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The effect of whole body vibration therapy on bone density in patients with thalassemia: A pilot study

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Abstract

Patients with thalassemia (Thal) have low bone mass which can lead to fracture and decreased quality of life. There are no noninvasive anabolic therapies available to improve bone health in Thal. A longitudinal cross-over pilot trial was conducted to evaluate the effectiveness of low magnitude whole body vibration (WBV) therapy on bone in 18 patients with Thal (9 adults, 10 male, 22.1 ± 10.7 years). Subjects were asked to stand on a vibrating platform (30 Hz, 0.3 g) for 20 min/day for 6 months. Areal bone mineral density (aBMD) by DXA and volumetric BMD by peripheral quantitative computed tomography (pQCT) was assessed at baseline, 6 and 12 months. Adherence in the first 3 months was greater when compared with the second 3 months (14 ± 6 vs. 10 ± 7 min/day, P=0.007). Intention to treat analysis revealed a significant increase in whole body BMC (2.6%; P = 0.021), BMC/Ht (2.6%, P = 0.02) and aBMD (1.3%; P = 0.036), as well as a net increase in serum markers of bone formation (Osteocalcin/CTx, P = 0.027) in the adult subjects. These preliminary findings suggest that vibration therapy may be an effective nonpharmacologic intervention in Thal. Future research is needed to confirm these findings in a larger sample for longer duration.

Patients with Thal have many risk factors that adversely affect bone mass including: ineffective erythropoiesis which leads to bone marrow hyperplasia and cortical thinning [1], poor growth, endocrine and growth hormone deficiencies [2], diabetes [3,4], and decreased circulating vitamin D levels [5]. Although many patients are small for age, bone mineral deficits are not completely explained by growth and lean mass deficits [1,6,]. Bone resorption is elevated in adult Thal compared to reference data, whereas reduced bone formation is a key component leading to the bone mineral deficits observed in young Thal patients [1,7]. Bone histomorphometry from iliac crest biopsies in children with Thal reveal impaired bone matrix, defective mineralization, and reduced formation rate, which are associated with iron deposits within bone [8].

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Additional Supporting Information may be found in the online version of this article.

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Despite the pervasiveness of low bone mass in Thal, there are few therapies available to young patients [2,9]; most are treated for hypogonadism through hormonal replacement and encouraged to take calcium and vitamin D supplements. Despite these efforts, the majority of patients continue to lose bone as they age, as much as 1 to 2% per year starting in the 3rd decade of life [10]. The primary pharmacologic treatment available to patients is bisphosphonate therapy aimed at reducing bone loss [8]. Alternative therapies focused on increasing bone formation have not been evaluated. Physical activity can increase bone mineral acquisition [11]; however, some cardiovascular exercises are not tolerated in Thal patients with cardiac complications. Recent advances in the field have shown that low magnitude (0.3 g), high frequency (20–90 Hz) mechanical stimulation can promote bone formation at a magnitude well below that which is reached from walking alone [12–14]. Whole body vibration (WBV) therapy has also been shown to improve strength and inhibit adipogenesis [14–16]. Seven studies have been published using WBV in postmenopausal women [17,18], young females with low bone mass [19,20], and children with cerebral palsy [21–23].

Given the paucity of research on noninvasive, bone enhancing therapies in Thal, a pilot trial of WBV therapy was devised. The primary aim of this short term trial was to examine the effects of WBV on trabecular and cortical bone density and strength variables by peripheral quantitative computed tomography (pQCT) and dual energy x-ray absorptiometry (DXA) in subjects with Thalassemia. The WBV intervention consisted of 20-min sessions, 6 days per week for 6 months in the subjects' home standing on an active vibration platform.

Eighteen subjects with Thal, 9 adults and 9 adolescents, completed all 5 assessment points (Supporting Information Table I). Two adult and two adolescent subjects had deficient vitamin D levels at the start of the study (25OH vitamin D < 20 ng/mL) despite being prescribed vitamin D supplementation. Only one adult subject was 100% adherent to the therapy (Supporting Information Table II). Adherence for both groups was greater during the first 3 months (13.5 ± 6.3 min/day) than the second 3 months (10.4 ± 6.5 min/day, P = 0.007).

The change in aBMD, vBMD, and markers of bone turnover are presented separately for the adult subjects (Tables I and II) and adolescents (Table II and Supporting Information Table III) due to the differences in age-related bone metabolism. Using intention to treat analysis, there was a significant 2.6% increase in whole body BMC, BMC/height (2.6%), and aBMD (1.3%) for the adult subjects during the 6-month intervention, which remained elevated at the 12 month time point (Table I). Individual absolute change in whole body BMC is presented in Supporting Information Fig. 1, illustrating a positive response of those most adherent to the protocol. However, the average increase in whole body BMC in the adult subjects (40 g) was less than our DXA instrument least significant change (LSC: 58 g). The same was true for the whole body aBMD increase in the adult subjects, (0.011 g/cm^2, data not shown) which was also less than our instrument LSC (0.023 g/cm^2). The rate of change in hip BMD during the 6-month intervention in the adult subjects (2.2%, 95%CI: −1.3, +5.7%) was significantly greater than the rate of change observed in the year prior to entry into the study (−2.7%, 95%CI: −0.2, −5.3%, P = 0.02). Of interest, there was also a highly significant correlation between the rate of change in hip a BMD assessed by DXA during the intervention period and the adherence to the protocol in minutes per month (r = 0.95, P = 0.001). There were no significant differences in any of the pQCT parameters assessed throughout the protocol for the adult group. Lean mass, assessed by DXA, trended to increase by 600 g after 6 months of vibration therapy (P = 0.06), without a significant change in absolute or percentage of body fat.

As expected for growing children, aBMD and BMC increased in the adolescent group, both before and during the intervention period. However, the rate of increase during the intervention did not differ from the 6 month prior to the start of intervention for any of the DXA bone parameters. The only difference observed for the adolescent group was an increase in cortical BMD. Given that fracture risk is related not only to trabecular but cortical bone density, this preliminary finding may elude to future benefits for these adolescent subjects.

Markers of bone formation and resorption were assessed at 4 time points in each age group (Table II). Overall, a net increase in bone formation was observed during the intervention period in the adults. This observation mirrored the findings observed in whole body BMC and aBMD. The largest increase (25%) in the marker of bone formation (osteocalcin) was observed at the 3-month time point, which corresponds with the period of greatest adherence. Bone resorption, assessed by serum CTx, continued to decrease throughout the 6 month intervention period, on average by 33%. Bone turnover markers were only assessed in one previous study of WBV, and were not found to change with therapy [17]. The increase in bone formation capacity in this study is promising and confirms the DXA results are not simply spurious findings in a small sample.

To our knowledge there are no anabolic therapies that have been tested in this population. Gains in BMC and BMD are not expected for adult subjects with thalassemia as they have already reached their peak bone mass, typically achieved in the third decade of life. In fact, young adults with Thal have been reported to lose bone mass at a young age, similar to what is observed in postmenopausal women. Pollak et al, [10] estimated that in young Israeli adults with Thal, spine BMD decreases annually by 1.1% per year and femoral neck by 0.9% per year.

Small but significant effects of WBV on the whole body DXA scans were observed, but curiously, no observable effects in the bone parameters assessed by pQCT in the adults. This is in contrast to the publication by Gilsanz et al. [19] where a QCT modality identified increases in specific bone compartments but assessments by DXA were unchanged. Differing results may be due to subject sample (Thal vs. young women), or differences in the precision of each modality at a center. Of note, this is the first published study of WBV to use whole body DXA in an adult population, which may have been more sensitive at picking up overall changes in BMC and aBMD in a small sample vs. compartmental analysis by pQCT.

There are a number of reasons why significant effects were observable in the adults but not in the adolescents. First, and perhaps most important, adolescents were captured during a period of rapid growth and pubertal development. Given that every child is on their own growth trajectory and bone accrual curve, observing changes in a small group of peri-pubertal adolescents may increase the variability in the data, and thus limit the ability to observe change. Of interest, adolescents trended towards participation in more minutes per day of vigorous activities compared to the adults (61 min vs. 7 min/day; $P = 0.13$) which perhaps limited the ability to see an effect of the vibration therapy. Third, all nine adults were on a chronic transfusion regimen, compared with only five of the adolescents ($P = 0.023$). The variability in erythropoeitic activity between transfused and nontransfused subjects may also contribute to variability in the bone assessments [24]. Finally, the adults tended to use the platform intervention for more minutes per month compared with adolescent subjects (357 (95%CI: 205, 308) vs. 229 (103,354), $P = 0.07$).

This pilot study was limited by its sample size, length, of intervention and lack of a control group. The differences in BMC and aBMD observed herein within the adults over a 6-month

time frame were statistically significant, though the magnitude of the effect was small, on the order of 1.3–2.6%. The magnitude may have been dampened by the short length of the intervention. Others have observed greater change in BMD when the intervention is longer [17]. The magnitude of the difference observed herein is similar to what has been observed in 24 young girls (15–20 years) with low BMD who used the platform for 1 year where a 2.0% net increase in spine vBMD and 2.3% increase in femoral cortical area was observed [19]. Budget constraints limited the design and scope of the current pilot project. There are also a limited number of subjects with Thal at any one medical center in the US, which prohibits a larger sample size without multicenter recruitment and accompanying budget. To increase the power of the sample, a cross-over, longitudinal design was chosen, where subjects were used as their own controls, thus making the use of a sham (nonvibrating) platform infeasible.

This is the first report of low magnitude mechanical stimulation (WBV) being used in subjects with Thal. Though the intervention was limited to a small number of subjects (n = 18), for a short duration (6 months), whole body BMC and aBMD increased in adults who had limited physical activity and low bone mass. A net increase in markers of bone formation was also observed for the adult group during the intervention period. Although these data are preliminary, they suggest promise of a noninvasive intervention in a group of patients who have a significant risk of osteoporosis morbidity. Future research should expand upon this study with a larger sample size for longer duration and include ways to improve adherence.

Methodology

This was a 12 month, cross-over longitudinal study design (6 months of intervention for each subject) in subjects with thalassemia. Adults participated in the active vibration therapy intervention for the first 6 months, while the adolescents participated in the intervention component of the trial from 6 to 12 months. Evaluations were made at baseline, 6 and 12 months of bone mass, density, and strength (by DXA and pQCT). Dietary intake, physical activity, anthropometry, and circulating markers of bone formation and resorption were also assessed as described below. Adherence to the therapy was assessed at the mid-point and end of intervention for the adults (3 and 6 months) and adolescents (9 and 12 months).

Specific procedures and methodology

Subjects—Subjects with Thal were recruited from hematology clinic at the Children's Hospital & Research Center, Oakland (CHRCO) and considered eligible if they were between 10 and 18 years (adolescent group) or over 18 years (adult group) with a DXA aBMD Z-score less than −1.0 at the spine, hip or whole body. Subjects were excluded if they had a history of bone marrow transplant (BMT), had taken a bisphosphonate in the previous year or where hypogonadal and treated for <6 months. Potentially eligible subjects were identified and approached. Informed written consent was obtained from all subjects or legal guardians and assent from the subjects <18 years. The protocol was approved by the Committee for the Protection of Human Subjects of the Institutional Review Board at CHRCO. A total of 23 subjects (12 adults, 11 adolescents) were initially enrolled into the study, of which 2 male subjects (1 adult, 1 adolescent) dropped after the baseline assessment. Two of the remaining 11 adults dropped during the intervention portion of the study, one subject after one month due to back pain, one after 2 months secondary to relocation out of the area for a job. One adolescent dropped after 1 month of intervention due to dizziness while standing on the platform; this subject was not on a chronic transfusion therapy program.

Vibration platform intervention—The Juvent 1000 Dynamic Motion Device (Juvent Medical, Inc. U.K.) was used for this study. The platform is portable (4”H × 20”D × 20”W; 15 pounds) and when stood upon, introduces a gentle vibration to the entire axial skeleton. Subjects were instructed to stand on the platform without shoes for 20 min each day, 6 days per week for 6 months. The platform was positioned in the home on a hard surface (non-carpet). Platforms were programmatically set to turn off after 20 min of vibration. Each vibrating platform had an internal electronic monitoring device which recorded date, time and length the subject stood on the platform. Adherence was then calculated as the number of minutes per day the subject stood on the platform, in relation to the requested intervention. Investigators communicated frequently (e.g., phone, text, and email) with subjects to trouble shoot any difficulties experienced during the intervention to enhance adherence.

Bone densitometry—A Discovery-A QDR bone densitometer (Hologic, Bedford, MA, software v12.6.1) was used to assess BMC and BMD at the PA spine, left hip and whole body on all subjects at baseline, 6 and 12 months. Prebaseline clinical BMD data was also available for all subjects one year prior to entry into the study, collected on the same instrument analyzed by the same staff. To minimize variability related to erythropoietic activity, bone scans were performed in all transfused subjects in the afternoon following their monthly transfusion. The following variables were collected from each DXA scan: bone mineral density (aBMD), bone mineral content (BMC), and bone area. Bone mineral apparent density (BMAD) was calculated as $BMC/Area^{1.5}$. *Z*-scores for adults were calculated from manufacturer's database and for the adolescents from the pediatric Hologic reference set. Peripheral quantitative computed tomography (pQCT, Stratec XCT2000, Pforzheim, Germany, software v5.5) was used to assess both cortical and trabecular bone density in the left distal tibia and radius. The distal tibia was scanned at two sites: 3 and 38%, and the radius at 4 and 50% proximal to the growth plate using standardized protocols [1,25]. Trabecular and cortical densities, bone area, cortical thickness, periosteal, and endosteal circumferences were assessed and section modulus calculated. The in vivo precision of the DXA and pQCT were determined by duplicate measurement of 30 healthy subjects of similar age. The in vivo coefficient of variation for the spine scan aBMD is 1.13%, and the tibial trabecular vBMD is 0.8%. All DXA and pQCT scans were analyzed by a single operator (EBF).

Anthropometric and pubertal assessment—Weight was measured on a digital electronic scale (Tanita BWB 800); and stature using a stadiometer (Holtain, Crymych, UK); at baseline 6 and 12 months. Body composition was assessed from the DXA whole body scan, fat (g), fat free mass (g), and % total body fat were used in the analysis. Pubertal status (in adolescents only) was determined at baseline using a validated self-assessment pictoral questionnaire [26].

Dietary intake and physical activity—Subjects were instructed not to change their use of nutritional supplements during the 12-month study. Calcium and vitamin D intake was assessed using a combined tool that was individually validated for calcium and vitamin D intake [27,28]. This tool was administered to each participant at baseline, 6- and 12-month time points. Physical activity was assessed using the validated Block Work and Home Activities Survey (Block EE©2004, Block Dietary Data Systems, Berkeley, CA) at the 6-month time point only [29].

Laboratory assessment—Blood was collected at 0, 3, 6, and 12 months for the adults and at 0, 6, 9, and 12 months for the adolescents. All blood was collected nonfasting, pretransfusion and at a similar time of day for each subjects' longitudinal samples. CBC with

differential, reticulocyte count, ALT, TSH, glucose, PTH, and serum ferritin were collected and analyzed as part of usual clinical care. 25-hydroxy vitamin D was assessed by ARUP national laboratories by chemiluminescent immunoassay (Salt Lake City, UT). Serum osteocalcin, an extra-hepatic vitamin K dependent protein produced primarily by osteoblasts was assessed using the Metra Osteocalcin immunoassay (Quidel Corp, San Diego, CA) and used as a marker of bone formation. Serum CTx was assessed using the CrossLaps Elisa (Immunodiagnostics, Fountain Hills, AZ) to quantify the degradation of products of C-terminal teleopeptides of type 1 collagen as an indication of bone resorption. Although markers of bone turnover are often collected in the fasted state, the circadian rhythm is often a stronger influence on variability, particularly for osteocalcin [30]. Therefore, blood in this study was collected at the same time of day for each subject, longitudinally. Neither transfusion nor chelation therapy regimens changed during the course of the study for the transfused subjects. Clinical information regarding chelation and transfusion history, fracture history, and disease characteristics were collected from subject interview and medical records.

Data analysis—Baseline comparisons of demographic and clinical variables between groups (adult vs. adolescent) were performed using a student's *T*-test for continuous variables, chi-squared test for categorical variables. Given adolescents were assessed at a time of rapid bone growth and mineralization, they were analyzed separately from the adult group. Repeated measures analysis of variance was used to assess the change in bone variables with time of study in the adult group. In the adolescent group, paired Student's *T*-tests were used to assess the difference in bone variables between the intervention period (6–12 months) and the nonintervention period (0–6 months). Pearson's correlation coefficients were used to assess the relationship between change in BMD and adherence to the protocol. After intention to treat analysis was complete, the relationship between potential confounding variables (e.g., gender, vitamin D and Tx status, adherence) and the variable of interest (ΔBMD) was explored. All analyses were completed using STATA, version 9.2 (College Station, Tx, 2000).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE I

Change in Bone Parameters at Baseline, 6 and 12 Months of a Longitudinal Whole Body Vibration Platform Intervention in Adult Subjects with Transfusion Dependent Thalassemia (n = 9)

Adult subjects	Intervention: Baseline	Intervention: 6 month	Post-Intervention: 12 month	***P*-value***
Bone Density by DXA**				
Spine aBMD, g/cm2	0.774 (0.620, 1.022)	0.782 (0.616, 1.006)	0.774 (0.614, 0.995)	NS
Spine BMAD, g/cm3	0.102 (0.080, 0.127)	0.103 (0.083, 0.125)	0.104 (0.082, 0.128)	NS
Total Hip aBMD, g/cm2	0.715 (0.624, 0.821)	0.726 (0.622, 0.815)	0.718 (0.619, 0.781)	NS
Total Hip BMC, g	22.67 (18.6, 27.3)	22.77 (17.8, 25.7)	22.76 (19.5, 25.8)	NS
Whole body BMC, g	1523 (1006, 1916)	1563* (1056, 1985)	1563* (1080, 2003)	0.021
Bone Density by pQCT				
Tibial Trabecular vBMD, g/cm3	193 (130, 243)	194 (123, 243)	192 (123, 234)	NS
Total Tibial vBMD, g/cm3	221 (163, 268)	223 (158, 270)	220 (159, 271)	NS
Peripheral Circumference, mm	65.1 (56.7, 78.2)	65.2 (57.1, 78.4)	65.2 (56.9, 78.3)	NS
Endosteal Circumference, mm	42.2 (27.7, 59.1)	42.2 (28.0, 59.2)	42.2 (28.1, 59.1)	NS
Tibial Cortical vBMD, g/cm3	1190 (1171, 1242)	1193 (1123, 1249)	1193 (1135, 1245)	NS
Tibial Cortical Thickness, mm	3.7 (2.9, 4.6)	3.7 (3.1, 4.6)	3.7 (3.1, 4.6)	NS
Body Composition by DXA				
Whole Body Fat mass, kg	12.7 (5.4, 22.5)	12.8 (4.4, 23.3)	13.0 (5.1, 22.1)	NS
Whole Body Lean mass, kg	39.2 (35.2, 48.0)	39.8^ (35.9, 49.4)	39.3 (35.3, 48.7)	0.06^

BMC, bone mineral content; aBMD, areal bone mineral density; vBMD, volumetric bone mineral density; BMAD, bone mineral apparent density.

Values are denoted as Mean (95%Confidence Interval)

* p-value is for the repeated measures ANOVA model,

* denotes time points that are significantly different from baseline by a $P < 0.05$.

^ denotes a trend ($P < 0.1$) from baseline.

** Least significant change (LSC) for our DXA instrument is: spine BMD: 0.022 g/cm2; hip BMD 0.025 g/cm2; and whole body BMC: 58 g.

TABLE II

Markers of Bone Turnover During Vibration Platform Therapy in Adolescent (n = 9) and Adult (n = 9) Subjects with Thalassemia

	Intervention				
	Baseline	3 month	6 month	12 month	*P*-value^
Adult subjects					
Osteocalcin, ng/mL	7.9 ± 2.1	9.9 ± 2.1*	8.4 ± 2.1	8.1 ± 2.8	0.005
CTx, ng/mL	0.70 ± 0.33	0.47 ± 0.22*	0.46 ± 0.28*	0.60 ± 0.33	0.005
Osteocalcin / CTx	13.2 ± 6.6	23.5 ± 9.4*	26.4 ± 19.9	15.9 ± 7.4	0.027
		Intervention			
	Baseline	6 month	9 month	12 month	
Adolescent subjects					
Osteocalcin, ng/mL	14.1 ± 6.3	14.9 ± 3.4	15.6 ± 4.7	16.8 ± 4.5	NS
CTx, ng/mL	1.48 ± 1.34	1.14 ± 0.87	1.13 ± 0.54	1.45 ± 0.68	NS
Osteocalcin/CTx	12.2 ± 4.4	16.9 ± 8.0	17.9 ± 11.8	12.9 ± 4.7	NS

P-value for the adolescent subjects is for the *t*-test difference in values between baseline-6 months and 6–12 months. Osteocalcin is a marker of bone formation. CTx, C-terminal teleopeptides of type 1 collagen is an indication of bone resorption. Osteocalcin/CTx: ratio is an indication of net bone formation. Values are denoted as Mean ± SD.

^ *P*-value for the adult subjects is for the repeated measures ANOVA model,

* denotes time points that are significantly different from baseline by a $P < 0.05$.