Prevention of Postmenopausal Bone Loss by a Low-Magnitude, High-Frequency Mechanical Stimuli: A Clinical Trial Assessing Compliance, Efficacy, and Safety

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ABSTRACT: A 1-year prospective, randomized, double-blind, and placebo-controlled trial of 70 postmenopausal women demonstrated that brief periods (<20 minutes) of a low-level (0.2 g, 30 Hz) vibration applied during quiet standing can effectively inhibit bone loss in the spine and femur, with efficacy increasing significantly with greater compliance, particularly in those subjects with lower body mass.

Introduction: Indicative of the anabolic potential of mechanical stimuli, animal models have demonstrated that short periods (<30 minutes) of low-magnitude vibration (<0.3 g), applied at a relatively high frequency (20–90 Hz), will increase the number and width of trabeculae, as well as enhance stiffness and strength of cancellous bone. Here, a 1-year prospective, randomized, double-blind, and placebo-controlled clinical trial in 70 women, 3–8 years past the menopause, examined the ability of such high-frequency, low-magnitude mechanical signals to inhibit bone loss in the human.

Materials and Methods: Each day, one-half of the subjects were exposed to short-duration (two 10-minute treatments/day), low-magnitude (2.0 m/s² peak to peak), 30-Hz vertical accelerations (vibration), whereas the other half stood for the same duration on placebo devices. DXA was used to measure BMD at the spine, hip, and distal radius at baseline, and 3, 6, and 12 months. Fifty-six women completed the 1-year treatment.

Results and Conclusions: The detection threshold of the study design failed to show any changes in bone density using an intention-to-treat analysis for either the placebo or treatment group. Regression analysis on the a priori study group demonstrated a significant effect of compliance on efficacy of the intervention, particularly at the lumbar spine (p = 0.004). Posthoc testing was used to assist in identifying various subgroups that may have benefited from this treatment modality. Evaluating those in the highest quartile of compliance (86% compliant), placebo subjects lost 2.13% in the femoral neck over 1 year, whereas treatment was associated with a gain of 0.04%, reflecting a 2.17% relative benefit of treatment (p = 0.06). In the spine, the 1.6% decrease observed over 1 year in the placebo group was reduced to a 0.10% loss in the active group, indicating a 1.5% relative benefit of treatment (p = 0.09). Considering the interdependence of weight, the spine of lighter women (<65 kg), who were in the highest quartile of compliance, exhibited a relative benefit of active treatment of 3.35% greater BMD over 1 year (p = 0.009); for the mean compliance group, a 2.73% relative benefit in BMD was found (p = 0.02). These preliminary results indicate the potential for a noninvasive, mechanically mediated intervention for osteoporosis. This non-pharmacologic approach represents a physiologically based means of inhibiting the decline in BMD that follows menopause, perhaps most effectively in the spine of lighter women who are in the greatest need of intervention.

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INTRODUCTION

OSTEOPOROSIS, A DISEASE CHARACTERIZED by the progressive loss of bone tissue, is one of the most common complications of aging. After menopause, BMD can continue to decline at a rate as high as 3%/year in some women, resulting in 70% of women over the age of 80 having BMD measurements more than 2.5 SDs below...
young normal values. Intervention strategies that slow the loss of bone soon after menopause may result in a significant reduction of fractures in those individuals at greatest risk.\(^7\)

To date, prevention of bone loss has been approached principally through pharmacologic intervention, the long-term safety of which remains uncertain.\(^8\) These pharmacologic approaches inherently ignore that a significant portion of the skeleton’s structural success can be attributed to bone’s sensitivity to alterations in its mechanical environment, with its “form follow function” characteristics ensuring that sufficient mass is placed to withstand the rigors of functional activity.\(^9\) In essence, physical stimuli represent both an endogenous anabolic stimulus to bone tissue\(^10\) and an antiresorptive factor that can actively inhibit osteoclastogenesis.\(^11\)

The skeleton’s sensitivity to its physical environment infers that such non-pharmacologic signals could provide an exogenous treatment regimen for the inhibition of bone loss. Whereas long-term exercise has been shown to increase BMD in young people,\(^12\) this sensitivity seems to be greatly reduced in the elderly.\(^13\) Moreover, exercise, and the predilection to falls that it may invoke, could promote the very fractures that the intervention is prescribed to prevent. In contrast to the relatively well-accepted anabolic influence of high mechanical forces, recent work has led to the hypothesis that extremely small physical stimuli, at sufficiently high, but physiologically relevant, frequencies, can be critical determinants of bone morphology\(^14\) and thus represent a unique means of mediating bone quantity and quality.

Using a surgically invasive model on the ulnae of aged (4 year old) turkeys, high-frequency (30 Hz), low-magnitude (200 microstrain) signals were successful in stimulating an increase in cortical bone, whereas high-amplitude (3000 microstrain), low-frequency (1 Hz) signals failed to be anabolic.\(^15\) Delivering these signals noninvasively for 10 minutes/day, a floor plate vibrating vertically at 90 Hz, inducing strain in the bone of less than 10 microstrain, successfully inhibited disuse osteopenia caused by 23 h and 50 minutes of tail suspension in the rat, whereas 10 minutes/day of normal weight-bearing activity failed to curb this loss.\(^16\)

In longer-term animal studies, 1 year of daily, 20-minute sessions of low-level (0.3 g, where g = earth’s gravitational field, or 9.8 m/s\(^2\)), high-frequency (30 Hz) mechanical stimulation to the hind limbs of adult female sheep stimulated a 43% increase in bone density in the proximal femur, measured by CT.\(^17\) This increase was achieved through a 36% increase in the thickness of individual trabeculae and a 45% increase in their number,\(^18\) contributing to a 12% increase in stiffness and 27% increase in strength of the cancellous bone from the femur.\(^19\)

The work reported here evaluates, in humans, whether such a noninvasive, low-level mechanical signal, induced noninvasively into the musculoskeletal system, is able to inhibit the bone loss that follows menopause. Considering the fiber type–specific sarcopenia that parallels aging,\(^20\) we believe the bone wasting that occurs in older adults results not only from the diminished levels of activity, but from the attenuated 20- to 50-Hz muscle dynamics that normally arise during long-duration activities such as quiet standing. Thus, we hypothesize that “reintroducing” the low-magnitude, high-frequency dynamics back into the musculoskeletal system will re-establish a key regulatory stimulus to the bone tissue and thus inhibit the reduction of BMD that follows menopause.

**MATERIALS AND METHODS**

**Study subjects**

The protocol and study design were reviewed and approved by Creighton University’s Human Use Committee, and all clinical work was completed at the Creighton University School of Medicine’s Osteoporosis Center. Women meeting the 3 to 8-year postmenopausal criteria were recruited from the greater Omaha area by newspaper, radio, and television advertising and from existing subjects within Creighton’s Osteoporosis Center. Informed consent was obtained from qualified volunteers who agreed to participate in the study. Inclusion criteria included normal nutritional status (as determined by questionnaire), stable weight maintenance (i.e., no elective weight loss or diet), estimated daily calcium intake of ≥500 mg/day, and the capability of following the protocol for daily use of the device as well as understanding and providing informed consent. Because of design constraints of the oscillating device, the body mass of included subjects had to be greater than 45 kg and less than 84 kg.

Exclusion criteria consisted of any pharmacologic intervention for osteopenia within the previous 6 months, any use of steroids, current smoking status, consumption of excessive alcohol (>2 drinks/day), evidence of osteomalacia, Paget’s disease, osteogenesis imperfecta, gastrointestinal disease, or history of malignancy, and/or any prolonged immobilization of the axial or appendicular skeleton within the last 3 years. Subjects were also excluded if they had evidence of spondyloarthrosis, thyrotoxicosis, psychomotor disturbances, hyperparathyroidism, renal or hepatic disease, and chronic diseases known to affect the musculoskeletal system (e.g., muscular dystrophy), and/or were engaged in high-impact activity at least three times per week (including but not limited to tennis, aerobics, running, weight-bearing activity or exercise more intense than fast walking).

Subjects not excluded by medical history and who met the inclusion criteria of 3–8 years past menopause underwent a battery of standard laboratory tests (e.g., Health Screen 20, urinalysis, hematology, and bone-specific markers; Metra, Sausalito, CA, USA), as well as lateral X-ray views of the thoracic and lumbar spine. In this second tier examination, subjects were excluded with physical or radiographic evidence of fractures or osteophytes. No patient exclusion was based on BMD status (T or Z scores). If the inclusion/exclusion criteria were satisfied by the medical history, laboratory data, and X-ray data, the subject was enrolled in the study. Over the course of 2 years, a total of 70 women were enrolled in the study.

Active and placebo devices were manufactured and assigned a device number to coincide with a randomization code. Each woman successfully recruited into the study was
provided with a mechanical device (see below), which was delivered to her home and set up by a technician. Throughout the course of the study, subjects and investigators were blinded as to which device was an active or placebo unit, and all information regarding the randomization scheme was kept confidential and secure.

**Design of the vibration platform**

To induce low-level physical stimulation in a controlled manner, an apparatus was designed that used a small, low-force (18N), but highly linear, moving coil actuator (model LA18–18; BEI San Marcos, CA, USA) to impose peak to peak vertical accelerations of 0.2g at a frequency of 30 Hz on a body mass of up to 85 kg. The device was designed such that a very small driving force would produce vertical accelerations of the subject’s body mass and the supporting spring loaded plate (Fig. 1). With incorporation of appropriate accelerometer feedback from the plate surface, control circuitry was sufficient to reduce non-translational modes of vibration caused by motion or positional changes of the subject. As demonstrated in human volunteers, foot-based, whole-body vibrations above 25 Hz (cycles per second) and below 1 g can safely be transmitted into the lower appendicular and axial skeleton without producing any detrimental skeletal resonances. The measured transmissibilities in the skeleton are all significantly below 1.0 at frequencies above 25 Hz, with ~70% of the ground-based signal reaching the trochanter of the femur and L3 in the spine.

**Experimental design**

Sample size projections (discussed below) determined that 64 women would be required to address the principal hypothesis, that is, women who used an active device at least 80% of the prescribed time would show a significant inhibition of the bone loss that follows menopause. The study was also designed such that subjects who dropped out within the first months of participation would be replaced. The initial cohort of 64 women was randomly distributed into one of two groups, and individual treatment began as soon as each subject was enrolled in the study. Each subject was randomly assigned to the active or placebo group according to a confidential, randomized number sequence generated by an independent statistical consultant and without regard to baseline BMD or matching between groups.

In the initial recruitment group, active group, which vibrated at 30 Hz, 0.2g peak to peak, were provided to 32 women, whereas 32 women received a placebo device. At this intensity level, with a total displacement of 55 μm, the motion of the active platform is slightly discernible because the intensity is just above the perception level for vibration. To help obscure the active/placebo status of the devices, each device emitted a low-frequency audible sound to suggest that every plate was “active.” Throughout the course of the study, neither the investigators nor the subjects were informed whether the device was active or placebo, reinforcing the blinded nature of the study.

Each coded device was delivered to the subject’s home, and the subject was instructed how to stand on it for two 10-minute treatments/day, separated by a minimum of 10 h, for 7 days/week. By delivering the devices to the subject’s home, each person was insulated from other participants in the study and intersubject device comparison was avoided, which also aided in the blinded study design. The subjects were advised to use the device in any location in their home that was convenient for them. Subject compliance was recorded by an electronic monitor integrated within the device, which tabulated time, date, and duration of each treatment, throughout the 1-year period. After the 10-minute treatment period, both active and placebo devices shut off automatically. If the subject interrupted any given 10-minute period (e.g., stepping off to answer the phone), this disruption was detected through a plate surface pressure switch, signaling the device to emit an acoustic warning and...
the treatment would pause until the subject returned. If the subject did not return within 10 minutes, the device would record the time activated and automatically shut off.

No incentive was given for maximizing compliance, the device emitted no visible or audible warnings if daily use was undersubscribed, and the study was designed such that the investigators did not prompt the subjects to use the device. Percent compliance was measured as the total number of treatments in which the subject stood on the device for at least 8 minutes, divided by two times the number of days the devices were in the subject’s home times × 100.

**Clinical assessment**

Baseline BMD was determined by DXA (QDR 2000; Hologic, Waltham, MA, USA), with measurements taken at four skeletal locations: proximal right and left femora, lumbar spine, and the distal one-third of the nondominant radius. Subjects were phoned to come in for follow-up scans at approximately 3, 6, and 12 months. Care was taken to position the patient in the same way at each scan, and the same bone density technician performed each scan. A bone phantom was used to calibrate the DXA machine each day. At baseline and completion of the study, to approximate change in bone remodeling status, serum and urine samples were taken, and markers of bone formation and resorption were measured. At completion of the study, a written “exit” questionnaire was requested from each subject, which asked about ease and convenience of use and whether, in the subject’s judgment, they were on a placebo or active device.

**Statistical analysis**

After 12 months of treatment, the primary outcome measure was, in subjects with at least 80% compliance, a significant difference between changes in BMD of the spine and femur in the active and placebo groups. Secondary outcome measures were serum indices of bone formation and resorption. The sample size was determined by anticipating a balanced study with a difference in bone density loss between active and placebo groups of 2% over 1 year, assuming a population SD of 2.4%. A final group size of 56 was calculated to be required to attain a power of 0.80 with an α of 0.05. With a 10% drop-out rate projected (N = 6), a recruitment goal of 64 was set (N = 32 in each group). While the active/placebo status of the devices was not revealed, any subject who withdrew within the first 3 months of treatment was replaced by a subject who received the same device status.

The study results were analyzed in collaboration with an independent statistical consultant (Boston Biostatistics, Wellesley, MA, USA), and no data imputation was performed. The data were initially evaluated in an “intention-to-treat” analysis using the 12-month DXA scan or the scan at the last follow-up visit, and included the results of all subjects enrolled in the study, both treatment and placebo. Analyses were performed a priori using all subjects, first by simple population t-test, and second by multiple linear regression, with body mass and compliance as covariates. Posthoc analyses were performed for all subjects with baseline and 12-month DXA data and for whom full electronically recorded compliance data were available. In posthoc testing, the interaction of compliance and treatment was assessed in a linear effects model, with least square means generated at the specified compliance levels reflecting the intercepts of the three compliance quartile boundaries (59.1%, 76.6%, 85.9%). Because of the reported relationship between osteoporotic fracture risk and body build,(25) a three-way interaction of treatment, compliance, and subject weight (bisected at 65 kg; consistent with NHANES II body weights of females in this age range(26)) was investigated both in a linear effect model and by a simple t-test dichotomizing compliance at the 80% and 60% levels. p values less than 0.05 were considered statistically significant; no posthoc corrections were undertaken.

**RESULTS**

In total, 70 (33 active and 37 placebo) subjects were randomized into the study and were included in the intention-to-treat analysis. Six (one active and five placebo) subjects withdrew within the first 3 months and therefore had no DXA follow-up. Each of the six people who withdrew was replaced by a new subject who entered into the same treatment type. Of the 64 subjects who had at least two DXA measurements, 8 did not have a 12-month DXA scan; therefore, the remaining 56 subjects (28 active and 28 placebo each with a 12-month DXA scan) formed the a priori analysis group. Complete electronically recorded compliance data on 10 of the remaining 56 subjects were not available, and thus the per-protocol analysis (group used for posthoc analysis purposes) considers only the subset of 46 subjects (26 active and 20 placebo) where a full electronic record of compliance was available. There was one adverse reaction of treatment reported (headache), which came from a woman in the placebo group. All active devices were reassessed at the end of the study and found to be within 5% of the 30 Hz, 0.2g criteria, as per the original dynamic parameters at the initiation of the study. Furthermore, at the end of the 12-month period, the audible acoustic signal, intended to obscure the active/placebo status of the platform, was functioning in all devices.

At the completion of the study, the randomization code was broken, and a comparison of the two groups, active and placebo, was determined. Although the study was not powered to detect demographic differences, age, height, femur, and spine BMD at baseline were not significantly different between the groups. However, at baseline, the placebo group’s average weight was 5 kg higher than the active group (p < 0.03), and the body mass index (BMI) of the placebo group was 2 kg/m² higher (p < 0.04; Table 1).

An intention-to-treat analysis of all 70 subjects was undertaken using a bootstrap technique to permit estimation of the response in subjects with incomplete data.(27) In neither the active nor placebo group did changes in bone density exceed the detection threshold of the study design. In the femoral neck, the active group lost 0.69% versus a 0.27% loss in the placebo group. In the trochanter, the active group lost 0.07% of their BMD versus a 0.19% loss in the placebo group. In the lumbar spine, the active
group lost 0.51% versus a loss of 0.65% in the placebo population \( (p = 0.45) \).

Fifty-six subjects (28 active and 28 placebo) had a 12-month DXA scan, and this group constituted the a priori study group. A wide range in compliance with device use was observed in this population, ranging from 1% to 95%. When the device was used, however, 98.4% of what constituted a complete treatment (>8 minutes) was a full 10-minute treatment. Thirty-seven percent of subjects completing the study were at least 80% compliant (10 active and 7 placebo), whereas 72% of subjects were at least 60% compliant (19 active and 14 placebo). Whereas the placebo population had consistently higher losses of BMD in the lumbar spine, femoral neck, and trochanter regions of the skeleton than that measured in the active treatment groups, no significant differences were observed on population averages.

Because of the large range of compliance, multiple regression analysis was performed on the a priori populations to identify the relationship between compliance and efficacy. Strong positive associations between device usage and changes in BMD were observed at all three sites of interest (Table 2). Using compliance and weight as covariates, a strong dependence on subject weight is also shown for the spine and femoral neck region of the placebo subjects \( (p = 0.004) \). Body mass index also showed a significant difference between the two groups \( (p = 0.04) \).

At the beginning of the protocol, there were no significant differences between the active and placebo groups in terms of age, height, months past the menopause, and femur, spine, or radius BMD. There were significant differences in body weight between the two groups, with the placebo group 5 kg heavier than the active group \( (p = 0.03) \). The table presents multiple regression data using the covariates of compliance and weight.

### TABLE 2. MULTIPLE REGRESSIONS OF ALL SUBJECTS WITH 12-MONTH DXA WITH COVARIATES OF COMPLIANCE AND WEIGHT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Error</th>
<th>t Value</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total spine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active y intercept</td>
<td>-4.11</td>
<td>2.96</td>
<td>-1.39</td>
<td>0.18</td>
</tr>
<tr>
<td>Active weight</td>
<td>-0.023</td>
<td>0.042</td>
<td>-0.54</td>
<td>0.59</td>
</tr>
<tr>
<td>Active compliance</td>
<td>0.0714</td>
<td>0.022</td>
<td>3.18</td>
<td>0.004</td>
</tr>
<tr>
<td>Placebo y intercept</td>
<td>-7.53</td>
<td>2.84</td>
<td>-2.65</td>
<td>0.014</td>
</tr>
<tr>
<td>Placebo weight</td>
<td>0.11</td>
<td>0.039</td>
<td>2.78</td>
<td>0.01</td>
</tr>
<tr>
<td>Placebo compliance</td>
<td>-0.01</td>
<td>0.014</td>
<td>-0.76</td>
<td>0.46</td>
</tr>
<tr>
<td>Femoral trochanter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active y intercept</td>
<td>-7.76</td>
<td>3.74</td>
<td>-2.08</td>
<td>0.048</td>
</tr>
<tr>
<td>Active weight</td>
<td>0.06</td>
<td>0.05</td>
<td>1.17</td>
<td>0.25</td>
</tr>
<tr>
<td>Active compliance</td>
<td>0.05</td>
<td>0.028</td>
<td>1.8</td>
<td>0.085</td>
</tr>
<tr>
<td>Placebo y intercept</td>
<td>-2.66</td>
<td>3.17</td>
<td>-0.84</td>
<td>0.41</td>
</tr>
<tr>
<td>Placebo weight</td>
<td>0.033</td>
<td>0.043</td>
<td>0.76</td>
<td>0.45</td>
</tr>
<tr>
<td>Placebo compliance</td>
<td>0.0026</td>
<td>0.014</td>
<td>0.19</td>
<td>0.85</td>
</tr>
<tr>
<td>Femoral neck</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active y intercept</td>
<td>-7.13</td>
<td>3.9</td>
<td>-1.83</td>
<td>0.08</td>
</tr>
<tr>
<td>Active weight</td>
<td>0.0796</td>
<td>0.055</td>
<td>1.44</td>
<td>0.16</td>
</tr>
<tr>
<td>Active compliance</td>
<td>0.018</td>
<td>0.029</td>
<td>0.62</td>
<td>0.54</td>
</tr>
<tr>
<td>Placebo y intercept</td>
<td>-3.25</td>
<td>3.39</td>
<td>-0.96</td>
<td>0.35</td>
</tr>
<tr>
<td>Placebo weight</td>
<td>0.10</td>
<td>0.046</td>
<td>2.18</td>
<td>0.04</td>
</tr>
<tr>
<td>Placebo compliance</td>
<td>-0.064</td>
<td>0.015</td>
<td>-4.34</td>
<td>0.001</td>
</tr>
</tbody>
</table>

The linear prediction model was constructed to investigate the general influence of compliance (i.e., percent of total possible treatments completed; Table 3). A significant interaction of treatment and compliance was observed for femoral neck BMD changes \( (p = 0.06) \), with the active treatment showing a relative benefit over placebo of 2.17% when the subjects were 86% compliant. Similar observations are seen at the trochanter (relative benefit of 1.23% at 86% compliance; \( p = 0.21 \)) and at the lumbar spine (1.5% relative benefit; \( p = 0.09 \)). Factoring in weight improves the effi-
Table 3. Percent Compliance Effect on Treatment Differences

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Active</th>
<th>Placebo</th>
<th>Diff.</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent change in total spine BMD (treatment and compliance interaction p value = 0.23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>59.1% Compliance</td>
<td>-1.55</td>
<td>-1.91</td>
<td>+0.36</td>
<td>0.69</td>
</tr>
<tr>
<td>59.1% Comp. and wt. &lt; 65 kg</td>
<td>-1.57</td>
<td>-3.63</td>
<td>+2.06</td>
<td>0.14</td>
</tr>
<tr>
<td>Mean compliance</td>
<td>-0.91</td>
<td>-1.77</td>
<td>+0.86</td>
<td>0.21</td>
</tr>
<tr>
<td>Mean comp. and wt. &lt; 65 kg</td>
<td>-0.70</td>
<td>-3.43</td>
<td>+2.73</td>
<td>0.02</td>
</tr>
<tr>
<td>85.9% Compliance</td>
<td>-0.10</td>
<td>-1.60</td>
<td>+1.50</td>
<td>0.09</td>
</tr>
<tr>
<td>85.9% Comp. and wt. &lt; 65 kg</td>
<td>+0.18</td>
<td>-3.17</td>
<td>+3.35</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Percent change in femoral trochanter BMD (treatment and compliance interaction p value = 0.035)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Active</th>
<th>Placebo</th>
<th>Diff.</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>59.1% Compliance</td>
<td>-0.30</td>
<td>-0.93</td>
<td>+0.63</td>
<td>0.67</td>
</tr>
<tr>
<td>59.1% Comp. and wt. &lt; 65 kg</td>
<td>-0.93</td>
<td>-1.89</td>
<td>+0.96</td>
<td>0.57</td>
</tr>
<tr>
<td>Mean compliance</td>
<td>+0.06</td>
<td>-0.73</td>
<td>+0.79</td>
<td>0.31</td>
</tr>
<tr>
<td>Mean comp. and wt. &lt; 65 kg</td>
<td>-0.16</td>
<td>-1.55</td>
<td>+1.39</td>
<td>0.28</td>
</tr>
<tr>
<td>85.9% Compliance</td>
<td>-0.76</td>
<td>-0.47</td>
<td>+1.23</td>
<td>0.21</td>
</tr>
<tr>
<td>85.9% Comp. and wt. &lt; 65 kg</td>
<td>+0.80</td>
<td>-1.12</td>
<td>+1.92</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Percent change in femoral neck BMD (treatment and compliance interaction p value = 0.02)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Active</th>
<th>Placebo</th>
<th>Diff.</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>59.1% Compliance</td>
<td>-1.18</td>
<td>-0.42</td>
<td>-0.76</td>
<td>0.52</td>
</tr>
<tr>
<td>59.1% Comp. and wt. &lt; 65 kg</td>
<td>-1.57</td>
<td>-0.94</td>
<td>-0.63</td>
<td>0.74</td>
</tr>
<tr>
<td>Mean compliance</td>
<td>-0.64</td>
<td>-1.18</td>
<td>-0.54</td>
<td>0.54</td>
</tr>
<tr>
<td>Mean comp. and wt. &lt; 65 kg</td>
<td>-0.93</td>
<td>-1.51</td>
<td>-0.58</td>
<td>0.69</td>
</tr>
<tr>
<td>85.9% Compliance</td>
<td>+0.04</td>
<td>-2.13</td>
<td>+2.17</td>
<td>0.06</td>
</tr>
<tr>
<td>85.9% Comp. and wt. &lt; 65 kg</td>
<td>-0.13</td>
<td>-2.23</td>
<td>+2.10</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Compliance was assessed as a single (linear) effect for percent compliance (59.09%, 76.62%, and 85.87%). Least-square means were generated at the specified compliance level. Weight was dichotomized to be either < 65 kg or ≥ 65 kg. Least-square means were generated estimating the < 65 kg means at that level of compliance (e.g., 59.1%).

Table 4. Percent Change as a Function of Compliance and Weight

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Active</th>
<th>Placebo</th>
<th>Diff.</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent change in total spine BMD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compliance ≥ 60%</td>
<td>-0.41</td>
<td>-0.84</td>
<td>+0.43</td>
<td>0.55</td>
</tr>
<tr>
<td>60% Comp. and wt. &lt; 65 kg</td>
<td>-0.28</td>
<td>-3.32</td>
<td>+3.04</td>
<td>0.03</td>
</tr>
<tr>
<td>Compliance ≥ 80%</td>
<td>-0.17</td>
<td>-1.11</td>
<td>+0.94</td>
<td>0.38</td>
</tr>
<tr>
<td>80% Comp. and wt. &lt; 65 kg</td>
<td>+0.49</td>
<td>-3.19</td>
<td>+3.68</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Percent change in femoral trochanter BMD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Active</th>
<th>Placebo</th>
<th>Diff.</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliance ≥ 60%</td>
<td>+0.57</td>
<td>-0.14</td>
<td>+0.71</td>
<td>0.40</td>
</tr>
<tr>
<td>60% Comp. and wt. &lt; 65 kg</td>
<td>+0.74</td>
<td>-1.25</td>
<td>+1.99</td>
<td>0.26</td>
</tr>
<tr>
<td>Compliance ≥ 80%</td>
<td>+0.90</td>
<td>+0.11</td>
<td>+0.79</td>
<td>0.56</td>
</tr>
<tr>
<td>80% Comp. and wt. &lt; 65 kg</td>
<td>+1.37</td>
<td>-1.10</td>
<td>+2.47</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Percent change in femoral neck BMD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Active</th>
<th>Placebo</th>
<th>Diff.</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliance ≥ 60%</td>
<td>-0.23</td>
<td>-1.28</td>
<td>+1.05</td>
<td>0.30</td>
</tr>
<tr>
<td>60% Comp. and wt. &lt; 65 kg</td>
<td>-0.41</td>
<td>-2.59</td>
<td>+2.18</td>
<td>0.27</td>
</tr>
<tr>
<td>Compliance ≥ 80%</td>
<td>0.17</td>
<td>-1.88</td>
<td>+2.05</td>
<td>0.16</td>
</tr>
<tr>
<td>80% Comp. and wt. &lt; 65 kg</td>
<td>-0.06</td>
<td>-2.18</td>
<td>+2.12</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Data are shown for the spine, femoral trochanter, and femoral neck as a function of 60% and 80% compliance. The analysis is repeated for those subjects that are also < 65 kg in weight. The subject numbers for each treatment type by category are Compliance ≥ 60%: Active = 19, Placebo = 14; Compliance ≥ 60% and weight < 65 kg: Active = 9, Placebo = 4; Compliance ≥ 80%: Active = 10, Placebo = 7; Compliance ≥ 80% and weight < 65 kg: Active = 7, Placebo = 3. The data illustrate a substantial increase in efficacy in the lumbar spine with both higher compliance levels and in lighter weight subjects.

Considering weight as an interacting influence on spine BMD, the subjects were stratified into groups above and below 65 kg (Fig. 2; Table 4). In the lower-weight cohort, in the highest quartile of compliance (86%), there was a 3.17% loss of bone in the spine in the placebo group compared with a 0.18% gain in BMD in the active group, suggesting a 3.35% relative benefit of treatment (p < 0.009; Table 3). Similarly, in this lower-weight, high-compliance group for the femoral neck, there was a 2.23% loss over the course of the year in the placebo group compared with a 0.13% loss in the active group, representing a 2.1% relative benefit of treatment. For the trochanter, the relative benefit was 1.92% over the course of 1 year of treatment.

Figure 3 provides a plot of the quartiles derived from the linear modeling with the placebo group providing the mean of the three-quartile values for each treatment site. In the lumbar spine, a 0.1% loss in the highest quartile of compliance was relatively better than the 1.55% loss experienced by the lowest compliance group. This 1.55% loss in the lowest compliance group was similar to the 1.76% loss measured in subjects standing on a placebo device. In the trochanter region, a 0.76% gain was determined for the highest-compliance group, whereas a 0.5% loss was experienced by the lowest compliance group, a loss that was similar to the 0.71% loss observed in the placebo group. The femoral neck, as well, demonstrated a dose-dependent response with a 0.04% gain in the highest-compliance group versus a 1.18% loss in the low-compliance group. This 1.18% loss was similar to the 1.24% loss measured in the placebo group. In the distal radius, there were no significant differences between any of the compliance groups and the placebo group.

Serum indices of bone formation and resorption were evaluated at baseline and at the end of the study to determine if the mechanical intervention influenced bone remodeling activity. Dietary calcium (self-reported) was the only variable that seemed significantly different at baseline. At 12 months, hydroxyproline levels fell 16% in the placebo group but only 3% in the active group, reflecting a 13% difference (p = 0.07). Phosphorus (baseline value = 3.7) was up 1.3% in the active group but fell 4% in the placebo group, reflecting a 5% difference (p = 0.08). No significant changes were seen in bone-specific alkaline phosphatase (which went up in both groups), total alkaline phosphatase (which went down in both groups), creatinine (which did not change), osteocalcin, or parathyroid hormone (PTH). Every 3 months, either by telephone or visits to the Center, patients were asked if they exercised more or changed any other aspect of their lifestyle. No trends were identified.

In their exit interviews, the subjects expressed concern that two 10-minute/day treatments were difficult to schedule but that they may be more encouraged to use the device if efficacy was demonstrated and if a single use per day were possible. Approximately 20% of the active subjects guessed incorrectly in terms of whether they had an active device,
and 30% of the placebo subjects guesses were incorrect as to the status of their device.

**DISCUSSION**

This study examines the safety and potential efficacy of a very-low-magnitude physical stimulus to inhibit loss of BMD, which is based on the musculoskeletal system’s strong sensitivity to mechanical stimuli. The physical stimulus is imposed noninvasively into the weight-bearing skeleton through ground-based accelerations. The nature of the vibratory stimulus is based on providing a surrogate for the spectra of high-frequency muscle-based signals that attenuate with aging. In addition to large amplitude mechanical forces (and resultant strains) associated with vigorous activity, smaller magnitude strain signals are continually evident in bone, and it is these signals that we are trying to mimic. When the 12-month human data are considered in an a priori analysis, the results indicate a potential benefit of treatment strongly dependent on compliance, as standing on the device for close to 20 minutes/day was associated with a greater ability to prevent bone loss. Using linear regression analysis to determine the effect of full 100% compliance indicates that an “idealized” subject who used the device for the full 20 minutes/day could have up to 7% higher lumbar spine BMD and 5% higher BMD in the trochanter than those who did not use the device at all. Compliance, however, is difficult to ensure in any study, and strategies to improve use must be considered.

The exit interviews indicated that a “twice per day” regimen made it difficult to fit into a working schedule. Possibly, exposure time could be reduced if the potency of the mechanical signal could be increased, perhaps by increasing the amplitude to above 0.2g, which may take advantage of the interdependence of cycle number and strain magnitude, or to identify alternative frequencies or waveform combinations that may be more effective. Examining subject commitment to a shorter treatment duration, a recent feasibility study has shown that, over 6 months of treatment in an elderly female population (75–90 years old), using a 10-minutes/day, 30 Hz stimulus at 0.3g, a mean compliance of 93% was maintained. Considering the difficulty in fitting in two 10-minute treatment regimens, it is also possible that compliance would have been improved had a single 20-minute session been used.

Posthoc analysis indicates that this intervention may be more effective in lighter women than in heavier women, particularly in the spine (Fig. 2). Considering that BMD is positively correlated with body mass, these data in turn also suggest that the mechanical stimulus works best in those women with lower BMD (i.e., effective in women who require it), specific to those skeletal sites that need treatment (no significant differences were observed in the radius between active and placebo subjects). The individualized “sensitivity” to the mechanical signal is consistent with findings in the mouse, where the anabolic potential of the mechanical stimulus is realized in inbred strains with low bone density (e.g., B6), whereas there is only low responsivity to altered mechanical environments in the high-density strains (e.g., C3H).

This study indicates that low-level mechanical stimuli may have the potential to prevent bone loss in the postmenopausal population, but failed to stimulate the formation of bone. In contrast, the stimulus used in this study was shown in animal studies to be strongly anabolic, an observation supported by recent work addressing the effects of 0.3g vibration on bone density in children with cerebral
gies it may exacerbate, including low back pain, (39) circu-

and

Considering that the bone strain resulting from these vibra-

it is entirely possible that the muscle may bene 

fi

does represent a surrogate for the signals lost by sarcopenia, (51) If the physical stimulus investigated here

stability and muscle strength contribute to fracture risk on a

associated with long bone fractures. For example, postural

activity, resulting in signiﬁcant effects on circulatory ﬂows

and clinical support for the hypothesis that extremely low

level physical stimuli may provide an effective means to

inhibit bone loss, particularly for those who cannot or will

not comply with traditional pharmacologic interventions for

osteooporosis. (53)

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REFERENCES

1. NIH Consensus Development Conference 2000 Osteoporosis

prevention, diagnosis, and therapy. NIH Consens Statement

17:1–45.

2. Dawson-Hughes B 1991 Calcium supplementation and bone loss:


280S.

3. Hannan MT, Felson DT, Anderson JJ 1992 Bone mineral density in

elderly men and women: Results from the Framingham osteo-


4. Riis B, Thomsen K, Christiansen C 1987 Does calcium supplemen-

tation prevent postmenopausal bone loss? A double-blind, con-


5. Ensrud KE, Palermo L, Black DM, Cauley J, Jergas M, Orwell ES,

Nevitt MC, Fox KM, Cummings SR 1995 Hip and calcaneal bone

loss increase with advancing age: Longitudinal results from the


6. Melton LJ 1995 How many women have osteoporosis now? J Bone

Miner Res 10:175–177.

7. Cummings SR, Black D 1995 Bone mass measurements and risk of

fracture in Caucasian women: A review of ﬁndings from prospec-


Schatzkin A, Schairer C 2002 Menopausal hormone replacement


von August Hirschwald, Berlin, Germany.

10. Lanyon LE 1996 Using functional loading to inﬂuence bone mass

and architecture: Objectives, mechanisms, and relationship with

estrogen of the mechanically adaptive process in bone. Bone

18:375–43S.

11. Rubin J, Murphy T, Nanes MS, Fan X 2000 Mechanical strain inhibits expression of osteoclast differentiation factor by murine


1992 Effects of resistance and endurance exercise on bone mineral

status of young women: A randomized exercise intervention trial.

J Bone Miner Res 7:761–769.


Deterring bone loss by exercise intervention in premenopausal and


14. Fritton SP, McLeod KJ, Rubin CT 2000 Quantifying the strain

history of bone: Spatial uniformity and self-similarity of low-


15. Rubin CT, Bain SD, McLeod KJ 1992 Suppression of the osteo-

16. Rubin C, Xu G, Judex S 2001 The anabolic activity of bone tissue, suppressed by disuse, is normalized by brief exposure to extremely

PREVENTION OF OSTEOPOROSIS BY LOW-LEVEL MECHANICAL SIGNALS

33. Judex S, Donahue LR, Rubin CT 2002 Genetic predisposition to osteoporosis is paralleled by an enhanced sensitivity to signals anabolic to the skeleton. FASEB J 16:1260–1283.
43. American Conference of Governmental Industrial Hygienists 1997 Threshold Limit Values for Chemical Substances and Physical Agents; Biological Exposure Indices, pp. 82–95.
49. Villanueva A, Madhavan G, McLeod K 2002 Changes in the non-linear dynamics of heart rate variability due to foot based vibration while in the seated position. Second Joint EMBS-BMES Conference. Houston, TX, USA, October 2002. p. 120.

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