

Research Article

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Calf Muscle Pump Stimulation Increases Lower Limb Bone Density in Perimenopausal Women

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Abstract

Nutrient delivery to bone tissue, as for all tissues in the body, is provided through interstitial fluid flow. This flow is driven by the differential fluid pressures between the intramedullary canal and the tissues outside of the bone. Correspondingly, reductions in tissue fluid pressure should enhance interstitial bone fluid flow, nutrient delivery, and thereby increase bone mineral density. This hypothesis was tested in a one year long pilot clinical study of healthy, employed, perimenopausal women (42 - 68 years). Soleus muscle (calf muscle pump) stimulation was utilized with the intent of increasing lower limb fluid return to the heart, serving to both reduce lower limb tissue pressures and to increase intramedullary pressures by increasing cardiac output. Dual-energy x-ray absorptiometry (DXA) assessments of bone mineral density (BMD) were obtained at 12 month intervals. Muscle stimulation usage ranged from 0.7 to 4.8 hours/work-day. Dose dependent responses between duration of daily soleus muscle stimulation and changes in both proximal femur BMD (+0.5% per hour of daily use; $p = 0.05$) and proximal tibia BMD (+1.5% per hour of daily use; $p = 0.0004$), were observed; no significant effect was observed at the lumbar spine. These results are consistent with the hypothesis that calf muscle pump stimulation, which is sufficient to reduce lower limb fluid pooling, is capable of significantly reducing the rate of bone loss in perimenopausal women as well as enhancing new bone formation.

Keywords: Bone fluid flow, Lower limb edema, Bone density, Secondary heart, Osteoporosis

Introduction

Bone tissue metabolism is critically dependent on Interstitial Fluid (ISF) flow [1]. ISF originates as fluid extravasated from the vascular supply, and then flows down fluid pressure gradients in the porous bone tissue where it provides nutritional support and collects extracellular waste products. As there are no lymphatic vessels in bone, ISF must traverse the bone tissue so that it can be collected by the lymphatics in the surrounding soft tissues and returned to the circulatory system.

The fluid pressure gradient driving ISF flow is primarily the pressure difference between the intramedullary canal and the soft tissue surrounding the bone. Correspondingly,

changes in these pressures have been shown to influence bone remodeling activity. For example, in animal models it has been shown that pressurizing the intramedullary canal increases ISF flow and produces periosteal bone formation [2]. Similarly, mechanical loading stimulates bone formation at sites of greatest strain (fluid pressure) gradients [3]. Clinically, both hypertension [4], and venous occlusion [5] raise intramedullary pressure and initiate new bone formation.

Raising the tissue pressure outside of the bone should correspondingly reduce the fluid pressure gradient for a constant intramedullary pressure. When recumbent, tissue pressures are close to venous pressure, or about 20 mmHg. However, when upright, lower limb tissue pressures can be

far higher due to the pooling of fluid into the lower body (lower limb edema) arising from the influence of gravity. Lower limb fluid pooling is normally prevented by the action of the calf muscle pumps, or soleus muscles, which serve as secondary hearts, pumping both venous blood and lymphatic fluid back to the cardiac muscle. However, in many individuals, soleus muscle insufficiency leads to substantial lower limb fluid pooling, a condition referred to clinically as lower limb edema. We propose that this fluid pooling inhibits transcortical ISF flow, thereby leading to bone resorption and osteoporosis.

We hypothesized that reduction of lower body tissue pressures, through calf muscle pump (soleus muscle) stimulation, and should result in increased in bone mineral density over an extended time period as a result of increased transcortical pressure gradients and ISF flow. If correct, the effect of reducing tissue fluid pressures should be most evident for bone tissues located in the lower regions of the body. We tested this hypothesis in a prospective, pilot clinical trial on healthy, employed, perimenopausal women extending over a one-year duration.

Methods

This study was approved by the Binghamton University IRB (Protocol #249-05). Healthy, employed (both salary and hourly) women, working in a local industrial facility, were recruited for participation. After obtaining informed consent, basic demographic information was collected. Individuals with body mass over 300 lbs (136 Kg) - the maximum allowable weight for our bone density scanner, or who had been diagnosed with hypertension, were excluded.

Each potential participant was screened to determine whether they experienced lower limb fluid pooling while seated. If lower limb pooling developed while seated, we then tested whether calf muscle pump (soleus muscle) stimulation was capable of reversing this fluid pooling. These assessments were accomplished using Air-plethysmography (APG) to measure calf volume changes, and micromechanical plantar stimulation of the soleus muscles as previously described [6]. Lack of pooling during quiet sitting, or inability of soleus muscle stimulation to reduce calf fluid volume, resulted in exclusion of the individual from the study.

Temporal changes in Bone Mineral Density (BMD) were obtained using dual energy absorptiometry (DXA; GE Lunar Prodigy, Waukesha, WI) measurements of the commonly assessed lumbar spine and proximal femur sites, as well

as for the proximal tibia to provide lower leg data [7]. Duplicate (separated in time by approximately one week) DXA measurements were obtained at enrollment and after one year [7]. The duplicate density measurements were averaged for analysis; if a difference greater than 3% was observed between the duplicate measurements, a third DXA measurement was requested from the participant and the two closest measurements were used in the analysis.

A soleus muscle stimulation device was installed at each participants work station, and participant's were encouraged to use the device daily for a minimum of one-half hour per day. The intervention required that the participants place the frontal plantar surface of their feet on the device while they were seated, and so essentially represented a form of "passive" muscle exercise. An electronic monitor built into the device recorded date, time of day, and duration, of use. At the end of the study, the stimulation devices were recovered and usage data downloaded. Participants were contacted monthly to determine if any difficulties with the protocol were being encountered.

Annualized changes in BMD were calculated and least squares linear regression analysis against average workday usage times was obtained (Origin 2017).

Results

A total of 82 subjects were recruited for initial screening. Sixty participants (73%) were found to demonstrate measureable pooling while sitting quietly for one-half hour, with the maximum pooling rate being 72 ml/hour. Fifty-one (85%) of this "pooling" subgroup experienced a reduction in pooling with soleus muscle stimulation. Of this subgroup who met all of inclusion criteria, thirty elected to participate in the one-year long intervention study. This enrolled group ranged in age from 42 years to 68 years (average age of 57.3 years; S.D. 8.1). Body mass for the group ranged from 51 Kg to 126 Kg, with an average of 71.0 Kg (S.D. 16.9). Average body mass index was 26.7 Kg/m² (S.D. 5.7). Resting blood pressures in the study group averaged 122/73 mmHg. During 30 minutes of quiet sitting APG volume was observed to increase by an average of 9.6 ml (S.D. 13.2) and during 30 minutes of soleus muscle stimulation was observed to decrease by an average of 10.7 ml (S.D. 12.9).

Twenty eight participants completed the one year protocol, one enrolled participant relocated out of the region, and one was lost to follow-up. Participant average daily usage of the secondary heart stimulation devices

ranged from 0.7 to 4.8 hours per day. No adverse events were reported.

Regression analysis on the change in lumbar spine BMD over the course of the year indicated that, in the absence of any soleus muscle stimulation, the average annual change in BMD would have been approximately -0.90% (± 0.77). Lumbar spine bone mineral density trended upward with increasing daily use of soleus muscle stimulation, with the point of no loss of bone mass occurring with about 4 hours/day of soleus muscle stimulation, but this trend was not statistically significant (Figure 1).

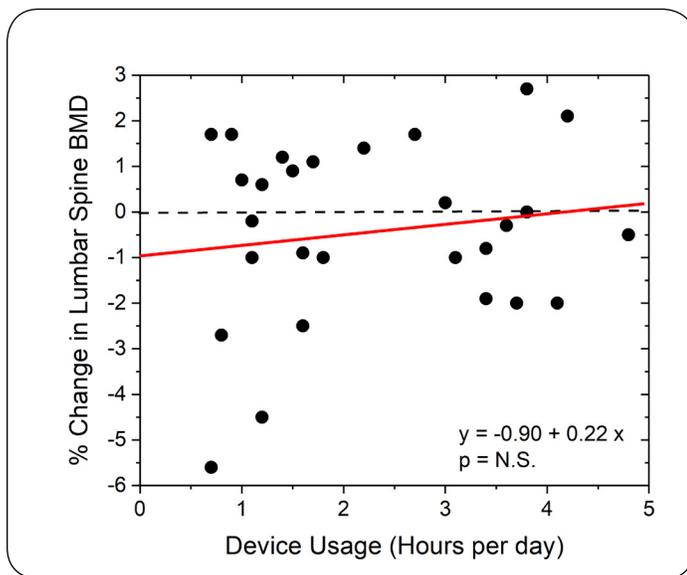


Figure 1: Influence of daily soleus muscle stimulation, and, as a direct consequence, reduction in lower limb fluid pooling, on annualized change in lumbar spine BMD in perimenopausal women. Daily stimulation use ranged from three-quarters of an hour per day to almost 5 hours per day. Least squares regression suggests a slight (0.22%/hour) increase in BMD associated with muscle stimulation, though the trend at this mid-body location was not found to be significant.

Change in proximal femur BMD in the absence of any soleus muscle stimulation was -1.28% (± 0.60) and demonstrated a significant positive correlation to average daily muscle stimulation usage time (Figure 2). Proximal femur BMD increased by 0.48% ($p = 0.05$) for each hour per day of use. 2.5 hours per day of muscle stimulation was associated with no net change in proximal femur BMD. Muscle stimulation for over 2.5 hours per day resulted in increased BMD for 9 of 11 individuals who exceeded this daily usage rate.

In the absence of any soleus muscle stimulation,

regression analysis indicated an annual loss in proximal tibia BMD of 3.99% (± 0.98). Change in proximal tibia BMD was also positively correlated with average daily device usage, with BMD increasing by 1.5% ($p = 0.0004$) for each hour per day of device use (Figure 3). Participants undertaking more than 2 hours per day, on average, typically saw net gains in proximal tibia BMD. Specifically, 11 of 13 participants with average daily use patterns of over 2 hours/day demonstrated increased BMD over the twelve month study period.

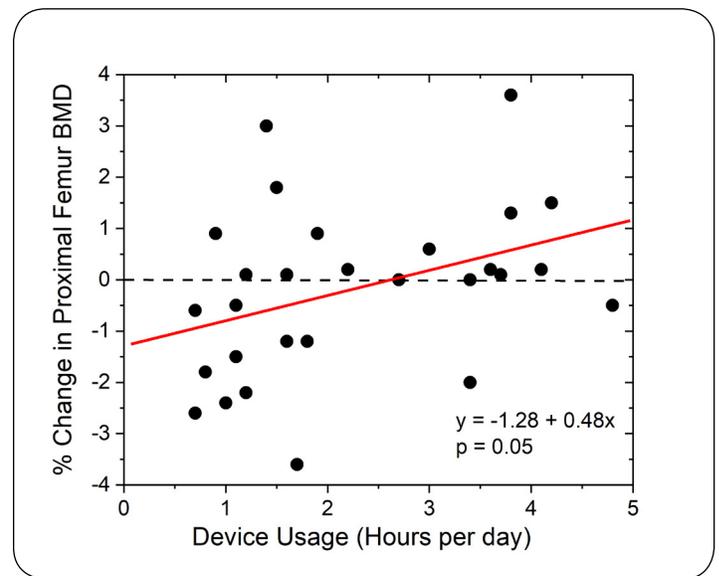


Figure 2: Influence of daily soleus muscle stimulation, on annualized change in proximal femur BMD in perimenopausal women. A significant dose response is observed at this site lower in the body, with each additional hour of daily stimulation associated with approximately a 0.5% increase in BMD.

Discussion

Due to the influence of gravity, blood and interstitial fluids pool into the lower limbs whenever an individual is sitting or standing upright, and soleus muscle contractions serve to return this fluid back to the heart. This “secondary heart” activity reduces lower limb tissue pressures, and as well, maintains sufficient fluid return to the heart to maintain normal cardiac output [8]. In individuals who pool excessively while upright, external soleus muscle stimulation can enhance venous return and lead to increased cardiac output and normalization of blood pressure [9]. Soleus muscle stimulation, therefore, can increase bone ISF pressure gradients both by increasing intramedullary pressures and reducing tissue pressures. Correspondingly, the effect of soleus muscle stimulation on bone remodeling would be expected to be greater in

the lower regions of the body, which is, in the foot, ankle, and lower leg regions, where hydrostatic tissue pressures are greatest.

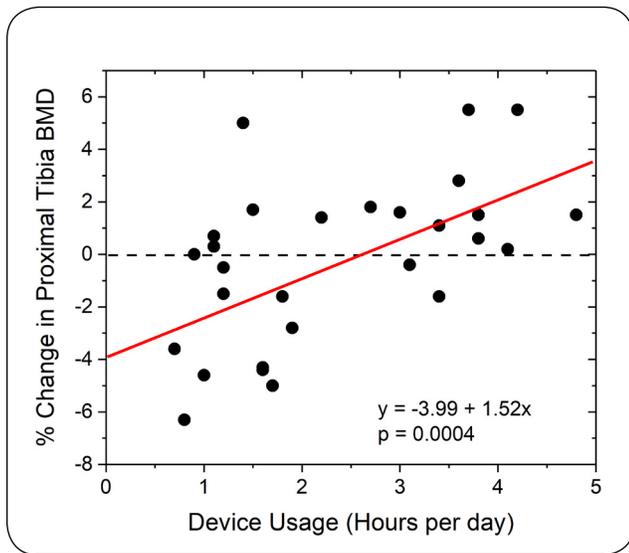


Figure 3: Influence of daily soleus muscle stimulation on annualized change in proximal tibia BMD in perimenopausal women. As with the femur data, a significant dose response is observed, with each additional hour of daily stimulation associated with a substantial 1.5% increase in BMD. The more robust response in the tibia is consistent with the tibia being much lower in the body where fluid pooling has a greater impact on transcortical fluid pressure gradients.

Consistent with the proposed fluid pressure influences on bone remodeling activity, daily soleus muscle stimulation was observed to have only a relatively minor influence on lumbar spine BMD over the course of one year. In our perimenopausal group of participants, the absence of muscle stimulation was associated with approximately a 1% annual loss of lumbar spine BMD, consistent with losses observed in previous reports [10]. Daily soleus muscle stimulation for 3.5 - 4 hours/day appeared to be sufficient to preclude this loss, though this apparent trend was not statistically significant.

A significant effect of soleus muscle stimulation was observed for the proximal femur. Regression analysis indicated that, in the absence of any soleus muscle stimulation, the study population would have lost approximately 1.3% of their proximal femur BMD. This change is also consistent with expected annual bone loss at this site for this age group of women. Daily soleus stimulation led to a reduction in bone loss at a rate of 0.48% per hour of daily stimulation. This effect resulted in prevention of bone loss for those undergoing 2.5 hours/day of soleus muscle stimulation, and increased BMD for

the vast majority of women performing “passive soleus muscle exercise” for more than 2.5 hours per day.

Finally, consistent with the anticipated increased effect at sites lower in the body, the influence of daily soleus muscle stimulation on proximal tibia BMD was rather dramatic. Regression analysis indicated that the population would have lost almost a 4% of their tibia BMD over the course of the year, in the absence of any soleus muscle stimulation. While there is a dearth of studies on age related bone loss in the tibia, studies on younger adults (age 25 - 55 years) have found proximal tibia bone loss rates of over 1.5% per year [11]. As many of our participants were well past menopause, the 4% annual loss rate may not be excessive.

Soleus muscle stimulation led to over a 1.5% increase in BMD for each hour per day of usage, such that, similar to what was observed in the proximal femur, those utilizing muscle stimulation for 2.5 hours per day were found to have no loss, on average, in tibia BMD. For those using the muscle stimulation for more than 2.5 hours per day saw increases in proximal tibia BMD, with the regression analysis indicating that five hours per day of use would be associated with over a 3% annual increase in BMD.

We have interpreted the results strictly in the context of our hypothesis that soleus muscle activity influences transcortical fluid gradients, and the observed bone remodeling activity simply reflects the improved transcortical ISF flow. However, in this study we did not specifically measure these internal fluid pressures, or the transcortical fluid flow rates, and so it is possible that the soleus muscle stimulation may have had some alternative, perhaps direct, effect on bone remodeling. This is certainly a possibility for the observed tibial BMD changes as the soleus originates on the proximal tibia. It is much more difficult to imagine how this lower leg muscle would directly influence proximal femur BMD, but the possibility cannot be dismissed.

Limitations of this study include the relatively small size of the study population and the fact that we did not include a placebo group. While a placebo treatment group would have strengthened the study, as the device utilized a vibratory type of stimulus it would have been obvious to the participants if they were in the placebo (no stimulus) group, which would have precluded any attempted blinding of the study. Utilization of an alternative means to activate the soleus muscles, such as electromagnetic stimulation, may allow for incorporation of an effective placebo treatment option in any future studies addressing the role of lower

limb edema, and secondary heart activity, on bone health. In addition, as this was a pilot study, we did not track diet, medication use, or other exercise activities, all of which may have affected bone adaptation over the course of the year, influences which could be quantified in a larger and more thorough study.

In conclusion, daily soleus muscle (calf muscle pump) stimulation was found to be associated with not only a slowing of lower body bone loss, but also significant increases in lower limb bone density. That the magnitude of the observed effects were related to the anatomical position of the bones, we believe, lends strength to the proposed mechanism of action being the soleus muscle's influence on reducing tissue pressures and increasing cardiac output. These results may have implications for the prevention and treatment of osteoporosis in this at-risk population.

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Competing Interests

Dr. Pierce reports no competing interests. Dr. McLeod is a principal in Sonostics, Inc, a Binghamton University spin-off venture focused on development of secondary heart diagnostics and therapeutics.

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