MUSCLE-BONE INTERACTION REGULATES BONE TISSUE REGENERATION AND REMODELING, AND MITIGATION OF OSTEOPOROSIS

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Mechanotransduction has demonstrated potentials for tissue adaptation in vivo and in vitro. Although a wide range of studies have been done, mechanism for this mechanical effect on bone regeneration is unknown and still under active investigation. A potential mechanism, by which bone responds to mechanotransductive signals, is through the skeletal muscle dynamics nearby bone. Dynamic mechanical signals have demonstrated promising for combating musculoskeletal deterioration trigged at proper loading rate, in which adequate combination of loading frequency, amplitude, and daily duration provides proper energy for maintain bone mass. It is essential to determine the components and mechanisms critical to the anabolic processes of musculoskeletal tissues. It has been shown that intramedullary pressure (ImP) and low-level bone strain induced by muscle stimulation (MS) has the potential to mitigate bone loss induced by disuse osteopenia. Optimized MS signals, i.e., low-intensity and high frequency, may be critical in maintaining bone mass and mitigating muscle atrophy.
Thus, the hypothesis for this study is that dynamic MS can enhance anabolic activity in bone, and inhibit bone loss in a functional disuse by sufficient short term daily duration of mechanical stimulation with relatively high frequency and physiological magnitude using muscle contraction. Using a hindlimb suspension (HLS) rat model, electro-induced dynamic MS was applied as replacement of the normal weight-bearing activity of the hindlimb with two skin patch electrodes at the right quadriceps muscles for total of 30 animals in six groups (N=5 per group): 1) baseline control, 2) age-matched control, 3) hindlimb suspended (HLS) sham control, 4) HLS+10 min MS, 5) HLS+30 min MS, 6) HLS+60 min MS. The stimulus was applied at 71 Hz, 0.2 ms pulse with 3s on and 8s rest, 5days per week, for a total of 4weeks. Distal metaphyseal regions and one epiphyseal region of the femurs (0.75mm per region) were scanned using □CT at 15μm resolution and evaluated to obtain bone volume fraction (BV/TV), connectivity (Conn.D), and trabecular number (Tb.N).
Disuse alone generated significant bone loss (-49.03% BV/TV, p=0.007, -58.55% Conn.D, -23.74% Tb.N, compared to the age-match control). Dynamic muscle contraction at 30 min demonstrated anabolic effects at the metaphyseal regions (52.72% BV/TV, p=0.24, 76.38% Conn.D, 11.97% Tb.N, compared to the HLS sham control). MS at 10 min showed a lesser response (7.31% BV/TV, 23.89% Conn.D, and 3.17% Tb.N). The most significant effective response occurred at 60 min MS loading [103.43% BV/TV (p=0.003), 164.65% Conn.D, and 22.35% Tb.N] in comparison to the HLS. Histomorphometry analysis and mid-diaphesis 4-pt bending mechanical testing showed consistent results with □CT.
These results demonstrated that dynamic muscle contraction can initiate adaptive response to mitigate bone loss under functional disuse with a daily loading duration dependent pattern, in which 30-60 min low-energy contraction at high frequency is able to recover 100% of bone loss induced by disuse osteopenia through muscle stimulation and it induced bone fluid flow.The results suggested awell design muscle-bone interaction approach may enhance the skeletal adaptation and potentially provide an alternative method for attenuation of osteoporosis and related bone diseases.