Bone Mineral Density in Survivors of Childhood Acute Lymphoblastic Leukemia

Farzaneh Rohani1,2, Khadijeh Arjmandi Rafsanjani2, Gholamreza Bahoush3*, Mansoureh Sabzehparvar4, Mohammad Ahmadi4

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 for LS, 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
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
Acute Lymphoblastic Leukemia

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 classification 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 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-Score 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 value of BMD Z-Score at any site, 32 patients had low BMD and 6 patients 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

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

| Site            | BMC (gr) | BMD (gr/cm²) | BMAD (gr/cm³) | BMD Z-score |
|-----------------|----------|--------------|---------------|-------------|
| Lumber spine    | 23.5 (1.24) | 1.0 (0.24) | 0.13 (0.03) | -1.6 (0.12) |
| Femoral 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) | 0.918 | -2.4 (0.17) |
| P.value         | 0.000 | 0.001 | 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

| Site            | Patients with FX | Patients without FX | P.value |
|-----------------|------------------|---------------------|---------|
| 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 LS  | -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
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 ALL diagnosis and found low BMD in 21% of patients, 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%.
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.

Acknowledgements

We are deeply indebted to MS Khodakarim for his statistical work conducted skillfully. This study is part of MD thesis of MS. Dr Mansoureh Sabzehparvar approved by Iran University of Medical Sciences. We are also grateful to staff of the Oncology Department of the Ali Asghar Hospital for their assistance in planning and performing this study.

References

Arikoski, Komulainen J, Riikonen P, et al (1999). Impaired development of bone mineral density during chemotherapy: a prospective analysis of 46 children newly diagnosed with cancer. J Bone Miner Res, 2002-9.

Arikoski P, Komulainen J, VuotilaJ S, et al (1998). Reduced bone mineral density in long-term survivors of childhood acute lymphoblastic leukemia. J Pediatr Hematol Oncol, 20, 234-40.

Arikoski P, Kroger H, Riikonen P, et al (1999). Disturbance in bone turnover in children with a malignancy at completion of chemotherapy. Med Pediatr Oncol, 33, 455-61.

Athanassiadou F, Tragiannidis A, Rouso I, et al (2006). Bone mineral density in survivors of childhood acute lymphoblastic leukemia. Turk J Pediatr, 48, 101-4.

Benmiloud S, Steffens M, Beaulyve Y, et al (2010). Long-term effects on bone mineral density of different therapeutic schemes for acute lymphoblastic leukemia or non-Hodgkin lymphoma during childhood. Horm Res Paediatr, 74, 241-50.

Bennadette MD, Brennan ZM, Stephan A, et al (2004). Bone mineral density in childhood survivors of acute lymphoblastic leukemia treated without cranial irradiation. J Clin Endocrinol Metab, 9, 689-94.

Bianchi ML, Baim S, Bishop NJ, et al (2010). Official positions of the international society for clinical densitometry (ISCD) on DXA evaluation in children and adolescents. Pediatr Nephrol, 25, 37-47.

Bonnick SL (1998). Bone densitometry in clinical practice. 1st ed. Totowa (NJ): Humana press Inc, pp 31-64.

Booth AM, Van den Heuvel-Eibrink MM, Hahlen K, et al (1999). Bone mineral density in children with acute lymphoblastic leukemia. Eur J Cancer, 35, 1093–97.

Brennan BM, Rahim A, Adams JA, et al (1999). Reduced bone mineral density in young adults following cure of acute lymphoblastic leukaemia in childhood. Br J Cancer, 79, 1859-63.

Carter DR, Bouxsein ML, Marcus R (1992). New approaches for interpreting projected bone densitometry data. J Bone Miner Res, 7, 137-45.

Cave H, Van der Werff ten Bosch J, Suciu S (1998). Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia. European organization for research and treatment of cancer-childhood leukemia cooperative group. N Engl J Med, 339, 591-8.

Clark EM, Ness AR, Bishop NJ, et al (2006). Association between bone mass and fractures in children: a prospective cohort study. J Bone Miner Res, 21, 1489-95.

Goulding A, Jones IE, Taylor RW, et al (2000). More broken bones: a 4-year double cohort study of young girls with and without distal forearm fractures. J Bone Miner Res, 15, 2011-8.

Gunes AM, Can E, Saglam H, et al (2010). Assessment of bone mineral density and risk factors in children completing treatment for acute lymphoblastic leukemia. J Pediatr Hematol Oncol, 32, 102-7.

Halton JM, Atkinson SA, Fraher L (1996). Altered mineral metabolism and bone mass in children during treatment for acute lymphoblastic leukaemia. J Bone Miner Res, 11, 1774–83.

Halton JM, Atkinson SA, Fraher L (1998). Mineral homeostasis and bone mass at diagnosis in children with acute lymphoblastic leukaemia. J Pediatr Hematol Oncol, 18, 367-71.

Henderson RC, Madsen CD, Davis C, et al (1996). Bone density in survivors of childhood malignancies. J Pediatr Hematol Oncol, 18, 367-71.

Henderson RC, Madsen CD, Davis C, et al (1998). Longitudinal evaluation of bone mineral density in children receiving chemotheraphy. J Pediatr Hematol Oncol, 20, 322–26.

Hesseling PB, Hough SF, Nel ED, et al (1998). Bone mineral density in long-term survivors of childhood cancer. Int J Cancer Suppl, 11, 44-7.

Hoorweg-Nijman JJ, Kardos G, Roos JC, et al (1999). Bone mineral density and markers of bone turnover in young adult survivors of childhood lymphoblastic leukaemia. Clin Endocrinol, 50, 237-44.
Farzaneh Rohani et al

Jarfelt M, Fors H, Lannerling B, et al (2006). Bone mineral density and bone turnover in young adult survivors of childhood acute lymphoblastic leukaemia. *Europ J Endocrinol*, **154**, 303-9.

Kadan-Lottick N, Marshall JA, Baron AE, et al (2001). Normal bone mineral density after treatment for childhood acute lymphoblastic leukemia diagnosed between 1991 and 1998. *J Pediatr*, **138**, 898-904.

Kanis JA, Johnell O, Odén A, et al (2000). Risk of hip fracture according to the World health organization criteria for osteopenia and osteoporosis. *Bone*, **27**, 585-90.

Kaste SC, Jones Wallace D, Rose SR, et al (2001). Bone mineral decreased in survivors of childhood acute lymphoblastic leukemia: Frequency of occurrence and risk factors for their development. *leukemiya*, **15**, 728-34.

Kaste SC, Rai SN, Fleming K, et al (2006). Changes in bone mineral density in survivors of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer*, **46**, 77 –87.

Kaushik A, Bansal D, Khandelwal N, et al (2009). Changes in bone Mineral density during therapy in childhood acute lymphoblastic leukemia. *Indian Pediatrics*, **46**, 245-48.

Kelly KM, Thornton JC, Hughes D, et al (2009). Total body bone measurements: a Cross-sectional study in children with acute lymphoblastic leukemia during and following completion of therapy. *Pediatr Blood Cancer*, **52**, 33-8.

Lequin MH, van der Sluis IM, van Rijn RR, et al (2002). Bone mineral assessment with tibial ultrasonometry and dual-energy xray absorptiometry in long-term survivors of acute lymphoblastic leukemia in childhood. *J Clin Densitom* **5**, 167-73.

Lewiecki EM, Gordon CM, Baim S, et al (2008). Special report on the 2007 adult and pediatric position development conferences of the international society for clinical densitometry. *Osteoporos Int*, **19**, 1369-78.

Mandel K, Atkinson S, Barr RD (2004). Skeletal morbidity in childhood acute lymphoblastic leukemia. *J Clin Oncology* **22**, 1215-21.

Maniadaki I, Stiakaki E, Germanakis I, et al (2006). Evaluation of bone mineral density at different phases of therapy of childhood all. *Pediatr Hematol Oncol*, **23**, 8-11.

Marinovic D, Dorgerest S, Lescoceure B, et al (2005). Improvement in bone mineral density and body composition in survivors of childhood acute lymphoblastic leukemia: a 1-year prospective study. *Pediatrics*, **116**, 102-8.

Nysom K, Holm K, Michaelson KF, et al (2001). Bone mass after treatment for acute lymphoblastic leukemia in childhood. *J Clin Oncol*, **19**, 2970-71.

Nysom K, Holm K, Michaelson KF, et al (1998). childhood. *J Clin Oncology* **22**, 1215-21.

Philip J (2000). Manual of pediatric hematology anb oncology. United State 3 rd edition, pp 378-79.

Thomas LB, Forkner CE Jr, Frei E III, et al (1961). The skeletal lesions of acute leukemia. *Cancer*, **14**, 608-21.

Tillmann V, Darlington AS, Eiser C, et al (2002). Male sex and low physical activity are associated with reduced spine bone mineral density in survivors of childhood acute lymphoblastic leukemia. *J Bone Miner Res*, **17**, 1073- 80.

Van der Sluis IM, Van den Heuvel-Eibrink MM, Hahlen K, et al (1998). Altered bone mineral density and body composition, and increased fracture risk in childhood acute lymphoblastic leukemia. *J Pediatr*, **141**, 204–10.

Van der Sluis IM, Van den Heuvel-Eibrink MM, Hahlen K, et al (2000). Bone mineral density, body composition, and height in long term survivors of acute lymphoblastic leukemia in childhood. *Med Pediatr Oncol*, **35**, 415-20.

Vassilopoulou-Sellin R, Brosnan P, Delpassand A, et al (1999). Osteopenia in young adult survivors of childhood cancer.