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REGENERATIVE REHABILITATION FOR LATERAL EPICONDYLALGIA

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Abstract

Lateral epicondylalgia (LE) is a common condition of the elbow that causes significant pain and disability resulting in economic burden and loss of function. Causes of LE include overuse leading to local tendinopathy, neuropathic mechanisms, and impairments in regions proximal and distal to the elbow such as the wrist, cervical spine, and shoulder girdle. Physical therapy and other forms of conservative rehabilitation are often utilized successfully and include interventions such as exercise, joint, and soft tissue manipulation, and various modalities such as ultrasound and extracorporeal shockwave therapy. However, despite the reported benefits of exercise and other rehabilitative interventions, most research regarding treatment efficacy has focused on functional outcomes without understanding the cellular and molecular effects. Moreover, inconsistencies in the literature remain regarding best-practice management for LE. Nevertheless, recent investigations have provided insight into the corrective processes that may occur with commonly employed rehabilitative procedures. This article will give an overview of the pathophysiological process associated with LE followed by a detailed discussion of the current understanding of the cellular and molecular mechanisms that may occur with conservative rehabilitation. The purpose of this paper is to present the current evidence regarding conservative rehabilitation to exemplify how these interventions may serve as an adjunct to biological therapies.

Keywords: *Lateral epicondylalgia; epicondylitis; regenerative rehabilitation; eccentric exercise; heavy-slow resistance exercise; tendinopathy*

INTRODUCTION

Lateral epicondylalgia (LE) is a musculoskeletal pain condition that affects up to 3% of the population annually[1] with approximately 40% of the population experiencing symptoms during their lifetime. Adults between 35-54 years are most often affected, with the highest incidence among individuals aged 40-49 and equal gender distribution.[2-5] While lateral epicondylalgia is commonly referred to as "tennis elbow," and nearly 40–50% of tennis players are affected at some point in their lifetime, [5] the condition is not limited to the tennis-playing population. LE causes significant work and recreation-related disability, a high financial burden due to work absence/productivity loss, and health care costs.[6] While LE is typically a unilateral condition, up to 12% of individuals have involvement of both upper extremities.[4] Despite the significant functional loss due to LE, evidence suggests that 90% of all cases can be addressed non-surgically.[6]

Conservative interventions, such as physical therapy, are often recommended as an initial treatment option for LE symptoms and associated impairments; however, they can also be used concurrently with regenerative medicine approaches to promote or augment cellular effects.[7] This paper will present an overview of the pathophysiological process of LE and an in-depth discussion of the evidence demonstrating the regenerative effects of common physical therapy interventions. Discussion of biologic therapies, such as platelet-rich plasma, is beyond this paper's scope. Instead, the intention is to promote an understanding of the underlying cellular responses to conservative treatment and provide insight into how physical therapy can serve as an adjunct to biologic therapies.

PATHOPHYSIOLOGY

Similar to other tendinopathies, the pathophysiology of LE is degenerative in nature and appears to originate with microtrauma from overuse contraction of the wrist extensors. The deep and anterior fibers of the extensor carpi radialis brevis are most commonly affected, although other tendons in the extensor mass, such as the extensor digitorum communis may be involved.[8] The traditional nomenclature of lateral epicondylitis or tendonitis implied the presence of inflammation; however, a body of research suggests that inflammatory markers are only present in the early phases and that degenerative changes in the tendon develop over time due to a failed healing response.[9,10] Moreover, evidence suggests that treatments to body regions away from the area of symptoms, such as the cervical spine and shoulder, may play an important role in recovery.[11-13] Therefore, the diagnosis of lateral epicondylitis is a misnomer and the term LE will be used to better represent the pathophysiological process.

The initial stages of tendon injury include several cellular and molecular processes to repair the affected structure. Inflammation plays a key role early in the reparative process, and cellular debridement's initial immune system response creates an optimal tendon repair environment.[7] Immediately following an injury, hemostasis occurs, which is comprised of: (a) vasoconstriction to decrease blood flow to the area, (b) formation of a platelet plug to seal the injured area, and (c) development of a blood clot. The hemostasis process can take seconds to hours, depending on the extent of the damage. The newly formed platelet plug serves as an established attraction point for the innate immune cells, such as neutrophils and macrophages, to begin the process of phagocytosis. Platelets release a number of cytokines that recruit circulating immune cells, which release additional cytokines responsible for fibroblast activation and, ultimately the reparative processes.[7,14]

Following hemostasis, the inflammatory phase continues with type I and type II immune responses, respectively pro- and anti-inflammatory. The type I response promotes clearance of cellular debris by macrophages and neutrophils, which are recruited within the first 3-5 days. Regulatory T cells (Tregs) then mediate a switch to the type II immune response, facilitating the formation of a new extracellular matrix (ECM) and secretion of growth factor.[7] Disruption of this initial inflammatory phase may play a pivotal role in developing tendon pathology.[15]

Cook and Purdam have proposed and revised a three-stage model of tendon pathology postulating that tendinopathy occurs on a continuum; therefore, a one-size fits all treatment approach is unlikely to lead to optimal results.[9,10] The three stages include reactive tendinopathy, tendon disrepair, and degenerative tendinopathy. Reactive tendinopathy is a short-term adaptive thickening of the tendon in response to acute overload or direct trauma, which aims to reduce stress and increase tendon stiffness. This tendon thickening is not an inflammatory reaction and is caused by the morphing of the tendon cell shape to resemble chondroid cells, and the upregulation of large proteoglycans and glycoproteins. This attracts water to the extracellular matrix, thereby thickening the tendon. It is important to note that this differs from the normal response to progressive loading, which is tendon stiffness without thickening.[10]

In the next stage, tendon disrepair, attempts are made to heal the tendon through the proliferation of chondrocytes and myofibroblasts, which increase proteoglycan and collagen production. This leads to

further breakdown and disorganization of collagen and the extracellular matrix, with subsequent reduction in the load-bearing capacity of the tendon. Imaging and histological studies indicate the presence of neovascularization and neuronal ingrowth [16], which may contribute to LE-related symptoms. The pathological changes resulting from the first two stages can reverse with the management of tendon loading and therapeutic interventions to stimulate repair; however, persistent or high-level loading can cause irreversible degenerative damage or rupture.[10]

The final phase of degenerative tendinopathy is characterized by a failed healing response and the progression of matrix and cellular changes. Tendon cell death causes further breakdown and disorganization of the matrix, neovascularization, neural ingrowth, and heterogeneity between pathological and normal cells. The capacity for reversing structural pathological changes is limited in this stage.[10,17,18] The importance of neovascularization in tendon pathology remains debatable and will be discussed later in this article.[19,20]

Since this initial Cook and Purdam model was published, evidence has shown conflicting data regarding the role of inflammatory cells in tendinopathy. Various cytokines commonly associated with inflammation, including interleukin-1 (IL-1) and interleukin-6 (IL-6), have been detected in pathological tendons. The process is still believed to be degenerative in nature, and the role of these substances in tendinosis is unclear.[9] Moreover, the increased presence of substance P (SP) and calcitonin-gene-related peptide (CGRP), both involved with pain transmission, has been identified in the presence of tendinopathy, specifically in the extensor carpi radialis brevis (ECRB) of patients with LE. Higher levels of SP and CGRP have been associated with more severe tendon degeneration.[21] Studies have also demonstrated elevated levels of messenger RNA (mRNA), changes in protein levels within the tendon, and other molecular changes relevant to rehabilitation benefits in tendinopathy cases. Furthermore, evidence suggests that estrogen may play an inhibitory role in the adaptive tendon response, which may explain why women are more susceptible to certain soft tissue overload injuries than their male counterparts.[22] Histological changes have also been detected in the common wrist extensor and ECRB tendons including moth-eaten fibers, fiber necrosis, signs of regeneration, and an increased proportion of fast-twitch muscle fibers. Concurrent lateral collateral ligament tears and intrasubstance tears of the involved tendons have also been identified and are associated with poor outcomes.[18,20,23]

In addition to the aforementioned tendon changes, motor system impairments and alterations in pain perception also contribute to LE-related symptoms. Motor system impairments associated with LE consist of weakness and altered motor control of the shoulder, wrist, and hand musculature, including unilateral or bilateral maximum grip.[18,20,23] Research has demonstrated reduced pressure-pain thresholds over the affected lateral epicondyle, which is consistent with peripheral excitation and sensitization caused by tissue injury, nociceptor activation, and the release of excitatory amino acids and neuropeptides, such as glutamate and SP.[18] On the contrary, evidence also indicates widespread mechanical hypersensitivity into the unaffected extremity, cervical spine, and lower extremity that is more prevalent in females and suggestive of sensitization of central nervous system pathways.[24-27]

EXERCISE/MECHANOTHERAPY

Several exercise programs have demonstrated efficacy in managing symptoms associated with tendinopathy at the lateral epicondyle, patella, and Achilles tendon. Evidence suggests that exercise should be a preferred intervention for LE rather than rest, as habitual training promotes collagen synthesis that peaks 24 hours after exercise and remains elevated for three days.[22] Numerous programs have been proposed with varying degrees of evidentiary support. Programs focused on isolated eccentric exercises, heavy-slow resistive exercises (HSR), general exercises, and others have shown improvement in functional outcomes, with some evidence that tendon regeneration may occur. Eccentric exercise involves the lengthening of a muscle while under load[28] whereas HSR exercise, which does not isolate the eccentric component, focuses on lifting

capacity and time under tension.[29] The literature also suggests that stretching the wrist extensors is essential to LE management.[30] This article will present the exercise evidence related explicitly to LE where available, as well as the evidence from tendinopathy in other body regions where evidence for LE is lacking.

Exercise may lead to regenerative changes in affected tendons through the process of mechanotransduction, in which cells convert mechanical stimuli into biochemical responses via three steps: (1) mechanocoupling, (2) cell-to-cell communication, and (3) a cellular response.[31] Mechanocoupling involves the application of shear, tensile, or compressive forces to cells within an extracellular matrix. The cells then communicate through the signaling proteins calcium and inositol triphosphate at the gap junctions, which allows for a response in distant cells that did not receive the mechanical stimulus. The cellular response of collagen synthesis occurs through two processes. First, the integrins that bridge the intracellular and extracellular regions pull on the cytoskeleton, which sends a physical signal to the cell nucleus. Second, the integrins activate biochemical signals that affect gene expression in the nucleus. Once the cell nucleus receives signals through these two mechanisms, mRNA is transcribed and shuttled to the endoplasmic reticulum in the cell cytoplasm, where it is translated into protein, secreted, and incorporated into the extracellular matrix for remodeling. Essentially, the mechanical stimulus or load outside the cell caused intracellular chemical processes leading to matrix remodeling.[31]

Exercise for tendinopathy has been extensively studied, yet no approach has demonstrated superiority in promoting tendon regeneration. Research previously focused on isolated eccentric strengthening, which positively affected functional outcomes and demonstrated potential benefits for tendon regeneration. Recent studies have compared eccentric strengthening to other programs such as HSR, which has shown promising results. Regardless of the exercise approach, mechanotransduction was the postulated mechanism for all regenerative cellular changes.

ECCENTRIC OVERLOAD RESISTANCE TRAINING

A substantial body of evidence has illustrated the benefits of eccentric strengthening exercises on LE and other tendinopathies.[32-36] Nonetheless, other studies have been contradictory. Initial evidence indicated that eccentric exercise posed significant benefits concerning functional outcomes when compared with concentric and isotonic exercise[37,38]; however, recent studies on HSR exercise have questioned this paradigm.[39-41] Furthermore, several studies have indicated improved outcomes in patients with LE using eccentric strengthening and other exercise programs without exhibiting structural, cellular, or molecular changes.[34,42] There is a paucity of evidence regarding the ability of exercises to induce cellular and molecular changes at the lateral elbow. The following section will focus on studies investigating exercise interventions' potential regenerative effects on LE and other tendinopathies. Where applicable, evidence will be expounded from body regions beyond the elbow to understand possible cellular and molecular changes.

Croisier et al.[43] compared a non-strengthening rehabilitation program of stretching, modalities, and deep friction massage to the addition of eccentric training of the wrist extensors and supinator using an isokinetic machine. Not only did the eccentric strengthening group demonstrate greater decreases in pain and improvement in self-reported disability, but ultrasound examination also revealed normalized tendon diameter in 48% of the intervention group.[43] This reduction in tendon diameter has also been noted in studies on Achilles tendinosis, where eccentric loading increased collagen synthesis in pathological tendons and not in healthy tendons.[44]

Clarke et al. examined the structural implications of non-operative management of LE through ultrasound assessment of echotexture, tendon thickness, neovascularity, intrasubstance tears, and concurrent lateral collateral ligament tearing. Eccentric strengthening exercises and stretching produced symptom improvement; however, 27% of patients responded poorly to treatment. This was attributed to intrasubstance tears greater than 8mm at the common

extensor origin in most of these poor responders. Eighty-four percent of the individuals that improved demonstrated tears smaller than 4 mm. The presence of a concurrent LCL tear was consistently associated with a poor outcome. While neovascularization has been implicated as a source of pain in LE, this study found no association or change in tendon diameter with improvement in symptoms or function. The authors concluded that neovascularization is part of the healing response and does not contribute to pain with nerve fiber ingrowth.[20]

On the contrary, exercise has demonstrated efficacy in promoting tissue regeneration in tendinopathic conditions similar to LE, such as patella and Achilles tendinopathy. Ohberg and Albertson investigated changes in tendon thickness and structure in patients with Achilles tendinopathy treated with eccentric exercises. Ultrasound indicated decreased tendon thickness and normalized tendon structure following eccentric exercises in 73% of patients, with an association between symptoms and tendon changes. In a follow-up study,[45] significant improvements in neovascularization were found in 89% of affected tendons.

Several studies indicate that Achilles tendon structure may not change with the performance of eccentric exercise.[46] Rabello et al.[41] investigated the association between imaging and clinical outcomes after performing eccentric strengthening and HSR exercises for Achilles and patellar tendinopathies. Neither eccentric strengthening nor HSR affected Achilles tendon thickness; however, both exercise programs reduced neovascularization upon long-term follow-up. There was no change in patellar tendon thickness with eccentric strengthening; however, there was a possible improvement with HSR. Moreover, findings suggested that both eccentric and HSR exercises improved clinical outcomes and were associated with changes in neovascularization in the Achilles and patellar tendons.[41]

In addition to the aforementioned structural changes, eccentrics and other forms of exercise may provide additional molecular benefits. Skeletal muscle has been called a "secretory organ," as a number of cytokines are released following contraction. Most of the cytokines the skeletal muscle produces have a local effect; however, some may have a systemic effect.[47] As previously mentioned, IL-1 and IL-6, two pro-inflammatory cytokines, have been detected in pathological tendons.[9] Interleukin-10 (IL-10), an important anti-inflammatory cytokine, has been shown to suppress pro-inflammatory cytokines such as IL-1, IL-6, interleukin -8 (IL-8), and tumor necrosis factor-α (TNF-α). IL-10 and granulocyte colony-stimulating factor (G-CSF) levels have been shown to increase following a bout of eccentric exercise,[48-50] and it has been postulated that G-CSF may have an anti-inflammatory effect via attenuation of TNF-α.[48] Moreover, IL-10 production may vary throughout the life cycle. For example, Conceicao et al.[51] compared the cytokine response to eccentric exercises in young and post-menopausal women. Results showed that young women had a significantly greater anti-inflammatory response than post-menopausal women, with IL-10 levels being the primary justification.[51] Additionally, cytokines may have a direct effect on the activity of tenocytes, as well as a role in the regulation of the matrix turnover in tendinopathy.[52,53]

Animal studies have provided some additional insight into the response of cytokines to eccentric exercises. Studies on rats have demonstrated that IL-10 increases after exercises and may act on local nociceptors to produce muscle hyperalgesia following eccentric exercise.[54] Moreover, increased levels of IL-6, have been reported in rats following eccentric exercises,[55] and although IL-6 is a pro-inflammatory cytokine, it is proposed to have an anti-inflammatory effect via induction of IL-10. Evidence suggests that any pro-inflammatory response generated from eccentric exercise has a short-lived and primarily local effect.[56]

HSR TRAINING

Recent efforts have concentrated on comparing an isolated eccentric exercise program to HSR, focusing more on load (i.e., resistance) than the eccentric component alone. HSR has been examined in LE, but most studies have investigated its effectiveness in addressing tendinopathies in other regions, with generally positive results.[57]

Performance of HSR exercises has resulted in normalization of patellar tendon fibril density and mean fibril area with decreased stiffness of pathologic tendons.[58] Beyer et al.[39] compared HSR training to eccentric training in the presence of chronic Achilles tendinopathy and found significant improvement in anterior-posterior tendon thickness and neovascularization in both groups. There was no difference between the groups in either the short-term or long-term, although the HSR group had better compliance, which was attributed to less time needed to perform the HSR program.[39]

In a systematic review comparing heavy load eccentric training with the natural history, traditional physical therapy, sham interventions, or other exercise interventions for Achilles tendinopathy, heavy load eccentric training appeared superior to the natural history and traditional physical therapy; however, it was not as effective as HSR training.[59] This has been corroborated by several studies demonstrating equal or greater effectiveness of HSR compared to eccentric strengthening.[60,61]

Despite evidence that mechanical changes occur with eccentric and HSR exercise, this may not be the reason for improved functional outcomes. Malliars et al.[62] performed a systematic review of the effectiveness of various loading programs on Achilles and patellar tendinopathy and concluded that there is little clinical or mechanical evidence for isolating the eccentric component. The authors also recommend using both concentric and eccentric loading in conjunction or instead of eccentric strengthening. The authors did note positive mechanical changes at the patella but not the Achilles tendons with HSR, such as decreased anterior-posterior tendon diameter and neovascularization, thus concluding that HSR is more likely to lead to tendon adaptation. There is a paucity of evidence regarding the potential molecular changes with HSR compared to the aforementioned molecular changes noted with eccentric training.

It is important to note the plausibility that different body regions respond to exercise therapy differently, and structural changes that occur in the patellar and Achilles tendon, may or may not occur at the lateral epicondyle. Drew et al.[40] investigated structural changes in Achilles, knee, elbow, and shoulder tendon disorders via diagnostic ultrasound, MRI, and computed tomography scan. Findings indicated that pain reduction or improved function is not associated with mechanical changes in tendon diameter and reduction in neovascularization after treatment with eccentric exercises. On the contrary, evidence suggests that the changes in tendon diameter and neovascularization that occur with HSR exercise are associated with pain reduction and improved function.

This literature review reinforces the proposed stages of the tendinopathy continuum and elucidates the complex relationship between tendon structure, pain, and function.[9] Given the variability in cellular response, tendon structure, and tolerance to loading in each of the three stages, the intensity and type of strengthening exercises should align with the potential for remodeling and the goal of treatment (i.e., pain, function, load capacity). Therefore, a uniform approach for all tendinopathies would be ineffective. According to Cook et al.,[9] heavy load eccentric strengthening would be highly provocative in the reactive tendinopathy stage. Performing eccentric strengthening or HSR exercises during the tendon disrepair stage would address deficits in tendon function and load-bearing capacity while also maximizing the regenerative qualities of the intervention, since structural changes are potentially reversible in this phase. In the degenerative tendinopathy stage, interventions to change tendon structure may be less important, as the likelihood of reversing the cellular changes is low.[9,40] Therefore, strengthening in this phase should focus on increasing the tendon's load-bearing capacity rather than stimulating healing or regeneration. An overview of the guidelines for a practical application can be found in Table 1.

MANUAL THERAPY

Manual therapy interventions are skilled passive movements of joints and soft tissue intended to improve tissue extensibility; increase range of motion; induce relaxation; manipulate soft tissue and joints; modulate pain; and reduce inflammation.[63] They are a preferred treatment for painful

Table 1. Evidence-Based Sample Regenerative Rehabilitation Program

Intervention	Dosing	Mechanism
Therapeutic Exercises: • Eccentrics and/or heavy-slow resistance of the wrist extensors (Figure 2) • Stretching of the wrist extensors	3 sets of 6-15 repetitions depending on load with a frequency of 3 times per week up to twice daily. Limit pain levels to 6/10 on verbal rating scale. 3 sets of 30 seconds performed daily.	• May have regenerative effect on tendon stiffness and tendon diameter.[39,43,58]May decrease neovascularization.[39,40] • Stretching may make the tendon more resistant to strain and potentially increase fiber orientation.[145]
Mobilization with Movement: • Mobilization with movement for pain-free grip (Figure 1) **Thrust and Non-thrust Joint Manipulation:** • Elbow joint • Cervical-thoracic region (see Figure 3)	Variable depending on source. The MWM is typically performed 6-10 repetitions per application until improvement plateaus.	• Correct positional fault[65] • Facilitation and decreased pain pressure[24] • Neurophysiological pain inhibition[71-76]
Soft Tissue Mobilization: • Cross friction massage to the wrist extensors	Limited evidence	• Break up adhesions[80] • Promote collagen fiber orientation[81] • Promote pro-inflammatory immune response and increase in blood flow
Neural Mobilization: • Radial nerve glides	60 seconds, 3 sets, 1-3 times per day	• Stimulate pro-inflammatory immune response[64] • Diminish mechanical and thermal hyperalgesia[91]
Blood Flow Restriction Training	Arterial occlusion of 30-50% for the upper extremity and 50-80% for the lower extremity[120] 20-40% of 1 repetition maximum for 30 repetitions, followed by 2 sets of 15 repetitions at submaximal arterial occlusion pressure[121]	• Heightens initial inflammatory response[122] • Increases expression of growth factors[123,124]
Extracorporeal Shockwave Therapy	Optimal dosage has not been determined Sample doses (radial intensity) 1-2 bars, 1500-2000 impulses, 10 Hz	• Stimulates influx of growth factors and protein[98] • Accelerates collagen synthesis and promotes fiber alignment[100] • Decrease pro-inflammatory mediators and substance P production[101]
Dry Needling	Pistoning of the affected tendon, 3 times up to 50 times[115]	• Increases gene expression for COX2 and MMP2[116] • Stimulates increase of type III collagen and GAGs[117]
Low Level Laser Therapy Class 3 (<500 mW)	Optimal dosing not established. Generally 20-30s treatments, 2-3×/week.	• Stimulates ATP and growth factor synthesis[131] • Promotes angiogenesis[131] • Promotes type III collagen synthesis[131] • Down-regulates pro-inflammatory cytokines in remodeling phase[131]

(Continues)

Table 1. (Continued)

Intervention	Dosing	Mechanism
Ultrasound	Continuous US at 1.0 and 2.0 W/cm^2, as well as pulsed US at 2.5 W/cm^2 and 20% duty cycle[139,140]	• In inflammatory phase: stimulates mast cells, platelets, macrophages and phagocytes[139,140] • In proliferative phase: upregulates fibroblasts, endothelial cells, and myofibroblasts[139,140,143] • In remodeling phase: promotes fiber alignment and stimulates transition from type III to type I collagen[139,140,143]

musculoskeletal conditions for many health care disciplines; however, the mechanisms by which they exert their therapeutic effects are multifaceted and complex including mechanical, neurophysiological, and neuroimmune responses.[64] Manual therapy interventions for LE include mobilization/manipulation of peripheral joints at the elbow complex, cervical spine, soft tissue structures, and neural tissues, and each offers unique reparative and regenerative properties.

PROPOSED MECHANISMS

The methods by which manual therapy exerts a hypoalgesic effect on LE-related symptoms are intricate with possible mechanical, neurophysiological, neuroimmune, and cognitive mechanisms of action. Mulligan initially postulated that the benefits of mobilization with movement (MWM) occurred from correcting minor positional faults that accompanied an injury and that treatment to correct this fault will affect muscle activity and vice versa. An MWM is the application of an accessory glide to a joint while the patient performs an active motion (Figure 1).[65] Therefore, by addressing this "mechanical block"[66] and performing the passive movement at the end of the accessory range, reflexogenic muscle guarding will decrease, muscles will be optimally positioned for recruitment, and nociception signals will wane.[66,67] Others have proposed using high-velocity techniques to correct joint mobility.[68-70]

The patient is positioned supine with the shoulder abducted 20°, elbow extended, and forearm pronated. The clinician stabilizes the distal humerus and applies a lateral glide to the proximal ulna and radius. The patient then performs a gripping motion while the glide is maintained. Each gripping isometric contraction should be maintained for a few seconds and repeated 6-10 repetitions per session. When appropriate, there is significant improvement in pain during the mobilization and enhanced grip strength directly following the intervention.[65]

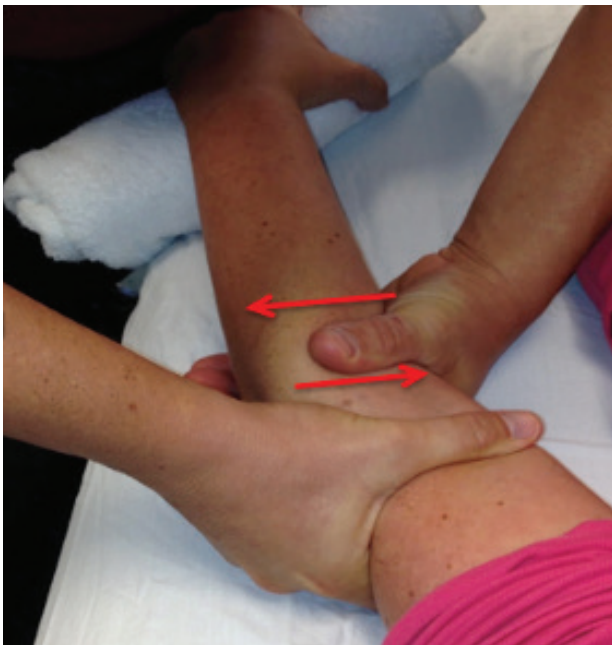

Figure 1. Mobilization with movement for pain-free grip.

The proposed neurophysiologic mechanism behind the hypoalgesic effect of cervical manipulations and the lateral glide-MWM has been attributed to activation of the endogenous descending pain inhibitory systems mediated by the dorsal periaqueductal gray region. This results in an immediate

Figure 2. Therabar® exercises for eccentric exercises of the wrist extensors.

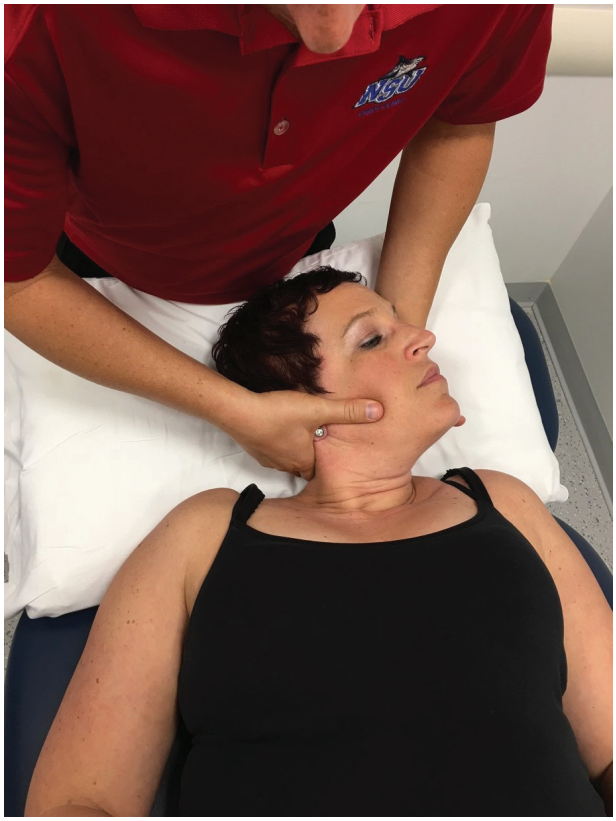

Figure 3. Cervical thrust manipulation.

hypoalgesia with concurrent excitation of the sympathetic nervous system, demonstrated through antinociception to mechanical but not thermal stimuli and changes in sudomotor, cutaneous vasomotor, cardiovascular, and respiratory function.[11,71-76] The pain-relieving effects of elbow mobilization, specifically, do not decay over repeated treatments and are not antagonized by naloxone, further suggesting a non-opioid mechanism of hypoalgesia.[77,78]

Additional manual therapy effects suggest a neuroimmune response, defined as the interaction between the immune and nervous systems. Changes in hormone and cytokine levels, such as cortisol and IL-1β, following manual therapy have been associated with this neuroimmune response, modulating inflammation and pain sensitivity. Neuroimmune responses have been noted both locally, at the spinal cord, supraspinal levels (including the brain), and systemically following the application of manual therapy.[64]

SOFT TISSUE MOBILIZATION

Soft tissue mobilization (STM) involves the application of targeted force through direct hand contact or instrumentation with the therapeutic goals of decreasing pain, reducing swelling, decreasing muscle guarding/spasm, enhancing tissue mobility/flexibility, elevating skin and muscle temperature, and promoting lymphatic and blood flow.[79] Deep transverse friction massage, or cross friction massage, is a specific STM technique that involves the application of deep friction in a perpendicular direction to the fiber orientation of the involved tissue. The intended purpose is to prevent or break up abnormal fibrous adhesions in remodeling collagen (cross-links or cross-bridges)[80] and realign the fibers in a longitudinal manner.[81] Despite extensive anecdotal evidence and long-standing clinical usage, research on the underlying mechanisms by which STM exerts its effect is lacking. However, considering STM as a non-invasive mechanical stimulus provides insight into its impact on cellular function, tissue structure, repair, and regeneration.[82,83]

Through mechanotransduction, STM facilitates endogenous repair and regenerative pathways, and

may be beneficial when used as an isolated intervention or implemented in conjunction with regenerative therapy such as platelet-rich plasma and stem cell treatments.[83] As mentioned previously, integrins facilitate communication of the mechanical load exerted on the extracellular matrix by physically altering the tendon cell membrane, which causes messenger RNA to transcribe the message and transport it to the cytoplasm, where collagen synthesis occurs.[31] In skeletal muscle, integrins propagate mechanotransduction signals by activating intracellular kinases, which uptick protein synthesis, glucose uptake, and immune cell recruitment.[84] Crane et al.[84] found an increase in intracellular kinases in muscles treated with massage, suggesting that the intervention may promote the mechanotransduction signaling needed for collagen repair and healing.

Water-Bankers et al.[85] postulates that mechanical compressive loads, such as massage, create an optimal inflammatory environment that promotes tissue repair. The intensity of a bout of massage affects M1 and M2 macrophages, and afferent nerve fibers. M1 macrophages are "classically activated" and considered pro-inflammatory cytokines since they produce IL-6 and TNF-α. M1 macrophages enter the tissue 24 hours post injury and are primarily involved in the phagocytosis of necrotic tissue. Around 48 hours after injury, they are replaced by M2 macrophages.

On the contrary, M2 macrophages are "alternatively activated" and considered anti-inflammatory cytokines since they produce interleukin-4 (IL-4), transforming growth factor β (TGF-β), and IL-10, which contribute to the myoblast proliferation and satellite cell activation that occurs during the repair and regeneration phase of healing.

Low to moderate load massage after injury may create the optimal inflammatory environment for tissue repair. This load intensity will minimize pro-inflammatory cytokine release from M1 macrophages, thereby limiting exposure of the damaged tissue to cytotoxic chemicals, reducing the potential for afferent nerve sensitization and plastic changes in the dorsal horn of the spinal cord, and promoting early activation of M2 macrophages.[85]

Furthermore, STM is often performed to accelerate tissue healing through vascularization and enhanced blood flow. The mechanical stimulus created by STM exerts pressure on local vasculature, which mobilizes the mast cells, macrophages, and endothelial cells necessary for forming new vessels.[83] These new vessels will ensure adequate blood supply to damaged and healing tissues to facilitate the repair and regeneration process previously discussed. In addition to the vasculogenesis (formation of new blood vessels) and angiogenesis (growth of new capillaries from existing blood vessels) resulting from mechanical stimulation, blood flow to an injured region is also augmented through elevation in skin and tissue temperature. This would theoretically facilitate the removal of inflammatory waste products and an influx of immunomodulators for cellular synthesis and repair. Increases in local tissue temperature occurs immediately, peaks after 25 minutes, and remains above baseline for over 60 minutes after either manual or instrument-assisted STM.[79,86]

NEUROMOBILIZATION

Neuromobilization is passive, or active movements focused on restoring the ability of the nervous systems to tolerate the normal vibration, compressive, tensile, and friction forces accompanied by daily activities.[87] Chemical or mechanical stimuli that exceed the physical capabilities of the nervous system from acute or chronic injury, respectively, can result in peripheral neuropathic pain, which may play a role in LE.[88,89] Injury of somatic tissues adjacent to neural structures affects the vascular, connective tissue, and impulse conducting properties of neural tissues, which in the presence of LE, would affect the radial nerve, specifically the posterior interosseus branch.[88,89] Mechanical or chemical stimuli activate the release of inflammatory mediators (cytokines, neuropeptides, neurotrophic factors, reactive oxygen species, and chemokines) that cause an immune response at the site of the lesion, proximally in the dorsal root ganglion and spinal cord, and in higher brain centers such as the midbrain, thalamus, and pre-frontal cortex.[64,90] At the injury site, the nervi nervorum (intrinsic innervation of nerve sheath) and sinuvertebral nerves become sensitized, and endoneurial edema inhibits the flow of inflammatory waste products. This leads to hyperalgesia,

fibrosis with subsequent limited tissue extensibility, myelin degradation, and resultant slowed impulse conduction.[87]

Studies suggest that the reparative and regenerative tissue effects of neuromobilization occur via reduced immune responses, diminished mechanical and thermal hyperalgesia, improved intraneural circulation and fluid dispersion, axoplasmic flow, and connective tissue viscoelasticity.[91] Neuromobilization appears to have a positive effect on neuropathic pain by decreasing Substance-P, nerve growth factor, and glial fibrillary acidic protein at the level of the dorsal root ganglion, increasing glial cells and brain-derived neurotrophic factor in the midbrain and activating endogenous opioid receptors in the periaqueductal gray area.[90] Furthermore, neuromobilization reduces levels of pro-inflammatory cytokines interleukin-1β (IL-1β), which attenuates inflammation around the dorsal root ganglion and surrounding non-neuronal cells,[64] ultimately facilitating a hypoalgesic response.

Mechanical stress caused by neuromobilization can activate the intracellular processes responsible for myelination and nerve homeostasis. In-vitro and ex-vivo studies have shown that graded tension to both sensory and motor nerves promotes neuron cell differentiation and growth, which is pivotal for repair after injury. Higgins et al.[92] found that seven days of intermittent mechanical stretching at 10% strain at 0.25 Hz for 120 minutes/day applied to sensory nerves promoted nerve cell differentiation and growth. In addition, neuromobilization with a tensile load between 0.1–1% strain minimized cell apoptosis, upregulated genes involved in nerve cell growth, and downregulated genes linked to mechanical allodynia.[92-94] On the contrary, higher levels of stretch, above 24% strain, negatively affect nerve cell regeneration and increase the rate of neuronal death.[93,95]

In summary, manual therapy interventions such as joint, soft tissue, and neural mobilization have the potential to aid in the regenerative process through mechanotransduction, immune responses, vascularization, and increased blood flow. These techniques should be included in the medical and rehabilitative plan for individuals with LE. A summary of the effects and proposed dosing of manual therapy applications can be found in Table 1.

MODALITIES

Physical therapy (rehabilitation) utilizes electrophysical and thermal agents to address symptoms and promote tissue healing in the presence of tendinopathy, including lateral epicondylalgia. These modalities include, but are not limited to, extracorporeal (radial) shockwave therapy (ESWT), dry needling, blood flow restriction (BFR), ultrasound (US), and photobiomodulation or low-level laser therapy (LLLT). Research on the mechanisms of action, efficacy, and utility of these modalities continues to expand and will be discussed in the following section focusing on the regenerative effects for LE.

EXTRACORPOREAL SHOCKWAVE THERAPY (ESWT)

ESWT involves the application of acoustic or electric energy to a specific tissue to promote remodeling or regeneration via interstitial or extracellular responses. The shockwaves, or pressure waves, are applied at what is described as low-, medium-, or high- intensities, based on energy flow through a given area, with a unit of measurement in mJ/mm^2.[96] The mechanism by which ESWT affects tendon repair is still under investigation and debated, but includes theories regarding improved blood supply and changes in inflammatory responses.[97]

ESWT promotes both vasculogenesis and partial ruptures of capillary vessels from the tendon and bone. This stimulates an influx of growth factors and proteins needed for tissue regeneration.[98] ESWT also activates mast cells, producing pro-inflammatory chemokines and cytokines that enhance tissue healing and regeneration.[97,99] Furthermore, ESWT accelerates collagen synthesis and promotes longitudinal alignment of fibers to increase tendon density and strength.[100]

Research has theorized that symptom relief after ESWT treatment occurs via mechanotransduction by decreasing the number of pro-inflammatory mediators, decreasing substance P production, and/

or descending inhibition.[101] ESWT produced degeneration of sensory nerve fibers in the epidermis of rats,[96] which may also contribute to a reduction in nociceptive somatic pain.

Animal studies have demonstrated the influx of new capillaries, muscularized vessels, and myofibroblasts at the bone-tendon junction in dogs.[102-104] The neovascularization produced with ESWT differs from the vasculogenesis associated with pathological tendons in that the latter occurs with concurrent neuronal ingrowth, which may be a source of symptoms.[105] Studies conducted on non-pathologic Achilles tendons in ponies and humans have not demonstrated resultant neovascularization from ESWT.[106,107] This illustrates the differences in physiological responses of healthy and pathologic tissues and body region.

Bosch et al.[102] found a short-term stimulation in protein metabolism in healthy tendons after ESWT and an up-regulation of gene expression for type-1 collagen, which may be beneficial for tissue repair.[107] One downside to ESWT was the disorganization and degradation of collagen fibers that lasted up to 6 weeks.[107] Although this occurred in healthy tendons, it may have implications for tissue regeneration and exercise prescription.

Furthermore, Zhang et al.[108] found that ESWT increased the amount of lubricin, a molecule that improves tendon gliding, in rat tendons. In-vitro studies by Vetrano et al.[109] and Han et al.[110] confirm increased proliferation and reduced pro-inflammatory markers, such as matrix metalloproteases (MMPs) and IL-6 in human tenocytes collected from semitendinosus and Achilles tendons during reconstructive surgeries. The aforementioned tenocytes were treated at medium intensity, with 1000 pulses and 500 pulses, respectively.

Studies on ESWT for LE are lacking; however, the available evidence demonstrates improvement in common extensor tendon thickness and deleterious neovascularization.[99] Despite these cellular changes, evidence of reduction of LE-related symptoms and improvement in function is inconsistent. However, it is not unreasonable to consider some of the physiological data for other regions as part of a comprehensive approach.[111,112]

DRY NEEDLING

Dry needling refers to the practice of inserting thin needles into tissue, without the use of an injectable substance. Although the underlying physiological mechanisms of dry needling are unclear, it is hypothesized to affect both peripheral and central pain by reducing local sensitivity and activating descending pain pathways.[113]

In physical therapy practice, many states limit the use of dry needling to trigger muscle points, but evidence has also shown that dry needling into tendons can be beneficial for reducing pain and enhancing tendon repair.[114] Regarding regenerative processes, it is postulated that repeated fenestration or "pistoning" of the tendon with the needle disrupts the chronic degenerative process and facilitates localized bleeding and fibroblast proliferation.[115] In a pilot study by Calderon-Diaz et al.,[116] healthy rat Achilles tendons were subjected to dry needling, and results showed an increase in expression of several genes related to tendon regeneration, including cyclooxygenase-2 (Cox-2) and matrix metalloproteinase 2 (Mmp2). A similar study performed on the supraspinatus tendons of rats hypothesized that the microtrauma caused by the dry needling stimulated a transient inflammatory response, increasing the presence of type III collagen, pro-inflammatory markers, and glycosaminoglycan.[117]

Specific to LE, a meta-analysis by Navarro-Santana et al.[118] indicated that dry needling produced short and long-term symptom reduction, improvement in pressure pain sensitivity, and reduced LE-related disability.[118] A recent randomized controlled study also found that dry needling was superior to corticosteroid injection in the short and long-term regarding self-reported function in patients with LE, with fewer potential adverse effects.[119]

BLOOD FLOW RESTRICTION TRAINING (BFRT)

BFR involves using a strap or pneumatic cuff to partially occlude arterial and completely occlude venous flow to the limb, creating a hypoxic environment that helps promote muscle adaptation with lower loads.[120] Traditional resistance training

requires the application of heavy loads with an intensity of 70-100% of 1 repetition maximum, whereas BFR uses significantly lower loads with intensities between 20-40% of 1 repetition maximum.[121] BFR is hypothesized to affect muscle hypertrophy via mechanotransduction and metabolic stress, leading to a heightened initial inflammatory response, including local recruitment of macrophages and neutrophils, IL-6, and TNF-α, as well as increased expression of growth factors.[122] The hypoxic environment also causes an increase in nitric oxide and vascular endothelial growth factor, which similarly promotes angiogenesis to traditional strength training.[123,124]

Most research involving BFR has focused on muscular changes in healthy individuals, but evidence has also shown tendinous changes. Some properties studied included tendon stiffness, or the ability to resist deformation, and cross-sectional area (CSA). This change in tendon size is a desirable, adaptive response that improves stiffness and tolerance to mechanical loading, as opposed to the pathological tendon thickening described in tendinopathy.[125] Centner et al.[126,127] noted increased tendon stiffness and CSA in the healthy patellar and Achilles tendons following protocols of BFR with low-load resistance training.[126,127] On the contrary, Brumitt et al.[128] did not find that BFR enhanced tendon size compared to individuals trained without the addition of BFR.[128] BFR has been shown to cause exercise-induced hypoalgesia endogenous opioid and endocannabinoid mechanisms and may reduce LE-related symptoms.[129] Further research is needed to investigate the cellular and metabolic effects of BFR on pathologic tendons, and specifically LE.

While there is a paucity of cellular and molecular evidence regarding the effects of BFR on tendinopathy, recent evidence has demonstrated some encouraging clinical results.[130] A recent systematic review showed that BFR, when used in cases of tendinopathy, leads to improved functional outcomes, decreased pain, and increased strength. Additionally, most of the studies included in this review noted beneficial changes in tendon morphology and mechanical properties.[130] Moreover, since BFR is performed at lower loads than the aforementioned eccentric and HSR exercises, exercises using BFR may be better tolerated in painful tendon conditions. Therefore, BFR should be considered an alternative to eccentric and HSR exercises training in patients with painful tendinopathy that are intolerant to other loading mechanisms (e.g., eccentric overload and slow resistance training).

LLLT (CLASS 3—NON-SURGICAL)

LLLT or photobiomodulation, has been used for various musculoskeletal conditions, including tendinopathy. LLLT induces a non-thermal, photochemical reaction in tissues which, during the initial phases of tendon injury, is hypothesized to increase adenosine triphosphate (ATP) synthesis and promote angiogenesis through hypoxia-induced growth factor stimulation. It has been found to encourage type III collagen synthesis and down-regulate pro-inflammatory cytokines (specifically TNF-α and IL-6), in the proliferative and remodeling stages of tendon healing, respectively.[131] It may also increase cellular metabolism in the mitochondrial cytochromes.[132]

Transected rat Achilles tendons treated with Class 3 LLLT for 20s, 3 times/week, were shown to have "increased proliferation of mesenchymal cells, improved collagen fiber alignment, reduced inflammation, and increased production of collagen II".[133] Using a Class 3 (40 mW, 50 Hz) laser application, Chen et al.[134] demonstrated similar results of an up-regulation of Type I collagen and increased tendon fibroblast proliferation in the Achilles tendons of pigs exposed to LLLT. However, these were treated for several minutes per exposure. Martinelli et al.[135] expounded on this by identifying the modulation of pro-inflammatory cytokines TNF-α and IL-6 in rat tendons treated with 40mW laser, for 10s on each of 8 points. While research shows promising data regarding the efficacy of LLLT on tendinopathies including LE,[136-138] further study is needed to extrapolate these findings regarding intra-cellular mechanisms of tendon repair and remodeling to human subjects.

ULTRASOUND (US)

Conventional ultrasound (US) is a modality that has historically been used clinically to induce thermal or non-thermal effects in injured or painful

tissues. US uses a piezoelectric crystal, housed in a transducer to generate high-frequency acoustic energy, which exerts mechanical effects that promote tissue regeneration and repair, increase protein synthesis and blood flow, resolve chronic inflammatory processes, and reduce symptoms.[139]

During the inflammatory phase, US stimulates mast cells, platelets, macrophages, and phagocytes, releasing arachidonic acid and synthesizing prostaglandins and leukotrienes. Continuous US at 1.0 and 2.0 W/cm^2, pulsed US at 2.5 W/cm^2 and 20% duty cycle have been shown to mediate inflammation and promote progression to the proliferative and remodeling phases.[139,140] Moura et al.[139] found lower concentrations of fibroblasts when US was used during the initial inflammatory phase, further indicating that US exerts an anti-inflammatory effect. In vitro animal studies have shown US to be effective at increasing cell migration, proliferation, and collagen synthesis in tendons via an up-regulation of IL-1 β and transformation of growth factor-beta (TGF-β) and vascular endothelial growth factor.[141,142]

When used during the proliferative phase, US upregulates fibroblasts, endothelial cells, and myofibroblasts, thereby maximizing and improving the efficiency of scar production. During the remodeling stage, US promotes more organized collagen fiber arrangement and alignment and stimulates the transition of newly formed collagen fibers from type III to type I, which increases tensile strength and scar mobility.[139,140,143] This evidence exemplifies the regenerative effects of conventional US along the continuum of tissue healing. Ultrasound use has fallen out of common clinical practice due to a lack of high-quality evidence confirming its effectiveness in addressing pain and function; however, its regenerative effects may warrant further exploration and clinical utility.

SUMMARY OF CONSERVATIVE TREATMENT OPTIONS

There is currently no consensus regarding the most appropriate administration of conservative rehabilitation for LE. However, considering the studies mentioned above and a recent consensus statement published by Bateman et al.,[144] the authors propose that a rehabilitative program consisting of the following interventions should be considered before more invasive measures or in conjunction with biologic procedures. These recommendations are listed in Table 1.

SAMPLE INTERVENTIONS

This description is for treatment of the left wrist extensors. The bar is grasped with left hand in wrist extension. The right-hand twists the Therabar® in the direction of flexion. The left wrist is allowed to slowly move into flexion using eccentric control of left wrist extensors [36]

High-velocity, low-amplitude thrust manipulation directed at the cervical vertebral is commonly performed in patients with LE due to facilitation and decreased pain pressure threshold at that spinal segment [24] and origination of the peripheral and central sensitization processes present in patients with LE.[146] The patient is supine with the cervical spine in sufficient ipsilateral lateral flexion and contralateral rotation to tension the tissues and the selected zygapophyseal joint. Using the index finger, the clinician exerts a rapid, small-amplitude thrust directed upward and medially toward the patient's contralateral eye.[11,147]

CONCLUSION

LE remains challenging for clinicians due to the evolution of pathologic tendons, tissue healing, and regeneration. While the condition appears to respond well to conservative management about symptom reduction, motor impairments, and function, there is a paucity of evidence regarding the underlying regenerative properties of these interventions. Nonetheless, the literature consistently demonstrates the efficacy of exercise and manual therapy in aiding recovery, two commonly performed physical therapy procedures. Despite variable evidence and a dearth of research, the potential does exist for a regenerative effect, as several studies clearly indicate cellular, structural, and metabolic changes with conservative treatment. In conclusion, rehabilitation should be considered before, or as an adjuvant intervention, to biologic therapy to maximize outcomes in individuals with LE.

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