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

Clinton Rubin,[1] Robert Recker,[2] Diane Cullen,[2] John Ryaby,[3] Joan McCabe,[3] and Kenneth McLeod[4]

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/s^2 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.[1] After menopause, BMD can continue to decline at a rate as high as 3%/year in some women,[2–5] resulting in 70% of women over the age of 80 having BMD measurements more than 2.5 SDs below

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[1]Department of Biomedical Engineering, State University of New York, Stony Brook, New York, USA; [2]Osteoporosis Research Center, Creighton University, Omaha, Nebraska, USA; [3]Clinical Research, Juveat, Inc., Somerset, New Jersey, USA; [4]Department of Bioengineering, State University of New York, Binghamton, New York, USA.

young normal values.[6] 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 invite, 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 ($0.3g$, 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 $\geq$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 0.2*g* 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.[21] 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 L_3 in the spine.[22]

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 devices, which vibrated at 30 Hz, 0.2*g* 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.[23] 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

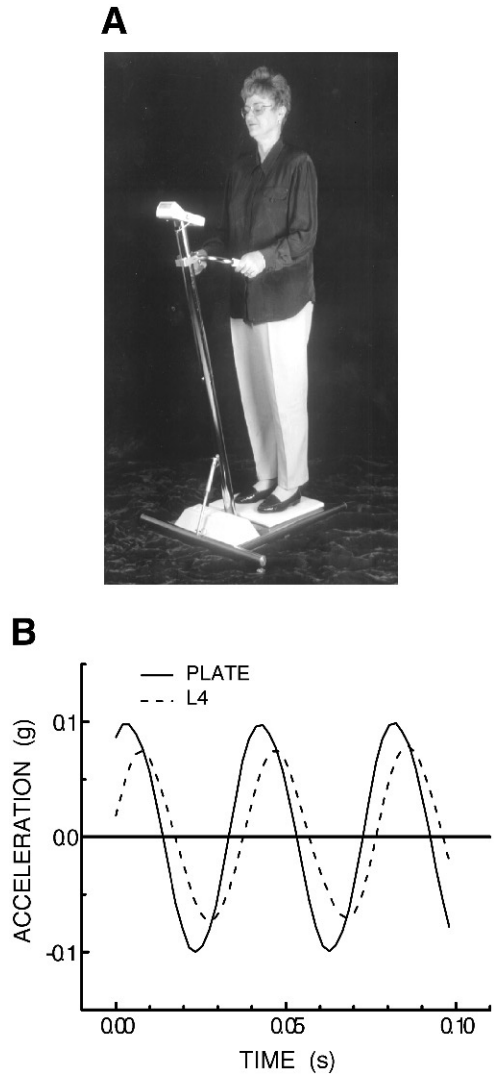

FIG. 1. (A) Noninvasive device to achieve low-magnitude mechanical stimulation consists of a spring-supported plate driven by an 18N peak force electromagnetic actuator. By incorporating the subject's mass as part of a resonating mechanical system, perturbation of up to 0.4*g* (peak to peak), over the range of 5–100 Hz, can be attained for subjects up to 80 kg. (B) Accelerations measured at L4 (dotted line), while slightly out of phase with the 0.2*g*, 30-Hz oscillation of the plate, demonstrated a high level of transmissibility.[22]

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 $\times$ 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.[24] 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/m^2 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% of their BMD 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

TABLE 1. BASELINE COMPARABILITY OF THE PLACEBO AND ACTIVE GROUPS (RANGES ARE PROVIDED IN THE PARENTHESES)

Parameter	*Placebo*	*Active*	p *Value*
Age (years)	57.33 (47–64)	57.34 (52–64)	0.99
Height (cm)	161.3 (150.4–177.1)	161.9 (155.3–176.1)	0.98
Weight (kg)	69.0 (53.4–85.6)	63.8 (48.3–81.0)	0.03
BMI (kg/m^2)	26.4 (20.1–32.1)	24.4 (18.4–30.4)	0.04
Postmenopausal (months)	69.9 (35.7–101.2)	68.2 (34.1–101.6)	0.74
Femur neck BMD	0.702 (0.57–1.01)	0.698 (0.50–0.93)	0.59
Femur trochanter BMD	0.62 (0.52–0.81)	0.60 (0.34–0.82)	0.53
Spine BMD	0.908 (0.69–1.34)	0.915 (0.65–1.18)	0.86
Radius BMD	0.65 (0.52–0.75)	0.66 (0.52–0.77)	0.65
N	28	28	

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 ($p = 0.03$). Body mass index also showed a significant difference between the two groups ($p = 0.04$).

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, BMD of the spine was found to increase 0.071% for each percent increase in compliance of device use ($p = 0.0039$). Projecting this correlation to an "idealized patient" who was 100% compliant, and assuming the bone remodeling response to be linear, this would correspond to a 7.1% increase in BMD over the course of the year. For the trochanter at 100% compliance, BMD would be projected to increase by 5.1% ($p = 0.085$), and for the femoral neck, BMD would increase at a projected rate of 1.8% over the course of the year ($p = 0.54$). Correspondingly, BMD changes in the placebo population demonstrated no association at the trochanter and lumbar spine and a negative association for the femoral neck ($p = 0.001$).

Posthoc analysis of the per protocol group, examining efficacy at each intercept of compliance quartiles, used least square means generated at the specified compliance level for those subjects in that quartile and treatment group performed without corrections. Based on the suggestion of a treatment and compliance interaction as seen in Table 2, a 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 2. MULTIPLE REGRESSIONS OF ALL SUBJECTS WITH 12-MONTH DXA WITH COVARIATES OF COMPLIANCE AND WEIGHT

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

The table presents multiple regression data using the covariates of subject weight and percent compliance of device use. A strong dependence on compliance is demonstrated for the spine of the active subjects ($p = 0.004$) and the femoral neck of the placebo subjects ($p = 0.001$). A dependence on subject weight is also shown for the spine and femoral neck region of the placebo subjects ($p = 0.01$ and $p = 0.04$, respectively).

Table 3. Percent Compliance Effect on Treatment Differences

Parameter	Active	Placebo	Diff. (A vs. P)	p Value
Percent change in total spine BMD (treatment and compliance interaction p value = 0.23)				
59.1% Compliance	−1.55	−1.91	+0.36	0.69
59.1% Comp and wt. < 65 kg	−1.57	−3.63	+2.06	0.14
Mean compliance	−0.91	−1.77	+0.86	0.21
Mean comp. and wt. < 65 kg	−0.70	−3.43	+2.73	0.02
85.9% Compliance	−0.10	−1.60	+1.50	0.09
85.9% Comp. and wt. < 65 kg	+0.18	−3.17	+3.35	0.009
Percent change in femoral trochanter BMD (treatment and compliance interaction p value = 0.35)				
59.1% Compliance	−0.50	−0.93	+0.43	0.67
59.1% Comp. and wt. < 65 kg	−0.93	−1.89	+0.96	0.57
Mean compliance	+0.06	−0.73	+0.79	0.31
Mean comp. and wt. < 65 kg	−0.16	−1.55	+1.39	0.28
85.9% Compliance	+0.76	−0.47	+1.23	0.21
85.9% Comp. and wt. ≤ 65 kg	+0.80	−1.12	+1.92	0.17
Percent change in femoral neck BMD (treatment and compliance interaction p value = 0.02)				
59.1% Compliance	−1.18	−0.42	−0.76	0.52
59.1% Comp. and wt. < 65 kg	−1.57	−0.94	−0.63	0.74
Mean compliance	−0.64	−1.18	−0.54	0.54
Mean comp. and wt. < 65 kg	−0.93	−1.51	−0.58	0.69
85.9% Compliance	+0.04	−2.13	+2.17	0.06
85.9% Comp. and wt. < 65 kg	−0.13	−2.23	+2.10	0.19

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

Parameter	Active	Placebo	Diff. (A vs. P)	p Value
Percent change in total spine BMD				
Compliance ≥ 60%	−0.41	−0.84	+0.43	0.55
60% Comp. and wt. < 65 kg	−0.28	−3.32	+3.04	0.03
Compliance ≥ 80%	−0.17	−1.11	+0.94	0.38
80% Comp. and wt. < 65 kg	+0.49	−3.19	+3.68	0.02
Percent change in femoral trochanter BMD				
Compliance ≥ 60%	+0.57	−0.14	+0.71	0.40
60% Comp. and wt. < 65 kg	+0.74	−1.25	+1.99	0.26
Compliance ≥ 80%	+0.90	+0.11	+0.79	0.56
80% Comp. and wt. < 65 kg	+1.37	−1.10	+2.47	0.25
Percent change in femoral neck BMD				
Compliance ≥ 60%	−0.23	−1.28	+1.05	0.30
60% Comp. and wt. < 65 kg	−0.41	−2.59	+2.18	0.27
Compliance ≥ 80%	0.17	−1.88	+2.05	0.16
80% Comp. and wt. < 65 kg	−0.06	−2.18	+2.12	0.40

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.

cacy of treatment, with the benefit of treatment ranging from 2% to 3% at all three sites, with p values ranging from 0.19 to 0.009.

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,

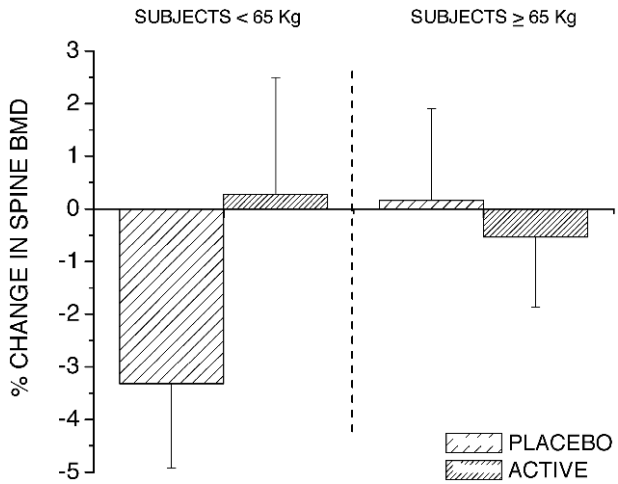

FIG. 2. Stratification based on body mass shows that the lighter women (<65 kg) lost 3.32% bone from the spine over the course of the year. In these lighter women who remained at least 60% compliant with the daily treatment of low-level mechanical stimulation, the loss was inhibited ($p = 0.032$). Heavier women lost essentially no bone over the course of the year, and thus it was not possible to show the efficacy of treatment to inhibit a loss that was not occurring ($p = 0.34$).

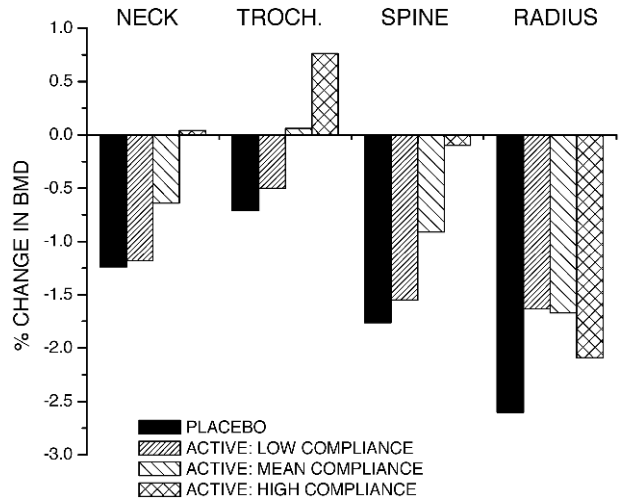

FIG. 3. The ability of low-level mechanical stimulation to inhibit bone loss in weight-bearing regions was strongly dependent on compliance (femoral neck, femoral trochanter, total spine), with trends showing the more the device was used, the greater the effect that was evident. Shown is each of the single linear effects model for active, low compliance (59.1%); active, medium compliance (mean); and active, high compliance (85.9%) groups for each site, and they are compared with the mean of the average placebo values from the linear model for all compliance levels (Table 3). There was no influence of the mechanical treatment on the radius.

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.[20] In addition to large amplitude mechanical forces (and resultant strains) associated with vigorous activity, smaller magnitude strain signals are continually evident in bone,[14,28] 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,[29] 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 0.2*g*, which may take advantage of the interdependence of cycle number and strain magnitude,[30] or to identify alternative frequencies or waveform combinations that may be more effective.[31] 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 0.3*g*, a mean compliance of 93% was maintained.[32] 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,[25] 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).[33]

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,[17–19] an observation supported by recent work addressing the effects of 0.3*g* vibration on bone density in children with cerebral

palsy[34] and adolescent females (10–13 years old) in the lowest quartile of BMD.[35] Whether the anabolic response was observed because the signal was delivered to the skeleton of children rather than adults or because the amplitude was 50% greater (0.3*g* rather than 0.2*g*) is not yet clear. Considering that the bone strain resulting from these vibrations are two orders of magnitude below those levels that initiate microdamage,[36] this indicates that anabolism can be achieved without putting the skeleton at structural risk. With this in mind, it is relevant to note that in a recent study reported by Torvinen et al.,[37] vibration 40 times greater than the signals examined here (8*g* as opposed to 0.2*g*) failed to stimulate any form of bone response. Whether this was because the study was relatively brief (8 months), used healthy young adults (and therefore there was no "signal" lacking that required replacement), or that the amplitude was so great as to be beyond any form of physiologic relevance (as in light that is too bright, sound that is too loud, or pressure that is too great), is difficult to determine at this point.

No adverse reactions were reported in the active group. Nevertheless, vibration of the human body is undeniably a complex issue,[38] and considering the variety of pathologies it may exacerbate, including low back pain,[39] circulation disorders,[40] and/or neurovestibular dysfunction,[41] it must be approached carefully. ISO 2631 gives *"provisional guidance as to acceptable human exposure"* to whole-body vibration in the 1- to 100-Hz band for a sitting or standing person,[42] defining numerical values of the *"fatigue-decreased proficiency boundary"* over a 24-h period. Sinusoidal frequencies in the range of 25–32 Hz allow for a 4-h exposure at 0.4*g*, well exceeding acceleration levels and times under investigation with this device. The safety of signals that exceed 1*g,* for even a short duration, may be of some concern.[43]

There is general perception within the skeletal disciplines that signals must be large to represent a positive influence on bone mass and morphology.[44] These data support the premise that extremely small mechanical signals may also be capable of serving as a regulatory influence on skeletal architecture, the "outcome" of which seems to be a more uniform distribution of stresses in trabecular bone under load.[45] This regulatory influence may be achieved directly, by mechanical strain, or indirectly, through amplification of the signal by intramedullary pressure[46] or fluid flow[47] in the bone tissue. Alternatively, the regulatory response may be regulated through a system such as neuromuscular feedback amplified by the low-level signals exceeding a stochastic threshold[48] or by stimulating skeletal muscle pump activity, resulting in significant effects on circulatory flows and fluid flow through the bone tissue.[49] Even considering the complicated nature of the physical mechanism, there can be little doubt that the biological means of controlling bone adaptation are even more complex.[50]

Bone architecture is but one of several critical risk factors associated with long bone fractures. For example, postural stability and muscle strength contribute to fracture risk on a par with BMD.[51] If the physical stimulus investigated here does represent a surrogate for the signals lost by sarcopenia, it is entirely possible that the muscle may benefit from treatment as well, enhancing muscle strength,[52] and coupled with the neurovestibular system, improve postural stability.[48]

This prospective, randomized, double-blind, and placebo-controlled study has provided important preliminary results, 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 osteoporosis.[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: A review of controlled clinical trials. Am J Clin Nutr **54:**274S–280S.
3. Hannan MT, Felson DT, Anderson JJ 1992 Bone mineral density in elderly men and women: Results from the Framingham osteoporosis study. J Bone Miner Res **7:**547–553.
4. Riis B, Thomsen K, Christiansen C 1987 Does calcium supplementation prevent postmenopausal bone loss? A double-blind, controlled clinical study. N Engl J Med **316:**173–177.
5. Ensrud KE, Palermo L, Black DM, Cauley J, Jergas M, Orwoll ES, Nevitt MC, Fox KM, Cummings SR 1995 Hip and calcaneal bone loss increase with advancing age: Longitudinal results from the study of osteoporotic fractures. J Bone Miner Res **10:**1778–1787.
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 prospective studies. Am J Med **98:**24S–28S.
8. Lacey JV Jr, Mink PJ, Lubin JH, Sherman ME, Troisi R, Hartge P, Schatzkin A, Schairer C 2002 Menopausal hormone replacement therapy and risk of ovarian cancer. JAMA **288:**334–341.
9. Wolff J 1892 Das Gesetz der Transformation der Knochen. Verlag 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:**37S–43S.
11. Rubin J, Murphy T, Nanes MS, Fan X 2000 Mechanical strain inhibits expression of osteoclast differentiation factor by murine stromal cells. Am J Physiol Cell Physiol **278:**C1126–C1132.
12. Snow-Harter C, Bouxsein ML, Lewis BT, Carter DR, Marcus R 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.
13. Smith EL, Gilligan C, McAdam M, Ensign CP, Smith PE 1989 Deterring bone loss by exercise intervention in premenopausal and postmenopausal women. Calcif Tissue Int **44:**312–321.
14. Fritton SP, McLeod KJ, Rubin CT 2000 Quantifying the strain history of bone: Spatial uniformity and self-similarity of low-magnitude strains. J Biomech **33:**317–325.
15. Rubin CT, Bain SD, McLeod KJ 1992 Suppression of the osteogenic response in the aging skeleton. Calcif Tissue Int **50:**306–313.
16. Rubin C, Xu G, Judex S 2001 The anabolic activity of bone tissue, suppressed by disuse, is normalized by brief exposure to extremely low-magnitude mechanical stimuli. FASEB J **15:**2225–2229.

17. Rubin C, Turner AS, Bain S, Mallinckrodt C, McLeod K 2001 Anabolism: Low mechanical signals strengthen long bones. Nature **412:**603–604.
18. Rubin C, Turner AS, Mallinckrodt C, Jerome C, McLeod K, Bain S 2002 Mechanical strain, induced noninvasively in the high-frequency domain, is anabolic to cancellous bone, but not cortical bone. Bone **30:**445–452.
19. Rubin C, Turner AS, Muller R, Mittra E, McLeod K, Lin W, Qin YX 2002 Quantity and quality of trabecular bone in the femur are enhanced by a strongly anabolic, noninvasive mechanical intervention. J Bone Miner Res **17:**349–357.
20. Huang RP, Rubin CT, McLeod KJ 1999 Changes in postural muscle dynamics as a function of age. J Gerontol A Biol Sci Med Sci **54:**B352–B357.
21. Fritton JC, Rubin CT, Qin YX, McLeod KJ 1997 Whole-body vibration in the skeleton: Development of a resonance-based testing device. Ann Biomed Eng **25:**831–839.
22. Rubin C, Pope M, Fritton J, Magnusson M, Hansson T, McLeod K 2003 Transmissibility of 15–35 Hz vibrations to the human hip and lumbar spine: Determining the physiologic feasibility of delivering low-level, anabolic mechanical stimuli to skeletal regions at greatest risk of fracture because of osteoporosis. Spine **28:**2621–2627.
23. Hollins M, Bensmaia SJ, Washburn S 2001 Vibrotactile adaptation impairs discrimination of fine, but not coarse, textures. Somatosens Mot Res **18:**253–262.
24. Deng HW, Lai DB, Conway T, Li J, Xu FH, Davies KM, Recker RR 2001 Characterization of genetic and lifestyle factors for determining variation in body mass index, fat mass, percentage of fat mass, and lean mass. J Clin Densitom **4:**353–361.
25. Aloia JF, Vaswani A, Ma R, Flaster E 1995 To what extent is bone mass determined by fat-free or fat mass? Am J Clin Nutr **61:**1110–1114.
26. Burmaster DE, Crouch EA 1997 Lognormal distributions for body weight as a function of age for males and females in the United States, 1976–1980. Risk Anal **17:**499–505.
27. Efron B, Halloran E, Holmes S 1996 Bootstrap confidence levels for phylogenetic trees. Proc Natl Acad Sci USA **93:**13429–13434.
28. Fritton S, McLeod K, Fritton J, Brand R, Rubin C 1995 Persistent, low magnitude strains as the dominant source of mechanical information in a bone's 24 hour strain history. Trans Orthop Res Soc **20:**547.
29. Powsner S, Spitzer R 2003 Sex, lies, and medical compliance. Lancet **361:**2003–2004.
30. Qin YX, Rubin CT, McLeod KJ 1998 Nonlinear dependence of loading intensity and cycle number in the maintenance of bone mass and morphology. J Orthop Res **16:**482–489.
31. Srinivasan S, Weimer DA, Agans SC, Bain SD, Gross TS 2002 Low-magnitude mechanical loading becomes osteogenic when rest is inserted between each load cycle. J Bone Miner Res **17:**1613–1620.
32. Hannan M, Rubin C, Cheng M, Swift C, Green E, Ryaby J, Kiel D 2003 A pilot study to determine daily compliance of elderly women enrolled to stand on a low-level vibration platform system to treat osteoporosis. IBMS-JSBMR Trans 510S.
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:**1260–1282.
34. Ward K, Alsop C, Brown S, Caulton J, Rubin C, Adams J, Mughal M 2003 Low magnitude, high frequency loading therapy increases volumetric tibial bone mineral density in children with disabling conditions. J Bone Miner Res **19:**360–369.
35. Pitukcheewanont P, Safani D, Gilsanz V, Rubin C 2002 Short-term low level mechanical stimulation increases cancellous and cortical bone density and muscle mass of female children with osteopenia/osteoporosis: A pilot study. 84th Meeting of the Endocrine Society. P2-725, p. 490.
36. Burr DB, Martin RB, Schaffler MB, Radin EL 1985 Bone remodeling in response to in vivo fatigue microdamage. J Biomech **18:**189–200.
37. Torvinen S, Kannus P, Sievanen H, Jarvinen TA, Pasanen M, Kontulainen S, Nenonen A, Jarvinen TL, Paakkala T, Jarvinen M, Vuori I 2003 Effect of 8-month vertical whole body vibration on bone, muscle performance, and body balance: A randomized controlled study. J Bone Miner Res **18:**876–884.
38. Griffin JJ 2001 Handbook of Human Vibration. Academic Press, London, UK.
39. Pope MH, Wilder DG, Magnusson ML 1999 A review of studies on seated whole body vibration and low back pain. Proc Inst Mech Eng [H] **213:**435–446.
40. Curry BD, Bain JL, Yan JG, Zhang LL, Yamaguchi M, Matloub HS, Riley DA 2002 Vibration injury damages arterial endothelial cells. Muscle Nerve **25:**527–534.
41. Seidel H, Harazin B, Pavlas K, Sroka C, Richter J, Bluthner R, Erdmann U, Grzesik J, Hinz B, Rothe R 1988 Isolated and combined effects of prolonged exposures to noise and whole-body vibration on hearing, vision and strain. Int Arch Occup Environ Health **61:**95–106.
42. Griffin MJ 1998 Predicting the hazards of whole-body vibration–considerations of a standard. Ind Health **36:**83–91.
43. American Conference of Governmental Industrial Hygenists 1997 Threshold Limit Values for Chemical Substances and Physical Agents; Biological Exposure Indices. pp. 82–95.
44. Frost HM 1990 Skeletal structural adaptations to mechanical usage (SATMU). 1. Redefining Wolff's law: The bone modeling problem. Anat Rec **226:**403–413.
45. Judex S, Boyd SK, Qin YX, Turner S, Ye K, Mueller R, Rubin C 2003 Adaptations of trabecular bone to low magnitude vibrations result in more uniform stress and strain under load. Ann Biomed Eng **31:**12–20.
46. Qin YX, Lin W, Rubin CT 2002 Load-induced bone fluid flow pathway as definded by in-vivo intramedullary pressure and streaming potentials measurements. Ann Biomed Eng **30:**693–702.
47. You L, Cowin SC, Schaffler MB, Weinbaum S 2001 A model for strain amplification in the actin cytoskeleton of osteocytes due to fluid drag on pericellular matrix. J Biomech **34:**1375–1386.
48. Gravelle DC, Laughton CA, Dhruv NT, Katdare KD, Niemi JB, Lipsitz LA, Collins JJ 2002 Noise-enhanced balance control in older adults. Neuroreport **13:**1853–1856.
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.
50. Karsenty G 2003 The complexities of skeletal biology. Nature **423:**316–318.
51. Nguyen T, Sambrook P, Kelly P, Jones G, Lord S, Freund J, Eisman J 1993 Prediction of osteoporotic fractures by postural instability and bone density. BMJ **307:**1111–1115.
52. Bosco C, Colli R, Introini E, Cardinale M, Tsarpela O, Madella A, Tihanyi J, Viru A 1999 Adaptive responses of human skeletal muscle to vibration exposure. Clin Physiol **19:**183–187.
53. Eisman JA 2001 Good, good, good, good vibrations: The best option for better bones? Lancet **358:**1924–1925.

Address reprint requests to:
Clinton T Rubin, PhD
Department of Biomedical Engineering
State University of New York
Stony Brook, NY 11794-2580, USA
E-mail: clinton.rubin@sunysb.edu

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