

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

Vicente Gilsanz,^{1,2} Tishya AL Wren,^{1,2} Monique Sanchez,¹ Frederick Dorey,³ Stefan Judex,⁴ and Clinton Rubin⁴

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, 0.3g); 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 paraspinal 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.

J Bone Miner Res 2006;21:1464–1474. Published online on June 26, 2006; doi: 10.1359/JBMR.060612

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

Dr Rubin is an inventor of the technology evaluated in this manuscript. He is also a founder of and consultant to Juvent, Inc. All other authors state that they have no conflicts of interest.

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

¹Department of Radiology, Childrens Hospital of Los Angeles, University of Southern California, Keck School of Medicine, Los Angeles, California, USA; ²Department of Orthopedics, Childrens Hospital of Los Angeles, University of Southern California, Keck School of Medicine, Los Angeles, California, USA; ³Department of Pediatrics, Childrens Hospital of Los Angeles, University of Southern California, Keck School of Medicine, Los Angeles, California, USA; ⁴Department of Biomedical Engineering, State University of New York, Stony Brook, New York, USA.

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 micro-damage 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 (Glaxo-SmithKline, 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 (mm²) and cortical bone area (mm²) 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 L₁, L₂, and L₃ and at the midshaft of the femur, the areas of paraspinal and quadriceps femoris muscles (mm²) were determined. For the purpose of this study, paraspinal 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 L₁, L₂, and L₃ 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/cm²) 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 0.3g, peak to peak (1.0g = Earth's gravitational field = 9.8 m/s²) 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, 0.3g, 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 (Stata-Corp, 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 0.2g, 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/cm³.⁽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)

	<i>Control</i>	<i>Experimental</i>	<i>p</i>
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 paraspinal 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 cm²; *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	<i>p</i>	Baseline	1 year	<i>p</i>
Axial						
Total paraspinus 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	<i>p</i>	Control	Experimental	<i>p</i>
Axial						
Total paraspinus 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 responsiveness 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

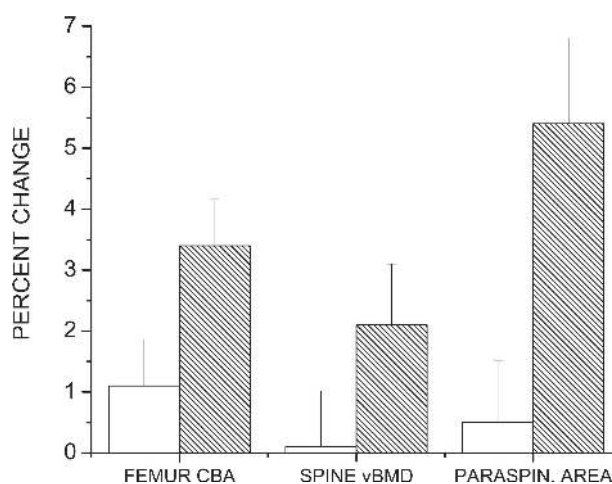


FIG. 1. Percent change (mean ± SE) occurring over the 1-year protocol, from both the control (white bars) and experimental (striped bars) subjects, using an intention-to-treat analysis and therefore including all 24 subjects who began the protocol in each group. The graph presents the CT data from the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

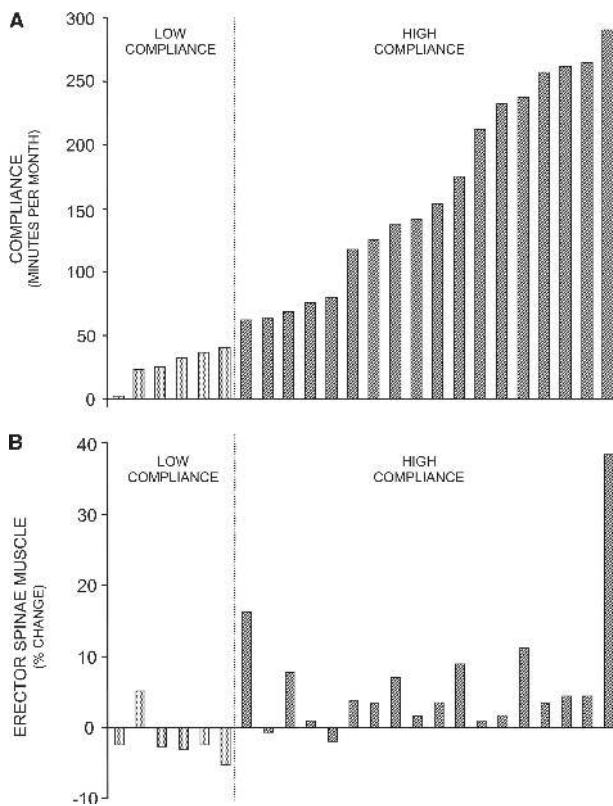


FIG. 2. (A) Compliance for each of the 24 subjects in the experimental group, as expressed in minutes per month. Each subject was requested to use the device for 10 minutes/day, such that 300 minutes/month would represent 100% compliance. Experimental subjects are represented either as those who used 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 paraspinal 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 paraspinal 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 paraspinal 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-

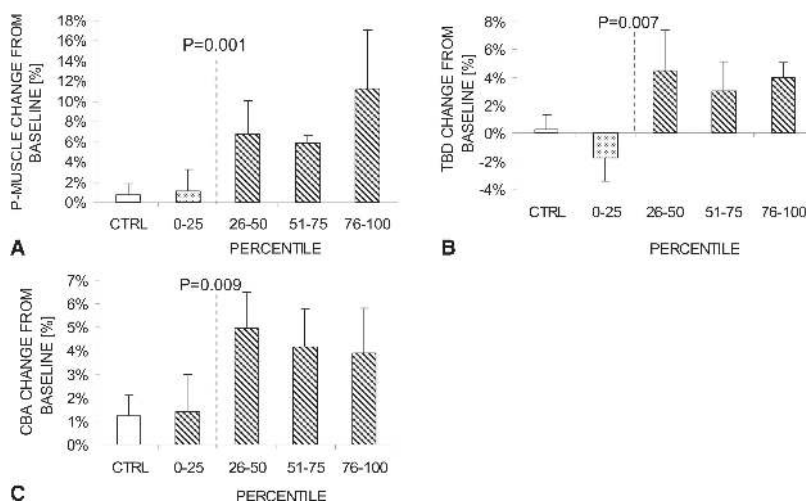


FIG. 3. Percent change (mean \pm SE) measured over the 1-year period for (A) paraspinus musculature, (B) vertebral cancellous BMD, and (C) femoral cortical area in control subjects (white bars; $N = 24$) compared with experimental subjects in each of the compliance quartiles ($N = 6$ each). p values 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 paraspinus 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.

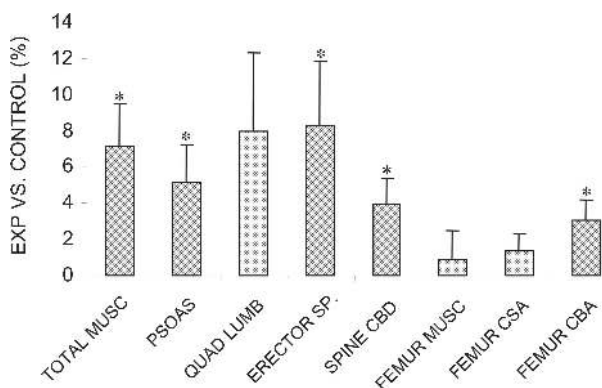


FIG. 4. Difference in the change (mean \pm SE) measured over the 1-year period for the those who used the device for >2 minutes/day compared with the controls pooled with the women in the lowest quartile of compliance. Each parameter evaluated, with the exception of musculature around the femur and femoral 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	<i>p</i>	Baseline	1 year	<i>p</i>
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	<i>p</i>	Control	Experimental	<i>p</i>
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 responsiveness 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 ana-

tomous 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 paraspinal 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 (8g) 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 (0.3g here, 8.0g 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., anti-resorptive 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.

ACKNOWLEDGMENTS

This project was sponsored by the Department of the Army (award number DAMD17-01-1-0817). The U.S. Army Medical Research and Materiel Command under the Bone Health and Military Medical Readiness (BHMMR) Program is the awarding and administering acquisition office. The content of this information does not necessarily reflect the position or the policy of the Government, and no official endorsement should be inferred. The investigators are grateful to Juvent for the use of the MST 1000 Mechanical Stress Technology devices and to GlaxoSmithKline for their generous gift of TUMS 500 mg calcium tablets. The authors thank Dr Kenny Ye and Cara Wah for technical comments and assistance on this manuscript. The authors are indebted to the encouragement and vision of John (Jack) Ryaby and for support from the start through completion of this study.

REFERENCES

- Loro ML, Sayre J, Roe TF, Goran MI, Kaufman FR, Gilsanz V 2000 Early identification of children predisposed to low peak bone mass and osteoporosis later in life. *J Clin Endocrinol Metab* **85**:3908–3918.
- Matkovic V, Jelic T, Wardlaw GM, Ilich JZ, Goel PK, Wright JK, Andon MB, Smith KT, Heaney RP 1994 Timing of peak bone mass in Caucasian females and its implication for the prevention of osteoporosis. Inference from a cross-sectional model. *J Clin Invest* **93**:799–808.
- Consensus Development Conference NIH 2000 Osteoporosis prevention, diagnosis, and therapy. *NIH Consens Statement* **17**:1–45.
- 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.
- Whyte MP, Wenkert D, Clements KL, McAlister WH, Mumm S 2003 Bisphosphonate-induced osteopetrosis. *N Engl J Med* **349**:457–463.
- Watts NB 1998 Treatment of osteoporosis with bisphosphonates. *Endocrinol Metab Clin North Am* **27**:419–439.
- Mashiba T, Hirano T, Turner CH, Forwood MR, Johnston CC, Burr DB 2000 Suppressed bone turnover by bisphosphonates

- increases microdamage accumulation and reduces some biomechanical properties in dog rib. *J Bone Miner Res* **15**:613–620.
8. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL 2004 Osteonecrosis of the jaws associated with the use of bisphosphonates: A review of 63 cases. *J Oral Maxillofac Surg* **62**:527–534.
 9. Rosenberg IH 1997 Sarcopenia: Origins and clinical relevance. *J Nutr* **127**:990S–991S.
 10. MacKellvie KJ, Khan KM, Petit MA, Janssen PA, McKay HA 2003 A school-based exercise intervention elicits substantial bone health benefits: A 2-year randomized controlled trial in girls. *Pediatrics* **112**:e447.
 11. Bass S, Pearce G, Bradney M, Hendrich E, Delmas PD, Harding A, Seeman E 1998 Exercise before puberty may confer residual benefits in bone density in adulthood: Studies in active prepubertal and retired female gymnasts. *J Bone Miner Res* **13**:500–507.
 12. Henderson NK, White CP, Eisman JA 1998 The roles of exercise and fall risk reduction in the prevention of osteoporosis. *Endocrinol Metab Clin North Am* **27**:369–387.
 13. Frost HM 1990 Skeletal structural adaptations to mechanical usage (SATMU): 1. Redefining Wolff's law: The bone modeling problem. *Anat Rec* **226**:403–413.
 14. Burr DB, Forwood MR, Fyhrie DP, Martin RB, Schaffler MB, Turner CH 1997 Bone microdamage and skeletal fragility in osteoporotic and stress fractures. *J Bone Miner Res* **12**:6–15.
 15. 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.
 16. Eisman JA 2001 Good, good, good... good vibrations: The best option for better bones? *Lancet* **358**:1924–1925.
 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, Muller R, Mitra 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.
 19. Rubin C, Recker R, Cullen D, Ryaby J, McCabe J, McLeod K 2004 Prevention of postmenopausal bone loss by a low-magnitude, high-frequency mechanical stimuli: A clinical trial assessing compliance, efficacy, and safety. *J Bone Miner Res* **19**:343–351.
 20. Ward K, Alsop C, Caulton J, Rubin C, Adams J, Mughal Z 2004 Low magnitude mechanical loading is osteogenic in children with disabling conditions. *J Bone Miner Res* **19**:360–369.
 21. Wilkins KE 2005 Principles of fracture remodeling in children. *Injury* **36**(Suppl 1):A3–11.
 22. Chan GM, Hess M, Hollis J, Book LS 1984 Bone mineral status in childhood accidental fractures. *Am J Dis Child* **138**:569–570.
 23. Goulding A, Cannan R, Williams SM, Gold EJ, Taylor RW, Lewis-Barned NJ 1998 Bone mineral density in girls with forearm fractures. *J Bone Miner Res* **13**:143–148.
 24. Landin L, Nilsson BE 1983 Bone mineral content in children with fractures. *Clin Orthop Relat Res* **178**:292–296.
 25. Goulding A, Jones IE, Williams SM, Grant AM, Taylor RW, Manning PJ, Langley J 2005 First fracture is associated with increased risk of new fractures during growth. *J Pediatr* **146**:286–288.
 26. Tanner JM 1986 Normal growth and techniques of growth assessment. *Clin Endocrinol Metab* **15**:411–451.
 27. Pyle SI, Waterhouse AM, Greulich WW 1971 Attributes of the radiographic standard of reference for the National Health Examination Survey. *Am J Phys Anthropol* **35**:331–337.
 28. Gilsanz V, Gibbens DT, Carlson M, Boechat MI, Cann CE, Schulz EE 1988 Peak trabecular vertebral density: A comparison of adolescent and adult females. *Calcif Tissue Int* **43**:260–262.
 29. Mora S, Gilsanz V 2003 Establishment of peak bone mass. *Endocrinol Metab Clin North Am* **32**:39–63.
 30. Morris FL, Naughton GA, Gibbs JL, Carlson JS, Wark JD 1997 Prospective ten-month exercise intervention in premenarcheal girls: Positive effects on bone and lean mass. *J Bone Miner Res* **12**:1453–1462.
 31. Genant HK, Engelke K, Fuerst T, Gluer CC, Grampp S, Harris ST, Jergas M, Lang T, Lu Y, Majumdar S, Mathur A, Takada M 1996 Noninvasive assessment of bone mineral and structure: State of the art. *J Bone Miner Res* **11**:707–730.
 32. Mora S, Goodman WG, Loro ML, Roe TF, Sayre J, Gilsanz V 1994 Age-related changes in cortical and cancellous vertebral bone density in girls: Assessment with quantitative CT. *AJR Am J Roentgenol* **162**:405–409.
 33. Arfai K, Pitukcheewanont PD, Goran MI, Tavare CJ, Heller L, Gilsanz V 2002 Bone, muscle, and fat: Sex-related differences in prepubertal children. *Radiology* **224**:338–344.
 34. Kalender WA 1992 Effective dose values in bone mineral measurements by photon absorptiometry and computed tomography. *Osteoporos Int* **2**:82–87.
 35. Rubin C, Pope M, Chris FJ, Magnusson M, Hansson T, McLeod K 2003 Transmissibility of 15-hertz to 35-hertz 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.
 36. International Standards Organization 1985 Evaluation of human exposure to whole-body vibration. *ISO* **2631**:2631–2634.
 37. Griffin MJ 1998 Predicting the hazards of whole-body vibration—considerations of a standard. *Ind Health* **36**:83–91.
 38. Rubin CT, Lanyon LE 1984 Regulation of bone formation by applied dynamic loads. *J Bone Joint Surg Am* **66**:397–402.
 39. Carter DR, Caler WE, Spengler DM, Frankel VH 1981 Fatigue behavior of adult cortical bone: The influence of mean strain and strain range. *Acta Orthop Scand* **52**:481–490.
 40. Powsner S, Spitzer R 2003 Sex, lies, and medical compliance. *Lancet* **361**:2003–2004.
 41. Rubin J, Rubin C, Jacobs CR 2006 Molecular pathways mediating mechanical signaling in bone. *Gene* **367**:1–16.
 42. Wang L, Fritton SP, Cowin SC, Weinbaum S 1999 Fluid pressure relaxation depends upon osteonal microstructure: Modeling an oscillatory bending experiment. *J Biomech* **32**:663–672.
 43. Qin YX, Kaplan T, Saldanha A, Rubin C 2003 Fluid pressure gradients, arising from oscillations in intramedullary pressure, is correlated with the formation of bone and inhibition of intracortical porosity. *J Biomech* **36**:1427–1437.
 44. Judex S, Zhong N, Squire ME, Ye K, Donahue LR, Hadjiargyrou M, Rubin CT 2005 Mechanical modulation of molecular signals which regulate anabolic and catabolic activity in bone tissue. *J Cell Biochem* **94**:982–994.
 45. Karsenty G 2003 The complexities of skeletal biology. *Nature* **423**:316–318.
 46. Judex S, Garman R, Squire M, Donahue LR, Rubin C 2004 Genetically based influences on the site-specific regulation of trabecular and cortical bone morphology. *J Bone Miner Res* **19**:600–606.
 47. Rubin CT, Lanyon LE 1984 Dynamic strain similarity in vertebrates; an alternative to allometric limb bone scaling. *J Theor Biol* **107**:321–327.
 48. 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.
 49. 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**:1280–1282.
 50. Rosen CJ 1994 Growth hormone, insulin-like growth factors, and the senescent skeleton: Ponce de Leon's Fountain revisited? *J Cell Biochem* **56**:348–356.
 51. Krakauer JC, Franklin B, Kleerekoper M, Karlsson M, Levine JA 2004 Body composition profiles derived from dual-energy X-ray absorptiometry, total body scan, and mortality. *Prev Cardiol* **7**:109–115.
 52. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, Cauley J, Black D, Vogt TM 1995 Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *N Engl J Med* **332**:767–773.

53. 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.
54. Bilezikian JP, Rubin MR, Finkelstein JS 2005 Parathyroid hormone as an anabolic therapy for women and men. *J Endocrinol Invest* **28**:41–49.
55. Seeman E 2001 The Achilles' heel of exercise-induced bone mass increments: Cessation of exercise. *J Bone Miner Res* **16**:1370–1373.
56. Kontulainen S, Heinonen A, Kannus P, Pasanen M, Sievanen H, Vuori I 2004 Former exercisers of an 18-month intervention display residual aBMD benefits compared with control women 3.5 years post-intervention: A follow-up of a randomized controlled high-impact trial. *Osteoporos Int* **15**:248–251.
57. Kontulainen S, Kannus P, Haapasalo H, Sievanen H, Pasanen M, Heinonen A, Oja P, Vuori I 2001 Good maintenance of exercise-induced bone gain with decreased training of female tennis and squash players: A prospective 5-year follow-up study of young and old starters and controls. *J Bone Miner Res* **16**:195–201.
58. Liu-Ambrose TY, Khan KM, Eng JJ, Gillies GL, Lord SR, McKay HA 2005 The beneficial effects of group-based exercises on fall risk profile and physical activity persist 1 year postintervention in older women with low bone mass: Follow-up after withdrawal of exercise. *J Am Geriatr Soc* **53**:1767–1773.
59. Winters KM, Snow CM 2000 Detraining reverses positive effects of exercise on the musculoskeletal system in premenopausal women. *J Bone Miner Res* **15**:2495–2503.
60. Gilsanz V 1998 Phenotype and genotype of osteoporosis. *Trends Endocrinol Metab* **9**:184–190.
61. Rubin CT, Bain SD, McLeod KJ 1992 Suppression of the osteogenic response in the aging skeleton. *Calcif Tissue Int* **50**:306–313.
62. Kohrt WM, Ehsani AA, Birge SJJ 1997 Effects of exercise involving predominantly either joint-reaction or ground-reaction forces on bone mineral density in older women. *J Bone Miner Res* **12**:1253–1261.
63. Ferrari SL, Chevalley T, Bonjour JP, Rizzoli R 2006 Childhood fractures are associated with decreased bone mass gain during puberty: An early marker of persistent bone fragility? *J Bone Miner Res* **21**:501–507.
64. 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.

Address reprint requests to:
Vicente Gilsanz, MD
Childrens Hospital Los Angeles
Department of Radiology, MS #81
4650 Sunset Boulevard
Los Angeles, CA 90027, USA
E-mail: vgilanz@chla.usc.edu

Received in original form November 17, 2005; revised form May 22, 2006; accepted June 16, 2006.