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Ultrasound and fragility fracture: is there a role?

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ABSTRACT

Osteoporotic fracture is known to have impaired healing capacity and therefore takes longer time to heal, as compared with younger one. The mechanism of impaired osteoporotic fracture healing is multi-factorial, where lower responsiveness to mechanical loading is generally believed to be one factor, yet not absolutely confirmed. In recent years, low intensity pulsed ultrasound (LIPUS) is demonstrated to have good efficacy in treating normal fracture healing, as proven by many randomized controlled trials, as well as in vitro and animal evidences. The effects of LIPUS on osteoporotic fracture healing was also validated in an animal study, which revealed that osteoporotic fractured bone of SD rats showed radiologically and biomechanically comparable responses to LIPUS as age-matched normal fracture healing, in terms of callus width, bridging rate, bone volume fraction, and stiffness etc. Gene expression profiling also confirmed that osteoporotic fractured bone responded to LIPUS very well by upregulating Col1 and BMP2 (osteogenesis) at early phase, VEGF (angiogenesis) at middle phase and RANKL (remodeling) at late phase. These confirm that osteoporotic bones respond well to LIPUS as good as normal bone. These findings may be associated with estrogen receptors (ERs), as estrogen depletion is sensed and relayed by ERs and ERs also function as mechano-sensors. A previous study observed a delayed ERs expression pattern in fracture callus of OVX rats, as compared with SHAM rats, which correlated well with the expression pattern of BMP-2 (callus formation-related gene). Hence, the responses of osteoporotic fractured bone to LIPUS may be related to the local ERs expression at fracture callus that needs further experiments to validate.

Osteoporotic fracture healing – responsiveness to mechanical stimulation?

Osteoporotic fracture is a critical medical challenge with increasing aging population and the prevalence is high too. In the USA, there are more than 1.5 million of such fracture cases each year [1] and therefore the related healthcare cost is very high. The capacity for fracture repair has been reported to decrease with age [2]. Many reports indicate the differences of mechano-biology between osteoporotic and normal bones [3] and osteoporosis impairs both early phase [4] and late phase of fracture healing with 40% reduction in callus cross-sectional area, 23% decrease of bone mineral density (BMD) and fivefold decrease in mechanical properties [5]. The mechanism of impaired osteoporotic fracture healing is multi-factorial and a number of evidences showed that poor sensitivity of osteoblasts to mechanical signals [6,7], impaired angiogenesis [8–10], and reduced mesenchymal stem cells [11,12] may play a role in the impaired healing. Acceleration of osteoporotic fractures is always the target of orthopaedic researchers to shorten the hospitalization and hence the economic benefits, where mechanical stimulation, e.g. weight bearing, is a common clinical approach. However, previous finding revealed that the osteoblasts from osteoporotic donors were less responsive to 1% cyclic strain stretching in terms of proliferation and TGFβ release, as compared with younger normal donors [6]. Hence, there is a general belief that osteoporotic bone is less responsive to mechanical stimulation; however, there were several reports telling opposite findings, e.g. Leppänen et al showed that osteoporosis was not attributable to impaired mechano-responsiveness of aging skeleton [13]; also, male adult rats with lower estrogen level demonstrated better mechanical responses than females [14]. Therefore, mechanical stimulation to enhance osteoporotic fracture healing remains controversial.

Efficacy of low intensity pulsed ultrasound on fracture healing

Low intensity pulsed ultrasound (LIPUS), a propagating acoustic wave that transfers energy onto the treated regions, has been well reported to accelerate fracture healing. Many randomized controlled clinical trials confirmed the accelerated fracture healing at different skeletal sites by LIPUS with 17–42% reduction in healing time [15,16]. Beneficial effects on complex

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tibial fractures [17] and non-unions of various bones [18] were demonstrated clinically. A few meta-analyses also verified the different extents of positive effects of LIPUS on fracture healing [19,20]. In vivo, LIPUS was shown to increase blood flow around the fracture site [21]. At cellular level, LIPUS was found to increase cellular activities of many cell types, e.g. increased calcium nodule formation and alkaline phosphatase activity in osteoblasts [22], more β-catenin nuclear translocation in osteocytes [23], promoted osteogenesis in mesenchymal stem cells [24] and stimulated proliferation/differentiation in periosteal cells [25], which are helpful to promote fracture healing at various phases. With all these positive scientific evidences, LIPUS is well accepted to be an effective biophysical modality to modulate mechanical micro-environment and blood flow in fracture site for accelerating fracture healing. However, all these animal or clinical evidences are on normal fracture in adults; the effect on osteoporotic fracture was not yet elucidated.

Effects of LIPUS on osteoporotic fracture healing – animal evidence

The first animal study to depict the efficacy of LIPUS on osteoporotic fracture healing was conducted on 120 female Sprague-Dawley (SD) rats divided into four groups – Sham ovariectomy with LIPUS treatment (Sham-T), Sham ovariectomy control (Sham-C), ovariectomy with LIPUS treatment (OVX-T) and OVX control (OVX-C) [26]. Half of the 6-month-old rats were bilaterally ovariectomized for OVX groups (FDA-verified animal model of osteoporosis [27]), while another half was sham operated for Sham groups. All the rats were housed for 3 months to develop osteoporosis and the reduction in BMD was confirmed by peripheral quantitative computed tomography (pQCT, Densiscan 2000, Scanco Medical, Bruttisellen, Switzerland), where –9.6%, –4.6% and –2.3% of BMD were detected at 5th lumbar vertebra, right femoral head and right femoral shaft respectively. They were then created closed fractures at femoral mid-shaft according to Einhorn's protocol [28]. LIPUS (pulsed 1.5 MHz, 30.0 mW/cm^2 spatial-averaged temporal-averaged intensity; Exogen 3000+, Smith & Nephew, Memphis, TN, USA) was given 20 min/day and 5 days/week for durations of 2, 4, or 8 weeks, at which radiography, BMD and microarchitecture measurement, histomorphometry and mechanical testing were performed. Results indicated that both the treatment groups (Sham-T and OVX-T) were of significantly enhanced callus formation, faster mineralization and better remodeling than their control groups (Sham-C and OVX-C) [26]. Interestingly, by comparing the results between Sham-T and OVX-T, OVX-T showed comparable healing responses with Sham-T group in most parameters, while OVX groups indicated relatively more significant differences in various assessments than Sham groups. The better healing responses in OVX-T than Sham-T included significantly higher CW (+15.0% at week 4), earlier appearance of callus bridging (week 4.17 vs. week 4.75) and higher percentages of completed healing (66.7% vs. 41.6% at week 4; 100% vs. 83.3% at week 8), higher ratio of increment in BV/TV value (+26% vs. +18.7% from week 2 to 4), faster response of endochondral ossification (faster drop in CW, faster decrease in cartilage area) and a higher stiffness value (+37.4% at week 4 and 36.9% at week 8) [26]. These findings were consistent with a previous study using low-magnitude high-frequency vibration (35 Hz, 0.3 g where g = gravitational acceleration) with the same study design and animal model, which also demonstrated relatively better effects on osteoporotic fracture healing than on the age-matched non-osteoporotic one [29]. Similar results were also found in Rubinacci's study which OVX non-fractured rats treated with vibration treatment (30 Hz, 3 g) showed significant increase in cortical and medullary areas,

Table 1
Gene expression levels relative to GAPDH in mechanical sensitivity related ER-α, ER-β, and osteogenic related Col-1 and BMP-2. (n=5 per group at each time point).

	ER-α						ER-β						Col-1						BMP-2					
	2		4		8		2		4		8		2		4		8		2		4		8	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SHAM	0.3069	0.1183	0.0540	0.0191	0.0005	0.0003	1.0238	0.5332	0.2066	0.0862	0.0360	0.0198	157.4	35.4	30.9	20.3	8.9	5.4	0.047	0.014	0.089	0.015	0.005	0.004
OVX	0.0016	0.0012	0.1344	0.1169	0.7091	0.2470	0.0226	0.0216	0.8081	0.4936	2.5582	0.9573	96.9	49.2	70.2	36.7	24.3	22.1	0.006	0.005	0.128	0.026	0.028	0.003
t-test	0.004	0.223	0.003	0.014	0.091	0.004	0.056	0.091	0.004	0.002	0.171	0.000												