RESEARCH ARTICLE

Bone Mineral Density in Survivors of Childhood Acute Lymphoblastic Leukemia

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Abstract

Background: The objective of this study was to evaluate bone mineral density (BMD) after completion of treatment for childhood acute lymphoblastic leukemia (ALL). **Methods:** In this cross-sectional study, 103 survivors of ALL aged 13.5 ± 0.45 who completed their treatment at least one year earlier were enrolled. Among these, 49.5% and 51.5% received chemotherapy alone and chemotherapy plus cranial radiotherapy, respectively. Bone mineral content, BMD, and bone mineral apparent density in the lumbar spine (LS), femoral neck (FN) and forearm were assessed using dual-energy X-ray absorptiometry (DEXA). BMD Z-scores were classified according to International Society for Clinical Densitometry (ISCD) criteria. **Results:** The mean BMD Z-scores ± SD forLS, FN and forearm were -1.60 ± 0.12, -1.21 ± 0.9 and -2.43 ± 0.14 respectively with significant differences (P<0.001). Considering the lowest BMD Z-score in LS and FN areas (at any site) and according to the ISCD classification, 62.1%, 33% and 4.9% of the patients had normal BMD, low BMD and osteoporosis, respectively. Also, 8.7% of patients had developed fractures after completion of the treatment period, 4.9% having BMD Z-Scores <-2 SD at any site. A direct relationship was apparent between BMD Z-scores at LS and FN at any sites and risk of fracture (P<0.001). **Conclusions:** ALL patients are at risk for low BMD and fracture. Therefore, applying DEXA scanning is recommended after completion of therapy for prevention of BMD reduction and osteoporosis.

Keywords: Acute lymphoblastic leukemia- treatment- bone- chemotherapy- fracture

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Introduction

Acute Lymphoblastic Leukemia (ALL) is the most common malignancy diagnosed childhood. Novel treatments including risk-adapted treatment protocols, increase cure rates in high risk patients, while they might result in long term complications like low bone mineral density (BMD) and osteoporosis in ALL patients (Cave et al.,1998). Osteoporosis predisposes the patients to increased risk of fractures of hip, spine, etc. High-risk patients should be detected in order to perform appropriate interventions. Children with ALL have reduced BMD at all phases of the disease. Although several studies have reported decreased BMD at diagnosis (Halton et al.,1998; Van der Sluis et al., 1998; Henderson et al., 1998) and during therapy (Halton et al.,1996; Arikoski et al.,1999; Boot et al.,1999; Marinovic et al., 2005; Maniadaki et al.,2006; Kelly et al., 2009; Kaushik et al., 2009), few studies have investigated whether these abnormalities last after completion of therapy of ALL patients. In addition, in older and even recent studies (Gunes et al.,2010; Benmiloud et al.,2010), BMD in children with ALL has been evaluated according to classification of World Health Organization (WHO) or the researchers' criteria.

The objective of this study is to determine BMD changes in children after completion of their treatment. To the best of our knowledge, this is the first study which evaluated BMD of children with ALL according to the recent classification of International Society for Clinical Densitometry (ISCO) Pediatric Official Positions.

Material and Methods

Study population

In this cross-sectional study, we recruited 103 patients (aged 13.5 ± 0.4 years) who were treated for ALL in Oncology Department of Ali Asghar Hospital. As inclusion criteria, they were all in their first remission and their treatment had been completed at least one year earlier. Exclusion criteria included history of bone marrow transplantation, any secondary malignancy, hormone replacement therapy or chronic illnesses that affect bone metabolism.

All patients were evaluated for age, weight, height, pubertal status, ALL type and kind of treatment. Written informed consent was obtained from parents of the patients

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and the study protocol was reviewed and approved by Ali Asghar Hospital Ethics Committee.

Treatment protocol

The patients had been treated according to the protocols of treatment of childhood leukemia (Philip et al., 2000), which included systemic administration of prednisolone, vincristine, daunorubicin, l-asparaginase, 6-mercaptopurine, cytarabine, cyclophosphamide, as well as intrathecal, intravenous and oral methotrexate. Treatment had been completed at least 1 year earlier (mean 4.2 ± 0.3 yrs) in all cases. Overall, 49.5% of the patients had received chemotherapy alone, 49.5% had received chemotherapy and cranial radiotherapy and 0.97% had received chemotherapy and local radiotherapy. Mean total corticosteroid dose used for treatment [corticosteroids as oral equivalent doses of prednisolone (g/m²)] was 6.83 ± 2.34 (range: 3-9).

Evaluation of BMD

Bone mineral content (BMC; grams), bone area (BA; square centimeters), bone mineral density (BMD; BMC divided by BA; grams per square centimeter) measurements were performed by dual-energy x-ray absorptiometry (DEXA) (Osteocor 2, France) in lumbar spine (L2-L4), femoral neck and forearm. BMD measurements were compared with age, sex and race specific-normative values provided by Osteocor 2, pediatric software and expressed as Z-scores. To minimize the effect of bone size on BMD values, bone mineral apparent density (BMAD; grams per cubic centimeter) was calculated for both lumbar spine and femoral neck, by dividing bone mineral content by bone area to the power of 1.5 and 2 respectively (Carter et al.,1992).

Definition of osteoporosis

According to International Society for Clinical Densitometry (ISCD) Pediatric Official Positions classification (Lewiecki et al.,2008; Bianchi et al.,2010) , low BMD or BMC were defined as BMD/BMC Z-score values equal or less than -2 SD adjusted for age, gender and race as appropriate. Osteoporosis can be also diagnosed as low BMD/BMC in presence of a clinically significant fracture history .Using the lowest Z-score of femoral neck or lumbar region; we defined low BMD and osteoporosis according to ISCD classification.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD) or number (percentage). We used the repeated measurement ANOVA test and multivariate logistic regression analysis for comparing quantitative and qualitative variables, respectively. To compare the differences between means we also utilized t test or Mann-Whitney U test. Chi-square test was utilized for determination of relationship between BMD Z-Score and risk of fracture. For all statistical tests a P-value<0.05 was considered as statistically significant, using two-tailed tests.

Results

Patients Characteristics

Of 103 patients, 52.4% were male and 47.6% were female with the mean age of 13.5 ± 0.4 years. Mean weight, height and BMI of patients were 45.86 ± 1.57 kg, 148.2 ± 1.64 cm and 45.9 ± 1.6, respectively. Patients' pubertal development (Tanner stage) was categorized into four groups, namely pre-puberty, early puberty, late puberty and adult. Those categories included 29 patients (28.2%), 19 patients (18.4%), 44 patients (42.7%) and 11 patients (10.6%) respectively. Most of the patients had ALL type L1 (86 patients; 86%) followed by type L2 (12 patients; 12%) and L3 (2 patients; 2%). Based on another

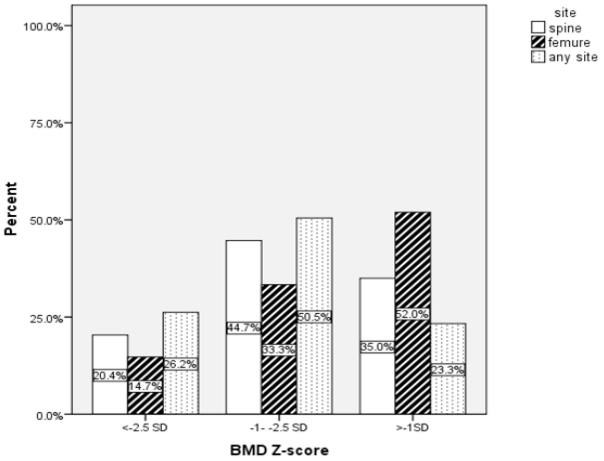

Figure1. Frequencies of Normal BMD, Osteopenia and Osteoporosis Based on WHO Classification of BMD Z-scores*
Abbreviations: BMD, Bone mineral density; WHO, World Health Organization.
*WHO classification of BMD Z-scores: Normal BMD, BMD Z-Score > -1 SD; Osteopenia; BMD Z-Score -1 - -2SD; Osteoporosis, BMD Z-Score <-2.5 SD

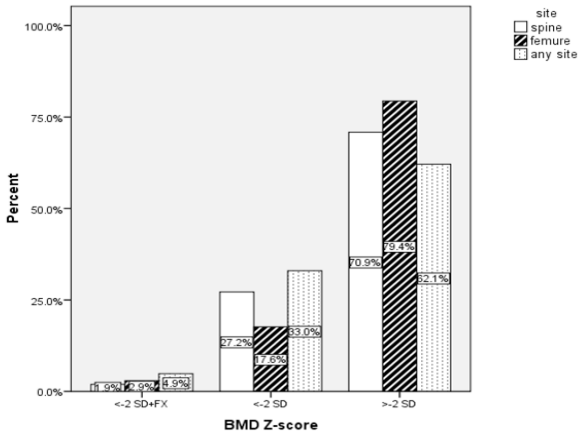

Figure 2. Frequencies of Normal BMD, Low BMD and Osteoporosis Based on ISCD Classification of BMD Z-Scores*
Abbreviations: BMD, Bone mineral density, ISCD: International Society for Clinical Densitometry.
*ISCD classification of BMD Z-scores: Normal BMD, Z-Score >-2SD; Low BMD, Z-Score < -2SD; Osteoporosis, Z-Score <-2SD + fracture

Table 1. Mean ± SD Values of BMC, BMD and BMAD at Lumber Spine, Femoral Neck Forearm

Site	BMC (gr)	BMD (gr/cm^2)	BMAD(gr/cm^3)	BMD Z-score
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Lumber spine	23.5 (1.24)	1.0 (0.24)	0.13 (0.03)	-1.6 (0.12)
Femural neck	3.3 (0.13)	0.7 (0.31)	0.13 (0.13)	-1.2 (0.14)
Forearm	0.6 (0.13)	0.3 (0.01)		-2.4 (0.17)
P.value	0.000	0.001	0.918	0.000

Abbreviations: BMC, Bone mineral content; BMD, bone mineral density ;BMAD, bone mineral apparent density; SD, Standard deviation; P-value <0.05 is significant

Table 2. Mean Values of BMC, BMD, BMAD, and BMD Z-Score at LS and FN Areas and BMD Z-Score at Any Site in Patients with Fracture and without Fracture

	Patients with FX	Patients without FX	P.value
	Mean±SD	Mean±SD	
BMC LS	2.33±7.4	2.54±11.5	0.63
BMD LS	0.73±0.07	0.96±1.8	0.74
BMAD LS	0.12±0.005	0.13±0.03	0.58
BMD Z-score LS	-1.80±0.51	-1.37±1.21	0.3
BMC FN	3.15±0.92	3.34±1.06	0.65
BMD FN	0.73±0.09	0.75±0.23	0.84
BMAD FN	0.11±0.02	0.13±0.13	0.66
BMD Z-score FN	-0.97±1.14	-1.09±1.34	0.78
BMD Z-score AS	-1.88±0.53	-1.77±1.19	0.77

Abbreviations: BMC, Bone mineral content; BMD, bone mineral density; BMAD, bone mineral apparent density; SD, Standard deviation ; LS, Lumbar Spine; FN, Femoral Neck; AS, Any Site; FX, Fracture; P-value <0.05 is significant

categorization, ALL patients were divided to Pre B cell (91 patients; 88.3%) and T cell (12 patients; 11.7%) leukemia. Mean time interval between the end of treatment and time of undergoing BMD was 4.2 ± 0.32 years ranged 1 to 15 years, while mean time interval between the onset of disease and end of treatment was 40.23 ± 0.62 months.

Bone Mineral Density

Mean BMD Z-score ± SD at LS, FN and forearm was -1.60 ± 0.12, -1.22 ± 0.9 and -2.43 ± 0.14 respectively with a significant difference (P<0.001). Mean values of BMD, BMC and BMAD at three aforementioned areas are depicted in table 1. Considering the lowest value of BMD Z-Score at LS and FN areas (at any site) and according to ISCD classification, 32 patients had low BMD and 6 patients had osteoporosis. Frequencies of normal BMD, low BMD and osteoporosis at LS, FN and any site according to WHO and ISCD classifications are depicted in Figures 1 and 2. Overall, 8.7% of the patients had developed fractures after completion of the treatment; among them 4.9% had BMD Z-Scores<-2 SD at any site. Mean values of BMC, BMD and BMAD at LS and FN areas and BMD Z-Score at LS and FN and any site in patients with or without fracture are depicted in table 2. Also, 66% of the patients with fractures and 36.2% of the patients without fracture had BMD Z-Scores<-2 SD at any site. Using Chi-square test, there was direct relationship between BMD Z-Score at LS, FN and any site and risk of fracture (P<0.001 for all).

Discussion

BMD in patients with ALL has been evaluated in several studies, while in most studies, "low BMD", "reduced BMD", "decreased BMD" or "osteopenia" have been recognized according to WHO classification (Z-Score -1 - -2.5 SD) or authors' criteria (Z-Score -1 - -2SD) and also osteoporosis has been recognized as Z-Score <-2.5 SD or <-2 SD. Our study was the first which evaluated the prevalence of low BMD and osteoporosis in patients with ALL according to ISCD classification (50% versus 33% and 26% versus 4.9% for low BMD and osteoporosis respectively). Considering the values of BMD Z-Scores according to the two aforementioned classifications, we concluded that the prevalence of low BMD and osteoporosis according to ISCD classification was significantly lower than that according to WHO classification. Results of our study revealed that considering the lowest values of BMD Z-Score at FN and LS areas (at any site) and according to ISCD classification, 33% of the patients had low BMD and 4.9% had osteoporosis. All survivors of childhood ALL are at risk of decreased BMD due to poor dietary habits, sedentary life style and administration of cytotoxic agents and irradiation, etc. Decreased BMD in ALL survivors has been reported at all phases of the disease, at diagnosis (Halton et al.,1998; Van der Sluis et al.,1998; Henderson et al.,1998), during treatment (Halton et al.,1996; Arikoski et al.,1999; Boot et al.,1999; Marinovic et al.,2005; Maniadaki et al.,2006; Kelly et al.,2009; Kaushik et al.,2009) and at the end of treatment. Several studies have reported both

supporting (Thomas et al.,1961;Marinovic et al.,2005; Arikoski et al.,1998; Hesseling et al.,1998;Nysom et al.,1998; Brennan et al.,1999; Hoorweg-Nijman et al.,1999; Arikoski et al.,1999; Vassilopoulou-Sellin et al.,1999;Nysom et al.,2001; Kanis et al.,2000; Kaste et al.,2001; Kaste et al.,2006; Athanassiadou et al.,2006) and refuting (Henderson et al.,1996;Van der Sluis et al.,1998; Bonnick et al.,1998; Van der Sluis et al.,2000; Kadan-Lottick et al.,2001; Leqin et al.,2002; Tillmann et al.,2002; Bernadette et al.,2004; Mandel et al.,2004; Jarfelt et al.,2006) findings about persistence of decreased BMD after treatment completion. We found low BMD in survivors of childhood ALL at an average of 4 years post treatment. Results of present study reconfirm previous studies that had reported high prevalence of reduced BMD among ALL Survivors. Arikoski et al., (1998) in their study on 29 survivors of ALL at an average of 8 years after completion of therapy, found decreased BMD in both lumbar and femoral regions. Also Nysom et al., (1998 and 2001) found reduced lumbar spine BMD in ALL survivors compared with controls, upon examining whole-body bone mass in 95 survivors of ALL at a median of 11 years after diagnosis. Moreover, Bernnan et al., (1999) examined BMD of ALL survivors approximately 17.8 years after ALL diagnosis and found low BMD in 31 adults. In the study undertaken by Gunes et al., (2010) on 70 survivors of childhood ALL, it was reported that 44% of the patients had osteoporosis and 41% had osteopenia. Benmiloud et al., (2010) in their study on 89 survivors of childhood cancers (75 survivors of ALL) also observed low BMD in 49% of their patients. Kaste et al., (2001) by using quantitative computed tomography (QCT), examined 141 ALL survivors (median age 15.9 years) at an average of 4 years after completion of therapy, and reported low BMD in 21% of the patients, a proportion significantly greater than the expected 5% in normal population. Kaste et al., (2006), following their two serial examinations of BMD in 57 survivors of childhood ALL which was undertaken by applying QCT, found that ALL survivors as a group achieved lower peak bone mass and were, thus, at increased risk of osteoporosis, later in life. They concluded that bone mineral accretion during adolescence is attenuated in childhood ALL survivors by a comparative deficit in trabecular versus cortical bone deposition. Thomas et al., (1961) followed ALL patients for an average of 24 years after ALL diagnosis by using DEXA bone densitometry in lumbar spine, femoral neck and total body. Their study showed low BMD in 24% of 74 randomly selected survivors of ALL. This was much higher than expected, based on the World Health Organization (WHO) report (Kanis et al.,2000). There are other studies indicating low BMD in ALL survivors after completion of treatment (Arikoski et al.,1998; Hesseling et al.,1998;Nysom et al.,1998; Brennan et al.,1999; Hoorweg-Nijman et al.,1999; Arikoski et al.,1999; Vassilopoulou-Sellin et al.,1999). On the contrary, there are other studies reporting no significant long term changes of BMD in survivors of childhood ALL (Bonnick et al.,1998; Van der Sluis et al.,2000; Kadan-Lottick et al., 2001; Leqin et al., 2002; Tillmann et al., 2002; Bernadette et al., 2004; Mandel et al., 2004; Jarfelt et al., 2006). Kadan–Lottick et al., (2001) showed no persistent abnormalities in total body BMD after treatment completion (mean 2.5 ± 1.8 yrs), in their study on 75 survivors of ALL ranging 11 to 82 months post diagnosis. Following examination of 53 survivors of ALL one year after completion of treatment and 187 healthy controls with DEXA of total body and lumbar spine as well as quantitative computer tomography at distal radial, Bernadette et al., (2004) reported that total body and lumbar spine BMD did not differ between ALL survivors and controls. They, however, found that distal radial BMD was lower in ALL survivors compared with controls. According to Tillmann et al., (2002), although mean lumbar BMD was lower in ALL survivors (28 patients), total body and lumbar area BMD were not different compared to controls at an average of 5 years post treatment.

We show that there is a significant difference in cortical and trabecular bone mass. Trabecular bone has a higher metabolic rate. Consequently changes in BMD will occur earlier in spine BMD than whole body BMD. Although Kadan, Bernadette, Tillman et al., found no persistent abnormalities in total body BMD in their study, they, however, measured whole body BMD and concluded that 80% of it is cortical bone (Bonnick,1998), whereas lumbar spine BMD mostly includes trabecular bone mass. In accordance with previous studies, steroids have the greatest impact on the spine, due to its rapid turnover in respect to cortical bone (Bonnick,1998). Mandel et al. (Mandel et al.,2004) in their study on 106 ALL survivors at an average of 5.8 years post treatment, measured BMD and reported that with respect to age and sex, spine or femur BMD were not significantly different with controls. Nine patients developed fractures after completion of the treatment period; among them 5 patients had BMD Z-Score<-2 SD at any site. There were not significant differences between mean BMD Z-Score at LS and FN in patients with fractures and without fractures (P=0.001).

There were positive relationship between BMD Z-Score at LS, FN and any site and risk of fracture (P<0.001). Some studies have been showed positive relationship between reduced BMD and risk of developing fractures. Clark et al., (2006) studied on 6213 children with mean age of 9.9 years during a 2-year follow up and reported that for every 1 SD decrease in BMC, risk of developing fractures increases by 89%. Goulding and colleagues (Goulding et al., 2000) conducted a 4-year double cohort study and compared 82 children with history of forearm fractures, with children without any history of fractures and reported that history of previous fractures and low BMD might increase risk of new fractures. Some other studies have reported increased risk of developing fractures in patients with ALL despite their normal BMD. Van der Sulis et al., (2000) examined BMD of lumbar spine and total body in 23 patients 9.6 years after cessation of therapy. They, following their study, reported normal mean SDS for Lumbar spine BMD, total body BMD and apparent lumbar spine BMD. According to them, while BMD SDS was normal in these patients, fracture risk was increased, particularly during and in the year after cessation of therapy. In another study, Van der

Sluis et al., (1998) reported that prior to chemotherapy and after initiation of therapy, lumbar spine BMD of ALL patients decreased significantly. Such decrements persisted up to 3 years after treatment completion. Van der sluis et al., in their comprehensive studies, showed higher rate of fracture in ALL patients compared to healthy controls. In these two studies they suggested that rather than the absolute values of BMD SDS, change in BMD plays a significant role in developing fractures. Studies conducted by Nysom, Thomas et al., (1961) on 95, 141 and 74 ALL survivors are among large and valuable studies on BMD changes in ALL survivors and all have reported reduced BMD in these patients.

We conducted a large study involving 103 participants treated with a single institutional protocol and followed up consistently. Results of this study confirms the assumption that low BMD is a potential serious consequence of childhood ALL and its treatment. As depicted in table 1, the differences between mean BMC, BMD and BMD Z-Scores at LS, FN and forearm were statistically significant. This shows that evaluation of one area is not sufficient for determining bone density and it is necessary to consider at least two areas including LS and FN. Forearm is not commonly used for determining BMD unless in special cases.

As a limitation, it was a cross-sectional study and we did not have any information about patients' BMD before initiation of treatment, at the end of treatment period and changes of BMD after the treatment period.

In conclusion , low BMD was observed in one third of the patients (<-2SD). Since reduced BMD predisposes the patient to low BMD, osteoporosis and fracture; application of DEXA scanning to evaluate and monitor BMD of children with ALL after completion of therapy is recommended. This contributes to identifying those patients at risk of developing low BMD, osteoporosis and pathological fractures.

Conflicts of Interest

The authors indicate no potential conflicts of interest.

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