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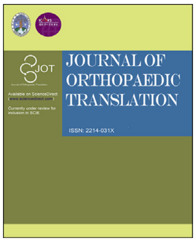

REVIEW ARTICLE

Ultrasound as a stimulus for musculoskeletal disorders

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Summary Ultrasound is an inaudible form of acoustic sound wave at 20 kHz or above that is widely used in the medical field with applications including medical imaging and therapeutic stimulation. In therapeutic ultrasound, low-intensity pulsed ultrasound (LIPUS) is the most widely used and studied form that generally uses acoustic waves at an intensity of 30 mW/cm^2, with 200 ms pulses and 1.5 MHz. In orthopaedic applications, it is used as a biophysical stimulus for musculoskeletal tissue repair to enhance tissue regeneration. LIPUS has been shown to enhance fracture healing by shortening the time to heal and reestablishment of mechanical properties through enhancing different phases of the healing process, including the inflammatory phase, callus formation, and callus remodelling phase. Reports from *in vitro* studies reveal insights in the mechanism through which acoustic stimulations activate cell surface integrins that, in turn, activate various mechanical transduction pathways including FAK (focal adhesion kinase), ERK (extracellular signal-regulated kinase), PI3K, and Akt. It is then followed by the production of cyclooxygenase 2 and prostaglandin E2 to stimulate further downstream angiogenic, osteogenic, and chondrogenic cytokines, explaining the different enhancements observed in animal and clinical studies. Furthermore, LIPUS has also been shown to have remarkable effects on mesenchymal stem cells (MSCs) in musculoskeletal injuries and tissue regeneration. The recruitment of MSCs to injury sites by LIPUS requires the SDF-1 (stromal cell derived factor-1)/CXCR-4 signalling axis. MSCs would then differentiate differently, and this is regulated by the presence of different cytokines, which determines their fates. Other musculoskeletal applications including bone—tendon junction healing, and distraction osteogenesis are also explored, and the results are promising. However, the use of LIPUS is controversial in treating osteoporosis, with negative findings in clinical settings, which may

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be attributable to the absence of an injury entry point for the acoustic signal to propagate, strong attenuation effect of cortical bone and the insufficient intensity for penetration, whereas in some animal studies it has proven effective.

Introduction

Ultrasound is an inaudible sound wave at frequencies higher than 20 kHz that is widely used in clinical imaging and sonography, and is also used in physiotherapy in medicine [1]. Therapeutic ultrasound is alternating compression and rarefaction of longitudinal sound waves with a frequency between 0.7 MHz and 3.3 MHz to maximise energy absorption at a depth of 2—5 cm of soft tissue. At intensities of 0.2—100 W/cm^2, the therapeutic benefits of ultrasound have also been explored and these benefits were generated using low-intensity pulsed ultrasound (LIPUS) [2]. LIPUS generally uses acoustic waves at intensity of 30 mW/cm^2, with 200 ms pulses and 1.5 MHz.

An ultrasound wave is generated when an electric current is applied to an array of piezoelectric crystals located on the transducer surface. Passing through the tissue, absorption of the ultrasound signal results in energy conversion to heat [3]. This thermal effect of ultrasound could cause various responses in biological tissues. Generally speaking, an increase of 1°C in temperature by ultrasound could increase metabolism; an increase of 2—3°C could decrease pain and muscle spasm; an increase of 4°C or above could increase collagen extensibility and decrease joint stiffness; meanwhile, at temperatures higher than 45°C, the thermal effect from ultrasound will be damaging. The thermal effect is extremely small using low intensity as in the LIPUS, which is advantageous in minimising the thermal effect observed in ultrasound forms at higher intensities; therefore, it is used to enhance bone and soft tissue healing [4]. Moreover, the nonthermal effects of ultrasound such as cavitation and acoustic microstreaming occur simultaneously with thermal effects. Therefore, ultrasound may be able to normalise or reestablish the effective metabolic temperatures in healing regions [1].

As LIPUS is reported to demonstrate clinical efficacy in enhancing repair in various musculoskeletal tissues, we review the related literatures on the effect of LIPUS on the most widely used musculoskeletal tissue repair, including fracture repair, the effect on stem cell recruitment and the mechanism of action of LIPUS during that process. We also look into the effect of LIPUS on other musculoskeletal injury repair such as distraction osteogenesis (DO), bone—tendon junction healing, muscle repair as well as osteoporosis.

Fracture repair

LIPUS was first reported to be able to accelerate fracture repair in 1983 [5] and was shown to accelerate biomechanical healing in the rabbit fibula osteotomy animal model [6]. In 1994, EXOGEN obtained approval from the United States Food and Drug Administration for accelerated healing of certain fresh fractures, and used this in clinical trials in tibial fracture healing [7] and distal radial fracture healing [8]. LIPUS was also shown to be an effective and safe treatment for delayed union or nonunions in clinical trials [9—12] and animal studies [13]. Recent studies showed that fracture healing in aged animal [14,15] in ovariectomy-induced osteoporotic bone was enhanced by LIPUS [16]. Four systematic review and meta-analysis journal articles found in Medline all concluded the positive effect of LIPUS on fracture repair [17—20]. These studies provided various lines of evidence that LIPUS had a positive effect on bone fracture healing in many types of fractures, especially on the processes of converting cartilaginous callus to hard callus, endochondral ossification, mineralised callus, and increasing the mechanical stability of the healing fracture [21] that spans over the various phases during the healing process. However, a recent large-scale TRUST randomised controlled trial involving 501 patients reported no positive effect of LIPUS on tibial fracture healing, in which the moderate compliance rate at 73% administered $>$ 50% of all recommended treatments might explain the differences from previous positive studies [22].

In Azuma et al's [23] study, a rat closed femoral fracture model was performed and treated at different periods of repair in order to determine the effect of LIPUS on each phase of the fracture repair process. Rats were divided into four groups based on the timing and duration of LIPUS treatment: Day 1—8 for the haematoma phase, Day 9—16 for the soft callus phase, Day 17—24 for the mineralisation phase and Day 1—24 for all phases of the fracture repair process. The results showed that even partial treatment with LIPUS during different phases of fracture healing could improve the fracture repair, but the treatment that lasted for all 24 days was the most effective. The results further confirmed the positive effect of LIPUS on fracture repair, and meanwhile indicated that LIPUS could act on various cellular reactions in all phases of fracture healing process such as inflammation, angiogenesis, chondrogenesis and endochondral ossification. Many studies showed the effect of LIPUS on different phases of fracture repair.

Inflammatory cells such as macrophages played an important role during the inflammatory phase of fracture repair. It was reported that LIPUS could accelerate macrophage phagocytosis, which removed debris and bacteria to facilitate fracture healing during the inflammation stage [24]. Ultrasound was also shown to stimulate the proliferation of fibroblasts within 24 hours after exposure [25,26].

After the inflammatory stage, angiogenesis was stimulated and activated. Vascularity was increased in an