured tendons from 891 patients in comparison with 445 tendon specimens obtained from similar local sites in similar age and sex group of "healthy" individuals who died accidentally. Degenerative changes were well documented in 865 ruptured tendons (97%) and only in 149 control tendons (27%). Similar statistical differences were observed comparing tendons of individuals who died three years after quadriplegia and those who died accidentally. Irreversible lipoid degenerations at the muscle tendon junctions were documented as early as three months after onset of quadriplegia. [79] Therefore, it is quite possible that radiofrequency denervations of MBDRs also lead to a progressive degeneration of the tissue innervated by MBDRs, which may partially explain the recurrence of pain after radiofrequency procedures.

There are free nerve endings, Pacini and Ruffini corpuscles in posterior lumbar ligaments. The free nerve endings were found in superficial layers of all ligaments including supraspinous and interspinous with a sharp increase in their quantity at the spinous processes attachments (enthesis). [120] **(Figure 7)**

Neoneurogenesis and neovasculogenesis have been observed in chronic connective tissue pathology. The nerve and vascular tissue ingrowth into diseased intervertebral discs, posterior spinal ligaments, hard niduses of fibromyalgia, as well as neuropeptides in the facet joint capsules make them potential sources of nociception. (115, 121-123)

BIOMECHANICAL PROPERTIES OF LIGAMENTS and TENDONS

The tensile strength of tendons is similar to that of bone and is about half that of steel. A tendon with a cross section of 10mm in diameter may support a load of 600 to 1000kg. (77, 79, 124)

Elongated below 4% of original length, ligaments and tendons return to their original crimp wave appearance; beyond 4% elongation, they lose the elasticity and may become permanently lax. Ligament laxity leads to joint hypermobility. In degenerated ligaments, subfailure was reported as early as at 1.5% of elongation. (124, 125)

There are three principal failure modes. The first most common is ligament failure. The second, more common, is a bone avulsion fracture, and the third, less common, is a shear or cleavage failure at the fibroosseous interface. The strongest connective tissue structures of the lumbar region are the zygapophyseal joint capsule and thoracolumbar fascia with average failure force at 680N and 500N respectively. (81, 124, 125)

Collagenous tissues are attenuated by inactivity and are favorably influenced by physical activity of an endurance nature, they are also deleteriously affected by NSAIDs and steroid administrations, and "[a]dministration of even a single dose of corticosteroids directly into ligaments or tendons can have debilitating effects upon their strength. Intraarticular injections of methyl-prednisolone acetate given either once or at intervals of several months may be less detrimental to ligament or tendon mechanical properties." (124, 125)

CLINICAL ANATOMY OF THE LUMBAR AND LUMBOPELVIC REGIONS IN RELATION TO RIT

A current review of the lumbosacral and pelvic ligamentous complex emphasizes that various ligamentous and fascial structures of the lower back form a continuous connective tissue stocking surrounding, interconnecting and supporting various soft tissue and osseous structures. [3, 80] This arrangement provides bracing and hydraulic amplification effect to the back muscles, enhancing their strength by up to 30%. [126, 127] Each of these structures was preserved in place by dissection of the osseous components. [80] **(Figure 8)** Although each of the connective tissues has a slightly different biochemical structure, they blend at their boundaries and function as a single unit. On the cross-section view, the lumbar interspinous ligaments have a triangular shape, but from the lateral aspect, they appear as a fan-like arrangement of fibers. [3, 80, 128] **(Figure 9)** The interspinous ligaments are anchored anteriorly to the ligamentum flavum and posteriorly to the supraspinous ligament, which is attached to the thoracolumbar fascia. **(Figure 10)** The fan-like shape allows the interspinous ligaments to expand without rupture when the lumbar vertebrae separate during flexion. It also transmits anteroposterior pull during flexion from the thoracolumbar fascia to the ligamentum flavum, preventing the latter from buckling into the spinal canal and helping align the lumbar vertebrae. Chondrocytes collect along the osseous borders of the interspinous ligament, predisposing them to chondrification after the third decade of life. [3, 80] Degenerative changes have been reported early in the second decade of life. Absence of the interspinous ligaments at L5-S1 level has also been reported. [129, 130]. The innervation is generally segmental and provided by the respective medial branches of the dorsal rami (MBDRs) that arise immediately below that vertebrae; the same applies to the muscles

arising from the lamina and spinous process. But innervation differs for z-joints where ascending and descending articular branches supply the z-joints above and below respectively. Thus, pain arising from z-joints may be referred to the interspinous areas in antidromic fashion and pain from the interspinous area may mimic z-joint pain in an orthodromic fashion and visa versa. [3, 80]

Differential diagnosis is based on a thorough understanding of the regional and segmental anatomy and pathology. Currently prevailing trends in diagnostic efforts address discogenic, facetogenic and neurocompressive components of spinal pain. Consequently prevailing therapy is directed towards neuromodulation or neurablation with radiofrequency generators, or surgical ablations and fusions to correct the mass effects in the neurocompressive models, or discogenic pain.

In the lumbar area, blocking the putative medial branches of the dorsal rami as the initial step in differential diagnosis is considered diagnostic and prognostic for z-joint pain. [81, 104, 106, 107] However, such approach as an initial step in differential diagnosis may be misleading , especially in the presence of midline tenderness, because it interrupts orthodromic and antidromic transmission at the proximal segment of the respective MBDR, excluding other putative nociceptors located distally on its course from the differential diagnosis. Similarly, the presence of a subligamentous plexus in the proximity of the sacral foramina may explain the failure of neurablative procedures in sacroiliac joint pain. [131] **(Figure 11)**

According to the spinal uncertainty principle, even a simple example of two motion segments, where disc, facets and musculotendinous compartment, each considered as one putative nociceptive unit, the total number of clinically indistinguishable combinations rises to sixty-three possibilities. It is practically impossible to address such a magnitude of possibilities

under fluoroscopic guidance. [132] Therefore, RIT offers an attractive practical alternative.

The following step-by-step approach for evaluation and treatment with RIT has been implemented based on earlier publications. [8-3738, 91, 92, 103-107]

In the presence of midline tenderness, interspinous ligaments are initially blocked. If the tenderness remains, lateral aspects of the spinous processes are blocked at the fibro-osseous junctions. Persistence of paramedial pain dictates blocks of the facet joint capsule. In this way all potential nociceptors in the vicinity of MBDRs are investigated. Should the pain persevere, investigation of the structures innervated by the intermediate branches of the dorsal rami follows. **(Figure 12)** Should the pain continue, investigation of structures innervated by the lateral branches is appropriate. Manipulation under local joint anesthesia (MUJA) may be attempted at any stage. [50, 51, 133]

Should the pain still persist, investigation of the middle column or anterior column (depending on MRI findings) follows the initial steps in the forms of translaminar, transforaminal or caudal approaches to epidural space, followed by evaluation of the discogenic component.

RIT is directed toward correction of posterior column pathology. In most instances, it is sufficient for adequate stabilization of hypermobile segments and abolishment of pain. The re-emerging application for RIT is the anterior column discogenic pain. [70-73]

RIT MECHANISM OF ACTION

The RIT mechanism of action is complex and multifaceted.

- Mechanical transection of cells and matrix by the needle causes cellular damage, stimulating inflammatory cascade and growth factors release. [51, 88, 112, 134, 136]

- Compression of cells by the extracellular volume of the injected solution and cell expansion or constriction due to osmotic properties of the injectate, stimulates release of intracellular growth factors. (9, 22, 51, 53-56, 84, 88, 136, 149-154)
- Chemomodulation of collagen through inflammatory proliferative, regenerative/reparative response is induced by the chemical properties of the proliferants and mediated by cytokines and multiple growth factors.(7-14, 51-56, 84, 88, 136, 149-154)
- Chemoneuromodulation of peripheral nociceptors provides stabilitzation of antidromic, orthodromic, sympathetic and axon reflex transmissions. (10-20, 88, 136)
- Modulation of local hemodynamics with changes in intraosseous pressure leads to reduction of pain. Empirical observations suggest that dextrose/lidocaine combination has a much more prolonged action than lidocaine alone. (10-21, 88, 117-119, 136)
- Temporary repetitive stabilization of the painful hypermobile joints, induced by inflammatory response to the proliferants, provides a better environment for regeneration and repair of the affected ligaments and tendons. (6-15, 23-37, 41-54, 56-68, 88, 136)

INDICATIONS FOR RIT

1. Chronic pain from ligaments or tendons secondary to sprains or strains.
2. Pain from overuse or occupational conditions known as “Repetitive Motion Disorder.”
3. Chronic postural pain of the lumbar and lumbosacral regions.
4. Painful recurrent somatic dysfunctions secondary to ligament laxity that improves temporarily with manipulation. Painful hypermobility and subluxation at given peripheral or spinal articulation(s) or mobile segment(s) accompanied by a restricted range of motion at reciprocal segment(s).

5. Lumbar vertebral compression fractures with a wedge deformity that exert additional stress on the posterior ligamento-tendinous complex.
6. Osteoarthritis of axial and peripheral joints, spondylosis, spondylolysis and spondylolisthesis.
7. Painful lumbar, lumbosacral and sacroiliac instability secondary to ligament laxity.
8. RIT may be the treatment of choice if the patient fails to improve after non-invasive modalities such as physical therapy, chiropractic or osteopathic manipulations, or NSAIDs, or intolerance to NSAIDs, opiates, steroid injections, radiofrequency denervation, or surgical interventions in the aforementioned conditions, or if such modalities are contraindicated.

SYNDROMES AND DIAGNOSTIC ENTITIES CAUSED BY LIGAMENT AND TENDON PATHOLOGY THAT HAVE BEEN SUCCESSFULLY TREATED WITH RIT

The majority of the following clinical entities represent a multi-etiological connective tissue diathesis with common pathogenesis.

1. Recurrent somatic lumbar dysfunctions
2. Iliolumbar Syndrome
3. Iliocostalis Friction Syndrome
4. Iliac Crest Syndrome
5. Internal Lumbar Disc Disruption
6. Interspinous Pseudoarthrosis (Baastrup’s Disease)
7. Lumbar Facet Syndrome

8. Lumbar Sprain/Strain Syndrome
9. Myofacial Pain Syndrome
10. Failed Back Syndrome
11. Lumbar instability
12. Lumbar ligament sprain
13. Spondylolysis
14. Sacroiliac joint pain
15. Sacrococcygeal joint pain
16. Gluteal tendinosis
17. Trochanteric Tendonosis
18. Ehlers-Danlos Syndrome
19. Ankylosing Spondylitis (Marie-Strumpell disease)
20. Fibromyalgia Syndrome

CONTRAINDICATIONS TO RIT

1. Allergy to anesthetic, proliferant solutions or their ingredients such as dextrose, sodium morrhuate or phenol
2. Acute non-reduced subluxations, dislocations or fractures
3. Acute sprains or strains of axial and peripheral joints
4. Acute arthritis (septic or post-traumatic with hemarthrosis)
5. Acute bursitis or tendinitis
6. Capsular pattern of the hip designating acute arthritis accompanied by tendinitis
7. Acute gout or rheumatoid arthritis

8. Recent onset of a progressive neurologic deficit, i.e., bladder dysfunction and bowel incontinence
9. Requests for large quantity of sedation and/or narcotics before and after treatment
10. Paraspinal neoplastic lesions involving the musculature or osseous structures
11. Severe exacerbation of pain or lack of improvement after local anesthetic blocks
12. Relative contraindications: central spinal canal, lateral recess or neural foramina stenosis

PUTATIVE NOCICEPTORS AND TISSUE PATHOLOGY TREATED WITH RIT

Putative nociceptors treated with RIT include: [3-38, 40-74]

1) Ligaments: Intraarticular, periarticular, capsular

2) Tendons

3) Fascia

4) Enthesis: the zone of insertion of ligament, tendon, or articular capsule to bone [3, 56, 79, 84, 136]

5) Intervertebral discs [26-31, 50, 70-73]

Tissue pathology treated with RIT includes:

1) Sprain: *Ligamentous injury at the fibro-osseous junction or intersubstance disruption. A sudden or severe twisting of a joint with stretching or tearing of ligaments*. [54, 55, 82, 137-139]

2) Pathologic Ligament Laxity: a post-traumatic or congenital condition leading to painful hypermobility of the axial and peripheral joints. [8-15, 23-25, 32-37, 40-61]

3) Tendinosis/Ligamentosis: A focal area of pathological degenerative changes due to a failure of cell matrix adaptation to excessive load and tissue hypoxia with a strong tendency to

chronic recurrent pain and dysfunction.[3, 55, 56, 63, 79]

4) Enthesopathy: *A painful pre- or post-traumatic pathological process that results in deposition of poorly organized tissue, degeneration and tendinosis at the fibro-osseous interface and transition towards loss of function.* [3, 55, 56, 79]

5) Internal disc disruptions. [26-29, 70-73] Note that the outer layers of the annulus represent a typical enthesis with Sharpey's fibers and may present histologically as a typical enthesopathy. [79]

The pathologic changes in items 2, 3, 4 and 5 above may be identical. Enthesopathy just delineates the location of these changes within the ligament or tendon in question and is equally applicable, with annular rent, to some of the painful disc problems.

CLINICAL PRESENTATIONS

Patients may present with various complaints that range from a single area of localized pain and tenderness to a combination of referred pain patterns known with disc, lumbar facet, sacroiliac joint or disc syndromes. Typical complaints include exacerbation of pain while standing or sitting in the same position for a given period of time, increased pain after exertion, and physical activity. A feeling of weakness in the low back or lower extremities and extreme fatigue are common as are pseudoradicular patterns of change in sensation, such as burning, numbness, tingling, the need for repetitive self manipulations, chiropractic or osteopathic manipulations, and painful clicking, popping or "locking" of axial or peripheral joints.

PHYSICAL EXAMINATION

The most common finding over chronically strained or sprained ligaments or tendons is

tenderness that, when provoked, rarely reproduces radiating or referral pain. The intensity of such tenderness may lessen or disappear completely after manipulation. Patients can point with a finger to pain sites in the lumbar, sacroiliac, pelvic and trochanteric regions.

Local tenderness, as well as referred and radiating pain, can often be abolished by infiltrating nociceptors in the involved tissue with local anesthetic. Tenderness is an objective finding especially when elicited over low back structures. (9, 10, 20, 140, 141)

RADIOLOGIC EVALUATION PRIOR TO RIT

1. Plain radiographs are of limited diagnostic value in painful pathology of the connective tissue but they may indicate:
    a) structural or positional osseous abnormalities
    b) anterior or posterior listhesis on lateral views (flexion, extension)
    c) degenerative changes in general and deformity of zygapophyseal articulation (142-145)
2. An MRI may detect intervertebral disc pathology, enthesopathy, ligamentous injury, interspinous bursitis, zygapophyseal joint disease, sacroiliac joint pathology, neural foraminal pathology, bone contusion, neoplasia, infection or fracture. An MRI can exclude or confirm spinal cord disease and pathology related to intradural, extramedullary and epidural spaces. (144-146)
3. A CT scan may detect small avulsion fractures of the facets, laminar fractures, fractures of vertebral bodies and pedicles, or degenerative changes, as well as sacroiliac joint pathology. (143, 144)
4. A bone scan is useful to assess the entire skeleton to rule out metabolically active

disease process. [143, 144]

SAFE INJECTION SITES AND TECHNIQUES

Safe injection sites are fibro-osseous junctions of ligaments and tendons. Common sites for injections are the enthesis of structures that insert or originate at spinous processes. At the lumbopelvic junction, from superficial to deep, those are superficial layers of the thoracolumbar fascia, the supraspinous ligaments, interspinous ligaments and multiple tendons. The apex of the spinous process may be considered a "spinous rotator cuff."

The cardinal rule is that solutions should be injected only after the needle has touched the bone. A total of .02 to .05 ml is injected after each bone contact. The needle is redirected after almost complete withdrawal of its length into subcutaneous tissue. In a fairly large structure, fan-wise or cone-wise reinsertions of the needle are utilized. There should not be a great resistance to injections, especially in degenerated structures. If a great resistance is felt, the needle is either in a healthy structure of a tendon or is abutting the bone and periosteum in such a way that its lumen is blocked. To be relatively painless, injections should be done slowly, in accordance with the patient's reaction. During the first visit, three- or two-stage techniques are appropriate, i.e., rising a skin weal with local anesthetic, followed by infiltration of deep structures, followed by proliferant injection. When the patient's confidence is won, the operator may resort to a one-stage technique, especially with mild solutions such as 12%-18% mixture of Dextrose with Xylocaine.

SOLUTIONS FOR INJECTIONS

There are four groups of proliferant solutions. These are:

i. Osmotic shock agents, such as hypertonic Dextrose and Glycerine

ii. Chemotactic agents such as Sodium Morrhuate

iii. Chemical irritants such as Phenol

iv. Particulates such as Pumice suspension.

The most common initial solution is 12.5% Dextrose. This concentration is achieved by a dilution of 50% Dextrose with local anesthetic in a 1:3 ratio, i.e. 1 ml of 50% Dextrose mixed with 3 ml of 1% Lidocaine. [5,27,110]

A gradual progression to 25% Dextrose with Xylocaine has been utilized. [107] If this proves ineffective, gradual progression to Sodium Morrhuate full strength has been described. [5,10] The fact that a solution of 25% Dextrose with Xylocaine abolishes pain for a longer duration than Xylocaine or Bupivacaine alone indicates that 25% Dextrose is neurolytic for small unmyelinated fibers.

5% Sodium Morrhuate is a mixture of sodium salts of saturated and unsaturated fatty acids of cod liver oil such as arachidonic acid, mediator of inflammation, and 2% benzyl alcohol, which acts as a local anesthetic and a preservative. Note that benzyl alcohol chemically is very similar to phenol.

Dextrose/Phenol/Glycerine solution (DPG, aka P2G): Originally produced in England by Boots company LTD of Nottingham for treatment of varicose veins, DPG was introduced to pain management by Ongley. [53] The solution consists of 25% Dextrose, 2.5% Phenol and 25% Glycerine. Prior to injection DPG is diluted in a 1:2; 1:1 or 2:3 ratio with a local anesthetic of the practitioner's choice. Some authors exclusively used this solution in 1:1 dilution. [51] Others modified it, reducing Glycerine to 12.5%

The 6% Phenol in Glycerine solution was utilized by proctologists in the beginning of the

last century and employed by Poritt in 1931 for treatment of pre-patellar and olecranon bursitis. (147) It was reintroduced in the late 1950s by Maher of England for intrathecal injections in the treatment of spasticity. (148) Subsequently Wilkinson, a neurosurgeon who trained at Massachusetts General Hospital, gained sufficient experience with intrathecal phenol administration, then began injecting it at the donor harvest sites of the iliac crests for neurolytic and proliferative responses. (58)

CONCLUSION

1. RIT/Prolotherapy is a valuable method of treatment for correctly diagnosed chronic, painful conditions of the locomotive systems. (1-141)
2. The practitioner's thorough familiarity with normal, pathologic, cross-sectional and clinical anatomy, as well as anatomical variations and function, is essential.(1-137)
3. Current literature supports manipulation under local joint anesthesia and a series of local anesthetic blocks for diagnosis of somatic pain. (133, 136)
4. Use of RIT in an ambulatory setting is an acceptable standard of care in the community.(1-74)

The future will be interesting when specific growth factors become readily available. The remaining challenge will be which specific or combination of growth factors to utilize. A combination of several growth factors together with specific genes responsible for the production of these growth factors is being developed in animal experiments. The use of mesenchymal stem cells for regeneration of bone, muscle and other connective tissues has been discovered. Injectable stem cells as a vehicle for regenerative/reparative response of the connective tissue is

on the horizon. The delivery mode for deep tissue will probably be injections or electronically guided transvascular systems whereas superficial will probably be addressed via transdermal systems. [134, 135, 149-155]

A physician, versatile in diagnostic and therapeutic injection techniques may have an ample opportunity to use RIT in the treatment of chronic pain arising from ligaments and tendons.

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