

Low Intensity Ultrasound for Promoting Soft Tissue Healing: A Systematic Review of the Literature and Medical Technology

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Abstract

Therapeutic ultrasound has been studied and used for the past seven decades to treat musculoskeletal injuries. Recently, a significant body of animal and human research has focused on the biomechanical effects of daily-applied, low intensity therapeutic ultrasound (LITUS) on soft tissue recovery. We performed a systematic review of the last two decades of LITUS literature to examine the effects on tendon, skeletal muscle, ligament, and tendon-bone junction injuries. LITUS facilitated tendon healing, with increased tensile strength and improved collagen alignment. For skeletal muscle and ligament injuries, LITUS increased cell proliferation during myoregeneration and improved tissue biomechanics (ultimate load, stiffness, energy absorption). LITUS aided tendon-bone junction healing through improved tissue function. Scientific evidence supports the use of LITUS to treat soft tissue injuries, and improve outcomes for musculoskeletal injuries and post-operative recovery. Lastly, we discuss the use of LITUS devices facilitating daily applied therapy in the home setting.

Keywords: Muscle; Tendon; Ligament; Healing; Bioeffects; Rehabilitation; Regeneration; Therapy; Therapeutic Ultrasound; Acoustic; Medicine

Introduction

Soft tissue injuries, both acute or chronic, are among the most frequent issues addressed by physical therapists, athletic trainers and primary care physicians; however, many currently available treatment options are costly, time consuming, and potentially harmful.^{1,2} Nonsteroidal anti-inflammatory pharmacotherapies can be deleterious to soft tissue healing and harmful to the gastrointestinal and renal systems.³ Interventions such as prescription painkillers, corticosteroid injections, and platelet-rich plasma injections can be addictive, costly, and of questionable efficacy, respectively.⁴ Traditional rest, time-off, and elevation therapy may not be feasible for all soft tissue injuries and patient lifestyles. Many use the regimen of rest, ice, compression, elevation and stabilization (RICES) to treat acute injury, but are unsure what to do if the injury becomes chronic.¹ Whereas, many of these current treatment options address inflammation and pain management, therapeutic ultrasound can both manage pain and facilitate healing. In the following systematic review, we examine the efficacy of low intensity therapeutic ultrasound (LITUS) in promoting healing of soft tissue injuries, and further discuss LITUS delivery systems

currently available for researchers, medical practitioners and patients.

Therapeutic ultrasound from 1-3 MHz has been used for over seven decades by physical therapists, athletic trainers and other health care providers to relieve pain and facilitate the healing process.⁵⁻⁷ Traditional therapeutic ultrasound has been used at intensities of 1-4 W/cm² in the physical therapy setting⁷ and at higher intensities up to 15,000 W/cm² for ablation of cancerous tissue,⁸ in either pulsed or continuous treatment modes. More recently, the use of therapeutic ultrasound at lower intensities (0.5-1W/cm²), in conjunction with other treatment modalities, has been used in both the home and the clinical setting to treat tendon, ligament, and muscle injuries.^{2,9-15} LITUS has been shown to alter tissue biomechanical properties,¹⁶ improve collagen alignment,^{17,18} and stimulate cell proliferation.¹⁹ The majority of the LITUS research in human subjects and animal models has investigated bone fracture healing.²⁰ This systematic review examines the efficacy of LITUS for improving healing in four tissue structures: (1) tendon, (2) muscle, (3) ligament, and (4) tendon-bone junctions. Additionally, two LITUS delivery systems and the benefits of longer duration

LITUS treatment are discussed following a summary of the literature.

Methods: Search Strategy and Criteria

A systematic literature review was executed and studies were identified on PubMed, Google Scholar, and in references from review articles that met the following inclusion criteria: 1) the study included at least one experimental arm that was treated with low intensity therapeutic ultrasound ($\leq 1.5 \text{ W/cm}^2$); 2) the study design had a control group that did not receive an active or alternative treatment to therapeutic ultrasound; 3) the study investigated biomechanical properties, histology (collagen synthesis/alignment), cell proliferation, and/or pain; 4) the study focused on skeletal muscle, tendon, ligament, or tendon-bone injury and healing; 5) the study was an original research article (review articles were excluded); 6) the study had appropriate local institutional review board (IRB) and informed consent procedures for human subjects, and appropriate local Institutional Care and Animal Use Committee (IACUC) approval for animal subjects; 7) the study was not focused only on bone or fracture healing; and 8) the study was written in English. All search results and studies were

independently evaluated by two authors (DD, TB) and further reviewed by research associates.

Results

The search yielded 35 applicable studies that met the inclusion criteria. These were subsequently categorized as: tendon (n=16), muscle (n=7), ligament (n=3), or tendon-bone junction (n=9). It should be noted that the majority of applicable studies utilized animal models, likely due to the experimental techniques required to elucidate the biomechanical and physiological processes resulting from LITUS.

LITUS was shown to have a beneficial effect on tendon strength and collagen synthesis following injury. Rupture strength in tendons treated with LITUS was significantly greater than controls from 5 to 42 days post-injury ($p < 0.05$; ^{16-18,21-23} Tensile strength and tendon extensibility in LITUS-treated tendons was also higher than in control tendons.^{16,22-25} Collagen synthesis, measured by conversion of radiolabeled proline to hydroxyproline, increased substantially from day 3 to day 5 post-injury and continued to show benefits through day 21 compared to controls ($p < 0.05$; ^{17,18} Collagen type I and III expression was

greater following LITUS treatment,²⁶ and higher birefringence (i.e., coherence of collagen alignment) was also observed in treated tendons compared to controls.^{27,28} Additionally, an examination of treatment time and duration found that introducing LITUS in the earlier stages of healing increased tensile strength and matrix synthesis compared to the later stages of healing.^{21,29} In three human studies examining epicondylitis and patellar tendinopathy, tendon pain was significantly decreased in a clinically meaningful way by up to 70% with daily applied continuous LITUS over the course of 6 weeks,⁴⁷ although in two of the studies pulsed LITUS produced similar decreases in pain with the control groups.^{11,14}

Application of LITUS increased cell proliferation and both myogenin and actin protein expression in skeletal muscle following a contusion injury. LITUS nearly doubled satellite cell proliferation compared to controls in an injured gastrocnemius muscle.¹⁹ A higher proliferation rate and cell number at days 6 and 8 were observed following the application of LITUS.³⁰ Cells treated with 8 doses of LITUS demonstrated a 40% increase in myogenin expression and a 47% increase in actin expression compared to controls.³⁰ Cyclooxygenase-2 (COX-2)

expression was also reduced in injured muscle tissue (both *in vivo* and *in vitro*) treated with LITUS compared to controls.^{31,32} Two human studies examining pain and trigger point depths demonstrated that LITUS significantly reduces pain,¹² and relaxes muscles, although muscle relaxation did not differ significantly from controls.⁹

Ligament healing benefitted from the application of LITUS. LITUS treated ligaments exhibited superior mechanical properties including ultimate load, stiffness, and energy absorption.³³⁻³⁵ LITUS-treated ligaments from one study were 34.2% stronger, 27.0% stiffer, and could absorb 54.4% more energy compared to sham-treated ligaments after 2 weeks of treatment.³⁵ Another study demonstrated that after six weeks of LITUS treatment, ligaments were 39.5% stronger, 24.5% stiffer, could absorb 69.1% more energy, and were 10.6% larger than sham-treated ligaments.³³ Collagen fibril diameter was larger in a group treated with LITUS compared to controls,³⁴ and there was a greater relative proportion of type II collagen in LITUS-treated ligaments compared to controls at both 3 and 6 weeks.³³

For tendon-bone junction healing, LITUS treatment significantly improved healing and osteogenesis. Application of

LITUS resulted in significantly more newly formed bone and improved tissue integration compared to controls.³⁶⁻⁴⁰ In one study,³⁹ reported the amount of new bone formed was 2.6 and 3.0 times greater in the treatment group compared to controls at weeks 8 and 16, respectively. Vascular endothelial growth factor (VEGF) in the tendon-bone interface was also significantly increased with LITUS treatment, particularly after 4 weeks.^{37,41} Type I and II collagen were increased with LITUS treatment,^{42,43} and collagen fibers demonstrated higher organization.⁴³ Similarly, there was up-regulation of type I collagen gene expression with LITUS treatment compared to controls.⁴⁴ Additionally, in procedures replacing ligaments with tendons (i.e., anterior cruciate ligament surgery; ACL), LITUS treated tendons showed greater stiffness and peak load compared to controls.^{36,40,45}

Discussion

LITUS improves the rate of tissue repair following tendon, skeletal muscle, ligament, and tendon-bone junction injuries. Injured tendons treated with LITUS recover with greater tensile strength and extensibility than similar tendons that received no treatment post-injury.^{16,22-25}

Recovering tendons treated with LITUS had greater amounts of collagen,²⁶ and improved organization and aggregation of collagen bundles.^{28,46} Also of importance, the intervention was most effective during the earlier stages of healing, with the most improvement noted during the first 14 days post-injury.²⁹ Tensile strength and collagen cellularity and stainability were more pronounced when LITUS was introduced during the granulation phase rather than the remodeling phase of tendon repair. The collective tendon results are promising when considering that 7% of all primary care physician visits and more than 30% of sports related injuries are related to tendinopathy, but there is currently no gold standard of treatment⁴⁷ Although the timing of intervention was found to be an important factor, similar effects were noted for continuous or pulsed mode ultrasound with the exception of one study.⁴⁶

Healing of skeletal muscle also benefited from the application of LITUS. Following contusion injuries to skeletal muscle, cell proliferation increased up to 96% in LITUS treated injuries compared to controls during the early stages of regeneration, although there was no effect on myotube production.¹⁹ LITUS produced a higher cell number and proliferation rate at

days 6 and 8; two factors related to muscle regeneration.³⁰ Myogenin and actin protein expression were increased at days 4, 6, and 8 in LITUS treated muscle compared to non-treated controls,³⁰ implying the existence of a cell process modulated by LITUS to affect the molecular biology of the cell, improving the rate of muscle repair and regeneration. Additionally, the reduction of inflammatory COX-2,^{31,32} suggests that LITUS accelerated the healing response. LITUS also reduced pain and improved relaxation of trapezius muscle tissue.^{9,12}

The three studies examining ligament healing revealed that LITUS-treated ligaments had superior mechanical properties including tensile strength and energy absorption.³³⁻³⁵ Ligaments treated with NSAIDs absorbed 33.3% less energy than those treated with a control vehicle that contained no COX-2 inhibitors.³⁵ These findings suggest that while NSAIDs address pain management, they may negatively impact the healing process. Comparatively, LITUS has the potential to provide both pain relief and anti-inflammatory effects without diminishing the healing process.

For tendon-bone junction injuries, LITUS treated animals had increased bone formation and greater mineral density than animals that did not receive any treatment.³⁶⁻

³⁹ New bone area was 2.6 and 3.0 times greater in LITUS treated groups compared to controls at weeks 8 and 16, respectively.³⁹ Radiographic measurements observed more newly formed bone and increased tissue integration in LITUS treated groups.³⁸ VEGF and collagen expression were also increased in the tendon-bone interface with the use of LITUS.^{37,41-44} Cumulatively, these results support the use of LITUS to shorten post-operative recovery time after procedures such as ACL surgery. Animal models indicate that the tendons used to replace ligaments in ACL surgery that are treated with LITUS are stiffer and can sustain greater peak loads,^{36,40,45} suggesting better clinical outcomes.

LITUS Delivery Systems & Clinical Applications

Collectively, these studies are encouraging for the use of LITUS to treat soft tissue injuries in human; however, the delivery of therapeutic ultrasound has been traditionally applied in the inpatient setting, which limits both the duration of treatment and frequency of application. Currently two wearable LITUS devices designed for daily home use have been approved by the United States FDA and CE-marked, including the Exogen[®] Bone Healing System (Bioventus

LLC, Durham, NC, U.S.), and the SAM[®] Sport Sustained Acoustic Medicine System (ZetrOZ Systems, LLC, Trumbull, CT, U.S.) Figure 1. The Exogen device operates a single ultrasonic collimated source at a frequency of 1.5 MHz, an intensity of 0.03 W/cm², temporal average power of 0.117 Watts with a pulsed 20% duty cycle for 20 min per day providing 140 Joules of ultrasound energy per treatment. The Exogen device is typically applied through a hole in a cast to a non-union fracture. The SAM device delivers low intensity continuous ultrasound at 3 MHz frequency, an intensity of 0.132 W/cm², temporal average power of 1.3 Watts for up to 4 hours per day from two divergent ultrasonic sources providing 18,720 Joules of ultrasound energy per treatment. The SAM device is applied with a star-shaped ultrasonic patch typically directly over and proximal to the soft-tissue injury. Both medical devices deliver low intensity ultrasound between 1-3 MHz, however the SAM device is 4.4x greater in intensity and 134x greater in energy delivery compared with Exogen, making the two devices considerably different and serving different clinical purposes.

The Exogen Bone Healing System is used in clinical practice to accelerate the

healing of established non-unions (excluding skull and vertebra), in addition to accelerating fracture healing time in fresh, closed, posteriorly displaced distal radius fractures and fresh, closed, or Grade I open tibial diaphysis fractures. The SAM device is used to reduce inflammation and pain, and accelerate the healing of soft tissues such as tendons, ligaments, and muscles. Both Exogen and SAM are non-invasive prescription-use devices that are administered and monitored by a licensed medical professional. Typically, patients prescribed wearable LITUS therapy self-apply the therapy daily in the home-setting, and have regularly scheduled follow up appointments with their healthcare provider who oversees use of the device. Overall, the use of these LITUS delivery systems has the clinical potential to accelerate healing and alleviate pain from a variety of disorders impacting soft tissues as well as bone.

Conclusions & Future Directions

The use of LITUS in the treatment of tendon, muscle, ligament, and tendon-bone junction injuries is supported by the literature. An advantage of using therapeutic ultrasound at lower intensities is that it can be safely used in the home-setting for long treatment times, in some cases up to 8

hours.¹² The vast majority of research to date has used animal models to understand the mechanisms underlying LITUS, and additional research with human subjects is worthwhile to expand our understanding on how physiological observations correlate to improved clinical outcomes of patients. Given the frequency and debilitating nature of soft tissue injuries, LITUS has the potential to reduce healing time, overall healthcare costs, and negative side effects, as well as improve quality of life.

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Figure 1: Wearable LITUS devices designed for daily home use: (A) SAM[®] Sport Sustained Acoustic Medicine System and (B) Exogen[®] Bone Healing System