Chapter 10
Ultrasound Stimulation of Tendon Healing: Current Strategies and Opportunities for Novel Therapeutic Approaches

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Abstract Tendons are mechanosensitive tissues that are critical to musculoskeletal mobility. An in-depth understanding of the mechanisms of tendon injury and healing is crucial to the development of new therapeutic strategies for tendon healing. Tendons do not possess a robust, intrinsic healing response, and conservative and surgical treatments have shown limited efficacy. For chronic tendon injuries (tendinopathies), the principal treatment of choice is exercise-based rehabilitation, which confers improvements in clinical symptoms and function. Therapeutic Ultrasound (TUS) is commonly incorporated within physiotherapy applications and provides pain relief, likely via a thermal modality, to soft skeletal tissues. While numerous animal studies have examined the efficacy of TUS in treating acute tendon injuries, few clinical studies have examined this treatment for chronic tendinopathies. Recently, focused ultrasound (FUS) methods have shown great promise for noninvasive tissue ablation and stimulation of tissue healing but have been minimally explored for musculoskeletal ailments. Precise and customizable therapeutic FUS methods offer the potential to achieve effective, functional tissue healing via thermal and/or mechanical stimulation pathways. This chapter explores the potential of FUS therapies as customizable, noninvasive treatment options for tendon injuries and offers insights into the current state and potential advancements of ultrasound stimulation for tendon healing.

Keywords Tendinopathy · Rehabilitation · Mechanotherapy · Therapeutic ultrasound · Focused ultrasound · Acoustic parameters

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10.1 Tendon: Anatomy, Injury, and Healing

10.1.1 Function and Anatomy

Tendons are dense, fibrous connective tissues that link muscle to bone and are critical to the overall function of the musculoskeletal system. While the primary function of tendons is to efficiently transmit tensile forces from muscle to bone, they are also subjected to compression and shear forces. Mature tendon is characterized by its hierarchical structure, and its mechanical function is dependent upon the biochemical composition and organization of its extracellular matrix (ECM) (Voleti et al. 2012; Screen et al. 2015; Snedeker and Foolen 2017). Tendon ECM is primarily composed of fibrillar collagens, proteoglycans, glycosaminoglycans, glycoproteins, and elastin (Sharma and Maffulli 2006) (Fig. 10.1). Collagen is the primary constituent of the tendon ECM, accounting for 60 to 85% of the dry weight of the tissue (Screen et al. 2015). Type I collagen is the dominant structural component, constituting nearly 95% of the total collagen content (Screen et al. 2015), while collagen types III, V, XI, XII, and XIV are present in much smaller proportions (Benjamin et al. 2008; Screen et al. 2015). The typical, highly organized collagen matrix can become disrupted in chronic injuries such as tendinopathy,

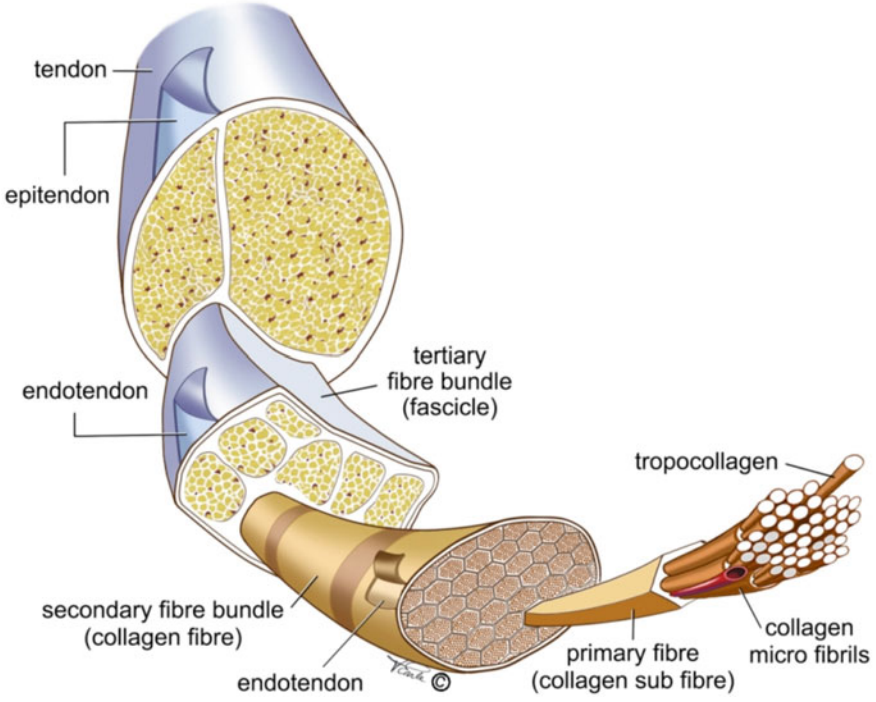

Fig. 10.1 Tendon hierarchical structure (reproduced with permission from Marqueti et al. (2019))

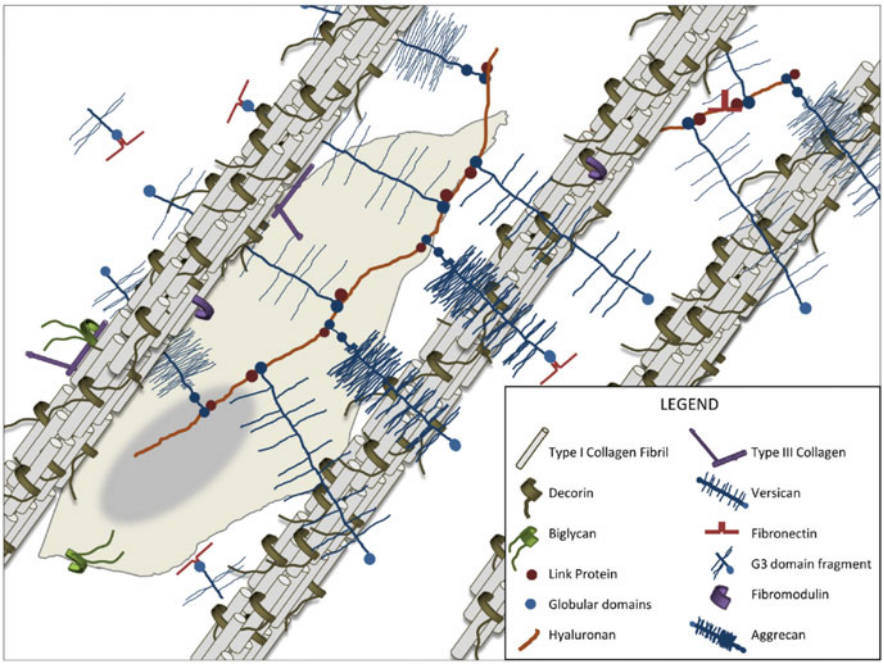

Fig. 10.2 Interactions of proteoglycans and other matrix macromolecules within the extracellular matrix of the tendon proper (reproduced with permission from Parkinson et al. (2011))

while the presence of collagen III, which typically amounts to 3–5% of the total collagen in a healthy tendon, may be elevated in tendinopathic tissue (Snedeker and Foolen 2017). Non-collagenous ECM components include: proteoglycans (whose hydrophilic nature allows for rapid diffusion of water-soluble molecules and cell migration), glycoproteins such as fibronectin (which contributes to tendon repair and regeneration processes), and elastic proteins such as Tenascin-C (which is associated with collagen fiber alignment and orientation, and is upregulated by mechanical strain) (Mackie and Ramsey 1996; Mehr et al. 2000) (Fig. 10.2).

Tendon cell populations are heterogeneous and contribute to ECM dynamics and homeostasis (Costa-Almeida et al. 2019; Zhang et al. 2019). Tenoytes, also referred to as resident cells, are fibroblast-like cells that are mainly responsible for ECM turnover, collagen production and assembly. They are arranged in longitudinal rows proximal to the collagen fibrils (Benjamin et al. 2008). Additionally, tendon stem/progenitor cells (TPSCs) replenish tendon cells by undergoing self-renewal and differentiation (Bi et al. 2007; Zhang and Wang 2010). Other cell populations include endothelial and synovial cells of the tendon sheaths as well as chondrocytes which are present within tendon-bone insertion sites and in tendon regions subjected to compressive forces during physiologic loading (Benjamin and Ralphs 1998; Kannus 2000; Zelzer et al. 2014). Tenocytes are *mechanosensitive*, and upon experiencing mechanical load, they stretch along the collagen fibrils longitudinally,

signaling collagen production. By modulating their alignment and signaling in accordance with their mechanical environment they alter ECM composition and structure (Humphrey et al. 2014; Muller et al. 2015; Popov et al. 2015). While little is known regarding the optimal loading conditions that may positively influence tendon healing, understanding how biophysical stimulation influences healing is critical to developing therapeutic treatments to restore pre-injury function.

10.1.2 Tendon Injuries and Healing

As tendons are frequently subjected to continuous or intermittent high magnitude forces, these tissues are prone to both acute and chronic injuries. Such injuries are debilitating, and are associated with ineffective healing, long-term pain, and loss of function (Nourissat et al. 2015). The type, severity, and prevalence of tendon injuries are dependent on multiple factors such as age, sex, activity levels, and genetic disposition (Sharma and Maffulli 2006; Thomopoulos et al. 2015). While tendon injuries are predominant in the elderly and athletic populations, they are becoming increasingly prevalent in the general population, due to increasing life expectancy, manual labor, and the popularity of strenuous loading activities such as exercise. Worldwide, more than half of the sport-related injuries involve tendons, and tendon damage is the most common orthopedic soft tissue injury (Walden et al. 2017). Apart from being highly prone to injury, tendons generally have a poor intrinsic capacity for healing, although the latter is dependent on the anatomic location and local environment (Thomopoulos et al. 2015). Intrasynovial tendon injuries do not exhibit spontaneous healing, while extrasynovial tendon injuries often result in fibrous tissue formation owing to a robust, scar-mediated healing response post-injury (Shen et al. 2021). Following its intrinsic repair response, tendon exhibits material properties which are inferior to those of native, uninjured tissue (Muller et al. 2015; Nourissat et al. 2015). Surgical and conservative medical interventions have limited, short-term efficacy and thus, there is significant motivation for the development of alternative approaches to improve tendon healing. Tendon injuries can be broadly categorized as acute or chronic, the former being the result of a "macro-trauma" such as a sudden mechanical overload, leading to a partial or complete rupture of the tendon. Chronic injuries typically present with an absence of inflammatory cells due to multiple stressors, including metabolic, biomechanical, genetic, and hypoxic factors; the latter may induce cellular responses that lead to disruption of matrix organization, loss of tissue material properties, and disrupted cell-matrix mechanotransduction (Nourissat et al. 2015; Sayegh et al. 2015). The etiology of chronic tendon disorders is multifaceted, and the subsequent degenerative pathway is triggered by dysregulated cell-cell and cell-matrix communication.

A primary etiologic factor in *tendinopathies* is repeated mechanical loading which exceeds the tendon's ability to heal (Steinmann et al. 2020; Millar et al. 2021). Although a biomechanical loading event individually may be of a magnitude within physiological limits, cumulative microtrauma from repetitive loading often

leads to localized collagen fiber damage (Herod and Veres 2018; Leek et al. 2020; Steinmann et al. 2020). When subjected to these stresses, a tendon may experience either inflammation of its sheath or degeneration of its body, or a combination of both (Sharma and Maffulli 2006). Recent evidence suggests the role of an inflammatory response in mediating tendon pathophysiology (Millar et al. 2017; Sunwoo et al. 2020; Millar et al. 2021). Specifically, various immune cell types (mast cells, macrophages, T cells) and inflammatory cytokines (interleukin (IL)-6, IL-5, IL-17, IL-18, IL-33, tumor necrosis factor alpha (TNF-α)) have been identified to play a critical role in the initiation and progression (early stages) of chronic tendon injuries (Millar et al. 2010; Garcia-Melchor et al. 2021). Interactions between resident and infiltrating immune cells and resident tenocytes are important in directing the inflammatory response phase of tendon healing, via secretion of cytokines and chemokines that regulate extracellular matrix remodeling. Pro-inflammatory cytokines (including members of the IL- and TNF-families) have been implicated in tendinopathy and are associated with immune cell recruitment, increased collagen type III and reduced collagen type I production, and reduced tendon biomechanical strength (Lin et al. 2006; Legerlotz et al. 2012; Dakin et al. 2014; Millar et al. 2017). Very recently, Garcia-Melchor et al. (2021) reported that tenocytes upregulate the genes involved in inflammation and T cell recruitment in vitro. T cell–tenocyte interactions, in turn, resulted in the upregulation of inflammatory cytokine expression and an increased expression of collagen III. It has been proposed that this autoregulated feedback loop plays a key role in chronicity and long-term complications of tendinopathy.

Largely due to the challenges presented in studying human tendinopathy, including the difficulty in identifying the onset of the disease as well as in procuring injured tissues at different stages of the post-injury response (Dirks and Warden 2011; Hast et al. 2014), our understanding of the precise mechanisms of tendon injury and healing remains incomplete. Tendon healing has primarily been studied using animal models of acute tendon injury (e.g., transection) or other experimentally induced tendon damage/injury models (Sharma and Maffulli 2005; Docheva et al. 2015). Tendon healing consists of sequential and overlapping phases (Docheva et al. 2015; Nourissat et al. 2015) including *inflammation, cell proliferation, migration, and remodeling* (Voleti et al. 2012; Docheva et al. 2015); however, it is common for incomplete healing to result in fibrovascular scar tissue which does not recapitulate native composition and material properties (Nourissat et al. 2015).

In order to study mechanisms of mechanical "overload" on the development of tendinopathy, researchers have developed a variety of preclinical approaches (Thomopoulos et al. 2015; Theodossiou and Schiele 2019). Some of these methods include uphill and downhill treadmill running in rats or mice (Heinemeier et al. 2012; Pingel et al. 2013; Zhang et al. 2020) and application of controlled, in vivo fatigue loading to rat or mouse tendons (Fung et al. 2010; Andarawis-Puri et al. 2012; Sereysky et al. 2012). Furthermore, biochemical induction of tendon injury has been studied using collagenase injections in various models including rabbits, sheep, and rats (Chen et al. 2014; Lacitignola et al. 2014; Solchaga et al. 2014; Urdzikova et al. 2014). Surgical repair following tendon transection has been

particularly useful in studying acute injury healing mechanisms (Yoshida et al. 2016; Moser et al. 2018). In vitro cell culture and tendon explant models (Goodman et al. 2004; Wunderli et al. 2020), as well as ex vivo rodent and equine tendon models, have been used to examine the effects of repetitive mechanical loading (e.g., cyclic strain or fatigue) on tendons (Arnoczky et al. 2007; Fung et al. 2009; Spiesz et al. 2015). Alteration of the tendon mechanical loading environment (e.g., by transection) can be effectively used to study biochemical responses (Maeda et al. 2011). An in vivo tendinopathy model was developed (Bell et al. 2013a) by injecting TGFβ-1 into adult mouse Achilles tendons. This injury model induces tendinopathic changes consistent with human histopathology (Bell et al. 2013a, b) and is amenable to therapeutic mechanical interventions (Bell et al. 2013a; Rezvani et al. 2021) simulating human treatments (Heinemeier et al. 2012; Dirks et al. 2013; Pingel et al. 2013; Reuther et al. 2013).

10.1.3 Mechanotherapy for Treatment of Chronic Tendon Disease

There exist several common, conservative, and surgical approaches for the treatment of chronic tendinopathies, such as rest and immobilization, anti-inflammatory drugs, growth factor injections (i.e., platelet-rich plasma), and surgical repair (Lim et al. 2019; Tsai et al. 2021) (Table 10.1). However, there is limited evidence of their long-term efficacy (Maffulli et al. 2010; Cardoso et al. 2019). The molecular mechanisms of disease initiation and progression, as well as the reasons for a failed healing response in lieu of restoration of tissue, are not well understood (Tsai et al. 2021). However, it is hypothesized that dysregulated and/or missing cues underlie the deficient healing response of a tendon; hence, a detailed understanding of such cues and mechanisms will greatly assist in the identification and design of novel therapeutic strategies to augment existing strategies to heal tendons. Rehabilitation protocols aim to robustly repair injured tissues in a manner that reduces their risk for reinjury (Gray and Brolinson 2001). This strategy involves the design of therapeutic modalities and rehabilitative exercises that address the type of injury (acute vs. chronic), symptoms, and tissue performance, via an in-depth understanding of tissue biomechanics and pathophysiology of injury (Gray and Brolinson 2001). Rehabilitation protocols generally utilize "*mechanotherapy*" to induce adaptation of the musculoskeletal tissues to mechanical forces and/or strain by directing cellular and molecular responses to achieve healing and/or regeneration. Identifying optimal mechanical loading regimes defined by transcriptional, molecular, and cellular responses is crucial in designing strategies for tendon repair and healing. For example, eccentric exercise (lengthening of the muscle and tendon while under load) is commonly used as a therapeutic modality to manage tendinopathy. These exercises have been shown to improve tendon structure and mechanical properties with corresponding improvements in clinical outcomes (Mafi et al. 2001; Fahlstrom

Table 10.1 Advantages and limitations of existing treatments for chronic tendon injuries

	Method	Advantages	Limitations
1	Topical/systemic anti-inflammatory drugs for pain relief	Effectively relieve pain and inflammation short-term; accessible and inexpensive	Insufficient evidence to support use in chronic injuries; may negatively alter natural tendon healing process; long-term use may cause adverse renal and gastrointestinal effects
2	Exercise-based rehabilitation	Principal treatment of choice across all tendinopathies; may tendon structural and biomechanical properties with corresponding improvements in clinical outcomes	Precise mechanisms of action are unknown; often require long periods of rehabilitation; customizing loading protocols to specific degrees of pathology is challenging; chronic pain may deter participation; requires patient compliance with protocols
3	Growth factor, i.e., platelet-rich plasma (PRP) treatment	Inexpensive; ease of administration (injections); low risk with autologous treatment; potentially beneficial in combination with therapeutic exercise	Variable and conflicting outcomes, potentially due to variability among PRP components
4	Therapeutic Ultrasound (TUS)	Widely accessible, noninvasive, painless	Few existing clinical trial data; conflicting data from preclinical studies of efficacy for treatment of acute injuries; no data on efficacy for chronic injuries
5	Low energy laser therapy (LLLT)	Evidence of reduction in inflammatory markers; provides pain relief when used in conjunction with exercise	Unclear mechanism of action; lack of standardized/reliable protocols (parameters) for administration; lack of homogeneous efficacy data
6	Extracorporeal Shockwave Therapy (ESWT)	Ease of administration; proven efficacy for treatment of specific types of tendinopathy	Unclear mechanism of action, lack of optimized treatment parameters for different types of tendon injuries

et al. 2003; Yu et al. 2013) and have emerged as the most efficacious therapy across numerous tendinopathies (Kingma et al. 2007; Murphy et al. 2018; Irby et al. 2020; Vander Doelen and Jelley 2020). Given that the goal of tendinopathy treatments is to restore normal tendon function, controlling the mechanical cues directed to the injured tendon can potentially promote healing via mechanotransduction mechanisms (Özer Kaya 2020). Regenerative rehabilitation approaches are, thus, central to translational tendon healing research (Gottardi and Stoddart 2018; Rando and Ambrosio 2018; Willett et al. 2020).

10.2 Therapeutic Ultrasound and Tendon Healing

10.2.1 Physical Principles, Characteristics, and Modalities

Therapeutic Ultrasound (TUS) utilizes acoustic pressures and/or intensities higher than those of diagnostic ultrasound to elicit biological responses in tissues. The ultrasound beam is directed into a specific area or a region within the tissue of interest to avoid damage to surrounding tissues. Existing TUS methods (e.g., in physiotherapy to provide deep heating to tissues such as tendons, ligaments, and skeletal muscles (Watson 2008) deliver low-intensity energy through the targeted tissue via the propagation of sound waves applied by an external source. The most common musculoskeletal application for TUS to date remains for pain and physiotherapy in conditions such as osteoarthritis-related knee pain, chronic back pain, lateral epicondylitis, and myofascial pain (Dedes et al. 2020; Gulati and Ottestad 2020; Petterson et al. 2020). Within the categorization of TUS, multiple ultrasound modalities have been developed and examined with various delivery modes, acoustic pressures, and duty cycles, to elicit different biological mechanisms in tissues (Fig. 10.3). Several examples include low-intensity pulsed ultrasound (LIPUS) (Warden et al. 2008; Hsu and Holmes 2016; Tanaka et al. 2020), low-intensity continuous ultrasound (cLIUS) (Lucchetti et al. 2020; Mittelstein et al. 2020), and pulsed focused ultrasound (pFUS) for soft tissue healing (Burks et al. 2011; Poliachik et al. 2014), nanoparticle delivery (O'Neill et al. 2009; Tharkar et al. 2019), physiotherapy for pain relief by providing deep heating to soft tissues (typically combined with physical therapy) (Brown et al. 2015; Papadopoulos and Mani 2020) and high-intensity focused ultrasound (HIFU) for thermal (tHIFU)

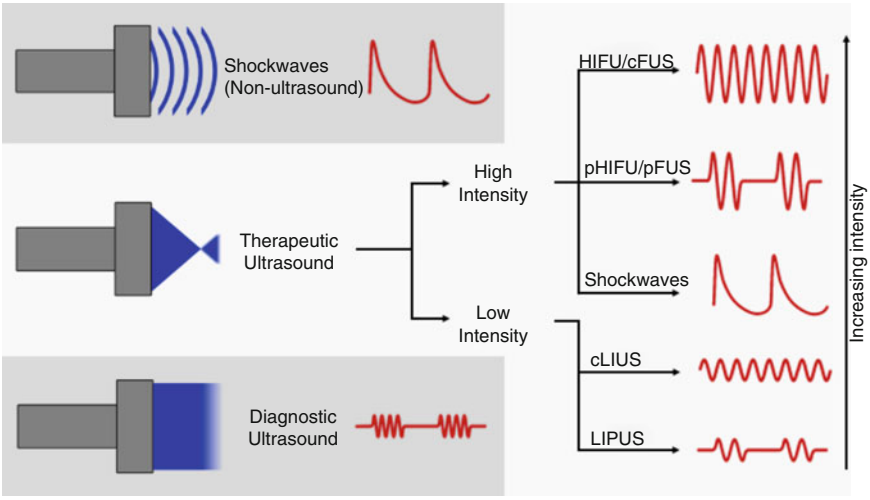

Fig. 10.3 Schematic of waveforms (different amplitudes) illustrating different modalities of TUS (Modified with permission from Liu et al. (2020))

ablation (Dubinsky et al. 2008; Vidal-Jove et al. 2015; Mauri et al. 2018) and non-thermal (histotripsy) tissue ablation (Vlaisavljevich et al. 2013; Bader et al. 2019; Xu et al. 2021).

A variety of labels have been utilized in published literature to describe different types of therapeutic ultrasound, with some overlap between commonly used terms. In general, these groups are broadly categorized based on the ultrasound intensity (high vs. low) and exposure mode (continuous vs. pulsed) (Liu et al. 2020). For clarity, in this chapter, we use the acronym *HIFU* to describe High Intensity Focused Ultrasound exposures that induce thermal and/or non-thermal irreversible changes within a short time frame (typically, it requires microseconds for direct effects during the pulse or histotripsy cavitation, milliseconds to elicit physiological responses such as in neuromodulation, to seconds or minutes for thermal changes). *FUS* refers to focused ultrasound methods (see Sect. 10.3 below), while *TUS* is used to describe low-intensity ultrasound exposures used currently for musculoskeletal physiotherapy and pain relief applications, as noted above. Different forms of TUS can be further categorized by understanding its basic physical parameters. A brief description of ultrasound parameters critical to the generated bioeffects and safety is given in Table 10.2.

Thermal bioeffects of ultrasound result from absorption of the applied ultrasonic energy. The amount of absorption and the accompanying heat generated depend upon ultrasound acoustic parameters as well as tissue properties. The primary determinants of thermal effects in tissues include tissue absorption coefficients and ultrasound exposure conditions, such as duration, intensity, beam width, and frequency. Importantly, there exists a direct relationship between the absorption capacity of a tissue and its protein content. Highly collagenous tissues such as tendon and ligament are known to absorb ultrasound energy more efficiently (Watson 2008). Other determinants of tissue temperature changes include ultrasound pulse repetition frequency and pulse duration, along with tissue characteristics such as density, acoustic impedance, and thermal conductivity (Dalecki 2004; Shankar and Pagel 2011).

Research suggests that an increase of temperature between 1 °C and 4 °C from baseline can provide therapeutic effects in tendons; however, higher elevations could potentially result in harmful effects such as thermal denaturation of collagen (Vlaisavljevich et al. 2015). An in vivo study investigated the ability of ultrasound to heat human patellar tendon and found that ultrasound frequency, intensity, duration of treatment, and size of the treatment area influenced heat production in tendon (Chan et al. 1998). The rate of temperature rise was found to be higher in the tendon compared to the adjoining muscle. Using a 3-MHz continuous ultrasound treatment lasting 4 minutes, temperature rises in the range of 8 °C to 10 °C were achieved using templates measuring two times the effective irradiation area of the transducer head. Such controlled thermal effects via TUS application are desirable to achieve pain relief, increased blood flow, decreased joint stiffness, and hyperdynamic tissue metabolism (Watson 2008; Papadopoulos and Mani 2020). Typically, physiotherapists utilize thermal effects of TUS to treat injuries such as tendonitis, joint pain, low back and neck pain, muscle strains, plantar fasciitis,

Table 10.2 Ultrasound parameters

	Parameter	Definition
1	Frequency (Hertz, Hz)	Number of US waves per second, or, number of times per second a particle experiences a complete compression and rarefaction cycle.
2	Duty Cycle (%)	The ratio of the time the transducer is "on" to the total exposure time (time "on" plus time "off")
3	Pulse Repetition Frequency (Hz)	Number of pulses transmitted per second
4	Intensity (W/cm^2)	A measure of ultrasound exposure that can be calculated based on maximum pressure measured in the field (Spatial Peak) or based on pressure averaged over a specific area (Spatial Average). When describing pulsed exposures, intensity may be applicable only while the pulse is "ON" (Pulse Average) or may be averaged over total time (Temporal Average). The most commonly reported intensity is Spatial Average Temporal Average (I_{SATA}); other reported indices include Spatial Average Pulse Average (I_{SAPA}), Spatial Average Temporal Peak (I_{SATP}), Spatial Peak Temporal Average (I_{SPTA}), and Spatial Peak Pulse Average (I_{SPPA}) (ter Haar 2007)
5	Acoustic power (Watts)	Total energy passing through a surface per unit time (measure of strength of ultrasound wave)
6	Mechanical index	Peak negative pressure of US waves divided by peak frequency; measures the likelihood of occurrence of a mechanical bioeffect due to cavitation.
7	Acoustic pressure (Pascal)	Changes in the local pressure of the medium, recorded as acoustic compression and rarefaction, typically measured as peak to peak pressure, peak negative pressure, or peak positive pressure. Defined as the difference between maximum or minimum pressure of the wave and average pressure of the medium in the absence of the wave
8	Attenuation (dB/cm/MHz)	Decrease in acoustic wave intensity per unit distance due to interactions between the wave and medium. It is usually expressed as a ratio of wave amplitudes in decibel notation, commonly per centimeter depth of tissue, per unit frequency, or at a specified frequency (e.g., dB/cm/MHz or dB/cm at 1 MHz)

ligament sprains, and arthritis pain (Brown et al. 2015; Papadopoulos and Mani 2020).

A combination of *non-thermal effects* such as acoustic streaming, acoustic cavitation, and radiation force displacement (Dalecki 2004; Izadifar et al. 2017) can also be produced by TUS or FUS application. Acoustic cavitation is the stable oscillation (inertial cavitation) or collapse (non-inertial cavitation) of a gas bubble in the presence of an acoustic field (Holland and Apfel 1990; Bader et al. 2019). Acoustic radiation force is that which results from momentum transfer from the sound field to the tissue of interest (Nightingale 2011; Urban 2018; Wang 2018). This effect itself is a consequence of radiation torque and acoustic streaming. The acoustic streaming phenomenon occurs when acoustic field propagation induces an increased rate of fluid flow (Dalecki 2004).

TUS is an appealing method to safely transfer mechanical energy to tendon tissue and elicit thermal and mechanical stimulation pathways in a prescribed manner. Although the therapeutic efficacy of TUS has been demonstrated in multiple studies, there is a substantial knowledge gap in understanding relationships between ultrasound dose (acoustic parameters) and the bioeffects elicited in these tissues. Optimal identification of TUS parameters and their correlation with molecular and tissue-level responses will largely benefit future research in ultrasound-induced tissue regeneration and rehabilitation.

10.2.2 TUS in Tendon Healing

The most widely studied form of TUS for musculoskeletal tissue repair and regeneration is low-intensity pulsed ultrasound (LIPUS), with applications in osteoporosis, fracture healing, mesenchymal stem cell recruitment and homing, and tendon–bone junction healing (Warden et al. 2008; Khanna et al. 2009; Zhang et al. 2017; Tanaka et al. 2020). Targeted application of TUS during different phases of tissue repair can produce a synergistic effect on healing (Saber and Saber 2017). During the inflammatory phase, TUS can stimulate mast cells, platelets, and macrophages, activating inflammatory mediators (Maxwell 1992; Leung et al. 2004). Efficiency of the proliferation phase of healing is also enhanced by TUS, by increasing collagen production and scar tissue formation (Zhou et al. 2004; Watson 2008). Lastly, TUS has also been shown to enhance the remodeling of scar tissue by improving collagen fiber orientation and increasing tensile strength (Nussbaum 1998; Maan et al. 2014).

The therapeutic potential of TUS, specifically low-intensity ultrasound (LIUS), in stimulating healing of acute tendon injuries has been investigated predominantly in animal studies, which enable the concurrent evaluation of tissue biomechanics and physiological responses to LIUS application (Table 10.3). Biomechanical metrics such as ultimate load, tensile strength and energy absorption, and structural metrics such as collagen organization and aggregation have been commonly characterized after applying treatments to assess the efficacy of TUS on healing (Ng et al. 2003; Yeung et al. 2006; Jeremias Junior et al. 2011). A 2016 review by Best et al. summarized the effects of LIUS on tendon, tendon–bone junction, muscle and ligament injuries (Best et al. 2016). The authors concluded that LIUS improves tendon strength and accelerates collagen formation after acute injury in preclinical models. Tensile strength and collagen expression (types I and III) were found to be greater in LIUS treated tendons compared to untreated controls (Jackson et al. 1991; da Cunha et al. 2001; Fu et al. 2008, 2010; Jeremias Junior et al. 2011; Kosaka et al. 2011). Regarding treatment time and duration (Fu et al. 2008, 2010), ultrasound treatment in the earlier (relative to later) stages of healing appears to improve tensile strength and matrix synthesis. While the available literature generally indicates that LIUS enhances biomechanical and structural properties of injured tendons, ultrasound parameters (e.g., intensity, stimulation frequency, and mode) and animal models (species, tendon of interest, and injury type) have varied across studies

Table 10.3 Results of studies investigating therapeutic ultrasound (TUS) treatment of tendon injuries

Author, Year	Species	Injury (or Injury Model)	Treatment paradigm	Key takeaways
da Cunha et al. (2001)	Rat	Achilles tenotomy	1 MHz, 0.5 W/cm^2, 5 min/day for 14 days	Improved collagen organization and aggregation when applied during early stages of healing in pulsed mode
Ng et al. (2003)	Rat	Achilles hemitransection	1 MHz, 1.0 or 2 W/cm^2, 4 min/session, for 22 sessions	Both treatment groups showed improved ultimate tensile strength compared to controls
Demir et al. (2004)	Rat	Achilles tenotomy	1 MHz, 0.5 W/cm^2, 5 min/day, 9 days	Increased tendon breaking strength following either TUS or laser therapy; treatment using combined modalities did not show additional positive effects.
Yeung et al. (2006)	Rat	Achilles tenotomy	1 MHz, 0.5 W/cm^2, 5 min/day, 3 times/week, for 2 or 4 weeks	Increased ultimate tensile strength and improved collagen bundle alignment.
Larsen et al. (2005)	Rabbit	Achilles tenotomy	3 MHz, varying intensities from 50 to 2000 mW/cm^2, 5 min/session, 10 sessions	No improvement in mechanical properties of healing tendons; mild decline in stiffness with increasing treatment intensity
Ng and Fung (2007)	Rat	Achilles tenotomy	1 MHz, varying intensities from 0.5 W/cm^2 to 2 W/cm^2 daily starting from day 5 after injury for 4 min/session for 22 sessions	Collagen fibril size increased with treatment, independent of intensity level.
Fu et al. (2008)	Rat	Patellar tendon mid-portion window defect	1.0 MHz, 30 mW/cm^2, 20 min/day, 5 days/week, for 2, 4, or 6 weeks	Beneficial effects of LIPUS (2-week treatment group) included improved ultimate tensile strength and collagen fiber alignment. 4 or 6 weeks of treatment was found to be detrimental to collagen remodeling.
Fu et al. (2010)	Rat	Central third patellar tendon removal	1.5 MHz, 150 mW/cm^2, 20 min/day for 14 or 28 days	Enhanced collagen synthesis during the granulation phase of healing.

(continued)

Table 10.3 (continued)

Author, Year	Species	Injury (or Injury Model)	Treatment paradigm	Key takeaways
Wood et al. (2010)	Rat	Achilles tendon partial rupture by direct trauma	3 MHz, 0.2 W/cm^2, 5 min/day, 5 days	Improved collagen organization; increased collagen type 1 in laser- and US-treated groups.
Jeremias Junior et al. (2011)	Rat	Achilles tenotomy	1 MHz, 0.1 W/cm^2, 5 min/day for 28 days	Increased ultimate load and tensile strength compared to controls.
Kosaka et al. (2011)	Rat	Achilles tenotomy	1.5 MHz, 45 mW/cm^2, 20 min/day	During the inflammatory phase, COX-2 and EP4 were overexpressed with LIPUS treatment, hence exaggerating inflammation. *TGF-β1*, *Col I*, and *Col III* expression levels were elevated in treated groups, encouraging tissue remodeling.
Farcic et al. (2013)	Rat	Achilles tenotomy	1 MHz, 0.5 W/cm^2, pulsed application for 1, 2, or 3 minutes per transducer area for 10 sessions	Collagen fibers showed better aggregation and organization in 3-minute treatment group
Farcic et al. (2018)	Rat	Achilles tenotomy	1 MHz, 0.5 W/cm^2, for 6 min/8 min/10 min for 10 days with 2 days of interval after fifth treatment day	10-minute treatment group showed the best collagen fiber aggregation and organization.
D'Vaz et al. (2006)	Human	Lateral epicondylitis	1.5 MHz, 30 mW/cm^2, 20 min/day for 12 weeks	Low-intensity ultrasound was not very effective compared to placebo.
Warden et al. (2008)	Human	Patellar tendinopathy	1.0 MHz, 100 mW/cm^2, 20 min/day for 12 weeks	Visual Analog Scale scores improved in both placebo and LIPUS treated groups; LIPUS provided no additional benefits over placebo.
Hsu and Holmes (2016)	Human	Achilles tendinopathy	Exogen® LIPUS device used for 20 min/day for 8 weeks over an area of maximum tenderness	Of 14 participants, 7 had excellent clinical outcomes with complete resolution of pain and other symptoms. 2 patients had good outcomes with mild tendon irritation and stiffness and 5 patients had minimal benefit with continued pain, swelling, and tenderness.

(continued)

Table 10.3 (continued)

Author, Year	Species	Injury (or Injury Model)	Treatment paradigm	Key takeaways
de Jesus et al. (2019)	Human	Patellar tendinopathy	1.0 MHz, 1.2 W/cm^2, 8 min/day, 2×/week for 8 weeks in combination with regimented exercise program	TUS enhanced the results obtained with rehabilitative exercise including pain and lower limb motor function.

COX-2 cyclooxygenase-2 enzyme, *EP4* Prostaglandin E_2 receptor 4, *TGF-β1* Transforming growth factor beta 1, *Col I* Collagen type I, *Col III* Collagen type III

(Tsai et al. 2011). In consideration of these inconsistencies, direct comparison of results is likely not warranted and researchers should exercise caution in deducing the cellular and molecular mechanisms attributable to treatments. Hence, there is not only an urgent need for standardization of TUS parameters and experimental conditions (treatment time, injury models) in future investigations, but also clinically relevant animal models whose tendon injury characteristics mirror those observed in human injuries.

Clinical studies have examined the influence of TUS on lateral epicondylitis (D'Vaz et al. 2006; Dedes et al. 2020), patellar tendinopathy (Warden et al. 2008; de Jesus et al. 2019) and Achilles tendinopathy (Hsu and Holmes 2016). A 2015 study on the short-term effectiveness of LIPUS on human Achilles tendinopathy revealed that all participants who had undergone traditional, nonsurgical treatment modalities prior to using LIPUS, showed good to excellent improvements in pain relief and function post-treatment (Hsu and Holmes 2016). In three studies that examined the influence of TUS on epicondylitis and patellar tendinopathy, a significant decrease in tendon pain was observed after daily treatments with continuous or pulsed LIUS treatment for 6 weeks (Best et al. 2016). However, two randomized controlled trials were used to assess the utility of LIPUS to treat chronic tendinopathies and reported that LIPUS provided no additional benefit to physical therapy for chronic tendinopathies (D'Vaz et al. 2006; Warden et al. 2008). Thus, while acute injury animal models demonstrate moderate effectiveness of LIUS in tendon healing, human studies specifically investigating chronic tendon injuries do not demonstrate promise as a noninvasive treatment option. Human studies investigating TUS effects on acute tendon injuries would provide further evidence to guide clinical practice, particularly if treatment paradigms across such studies were standardized, as noted above.

Extracorporeal Shockwave Therapy (ESWT) utilizes rapid, short-duration pressure waves ("shockwaves") intended to elicit physicochemical and cellular reparative responses and has shown promise in treating a variety of musculoskeletal conditions (Simplicio et al. 2020). ESWT can be regarded as high-intensity therapeutic ultrasound, since shockwaves can be generated under both continuous and pulsed modes via transducers that induce nonlinear propagation effects resulting in shock formation. Alternatively, shockwaves can also be generated by non-ultrasonic

sources such as electrohydraulic and electromagnetic systems (Simplicio et al. 2020). To date, the US FDA has only approved the use of ESWT for plantar fasciitis and lateral epicondylitis (Wang 2012). Studies have shown that ESWT acts as a mechanical stimulus and promotes healing via mechanotransduction (Moya et al. 2018; Simplicio et al. 2020) and may also alleviate pain (Hausdorf 2008). In humans, ESWT may aid tendon healing by providing mechanical stimulation to aid inflammatory and catabolic processes that are associated with damaged matrix constituents (Waugh et al. 2015). A recent study compared the effectiveness of ESWT and LIUS on pain, return to functionality, and quality of life in patients with Achilles tendinopathy (Dedes et al. 2020). Although both interventions resulted in significant improvements in pain and functionality immediately and 4 weeks post-treatment, the effects of ESWT were more pronounced compared to LIUS. Another recent, randomized controlled trial evaluated the effectiveness of point-focused (small treatment volume focused on the point of maximum pain) and line-focused (larger treatment volume with equally distributed energy density but smaller maximum pressure compared to point-focused) ESWT on patients with confirmed Achilles tendinopathy and concluded that both modalities showed superior outcomes in terms of pain relief compared to placebo treatment (Gatz et al. 2021). Previous in vitro studies have shown the positive effects of ESWT on tenocyte viability and proliferation, collagen fiber synthesis and organization, expression of TGF-β1 and IGF-1, and decreased expression of MMPs and pro-inflammatory interleukins (ILs) (Banes et al. 1999; Chen et al. 2004; Notarnicola and Moretti 2012). While ESWT is currently deemed as a safe and effective "mechanotherapy" to treat many musculoskeletal pathologies including chronic tendon injuries, unfortunately, there exists very little guidance with regard to parameter selection to ensure repeatability and effectiveness for degenerative tendinopathy (d'Agostino et al. 2017; Fan et al. 2020).

10.3 Focused Ultrasound: A Novel Therapeutic for Tendon Healing?

Recently, Focused Ultrasound (FUS) methods have shown great promise for non-invasive tissue ablation, neuromodulation, and drug delivery (Daoudi et al. 2017; Miller and O'Callaghan 2017; Chua and Faigel 2019). FUS treatments are currently approved for numerous applications including treatment of painful bone metastases, essential tremor, uterine fibroids, and prostate cancer (Duc and Keserci 2019). FUS is also gaining considerable interest as a musculoskeletal treatment option, with clinical research in applications such as osteoarthritis, bone and desmoid tumors, epicondylitis, rotator cuff injury, and plantar fasciitis (Liberman et al. 2009; Weeks et al. 2012; Masashi Izumi et al. 2013; Chan et al. 2017). Another emerging application of FUS is pain relief. Although the precise mechanisms of FUS-induced analgesia are not clear, localized denervation of tissue targets and neuromodulatory effects have been presumed (Brown et al. 2015).

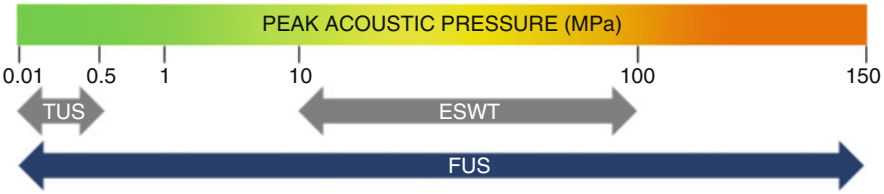

Fig. 10.4 Comparison of an approximate range of peak acoustic pressures delivered by FUS, ESWT, and Low-Intensity TUS

The multitude of diverse applications of FUS are largely dependent on the exposure conditions and the manner in which they are delivered (Fishman and Frenkel 2017). In contrast to HIFU (which is primarily used for tissue ablation), *therapeutic FUS* can be leveraged to achieve effective, functional tissue healing via thermal and/or mechanical stimulation pathways, without inducing irreversible tissue damage. Furthermore, FUS can achieve higher precision with a wide range of acoustic exposures that can encapsulate those utilized in LIUS and ESWT (Fig. 10.4). Additionally, the pulsing parameters can be modulated in real-time during treatment across a wide parameter space. With the advent of state-of-the-art, customizable, reliable, and safe FUS systems, researchers and clinicians are beginning to leverage the potential of image-guided, therapeutic FUS for the treatment of many debilitating conditions.

Focusing on the ultrasound beams prevents them from being applied to other regions, and minimizes the potential for thermal or mechanical damage to tissues located outside the focal zone, allowing for precise treatments of targeted tissues or tissue regions. To achieve localized biological effects, FUS transducers are designed such that focused ultrasound beams converge at a single focal point, using techniques such as geometric focusing (concave transducers that cause waves to arrive at a single focal point), electronic focusing (using phased array transducers composed of multiple piezoelectric elements), or by using acoustic lenses (mimicking a concave transducer surface) (Elhelf et al. 2018).

Ultrasound waves interact with tissues to produce thermal and non-thermal bioeffects (Sect. 10.2.1). Acoustic cavitation, which is one of the most widely studied non-thermal mechanisms, is not significant at lower intensities and is often associated with "high" acoustic pressures (Bader et al. 2019). Typically, at high-pressure amplitudes, microscopic gas bubbles form and oscillate (non-inertial cavitation) or steadily grow in size and collapse above certain pressure thresholds (inertial cavitation). Stable or non-inertial cavitation may induce reversible tissue effects such as sonoporation, whereas inertial cavitation induces large stresses and strains on the tissue, ultimately leading to irreversible tissue damage, i.e., histotripsy ablation. Cavitation can also enhance thermal effects by increasing energy absorption at the focal point. Thus, acoustic amplitudes can directly alter the threshold for inertial cavitation as they can change bubble response from non-inertial to inertial cavitation. Mechanical Index (MI) is another parameter that is commonly used to

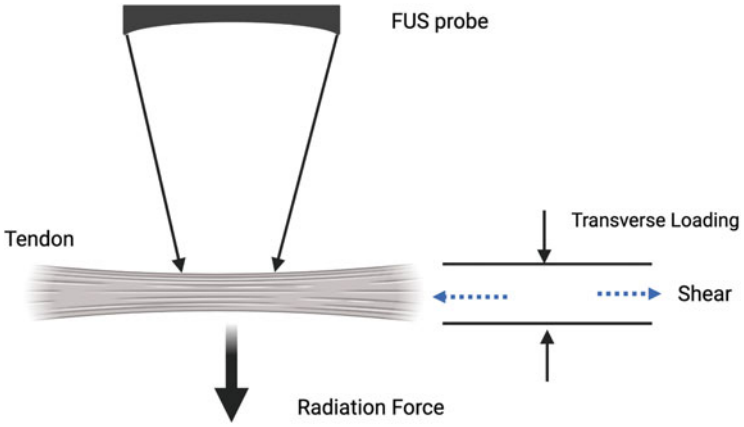

Fig. 10.5 An FUS transducer producing Acoustic Radiation Force to generate tissue displacements and/or deformation

determine the likelihood of cavitation. It is defined as the maximum value of negative peak pressure divided by the root square of the acoustic center frequency. The MI is frequently used to determine the exposures below which cavitation and related bioeffects would not be observed.

In the absence of cavitation, tissue displacement due to FUS application typically occurs as a result of radiation forces. Acoustic Radiation Force (ARF) is defined as the time-averaged force exerted by acoustic waves on the tissue (Urban 2018). As a result of these forces, localized tissue displacement and deformation can be observed, due to transfer of momentum from the sound field to the tissue. Depending on variables such as probe orientation, ultrasound can induce mechanical loading of the extracellular matrix, which in turn provides a biophysical stimulus to the resident cells. ARFs are known to influence cellular proliferation and protein synthesis as evidenced by augmented wound healing and bone remodeling and healing (Curra and Crum 2003; Zhang et al. 2012; Tang et al. 2015). Figure 10.5 depicts the application of radial forces, which deform the tendon transversely while, simultaneously, shear loading of the tendon occurs longitudinally (i.e., along the tendon's long axis). Irrespective of the mode of mechanical loading, tissue deformation can be spatially and temporally quantified using speckle-tracking methods in conjunction with high-frequency imaging (Bercoff et al. 2004; Liu and Ebbini 2010; Ebbini and ter Haar 2015). Perhaps the most prominent biomedical application utilizing ARFs is in conjunction with imaging, to determine the mechanical properties of tissue by utilizing radiation forces (Wells and Liang 2011; Doherty et al. 2013; Urban 2018). Acoustic Radiation Force Impulse (ARFI) imaging utilizes short-duration acoustic radiation forces to generate localized, quantifiable tissue deformation, thereby providing a noninvasive method to quantify tissue biomechanical properties. Recently, the utility of ARFI imaging has been recognized for multiple tissue types including tendon, thyroid, breast, kidney, and pancreas (Bojunga et al. 2012; Wang 2016; Kaya et al. 2018).

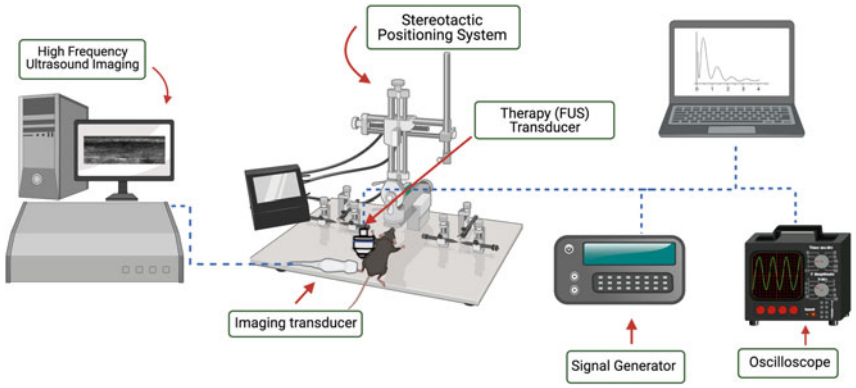

Fig. 10.6 Schematic of a custom-built small animal FUS system allowing interchangeable transducers and driving systems (for different FUS exposures) and a high-frequency imaging system for real-time treatment monitoring and guidance

Currently, FUS methods are being explored to achieve effective tendon healing. One approach is to utilize "low intensity" FUS methods to promote tendon healing via radiation forces (predominantly mechanical stimulation) without producing thermal damage and cavitation-like bioeffects (Meduri et al. 2020). Higher amplitude pulses (compared to traditional physiotherapy applications) are expected to induce larger tendon matrix strains, and this mechanical effect, similar to existing mechanical loading (exercise) therapies typically used for the treatment of chronic tendon injuries (Mafi et al. 2001; Kingma et al. 2007; Irby et al. 2020), in turn, can effectively stimulate tendon repair. Researchers are also exploring histotripsy, a cavitation-based therapy that utilizes short, high-intensity pulses to mechanically homogenize tissue with negligible heating in the tissue (Smallcomb and Simon 2019). Such cavitation effects can induce targeted microdamage within the tendon and promote a healing response, thus serving as an improved, noninvasive alternative to traditional dry needling approaches (Khandare et al. 2021). Initial studies have shown that this approach preserves the mechanical properties of tendons better than dry needling, without damaging the surrounding tissue.

The wide range of FUS applications utilizing both thermal and non-thermal bioeffects indicate the need for robust, real-time image guidance systems with high sensitivity and specificity, for target visualization, beam focusing, and accuracy verification. An ideal, innovative FUS system for tendon healing applications can precisely target tendons, accurately measure the resulting thermal and mechanical bioeffects and facilitate the investigation of cell/tissue responses. Given the paucity of published data on acoustic parameters and mechanisms of action associated with focused ultrasound therapies for tendon injuries, a thorough investigation of such methods in suitable preclinical models is necessary. Controlled studies in relevant animal models will provide a rigorous basis for optimizing acoustic pulsing parameters for FUS tendon treatments, strengthen the rationale for using FUS as a noninvasive treatment method of stimulating tendon healing and will establish a

modular, scalable experimental platform upon which further studies of different species (e.g., rabbit, equine, and human) can readily be undertaken. Figure 10.6 depicts a modular, custom designed system that can apply controlled mechanical, thermal, and mechanical-thermal (dual) stimulation to murine Achilles tendons, under image guidance (Meduri et al. 2020). To establish the feasibility and efficacy of applying different pulsing schemes to injured tendons, investigators may utilize reliable preclinical tendon injury models such as tenotomy for acute injuries or a previously established murine Achilles model (Bell et al. 2013a; Rezvani et al. 2021) of degenerative tendinopathy. The concurrent utilization of real-time, high-frequency ultrasound imaging (as depicted in Fig. 10.6), high field magnetic resonance imaging (MRI) methods, or laser vibrometry enables the quantification of mechanical effects.

Noninvasive (MRI thermometry) or invasive (thermocouple) assessment of dynamic temperature changes accompanying FUS treatment of tendons is a crucial component in analyzing thermal effects of pulsing. Experimental, regional measurements of temperature may further be used to validate computational simulations of predicted heating effects from FUS fields. The effect of predominantly thermal and predominantly mechanical stimulation on the healing profiles of injured tendons can then be established using biomechanical, geometric, cellular, and histologic analyses.

10.4 Future Advancements in Ultrasound-Based Stimulation of Tendon Healing

Although therapeutic ultrasound approaches are widely used for physiotherapy applications, *the mechanism of action and optimal acoustic parameters are poorly understood* and have not been systematically investigated in comparative studies utilizing in vivo tendon injury models. Novel in vivo data from small animal FUS studies will serve as a foundation upon which the methodology can be readily adapted to larger species in order to explore a wider range of FUS treatments in more clinically relevant animal models. Future studies aimed at identifying optimal TUS modalities (e.g., FUS and ESWT) and the corresponding acoustic parameter sets for the treatment of specific tendon injuries (acute and chronic) will strengthen the rationale for using ultrasound modalities for noninvasive stimulation of tendon healing and regeneration.

Specifically, for the treatment of chronic tendon injuries, it is widely known that mechanical loading-based treatments such as exercise-based rehabilitation can effectively treat symptomatic tendinopathy; however, the mechanism of this healing response is not well understood. Furthermore, physiotherapy requires patient compliance, frequently causes discomfort, and may require lengthy treatment periods (e.g., up to 5 years) for symptomatic relief and restored functionality. Successful development of US-based treatments for chronic tendon injuries may provide further

insights into the aforementioned healing pathways in response to mechanical loading. Finally, FUS approaches for treatment of tendon injuries alone or in combination with other therapies could represent an attractive alternative for individuals who are unable or unwilling (e.g., due to pain or injury severity) to pursue physical therapy. In turn, prompt and effective treatment of injured tendons is expected to halt the progression of long-term, degenerative changes that may lead to chronic mobility issues.

References

Andarawis-Puri N, Sereysky JB, Sun HB, Jepsen KJ, Flatow EL (2012) Molecular response of the patellar tendon to fatigue loading explained in the context of the initial induced damage and number of fatigue loading cycles. J Orthop Res 30(8):1327–1334

Arnoczky SP, Lavagnino M, Egerbacher M (2007) The mechanobiological aetiopathogenesis of tendinopathy: is it the over-stimulation or the under-stimulation of tendon cells? Int J Exp Pathol 88(4):217–226

Bader KB, Vlaisavljevich E, Maxwell AD (2019) For whom the bubble grows: physical principles of bubble nucleation and dynamics in histotripsy ultrasound therapy. Ultrasound Med Biol 45(5):1056–1080

Banes AJ, Horesovsky G, Larson C, Tsuzaki M, Judex S, Archambault J, Zernicke R, Herzog W, Kelley S, Miller L (1999) Mechanical load stimulates expression of novel genes in vivo and in vitro in avian flexor tendon cells. Osteo Cart 7(1):141–153

Bell R, Li J, Gorski DJ, Bartels AK, Shewman EF, Wysocki RW, Cole BJ, Bach BR Jr, Mikecz K, Sandy JD, Plaas AH, Wang VM (2013a) Controlled treadmill exercise eliminates Chondroid deposits and restores tensile properties in a new murine tendinopathy model. J Biomech 46(3): 498–505

Bell R, Li J, Shewman EF, Galante JO, Cole BJ, Bach BR Jr, Troy KL, Mikecz K, Sandy JD, Plaas AH, Wang VM (2013b) ADAMTS5 is required for biomechanically-stimulated healing of murine tendinopathy. J Orthop Res 31(10):1540–1548

Benjamin M, Ralphs JR (1998) Fibrocartilage in tendons and ligaments-an adaptation to compressive load. JAnat 193:481–494

Benjamin M, Kaiser E, Milz S (2008) Structure-function relationships in tendons: a review. J Anat 212(3):211–228

Bercoff J, Tanter M, Fink M (2004) Supersonic shear imaging: a new technique for soft tissue elasticity mapping. IEEE Trans Ultrason Ferroelectr Freq Control 51(4):396–409

Best TM, Wilk KE, Moorman CT, Draper DO (2016) Low intensity ultrasound for promoting soft tissue healing: a systematic review of the literature and medical technology. Intern Med Rev (Wash D C) 2(11):271

Bi Y, Ehirchiou D, Kilts TM, Inkson CA, Embree MC, Sonoyama W, Li L, Leet AI, Seo BM, Zhang L, Shi S, Young MF (2007) Identification of tendon stem/progenitor cells and the role of the extracellular matrix in their niche. Nat Med 13(10):1219–1227

Bojunga J, Dauth N, Berner C, Meyer G, Holzer K, Voelkl L, Herrmann E, Schroeter H, Zeuzem S, Friedrich-Rust M (2012) Acoustic radiation force impulse imaging for differentiation of thyroid nodules. PLoS One 7(8):e42735

Brown MR, Farquhar-Smith P, Williams JE, ter Haar G, deSouza NM (2015) The use of high-intensity focused ultrasound as a novel treatment for painful conditions-a description and narrative review of the literature. Br J Anaesth 115(4):520–530

Burks SR, Ziadloo A, Hancock HA, Chaudhry A, Dean DD, Lewis BK, Frenkel V, Frank JA (2011) Investigation of cellular and molecular responses to pulsed focused ultrasound in a mouse model. PLoS One 6(9):e24730

Cardoso TB, Pizzari T, Kinsella R, Hope D, Cook JL (2019) Current trends in tendinopathy management. Best Pract Res Clin Rheumatol 33:122–140

Chan AK, Myrer JW, Measom GJ, Draper DO (1998) Temperature changes in human patellar tendon in response to therapeutic ultrasound. J Atthl Train 33(2):130–135

Chan M, Dennis K, Huang Y, Mougenot C, Chow E, DeAngelis C, Coccagna J, Sahgal A, Hynynen K, Czarnota G, Chu W (2017) Magnetic resonance-guided high-intensity-focused ultrasound for palliation of painful skeletal metastases: a pilot study. Technol Cancer Res Treat 16(5):570–576

Chen YJ, Wang CJ, Yang KD, Kuo YR, Huang HC, Huang YT, Sun YC, Wang FS (2004) Extracorporeal shock waves promote healing of collagenase-induced Achilles tendinitis and increase TGF- p 1 and IGF-I expression. J Ortho Res 22:854–861

Chen L, Liu JP, Tang KL, Wang Q, Wang GD, Cai XH, Liu XM (2014) Tendon derived stem cells promote platelet-rich plasma healing in collagenase-induced rat achilles tendinopathy. Cell Physiol Biochem 34(6):2153–2168

Chua T, Faigel D (2019) Endoscopic ultrasound-guided ablation of liver tumors. Gastrointest Endosc Clin N Am 29(2):369–379

Costa-Almeida R, Calejo I, Gomes ME (2019) Mesenchymal stem cells empowering tendon regenerative therapies. Int J Mol Sci 20(12):3002

Curra FP, Crum LA (2003) Therapeutic ultrasound: surgery and drug delivery. Acoust Sci Technol 24(6):343–348

d'Agostino MC, Tibalt E, Craig KV, Respizzi S (2017) Shock wave therapy for tendinopathies. In: Muscle and tendon injuries. Springer, Berlin, pp 421–439

da Cunha A, Parizotto NA, Vidal B d C (2001) The effect of therapeutic US on Achilles tendon repair of the rat. Ultrasound Med Biol 27(12):1691–1696

Dakin SG, Smith RK, Heinegard D, Onnerfjord P, Khabut A, Dudhia J (2014) Proteomic analysis of tendon extracellular matrix reveals disease stage-specific fragmentation and differential cleavage of COMP (cartilage oligomeric matrix protein). J Biol Chem 289(8):4919–4927

Dalecki D (2004) Mechanical bioeffects of ultrasound. Annu Rev Biomed Eng 6:229–248

Daoudi K, Hoogenboom M, den Brok M, Eikelenboom D, Adema GJ, Futterer JJ, de Korte CL (2017) In vivo photoacoustics and high frequency ultrasound imaging of mechanical high intensity focused ultrasound (HIFU) ablation. Biomed Opt Express 8(4):2235–2244

de Jesus JF, de Albuquerque TAB, Shimba LG, Bryk FF, Cook J, Pinfildi CE (2019) High-energy dose of therapeutic ultrasound in the treatment of patellar tendinopathy: protocol of a randomized placebo-controlled clinical trial. BMC Musculoskelet Disord 20(1):624

Dedes V, Tzirogiannis K, Polikandrioti M, Dede AM, Mitseas A, Panoutsopoulos GI (2020) Comparison of radial extracorporeal shockwave therapy with ultrasound therapy in patients with lateral epicondylitis. J Med Ultrason (2001) 47(2):319–325

Demir H, Menku P, Kirnap M, Calis M, Ikizceli I (2004) Comparison of the effects of laser, ultrasound, and combined laser + ultrasound treatments in experimental tendon healing. Lasers Surg Med 35(1):84–89

Dirks RC, Warden SJ (2011) Models for the study of tendinopathy. J Musculoskelet Neuronal Interact 11(2):141–149

Dirks RC, Richard JS, Fearon AM, Scott A, Koch LG, Britton SL, Warden SJ (2013) Uphill treadmill running does not induce histopathological changes in the rat Achilles tendon. BMC Musculoskelet Disord 14:90

Docheva D, Muller SA, Majewski M, Evans CH (2015) Biologics for tendon repair. Adv Drug Deliv Rev 84:222–239

Doherty JR, Trahey GE, Nightingale KR, Palmeri ML (2013) Acoustic radiation force elasticity imaging in diagnostic ultrasound. IEEE Trans Ultrason Ferroelectr Freq Control 60(4):685–701

Dubinsky TJ, Cuevas C, Dighe MK, Kolokythas O, Hwang JH (2008) High-intensity focused ultrasound: current potential and oncologic applications. AJR Am J Roentgenol 190(1):191–199
Duc NM, Keserci B (2019) Emerging clinical applications of high-intensity focused ultrasound. Diagn Interv Radiol 25(5):398–409
D'Vaz AP, Ostor AJ, Speed CA, Jenner JR, Bradley M, Prevost AT, Hazleman BL (2006) Pulsed low-intensity ultrasound therapy for chronic lateral epicondylitis: a randomized controlled trial. Rheumatology (Oxford) 45(5):566–570
Ebbini ES, ter Haar G (2015) Ultrasound-guided therapeutic focused ultrasound: current status and future directions. Int J Hyperth 31(2):77–89
Elhelf IAS, Albahar H, Shah U, Oto A, Cressman E, Almekkawy M (2018) High intensity focused ultrasound: the fundamentals, clinical applications and research trends. Diagn Interv Imaging 99(6):349–359
Fahlstrom M, Jonsson P, Lorentzon R, Alfredson H (2003) Chronic Achilles tendon pain treated with eccentric calf-muscle training. Knee Surg Sports Traumatol Arthrosc 11(5):327–333
Fan Y, Feng Z, Cao J, Fu W (2020) Efficacy of extracorporeal shock wave therapy for Achilles tendinopathy: a meta-analysis. Orthop J Sports Med 8(2):2325967120903430
Farcic TS, Baldan CS, Cattapan CG, Parizotto NA, Joao SM, Casarotto RA (2013) Treatment time of ultrasound therapy interferes with the organization of collagen fibers in rat tendons. Braz J Phys Ther 17(3):263–271
Farcic TS, Baldan CS, Machado AFP, Caffaro LAM, Masson IFB, Casarotto RA (2018) Collagen fibers in the healing process of rat Achilles tendon rupture using different times of ultrasound therapy. Adv Wound Care (New Rochelle) 7(4):114–120
Fishman PS, Frenkel V (2017) Treatment of movement disorders with focused ultrasound. J Cent Nerv Syst Dis 9:1179573517705670
Fu SC, Shum WT, Hung LK, Wong MW, Qin L, Chan KM (2008) Low-intensity pulsed ultrasound on tendon healing: a study of the effect of treatment duration and treatment initiation. Am J Sports Med 36(9):1742–1749
Fu SC, Hung LK, Shum WT, Lee YW, Chan LS, Ho G, Chan KM (2010) In vivo low-intensity pulsed ultrasound (LIPUS) following tendon injury promotes repair during granulation but suppresses decorin and biglycan expression during remodeling. J Orthop Sports Phys Ther 40(7):422–429
Fung DT, Wang VM, Laudier DM, Shine JH, Basta-Pljakic J, Jepsen KJ, Schaffler MB, Flatow EL (2009) Subrupture tendon fatigue damage. J Orthop Res 27(2):264–273
Fung DT, Wang VM, Andarawis-Puri N, Basta-Pljakic J, Li Y, Laudier DM, Sun HB, Jepsen KJ, Schaffler MB, Flatow EL (2010) Early response to tendon fatigue damage accumulation in a novel in vivo model. J Biomech 43(2):274–279
Garcia-Melchor E, Cafaro G, MacDonald L, Crowe LAN, Sood S, McLean M, Fazzi UG, McInnes IB, Akbar M, Millar NL (2021) Novel self-amplificatory loop between T cells and tenocytes as a driver of chronicity in tendon disease. Ann Rheum Dis 80(8):1075–1085
Gatz M, Schweda S, Betsch M, Dirrichs T, de la Fuente M, Reinhardt N, Quack V (2021) Line- and point-focused extracorporeal shock wave therapy for Achilles tendinopathy: a placebo-controlled RCT study. Sports Health 13(5):511–518
Goodman SA, May SA, Heinegard D, Smith RKW (2004) Tenocyte response to cyclical strain and transforming growth factor beta is dependent upon age and site of origin. Biorheology 41(5): 613–628
Gottardi R, Stoddart MJ (2018) Regenerative rehabilitation of the musculoskeletal system. J Am Acad Orthop Surg 26(15):e321–e323
Gray G, Brolinson PG (2001) Principle-centered rehabilitation. In: Principles and practice of primary care sports medicine. Lippincott Williams & Wilkins, Philadelphia, PA, pp 645–652
Gulati A, Ottestad E (2020) Hearing the call for therapeutic ultrasound. Pain Med 21(7):1317–1318
Hast MW, Zuskov A, Soslowsky LJ (2014) The role of animal models in tendon research. Bone Joint Res 3:193–202

Hausdorf J (2008) Selective loss of unmyelinated nerve fibers after extracorporeal shockwave application to the musculoskeletal system. J Neuroscience 155(1):138–144
Heinemeier KM, Skovgaard D, Bayer ML, Qvortrup K, Kjaer A, Kjaer M, Magnusson SP, Kongsgaard M (2012) Uphill running improves rat Achilles tendon tissue mechanical properties and alters gene expression without inducing pathological changes. J Appl Physiol (1985) 113(5):827–836
Herod TW, Veres SP (2018) Development of overuse tendinopathy: a new descriptive model for the initiation of tendon damage during cyclic loading. J Orthop Res 36(1):467–476
Holland CK, Apfel RE (1990) Thresholds for transient cavitation produced by pulsed ultrasound in a controlled nuclei environment. J Acoust Soc Am 88(5):2059–2069
Hsu AR, Holmes GB (2016) Preliminary treatment of Achilles tendinopathy using low-intensity pulsed ultrasound. Foot Ankle Spec 9(1):52–57
Humphrey JD, Dufresne ER, Schwartz MA (2014) Mechanotransduction and extracellular matrix homeostasis. Nat Rev Mol Cell Biol 15(12):802–812
Irby A, Gutierrez J, Chamberlin C, Thomas SJ, Rosen AB (2020) Clinical management of tendinopathy: a systematic review of systematic reviews evaluating the effectiveness of tendinopathy treatments. Scand J Med Sci Sports 30(10):1810–1826
Izadifar Z, Babyn P, Chapman D (2017) Mechanical and biological effects of ultrasound: a review of present knowledge. Ultrasound Med Biol 43(6):1085–1104
Jackson BA, Schwane JA, Starcher BC (1991) Effect of ultrasound therapy on the repair of Achilles tendon injuries in rats. Med Sci Sport Exer 23(2):271–176
Jeremias Junior SL, Camanho GL, Bassit AC, Forgas A, Ingham SJ, Abdalla RJ (2011) Low-intensity pulsed ultrasound accelerates healing in rat calcaneus tendon injuries. J Orthop Sports Phys Ther 41(7):526–531
Kannus P (2000) Structure of the tendon connective tissue. Scand J Med Sci Sports 10:312–320
Kaya M, Degirmenci S, Goya C, Tuncel ET, Ucmak F, Kaplan MA (2018) The importance of acoustic radiation force impulse (ARFI) elastography in the diagnosis and clinical course of acute pancreatitis. Turk J Gastroenterol 29(3):342–347
Khandare S, Smallcomb M, Klein B, Geary C, Simon JC, Vidt ME (2021) Comparison between dry needling and focused ultrasound on the mechanical properties of the rat Achilles tendon: a pilot study. J Biomech 120:110384
Khanna A, Nelmes RT, Gougoulias N, Maffulli N, Gray J (2009) The effects of LIPUS on soft-tissue healing: a review of literature. Br Med Bull 89:169–182
Kingma JJ, de Knikker R, Wittink HM, Takken T (2007) Eccentric overload training in patients with chronic Achilles tendinopathy: a systematic review. Br J Sports Med 41(6):e3
Kosaka T, Masaoka T, Yamamoto K (2011) Possible molecular mechanism of promotion of repair of acute Achilles tendon rupture by low intensity-pulsed ultrasound treatment in a rat model. West Indian Med J 60(3):263–268
Lacitignola L, Staffieri F, Rossi G, Francioso E, Crovace A (2014) Survival of bone marrow mesenchymal stem cells labelled with red fluorescent protein in an ovine model of collagenase-induced tendinitis. Vet Comp Orthop Traumatol 27(3):204–209
Larsen A, Kristensen G, Thorlacius-Ussing O, Oxlund H (2005) The influence of ultrasound on the mechanical properties of healing tendons in rabbits. Acta Orthop 76(2):225–230
Leek CC, Soulas JM, Sullivan AL, Killian ML (2020) Using tools in mechanobiology to repair tendons. Curr Tissue Microenviron Rep 1(2):31–40
Legerlotz K, Jones ER, Screen HR, Riley GP (2012) Increased expression of IL-6 family members in tendon pathology. Rheumatology (Oxford) 51(7):1161–1165
Leung MC, Ng GY, Yip KK (2004) Effect of ultrasound on acute inflammation of transected medial collateral ligaments. Arch Phys Med Rehabil 85(6):963–966
Liberman B, Gianfelice D, Inbar Y, Beck A, Rabin T, Shabshin N, Chander G, Hengst S, Pfeffer R, Chechick A, Hanannel A, Dogadkin O, Catane R (2009) Pain palliation in patients with bone metastases using MR-guided focused ultrasound surgery: a multicenter study. Ann Surg Oncol 16(1):140–146

Lim WL, Liau LL, Ng MH, Chowdhury SR, Law JX (2019) Current Progress in tendon and ligament tissue engineering. Tissue Eng Regen Med 16(6):549–571
Lin TW, Cardenas L, Glaser DL, Soslowsky LJ (2006) Tendon healing in interleukin-4 and interleukin-6 knockout mice. J Biomech 39(1):61–69
Liu D, Ebbini ES (2010) Real-time 2-D temperature imaging using ultrasound. IEEE Trans Biomed Eng 57(1):12–16
Liu DD, Ullah M, Concepcion W, Dahl JJ, Thakor AS (2020) The role of ultrasound in enhancing mesenchymal stromal cell-based therapies. Stem Cells Transl Med 9:850–866
Lucchetti D, Perelli L, Colella F, Ricciardi-Tenore C, Scoarughi GL, Barbato G, Boninsegna A, De Maria R, Sgambato A (2020) Low-intensity pulsed ultrasound affects growth, differentiation, migration, and epithelial-to-mesenchymal transition of colorectal cancer cells. J Cell Physiol 235(6):5363–5377
Maan ZN, Januszyk M, Rennert RC, Duscher D, Rodrigues M, Fujiwara T, Ho N, Whitmore A, Hu MS, Longaker MT, Gurtner GC (2014) Noncontact, low-frequency ultrasound therapy enhances neovascularization and wound healing in diabetic mice. Plast Reconstr Surg 134(3):402e–411e
Mackie EJ, Ramsey S (1996) Expression of tenascin in joint-associated tissues during development and postnatal growth. J Anat 188:157–165
Maeda T, Sakabe T, Sunaga A, Sakai K, Rivera AL, Keene DR, Sasaki T, Stavnezer E, Iannotti J, Schweitzer R, Ilic D, Baskaran H, Sakai T (2011) Conversion of mechanical force into TGF-beta-mediated biochemical signals. Curr Biol 21(11):933–941
Maffulli N, Longo UG, Denaro V (2010) Novel approaches for the management of tendinopathy. J Bone Joint Surg Am 92(15):2604–2613
Mafi N, Lorentzon R, Alfredson H (2001) Superior short-term results with eccentric calf muscle training compared to concentric training in a randomized prospective multicenter study on patients with chronic Achilles tendinosis. Knee Surg Sports Traumatol Arthrosc 9(1):42–47
Marqueti R, Neto I, Barin F, Ramos G (2019) Exercise and tendon remodeling mechanism. In: Sozen H (ed) Tendons. IntechOpen Publishing, pp 37–56
Masashi Izumi MI, Kawasaki M, Ushida T, Morio K, Namba H, Graven-Nielsen T, Ogawa Y, Tani T (2013) MR-guided focused ultrasound for the novel and innovative management of osteoarthritic knee pain. BMC Musculoskelet Disord 14:267
Mauri G, Nicosia L, Xu Z, Di Pietro S, Monfardini L, Bonomo G, Varano GM, Prada F, Vigna PD, Orsi F (2018) Focused ultrasound: tumour ablation and its potential to enhance immunological therapy to cancer. Br J Radiol 91(1083):20170641
Maxwell L (1992) Therapeutic ultrasound: its effects on the cellular and molecular mechanisms of inflammation and repair. Physiotherapy 78(6):421–426
Meduri C, Simon, A, De Konick L, Coffey M, Claros E, Velazquez M, Brolinson PG, McCrady B, Vlaisavljevich E, Wang VM (2020) Design of a Focused Ultrasound System for the non-invasive treatment of injured tendons. In: 7th International Symposium on Focused Ultrasound
Mehr D, Pardubsky PD, Martin JA, Buckwalter JA (2000) Tenascin-C in tendon regions subjected to compression. J Orthop Res 18:537–545
Millar NL, Hueber AJ, Reilly JH, Xu Y, Fazzi UG, Murrell GA, McInnes IB (2010) Inflammation is present in early human tendinopathy. Am J Sports Med 38(10):2085–2091
Millar NL, Murrell GA, McInnes IB (2017) Inflammatory mechanisms in tendinopathy - towards translation. Nat Rev Rheumatol 13(2):110–122
Millar NL, Silbernagel KG, Thorborg K, Kirwan PD, Galatz LM, Abrams GD, Murrell GAC, McInnes IB, Rodeo SA (2021) Tendinopathy. Nat Rev Dis Primers 7(1):1
Miller DB, O'Callaghan JP (2017) New horizons for focused ultrasound (FUS) - therapeutic applications in neurodegenerative diseases. Metabolism 69S:S3–S7
Mittelstein DR, Ye J, Schibber EF, Roychoudhury A, Martinez LT, Fekrazad MH, Ortiz M, Lee PP, Shapiro MG, Gharib M (2020) Selective ablation of cancer cells with low intensity pulsed ultrasound. Appl Phys Lett 116(1):013701

Moser HL, Doe AP, Meier K, Garnier S, Laudier D, Akiyama H, Zumstein MA, Galatz LM, Huang AH (2018) Genetic lineage tracing of targeted cell populations during enthesis healing. J Orthop Res 36(12):3275–3284

Moya D, Ramon S, Schaden W, Wang CJ, Guiloff L, Cheng JH (2018) The role of extracorporeal shockwave treatment in musculoskeletal disorders. J Bone Joint Surg Am 100(3):251–263

Muller SA, Todorov A, Heisterbach PE, Martin I, Majewski M (2015) Tendon healing: an overview of physiology, biology, and pathology of tendon healing and systematic review of state of the art in tendon bioengineering. Knee Surg Sports Traumatol Arthrosc 23(7):2097–2105

Murphy M, Travers M, Gibson W (2018) Is heavy eccentric calf training superior to wait-and-see, sham rehabilitation, traditional physiotherapy and other exercise interventions for pain and function in mid-portion Achilles tendinopathy? Syst Rev 7(1):58

Ng GY, Fung DT (2007) The effect of therapeutic ultrasound intensity on the ultrastructural morphology of tendon repair. Ultrasound Med Biol 33(11):1750–1754

Ng C, Ng G, See E, Leung M (2003) Therapeutic ultrasound improves strength of achilles tendon repair in rats. Ultrasound Med Biol 29(10):1501–1506

Nightingale K (2011) Acoustic radiation force impulse (ARFI) imaging: a review. Curr Med Imaging Rev 7(4):328–339

Notarnicola A, Moretti B (2012) The biological effects of extracorporeal shock wave therapy (ESWT) on tendon tissue. MLTJ 2(1):33–37

Nourissat G, Berenbaum F, Duprez D (2015) Tendon injury: from biology to tendon repair. Nat Rev Rheumatol 11:223–233

Nussbaum E (1998) The influence of ultrasound on healing tissues. J Hand Ther 11(2):140–147

O'Neill BE, Vo H, Angstadt M, Li KP, Quinn T, Frenkel V (2009) Pulsed high intensity focused ultrasound mediated nanoparticle delivery: mechanisms and efficacy in murine muscle. Ultrasound Med Biol 35(3):416–424

Özer Kaya D (2020) Architecture of tendon and ligament and their adaptation to pathological conditions. In: Angin S, Simsek I (eds) Comparative kinesiology of the human body. Elsevier, pp 115–147

Papadopoulos ES, Mani R (2020) The role of ultrasound therapy in the management of musculoskeletal soft tissue pain. Int J Low Extrem Wounds 19(4):350–358

Parkinson J, Samiric T, Ilic MZ, Cook J, Handley CJ (2011) Involvement of proteoglycans in tendinopathy. J Musculoskelet Neuronal Interact 11(2):86–93

Petterson S, Plancher K, Klyve D, Draper D, Ortiz R (2020) Low-intensity continuous ultrasound for the symptomatic treatment of upper shoulder and neck pain: a randomized, double-blind placebo-controlled clinical trial. J Pain Res 13:1277–1287

Pingel J, Wienecke J, Kongsgaard M, Behzad H, Abraham T, Langberg H, Scott A (2013) Increased mast cell numbers in a calcaneal tendon overuse model. Scand J Med Sci Sports 23(6):e353–e360

Poliachik SL, Khokhlova TD, Wang YN, Simon JC, Bailey MR (2014) Pulsed focused ultrasound treatment of muscle mitigates paralysis-induced bone loss in the adjacent bone: a study in a mouse model. Ultrasound Med Biol 40(9):2113–2124

Popov C, Burggraf M, Kreja L, Ignatius A, Schieker M, Docheva D (2015) Mechanical stimulation of human tendon stem/progenitor cells results in upregulation of matrix proteins, integrins and MMPs, and activation of p38 and ERK1/2 kinases. BMC Mol Biol 16:6

Rando TA, Ambrosio F (2018) Regenerative rehabilitation: applied biophysics meets stem cell therapeutics. Cell Stem Cell 22(3):306–309

Reuther KE, Thomas SJ, Sarver JJ, Tucker JJ, Lee CS, Gray CF, Glaser DL, Soslowsky LJ (2013) Effect of return to overuse activity following an isolated supraspinatus tendon tear on adjacent intact tendons and glenoid cartilage in a rat model. J Orthop Res 31(5):710–715

Rezvani SN, Nichols AEC, Grange RW, Dahlgren LA, Brolinson PG, Wang VM (2021) A novel murine muscle loading model to investigate Achilles musculotendinous adaptation. J Appl Physiol (1985) 130(4):1043–1051

Saber AA, Saber A (2017) Therapeutic ultrasound: physiological role, clinical applications and precautions. J Surg 5(3–1):61–69
Sayegh ET, Sandy JD, Virk MS, Romeo AA, Wysocki RW, Galante JO, Trella KJ, Plaas A, Wang VM (2015) Recent scientific advances towards the development of tendon healing strategies. Curr Tissue Eng 4(2):128–143
Screen HR, Berk DE, Kadler KE, Ramirez F, Young MF (2015) Tendon functional extracellular matrix. J Orthop Res 33(6):793–799
Sereysky JB, Andarawis-Puri N, Jepsen KJ, Flatow EL (2012) Structural and mechanical effects of in vivo fatigue damage induction on murine tendon. J Orthop Res 30(6):965–972
Shankar H, Pagel PS (2011) Potential adverse ultrasound-related biological effects. Am S Anes 115(5):1109–1124
Sharma P, Maffulli N (2005) Tendon injury and tendinopathy: healing and repair. J Bone Joint Surg 87-A(1):187–202
Sharma P, Maffulli N (2006) Biology of tendon injury-healing, modeling and remodeling. J Musculoskelet Neuronal Interact 6(2):181–190
Shen H, Yoneda S, Sakiyama-Elbert SE, Zhang Q, Thomopoulos S, Gelberman RH (2021) Flexor tendon injury and repair: the influence of synovial environment on the early healing response in a canine mode. J Bone Joint Surg Am 103(9):e36
Simplicio CL, Purita J, Murrell W, Santos GS, Dos Santos RG, Lana J (2020) Extracorporeal shock wave therapy mechanisms in musculoskeletal regenerative medicine. J Clin Orthop Trauma 11 (Suppl 3):S309–S318
Smallcomb M, Simon J (2019) Histotripsy in collagenous tendons. In: 178th Meeting of the Acoustical Society of America
Snedeker JG, Foolen J (2017) Tendon injury and repair - a perspective on the basic mechanisms of tendon disease and future clinical therapy. Acta Biomater 63:18–36
Solchaga LA, Bendele A, Shah V, Snel LB, Kestler HK, Dines JS, Hee CK (2014) Comparison of the effect of intra-tendon applications of recombinant human platelet-derived growth factor-BB, platelet-rich plasma, steroids in a rat achilles tendon collagenase model. J Orthop Res 32(1): 145–150
Spiesz EM, Thorpe CT, Chaudhry S, Riley GP, Birch HL, Clegg PD, Screen HR (2015) Tendon extracellular matrix damage, degradation and inflammation in response to in vitro overload exercise. J Orthop Res 33(6):889–897
Steinmann S, Pfeifer CG, Brochhausen C, Docheva D (2020) Spectrum of tendon pathologies: triggers, trails and end-state. Int J Mol Sci 21(3):844
Sunwoo JY, Eliasberg CD, Carballo CB, Rodeo SA (2020) The role of the macrophage in tendinopathy and tendon healing. J Orthop Res 38(8):1666–1675
Tanaka E, Liu Y, Xia L, Ogasawara N, Sakamaki T, Kano F, Hashimoto N, Feng X, Yamamoto A (2020) Effectiveness of low-intensity pulsed ultrasound on osteoarthritis of the temporomandibular joint: a review. Ann Biomed Eng 48(8):2158–2170
Tang J, Guha C, Tome WA (2015) Biological effects induced by non-thermal ultrasound and implications for cancer therapy: a review of the current literature. Technol Cancer Res Treat 14(2):221–235
ter Haar G (2007) Therapeutic applications of ultrasound. Prog Biophys Mol Biol 93(1–3):111–129
Tharkar P, Varanasi R, Wong WSF, Jin CT, Chrzanowski W (2019) Nano-enhanced drug delivery and therapeutic ultrasound for cancer treatment and beyond. Front Bioeng Biotechnol 7:324
Theodossiou SK, Schiele NR (2019) Models of tendon development and injury. BMC Biomed Eng 1:32
Thomopoulos S, Parks WC, Rifkin DB, Derwin KA (2015) Mechanisms of tendon injury and repair. J Orthop Res 33(6):832–839
Tsai WC, Tang ST, Liang FC (2011) Effect of therapeutic ultrasound on tendons. Am J Phys Med Rehabil 90(12):1068–1073

Tsai SL, Nodl MT, Galloway JL (2021) Bringing tendon biology to heel: leveraging mechanisms of tendon development, healing, and regeneration to advance therapeutic strategies. Dev Dyn 250(3):393–413

Urban MW (2018) Production of acoustic radiation force using ultrasound: methods and applications. Expert Rev Med Devices 15(11):819–834

Urdzikova LM, Sedlacek R, Suchy T, Amemori T, Ruzicka J, Lesny P, Havlas V, Sykova E, Jendelova P (2014) Human multipotent mesenchymal stem cells improve healing after collagenase tendon injury in the rat. BioMed Eng OnLine 13:42

Vander Doelen T, Jelley W (2020) Non-surgical treatment of patellar tendinopathy: a systematic review of randomized controlled trials. J Sci Med Sport 23(2):118–124

Vidal-Jove J, Perich E, Del Castillo MA (2015) Ultrasound guided high intensity focused ultrasound for malignant tumors: the Spanish experience of survival advantage in stage III and IV pancreatic cancer. Ultrason Sonochem 27:703–706

Vlaisavljevich E, Kim Y, Allen S, Owens G, Pelletier S, Cain C, Ives K, Xu Z (2013) Image-guided non-invasive ultrasound liver ablation using histotripsy: feasibility study in an in vivo porcine model. Ultrasound Med Biol 39(8):1398–1409

Vlaisavljevich E, Xu Z, Arvidson A, Jin L, Roberts W, Cain C (2015) Effects of thermal preconditioning on tissue susceptibility to histotripsy. Ultrasound Med Biol 41(11):2938–2954

Voleti PB, Buckley MR, Soslowsky LJ (2012) Tendon healing: repair and regeneration. Annu Rev Biomed Eng 14:47–71

Walden G, Liao X, Donell S, Raxworthy MJ, Riley GP, Saeed A (2017) A clinical, biological, and biomaterials perspective into tendon injuries and regeneration. Tissue Eng Part B Rev 23(1): 44–58

Wang CJ (2012) Extracorporeal shockwave therapy in musculoskeletal disorders. J Ortho Surg Res 7:11

Wang L (2016) Applications of acoustic radiation force impulse quantification in chronic kidney disease: a review. Ultrasonography 35(4):302–308

Wang L (2018) Acoustic radiation force based ultrasound elasticity imaging for biomedical applications. Sensors (Basel) 18(7):E2252

Warden SJ, Metcalf BR, Kiss ZS, Cook JL, Purdam CR, Bennell KL, Crossley KM (2008) Low-intensity pulsed ultrasound for chronic patellar tendinopathy: a randomized, double-blind, placebo-controlled trial. Rheumatology (Oxford) 47(4):467–471

Watson T (2008) Ultrasound in contemporary physiotherapy practice. Ultrasonics 48(4):321–329

Waugh CM, Morrissey D, Jones E, Riley GP, Langberg H, Screen HR (2015) In vivo biological response to extracorporeal shockwave therapy in human tendinopathy. Eur Cell Mater 29:268–280. discussion 280

Weeks EM, Platt MW, Gedroyc W (2012) MRI-guided focused ultrasound (MRgFUS) to treat facet joint osteoarthritis low back pain--case series of an innovative new technique. Eur Radiol 22(12):2822–2835

Wells PN, Liang HD (2011) Medical ultrasound: imaging of soft tissue strain and elasticity. J R Soc Interface 8(64):1521–1549

Willett NJ, Boninger ML, Miller LJ, Alvarez L, Aoyama T, Bedoni M, Brix KA, Chisari C, Christ G, Dearth CL, Dyson-Hudson TA, Evans CH, Goldman SM, Gregory K, Gualerzi A, Hart J, Ito A, Kuroki H, Loghmani MT, Mack DL, Malanga GA, Noble-Haeusslein L, Pasquina P, Roche JA, Rose L, Stoddart MJ, Tajino J, Terzic C, Topp KS, Wagner WR, Warden SJ, Wolf SL, Xie H, Rando TA, Ambrosio F (2020) Taking the next steps in regenerative rehabilitation: establishment of a new interdisciplinary field. Arch Phys Med Rehabil 101(5):917–923

Wood VT, Pinfildi CE, Neves MA, Parizoto NA, Hochman B, Ferreira LM (2010) Collagen changes and realignment induced by low-level laser therapy and low-intensity ultrasound in the calcaneal tendon. Lasers Surg Med 42(6):559–565

Wunderli SL, Blache U, Snedeker JG (2020) Tendon explant models for physiologically relevant in vitro study of tissue biology - a perspective. Connect Tissue Res 61(3–4):262–277

Xu Z, Hall TL, Vlaisavljevich E, Lee FT Jr (2021) Histotripsy: the first noninvasive, non-ionizing, non-thermal ablation technique based on ultrasound. Int J Hyperth 38(1):561–575

Yeung CK, Guo X, Ng YF (2006) Pulsed ultrasound treatment accelerates the repair of Achilles tendon rupture in rats. J Orthop Res 24(2):193–201

Yoshida R, Alaee F, Dyrna F, Kronenberg MS, Maye P, Kalajzic I, Rowe DW, Mazzocca AD, Dyment NA (2016) Murine supraspinatus tendon injury model to identify the cellular origins of rotator cuff healing. Connect Tissue Res 57(6):507–515

Yu J, Park D, Lee G (2013) Effect of eccentric strengthening on pain, muscle strength, endurance, and functional fitness factors in male patients with achilles tendinopathy. Am J Phys Med Rehabil 92(1):68–76

Zelzer E, Blitz E, Killian ML, Thomopoulos S (2014) Tendon-to-bone attachment: from development to maturity. Birth Defects Res C Embryo Today 102(1):101–112

Zhang J, Wang JH-C (2010) Characterization of differential properties of rabbit tendon stem cells and tenocytes. BMC Musculoskelet Disord 11:10

Zhang S, Cheng J, Qin YX (2012) Mechanobiological modulation of cytoskeleton and calcium influx in osteoblastic cells by short-term focused acoustic radiation force. PLoS One 7(6): e38343

Zhang N, Chow SK, Leung KS, Cheung WH (2017) Ultrasound as a stimulus for musculoskeletal disorders. J Orthop Translat 9:52–59

Zhang C, Zhu J, Zhou Y, Thampatty BP, Wang JH (2019) Tendon stem/progenitor cells and their interactions with extracellular matrix and mechanical loading. Stem Cells Int 2019:3674647

Zhang J, Nie D, Williamson K, McDowell A, Hogan MV, Wang JH (2020) Moderate and intensive mechanical loading differentially modulate the phenotype of tendon stem/progenitor cells in vivo. PLoS One 15(12):e0242640

Zhou S, Schmelz A, Seufferlein T, Li Y, Zhao J, Bachem MG (2004) Molecular mechanisms of low intensity pulsed ultrasound in human skin fibroblasts. J Biol Chem 279(52):54463–54469