Effect of Low Intensity Ultrasound Stimulation on Bone Strength Improvement for Prevention of a Risk of Osteoporotic Bone Fracture

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Introduction:

Osteoporosis is a metabolic bone disease characterized by low bone mass, which increases the bone fragility and the risk of fracture. Considerable works have been done to treat osteoporotic bones. A low intensity ultrasound (US) has been recently introduced as a potential intervention capable of preventing osteoporotic bone fracture, based on the fact that the low intensity US transfers mechanical energy, which is concerned in regulation of bone modeling/remodeling, into the bone tissues. It has been, however, still controversial whether or not the low intensity US is effective for prevention of osteoporotic bone fracture. The current study is, therefore, performed to identify quantitatively if the low intensity US stimulation is effective mechanically on prevention of osteoporotic bone fracture.

Materials and Methods:

Eight virgin ICR mice (14-week-old, approximate weight 25g) were housed in individually ventilated and cleaned cages (room temperature 23°±2°C, humidity 50%±10%). All mice were ovariectomized (OVX) to induce osteoporosis and a degree of occurrence of the osteoporosis for each mouse was confirmed morphologically through in-vivo micro-CT (Skyscan 1076, Skyscan, Belgium) images with at a resolution of 18μm. One right hind limb for each mouse was then stimulated with the low-intensity US (assigned to US Group), but the left hind limb was not stimulated and served as an internal control (assigned to CON Group) (Fig 1). Here, US stimulation was applied to the proximal tibia with following parameters: 1.0 kHz frequency, 30mW/cm^2 intensity, 200μs pulse width, and stimulation for 20 minutes/day and 5 days/week over a 6-week period. All procedures were in accordance with approved National Institutes of Health (NIH) Guideline for care and use of laboratory animals under a protocol approved by Yonsei university school of animal care and ethics committee.

The hind limbs of all mice were scanned by in-vivo micro-CT for acquisition of 2D images necessary to generate finite element (FE) models. The 2D images scanned for the hind limbs of all mice were converted to 3D voxel FE models by Mimics 11.11 (Materialise, Belgium) and Hypermesh 7.0 (Altair Co., USA). Material properties for the FE models were then determined by the gray values for each element calculated by Mimics 11.11 (Fig 2). To determine quantitatively the effect of the low intensity US stimulation on the bone strength, structural modulus was computed by applying a compressive displacement of 0.5% strain to the bone (Fig 2). Here, all FE analyses were performed by using ABAQUS 6.5 (HKS Inc, U.S.A) and one-way ANOVA test with Tukey'B post hoc multiple comparisons to identify that the structural moduli in US or CON Group are constant, increased or decreased over time. The significance level (p) for the statistical analysis was then set at 0.05.

Results:

The histogram analyses of the gray value distributions showed that the gray values in US Group were generally higer than those in CON Group (Fig 3). The distributions of the high gray values were gradually increased in US Group over time, whereas those in CON Group were generally decreased over time.

The structural moduli computed from the FE analyses showed that the structural moduli in US Group were significantly increased over time ($p<0.05$). It was, however, identified that the structural moduli in CON Group were statistically constant over time ($p>0.05$) (Fig 4).

Discussions and Conclusions:

In the current study, positive effects of US stimulation on the osteoporotic bone were identified. The results of the histogram and the FE analyses indicated that bone qualities such as the gray value distribution and structural modulus (indexes of bone strength in the current study) were increased through application of the low intensity US stimulation to the bone weaken mechanically by osteoporosis. These findings may indicate that the low intensity US may prevent effectively a risk of the osteoporotic bone fracture through achievement of the bone strength improvement. However, the findings in the current study require further confirmation using concepts incorporated in micro-mechanics and molecular biology. Also, the current study is limited to the analyses of the gray value distributions and the structural moduli for the cortical bone without consideration of the trabecular bone together. We are, therefore, currently investigating those in an ongoing study, the results of which may increase the confidence levels of the results presented here.

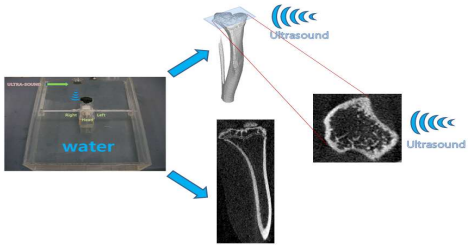

Fig 1. Ultrasound stimulation and its site

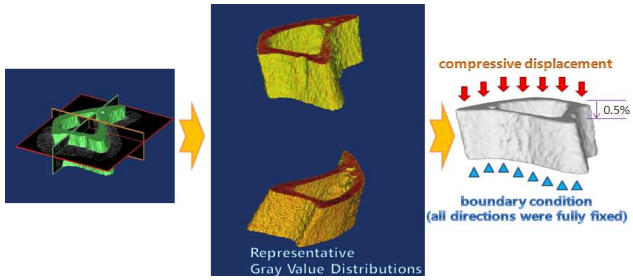

Fig 2. Process of FE model construction and analysis, a) micro- CT scan, b) material property assignment for US (down) and CON (up) Groups (high gray values were generally distributed in US Group compared with CON Group), c) application of compressive dispacement to FE model for calculation of structural modulus

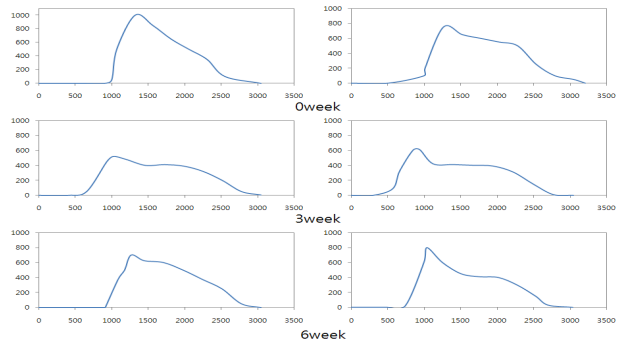

Fig 3. Changes of the gray value distributions in US (left) and CON (right) Groups over time, x axis: hounsfield unit (gray value), y axis: the number of elements with the same gray value

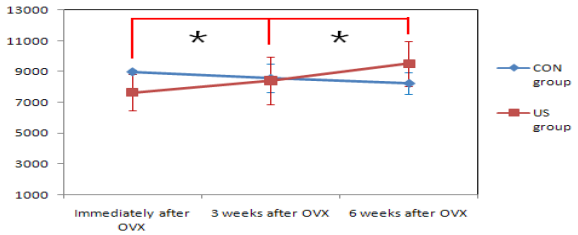

Fig 4. Changes of Structural moduli in US and CON Groups over time, *: significant change of the structural modulus over time ($p<0.05$)