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Bone Mineral Density, Lean Body Mass and Bone Biomarkers Following Physical Exercise in Children with Acute Lymphoblastic Leukemia Undergoing Chemotherapy

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ABSTRACT

Background: This study was aimed to evaluate the effects of physical exercise on bone mineral density (BMD), lean body mass (LBM) and bone biomarkers in children with acute lymphoblastic leukemia on chemotherapy.
Methods: forty-six leukemic children were randomly assigned to two groups; exercise group (E) undergoing supervised mixed exercise program consisting of aerobic, resistance and flexibility training and control group (C) who did not receive any kind of exercise. BMD and LBM were measured by Densitometry (DEXA) and bone biomarkers were assessed through blood sample analysis at baseline, and then 6 and 12 months later.
Results: There was marked increase in BMD, LBM and bone biomarkers in response to exercise with the time compared with control group ($P<0.001$). At the end of the study, the results of the study showed that the percentage of patients with normal lumbar BMD (LBMD) and total BMD (TBMD) in exercise group were 13% and 17.4%, respectively compared to 0% in control group. In addition, the percentage of osteoporotic patients at LBMD & TBMD in exercise group were 21.7% and 17.4%, respectively compared to 78.3% and 52.18% in control group, respectively ($P<0.05$).
Conclusion: It can be concluded that physical exercise could be effective in increasing BMD, LBM and bone biomarkers in children with ALL.

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Introduction

Leukemia is a malignant disease affecting bone marrow in which normal marrow hematopoietic cells is replaced by lymphoblasts.[1] Acute Lymphoblastic Leukemia (ALL) is the most common type of leukemia in childhood accounting for 25% of all childhood cancers.[2, 3] Survival rate of pediatric ALL has improved dramatically in the last 40 years.[4, 5]

Leukemic children are liable to have lower BMD due to either the disease itself or chemotherapeutic agents. Chemotherapeutic agents have thought to negatively impact osteoblastic activity and cause bone mineral loss, in addition to impairment on renal and parathyroid function, growth hormone axis and type I and II collagen degradation.[6-13] These factors all contribute to deterioration of BMD in children with ALL.[14, 15] Various studies have reported that up to 30% of children with ALL have decreased BMD at diagnosis and 15–29% of ALL survivors have diminished BMD following chemotherapy.[16-18]

Children with ALL exhibit lack of energy, some degrees of fatigue, decrease functional mobility, weakness in lower extremities and muscle strength and decreased range of motion of different joints within the first year after the diagnosis.[5, 19] Low level of physical activity is particularly an additional detrimental factor for reduced

BMD in children with ALL. Published literature lacks clinical studies addressing the effects of physical exercise on BMD in pediatric leukemia patients.[20] Therefore, we hypothesized that physical exercise might attenuate bone loss, improve BMD and LBM and affect bone biomarkers in pediatric patients with ALL undergoing chemotherapy.

Materials and Methods

This randomized controlled trial recruited ALL children from King Khalid hospital in Majmaah city, KSA. The Declaration of Helsinki principles were followed in this research. The study protocol was submitted to the Institutional Review Board of the Basic & Health Science Research Center at Majmaah University and ethical approval was obtained under the number MUREC-64/52362/12/1437. An informed written consent form was provided to parents or guardians before entering the study.

Inclusion Criteria included: Children with ALL with age range from 6-14 years while receiving maintenance phase of chemotherapy, no need for physical assistance in the patients, absence of any medical disability such as acute thrombosis, active ischemia, hemodynamic instability, uncontrolled pain and absence of cognitive impairment. Exclusion criteria included: cranial irradiation, any other comorbidities or treatments associated with altered bone metabolism, growth hormone deficiency and adrenal insufficiency.

The sample size was estimated using a software program, [G-power (version 3.0.10)]. To avoid a type II error, study researchers aimed to recruit 68 participants, giving 90 % power at α=0.05 and effect size of 0.8. To select the samples, medical records were reviewed and physical examination was performed to assess patients who were eligible for the study. After screening potentially eligible patients, a registration officer was instructed to randomly assign the patients to either the exercise group or the control group. Randomization involved opening an opaque envelope prepared with random number generation using excel to generate the allocation sequence by registration officer who was not involved in any part of the study.

Measurements of Height, Weight and BMI

Height and weight were measured for each child by height and weight scales, respectively. Body mass index (BMI) was calculated using the standard formula: mass (kg)/height^2 (m).

Bone Biomarkers to Assess Bone Metabolism

Fasting blood samples were obtained in the morning on the same day as BMD measurements. For all patients, bone biomarkers including levels of calcium (Ca), phosphorus (P), parathyroid hormone (PTH) and alkaline phosphatase (ALP) were measured at baseline, six months and 12 months for all patients.

Assessment of BMD and LBM

All children were assessed for BMD and LBM by Dual Energy X-ray Absorptiometry (DEXA) (DXA, Lunar DPXL/PED, Madison, Wisconsin, U.S.A.). DEXA is the most commonly used method for assessing BMD and LBM in children which takes age, height, weight and sexual maturity rating into consideration. DEXA is composed of a central apparatus with a padded platform and X-ray generator used to emit low dose x-ray on the area required to be measured with adjustment of the mechanical arm (scanner). Lumbar spine (L2-L4) and total body BMD were measured. It demonstrates high accuracy, low irradiation dosage and fast scanning time. In our study, in order to detect the efficiency of exercise, BMD measures were performed at baseline and repeated within six and 12 months. World Health Organization defines osteopenia as Z-score between -1 and -2.5 and osteoporosis as Z-score equal or less than -2.5. Z-Score equal or greater than -1 was considered as normal BMD.[21, 22]

Intervention

Exercise Group

Each patient in exercise group received an individualized, supervised, mixed-modality exercise program. Each patient underwent two sessions per week for six months and one session per week for another six months. The intensity of exercise was light to moderate intensity. The exercise training was preceded by five minutes of warm-up exercise involving light stretch or walking back and forth inside the room. Each exercise session included three types of exercises; 1) aerobic exercise such as walking or stationary cycling, 2) resistance training using resistance bands, 3) flexibility training such as static stretching. Duration of each session was ranged between 30-45 minutes.

The aims and procedures of the exercises were illustrated to each child before starting exercise session. Intensity of aerobic exercise was determined using the rating of perceived exertion (RPE) scale.[23] Children were instructed to exercise at 3-6 out of ten at RPE.[24] It is concentrated on large muscle groups while performing resistance and flexibility training. Before each session researcher ensured that there were no contraindications to exercise and discussed current status with the physician. Necessary written instructions and tools such as resistance bands for prescribed exercises were given to each child. Shared tools and equipment were cleaned after each use to ensure proper infection control. Progression of exercise for each patient depended on patient tolerance. Each patient in control group was advised to be active as possible as. No exercise equipment, nor formal instructions were provided.

Statistical Analysis

Statistical analysis was carried out using SPSS (v22.0; IBM software cooperation group). Continuous variables were summarized as mean ± standard deviation (SD) and categorical variables as frequency and percentage (%). Shapiro–Wilk test was used to detect a normal distribution of data. Repeated Measures ANOVA test was used to compare changes within groups at baseline, six months and 12 months for normally distributed variables. Independent T-test was used to compare parametric variables with normally distributed between both groups

and Mann-Whitney test used for parameters with a skewed distribution. P≤0.05 was considered statistically significant.

Results

Figure 1 illustrated participating patients and dropout through the study. Data of forty-six (23 patients in exercise group and 23 in control group) subjects were available for final analysis. Our findings were classified as follows: Demographic data, bone biomarkers, and densitometry results including quantitative lumbar spine (LBMD) and total body (TBMD), body composition measurements (Lean body mass and percentage of body fat) and qualitative results of BMD based on WHO definition. There were no differences between demographics of the children composing the exercise group and the control group. These results showed that both groups had similar characteristics regarding age, sex, height, weight and BMI (P>0.05) (Table 1).

Bone Biomarkers Assessment

There was no significant difference in bone biomarkers at baseline between two groups (P>0.05). However, a significant increase in bone biomarkers among patients in exercise group at six months and 12 months compared with baseline was observed. In comparing both groups, there was no significant difference at the baseline P>0.05 while there were highly significant differences at six months and one-year, P<0.001 (Table 2).

Densitometry Measurements

Quantitative Densitometry Measurements

There were significant improvements in LBMD and TBMD among patients in exercise group at six months and 12 months compared with baseline. Again, in comparing both groups, there was no significant difference at the baseline between two groups in terms of bone markers

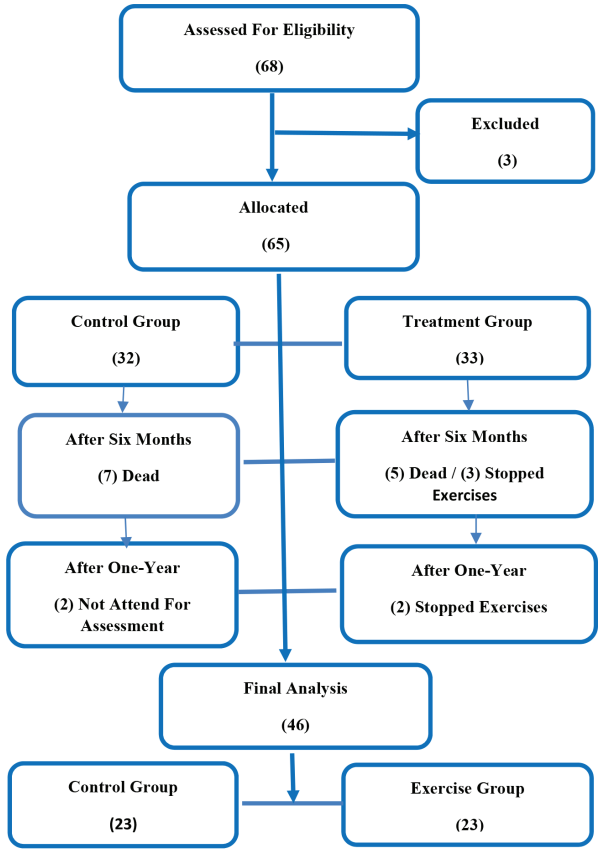

Figure 1: Flow diagram illustrating participating patients and dropout

Table 1: Demographic characteristics of the patients

	Exercise group (23)	Control group (23)	P value
Age (Year)	9.26±2.39	9.91±2.09	0.330*
Height (cm)	124.13±11.95	129.30±10.8	0.130*
Weight (Kg)	28.52±7.39	32.26±6.57	0.077*
BMI (Kg /m^2)	18.15±1.79	19.12±1.56	0.067*
Gender N (%)			
Female	8(65.2%)	5 (21.7%)	0.331*
Male	15 (34.8%)	18 (78.3%)	

Data are mean±SD; * No significant difference

Table 2: Bone biomarkers measurements

Variable	Baseline		Six months		12 months	
	Group E	Group C	Group E	Group C	Group E	Group C
Ca (mg/dL)	8.57±0.40	4.48±0.25	9.37±0.354†	8.55±0.26*	9.55±0.344†	8.58±0.35*
	0.400*		0.001†		0.001†	
PTH (ng/l(	24.38±4.17	23.55±3.15	29.65±4.60†	23.88±3.12*	35.83±3.64†	23.98±3.21*
	0.452*		0.001†		0.001†	
ALP (U/l)	146.52±10.21	148.61±8.20	164.61±9.60†	149.22±6.55*	178.17±10.58†	149.57±6.05*
	0.449*		0.001†		0.001†	
P (mg/dL)	3.42±0.28	3.51±0.3	4.03±0.35†	3.57±0.22*	4.42±0.26†	3.65±0.18*
	0.324*		0.001†		0.001†	

Data are mean±SD; E: exercise, C: control, PTH: parathyroid hormone, ALP: Alkaline phosphate; *No significant difference; † highly significant difference

Table 3: Quantitative BMD measurements

Variable	Baseline		Six months		12 months	
	Group E	Group C	Group E	Group C	Group E	Group C
LBMD (g/cm^2)	0.727±0.059	0.712±0.050	0.778±0.035†	0.716±0.040*	0.808±0.058†	0.724±0.032*
	0.335*		0.001†		0.001†	
TBMD (g/cm^2)	0.811±0.072	0.814±0.071	0.842±0.076†	0.805±0.056*	0.869±0.069†	0.797±0.055*
	0.898*		0.027†		0.001†	

Data are mean ± SD, LBMD: Lumbar bone mineral density, TBMD: Total body bone mineral density. *No significant difference; † highly significant difference

while there were highly significant differences at six months and 12 months, P<0.001 (Table 3).

Body Composition Measurements

There was significant improvement in LBM in exercise group at six months and 12 months compared with baseline. F (1.2, 26.32) =70.15, P<0.001, while there was no improvement in LBM in control group at six months and 12 months compared with baseline. F (1.02, 22.54) =2.38, P<0.136. The results of the study also showed positive correlation between BMD and LBM (P<0.05). Body fat decreased significantly with time from baseline to 12 months in exercise group, while in control group the percentage of body fat was increased with time from baseline to 12 months, P=0.021 and P=0.043, respectively (Table 4).

Qualitative Densitometry Measurements Based on WHO Definition

BMD at lumbar spine (LBMD) was measured and compared between exercise and control groups. At the beginning of the study, the Mann-Whitney test showed that 20 (87%) and 3 (13%) patients in exercise group had osteoporosis and osteopenia compared to 19 (82.6%) and 4 (17.4%) subjects in control group, respectively (P=0.685). At the end of study, three (13%) patients had normal BMD and 20 patients (87%) had a reduction in BMD of whom 5 (21.7 %) had osteoporosis. In control group, none of the patients had normal BMD, 23 (100%) had a reduction in BMD, of whom 21 (78.3%) had osteoporosis (Figure 2) (P=0.028).

TBMD at the beginning of the study showed that 19 (82.6%) and 4 (17.4%) patients in exercise group had osteoporosis and osteopenia compared to control group, 18 (78.3%) and 5 (21.7%) subjects had osteoporosis and osteopenia, respectively (P=0.713). At the end of study, in exercise group; four (17.4%) patients had normal TBMD, 19 patients (82.6%) had a reduction in TBMD, of whom 4 (17.4%) had osteoporosis. In control group, none of the

Table 4: Body composition (Lean body mass and percentage of fat measurements)

Variable	Baseline		Six months		12 months	
	Group E	Group C	Group E	Group C	Group E	Group C
LBM	16346±404.14	16587±524.41	17069±531.49†	16683±464.36*	18726±1102.55†	16686±457.81*
(g)	0.087*		0.012†		0.001†	
PBF %	17.90 (17.70, 18.70)	17.50 (16.80, 18.70)	17.50 (16.80,18,00)	18.70 (17.50, 19.80)	16.00 (14.90,16.80)	19.20 (18.50, 20.30)
	0.235*		0.001†		0.001†	

E: Exercise, C: Control, LBM: lean body mass (Data are expressed as mean ± SD), PBF: percentage of body fat (Values of PBF are expressed as median (25th; 75th percentiles)

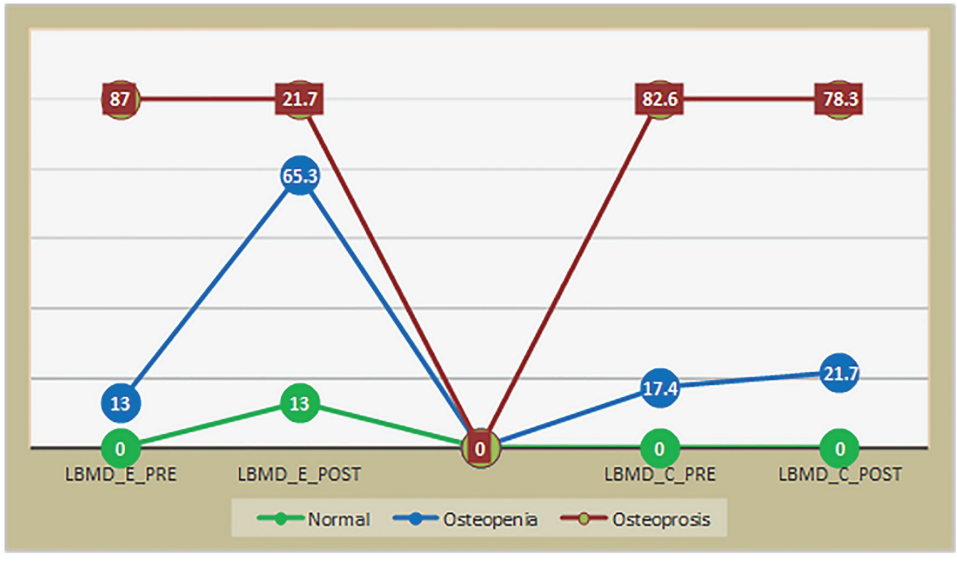

Figure 2: LBMD in both groups according to WHO classification at the beginning and end of the study

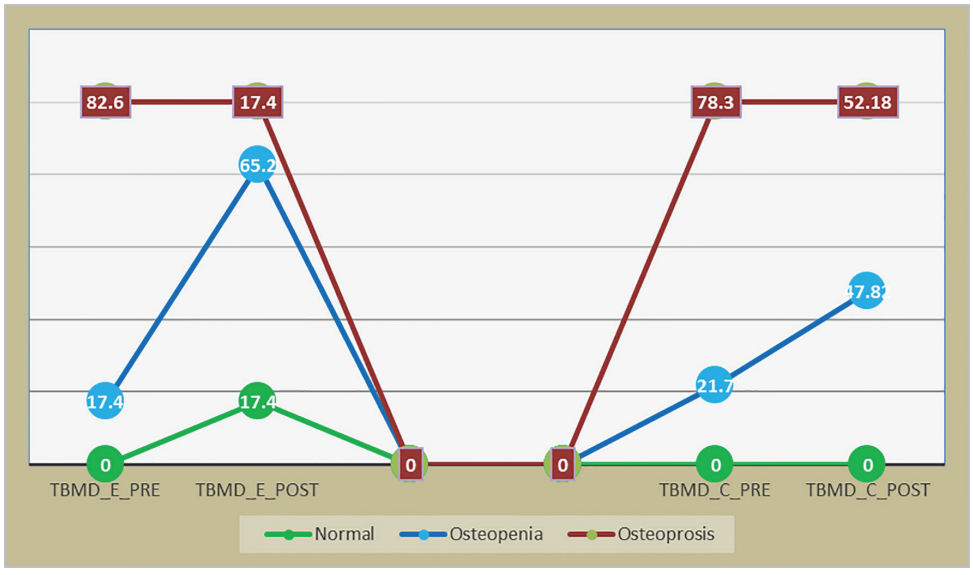

Figure 3: TBMD in both groups according to WHO classification at the beginning and end of the study

patients had normal TBMD at the end of the study, 23 (100%) had a reduction in TBMD, of whom 12 (52.18%) had osteoporosis (Figure 3) (P=0.004).

Discussion

Childhood cancer treatment is a potential etiologic factor for low BMD among children who survive. Risk factors which cause a long term decline in bone density include cancer itself, chemotherapy, poor nutrition, decreased exposure to sunlight and low levels of physical activity during treatment.[11, 25] Children with ALL are less physically active compared with healthy peers. Lower activity is proved to correlate with lower lumbar BMD.[26] The current study was designed to investigate the response of BMD, body composition and bone biomarkers to physical exercise in ALL children undergoing maintenance phase of chemotherapy.

The results of the study showed that there was a significant improvement in bone biomarkers (Ca, PTH, ALP, P) among patients in exercise group at six months and 12 months compared with baseline (P<0.001), while no improvement was observed in control group at six months and 12 months compared with baseline (P>0.05). Physical activity had substantial effects on bone turnover. Results of our study are in agreement with the findings of previous studies which suggested that physical exercise could lead to a favorable response in overall bone turnover and increase bone formation biomarkers.[27-31]

There are also studies which have reported that bone resorption was stimulated and bone formation was decreased following physical exercise, however; in those studies other kinds of exercises such as endurance exercise, anaerobic training, brisk treadmill walking were employed.[32-34] Therefore, the impact of physical exercise on bone markers vary depending on the kind, intensity and frequency of the exercise and timing of the biomarker measurement.

The results obtained from this study also revealed that BMD (LBMD, TBMD) was increased significantly in six months and 12 months compared with baseline in exercise group (P<0.001); however no improvement was observed in control group in this period compared with baseline (P>0.05). This can be referred to the increase of bone mineral content by the effect of physical exercise. Exercise increases mechanical load exerted on bone (muscle pull) which stimulates osteogenesis.[35] According to Wolff's law, application of external forces (or muscle pull) repeatedly or over time causes osteoblast activity to increase, and as a result, bone mass increase. Without these forces, osteoclast activity predominates and bone mass decreases. Resistance exercise and aerobic training provide stress on bone that in turn results in increasing bone strength and BMD.

Our results revealed significant increase in LBM and decrease in percentage of body fat mass in exercise group compared to control group. We found that BMD was correlated with LBM (P<0.05). Exercise-induced weight loss, particular loss in fat mass, had no significant association with the changes in BMD (P>0.05). Meanwhile, the effects of LBM on bone was a strong positive effect on BMD.[36] As such, it is essential to maintain appropriate body weight and increase LBM by physical exercise.

Conclusion

It can be concluded that physical exercise including resistance and aerobic exercise are mechanical stimulators of bone formation, hence effective in increasing BMD and LBM in children with ALL.

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Conflict of Interest:

The authors deny any financial or personal relationships with other people or organizations that could inappropriately influence (bias) their work.

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