Original Investigation

Effect of Low-Magnitude, High-Frequency Mechanical Stimulation on BMD Among Young Childhood Cancer Survivors
A Randomized Clinical Trial

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IMPORTANCE Bone accrual during youth is critical to establish sufficient strength for lifelong skeletal health. Children with cancer may develop low bone mineral density (BMD) any time before or after diagnosis.

OBJECTIVE To evaluate the ability of low-magnitude, high-frequency mechanical stimulation to enhance BMD among childhood cancer survivors.

DESIGN, SETTING, AND PARTICIPANTS Double-blind randomized clinical trial conducted at St Jude Children's Research Hospital from June 1, 2010, to January 22, 2013, using cancer survivors, ages 7 to 17 years, who were previously treated at St Jude Children's Research Hospital, were in remission, and at least 5 years from diagnosis, with whole-body or lumbar spine BMD *z* scores of −1.0 or lower. Participants were randomized (stratified by sex and Tanner stage) to either a placebo device or low-magnitude, high-frequency mechanical stimulation device, which was used at home.

INTERVENTIONS Placebo or low-magnitude, high-frequency mechanical stimulation (0.3 g; 32-37 Hz) for 2 sessions lasting 10 minutes each, 7 days per week for 1 year. All participants were prescribed daily cholecalciferol (vitamin D) and calcium.

MAIN OUTCOMES AND MEASURES Changes in areal and volumetric BMD and bone biomarkers were compared by analysis of variance, adjusted for strata.

RESULTS Of the 65 participants, 32 were randomized to the intervention group (mean [SD] age was 13.6 [3.7] years, 18 [56.2%] were male, and 27 [84.4%] were white), and 33 were randomized to the placebo group (mean [SD] age was 13.6 [2.9] years, 17 [51.5%] were male, and 26 [78.8%] were white). Forty-eight participants completed the trial, 22 in the intervention group and 26 in the placebo group with median adherence of 70.1% for intervention and 63.7% for placebo groups. With intention-to-treat analysis, mean (SD) whole-body BMD *z* score by dual x-ray absorptiometry improved by 0.25 (0.78) in the intervention (n = 22), but decreased by −0.19 (0.79) in the placebo group (n = 26, *P* = .05). Circulating osteocalcin at 12 months correlated with change in total body BMD (r = 0.35, *P* = .02). Tibial trabecular bone among participants completing 70% or more of the prescribed sessions increased by a mean of 11.2% (95% CI 5.2 to 17.2%) compared with those completing less than 70% who decreased by a mean of −1.3% (95% CI −7.3 to 4.7%; P=.02). Change in circulating receptor activator of nuclear factor κ-B ligand was higher in the intervention than in the placebo group (0.06 [0.16] vs −0.04 [0.17] pmol/L) (*P* = .04).

CONCLUSIONS AND RELEVANCE Pediatric cancer survivors with low BMD may benefit from low-magnitude, high-frequency mechanical stimulation as a novel and safe intervention to optimize peak bone mass during youth, alone or in conjunction with other therapies.

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Accrual of bone mineral density (BMD) during childhood and adolescence is critical to establish sufficient bone mass to support and maintain skeletal health throughout life. For children diagnosed with cancer, the cumulative effects of disease,[1,2] chemotherapy,[3] radiation exposure,[4] physical inactivity,[5] and poor nutrition[6] are detrimental to bone mineralization and may result in suboptimal BMD that persists into adulthood.[7,8] The percentage of childhood cancer survivors with low BMD is reported to be as high as 47%, depending on tumor type and treatment exposure.[7-10] Bisphosphonate therapy successfully improved BMD in small studies among childhood cancer survivors,[11] but has potential adverse effects.[12,13] Randomized trials evaluating weight-bearing exercise[14] or nutritional supplementation[15] have not shown that these improve BMD in this population.

Designed to harness bone's sensitivity to mechanical signals,[16] low-magnitude (<1.0 g) mechanical stimulation (LMS) improves quantity and quality of bone in animal models[17] and humans, with particular efficacy in younger populations.[18-20] In humans, low-magnitude acceleration is applied through the feet, by standing on a platform oscillating at relatively high frequency. The mechanical signal transmits to the hip and spine with approximately 80% efficiency[21] and is anabolic to bone,[22] biasing mesenchymal stem cell populations toward osteoblastogeneis[23] and enhancing cytoskeletal adaptation in stem cell progenitors.[24] Examined in mouse models of cancer,[25,26] LMS protects bone tissue without compromising longevity or promoting tumor growth. Because LMS is noninvasive and nonpharmacologic with minimal risk for adverse events, the aims of this study were to evaluate the effects of LMS on BMD and markers of bone turnover among survivors of childhood cancer with low BMD.

Key Points

Question What is the efficacy of low-magnitude, high-frequency mechanical stimulation (LMS) to preserve BMD (BMD) in young survivors of childhood cancers?

Findings Among 48 survivors (ages 7-17 years) who completed this 1-year, placebo-controlled randomized clinical trial of LMS, those who participated in prescribed LMS sessions gained total body BMD vs a loss BMD for the placebo group, a significant difference.

Meaning LMS may represent a promising novel and safe therapy to preserve bone mass in survivors of childhood cancer.

Methods

Design

This prospective, double-blind, placebo-controlled trial was conducted at St Jude Children's Research Hospital (SJCRH), and approved by the institutional ieview board. Written informed consent was obtained from parents or legal guardians. The trial protocol is included as Supplement 1.

Participants

Childhood cancer survivors, 7 to 17 years of age, 5 or more years from diagnosis, and not currently receiving treatment for cancer, with age- and sex-specific lumbar or whole-body BMD *z* scores of less than −1.0 were contacted for recruitment 1 month prior to annual after completion of therapy clinic appointments. Eligibility criteria included verification of a BMD *z*-score of less than −1.0, ability to stand independently for 10 minutes, and ability to tolerate calcium and vitamin D supplements. Children requiring chronic oral glucocorticoid therapy, pharmacologic agents for reduced BMD other than calcium or vitamin D, with metal implants or spinal deformity requiring bracing, and pregnant females were not eligible. Potentially eligible participants with baseline 25-hydroxy vitamin D (25[OH]D) levels lower than 50 nmol/L (to convert to ng/mL divide by 2.496) were treated with 5000 IU of vitamin D to normalize 25(OH)D status prior to randomization.[27]

Randomization

Personnel not involved with study participants randomized those enrolled using a computer program written in C++ to intervention or placebo groups in block sizes of 4 by Tanner stage (1, 2, 3 vs 4, 5) and sex.[28]

Intervention

Participants were instructed to stand on a platform for 10 minutes twice daily[29] for 1 year. Those assigned to the intervention stood on an active platform. The mechanical signal (0.3 g at 32-37 Hz) produced a subtle, sinusoidal, vertical translation less than 100 µm via a linear electromagnetic actuator.[30] The placebo group stood on a device identical in appearance to the active platform. The placebo device emitted a 500-Hz audible hum but did not deliver the signal. Both groups received calcium (800-1200 mg/d) and vitamin D supplements (cholecalciferol, 400 IU/d) as recommended by the Children's Oncology Group.[31]

Adherence

Participants received log sheets to record daily sessions. An inboard monitor[32] also recorded the number and time of each session. Session counts were visible when the device was turned on. To encourage adherence, participants were contacted weekly to inquire how many sessions they completed, and were provided with problem-solving strategies if they had difficulty. Participants were encouraged to put the device in an accessible location and to use it while engaged in another activity (eg, watching television, listening to music). In addition, $5 gift cards were mailed after completion of every 50 sessions, report cards were sent monthly with statements to reinforce adherence, and participants received an iPod shuffle at the end of the study. Actual adherence (ratio of time the device was used to total prescribed use) was determined from device monitor data at study completion.

Assessments

Areal BMD was measured with dual x-ray absorptiometry (DEXA, 4500 QDR-A/Discovery fan beam; Hologic). Scans were performed in fast transverse speed mode, and the scanner was calibrated monthly. Data were analyzed using QDR software

for Windows (version 13.3:3, CV <1%). Normative data provided by the manufacturer were used to calculate age- and sex-specific *z* scores.

Average lumbar volumetric BMD was assessed with quantitative computed tomography (QCT) (Lightspeed Ultra 8-detector; GE Healthcare). Participants were scanned lying on cushions containing phantoms of potassium sulfate mineral equivalents (Mindwaves, CV <2.8%). Mineral content was determined via axial images of mid bodies of L1 and L2, using sagittal or coronal scout images of the upper abdomen.[33] A total of 28 to 32 three-millimeter slices were obtained for complete assessment of target vertebrae.

Tibial cortical and trabecular bone content were also assessed with QCT. To assure identical scan locations, left tibial length was measured with a Segmometer (Rosscraft). A scout view was used to position the scanner 50% from the distal tibial end plate. A single slice of 2.3 mm was taken with a voxel size of 0.4 mm. Image processing and numerical values were generated (Mindwaves QCT ProTM BIT) to calculate cortical cross-sectional area (in square millimeters between endosteal and periosteal borders). A region 2×2 voxels between endosteal and periosteal bone envelopes defined the cortical compartment.

Fasting blood and urine samples were taken at baseline and at 12 months. To detect and resolve potential endocrinopathies, including vitamin D deficiency, prior to randomization, serum was assayed for estradiol (female), testosterone (male), free thyroxine, triiodothyronine, thyroid stimulating hormone, intact parathyroid hormone, 25(OH)D, and 1,25-dihydroxyvitamin D_2 [1,25$(OH)_2$-D_2].[27] To evaluate bone turnover, thawed samples obtained at baseline and at 12 months (stored at −80°C) were assayed for osteocalcin (OC), skeletal alkaline phosphatase (BSAP), carboxyterminal telopeptide of type 1 collagen (CTx), collagen cross-linked N-telopeptide (NTx), N-terminal propeptide of type 1 procollagen (PINP), osteoprotegerin (OPG), and receptor activator of nuclear factor κ-B ligand (RANKL).

Dietary intake was assessed with the Block Kids Food Frequency Questionnaire 2004 (NutritionQuest).[34] Average daily minutes of moderate or vigorous physical activity was measured over 7 days with an accelerometer (GT3X; ActiGraph) worn over the right hip during waking, nonbathing hours.[35,36]

Outcomes

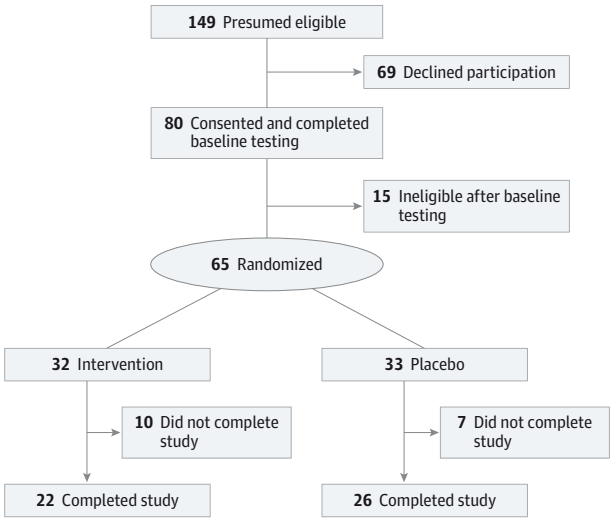
Primary outcome measures were changes from baseline to 12 months in age- and sex-specific *z* scores for total body and lumbar spine areal BMD, in total and lumbar areal BMD, and in lumbar volumetric BMD, tibia bone content and strength. Secondary outcome measures were changes in biomarkers of bone turnover. Adverse events were collected from on-study date until 12 months after the start of the intervention and reported in real time.

Statistical Analysis

Descriptive statistics summarized demographic, skeletal, endocrine characteristics, macronutrient intake, and daily physical activity among participants. Two-sample *t* tests compared characteristics of intervention and control groups. Mean changes in BMD measures and biomarkers of bone turnover were calculated from baseline to 12 months after intervention. Preestablished comparisons (intention-to-treat) between intervention and placebo groups, and post hoc comparisons (per-protocol analyses) between intervention group participants who completed 70% or more of the assigned sessions and those who completed less than 70% of the sessions, used analyses of variance, adjusting for Tanner stage and sex. Associations between measures of BMD and biomarkers of bone turnover were evaluated with Pearson product-moment correlation. SAS statistical software (version 9.3, SAS Institute, Inc) was used for all analyses.

Power estimates for primary outcomes were based on 2-sided 2-sample *t* tests. A priori, we estimated that 30 participants in each group, assuming no change in the placebo group, and a common standard deviation (SD) of 6.8%,[29] resulted in 87% power to detect a 5.5% change in BMD measures in the intervention group, with type 1 error of 0.05.[30,31] We did not adjust for multiple comparisons.

Figure 1. CONSORT Flow Diagram



Results

Among 149 children with a mean (SD) age of 13.6 (3.7) years scheduled for follow-up between May 13, 2010, and November 9, 2011, with previous total body or lumbar BMD *z* scores lower than -1.0, 80 (54%) consented and completed testing. Twelve were not eligible because *z* scores had improved to more than −1.0 since their last visit, 2 had vitamin D levels that did not recover enough to allow participation, and 1 was receiving long-term glucocorticoid therapy, leaving 65 for randomization. Of the 65 participants, 32 were randomized to the intervention group (mean [SD] age was 13.6 [3.7] years, 18 [56.2%] were male, and 27 [84.4%] were white), and 33 were randomized to the placebo group (mean [SD] age was 13.6 [2.9] years, 17 [51.5%] were male, and 26 [78.8%] were white). The groups shared other similar baseline characteristics (eTable in Supplement 2). Ten participants in the intervention and 7 in the placebo group did not complete the study (**Figure 1**). Nine

Table 1. Mean Change in Bone Mineral Density (BMD), Content, and Strength From Baseline to 12 Months

	Intervention (n = 22)		Placebo (n = 26)		
Measure	Mean[a] (SD)	[95% CI]	Mean[a] (SD)	[95% CI]	*P* Value
Total body BMD *z* score	0.25 (0.78)	[−0.09 to 0.59]	−0.19 (0.79)	[−0.51 to 0.12]	.05
L1,L2 BMD *z* score	0.08 (0.51)	[−0.13 to 0.30]	0.14 (0.51)	[−0.06 to 0.35]	.68
Bone mineral content/height, total, %	1.71 (9.01)	[−2.15 to 5.60]	3.99 (8.97)	[0.44 to 7.55]	.38
BMD/height, total, %	6.56 (7.64)	[3.27 to 9.85]	3.45 (7.60)	[0.43 to 6.46]	.12
L1, L2 bone mineral content/height, %	3.70 (21.20)	[−5.41 to 12.82]	2.54 (21.06)	[−5.81 to 10.89]	.84
L1, L2 BMD/height, %	4.91 (10.34)	[0.46 to 9.36]	5.01 (10.29)	[0.94 to 9.06]	.97
L1, L2 volumetric BMD, %	5.64 (10.83)	[0.98 to 10.31]	5.30 (11.06)	[0.92 to 9.68]	.91
Tibia cortical bone, %	3.00 (4.69)	[0.87 to 5.02]	1.77 (4.90)	[−0.17 to 3.71]	.40
Tibia trabecular bone, %	4.89 (10.27)	[0.47 to 9.31]	0.64 (10.45)	[−3.51 to 4.79]	.08
Tibia cortical bone and/or length, %	−1.19 (6.63)	[−4.05 to 1.66]	−1.86 (6.77)	[−4.54 to 0.82]	.73

[a] Adjusted for sex and tanner stage (from analysis of variance).

Table 2. Mean Change From Baseline to 12 Months in Biomarkers of Bone Turnover

	Intervention (n = 22)		Placebo (n = 26)		
Biomarker	Mean[a] (SD)	[95% CI]	Mean[a] (SD)	[95% CI]	*P* Value
PINP, µg/L	22.75 (241.40)	[−81.22 to 126.71]	−62.41 (235.98)	[−159.56 to 34.73]	.23
OC, ng/mL[b]	−5.87 (40.61)	[−23.38 to 11.65]	−14.15 (39.36)	[−29.77 to 1.47]	.47
BSAP, g/L	−3.90 (18.71)	[−11.97 to 4.17]	−13.96 (19.01)	[−21.51 to −6.41]	.07
CTx, µg/mL	−21.36 (466.50)	[−222.24 to 179.52]	−187.57 (473.90)	[−375.27 to 0.13]	.23
NTx, mmol BCE/mmol creatinine	−61.29 (207.22)	[−150.52 to 27.94]	−46.35 (210.48)	[−129.74 to 37.02]	.81
OPG, pmol/L	−0.29 (1.43)	[−0.90 to 0.33]	0.30 (1.41)	[−0.26 to 0.86]	.16
RANKL, pmol/L[c]	0.06 (0.16)	[−0.01 to 0.13]	−0.04 (0.17)	[−0.11 to 0.02]	.04
RANKL/OPG index[c]	0.13 (0.50)	[−0.09 to 0.34]	−0.13 (0.50)	[−0.33 to 0.08]	.09

Abbreviations: BCE, bone collagen equivalent; BSAP, bone-specific alkaline phosphatase; CTx, carboxyterminal telopeptide of type I collagen; NTx, collagen cross-linked N-telopeptide; OC, osteocalcin; OPG, osteoprotegerin; PINP, aminoterminal propeptide of type 1 procollagen; RANKL, receptor activator nuclear factor κ-B ligand.

[a] Adjusted for sex and tanner stage (from analysis of variance) [b]Levels of OC were determined by immunoradiometric assay (Quest Diagnostics Inc; sensitivity 2.0 ng/mL), BSAP by immunochemiluminometric assay (Quest Diagnostics Inc; sensitivity 0.1 µg/L), CTx by electrochemiluminescent assay (Quest Diagnostics Inc; sensitivity 30 pg/mL), and PINP by radioimmunoassay (Arup Laboratories; sensitivity, 2 µg/L). Urine NTx was analyzed by immunochemiluminometric assay (Quest Diagnostics Inc; sensitivity 10 nmol BCE/L). [c]The RANKL assay, a sandwich enzyme-linked immunosorbent assay (sensitivity 0.02 pmol/L), and the Luminex ELISA for OPG (sensitivity 10 pg/ml) were performed by Rules Based Medicine.

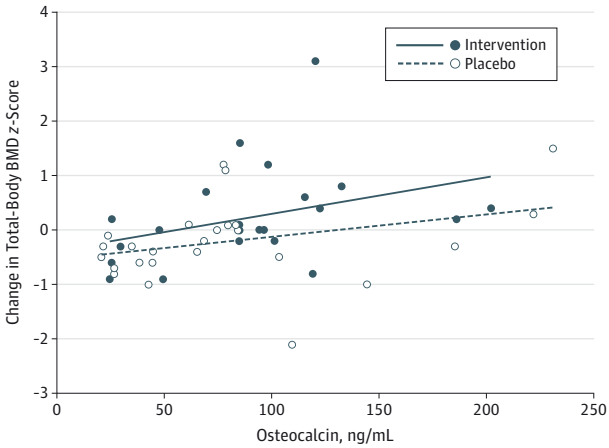
participants reported being too busy, 1 had attention issues that precluded standing on the device, and 7 were lost to follow-up. Those completing did not differ from those not completing the study with respect to sex, race, Tanner stage, age, diagnostic group, or treatment exposure. Adherence did not differ between groups with median (interquartile range) values of 70.1% (35.4%-91.5%) in the intervention and 63.7% (33.3%-86.5%) in the placebo group (P = .40). There were no adverse events associated with standing on either device.

Table 1 displays changes in BMD measurements by treatment group. In an intention to treat analysis, age- and sex-specific total-body BMD *z* scores improved, on average, by 0.25 in the intervention and decreased by -0.19 in the placebo group (P = .05). Because there were no differences between groups in changes in lumbar BMD measures, this difference is likely accounted for by accrual of bone in the lower extremity or other sites. Percentage changes in tibia cortical and trabecular bone trended greater in the intervention group than in the placebo group but did not seem to keep up with linear growth because percentage change in tibial cortical bone content per length declined in both groups.

In a per-protocol analysis, changes in percentage of tibial trabecular bone were associated with adherence in the intervention group. After adjusting for sex and Tanner stage, the 11 intervention group participants who completed 70% or more of the assigned intervention had a mean (95% CI) 11.2% (5.2 to 17.2%) increase, whereas the 11 who completed less than 70% of the sessions had a mean (95% CI) −1.3% (−7.3-4.7%) decrease in tibia trabecular bone (P=.02). There was no association between adherence and change in percentage tibial trabecular bone in the placebo group (P = .49).

Table 2 shows changes from baseline to 12 months after intervention among biomarkers of bone turnover. Although differences between groups were not statistically significant, after accounting for sex and Tanner stage, means for biomarkers of bone formation (PINP, OC, and BSAP) tended to increase or slightly decrease from baseline to 12 months in the intervention group, with a larger magnitude decrease in the pla-

Figure 2. Correlation Between Osteocalcin at 12 Months and Change in Total-Body Bone Mineral Density (BMD) *z* Score



cebo group. Osteocalcin values at 12 months after intervention correlated positively with change in total body BMD *z* score (r = 0.35, P = .02) (**Figure 2**). Changes in biomarkers of bone resorption did not differ between groups. Receptor activator of nuclear factor κ-B ligand values increased in the intervention and decreased in the placebo group.

Discussion

To our knowledge, this is the first prospective, randomized clinical trial that suggests benefit of LMS to prevent or reverse decline in BMD among young survivors of childhood cancer. Participants in the intervention group demonstrated increased total-body BMD, in contrast to decreased BMD among those in the placebo group. Overall trends in bone formation biomarkers (OC, PINP, BSAP) among those who received the intervention, in combination with a suggested increase in tibial trabecular and cortical bone, indicate effects favoring bone formation as a result of LMS. Moreover, intervention adherence influenced favorable change in BMD; those in the LMS group who completed at least 70% of the prescribed sessions displayed a better outcome than those less adherent.

Accruing bone tissue during childhood and adolescence carries lifelong benefits.[37] Although reports fail to demonstrate an association between low BMD and idiopathic fracture,[38] and do not provide evidence of increased fracture risk among adult survivors of childhood cancer when compared with siblings,[39] such studies included survivors who were in their second and fourth decades of life. The impact of persistently low BMD on fracture risk among childhood cancer survivors as they enter their fifth and sixth decades of life is not known. However, it is clear from the general population literature that the higher the BMD, the lower the risk of complications of osteoporosis. Models that incorporate BMD with clinical risk factors among postmenopausal women, to predict age at onset of osteoporosis, indicate that a 10% increase in peak bone mass is associated with delayed onset of osteoporosis of 13 years.[40] In addition, epidemiologic data indicate that a 10% increase in peak bone mass reduces risk for fracture among women by 50% after menopause.[41] Thus, gaining BMD during adolescence, as demonstrated herein following 1 year of LMS, has potential to reduce long-term risk for osteoporosis, fractures, and associated mortality among childhood cancer survivors. Although prospective studies that follow survivors through adulthood will be required to determine if this hypothesis is valid, LMS seems to be a safe, nonpharmacologic intervention that could be started during or immediately following therapy to boost bone health among young people whose cancer and/or therapy interferes with achieving optimal skeletal health.

Bone metabolism is a complex process involving resorption and formation, mediated by osteoclasts and osteoblasts, enabled by hematopoietic and mesenchymal stem cells that reside in a bone marrow niche susceptible to disruption by cancer and/or its treatment.[42] These processes are tightly coupled during bone cell recruitment and remodeling, and are influenced by hormonal status, especially during childhood and adolescence, the most important period of bone growth.[43] Balanced hormonal status across treatment and placebo groups in our study allowed evaluation of changes in biomarkers of bone formation and resorption. Although we found a modest correlation between OC values at the end of the intervention and change in total body BMD *z* score, RANKL was the only biomarker of bone turnover in which change over 12 months differed between groups. Mean RANKL increased in the intervention but decreased in the placebo group, indicating increased osteoclast activity and elevated bone resorption.[44] This, associated with a trend toward an increase in BSAP (index of bone formation) among those in the intervention group, suggests that mechanical signals promote bone turnover, with a net balance toward bone accrual. It is possible, although not demonstrated herein, that a bone-organ system suppressed by disease and/or treatments is "activated" by the mechanical signals, either mobilizing stem cell progenitors or stimulating resident bone cell populations. We did not observe a correlation between RANKL and any BMD measures. This may be because peak RANKL and other bone turnover markers occurred after baseline but prior to the 12-month follow-up.

Our results suggest an increase in appendicular rather than spinal bone mass, results similar to those reported by Ward et al[20] in their study of 20 children with cerebral palsy where they reported increased volumetric tibial trabecular bone (6.3% intervention vs −11.9% control), but not lumbar spine or tibial cortical bone, after 6 months of 5 weekly, 10-minute LMS sessions (0.3 g, 90 Hz). Wren et al[45] reported changes in tibial cortical bone density, but not tibial or spinal trabecular BMD, among 31 children with cerebral palsy during LMS vs during a standing period. Studies of LMS among young females with idiopathic scoliosis and low BMD,[46] or with fracture history and low BMD,[18] also reported improvements in appendicular rather than in spinal BMD. These regional differences in the effects of LMS on BMD may relate to the proximity of the device to body region, with potential loss of vibratory energy as the signal travels from the distal lower extremity to the trunk,[47] or to differences in capacity to respond to mechanical signals, with some regions more attuned to functional adaptation than others.[48]

These data point toward the anabolic potential of LMS for the skeleton. Considering the health history of children previously treated for malignant disease, it is important to ensure that any intervention, even one that is nonpharmacologic, is safe. Vibration is recognized as a pathogen, provoking low back pain, white finger diseases, blurred vision, and hearing loss.[49] Indeed, measures of human exposure to high-magnitude vibration emphasize that its use should be approached with caution, particularly among those at greatest risk for fracture.[50-52] That being said, International Organization for Standards (ISO)-2631 standards for human exposure to vibration indicate that the frequency and intensity of the signal in this study is considered safe for up to 4 hours each day.[53] In addition, in murine models of ovarian cancer and myeloma, LMS did not compromise survival or exacerbate disease, yet protected bone quality in the axial and appendicular skeleton and reduced pathologic abnormalities in skeletal tissue,[25,26] suggesting that mechanical signals that are salutary to bone tissue do not result in progression of malignant disease. Finally, in our study, we observed no adverse events associated with LMS over 1 year of twice-daily use.

Our results should be considered in the context of some limitations. First, although 74% of enrolled participants completed the study, retaining our ability to detect a change in total-body BMD *z* score, our final sample size limited statistical power to detect differences in other outcomes. Second, only half of participants in the intervention group completed 70% or more of prescribed sessions. This may limit the feasibility of this intervention in a nonresearch setting. Third, our data lack early and repeated measures of the biomarkers of bone turnover, limiting ability to determine and understand initial and longitudinal metabolic responses of bone to LMS in this population. Failure to detect differences between groups, with respect to mean changes in some biomarkers of bone turnover, may be because the biomarker response to LMS was acute (within days or weeks of the intervention start), with values attenuating over the study period.[54] Finally, even though we used a double-blind, placebo-controlled study design, we could not control for potential confounding by differences in other factors that influence bone growth (eg, genetics, sun exposure).

Conclusion

This study suggests that pediatric cancer survivors with low BMD may benefit from LMS as a safe intervention to promote accrual of bone mass during childhood and adolescence. These results are preliminary. Further work needs to be done to define mechanisms of action of LMS in this population and to determine if modifications in dose and/or duration of LMS can provide greater improvements in BMD. There is also a need to determine if LMS works synergistically with pharmacologic or exercise interventions, prevents bone loss among children during cancer therapy, or improves BMD among survivors who have achieved skeletal maturity, and to determine if bone accrual is retained following cessation of use.

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Mogil, Kaste, Ferry, Ness.
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