
Why We Still Cannot Answer Clearly If Low-Intensity Pulsed Ultrasound Treatment Can Repair Articular Cartilage?

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Received: 04 November 2019

Published: 26 November 2019

Keywords: *Low Intensity Pulsed Ultrasound; Articular Cartilage; Treatment Protocol*

Five years ago a question was raised. Is it possible for Low-intensity pulsed ultrasound treatment (LIPUS) to repair articular cartilage? A daily 20-minute treatment for 3 months was given to surgically created cartilage defects of 5mm in diameter on the right side distal femoral condyle of rabbits. The ultrasonic device used was an Exogen low-intensity pulsed ultrasound device (Smith & Nephew Inc, Memphis, TN, USA) which provided a peak intensity of 30mW/cm² at a frequency of 1.5MHz. After treatment, the cartilage defects of the LIPUS-treated group were covered by proliferative tissue, where the non-treated were not. The study concluded that there was no significant therapeutic effect.

In a recent similar type study, the treatment was for 10 min per day for 14 days at 1W/cm² at a frequency of 1MHz (the ultrasonic device was not disclosed). This study suggested that LIPUS has therapeutic potential for the treatment of mandibular condylar cartilage defects of 2mm in diameter. In [12], normal and osteoarthritis chondrocytes in culture dishes were treated with 3MHz ultrasound for 6 days, 20 min per day at intensities of 20, 30, 40 and 50mW/cm². In [1], a frequency of 1MHz, with an intensity of 0.1 W/cm² was used on human osteoarthritic knee showed no significant difference in the treatment effect. In [4] 1MHz with a peak intensity of 1W/cm² at a 20% duty cycle was applied for cartilage repair in humans. In this study it is mentioned that there is limited understanding about the important factors that may influence the effects of the treatment, such as dose, intensity, mode, or application techniques. A previous meta-analysis study [5] was inconclusive. Human chondrocytes and explants were exposed to LIPUS (30mW/cm²; 20min/day, 6 days) in [2]. Li *et al* [3] used 3MHz ultrasound with 20% duty cycle and 30mW/cm²

acoustic intensity for 20 min a day, 5 days a week for a total of 6 weeks. This study concluded that low intensity ultrasound could improve cartilage degeneration. Chondrocytes in culture dish treated with LIPUS for 20 min at 3.0MHz frequency and 60mW/cm² intensity showed increased gene expressions [8]. A review article state that LIPUS increases proliferation in articular cartilage [7] and state that the desired biological effect depends on the type of signal used. Oyonarte *et al* concluded that LIPUS (30mW/cm² 1MHz, 5 times a week over a 26-day period) may alter the histology of cartilage when treated for 10 or 20 min and the sensitivity of condylar tissues to LIPUS stimulation differs between the anterior and posterior regions of the condyle, and will also depend on the duration of daily stimulation. Also Sahu *et al* [10] concluded that continuous ultrasound at 5MHz (intensity < 20mWcm⁻²) for 20 min 4 times per day for 28 days improved cartilage repair and also claim that the bio-effects are frequency dependent. Cyclic tensile strain has shown by Yank *et al* to have no therapeutic effects on normal articular cartilage and chondrocytes [15] Xia *et al* exposed to LIPUS New Zealand White rabbits with osteoarthritis (3MHz, 20% duty cycle,). They concluded that LIPUS protects cartilage from damage in early-stage osteoarthritis. Uddin *et al* [11] concludes that LIPUS (20min per day at 30mW/cm², 1MHz, 40mW/cm², 20 min/day 6d/wk for 5 weeks) has potential therapeutic effects in preventing cartilage degradation and treating osteoarthritis. Zhou *et al* also concluded that LIPUS (1MHz, 1W/cm², 10 min, for 14 days for once a day) decreased the severity of cartilage injury [16]. Furthermore, in real life, when walking pressures in a joint are in the range from 3 to 10MPa with a frequency around 1Hz [6].

As it can be noticed, the majority of the published research shows that LIPUS has some effect on articular cartilage. But why some studies come to different conclusions? Is it really because the size of the surgically induced defects or the treatment protocol? Or is it because the type of the LIPUS device, its frequency, its intensity, all the above, or something else? Ultrasound research in Medicine and Biology suffers from the fact that are too many parameters involved. It is clear that if we want LIPUS to become a clinical practice, we all have to put some more effort on producing standardized and repeatable research with evidence on how to design treatment protocols for LIPUS.

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