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Low-Level, High-Frequency Mechanical Signals Enhance Musculoskeletal Development of Young Women With Low BMD

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ABSTRACT: The potential for brief periods of low-magnitude, high-frequency mechanical signals to enhance the musculoskeletal system was evaluated in young women with low BMD. Twelve months of this noninvasive signal, induced as whole body vibration for at least 2 minutes each day, increased bone and muscle mass in the axial skeleton and lower extremities compared with controls.

Introduction: The incidence of osteoporosis, a disease that manifests in the elderly, may be reduced by increasing peak bone mass in the young. Preliminary data indicate that extremely low-level mechanical signals are anabolic to bone tissue, and their ability to enhance bone and muscle mass in young women was investigated in this study.
Materials and Methods: A 12-month trial was conducted in 48 young women (15–20 years) with low BMD and a history of at least one skeletal fracture. One half of the subjects underwent brief (10 minutes requested), daily, low-level whole body vibration (30 Hz, 0.3*g*); the remaining women served as controls. Quantitative CT performed at baseline and at the end of study was used to establish changes in muscle and bone mass in the weight-bearing skeleton.
Results: Using an intention-to-treat (ITT) analysis, cancellous bone in the lumbar vertebrae and cortical bone in the femoral midshaft of the experimental group increased by 2.1% ($p = 0.025$) and 3.4% ($p < 0.001$), respectively, compared with 0.1% ($p = 0.74$) and 1.1% ($p = 0.14$), in controls. Increases in cancellous and cortical bone were 2.0% ($p = 0.06$) and 2.3% ($p = 0.04$) greater, respectively, in the experimental group compared with controls. Cross-sectional area of paraspinous musculature was 4.9% greater ($p = 0.002$) in the experimental group versus controls. When a per protocol analysis was considered, gains in both muscle and bone were strongly correlated to a threshold in compliance, where the benefit of the mechanical intervention compared with controls was realized once subjects used the device for at least 2 minute/day ($n = 18$), as reflected by a 3.9% increase in cancellous bone of the spine ($p = 0.007$), 2.9% increase in cortical bone of the femur ($p = 0.009$), and 7.2% increase in musculature of the spine ($p = 0.001$) compared with controls and low compliers ($n = 30$).
Conclusions: Short bouts of extremely low-level mechanical signals, several orders of magnitude below that associated with vigorous exercise, increased bone and muscle mass in the weight-bearing skeleton of young adult females with low BMD. Should these musculoskeletal enhancements be preserved through adulthood, this intervention may prove to be a deterrent to osteoporosis in the elderly.
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Key words: osteoporosis, treatments, mechanical, loading, novel entities, osteopenia, frequency, bone, adaptation, muscle, anabolic, osteogenic, CT diagnostics, therapeutics

INTRODUCTION

SUSCEPTIBILITY FOR LOW bone mass is present early in life, the amount of bone gained during adolescence is a main contributor to peak bone mass in the young adult, and peak bone mass in the young adult is a likely determinant of osteoporosis in the elderly.[1,2] Whereas research continues to identify means of reversing osteoporosis in the elderly, these data from children, adolescents, and young adults indicate that enhancing bone health early in life represents a viable means of deterring osteoporosis decades before it arises.[3] However, the benefits of early pharmacological interventions to prevent a disease that will not manifest for

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decades must be weighed against the possible complications of extended treatment.[4,5] To date, most interventions have focused on antiresorptive medications that inhibit the cellular processes of bone turnover,[6] yet, when prescribed as a decades-long prevention strategy, may compromise both bone quality[7] and viability.[8] As importantly, the critical roles of muscle strength and neuromuscular control in the reduction of falls and fractures fail to be addressed with interventions that specifically and exclusively targets bone.[9]

Considerable interest has, therefore, been placed on studying controllable environmental factors, such as physical exercise, which can promote bone and muscle gains during growth,[10] well before bone mass has reached its peak.[11,12] Maximizing the benefits of the mechanical regimen without putting the skeleton at risk creates a challenge to identify, and thus focus on, the anabolic components of the loading environment. A common perception of skeletal adaptation to exercise is that the mechanical loads must be great to augment bone mass, such that vigorous physical exercise will induce bone strains sufficient to cause microdamage and stimulate bone formation through the repair of damaged tissue.[13,14] In contrast to these large loads and the potential damage they may cause, extremely low-level, high-frequency strains on bone mass, similar to those caused by muscle contractibility during postural control,[15] have recently been shown to be anabolic to bone tissue.[16] Animal studies indicate that low-magnitude high-frequency strains, induced through vibration, can stimulate bone formation in weight-bearing regions of the skeleton.[17,18] Translating this potential to the clinic, preliminary evidence indicates such signals can effectively inhibit bone loss in postmenopausal women[19] and enhance bone acquisition in children with disabling conditions.[20]

Approximately one in three children suffer a bone fracture by the time they reach skeletal maturity.[21] Whereas strenuous physical activity and occupational hazards are key factors in the pathogenesis of these fractures, several studies indicate that teenagers who sustain fractures also have decreased bone mass.[22–25] Therefore, the use of low-level mechanical signals to strengthen bone in young subjects with low bone mass may be relevant not only to the treatment of existing skeletal fragility, but, by enhancing peak bone mass and retaining it through adulthood, reduce the risk of osteoporosis and fractures later in life. This study was designed to establish whether brief, daily exposure to extremely low-level mechanical stimuli was anabolic to musculoskeletal development in young females, 15–20 years of age, each with low BMD and who had already sustained a fracture. Considering that these young women are highly likely to achieve only a low peak bone mass and therefore may be at greater risk of osteoporosis later in life, it was projected that a nonpharmacologic enhancement of the musculoskeletal system early on, if retained, could help diminish this debilitating disease.

MATERIALS AND METHODS

The study design, protocol, and consent forms were reviewed and approved by the institutional review board at Childrens Hospital Los Angeles (CHLA) and The Surgeon General's Human Subjects Research Review Board, and all participants and the parents of those <18 years of age signed informed consent.

Study subjects

The subjects for this study were healthy white females 15–20 years of age, all of whom had previously sustained at least one fracture. An initial interview was conducted with the subjects and their parents to describe the purpose and the aims of the study and the tests that would be performed. Candidates for this study were excluded if they had a diagnosis of any underlying disease or chronic illness, if they had been ill for >2 weeks during the previous 6 months, if they had been admitted to the hospital at any time during the previous 3 years, or if they were taking any medications including oral contraceptives. Candidates who were pregnant, had ever been pregnant, or with an absence of menses for >4 consecutive months or two cycle lengths after establishing regular cycles were also excluded from the study.

All potential candidates underwent a physical examination to determine their general health, vital signs, and stage of sexual development. Only females who had completed puberty (Tanner stage V of sexual development) were considered eligible for this study.[26] Thereafter, height, sitting height, weight, and body mass index (BMI) were determined, and skeletal age was determined from roentgenograms of the left hand and wrist.[27] Females in whom the epiphyses of the phalanges and the metacarpals had not fused completely were excluded to avoid inclusion of subjects with constitutional delay of growth.

Using this approach, candidates were evaluated until 150 were enrolled. Subsequently, CT measures were obtained, and the 50 subjects with the lowest CT values for vertebral cancellous BMD (~1 SD below mean peak BMD values) were invited to participate in the intervention phase of this study.[28] These subjects were assigned to the mechanical intervention or the control group based on their home address, with the 25 subjects living closest to CHLA selected to participate in the mechanical intervention and the remaining 25 serving as controls. Subjects assigned to the control group did not participate in the mechanical intervention schedule, but underwent the same baseline and follow-up examinations as the subjects in the intervention group.

Dietary and physical activity assessments

Dietary and physical activity questionnaires were completed at baseline and 6 and 12 months. Nutritional status was assessed using written recall records of dietary intake.[29] To account for the possible confounding effect of calcium intake, all participants were provided with a daily dose of one tablet of fruit-flavored TUMS 500 (GlaxoSmithKline, Pittsburgh, PA, USA), consisting of 500 mg of elemental Ca as Ca carbonate/tablet, for 1 year. Compliance was maximized through weekly telephone contacts.

Levels of physical activity in all study participants were examined using a 7-day physical activity recall questionnaire at baseline, 6 months, and completion of the study.

Participants were asked to indicate the number of times in the past week they engaged in strenuous, moderate, and mild forms of physical activity for >15 minutes. Definitions of each type of physical activity, as well as several examples of sport types in each category, were provided so that subjects fully understood these terms. A total score was obtained by multiplying responses in each intensity category by values corresponding to multiples of resting energy expenditure and summing the products. Thus, this measure represents frequency, intensity, and duration elements of physical activity with a test–retest reliability coefficient of 0.81.[30,31]

CT measurements of bone and muscle mass

All participants were assessed by CT using the same scanner (Hilite Advantage; General Electric, Milwaukee, WI, USA) and the same mineral reference phantom for simultaneous calibration (CT-T bone densitometry package; General Electric), and all studies were performed by the same technologist. In the axial skeleton, identification of the sites to be scanned was performed with lateral scout views and measurements of the density of cancellous bone and the cross-sectional dimensions of the vertebral bodies were obtained at the first, second, and third lumbar vertebrae; these measures are a reflection of the tissue density of bone in milligrams per cubic centimeter. In the femur, location of the site to be scanned was determined by physical examination, and the cross-sectional area (mm^2) and cortical bone area (mm^2) at the midshaft of the bone were obtained. A critical consideration in any CT study,[31] the CVs for repeated CT measurements of vertebral cancellous BMD and vertebral body cross-sectional area and of cortical BMD, cortical bone area, and the cross-sectional area of the femur ranged between 0.6% and 1.5% at our facility.[32]

From the same CT cross-sectional images obtained at L_1, L_2, and L_3 and at the midshaft of the femur, the areas of paraspinous and quadriceps femoris muscles (mm^2) were determined. For the purpose of this study, paraspinous musculature was defined as the combined area of the iliopsoas, erector spinae, and quadratus lumborum muscles. At our facility, the CVs for repeated CT measurements of muscle in the thigh and trunk fell between 1% and 2%.[33]

The time required to complete CT scans in individual patients was ~10 minutes. CT measurements were obtained at 1.5 or 1.0 mm thickness, 80 kVp, 70 mAmp, and 2 s. Radiation was 100–150 mrems (10–15 mJ/kg) localized to the 10-mm-thick section of imaging in the midportions of the L_1, L_2, and L_3 vertebral bodies and the 1.5-mm-thick section of the midthigh. The effective radiation dose was ~10 mrem (0.10 mJ/kg), including that associated with the scout view.[34]

DXA determinations of bone and body composition

All participants were also assessed with the Hologic QDR4500 (General Electric) DXA scanner, and all studies were performed by the same technologist. BMC (g) and areal BMD (aBMD, g/cm^2) were measured for the total body and lumbar spine. In addition, total fat mass (kg) and total lean mass (kg) were determined from the total body scan. Precision for aBMD values of the total body and spine was 0.4% and 1.6%, respectively, and for total fat mass and total lean mass was 3.1% and 0.6%, respectively. Total body scans required <5 minutes and have a total body radiation exposure of 0.4 mrem, whereas spine scans were obtained in 30 s with a skin entrance exposure of 3.7 mrem.[29]

Mechanical stimulus intervention

The mechanical intervention device has been previously described in detail.[35] Briefly, to deliver low-level mechanical signals to the weight-bearing skeleton in a controlled manner, a small (36 × 36 × 9 cm) platform was designed to induce a vertical, sinusoidal acceleration. The top platen of the platform accelerated at 0.3*g*, peak to peak (1.0*g* = Earth's gravitational field = 9.8 m/s^2) and at a frequency of 30 Hz (cycles per second) through a low force (18N) coil actuator (model LA18–18; BEI, San Marcos, CA, USA). This acceleration is well below International Organization for Standardization (ISO) and Occupational Safety and Health Administration (OSHA) recommendations for human limits of vibration exposure.[36,37] Displacement of the top platen at 30 Hz, 0.3*g*, was <50 μm.

The intervention was performed after the installation of the mechanical devices in the homes of the young women. Subjects were instructed to stand on the platform for 10 minutes each day for 12 months. Each device was equipped with a built-in electronic monitoring system that automatically recorded the duration the device was used each day. Compliance was assessed through monthly calibrations and data downloading, as well as weekly telephone contacts.

Statistical analysis

Both an intention-to-treat (ITT) analysis, which included all experimental and control subjects who began the protocol at baseline, and a per protocol (PP) analysis, designed to exclude drop-outs and poor compliers, were performed. Statistical analysis was performed using Stata 8.0 (StataCorp, College Station, TX, USA) and SPSS 13.0 for Windows (Chicago, IL, USA). All values shown are presented as mean ± SD, unless otherwise stated. The sample size was determined a priori by anticipating a balanced study with a difference in vertebral cancellous BMD gains between experimental and control subjects of 4% over 12 months, assuming an enhanced response over that achieved in the spine when a 0.2*g*, 30-Hz signal was used in a group of postmenopausal women,[19] and values for cancellous BMD in the lowest quartile to be 178 ± 9 mg/cm^3.[1] A sample size of 25 subjects in each group resulted in a power of 0.80 with an α of 0.05.

In the ITT analysis, baseline characteristics were compared with a two-sample *t*-test. Paired *t*-tests evaluated changes in measurements over baseline, and an unpaired *t*-test was used to compare both actual changes as well as the relative (percentage) changes over time for the control and treatment groups. This evaluation is equivalent to a repeated-measures ANOVA, which was used to include baseline measures such as bone age or height as covariates. Multivariate ANOVA simultaneously compared various changes over time in the axial and appendicular skeleton.

TABLE 1. BASELINE MEASURES AND *p* VALUES FOR ANTHROPOMETRIC PARAMETERS, PHYSICAL ACTIVITY, AND CALCIUM INTAKE FOR THE CONTROL AND EXPERIMENTAL GROUPS ($N = 24$ IN EACH GROUP)

	Control	*Experimental*	*p*
Age (years)	17.6 ± 1.3	17.3 ± 1.5	0.45
Bone age (years)	17.4 ± 0.7	17.0 ± 1.0	0.12
Height (cm)	164.0 ± 6.1	160.8 ± 3.8	0.037
Weight (cm)	67.5 ± 15	63.3 ± 13.7	0.32
BMI (kg/m^2)	25.1 ± 5.5	24.5 ± 5.5	0.72
Physical exercise index (h/wk)	9.9 ± 9.0	11.3 ± 11	0.74
Inactivity index (h/wk)	8.9 ± 9.3	5.6 ± 3.9	0.11
Calcium intake (mg/day)	1138 ± 814	1354 ± 1251	0.48

The single significant difference in these baseline parameters was height, where controls were 3.2 cm taller ($p = 0.037$).

The PP analysis was designed to identify any dose:response relationship, in which efficacy of the device could be shown as dependent on compliance, or if a "threshold" response, similar to that observed in animal experiments, arose where once a given number of loading cycles was passed, additional loading provided no additional benefit to bone tissue.[38] In this posthoc analysis, the experimental cohort was subdivided into quartiles[19] to allow a comparison between the women who were the lowest 25% of compliers relative to those who fell between 25% and 50%, 50% and 75%, and 75% and 100%, representing those women who were closest to the requested 10 minute/day treatment regimen, and thus to determine if a minimal use for the device could be approximated.[20]

RESULTS

Of the 150 women who volunteered for the study, the 50 women with the lowest BMD were enrolled in the study. Two subjects, one in the experimental group and one in the control group, began the use of oral contraceptives between the time of enrollment and the start of protocol and were removed from the study before the start of protocol. Those women closest to the hospital were enrolled in the treatment arm of the study, and Table 1 shows the baseline characteristics of the control ($N = 24$) and treatment groups ($N = 24$). Despite a subject pooling based on the proximity of their residence to CHLA, the sole measure that was significantly different between groups at baseline was height; women in the control group were 1.8% taller than those in the experimental group ($p = 0.037$).

ITT analysis

Over the course of the 1-year study, experimental and control subjects showed identical increases in height (0.4%) and similar increases in weight (2.6% and 2.1%, respectively), BMI (1.9% and 1.4%, respectively), and calcium intake (42% and 36%, respectively), with no significant differences at follow-up in measures of physical activity or inactivity. There were no reported adverse reactions to the treatment.

Table 2 summarizes the results from the ITT analysis, with baseline and follow-up CT values for muscle and bone in the axial and appendicular skeleton presented for all control and experimental subjects ($n = 24$ in each group). Baseline values for the panel of musculoskeletal measures were not significantly different in the experimental group than those measured in the controls. Whereas significant increases were present at follow-up for all morphological traits in the experimental group, the only significant change observed in the control group was evident in the cross-sectional area of the femur.

Table 3 presents the absolute changes and percent changes for all women in each of the two groups. In the axial skeleton, significantly greater increases were evident in the absolute and/or percent change of paraspinous musculature of the experimental group over all controls, with 6.0% greater gains measured in the psoas ($p < 0.003$) and 4.4% in the erector spinae ($p = 0.03$). The spine had 2.0% more cancellous bone in the experimental than the control cohort ($p = 0.06$).

In the appendicular skeleton, experimental subjects had 2.3% greater increase than controls in femoral cortical bone area ($p < 0.04$; Fig. 1). Considering that the cross-sectional area defined by the periosteal envelope (femur cross-sectional area) was similar in the two groups (mean area increase in each cohort increased 0.1 cm^2; $p = 0.25$), the increase in bone area was achieved through apposition on the endosteal surface.

None of the baseline variables showed a significant correlation with any of the absolute or percent changes over the 12-month experimental period. As a result, *p* values changed insignificantly when any of these baseline characteristics were considered as covariates for the absolute and relative comparison between controls and experimental subjects.

Statistically significant differences between experimental and controls were also found when the changes from all outcome variables were analyzed as a vector of observation using a multivariate repeated-measure ANOVA; this was true whether the analysis was based on absolute change or percent changes, with or without covariates ($p < 0.05$). When separated into two anatomical regions, significant differences were observed for the axial, but not for the appendicular, skeleton.

PP analysis

Compliance in the 24 women in the experimental group was highly variable, ranging from 1% to 100%, with a mean compliance of 130.3 ± 92.1 minutes/month or 4.3 minutes/day (Fig. 2A). A posthoc, PP analysis was used to determine whether there was a dose:response benefit of treatment duration or whether a compliance threshold existed, beyond which exposure to mechanical intervention no longer provided additional benefit. The experimental cohort was stratified into quartiles according to their percent compliance, with the bottom quartile including compliance values between 1% and 13% ($n = 6$), the second lowest quartile of compliance between 21% and 39% ($n = 6$), the second highest quartile fell between 41% and 71% of compliance ($n = 6$), and the quartile with the highest compliance was between 77% and 100% of compliance ($n = 6$).

TABLE 2. BASELINE AND 1-YEAR CT MEASURES AND *p* VALUES FOR SPECIFIC MUSCULOSKELETAL REGIONS WITHIN THE AXIAL AND APPENDICULAR SKELETON FOR BOTH CONTROL AND EXPERIMENTAL GROUPS ($N = 24$ IN EACH GROUP)

	Control			*Experimental*		
	Baseline	*1 year*	*p*	*Baseline*	*1 year*	*p*
Axial						
Total paraspinous musculature (cm^2)	181.6 ± 26	182.8 ± 27	0.52	167.5 ± 29	177.5 ± 31	<0.001
Psoas (cm^2)	48.7 ± 8.2	48.7 ± 7.70	0.99	45.0 ± 9.5	48.0 ± 10.9	<0.001
Quadratus lumborum (cm^2)	20.9 ± 5.9	21.9 ± 6.70	0.08	19.1 ± 3.6	21.2 ± 4.3	<0.001
Erector spinae (cm^2)	112.0 ± 15.0	112.2 ± 15.0	0.89	103.4 ± 21	108.3 ± 21	0.03
Spine cancellous BMD (mg/cm^3)	171.3 ± 17.1	171.5 ± 14.9	0.93	164.8 ± 25	168.6 ± 25	0.03
Appendicular						
Quadriceps femoris muscle (cm^2)	112.0 ± 16.0	114.6 ± 14.0	0.14	104.4 ± 13	108.5 ± 15	<0.001
Femur cross-sectional area (cm^2)	5.12 ± 0.77	5.17 ± 0.82	0.05	4.82 ± 0.53	4.92 ± 0.52	0.003
Femur cortical bone area (cm^2)	4.18 ± 0.51	4.24 ± 0.58	0.14	3.96 ± 0.43	4.10 ± 0.42	<0.001

The only significant change in the control group was in cross-sectional area of the femur ($p = 0.05$). In contrast, there were significant changes measured in each region of the axial and appendicular skeleton of the experimental group.

TABLE 3. AFTER THE 1-YEAR EXPERIMENTAL PROTOCOL, ABSOLUTE AND PERCENT CHANGE IN CT MEASURES OF SPECIFIC MUSCULOSKELETAL REGIONS OF THE AXIAL AND APPENDICULAR SKELETON FOR ALL THE WOMEN IN THE CONTROL AND EXPERIMENTAL GROUPS ($N = 24$ IN EACH GROUP)

	Absolute change			*Percent change*		
	Control	*Experimental*	*p*	*Control*	*Experimental*	*p*
Axial						
Total paraspinous musculature (cm^2)	1.2 ± 9.0	10.1 ± 12.5	0.007	0.5 ± 5.0	5.4 ± 6.9	0.002
Psoas (cm^2)	0.0 ± 2.9	3.1 ± 3.5	0.002	–0.1 ± 0.1	5.9 ± 6.7	0.003
Quadratus lumborum (cm^2)	1.0 ± 2.7	2.2 ± 2.6	0.16	3.0 ± 14.7	9.0 ± 11.7	0.17
Erector spinae (cm^2)	0.2 ± 5.6	5.3 ± 11.0	0.05	–0.1 ± 0.9	4.3 ± 8.8	0.03
Spine cancellous BMD (mg/cm^3)	0.1 ± 7.7	3.8 ± 7.7	0.11	0.1 ± 4.5	2.1 ± 4.9	0.06
Appendicular						
Quadriceps femoris area (cm^2)	2.6 ± 8.4	4.1 ± 4.5	0.45	2.2 ± 2.7	3.6 ± 3.6	0.36
Femur cross-sectional area (cm^2)	0.1 ± 0.1	0.1 ± 0.2	0.25	0.9 ± 2.2	1.9 ± 3.4	0.28
Femur cortical bone area (cm^2)	0.05 ± 0.17	0.14 ± 0.15	0.08	1.1 ± 3.7	3.4 ± 3.7	0.04

p values reflecting the difference between the control and experimental groups are also given.

A dose effect was evident in the erector spinae muscle, providing a first indication of a significant increase in muscle mass achieved at 20% compliance (2 minutes/day; Fig. 2B). When assessed by the responsivity of specific quartiles of compliance, clear threshold characteristics were observed in a number of musculoskeletal sites, with the lowest quartile failing to respond at all to the intervention, and the three highest quartiles being very similar in their responses (Fig. 3). Given the nonresponsivity of those in the lowest quartile of compliance, these subjects were pooled with controls. Moving these low compliers into the control groups further reduced the small differences in baseline characteristics between control and experimental subjects, including the *p* value for the difference in height from <0.05 to 0.8.

As summarized in Table 4, women who used the intervention at least 2 minutes/day ($n = 18$) showed significant increases over the group pooling controls and those in the lowest quartile of compliance ($n = 30$). Figure 4 shows the differences between groups and includes an 8.3% greater cross-sectional area of the erector spinae musculature in highly compliant women over controls and low compliers ($p = 0.006$), a 5.2% increase in the cross-sectional area of

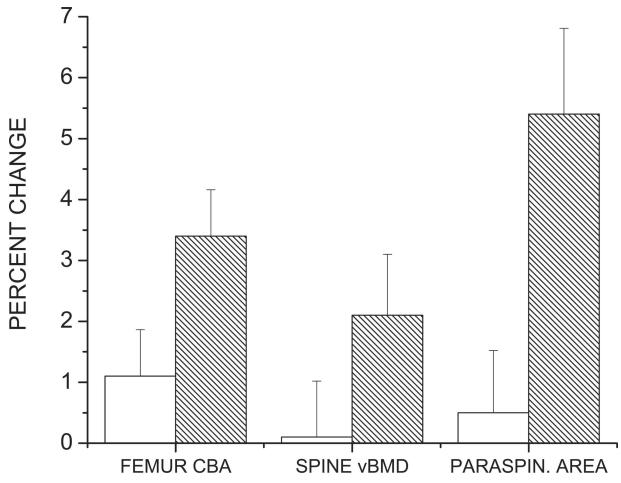

FIG. 1. Percent change (mean ± SE) occurring over the 1-year protocol, from both the control (white bars) and experimental (striped bars) subjects, using an intention-to-treat analysis and therefore including all 24 subjects who began the protocol in each group. The graph presents the CT data from the cortical bone area of the femur ($p = 0.04$), the cancellous BMD of the spine ($p = 0.06$), and the total paraspinous musculature ($p = 0.002$).

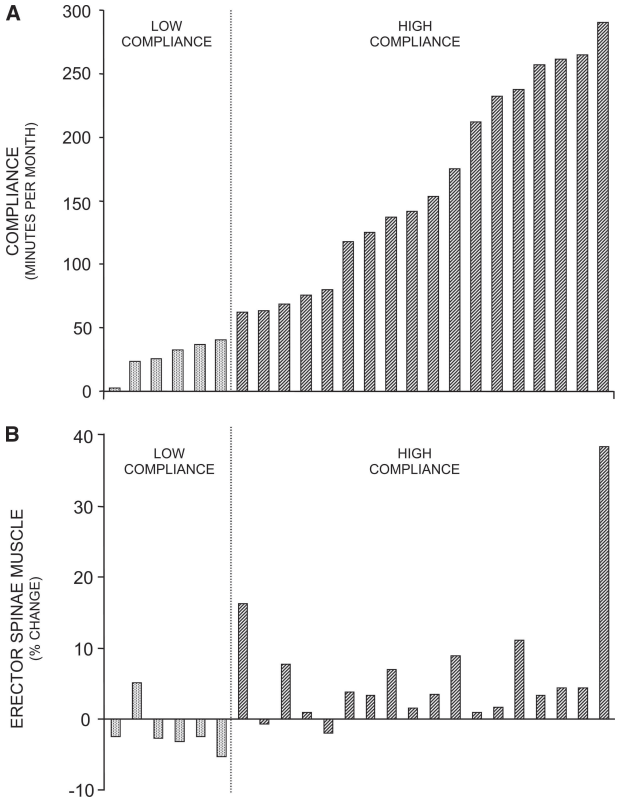

FIG. 2. (A) Compliance for each of the 24 subjects in the experimental group, as expressed in minutes per month. Each subject was requested to use the device for 10 minutes/day, such that 300 minutes/month would represent 100% compliance. Experimental subjects are represented either as those who used the device <20% of the allotted time (stippled bars) and are indicated as low compliance ($N = 6$) or those who used the device for >20% of the time (striped bars) and are indicated as high compliance ($N = 18$). (B) Percent change in the cross-sectional area of the erector spinae muscle of each experimental subject, as related to their compliance (above).

the psoas ($p = 0.02$), 7.2% greater mass in the total paraspinous musculature of high compliers ($p = 0.001$), a 3.9% greater density in the cancellous bone of the spine ($p = 0.007$), and a 2.9% greater cortical bone area in the femur ($p = 0.009$). No significant differences were observed in the musculature of the femur or in the cross-sectional area—in contrast to cortical bone area—of the femur.

DXA

Baseline and follow-up DXA values are shown in Table 5. Mean values for spine BMC and aBMD and for total body BMC were significantly higher in both groups at follow-up. In addition, in the experimental group, values for total body aBMD were higher after the intervention. There were, however, no significant differences between groups in the absolute and/or percent change for any of these DXA measures of bone and body composition (Table 6).

DISCUSSION

The data from this study indicate that the formation of bone and muscle can be enhanced in young women with low BMD by short daily exposure to extremely low-magnitude mechanical signals. It is presumed that the physiologic basis of these exogenous signals is that they serve to amplify the spectral content of endogenous muscle contractibility that are projected to the skeleton during even passive activities such as standing.[15] That the controls and women with low compliance significantly increased only a single musculoskeletal parameter over the course of a year, whereas there were significant increases in each musculoskeletal parameter in the experimental group, emphasizes that the skeleton is readily responsive to mechanical signals, and they do not need to be "big" to be anabolic.

This study supports the premise that mechanical signals, orders of magnitude below that which might cause damage to the bone matrix,[39] can enhance musculoskeletal development. The ITT analysis revealed that 1 year of these mechanical signals increased cancellous bone in the axial skeleton and cortical bone in the appendicular skeleton by 2.0% and 2.3% over controls, respectively. Simultaneous to these gains in bone, low-magnitude high-frequency mechanical signals significantly increased muscle mass; close to a 5% greater increase in cross-sectional area of paraspinous musculature was detected in women in the intervention group compared with controls.

As with any intervention, it is important to emphasize that the treatment will only be effective if it is actually used.[40] The PP analysis revealed a direct dependence of efficacy on compliance; women using the vibration system at least 2 minutes/day realized a benefit of the intervention through gains in cancellous and cortical bone and paraspinous musculature as opposed to women who used it <2 minutes/day, who showed no changes in their skeletal parameters that were different than measured in controls. In those women who used the device at least 2 minutes/day, increases reached 7.2% in the spinal musculature, 3.9% in the cancellous bone of the spine, and 2.9% in the cortical bone of the femur compared with controls pooled with poor compliers. Once the 2-minute duration was surpassed, women, even in the highest quartile of compliance, reaped no additional benefit of use, suggesting that a biologic response was triggered rather than accumulated.[38]

The mechanism(s) by which extremely low-level mechanical signals can enhance the musculoskeletal system are currently unknown.[41] The physical basis of translating low-level mechanical signals into a biological response could result from an amplification system achieved through fluid movement through the canalicular system of osteocytes[42] and promoted by the interdependence of fluid pressure and frequency.[43] From a biologic perspective, the enhanced skeletal mass could result from alterations in the transcriptional control of the bone tissue either by upregulating genes involved in bone formation, downregulating genes involved in the resorption of bone, or both.[44] Certainly, it is possible that adaptation of the musculoskeletal system to exogenous signals is preferentially sensitive to higher frequency signals, similar to other physiologic systems designed to monitor "exogenous stimuli," such as vi-

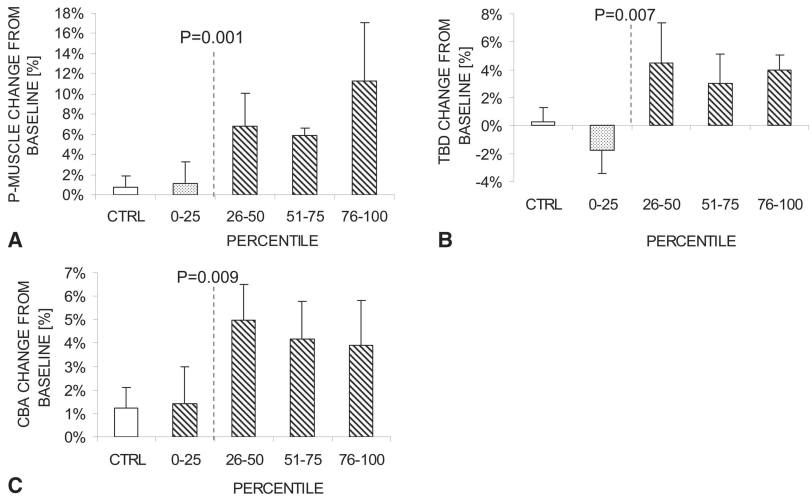

FIG. 3. Percent change (mean ± SE) measured over the 1-year period for (A) paraspinous musculature, (B) vertebral cancellous BMD, and (C) femoral cortical area in control subjects (white bars; $N = 24$) compared with experimental subjects in each of the compliance quartiles ($N = 6$ each). p values reflect comparison of subjects pooled from the three top compliance quartiles (compliance >20%) to the pooled low compliance (<20% compliance) plus the control group. Note very little change was measured in either the controls or the quartile representing the lowest compliers over the 1-year period, whereas the anabolic response to the mechanical signal did not increase beyond the 2-minute "threshold," implying a triggered response of bone to mechanical signals rather than an accumulated dose:response adaptation.

TABLE 4. USING A PER PROTOCOL ANALYSIS, SUBJECTS ($N = 6$) WITHIN THE LOWEST QUARTILE OF COMPLIANCE WERE POOLED WITH CONTROLS (CONTROLS + POOR COMPLIERS: TOTAL $N = 30$) AND COMPARED WITH THE ABSOLUTE AND PERCENT CHANGES MEASURED FROM CT IN THE SUBJECTS IN THE THREE HIGHEST QUARTILES OF COMPLIANCE (HIGH COMPLIERS: $N = 18$)

	Absolute change			*Percent change*		
	Control + poor compliers	*High compliers*	*p*	*Control + poor compliers*	*High compliers*	*p*
Axial						
Total paraspinous musculature (cm^2)	1.4 ± 8.9	12.6 ± 12.6	0.001	0.8 ± 5.1	8.0 ± 9.1	0.001
Psoas (cm^2)	0.6 ± 3.6	3.1 ± 2.8	0.01	1.6 ± 8.2	6.8 ± 6.0	0.02
Quadratus lumborum (cm^2)	1.1 ± 2.5	2.4 ± 2.7	0.11	5.4 ± 13.7	13.4 ± 15.0	0.07
Erector spinae (cm^2)	–0.3 ± 5.3	7.1 ± 10.4	0.002	–0.2 ± 4.7	8.1 ± 14.5	0.006
Spine cancellous BMD (mg/cm^3)	–0.4 ± 7.4	5.9 ± 7.2	0.006	–0.1 ± 4.5	3.8 ± 4.9	0.007
Appendicular						
Quadriceps femoris area (cm^2)	3.0 ± 7.8	4.0 ± 4.5	0.59	3.0 ± 6.8	3.9 ± 4.2	0.63
Femur cross-sectional area (cm^2)	0.05 ± 0.12	0.12 ± 0.16	0.10	1.0 ± 2.2	2.4 ± 3.7	0.12
Femur cortical bone area (cm^2)	0.05 ± 0.17	0.17 ± 0.13	0.02	1.3 ± 3.9	4.3 ± 3.6	0.009

Highly significant differences were observed in several regions of the spine musculature, as well as the cancellous bone of the spine and cortical bone area of the hip, whereas musculature around the femur and cross-sectional area of the femur were not significantly different between groups.

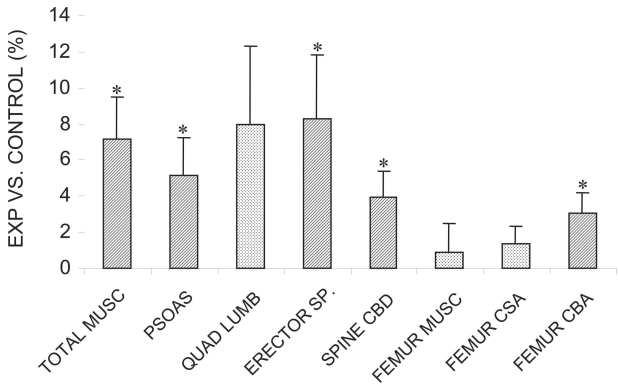

FIG. 4. Difference in the change (mean ± SE) measured over the 1-year period for the those who used the device for >2 minutes/day compared with the controls pooled with the women in the lowest quartile of compliance. Each parameter evaluated, with the exception of musculature around the femur and femoral cross-sectional area, showed that the experimental group benefited significantly (*) from the mechanical intervention.

sion (color), hearing (tone), and tactile sense (pressure), and that these external signals are processed within specific windows of sensitivity and begin to shut down when the signal becomes too bright, too loud, or too heavy.

The physical and biologic mechanisms that control the adaptation of bone to its loading environment are complex[45] and involve the interaction of pathways mediated through gravity, muscle contractions, and physical activity, as well as a genetic component that defines the musculoskeletal system's susceptibility to mechanical signals.[46] Whereas the strain signals in this study fell well below those that are imposed on the skeleton by vigorous exercise,[47] they were significantly more robust than those experienced during minimal activities of daily life.[48] These extremely low-level strain magnitudes are intended to augment those mechanical signals that arise through muscle contractions during passive activities, such as maintaining posture, whereas remaining orders of magnitude below those strain levels may cause microdamage to bone tissue.[39,47] These data also support the proposed interdependence of the

Table 5. Baseline and Follow-Up DXA Values for Specific Regions of the Musculoskeletal System and Whole Body Measures for Both Control and Experimental Subjects (N = 24 in Each Group)

	Control			*Experimental*		
	Baseline	*1 year*	*p*	*Baseline*	*1 year*	*p*
Spine BMC (g)	56.1 ± 8.4	58.3 ± 7.8	<0.001	50.7 ± 6.1	52.7 ± 6.0	<0.001
Spine aBMD (g/cm^2)	1.02 ± 0.1	1.04 ± 0.1	0.003	0.95 ± 0.1	0.98 ± 0.8	0.002
Whole body BMC (g)	1614 ± 258	1676 ± 270	<0.001	1481 ± 184	1535 ± 177	<0.001
Whole body aBMD (g/cm^2)	0.98 ± 0.08	0.99 ± 0.07	0.15	0.94 ± 0.06	0.95 ± 0.06	0.05
Trunk lean mass (kg)	19.8 ± 2.7	20.0 ± 2.5	0.34	18.4 ± 2.4	18.9 ± 2.6	0.07
Total lean mass (kg)	40.1 ± 5.9	40.8 ± 5.6	0.06	37.8 ± 5.2	38.6 ± 5.8	0.15

Whereas significant changes were measured in several parameters within each group, the magnitude of these changes were not significantly different between groups (Table 6).

Table 6. Absolute and Percent Change in DXA Measures for Women in the Control and Experimental Groups (N = 24 in Each Group)

	Absolute change			*Percent change*		
	Control	*Experimental*	*p*	*Control*	*Experimental*	*p*
Spine BMC (g)	2.14 ± 2.18	2.07 ± 1.97	0.91	3.82 ± 4.07	3.93 ± 3.84	0.92
Spine aBMD (g/cm^2)	0.02 ± 0.03	0.02 ± 0.03	0.99	2.11 ± 3.22	2.25 ± 3.19	0.88
Whole Body BMC (g)	59.5 ± 57.8	53.5 ± 53.8	0.71	3.45 ± 3.45	3.52 ± 3.34	0.94
Whole body aBMD (g/cm^2)	0.01 ± 0.02	0.01 ± 0.02	0.57	0.65 ± 1.87	0.96 ± 2.29	0.61
Trunk lean mass (g)	214 ± 1058	460 ± 1174	0.45	1.06 ± 4.93	2.19 ± 6.03	0.49
Total lean mass (g)	702 ± 1704	754 ± 2456	0.93	1.75 ± 4.07	1.61 ± 5.95	0.93

No significant differences between control and experimental subjects were identified.

musculoskeletal "system," in that conditions such as sarcopenia[9] and the deterioration of the spectral content of muscle contraction[15] would diminish key regulatory components to the skeleton and thus conspire to contribute to the etiology of osteopenia.

The anabolic effects of the intervention on muscle and bone were present even after accounting for body weight, despite previous suggestions that low-magnitude mechanical stimulation would be most beneficial in subjects with lesser body weight.[19] Whereas it is entirely possible that the responsivity of the experimental group was caused by the signal magnitude being 50% higher than the study on postmenopausal women (0.3g versus 0.2g), it may also be that all the women in this study began with low BMD, and thus the entire cohort was more sensitive to the mechanical signals. This can be considered in the context that mice with low BMD are more sensitive to the high-frequency mechanical signal than mice with dense bone,[49] but whether this is by virtue of the signal being greater in lighter bones or because bones more prone to disuse osteoporosis are, in turn, more sensitive to mechanically based augmentation, is not yet clear. It is also possible that the women in this study, like the children with disabling conditions,[20] were responsive because they were young, and that the ability to proliferate and differentiate pre-osteoblasts into bone-producing cells is more readily achieved in younger organisms.[50]

The use of CT to obtain measures of muscle and bone in the appendicular and axial skeleton provided unique insight into the means by which the low-level mechanical signal worked and helped to identify the specific tissues and anatomic compartments that it influenced. In contrast, DXA cannot fully correct for errors associated with changes in body and skeletal size[29,31] and does not allow for the independent assessment of muscle mass from other lean tissues.[51] Along these lines, it is noteworthy that, in this study, CT helped identify significant differences in bone and in muscle between control and experimental subjects, which were not evident with DXA. For example, the use of CT showed that the experimental group realized a significant increase in the cross-sectional area of paraspinous musculature compared with controls, thus indicating a benefit of the mechanical intervention beyond that specific to bone. These data suggest that mechanical signals have the potential to influence both bone and muscle, and considering the importance of muscle function to the incidence of falls and fall-related injuries, indicates that this intervention may be useful in reducing osteoporosis risk factors for fracture that drug therapies fail to address.[52]

There are several limitations in this study, and the results must be addressed and interpreted in context with its design. First, it is important to emphasize that this was not a randomized study because, by design, subjects were assigned to either the mechanical intervention or the control group based on their residential address; participants living closer to CHLA were assigned to the mechanical intervention to facilitate equipment maintenance, calibration, and data downloading. Whereas randomization did not occur, the baseline measures identified only height to be significantly different between the experimental and control subjects, and considering height as a covariate did not alter the statistical outcomes. Additionally, the subjects were not re-

cruited from the community at large, but were selected from young white female volunteers with low BMD and a history of fracture(s). It should be realized, however, that the intent of this study was specifically to determine if the skeletons of young women with low BMD could be enhanced with low-level mechanical signals, not if any given individual could realize a benefit from treatment. It is entirely possible that our results may not apply to subjects with denser bones, older (or younger) women, other ethnic groups, or men. Similarly, our findings apply to a specific type of mechanical stimulus, and it is likely that other types of vibration loading may result in varying effects on bone mass. Indeed, a recent 8-month study in healthy young adults found no effect of brief (4 minute), three to five times per week, high-magnitude (8*g*) whole body vibration training on bone mass, although this stimulus improved vertical jump height.[53] The differing study populations, the assays used to measure musculoskeletal response, and the wide disparity in magnitude of the mechanical stimulation (0.3*g* here, 8.0*g* there) are likely explanations for the discrepancy between results. It is also possible that musculoskeletal tissues of healthier subjects with stronger bones may not be as responsive to this range of loading. Data from animal studies suggest an individualized set point to mechanical signals; the anabolic potential of mechanical stimulus is greater in inbred mice strains with low BMD, whereas strains with high BMD have a lesser response to mechanical signals.[38]

It is important to emphasize that this study also does not address what will happen to the bone and muscle gains achieved in the mechanically stimulated cohort once treatment ceases. As with other anabolic interventions, such as PTH,[54] it is possible that gains in bone will be lost once treatment has stopped, and that other strategies (e.g., antiresorptive drugs, exercise) will have to be implemented to curb progressive deterioration. Whether gains realized even by exercise are preserved over time is controversial,[55] with evidence indicating that the bone accretion achieved through high-impact loading in premenopausal[56,57] and elderly[58] women is readily maintained after cessation of exercise, whereas other studies indicate that bone gains achieved in premenopausal women are at risk once exercise stops.[59] Extrapolating from the increases in muscle mass that parallel the gains in bone shown in this study, there is some possibility that the additional mechanical challenge derived from the muscle to the bone will contribute to the retention of the skeletal tissue even in the absence of the anabolic surrogate provided by the low-magnitude vibration.

At least 20% of the variance in bone mass is caused by controllable environmental factors, such as physical activity.[60] Unfortunately, exercise interventions have not proven overtly effective in the elderly because of difficulties with long-term compliance, a decline in the adaptive response to load bearing with aging,[61] and an increased risk of injury during vigorous exercise.[62] In contrast, enhancing the musculoskeletal system during early adulthood, and thus raising the peak bone and muscle mass as an adult, may serve to mitigate the consequences of their inevitable age-related decline in strength and integrity.[12] This is particularly true for adolescents with fractures, because they are at greater risk of decreased bone mass after puberty.[63] This study suggests that noninvasive mechanical loading, induced orders of magnitude below that that associated with exercise, could represent a unique means of augmenting the musculoskeletal system, and perhaps reducing bone fragility. That these signals seem to enhance both bone and muscle also suggest that the mechanical modality addresses risk factors for osteoporosis beyond "simply" bone quantity and quality. Moreover, it seems that these low-intensity mechanical signals incorporate many aspects of the complex remodeling cycle, enhancing bone formation while suppressing bone resorption.[64] Many questions remain as to whether the musculoskeletal benefits observed in this study will persist over time or whether such an intervention will ultimately reduce falls and/or fractures. Certainly, such information will be of great value in evaluating the potential of a nondrug measure for the prevention of postmenopausal osteoporosis decades before it occurs.

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