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Original Article

Hylonome

Whole body vibration therapy in patients with Duchenne muscular dystrophy – A prospective observational study

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Abstract

Objectives: To study the tolerability of whole body vibration (WBV) exercise in patients with Duchenne muscular dystrophy (DMD) and its effects on muscle and bone. **Methods:** WBV was performed two to three times a week for three months. Motor function, muscle strength, bone mass and biochemical markers of bone and mineral metabolism were analyzed before and after the WBV period at 0, 3, 6 and 12 months. **Results:** Six ambulatory patients with DMD aged 5.7-12.5 years completed the study. No changes in creatine kinase activity were found, indicating that the WBV exercise did not further damage the skeletal muscle. No significant changes in bone mass, muscle strength or bone markers were found. However, there was a non-significant trend for the bone formation marker, bone-specific alkaline phosphate, to increase from a mean of 59 U/L to 73 U/L after three months of WBV. The bone formation marker levels returned to baseline three months after discontinuing WBV and were still at that level after nine months. **Conclusions:** WBV therapy appears to be safe and well tolerated among ambulatory DMD patients. The potential benefits of WBV on bone and muscle in DMD remain to be elucidated.

Keywords: Vibration Therapy, DXA, DXL, pQCT, Bone Mineral Density, Sclerostin

Introduction

Duchenne muscular dystrophy (DMD), an inherited X-linked recessive disorder and the most common muscular dystrophy in childhood, involves an increased risk of osteoporosis[1-4]. Patients with DMD suffer from a progressive deterioration in muscle function from early childhood, with increasing difficulty walking, and most patients lose the ability to walk between seven and 13 years of age. Following the muscle deterioration, increased levels of creatine kinase (CK) are found. Moreover, in a recent cross-sectional study, it was shown that DMD patients have reduced bone turnover[5].

Whole body vibration (WBV) is a method for strengthening muscle which was initially developed in the 1970s in order to prevent the loss of muscle and bone mass in cosmonauts during prolonged space flights[6]. Nowadays, the method is being used increasingly to treat a variety of clinical conditions[7,8]. The mechanism behind the effect of vibration on bone is not fully understood, but WBV has been shown to be osteogenic in children with disabling conditions, according to Ward et al.[9]. There are also some data indicating that WBV is able to reduce bone resorption. For example, Turner et al.[10] found a reduction in the cross-linked amino-terminal telopeptide of type I collagen (NTX), a bone resorption marker, after eight weeks of WBV in postmenopausal women.

Physical activity and mechanical loading are thought to be beneficial to bone health. However, intensive exercise may also cause muscular lesions. A temporary increase in CK levels has been demonstrated following WBV in healthy, inactive subjects[6].

This observational pilot study was designed to investigate the tolerability of WBV in children with DMD, in addition to studying the effects on muscle function, bone mass, bone turnover and body composition after three months of WBV therapy and during a post-intervention follow-up period of nine months.

The authors have no conflict of interest.

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Subjects and methods

Subjects

The subjects in this study were recruited from the Queen Silvia Children's Hospital in Gothenburg, Sweden. Six patients with DMD, 5.7-12.5 years of age (median 6.8 years), were included between June 2008 and September 2009. All the patients had immunohistochemically and genetically verified DMD, they were all able to walk without assistance and they were all being treated with 0.35 mg/kg/day of prednisolone in accordance with the DMD treatment recommendations in Sweden at that time.

Study procedure

Muscle strength tests and measurements of bone and muscle parameters and biochemical markers of bone and mineral metabolism were performed at inclusion, at three months, i.e. immediately after completion of the WBV, at six months and at 12 months. Height was measured to the nearest 0.1 cm using a wall-mounted ruler. Weight was measured on analog scales to the nearest 0.1 kg. A questionnaire about general health, well-being and fractures was designed for the participating children and their parents to complete at inclusion and at every follow-up. Information on previous fractures was also collected from clinical files.

Informed consent was obtained from all the children and their parents. This study was approved by the Human Ethics Committee at the Medical Faculty, Sahlgrenska Academy at Gothenburg University.

Intervention

Participating patients were trained on a Galileo Delta (Novotec Medical GmbH, Pforzheim, Germany) for three months. This device has been described elsewhere by Semler et al.[7]. In short, the Galileo Delta generates vibrations by oscillating along the sagittal axis, which induces side-alternating oscillations that provoke apical gait-like movements of the body. The patients and their parents were well informed about and instructed on how to use the Galileo Delta and how to perform the WBV exercise. The feet should be placed in a position that gives a vibration amplitude of 2 mm, which means a peak-to-peak displacement of 4 mm. The vibration exercise was performed at 16-24 Hz two to three times a week, for two minutes per session during the first two weeks and then for six minutes per session during the remaining 10 weeks (treatment protocol, Table 1). With a vibration at 16-18 Hz, a peak acceleration of 2.1-2.6 g was transmitted to the body, while the corresponding figures at 20-24 Hz were 3.2-4.6 g, using this set-up.

Weeks 1 and 2	2 to 3 times/week
	1 min 16-18 Hz (warming up) 2 min resting 1 min 20 –24 Hz
Weeks 3-12	2 to 3 times/week
	1 min 16-18 Hz (warming up) 1 min 20-24 Hz 2 min resting 2 min 20-24 Hz 2 min resting 2 min 20-24 Hz

Table 1. Treatment protocol for whole body vibration therapy on the Galileo Delta vibration plate.

Assessment of bone and muscle mass

Bone mineral density (BMD) and bone mineral content (BMC) values were assessed by the Lunar DPX IQ (pencil beam), (GE Lunar Corp., Madison, WI, USA) for total body (TB), total hip and lumbar spine (L_1-L_4). Age- and gender-specific Z-scores were calculated. Lean body mass and fat mass were also assessed. Measurements of the left heel bone mass were performed using the dual-energy X-ray absorptiometry (DXA) and laser (DXL) Calscan technique, where the measurement by DXA is combined with a laser measurement of the total heel thickness. This technology reduces the uncertainty related to the variable composition of soft tissue in adults[11]. For heel BMD, the DXL Calscan (Demetech AB, Täby, Sweden) has been used to diagnose osteoporosis in adults and it is used in conjunction with measurements made using axial DXA technology[12,13]. The DXL Calscan pediatric version includes a function which makes it possible to measure calcaneal height[14]. This height, together with the BMD value, provides an opportunity to calculate the volumetric bone mineral apparent density (BMAD), which could be valuable when measuring bones of different sizes in growing individuals, for example[15].

The peripheral quantitative computed tomography (pQCT) measurements were performed on the left tibia at 4% and 66% of the tibia length using an XCT 2000 (Stratec Medizintechnik GmbH, Pforzheim) with software version 6.00. Quality assurance was performed every day using the phantom provided by the manufacturer. The tibia length was measured with a ruler from the medial malleolus to the tibial plateau. A voxel size of 0.5 mm and a scan speed of 20 mm/s were used. The exact position of the CT scans was defined in a coronal scout scan at the distal lower leg. The mass, area and density of muscle and bone were calculated in two steps. At the 4% site, the analysis was performed using a threshold of 180 mg/cm^3 to separate bone from soft tissue (contour mode 1). From the total bone area, the inner 45% were determined as trabecular bone, while the outer 55% were defined as cortical and subcortical bone (peel mode 1). At 66%, an overall threshold of 710 mg/cm^3 was used to separate cortical bone from soft tissue and marrow (cort mode 1). The muscle area was isolated using a threshold-based algorithm which determined all voxels with a density between 40 and 180 mg/cm^3 as muscle. To reduce noise, the image was filtered using a median filter before the analysis. The performance and reference values of the device have been reported elsewhere[16].

Assessment of muscle strength

Isometric muscle strength tests were performed according to Eek et al.[17] and measured using an electronic hand-held my-

	Age (years)	**Height** (Z-score)	**Weight** (Z-score)	**CK (µkat/L)**			
		Start to Follow-up	Start to Follow-up	Start	3 months	6 months	12 months
Patient 1	6.7	-0.3 to -0.4	2.6 to 3.2	323	238	283	476
Patient 2	12.5	-3.0 to -4.2	-0.9 to -0.6	145	102	93	86
Patient 3	7.9	-1.2 to -1.6	1.1 to 0.4	356	171	320	269
Patient 4	7.0	-0.8 to -1.2	0.0 to 0.0	–	351	106	249
Patient 5	5.7	-2.0 to -2.4	-0.1 to 0.1	201	–	–	228
Patient 6	6.5	-2.2 to -2.6	-1.4 to -1.2	165	104	187	240
All patients (median values)	6.8	-1.6 to -2.0	-0.1 to 0.0	201	171	187	244

CK = creatine kinase. No significant changes were found during the study period. Height and weight Z-scores at the start and at follow-up at 12 months.

Table 2. Auxological data for the investigated children.

ometer. Torque values in Nm were calculated for each muscle group. The knee extensor strength values and the foot plantar- and dorsi-flexion strength values were analyzed. In order to determine muscle strength regardless of the age of the patients, quotients were also calculated between torque values obtained from the patients and reference values collected from healthy individuals of corresponding ages and weights[17].

Assessment of biochemical markers of bone and mineral metabolism

Serum sclerostin was assessed by a quantitative enzyme-linked immunosorbent assay (ELISA) (Biomedica, Vienna, Austria)[18]. The serum bone-specific alkaline phosphatase (BALP) activity was determined by ELISA (Quidel Corp., San Diego, CA, USA)[19]. Serum osteocalcin was determined using a chemiluminescence immunoassay (DiaSorin Inc., Stillwater, MN, USA). Type I collagen degradation was assessed by the serum CrossLaps ELISA (IDS Nordic a/s, Herlev, Denmark), which is reported to measure a cathepsin K degradation product of trivalently cross-linked type I collagen (CTX)[20]. An insulin-like growth factor binding protein (IGFBP) blocked radioimmunoassay (RIA) with a large excess of insulin-like growth factor-II (IGF-II) was used to determine IGF-I and an RIA was used for IGFBP-3 (Mediagnost GmbH, Reutlingen, Germany)[21]. The serum CK activity was analyzed for safety purposes with a Cobas instrument (Roche Diagnostics Scandinavia AB, Bromma, Sweden).

Statistics

For continuous variables, the results are presented as minimum, maximum and median values. The overall trend for each variable is estimated by using the slope from a linear regression (model: the variable=months since first exam) within each patient. The overall trend test was made using the Wilcoxon signed rank test for all patients. Correlation analyses were performed with Spearman's non-parametric rank correlation. All the tests were two-tailed and conducted at the 5% significance level.

Results

Subjects

All six patients with DMD completed the vibration treatment period and the follow-up examinations without any adverse events. From the questionnaires, it was concluded that the patients subjectively experienced that their well-being was unchanged or improved after the vibration period. All the patients remained ambulatory throughout the study period. No fractures were reported before the study in the patient group and no fractures occurred during the study period. The height and weight of each patient are presented in Table 2.

DXA and DXL measurements

Bone mass measurement data at baseline and during the follow-up period are presented in Table 3. No significant changes were found in terms of BMD or BMC in TB, spine, hip or heel bone after the WBV treatment period. When it came to body composition, the DXA measurements did not reveal any significant changes in lean mass or fat mass at any time point.

pQCT measurements

Values from pQCT measurements are shown in Table 4. There was a trend towards increasing muscle density after three months of WBV (numerical values), but these changes did not reach statistical significance.

Muscle strength measurements

No significant changes were observed in knee extensor muscle strength or foot plantar- and dorsi-flexor muscle strength at any time point during the study period.

Measurements of biochemical markers

The results for the biochemical markers of bone and mineral metabolism are presented in Table 3. Although non-significant, we observed a trend for BALP to increase from a mean of 59

	Start	3 months	6 months	12 months
TB BMD (g/cm^2)	0.799	0.796	0.777	0.816*
TB BMC (g)	714	761*	773	779*
BMD $L_1 – L_4$ (g/cm^2)	0.630	0.617	0.629	0.629
BMD $L_1 – L_4$, Z-score	-0.9	-1.1	-1.05	-1.1
Total hip BMD (g/cm^2)	0.560	0.555	0.563	0.563
Heel BMD (g/cm^2)	0.160	0.177	0.166	0.168
Heel BMC (g)	0.118	0.130	0.121	0.126
Heel BMAD (mg/cm^3)	57.7	59.8	56.7	61.0
Osteocalcin (µg/L)	28	25	22	22
BALP (U/L)	59	73	56	55
CTX (µg/L)	0.555	0.540	0.605	0.635
Sclerostin (pmol/L)	17.2	16.1	17.0	-
IGF-I (µg/L)	182	164	181	206
IGFBP-3 (µg/L)	3337	3329	3308	3395

BMD = bone mineral density, TB BMD = total body BMD, BMC = bone mineral content, BMAD = bone mineral apparent density
*Values are given as the median. * Significant changes since the start: $p<0.05$.*

Table 3. DXA and DXL measurement values and markers of bone and mineral metabolism.

	Start	3 months	6 months	12 months
Trabecular density (mg/cm^3)	168.1	183.8	179.0	165.6
Cortical density (mg/cm^3)	1023	1087	1041	1106
Muscle density (mg/cm^3)	74.9	76.7	72.9	72.4
Muscle area (cm^2)	4906	5247	5528	6106
Bone-muscle area ratio	2.44	2.40	2.32	2.29

Values are given as the median. No significant changes were found during the study period.

Table 4. pQCT measurement values.

U/L to 73 U/L after three months. The levels of BALP returned to baseline after six months (56 U/L) and were still at this lower level at 12 months (55 U/L). No significant changes were observed for sclerostin, osteocalcin, CTX, IGF-I or IGFBP-3 during the study period. There was no significant change in CK activity (Table 2).

Discussion

To our knowledge, this is the first study of WBV treatment in patients with DMD. The present work indicates that three months of WBV is well tolerated by ambulatory patients with DMD. There were no indications of muscle damage due to the WBV. The patients' muscle strength and motor function remained at the same level during the follow-up period and no changes in circulating CK activity were observed. In addition, most bone parameters assessed by DXA, DXL and pQCT showed no significant changes during the study period.

It is known that physical activity is necessary and beneficial for many human body functions, including muscle strength, motor function and bone strength. The natural course of the DMD disorder includes the progressive destruction of muscle tissue and a reduction in physical activity level with time[22]. This also includes an increased risk of osteoporosis and fractures[4]. DMD patients are often treated with glucocorticoids, which have been shown to slow the progression of the disease and preserve muscle function and strength[23]. In mdx mice, which lack dystrophin, Novotny et al.[24] recently showed that restricted activity, together with prednisolone treatment, independently influence and reduce bone strength. This indicates the importance of encouraging patients with DMD to maintain a certain level of physical activity. Submaximum functional strength training and activities are recommended for boys in the ambulatory or the early non-ambulatory stage of the disease in order to avoid disuse atrophy[25]. However, patients with DMD have vulnerable muscle tissue and the question of whether physical activity could harm the muscles even more has been discussed. High-resistance strength training and eccentric exercise are considered to be inappropriate due to concerns about contraction-induced muscle fiber injury[26]. It is therefore important to investigate the kind of physical activity that might be suitable and feasible for patients with DMD. The present study does not show any increases in bone or muscle

parameters that could be convincingly related to the WBV, nor were any significant decreases in these parameters noted during the study period of 12 months.

Biochemical markers of bone and mineral metabolism can be useful for evaluating bone resorption and formation in specific conditions. Turner et al.[10] noted a significant reduction in the bone resorption marker, NTX, after two months of WBV in postmenopausal women. In the present study, there was no change in bone resorption measured by CTX, but there was a numerical increase in the formation marker, BALP, after three months of WBV. Even if this change did not reach statistical significance, it may indicate an increase in bone formation during WBV. Sclerostin is a novel regulatory marker of bone remodeling produced almost exclusively by osteocytes. The precise physiologic role of sclerostin is not yet fully understood, but several studies indicate that sclerostin expression decreases in the presence of mechanical loading leading to enhanced osteogenesis[27]. In the present study, no significant changes in sclerostin were, however, observed and all the patients were within the reported reference interval for healthy children[28]. All in all, no major findings were observed in the investigated bone markers in the present study, which may suggest that the remodeling cycle was not disrupted during the nine-month follow-up period, i.e. longer than a normal remodeling cycle, and there was therefore no negative effect at cellular level.

The present study does not demonstrate that WBV therapy increases or preserves bone mass or bone strength in patients with DMD. There are several reasons for this, such as the small study group, too low vibration frequency or too short duration, or the fact that WBV might not influence bone. The fact that no matched controls were used is also a limitation. It is therefore difficult to draw any major conclusions from this small observational study. However, with the CK activity at a stable level throughout the study period, there are no indications of muscle damage due to the WBV performed in this study. The vibration treatment appears to be a safe, well-tolerated treatment in patients with DMD, but the effect on bone and muscle remains to be further elucidated.

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