Original Article

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Prevalence of Low Bone Mass for Chronological Age in Children with Acute Leukemia in Southern Iran

Mohammad Reza Bordbar MD[1], Sezaneh Haghpanah MD [1], Forough Saki MD [2,*]

1. Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
2. Shiraz Endocrinology and Metabolism Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
*Corresponding author: Dr. Forough Saki, Shiraz Endocrinology and Metabolism Research Center, Shiraz University of Medical Sciences, Shiraz, Iran. E-mail: forughs@yahoo.com.

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Abstract

Background: Total bone mass acquired during childhood is known to be the most important determinant and base of lifelong skeletal health. The present study investigated the prevalence of low bone mass for chronological age (LBM) in lumbar and femoral areas of leukemic children in the south of Iran and evaluated the association of anthropometric, clinical and laboratory data of these children with low bone mass.

Materials and Methods: This cross sectional study was conducted on 106 patients with proven diagnosis of acute leukemia who aged 4-18 years old. Anthropometric data, physical activity, sun exposure, pubertal stage and mineral biochemical parameters were assessed. Bone mineral density was measured by Dual-energy X-ray absorptiometry. The data were analyzed using SPSS (version21).

Results: The prevalence of low bone mass for chronological age in leukemic children of southern Iran was 28.3% and 27% in lumbar and femoral regions, respectively and it was not sex dependent. This prevalence was associated with duration of disease, serum calcium, serum level of vitamin D, Body mass index (BMI), and radiotherapy. Among these factors, serum calcium had independent predictive effects.

Conclusion: The present investigation revealed high prevalence of low bone mass in Iranian leukemic children. The most important associated factors with bone mineral density were radiotherapy, BMI, duration of illness, and serum calcium level. Further studies are recommended on bone mineral density in leukemic children, especially in Asian countries, with attention to patients' fractures to find out the important risk factors for future osteoporosis.

Key words: Children, Leukemia. Low bone mass, Iran

Introduction

Total bone mass acquired during childhood is known to be the most important determinant and base of lifelong skeletal health (1). Acute leukemia consisting of acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) is the most common childhood malignancy, accounting for about 30% of all childhood cancers (2, 3). Dramatic improvements in treatment and cure rate of these patients over the last two decades (4, 5) have produced a large group of leukemia survivors who are at risk of long term complications related to cancer therapy (6).Poor bone acquisition and low bone mineral density (BMD) are important potential sequels in these children (7-15). Numerous factors might contribute to decrease of bone mass in leukemic children, including the underlying disease (16), malnutrition (17), reduced muscle strength (18), lower physical activity (19), chemotherapy (20), radiotherapy (21), and endocrinopathies (22). Nowadays, Dual-energy X-ray absorptiometry (DXA) is the most widely used technique to evaluate BMD in children (23).Some studies have investigated the BMD of leukemic children in the United Kingdom (14), the United States (7-10,15,26), Korea (11), Poland (24) and the Netherlands (13, 25). However, there is lack of relevant data in the Middle East, especially about the prevalence of low bone mass and its associated factors in leukemic children.

The present study investigated the prevalence of low bone mass for chronological age (LBM) in lumbar and femoral areas of leukemic children in south of Iran and evaluated the association of anthropometric, clinical, and laboratory data of these children with low bone mass.

Materials and Methods

This study was conducted in a 12-month period during 2015-2016 in a tertiary clinic for care of pediatric oncology patients affiliated to Shiraz University of Medical Sciences in Shiraz, in south of Iran. All patients with proven diagnosis of acute leukemia based on the results of bone marrow aspiration exam and flowcytometry who were on the maintenance phase of their chemotherapy were included. Patients younger than 3 years, and those with preexisting metabolic disorder, endocrine, and renal dysfunctions were excluded. Chemotherapy protocol in the maintenance phase of treatment in ALL patients consisted of monthly injection of Vincristine, oral prednisolone 40 mg/m2 or dexamethasone 6mg/m2 for 5 consecutive days every month, oral 6-mercaptopurine nightly, and oral methotrexate weekly. The patients should pass this phase of treatment for at least 6 months. Additionally, those patients with central nervous system involvement by leukemic cells as well as T-cell ALL patients were given craniospinal irradiation as a therapeutic or prophylactic indication, respectively. Given the inclusion and exclusion criteria, 106 patients with the age range of 4-18 years old were included.

Anthropometric data, pubertal stage, physical activity, and sun exposure

Weight, height, and pubertal stage of children were evaluated by a trained physician. Patients's height was measured while they were standing without shoes, with a standard wall-mounted meter, and rounded to the nearest 0.5 cm. Weight was measured while the patient wore a light cloth and no shoes, with a standard scale (Seca, Germany) and rounded to the nearest 0.1 kg.

Body mass index (BMI) was calculated as below:

BMI (kg/m2) = weight (kg) / (height (m))^2

Pubertal stage was evaluated according to the Tanner standard classification (27). However, Tanner stages 1 was considered as prepubertal, 2 and 3 were considered as early pubertal, 4 and 5 were considered as late pubertal. According to the American College of Sports Medicine recommendations, children need at least 3 days of physical activity weekly (27). Therefore, we divided the patients into two groups based on whether they followed this recommendation or not. Moreover, they were classified into three groups, according to their average daily sun exposure; those with less than 15 min/day, 15-30 min/day, and more than 30 min/day sun exposure (27).

Mineral biochemical parameters

An experienced technician took all the blood samples in the Shiraz Endocrinology Research Center after 8-12 hr of fasting. We checked serum for calcium (Ca), phosphorous (P), magnesium (Mg), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH) by colorimetric assay with an auto-analyzer (Biosystems SA, Barcelona, Spain). Moreover, concentration of 25-hydroxy vitamin D (25OHD) was checked during autumn by high performance liquid chromatography (Young Lee 9100, South Korea) in ng/ml. TSH was checked quantitatively by Electro-chemo-luminescence method, Cobas E411, Japan. The intra- and inter-assay coefficients of variation were 8.6% and 8.7%. Serum intact-PTH was measured by ELISA (SRL, Inc., Japan). Urinary calcium and urinary creatinine were measured by standard colorimetric methods with an auto-analyzer (Biosystems SA, Barcelona, Spain). U-Ca/Cr was calculated as urinary calcium (mg/dL)/urinary creatinine (mg/dL).

Measurement of BMD and definition of low bone mass for chronological age

BMD was measured using Hologic system DXA (Discovery QDR, USA). The coefficient of variation in our laboratory was 2.4% for the femoral neck, and 0.51% for the lumbar spine (based on measurements in ten children). BMD (g/cm2) Z score less than -2 for the patient's age and sex was considered as low bone mass for chronological age (LBM). The normative data of Iranian children(28) was used for 9-18 years old children and the standard data of Hologic system DXA (Discovery QDR, USA) was obtained which was from the U.S. Centers for Disease Control's "National Health and Nutrition Examination Survey" (NHANES) for those of < 9 years old(27) for our source. DXA was performed while the child used special clothing without shoes.

Statistical Analysis

Data were analyzed using SPSS (Version 21). Descriptive data were presented as mean, standard deviation, and percentage. Qualitative variables were compared between the two groups by Chi-square test. Comparison of quantitative data was done between two groups by student t test. To determine the independent factors influencing bone mineral density, multiple logistic regressions by step-wise methods was used. P values less than 0.05 were considered statistically significant.

Ethics

The Ethics Committee of the Shiraz University of Medical Sciences approved the current study with the Grant No.93-01-32-7165. The children or their parents signed the informed consent form.

Results

One hundred and six leukemic children aged 8.1±3.9 years (mean± SD) were recruited for the current study, including 63 boys and 43 girls. The diagnosis of 94 patients (85.8%) was pre-B cell ALL, and 12patients (9.4%) had T cell ALL. Most of the patients (76%) were in early pubertal stages. Mean duration of disease was 23.1±15.3 months. Lumbar and femoral LBM were seen in 28.3% and 27% of leukemic children, respectively. There was no significant difference in the prevalence of femoral or lumbar LBM in boys and girls (p value =0.329 and 0.651, respectively) (Figure 1).

Tables I, II and III reveal the general characteristics and laboratory data of leukemic children, considering low bone mass in lumbar and femoral area. In all the leukemic children, femoral LBM was associated with BMI (p=0.044), while lumbar LBM was associated with serum calcium (P<0.001). In male leukemic children, femoral LBM was associated with duration of disease (p=0.031) and serum level of 25(OH) D3 (p=0.015), and lumbar LBM was associated with serum calcium (p<0.001), serum level of 25(OH) D3 (p=0.025) and radiotherapy (p=0.03). In female subjects, femoral LBM was associated with BMI (p=0.02) and serum Ca (p=0.01); and lumbar LBM was associated with duration of disease (p=0.008) and BMI (p=0.029).

After univariate analysis of the relationship between femoral and lumbar LBM with clinical and laboratory data, logistic regression was done and all variables with P value less than 0.2 were entered into this model to find the independent factors influencing LBM. In this model, serum calcium was determined as an independent protective factor on lumbar LBM of all children (p-value=0.001, OR 0.218, 95% CI 0.087-0.543). When this analysis was done in males and females separately, serum calcium was determined again as a significant protective factor for lumbar LBM of boys (p-value=0.017, OR 0.138, 95% CI 0.027-0.699), and for femoral LBM of girls (p-value=0.035, OR 0.090, 95% CI 0.010-0.842).

Table I: General characteristics and laboratory data of leukemic children considering low bone mass in lumbar and femoral area

variable	low femoral bone mass			low lumbar bone mass		
	yes	No	P value	yes	no	P value
Age (yr)	7.5 ± 4.3	8.5 ± 3.9	0.971	8.4 ± 4.6	7.6 ± 3.8	0.865
Duration of illness (m)	19.3 ± 11.9	25.8 ± 16.5	0.346	21 ± 19.6	23.9 ± 13.1	0.371
BMI (kg/m^2)	15.4 ± 2.9	16.5 ± 4	0.044	15.3 ± 3.1	16.4 ± 3.9	0.473
Sex (M/F)	17/7	37/28	0.23	16/13	45/29	0.6
Puberty (n)						
-pre pubertal	17	38	0.5	17	51	0.6
-early pubertal	4	18		8	15	
-late pubertal	3	9		4	8	
LDH	386 ± 90	420 ± 115	0.186	419 ± 113	417 ± 99	0.744
Ca	9.2 ± 0.6	9.5 ± 0.61	0.09	9.1± 0.6	9.6 ± 0.56	<0.001
Ph	5.1 ± 0.81	5.2±0.8	0.55	4.9 ± 0.9	5.2±0.8	0.31
Mg	2.1 ± 0.44	2.2±0.4	0.54	2.4 ± 0.4	2.2±0.4	0.32
Alkaline phosphatase	457 ± 139	504 ± 219	0.35	450 ± 203	507 ± 192	0.2
25(OH) D_3	17.9 ± 7.9	22.8 ± 18	0.21	19.6 ± 12.5	24.1 ± 20	0.27
Urine Ca/Cr	0.13 ± 0.13	0.19 ± 0.4	0.49	0.18 ± 0.16	0.16 ± 0.4	0.69
PTH	44.5 ± 42.6	43.5 ± 25.6	0.49	46.7 ± 42	41 ± 22.5	0.37
TSH	2.9 ± 1.8	5 ± 16.5	0.3	2.9 ± 1.7	4.7 ± 1.5	0.54
Sun exposure	---	---	0.361	---	---	0.64
Physical activity	---	---	0.387	---	---	0.823
Chemotherapy protocol	---	---	0.635	---	---	0.094
Radiotherapy	---	---	0.981	---	---	0.185

Table II: General characteristics and laboratory data of leukemic children considering low bone mass in lumbar and femoral area in girls

variable	low femoral bone mass			low lumbar bone mass		
	yes	No	P value	yes	no	P value
Age (yr)	5.5 ± 2.5	8.3 ± 3.9	0.086	7.2 ± 3.6	7.2 ± 3.8	0.951
Duration of disease (m)	17.7 ± 10.8	21.3 ± 13.7	0.52	13.6 ± 7	22.6 ± 13.3	0.008
BMI (kg/m^2)	13.6 ± 2.4	17.2 ± 4.6	0.02	14.2 ± 3.1	16.9 ± 4.4	0.029
Puberty						
-pre pubertal	9	13	0.68	8	18	0.4
-early pubertal	1	12		5	8	
-late pubertal	0	3		0	3	
LDH	392 ± 81	432 ± 133	0.47	451 ± 110	428 ± 133.6	0.56
Ca	8.9 ± 0.79	9.6 ± 0.6	0.01	9.3 ± 0.74	9.6 ± 0.6	0.07
Ph	5.4 ± 0.75	5.05±0.8	0.63	4.9 ± 1	5.2±0.7	0.319
Mg	2.1 ± 0.32	2.2 ± 0.52	0.61	2.15 ± 0.24	2.19 ± 0.53	0.76
Alkaline phosphatase	539 ± 118	490 ± 242	0.61	497 ± 208	512 ± 213	0.84
25(OH) D_3	20.5 ± 8.4	17.3 ± 9.4	0.42	0.24 ± 0.17	0.19 ± 0.6	0.87
Urine Ca/Cr	0.15 ± 0.12	0.25 ± 0.2	0.45	23 ± 15	22.1 ± 20	0.78
PTH	37.4 ± 18.5	43.5 ± 26.9	0.58	43 ± 30	39 ± 21	0.64
TSH	2.1 ± 1.5	2.5 ± 1.6	0.5	2.4 ± 1.6	2.5 ± 1.5	0.87
Sun exposure	---	---	0.168	---	---	0.168
Physical activity	---	---	0.178	---	---	0.178
Chemotherapy protocol	---	---	0.731	---	---	0.731
Radiotherapy	---	---	0.62	---	---	0.62

Table III: General characteristics and laboratory data of leukemic children considering low bone mass in lumbar and femoral area in boys

variable	low femoral bone mass			low lumbar bone mass		
	yes	No	P value	yes	no	P value
Age (yr)	8.4 ± 4.7	8.6 ± 4	0.8	9.3 ± 4.8	7.8 ± 3.8	0.264
Duration of disease (m)	19.9 ± 12.5	29.4 ± 17.9	0.031	27.3 ± 24.6	24 ± 13	0.696
BMI (kg/m^2)	16.2 ± 2.8	16.1 ± 3.5	0.91	16.2 ± 2.8	16.1 ± 3.5	0885
Puberty						
-early pubertal	11	25	0.97	9	33	0.34
-mid pubertal	3	6		3	7	
-late pubertal	3	6		4	5	
LDH	382 ± 81	412 ± 103	0.29	375 ± 77	410 ± 100	0.212
Ca	9.4 ± 0.49	9.4 ± 0.6	0.83	9.03 ± 0.43	9.6 ± 0.56	<0.001
Ph	4.9 ± 0.9	4.9 ± 0.9	0.89	4.9 ± 0.9	5.06 ± 0.9	0.58
Mg	2.1 ± 0.48	2.2±0.4	0.49	2.1 ± 0.48	2.2±0.4	0.55
Alkaline phosphatase	422 ± 135	514 ± 202	0.11	406 ± 196	504 ± 180	0.08
25(OH) D_3	16.8 ± 7.6	27.2 ± 21	0.015	16.7 ± 9.3	25.6 ± 19.9	0.025
Urine Ca/Cr	0.12 ± 0.14	0.15 ± 0.2	0.5	0.13 ± 0.13	0.14 ± 0.19	0.9
PTH	47.5 ± 49	43.5 ± 24.9	0.69	49.4 ± 5	41.7 ± 23.6	0.428
TSH	3.3 ± 1.8	6.8 ± 2	0.5	3.3 ± 1.8	6.1 ± 1.9	0.57
Sun exposure	---	---	0.979	---	---	0.979
Physical activity	---	---	0.917	---	---	0.917
Chemotherapy protocol	---	---	0.743	---	---	0.743
Radiotherapy	---	---	0.59	---	---	0.03

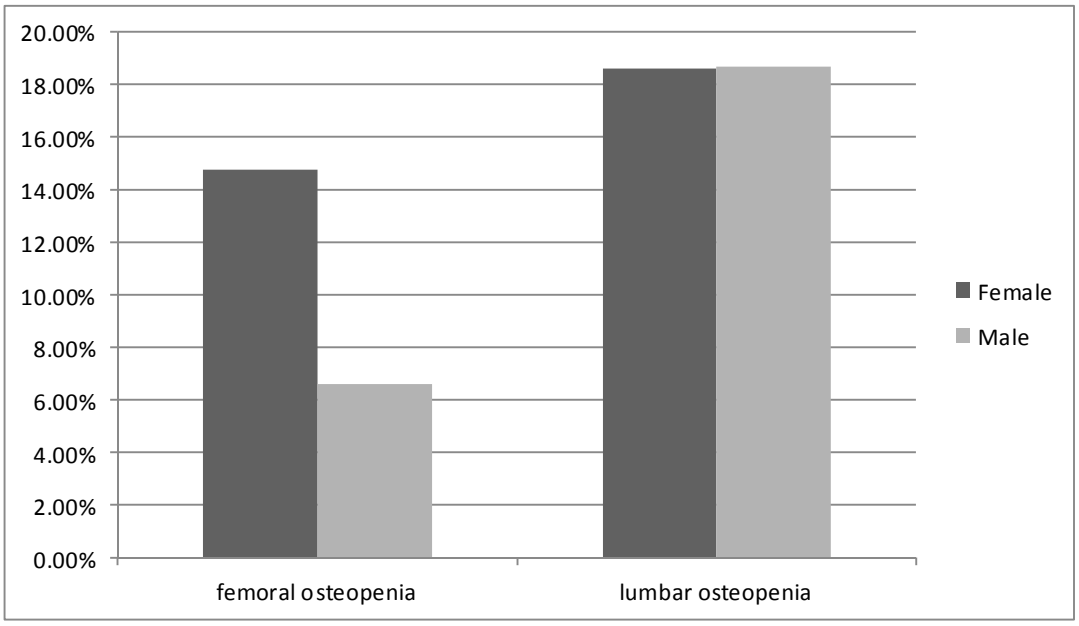

Figure1. Prevalence (%) of femoral and lumbar LBM in leukemic boys and girls

Discussion

To the best of our knowledge this study was the first study investigated the prevalence of LBM in leukemic children in the Middle East. The present investigation revealed that the prevalence of low bone mass for chronological age in leukemic children of southern Iran was 28.3% and 27% in lumbar and femoral regions, respectively and was not sex dependent. This prevalence was associated with duration of disease, serum calcium, serum level of 25(OH) D, BMI and radiotherapy. Among these factors, serum calcium had independent predictive effects.

The American Cancer Society in 2008 published a study by Thomas et al, which investigated the prevalence of osteopenia in young adult survivors of childhood ALL. They found that 24% of their participants had a BMD of >1 SD below the mean, which is a higher percentage than expected based on the reports of the World Health Organization (7). Another Cohort study in the USA revealed that only 5.7% of adult survivors of childhood ALL had a BMD Z score of less than -2SD, consistent with osteoporosis. However, they had not measured BMD before or during the disease at regular intervals following treatment completion (9).

Choi et al., showed that 25.7% of childhood cancer survivors had BMD less than -2SD (11). Several studies from the UK (14), the USA (8, 10, 15), Poland (24) and the Netherlands (25) also reported that BMD in leukemic children was less than the values in normal population, though they did not report any data about the prevalence of LBM in their research. The results of current study showed that the prevalence of LBM in Iranian children suffering from leukemia was higher than their age-matched counterparts in the USA, but somehow similar to the Korean leukemic children which were about 26%. Burrows et al., highlighted the importance of considering ethnic differences in pediatric bone studies (29). They showed that many of the risk factors for osteoporosis such as low calcium intake, smaller body size, and lower physical activity were present in the Asian children and this might be reflected in their lower bone mass across sites. Further studies in Asian population should be done to find out the higher prevalence of LBM in leukemic children. Moreover, Vitanza et al., demonstrated that BMD of leukemic children increases over time after completion of chemotherapy, but still remains below the normal range for at least 6 years (26). This is consistent with our findings that showed duration of illness is conversely related to LBM in leukemic children. It seems that the intensity of chemotherapy is a key factor affecting BMD in leukemia, and as the patient continues his or her treatment particularly in the maintenance phase, the chemotherapy becomes less intense. This may justify the improvement of LBM over time in patients undergoing chemotherapy for whatever reason.

Many studies were done to identify factors associated with low bone mass in leukemic children and also adult survivors of childhood leukemia (7-15, 24, 25). The strongest risk factor for persistent LBM during young adulthood was high dose cranial radiotherapy (9, 11). Another study showed that ALL treatment in childhood without cranial radiation did not result in long term adverse effects on bone development (8). This study showed that lumbar bone density in male leukemic children was more reduced in those who received radiotherapy during treatment course. Some studies suggested that cranial radiotherapy might produce subclinical growth hormone deficiency which results in disturbances in bone mineral accumulation (30). Diminished growth hormone production in the pituitary gland leads to a decrease in the

IGF-1 / IGFBP3 ratio that is harmful for the proliferation of the epiphyseal growth plates until sex hormone-mediated epiphyseal closure occurs (31).

Positive correlation between body mass index and BMD has been shown in different age groups (32). Similarly, Choi et al., reported that BMI SDS was associated with decreased lumbar BMD SDS (11). Current probe also showed the prevalence of LBM in both femoral and lumbar areas of female leukemic children as well as femoral area of all leukemic children was higher in those subjects who had lower BMI. Potentially, beneficial effects of increased body weight may result from the increased mechanical load exerted on bone, which stimulates osteogenesis (33).

Another finding of this study was the independent predictive effect of serum calcium level with both lumbar and femoral low bone mass. This finding merits further investigation in future studies. Some studies revealed that calcium and vitamin D intake were important factors in bone turnover in prepubertal children with childhood leukemia (10, 15).

However, this study would have been more robust if BMD had been done initially before starting chemotherapy to find out the impact of cancer therapy. Longitudinal evaluation of patients at diagnosis and during therapy with attention to patients' fractures is warranted.

Conclusion

The present investigation revealed that prevalence of low bone mass in Iranian leukemic children was 28.3% and 27% in lumbar and femoral area, respectively. The most important associated factors were radiotherapy, BMI, duration of illness and serum calcium level. Further studies are suggested to investigate bone mineral density in leukemic children, especially in Asian countries, with attention to patients' fractures in order to find out the important risk factors of future osteoporosis, and its disabilities.

Acknowledgments

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Conflict of interest

All authors declare that they have no conflict of interest.

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