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Response of bone to whole body vibration in children with acute lymphoblastic leukemia

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Abstract : Objectives: The objective of this study was to evaluate the effect of whole body vibration (WBV) on bone mineral density (BMD) in children with acute lymphoblastic leukemia. **Methods**: Forty children with acute lymphoblastic leukemia in the maintenance phase participated in this study with age range 10 to 14 years. They were randomly allocated into either study or control groups, study group received WBV training for 20 weeks, 5 times/week, every session composed of 10 repetitions (30-60 sec) and 1 min rest, peak to peak displacement 2mm and frequency of 30 HZ plus traditional physiotherapy program. Control group received the traditional physiotherapy program only. The outcome measure was BMD, which was assessed by dual-energy X ray absorptiometry. **Result**: Children in WBV group showed a significant increase in BMD of L1-L4 and proximal femur compared with that of the control group post treatment ($p > 0.05$). Both groups showed a significant increase in BMD post treatment compared with that of the pre-treatment ($p > 0.001$). **Conclusion**: Adding WBV to the treatment program is an effective modality in improving BMD in children with ALL.

Keywords : Acute Lymphoblastic Leukemia, Whole Body Vibration, Bone Mineral Density, Osteoporosis.

Introduction

Due to high rates of survival among children with acute lymphoblastic leukemia (ALL), the short-term repercussions and long-term consequences from the tumor itself or the antineoplastic drugs are being considered [1,2].

Disease consequences may include neuro-muscular and musculoskeletal intricacies that involve pain, weaker deep tendon reflexes, diminished sensation, muscle spasms, decreased muscle strength, retarded fine and gross motor performance, less energy expenditure, limitations of ankle dorsiflexion ROM, learning inabilities, osteopenia, avascular necrosis and decreased bone density [3,4].

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Children managed for ALL, the most well-known pediatric tumor, are more prone to bone mineral density (BMD) deficits that may continue to adulthood. The main cause of that may include the malignancy itself, sex hormone and/or growth hormone (GH) deficiency, radiation, chemotherapy, low vitamin D and calcium intake, and physical activity reduction [5,6].

Aggregation of bone minerals during childhood is a vital factor that determines the risk of developing osteoporosis later in life [7]. The decrease in estimated balance of bone mineral content (BMC) during childhood is one of the main causes that can lead to fractures [8]. Physical activity and mechanical loading are considered as the best non-pharmacological methods to improve general health and specifically bone size and density[9].

Whole body vibration (WBV) is considered as a weight bearing exercise, that provides low magnitude, and high- frequency mechanical stimuli. WBV is produced by standing on an oscillating platform that generates sinusoidal vertical vibrations which transmit the force to the body, thus provoking reflexive muscle contraction and loads the bone [10].

WBV has been examined as a procedure to stimulate calcium deposition in bones [11]. It showed good results in improving bone size and strength in many experimental trails carried on normal children [12], children with crippling conditions such as C.P [13], young ladies with decreased bone mass and ladies with post-menopausal osteoporosis. WBV has likewise revealed an increase in bone density at the spine, tibia, femur, and forearm [14].

There is little data on the impact of WBV on bone density of children affected by acute lymphoblastic leukemia. This study is carried out on children with acute lymphoblastic leukemia to investigate the effect of Whole body vibration as an alternative and safe technique to enhance the strength of bones and as a treatment for osteoporosis or osteopenia for these patients.

Materials and Methods

Design of the study

This is a randomized controlled trial. The study was ethically approved by the ethics committee of the university.Informed consent was obtained from all parents. The patients were randomly allocated into the study or the control group.

Subjects:

Forty survivor children with acute lymphoblastic leukemia in the maintenance phase of treatment, their ages ranged from 10: 14 years, were recruited from king Khalid hospital, Najran, Saudi Arabia. The participants enrolled had an initial BMD below the mean for sex- and age-matched controls and were eligible for participation and randomization in the intervention trial. They were able to stand and walk normally and to tolerate vitamin D and calcium supplements.

The exclusion criteria included any contraindications for WBV as instable bone metastases, acute leg thrombosis, a fracture in the lower extremities in the past 2 years, foot ulcers, artificial hips or other osteosynthesis, myocardial infarction, angina pectoris or heart disease within the past six months. Also, Children requiring chronic glucocorticoid therapy, or pharmacologic agents for reduced BMD other than calcium or vitamin D, and children with metal implants or spinal deformity that requires bracing were excluded. Therefore, the participants were assessed clinically prior to randomization.

Randomization

The randomization process was performed using closed envelopes. The investigator prepared 40 closed envelopes with each envelope containing a card labeled with either study or control group. Finally, each patient was asked to draw a closed envelope that contains whether they were allocated to group A or group B. The patients were randomly allocated to either study group (n = 20) or control group (n = 20).

Intervention

Study group received the treatment for 20 weeks with a protocol that consists of traditional physical therapy for the children (stretching, aerobic , and strengthening exercise) in addition to WBV on a vibration platform (Fitvibe medical pro, Uniphy®, Germany). The protocol included 5 sessions/week, every session composed of 10 repetitions (30-60 s) and 1-min rest, peak-to-peak displacement of 2 mm (peak acceleration 2.5-3.6 g) and frequency 30 Hz. During all sessions, participants wore similar cotton socks only, to standardize the possible dampening effects of different footwear. The exercises performed were standard squats (knee angle 90-130°) while applying the vibration protocol. The participants were carefully monitored for pain, numbness, discomfort, redness, itching, or muscle soreness, and the session was discontinued if any of these symptoms were present.

The control group received the same protocol of the traditional physical therapy intervention as the study group. They also received sham WBV by standing on the vibration platform device with the device being turned off.

Both groups received calcium and vitamin D supplements as recommended by the Children's Oncology Group [15].

Measurement

The bone mineral density of the femoral neck and lumbar spine were measured at two time points; pre- and post-intervention (20 weeks post treatment) using dual-energy x-ray absorptiometry (DXA), which is used to assess the mineral content of the bone while keeping radiation exposure to a minimum [16], and scanned with the QDR-Explorer software, pediatric version (Hologic Corp. Software version 12.4, Bedford, MA 01730). Daily calibration of DXA equipment was performed with a lumbar spine phantom and step densities phantom following the Hologic guidelines. The assessments in pre- and post-training moments were performed by the same technician who had been fully trained on the operation of the scanner, the positioning of subjects, and the analysis of results, according to the manufacturer's guidelines.

Statistical analysis

T test was conducted for comparing subject characteristics between both groups. Mixed MANOVA was conducted for comparing BMD pre and post treatment conditions in each group and between groups. Post-hoc tests using the Bonferroni correction were carried out for subsequent multiple comparison. The level of significance for all statistical tests was set at $p < 0.05$. All statistical analysis were conducted through the statistical package for social studies (SPSS) version 19 for windows (IBM SPSS, Chicago, IL, USA).

Results

Subject characteristics:

Table 1, showed the mean ± SD age, weight, and height of study and control groups. There was no significant difference between both groups in the mean age, weight, and height ($p > 0.05$).

Table (1): Mean age, weight, and height of study and control groups:

	$\bar{x}$**±SD**			
	Study group	**Control group**	**t- value**	**p-value**
Age (years)	11.46 ± 1.24	12.06 ± 1.38	-1.24	0.22*
Weight (kg)	28.4 ± 3.39	29 ± 2.13	-0.57	0.56*
Height (cm)	132.33 ± 2.05	131.93 ± 2.65	0.46	0.64*

$\bar{x}$**, Mean; SD, standard deviation; p-value, level of significance; * Non significant.**

Effect of treatment on BMD:

Mixed MANOVA showed a significant interaction of time x group (*F = 16.9, p = 0.0001*), a non significant group effect (*F = 0.7, p = 0.5*), and a significant time effect (*F = 68.32, p = 0.0001*).

Between group comparison:

There was no significant difference between the study group and control group in BMD pre-treatment ($p > 0.05$). Comparison between study group and control group post treatment revealed a significant increase in BMD of L1-L4 and proximal femur in the study group compared with that of the control group ($p < 0.05$). (table 2, figure 1).

Within group comparison:

There was a significant increase in BMD of L1-L4 and proximal femur of the study and control group post-treatment compared with pre-treatment ($p < 0.01$). (table 2, figure1).

Table (2): Mean BMD of L1-L4 and proximal femur pre and post treatment in study and control groups.

	Study group			Control group			Between groups	
	Pre	Post		Pre	Post		Pre	Post
BMD (g/cm²)	x̄±SD	x̄±SD	P value	x̄±SD	x̄±SD	P value	P value	P value
L1-L4	0.58 ± 0.17	0.85 ± 0.1	0.0001**	0.61 ± 0.07	0.72 ± 0.16	0.003**	0.51*	0.02**
Proximal femur	0.57 ± 0.1	0.75 ± 0.11	0.0001**	0.59 ± 0.09	0.64 ± 0.12	0.006**	0.64*	0.01**

x̄, Mean; SD, standard deviation; p-value, level of significance; * Non significant; ** Significant

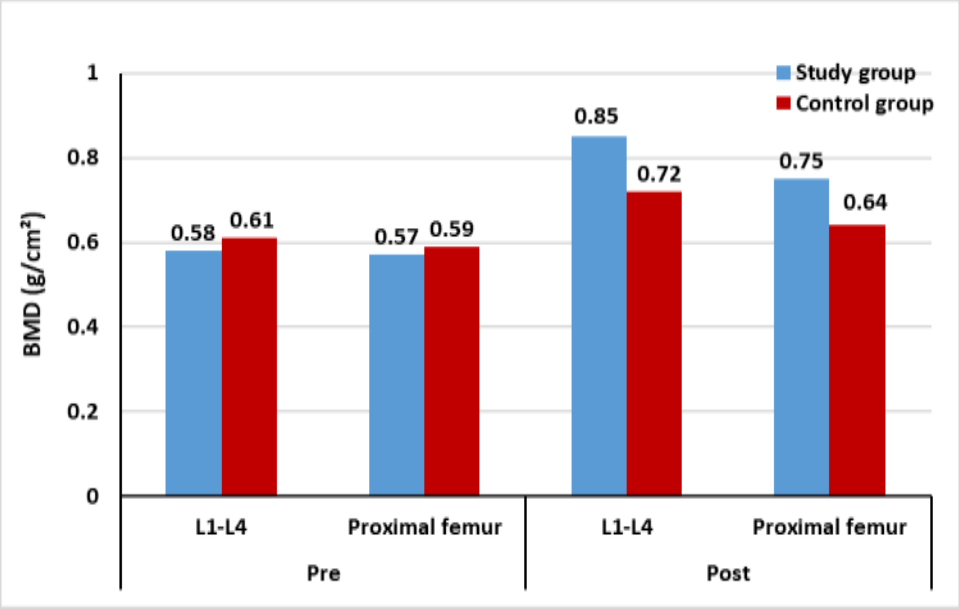

Figure (1). Mean BMD of L1-L4 and proximal femur pre and post treatment in study and control groups

Discussion

The 5-year incidence of musculoskeletal complications through or after the treatment of ALL is 32.7% and the relative risk of fractures, according to age and gender, is 2.03 compared to the reference data of the general Practice Research Database of the United Kingdom. Childhood cancer survivors are highly vulnerable to musculoskeletal complications as they are affected at the period of achievement of peak bone density [17]

The earlier the therapy for bone loss, the greater the benefits for the children, as the peak bone density is acquired during teenage years and present a basis for bone strength, quality and integrity later on in life [18, 19].

It is known that mechanical stimulation helps bone tissue to remain healthy [20]. Along with the force of gravity, muscular power and ground stress reaction forces, which are the main forces that are empowered daily via the human skeleton, and so, share in bone building and re-building. This subsequently leads to an increase in bone mass combined with an increase in physical activity [21].

The impact of WBV on bone tissue metabolism was previously investigated in children with physical health problems involving D.M, idiopathic osteoporosis, C.P, or muscular atrophy [22, 23]. Post therapy outcomes for those two studies reported a significant increase in trabecular (2.1%; 6.2%) and cortical (3.4%; 2.1%) BMD in contrast to control groups when utilizing a mechanical vibratory stimulus.

Abercromby and colleagues [23, 24] investigated the transmission of WBV through the skeleton utilizing two vibration platforms: the main one was the perpendicular vibration equipment similar to the one utilized in our study while the other was the rotational vibration equipment. Upon utilizing an accelerometer connected to a bite bar, they demonstrated that an effective amount of vibration was passed from the plate to the head. More transmission was confirmed to pass through the skeleton by utilizing the main perpendicular vibration machine than the rotational one. With time, the passage of mechanical power from WBV can be beneficial.

The results of this study showed that training for 20-weeks with whole body vibration plus conventional treatment improved the BMD in children with ALL in comparison with conventional treatment only.

The results of this study are supported by previous studies that showed the anabolic effect of WBV on BMD in children with compromised bone such as Down syndrome, idiopathic scoliosis, children with thermal injury, and cerebral palsy. Slatkosvka et al., [25] in their meta-analysis concluded that WBV could be effective in children and adolescents with compromised bone. Dalen et al., [26] showed that WBV increased bone mineral content in both legs and the lumbar spine in children with cerebral palsy. Edionwe et al., [27] concluded that the use of WBV in combination with exercise may help decrease regional bone loss in children recovering from burns than the use of exercise alone. Matute-Llorente et al., [28] concluded that a 20-week WBV might be useful to improve subtotal bone mineral content and density in adolescents with down syndrome.

There are many probable explanations for the experimental outcomes that State that whole body vibration has a positive effect on bone building, and different fluid composition intermixed within the intratrabecular space in bone. Bone marrow is the main fluid component, but blood, lymph cells, and interstitial fluid also exist in different quantities. Dynamic loading causes fluid flow in the bone's structural network, which creates shear forces on the plasma membranes of existing osteocytes, osteoblasts, and bone lining cells. Bone tissues are highly affected by fluid shear forces [29- 31].

Increased bone density following mechanical input can be explained as an adaptation response of skeletal system to the amount of physical activity exerted [29, 32]. Frost [33] reported that the mechanical input must produce a heavy stress in order to affect bone morphology. Osteogenic impact of vibration therapy is proven, although, the mechanism underlying it have not been fully explained yet. It is proposed that the vibrations trigger micro injury in the bone which is repaired by the osteoblasts. [34].

WBV input also influences bone rebuilding in an indirect way via the response of the endocrine system. As reported in some preceding participated in this study. The beneficial effects of testosterone on bone density were observed in the lumbar spine, hips and forearm in healthy males and females [36, 37].

The bone's response to WBV might be the result of a direct reaction inside the bone tissue itself to pressure force or via muscle; either by contractions which stress the bone or because of more muscle mass and/ or force exerting stresses on the bone. Increased muscle activity and blood flow as a result of WBV has been stated in many researches [38, 39].

The mechanism by which WBV treatment works can be indicated by changes that take place in blood flow. There is a positive relationship between blood flow and muscle oxygenation. During physical activities, blood flow increases to the muscles to cope with the elevated demand for oxygen and to remove accumulated carbon dioxide and hydrogen ions. By Utilizing near-infrared spectroscopy (NIRS), several studies [30, 41] reported that WBV could stimulate peripheral blood circulation. Energy can be decreased by ischemia as oxygen acts as the final electron receptive in the electron transport chain.

The design of WBV protocol used in this study was based upon the recommendations of the previous studies which showed improvement in BMD using the following parameters : 10-20 minutes at least three times per week, for a minimum of 20 weeks, with low amplitude (less than or 4 mm of peak-to-peak displacement) and high frequency (15 : 35 Hz) [42].

The vibration might cause some side effects like low back pain, hearing loss, white finger diseases, and blurred vision [43] . Therefore the measures of exposure to vibration with high-magnitude emphasize on use with caution, especially to those with a high risk of fracture [44]. According to the standards for human exposure to vibration of International Organization for Standards (ISO)-2631 the intensity and frequency used in this study is safe up to 4 hours per day [45]. In addition to animal models of cancer, vibration didn't exacerbate the disease or compromise survival. This suggests that mechanical vibration doesn't result in malignant disease progression [46]. Finally, during this study, no adverse effects associated with WBV were observed.

The limited number of participating children is a limitation in this study. Previously reported WBV studies in children do not, however, comprise large study groups.

In conclusion, WBV therapy for low BMD during maintenance phase in children with ALL appears to be safe and effective. Further studies on a larger population are needed to evaluate the long-term outcomes and safety.

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