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The effect of whole body vibration training on bone and muscle function in children with osteogenesis imperfecta

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Abstract

Context: Osteogenesis imperfecta (OI) is a bone fragility disorder associated with reduced muscle size, dynamic muscle function and mobility.

Objective: To assess the effect of whole body vibration (WBV) training on bone density and geometry, muscle size and function, mobility, and balance in children with OI.

Design: Randomised controlled pilot trial

Setting: Tertiary paediatric research centre

Participants: Twenty-four children (5-16 years) with OI types 1,4 and limited mobility (CHAQ score ≥0.13) recruited in gender- and pubertal stage-matched pairs. Incident fractures in two boys (WBV arm) led to exclusion of two prepubertal male pairs.

Intervention: 5 months of WBV training (3x3min twice daily) or regular care.

Main Outcome Measures: Bone and muscle variables measured by dual-energy X-ray absorptiometry (lumbar spine, hip, total body) and peripheral quantitative computed tomography (distal and proximal tibia). Mobility assessed by six-minute walk tests and CHAQ; dynamic muscle function by mechanography.

Results: All participants had reduced walking distances and dynamic muscle function ($p<0.001$). BMI Z-score was associated with higher CHAQ scores (rho +0.552; $p=0.005$) and lower walking and two-leg jumping performance (rho -0.405 to -0.654, $p<0.05$). The WBV and control groups did not differ in the 5-month changes in bone density or geometry. Total lean mass increased more in the WBV group (+1119g [+224 to +1744]) compared to controls (+635g [-951 to +1006]), $p=0.01$, without improving mobility, muscle function or balance.

Conclusions: The increase in lean mass without changes in muscle function or bone mass suggests reduced biomechanical responsiveness of the muscle-bone unit in children with OI.

INTRODUCTION

Osteogenesis imperfecta (OI) is an inherited bone fragility disorder with low bone mass, high bone material density and altered geometry, leading to increased fracture risk, but also to reduced muscle size, dynamic muscle function (1,2), isometric muscle force (3,4), and limited mobility (5). Intravenous bisphosphonate (BP) therapy in children with OI increases bone mass (6) by inhibiting bone resorption, but evidence of fracture reduction remains limited (7). To date, there is a complete lack of anabolic therapy to directly target the impaired bone formation and muscle function in OI.

Whole body vibration (WBV) training (high frequency, low or variable magnitude, using a vibrating platform) is widely used to improve physical fitness (8,9). Several small randomised controlled trials and observational studies in children with cerebral palsy (10-17) and other paediatric disabling conditions (12,18-21) have demonstrated a beneficial effect of WBV on walking speed, muscle strength, spasticity and balance. The underlying concept of mechanical stimulation to bone is the mechanostat theory (22), which states that bone adapts its strength to mechanical forces which are mostly imposed by muscle. Accordingly, any treatment that strengthens muscle should lead to improvements in bone structure and mass, mobility, balance and risk of fall. Of note, bone formation increases significantly and in excess of bone resorption after short-term use of WBV in healthy children (23).

Using WBV therapy as an adjunctive therapy in children with OI and limited mobility is therefore tempting, especially since significant improvements in cortical thickness of femora and tibiae, and higher trabecular tibial bone volume have been reported following WBV in a mouse model of OI (24). In addition, data from an uncontrolled observational study in 53 children with OI treated with WBV within an intensive rehabilitation program showed

increased muscle strength and mobility (25,26). To date, there are no randomised controlled studies using WBV in children or adults with OI.

This paired randomised controlled pilot trial aimed to assess the effect of 5-months of WBV training on bone mass, geometry and density, as well as muscle function and size, mobility and balance in children with OI.

SUBJECTS AND METHODS

Between May 2012 and May 2015, 24 children (5-16 years) with clinically mild to moderate OI (Sillence types 1,4) with limited mobility were recruited from OI specialist clinics at tertiary Children's Hospitals in Birmingham, Sheffield and Manchester, as well as through an advertisement placed on the Brittle Bone Society website. Limited mobility was defined by a Child Health Assessment Questionnaire (CHAQ) score of ≥0.13 (27), with the minimum ability to rise from a chair.

Bisphosphonate therapy increases mobility and isometric grip force during the first treatment years (28,29). In order not to confuse such secondary improvements in muscle function due to BP therapy with primary effects from WBV, children had to be either naïve to BP therapy, or had to have received BP therapy for more than 2 years (current therapy), or stopped BP therapy at least 6 months prior to enrolment (previous therapy). Children were excluded if they had experienced a lower limb fracture within 3 months of enrolment, or a recent upper limb fracture still in plaster, if they had heart or lung disease, or if on steroid therapy (oral, systemic, topical or inhaled, for more than 3 weeks in the last 12 months) or any other bone-active treatment. The study design required children to be recruited in pairs matched for gender and pubertal stage group (pre-pubertal [Tanner stage 1], pubertal [Tanner stage 2-4],

post-pubertal [Tanner stage 5]). Eligible pairs of children were invited to attend the Wellcome Trust Clinical Research Facility at Birmingham Children's Hospital (WTCRF), where informed consent was taken from the participant and their parent or guardian, and all study investigations took place. Specific history recorded included details of medication, duration, dose and frequency of previous/current BP therapy, recent medical history, fracture and rodding surgery. Pairs of children were then randomized so that one received 5 months of twice-daily vibration training (n=12) and the other regular care (n=12), using sealed envelopes. This registered trial (NCT03029312) complied with the ethical principles for medical research set by the Declaration of Helsinki and was approved by the regional ethics committee.

Outcome measures

The following outcome measures were taken in both groups before and following the 5 months intervention.

Anthropometry and incident fractures:

Height and weight were measured using a Harpenden Stadiometer and electronic scales, respectively, wearing light indoor clothing. Pubertal stages were assessed according to Tanner (30), either by physical examination or through self-rating using standard graphical illustrations. Body mass index (BMI) was calculated as kg/m^2. Gender- and age-specific Z-scores for height, weight and BMI were calculated according to UK reference data (31,32). Location and nature of radiographically confirmed incident fractures during the study were recorded.

Dual Energy X-Ray Absorptiometry (DXA):

DXA scans of the lumbar spine, hip and total body were performed on a Lunar iDXA (GE, Madison, Wisconsin, USA). Size-corrections included calculation of bone mineral apparent density (BMAD) at the lumbar spine (33) and removing the head from the total body scan (TBLH) (34). Hip scans are reported for the right, or non-rodded, femoral neck and hip. Bone density results are presented as Z-scores for age. Lumbar spine Z-scores were generated from our large local cohort of 1500 healthy children (35). Hip and TBLH Z-scores, lean mass for height Z-scores and percent body fat were derived from the manufacturer's database. Leg bone mass and leg lean mass were derived from the total body scan.

Peripheral QCT tibia (pQCT):

A pQCT scan of the tibia using a Stratec XCT2000 scanner (Stratec Medizintechnik, Pforzheim, Germany) was performed at the distal (4% of tibia length) and proximal tibia (66% of tibia length). Outcome measures included trabecular and total bone densities at the 4% site, and cortical density, bone and muscle cross sectional areas, muscle density and estimated cortical thickness at the 66% site. Reproducibility of tibia bone and muscle pQCT parameters has been described previously (36,37).

Mobility, Muscle function and Balance:

Childhood Health Assessment Questionnaire (CHAQ):

The CHAQ score is a common tool to measure mobility/disability in children, assessing various motor function skills involved in dressing, arising, eating, walking, hygiene, reach, and grip (27). The possible score range is 0 to 3, with limited mobility defined as a score ≥0.13. Pain was assessed separately using a faces pain scale (38).

Six-minute walk test (6MWT):

The 6MWT is a standardized endurance test where children are asked to walk as far as possible over six minutes. The maximum distance covered during this 6 minute walk (6MWD) in 30 meter laps with cones at the turning points was measured, using standardized encouragement (39). Gender-specific Z-scores for age and height were calculated as previously reported (40).

Mechanography:

Dynamic muscle function was assessed using a Leonardo™ Mechanograph Ground Reaction Force Plate (Novotec Medical Inc, Pforzheim, Germany) (41) with proprietary software. The following tests were performed using standard procedures, with best of three repetitions retained (42,43): 1) Single two-legged jump, a vertical countermovement jump to achieve maximum jumping height; 2) multiple one-legged hopping on the dominant forefoot (like rope-skipping) to achieve maximal vertical ground reaction forces during eccentric muscle contraction; 3) chair rise test (5 sit-to-stand repetitions); and 4) heel rise test (5 bilateral heel rises with knees kept stiff) with the aim to achieve maximal speed during the upward movement. High reproducibility of all muscle force-time data reported here has been recently described (43).

Outcome variables were 1) peak power per body weight (W/kg), peak force per body weight (N/kg being dimensionless), peak velocity (m/s) and jumping height (m) during eccentric muscle contraction for the single two-legged jump, 2) peak force for the multiple one-legged hop, and 3+4) mean time per repetition (sec) and peak power in the rising phase (W/kg) in the chair and heel rise tests. Peak ground reaction force per body weight measured in multiple

one-legged hopping is considered the most appropriate variable for assessing the muscle-bone unit at the tibia in children, as bone is expected to adapt to the peak forces (44).

This device also measures balance (swaying area), and manufacturer's instructions were followed. Depending on their individual ability, participants were asked to stand for ten seconds, 1) on one foot, 2) on two feet in tandem stand, 3) in semi-tandem stand and 4) in parallel feet stand. Categories 1-4 reflect decreasing balance abilities. Both decreasing balance category, and decreasing swaying area, reflect improvement.

Intervention

Children randomised to 'regular care' (controls) continued to receive routine care including physiotherapy. Children randomised to 'vibration' had their first WBV training sessions under supervision in the WTCRF and were subsequently supplied with a vibration device (Galileo M™, Novotec Medical, Pforzheim, Germany) for home use. Vibration training was supervised by a research physiotherapist (JS) and included several scheduled home visits to ensure correct, individualised training and adherence. Children were asked to keep a training record, and the device recorded adherence data (date, time, frequency, and duration of use).

The Galileo M™ device has a motorized board that produces side-to-side alternating vertical sinusoidal (rotational) vibrations around a fulcrum in the mid-section of the plate. The vibration frequency can be selected by the user who stands on the board with both feet, wearing shoes. The peak-to-peak displacement to which the feet are exposed increases with the distance of the feet from the centre line of the vibrating board. Three positions marked 1, 2 and 3 are indicated on the vibrating board, corresponding to peak-to-peak displacements of

2, 4, and 6mm. The peak acceleration exerted by vibration exercise increases with higher frequencies and higher amplitudes.

Children used the device twice daily for 3 x 3 minutes, with 3 minute breaks (total active training time daily 18 min) for 5 months. Children were asked to stand upright on the platform, with knees bent (10-45 degrees, semi-squat or squat position). A schedule of increasing intensity of vibration exercise was used over time, allowing some adjustment to the patient's physical capability. Amplitude 1 was used for the first 2 weeks, then increased to amplitude 2 and further increased up to amplitude 3, if individually possible, always using frequencies between 20-25Hz. Children were also asked to perform exercises on the platform, including shifting their weight from one side to the other or increase/decrease their knee and hip angle. Other exercise included weight shift with rotation of the trunk, and alternate flexion and extension of knees. Where possible, active squats or semi-squats were done on the platform.

The safety of vertical and rotational WBV treatment regimens have been demonstrated in previous studies in children with disability (10-17) and OI (25,26). In all paediatric and adult studies, vibration treatment was well tolerated, including children with OI carrying intramedullary rods. Since forces produced during WBV therapy are lower compared to forces applied during walking and running in daily life (45-47), and participants were at least partially ambulant, WBV was not considered a safety risk. Nevertheless, children were asked to report any discomfort, fatigue or pain.

Statistical Analysis

In the absence of pilot data for OI children, the primary endpoint variable chosen for sample size calculation was total tibial volumetric BMD at the tibial 4% site, measured by pQCT,

guided by a pilot WBV study in disabled children, accepting their use of different vibration and scanning technology (12).

Matching by gender and pubertal stage was done to optimise comparability of results. Randomization allocated one of each pair to vibration or no vibration. All outcome variables were tested for normal distribution and, given the small sample sizes, descriptive statistics are presented as median (range). To describe the extent of disease and immobility, baseline data were compared against reference data from healthy children (zero) for anthropometry (31,32), DXA (35), and dynamic muscle function (single two-leg jumps, multiple one-leg hops (42) and chair rise test (48)) using one-sample T-tests. Spearman's correlation was used to assess associations amongst variables at baseline.

Study results are reported according to the standards set by the International Society of Musculoskeletal and Neuronal Interactions (49). The 5-month change in absolute values and Z-scores in all outcome variables in the vibration group was compared with those of the control group using Wilcoxon signed rank test, or paired T-test, as appropriate. All tests were two-tailed and throughout the study $p<0.05$ was considered significant. Calculations were performed using SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA) by a qualified biostatistician (PN).

RESULTS

Baseline Characteristics

Twenty-four children (12 pairs, matched by gender and pubertal stage) were recruited into the study. Their baseline characteristics are shown in **Table 1**. As expected, the total group of OI children were shorter ($p<0.001$) compared to the reference population (zero). The vibration

group had slightly greater BMI Z-scores and percent body fat compared to the control group. The total group's limited mobility was demonstrated by their median (range) CHAQ score of 1.187 (0.375 to 1.875) and low 6MWD Z-scores for age (-2.34 [-6.51 to -0.58]; p<0.001) and height (-1.49 [-5.60 to 0.82]; p<0.001), with no significant differences between the vibration and control groups. Similarly, dynamic muscle function variables of the total cohort were significantly lower in all patients compared to the reference population (p≤0.001), with no difference between the two groups.

Figure 1 demonstrates the effect of body mass on mobility. BMI Z-score correlated positively with CHAQ scores (rho=0.552, p=0.005) and negatively with 6MWD Z-scores (rho=-0.405, p=0.049), weight-related, two-legged peak jumping power (rho=-0.557, p=0.007), velocity (rho=-0.654, p=0.001) and jumping height (rho=-0.585, p=0.004). Very similar significant relationships of these functional variables were observe with percent body fat, but not with lean mass/height Z-score (data not shown).

Response to 5 months of vibration therapy

Two prepubertal, male pairs had to be excluded since two boys randomised to WBV, both previously treated with BP, dropped out of the study due to incident fractures. One boy had a suspected leg fracture after consent and before starting WBV therapy which delayed the start of therapy. He later suffered an atraumatic pelvic fracture towards the end of the 5-month intervention. The other boy sustained a left fibula fracture and experienced intermittent pain in his right tibia during WBV training from a pre-existing mal-positioned rod. None of these fractures occurred during a WBV training session. In both cases, prolonged rehabilitation did not allow regular use of the device and caused an unacceptably long delay to the post-intervention visits, leading to secondary exclusion. Of note, their 6MWD (age Z-scores -6.14;

-6.51) and peak two-legged jumping force (Z-scores -5.04; -5.10) at baseline were the lowest, by far, of the entire cohort with no apparent difference in bone mass.

The remaining 10 pairs therefore consisted of 4 male pairs (3 prepubertal, 1 post-pubertal) and 6 female pairs (5 prepubertal, 1 postpubertal), including a pair of identical twins. Five children each in the vibration and control groups, had previous or current BP therapy for more than 2 years, and five children each were naïve to BP therapy. Median (range) adherence to WBV was 84% (63 to 96%), with recorded average frequency of 24.1Hz (23.2 to 24.5), and highest amplitudes between 2 to 3.

There were no significant differences between the vibration and control group in the 5-month changes in growth, bone density or geometry (**Table 2**). The vibration group had a significantly greater increase in total lean mass (+1119g [224 to +1744]) over 5 months compared to controls (+635g [-951 to +1006]), p=0.01, and a corresponding change in lean mass/height Z-score. Similar changes were observed in other muscle variables such as leg lean mass and cross-sectional muscle area at the 66% site, but these did not reach statistical significance (**Figure 2**). However, the increase in lean mass was not associated with substantive improvements in mobility or dynamic muscle function, as measured by CHAQ, 6MWT and mechanography (**Table 3**). There was no significant difference between the two groups in variables of balance (data not shown). Adjustment for previous or current BP therapy did not alter the results. The results of the entire study population were reflected in those of the identical twin pair (both on BP therapy, data not shown).

In addition to the low impact fractures that had led to exclusion of two boys, one child sustained an accidental nose fracture and another one a finger fracture in the WBV group during the study period (unrelated to WBV training sessions). There were no fractures in the

control group, apart from one child who had incidental vertebral fractures detected during the study.

DISCUSSION

This first randomised controlled study in children with OI demonstrated no effect of 5 months, twice-daily rotational WBV on bone mass, density or geometry despite a significant increase in total lean mass. Muscle mass or size are often used as surrogates for muscle force in able-bodied children. This study in children with OI indicates that increments in lean mass are not necessarily associated with improvements in mobility, 6MWD, dynamic muscle function or balance. In line with the recent observation that children with OI produce less peak force per muscle size (2), our results suggest reduced biomechanical responsiveness of their muscle-bone unit. Together with the potential safety concern that significant incident fractures occurred in the two muscularly weakest children only in the WBV group, our results do not encourage the use of WBV in OI children.

Vibration training (whether vertical or rotational) is designed to improve peak muscle forces, and secondary effects on bone are expected according to the mechanostat theory (22). The fairly large number of randomised studies demonstrating positive effects of WBV on walking speed, muscle strength, spasticity and balance in children with cerebral palsy (10-15,17) or other disabilities (12,19), indicate that this treatment modality appears efficacious and safe in children without a primary bone formation defect. Therefore, the results of this study raise several questions.

Our results are in contrast with evidence from a murine model of OI, where 5 weeks of vertical WBV increased cortical thickness of femur and tibia (24), and to some extent from an

observational study in children with a wide range of OI severity which suggested rotational WBV improves motor function and walking distance (25,26). The lack of a bone effect despite improved total lean mass in this study questions whether OI bone may respond less to vibration therapy compared to non-OI bone. Such decreased responsiveness may be caused by the high material density altering the biomechanical signal (increased mechanostat set-point) or by the reduced bone formation capacity typical for OI bone. Given the reduced peak force per muscle area reported in OI children (2), we speculate that the biomechanical bone strain imposed by muscle forces may possibly be translated more slowly in OI bone compared to that of able-bodied children. Whilst disease-specific bone material properties may offer an explanation for decreased biomechanical responsiveness of OI bone, the decreased responsiveness of OI muscle function to WBV therapy may also have its origin in defective collagen type I. Tendons contain plenty of collagen type I and transmit forces from muscles to bones. In OI, the biomechanical properties of tendons are impaired (50), possibly altering transmission of forces and dynamic function. Of note, reduced muscle forces and dynamic function at baseline are not just found in children with OI, but also in the OI mouse model (51).

Whether and how much an individual can improve his/her muscle function in response to WBV therapy depends to some extent on the mobility and function of the individual at baseline and the intensity of training. Our cohort did not include children with severe forms of OI, in fact all were at least partially mobile by design. In their observational study of children with more severe OI, Hoyer-Kuhn et al (25) reported the effect of a rehabilitation concept including WBV, not a direct effect of WBV in isolation. In general, the forces applied during WBV are lower than during walking or running (45-47). Whilst the level of immobility in our cohort was not severe, with habitual loading forces greater than those employed during WBV, it is a fact that WBV is used as an effective fitness tool in able-

bodied individuals (8). Therefore, one would still expect positive results even in our patient group with limited mobility.

The intensity and duration of training in the current study (20-25Hz, 3x3min, twice daily, for 5 months) was comparable with other WBV studies in children. In fact, most studies in CP used a once daily or five times/week vibration regimen, for 5-6 months. In addition, adherence to WBV was comparable with a recent larger scale WBV study in children (52). Finally, there are different brands, models, and types (vertical, rotational) of WBV devices available on the market, with variable levels of evidence supporting their effectiveness (53).

This study found that higher BMI Z-score correlated with higher CHAQ score and lower 6MWD, body-weight-related peak power, velocity and jumping height in the two-legged jump at baseline. Such negative associations between overweight and weight-related jumping outcomes have been previously described in able-bodied children (54). Our results indicate decreased mobility and whole-body muscle performance in overweight children with OI. Since overweight in OI is also associated with higher fracture rates (55), lifestyle modification should be an integral part of OI management (56).

Limitations of this study include its small sample size. Care was taken not to include patients who had started BP therapy in the last 2 years, which is associated with secondary gains in mobility. The number of patients with previous and current BP therapy happened to be identical in both groups. Whilst we cannot completely exclude an effect, we consider it unlikely given that the 5-month changes observed in the pair of identical twins was in line with the overall study results.

Conclusion

Whilst it is possible that treatment response in dynamic muscle function and bone may require longer training durations in children with OI, the effort and engagement required from the child and parents for this training is substantial. Therefore, the lack of a measurable bone effect over 5 months suggest that rotational WBV therapy is not a practical, effective treatment tool to increase bone formation and strength in OI. The incident low-impact fractures in the two weakest subjects on WBV therapy also raise concerns about safety in children with OI. Whether rotational or other forms of WBV are more efficacious in more severely immobile children with OI, or as an adjunct to an intensive rehabilitation program, requires further study. The association of overweight with impaired mobility highlights the need for active weight management in children with OI.

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Figure Legends:

Figure 1:

Baseline correlations between BMI Z-scores of 24 children with osteogenesis imperfecta with their CHAQ score, 6-minute walk distance (Z-scores for age and height), and weight-related peak power, velocity and jumping height in the single two-legged jump (S2LJ).

Figure 2

A) The vibration group (white boxes) had greater increments in total lean mass over 5 months compared to pubertal stage- and gender-matched controls (grey boxes), with similar trends in leg lean mass and cross-sectional muscle area at the proximal tibia (66% site). B) There were no corresponding differences in total or leg bone mineral content (BMC) or proximal tibia cross-sectional bone area (CSA). Box-plots depict median, interquartile range and 5/95% percentiles.

Table 1: Baseline characteristics of the Study Population

	Total group (n=24)	**Vibration (n=12)**	**Control (n=12)**	**p-value**
Age (years)	8.72 (5.03 to 16.73)	9.38 (6.59 to 16.73)	6.49 (5.03 to 16.16)	0.088
Non-vertebral fractures last 2 years	1 (0 to 8)	1 (0 to 8)	1 (0 to 3)	0.358
Female/Male	12/12	6/6	6/6	
Anthropometry				
Height Z-score	-0.96 (-2.73 to 0.89)***	-1.02 (-2.73 to 0.89)	-0.86 (-2.50 to 0.36)	1.000
Weight Z-score	-0.30 (-2.33 to 1.68)	0.67 (-1.59 to 1.68)	-0.75 (-2.33 to 1.27)	0.057
BMI Z-score	0.25 (-2.43 to 2.73)	0.85 (-0.21 to 2.73)	-0.15 (-2.43 to 2.38)	0.013
Mobility				
CHAQ score	1.187 (0.375 to 1.875)	1.187 (0.375 to 1.625)	1.187 (0.375 to 1.875)	0.907
Faces Pain score	20 (0 to 80)	20 (0 to 80)	25 (0 to 80)	0.573
6 MWD (m)	462 (246 to 693)	456 (246 to 693)	468 (331 to 592)	0.817
6 MWD age Z-score	-2.34 (-6.51 to -0.58) ***	-3.30 (-6.51 to -0.58)	-1.90 (-2.94 to -0.79)	0.204
6 MWD height Z-score	-1.49 (-5.60 to 0.82) ***	-2.41 (-5.60 to 0.54)	-0.90 (-2.46 to 0.82)	0.184
DXA				
Lumbar spine BMD Z-score	-0.25 (-3.60 to 2.60)	0.00 (-2.40 to 2.60)	-0.35 (-3.60 to 2.20)	0.193
Lumbar spine BMAD Z-score	0.50 (-3.50 to 4.80)	0.90 (-2.40 to 4.80)	-0.05 (-3.50 to 4.20)	0.236
Femoral neck BMD Z-score (R)	-1.35 (-3.70 to 1.50)***	-2.10 (-3.70 to 1.50)	-1.10 (-3.60 to 0.50)	0.948
Hip BMD Z-score (R)	-1.45 (-4.30 to 1.30)**	-1.70 (-4.30 to 1.30)	-1.40 (-3.20 to 1.20)	0.870
TBLH BMD Z-score	-0.75 (-2.90 to 1.60)***	-0.75 (-2.90 to 0.10)	-0.85 (-2.60 to 1.60)	0.908
Lean Mass/Height Z-score	-0.36 (-2.33 to 1.64)	-0.26 (-1.13 to 1.48)	-0.36 (-2.33 to 1.64)	0.425
Percent body fat (%)	32.3 (21.7 to 50.8)	37.2 (24.6 to 50.8)	30.2 (21.7 to 39.4)	0.019
Single Two-Leg Jump				
Peak power Z-score	-2.17 (-10.90 to -0.49)***	-3.10 (-10.90 to -0.57)	-1.71 (-2.89 to -0.49)	0.128
Peak force Z-score	-2.85 (-5.10 to 1.52)***	-3.40 (-5.10 to -0.35)	-2.40 (-4.49 to 1.52)	0.422
Jumping height Z-score	-2.50 (-8.50 to -0.83)***	-3.16 (-8.50 to -1.47)	-2.00 (-3.41 to -0.83)	0.052
Multiple One-Leg hop				
Peak force Z-score	-2.26 (-4.33 to -1.26)***	-2.18 (-4.33 to -1.31)	-2.33 (-4.20 to -1.26)	0.875
Chair Rise test				
Time per repetition Z-score	1.93 (-1.30 to 8.66)***	1.93 (0.70 to 5.57)	2.43 (-1.30 to 8.66)	0.655
Peak power Z-score	-1.87 (-3.01 to 0.58)***	-2.09 (-3.01 to 0.39)	-1.55 (-2.50 to 0.58)	0.205

** <0.01, *** <0.001, p-value for comparison with reference values from healthy children

Table 2. Comparison of the Change in Growth and Bone Variables over 5 Months

Change	Vibration (n=10)	Control (n=10)	Difference*	p-value
Anthropometry				
Height Z-score	-0.10 (-0.58 to 0.19)	-0.12 (-0.30 to 0.20)	+0.02	0.982
Weight Z-score	0.11 (-0.08 to 0.39)	-0.05 (-0.57 to 0.27)	+0.16	0.104
BMI Z-score	0.33 (-0.24 to 0.50)	0.05 (-0.60 to 0.43)	+0.28	0.171
DXA				
Lumbar spine BMD Z-score	0.0 (-0.5 to 0.5)	-0.1 (-0.4 to 0.6)	+0.1	0.918
Lumbar spine BMAD Z-score	-0.1 (-2.1 to 0.7)	-0.1 (-0.3 to 0.9)	0	0.296
Femoral neck BMD Z-score (R)	-0.1 (-0.5 to 0.3)	0.1 (-0.8 to 0.5)	-0.2	0.418
Hip BMD Z-score (R)	0.0 (-0.4 to 0.5)	-0.1 (-0.3 to 0.2)	+0.1	0.746
TBLH BMD Z-score	0.1 (-0.2 to 0.3)	-0.1 (-0.4 to 0.7)	+0.2	0.280
Lean Mass/Height Z-score	0.09 (-0.56 to 0.42)	-0.07 (-0.47 to 0.27)	+0.16	0.038
Percent body fat (%)	1.7 (-0.7 to 3.1)	2.3 (-2.0 to 3.7)	-0.6	0.948
pQCT distal tibia (4%)				
Total BMD (mg/cm^3)	3.0 (-4.2 to 46.4)	5.4 (-38.9 to 42.6)	-2.4	0.634
Trabecular BMD (g/cm^3)	5.6 (-47.1 to 78.5)	-10.7 (-34.4 to 94.4)	+16.3	0.508
pQCT proximal tibia (66%)				
Cortical BMD (mg/cm^3)	4.2 (-26.4 to 30.3)	8.8 (-27.4 to 115.2)	-4.6	0.805
Cortical area (mm^2)	8.3 (-10.5 to 17.6)	9.3 (-4.5 to 30.5)	-1	0.508
Cortical thickness (mm)	0.18 (-0.31 to 0.44)	0.20 (-0.20 to 0.92)	-0.02	0.445
Bone/muscle ratio	-0.03 (-0.35 to 0.52)	0.19 (-0.54 to 2.64)	-0.22	0.277
Muscle Density (g/cm^3)	0.54 (-2.26 to 3.94)	0.35 (-1.03 to 4.56)	+0.19	0.586

*Mean numerical difference of changes of the vibration group relative to the control group

Table 3. Comparison of the Change in Muscle Function and Mobility over 5 Months

Change	n	Vibration	n	Control	Difference*	p-value
Mobility, Pain, Endurance						
CHAQ score	10	-0.25 (-1.00 to 0.63)	10	-0.19 (-0.63 to 0.75)	-0.06	0.319
Faces pain score	10	5 (-30 to 40)	10	0 (-30 to 60)	+5	0.933
6 MWD (m)	10	-17 (-83 to 122)	10	-18 (-70 to 51)	+1	0.278
6 MWD age Z-score	10	-0.39 (-1.51 to 1.95)	10	-0.56 (-1.35 to 0.43)	+0.17	0.184
6 MWD height Z-score	10	-0.41 (-1.41 to 1.74)	10	-0.50 (-1.20 to 0.53)	+0.09	0.211
Single Two Leg Jump						
Peak power (W/kg)	10	0.23 (-5.98 to 7.49)	8	-0.82 (-7.26 to 6.25)	+1.05	0.527
Peak velocity (m/s)	10	-0.01 (-0.16 to 0.57)	8	-0.12 (-0.35 to 0.31)	+0.11	0.327
Peak force (N/kg)	10	0.03 (-1.03 to 0.50)	8	-0.08 (-0.76 to 0.34)	+0.11	0.779
Jumping height (m)	10	0.00 (-0.04 to 0.07)	8	-0.02 (-0.08 to 0.17)	+0.02	0.624
Multiple One Leg Hop						
Peak force (N/kg)	10	-0.06 (-0.23 to 0.14)	10	-0.09 (-0.17 to 0.50)	+0.03	0.600
Chair Rise Test						
Time per repetition (sec)	10	-0.01 (-0.71 to 0.29)	10	-0.12 (-1.34 to 0.34)	+0.11	0.240
Peak power (W/kg)	10	0.29 (-2.21 to 4.76)	10	0.15 (-2.44 to 4.59)	+0.14	0.868
Heel Rise Test						
Time per repetition (sec)	10	0.02 (-0.28 to 0.32)	9	-0.08 (-0.57 to 0.45)	+0.1	0.714
Peak power (W/kg)	10	0.58 (-2.38 to 3.53)	9	-0.50 (-4.87 to 5.52)	+1.08	0.764

*Mean numerical difference of changes of the vibration group relative to the control group