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Evaluation of bone mineral density in long-term survivors of childhood acute lymphoblastic leukemia

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Abstract

Background: The purpose of this study was to evaluate long-term changes in bone density profile among survivors of childhood acute lymphoblastic leukemia.

Patients and Methods: This was a 5 year prospective study comprised of thirty-one survivors of childhood acute lymphoblastic leukemia with a mean age of 11.8 (4.6) years, who completed therapy at least 1 year previously (according to the ALL-6 therapeutic protocol), and remained in complete continuous remission. BMD was measured from the lumbar spines (L2 to L4) and femoral neck, at baseline (2006) and after 5 years (2011), using dual energy x-ray absorbtiometry. Bone mineral density Z score and bone mineral content were calculated for both lumbar spine and femoral neck.

Results: The mean femoral bone mineral density was 0.69 in 2006 and 0.82 in 2011 (p=0.005). The mean femoral Z score was -1.38 in 2006 and -0.55 in 2011 (p=0.006). For the lumbar spine, the mean bone mineral density was 0.71 in 2006 and 0.88 in 2011 (p=0.000); and the mean Z score was -2.08 in 2006 and -0.93 in 2011 (p=0.000) respectively. All three indices significantly changed through-out the study period. The general linear regression analysis revealed that daily calcium intake was an important predictor of lumbar spine BMD Z score. Femoral neck BMD Z score was correlated with the serum vitamin D level.

Conclusion: Osteopenia in survivors of childhood acute lymphoblastic leukemia constitutes an important health risk. Patients and their families should be encouraged to take sufficient amount of calcium and vitamin D during chemotherapy and afterward.

Keywords: Acute lymphoblastic leukemia, bone mineral density, bone mineral content, dual energy x-ray absorbtiometry (DXA), Iran.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, accounting for 26% of all childhood cancers. In recent years, survival of ALL patients has increased and 5 years event free survival has reached up to 80% with the application of intensive chemotherapy protocols [1, 2]. However, as survival rates have improved, there has been an increasing recognition of adverse long-term effects of the disease and its treatment such as effects on neuropsychological cardiac, growth, and endocrine functioning including osteoporosis and obesity [3, 4]. Survivors of childhood ALL have been reported to be at increased risk of decreased bone mineral density (BMD(, compared to appropriately matched healthy peers, long after they have completed therapy [4-14]. Probable causes of decreased BMD in ALL are the leukemic process itself [15], ectopic production of parathyroid hormone (PTH)[16], paracrine secretion of lymphokines [17, 18], and decreased physical activity. Furthermore, the negative effects of the treatment may play a major role, such as chemotherapy with steroids

[13] and methotrexate (MTX) [19-21], as well as cranial irradiation [22-24].

Reported frequencies of BMD more than 1–2 standard deviations below age matched controls range from 8 to 77% [25-28]. Some studies have shown no difference in BMD among children with ALL compared to healthy controls after adjusting for bone size [29], whereas others reported decreased BMD in children with ALL at diagnosis compared to controls, with the difference disappearing as treatment progressed. Given these inconsistencies, there is a need to accurately determine the risk factors for bone related problems, including low bone mass, in children with ALL. This may help guide the institution of appropriate interventions to reduce morbidity from later osteoporosis. The aim of this study was to assess BMD in a group of survivors of childhood ALL, all treated according to the ALL-6 protocol.

Patients and Methods

This 5-year prospective study comprised of 31 survivors of childhood pre-B cell ALL who had been treated in Ali-Asghar pediatrics hospital, Tehran, Iran. Patients had completed therapy at least 1 year prior to enrollment in the present study. Patients were eligible to participate in the study if they remained in complete continuous remission

and had no second malignancies. None of them had received any hormone replacement therapy. Other exclusion criteria included a history of spinal or cranial irradiation, allogeneic bone marrow transplantation, growth hormone deficiency, hypothyroidism, and hypogonadism.

All patients were treated according to the ALL-6 protocol. Systemic chemotherapy involved prednisolone, dexamethasone, methotrexate (MTX), 6-mercaptopurine, L-asparaginase, vincristine, cytarabine, cyclophosphamide and daunorubicin. None of them received cranial irradiation but they received intrathecal MTX as CNS prophylaxis. Prednisolone therapy during remission induction consisted of 60 mg/m2 daily divided into three doses for 4 weeks, then tapered to 0 mg in 36 days. Maintenance treatment consisted of MTX 20 mg/m2/week for 12 cycles, alternated with prednisolone 60 mg/m2 daily for 2 weeks.

Body weight and height was measured for all subjects, and body mass index (BMI) was calculated as weight in kg divided by the square of the height in m (m2). Standard deviation scores (SDS) for weight, height, and BMI were derived from the CDC (centers for disease control and prevention) 2000 growth curves.

Pubertal stages of the patients were assessed by a pediatric endocrinologist according to the Tanner stages.

Participants completed a questionnaire to assess their use of calcium supplements and daily dairy product consumption, and according to their responses, the amount of daily calcium intake was estimated.

Serum calcium (Ca), phosphate (P), alkaline phosphates (ALP), and 25 (OH) Vitamin D. (radioimmunoassay), levels were measured.

BMD was measured from the lumbar spines (L2 to L4) and femoral neck, at baseline (2006) and after 5 years (2011), by dual energy x-ray absorbtiometry (DXA) method using a computed densitometry device (Hologic QDR Delphi W S/N 70232) and z-scores of BMD were calculated by subtracting the age and sex-specific mean reference BMD score from the observed score and dividing the difference by the standard deviation of BMD in the age and sex-matched reference group. The lumbar spine and femoral neck bone mineral content (BMC; grams), and bone area (BA; square centimeters), were also measured. The following bone density indices were used in the subsequent statistical analysis:

LSBMD: lumbar spine BMD (gr/cm2), LSBMD ZS: lumbar spine BMD Z-score, LSBMC: lumbar spine BMC

(gr), FBMD: femoral neck BMD (gr/cm2), FBMD ZS: femoral neck BMD Z-score, FBMC: femoral neck BMC (gr).

Statistical analysis

The statistical analysis was performed using SPSS software (version 19.0, SPSS Co, Chicago IL). The frequency of abnormal Z scores were calculated at both measurements and the statistical significance of the difference was tested by Chi square test. Mean bone density indices were compared between two measurements, and the statistical significance of changes were tested. Two sample t-tests were used to compare continuous data. For continuous variables that did not meet the parametric criteria, a nonparametric test was used. A comparison was also performed between

males and females for both measurements (paired t-test for normally distributed variables and the Wilcoxon signed-rank test for non-normally distributed variables). To investigate whether any of the background variables were predictor of bone density indices, we conducted univariate linear regression analyses.

Results

A total of 31 patients (20 boys and 11 girls) diagnosed as ALL and treated in the division of pediatric hematology were enrolled into the study. They all completed the full courses of ALL-6 chemotherapy protocol and were in first complete remission. Their anthropometric characteristics and laboratory features related to the bone mineral density are presented in table1. The mean (standard deviation; SD) age was 11.8 (4.6) years. The youngest patient was 6 and the oldest one was 21 years old. The mean age (SD) at which the subjects were diagnosed as ALL was 52.3 (35.3) months with maximum of 13 years and minimum of approximately 5 months.

The mean femoral BMD was 0.69 in 2006 and 0.82 in 2011 (p=0.005). The mean femoral Z score was -1.38 in 2006 and -0.55 in 2011 (p=0.006). For the lumbar spine, the mean BMD was 0.71 in 2006 and 0.88 in 2011 (p=0.000); and the mean Z score was -2.08 in 2006 and -0.93 in 2011 (p=0.000) respectively. All the three indices significantly changed through-out the study period.

The boys and girls were not significantly different regarding the age at the diagnosis of ALL, the age at enrollment

in the study, post-treatment time, weight, BMI, serum levels of Ca, P, ALP, and 25 (OH) Vitamin D level, and the daily calcium intake (Table1). However, the mean height (SD) was 159 (17.7) for boys and 147 (14.8) for girls. The two-tailed p value (Table 1) for the difference was 0.05 which is of borderline significance. The mean height HDS and weight SDS were not significantly different between two groups (p values were 0.4 and 0.5 respectively).

Figure 1 illustrates the mean lumbar spine and femoral neck BMD, for males and females separately, and their change with time throughout the study period. Figure 2 presents the same findings related to the Z scores. The majority of indices were lower in males at the first measurement; the differences were statistically significant for LSBMD, LSBMD ZS, and FBMAD (2 tailed p= 0.01, and 0.003 respectively), but not for FBMD, and FBMD ZS (p=0.6, and p=0.8 respectively). However, after 5 years, the differences between two sexes decreased, and at the second measurement, males got higher scores, or if not, their scores were no longer significantly lower than females (p=0.1, for FBMD, 0.4 for LSBMD, 0.5 for FBMD ZS, 0.3 for LSBMD ZS, figures 1, and 2).

Bone parameters improved during the study period more rapidly in boys than girls. At the beginning, 44 % (54.5% males, 45.5% females) of the patients had abnormal FBMD ZS and 72% (77.8% males, 22.2% females) had abnormal LSBMD ZS. After 5 years this values changed to 12% (66.7% males, 33.3% females), and 32% (75% males, 25% females). Most of the patients with abnormal Z scores were boys in both measurements.

The general linear regression analysis revealed that daily calcium intake was an important predictor of lumbar spine BMD ZS and BMAD. Interestingly this strong correlation was not seen between femoral neck bone density and calcium intake. Instead, femoral neck BMD ZS was correlated with the serum vitamin D level. Another difference between lumbar spine and femoral neck bone density was seen in their correlation with height and weight. Table 2 presents general linear regression models, constructed for femoral and lumbar spine BAMD ZS.

Discussion

There are several cross-sectional studies in which BMD status has been assessed in long-term survivors of childhood ALL. Studies on patients who were treated with cranial irradiation have shown significantly reduced BMD, even >8 years after completion of treatment [5, 6, 8, 9, 30]. Defects in the hypothalamic-pituitary axis leading to abnormalities in growth hormone and gonadotropin secretion are probable causes, leading to disturbed bone metabolism [31]. The effect of chemotherapy alone on BMD is much less clear; in the absence of cranial radiation, normal [32, 33] or [34, 35] reduced BMD have been reported.

Arikoski et al. [36] showed reduced femoral and lumbar spine BMD after ALL treatment; a history of cranial irradiation appeared to be a risk factor for osteopenia. This risk factor has been reported by

others as well [32]. Nysom et al. [9] reported reduced BMD in irradiated and non-irradiated patients 11 years after diagnosis.

Brennan et al. [37] studied fifty-three survivors of ALL (aged 6-17 years), who had completed their treatment without cranial irradiation, at least 1 year previously, and 187 (5-19 years) healthy controls and found that after adjustment for age, gender, and pubertal stage, the median total body BMC, total body aBMD, and LSBMAD of ALL subjects were not different from those of controls.

There was significant overlap between the two groups. Nysom et al. [9] examined aBMD in a large cohort of ALL survivors. The ALL subjects had significantly lower LS aBMD compared with controls, partially explained by reduced bone size [9]. Arikoski et al. showed that aBMD was normal in long-term survivors of ALL treated without cranial irradiation [36].

Marinovic et al., found a slight decrease in total body BMD after a median time of 2.2 years after the completion of therapy for ALL in childhood. Patients showed a significantly lower median BMD when evaluated <1.5 years as compared with those at >1.5 years since completion of therapy. A significant increase in total body BMD were observed during the study period in ALL patients as compared with age, gender, and pubertal stage-matched control subjects [38].

The findings of our study are consistent with those reported by Arikoski et al. [7] and Nysom et al. [9]. In our study, at the time of enrollment, the subjects were on average 3.2 years old in complete continuous remission. Fourty four percent of them had abnormal FBMD ZS and 72% had abnormal LSBMD ZS and none of them had experienced cranial irradiation, and the chemotherapy protocol was the same for all of them. After 5 years follow-up, a catch-up increment was noticed in bone mineral parameters. The frequency of abnormal FBMD ZS and LSBMD ZS changed to 12%, and 32%.

When we investigated the predictors of BMD, daily calcium intake was the important one for LSBMAD and LSBMD ZS. Various other studies have also emphasized the importance of adequate calcium intake [5, 39, 40].

The cause of the inverse correlation between longitudinal growth and LSBMD decrement is unclear. Accelerated bone accretion occurs during puberty as a result of the direct sex hormone effect on both bone and cartilage, coincident with the epiphyseal fusion process. Indeed, our patients with Tanner stages I, II, or III had lower BMD Z scores than did our patients with Tanner stages IV or V. Many children treated for ALL exhibit earlier entry into puberty, and sometimes exhibit accelerated tempos of pubertal progression [41, 42]. Patients who rapidly progress through puberty would, by definition, have undergone more rapid bone accretion during this finite time period because of the sex hormone effect. This finding is expected because the sex hormones promote increased BMD [43, 44].In our study, BMD decrements occurred more often and, with greater severity in boys. However, during the study period, boys improved more rapidly in bone parameters. Male gender as a risk factor for decreased BMD after completion of treatment has also been indicated in 2 other studies [5, 7]. One hypothesis is that skeletal maturation is more delayed in boys than in girls and that progression through puberty is accelerated in adolescent girls [42]. This accelerated maturation results in an earlier and potentially greater estrogen effect on BMD accretion. In addition, estrogen is thought to have a greater effect on bone mineral accretion than does androgen [45]. In Arikoski et al. study [7] in stepwise regression analysis male gender remained the only significant negative predictor of both lumbar and femoral neck BMD. Male gonads are more sensitive to certain cytotoxic drugs than the female [46,47] However, none of our patients received direct gonadotoxic agents such as alkylating agents, procarbazine, vinblastine, cisplatin etc. Another possible explanation is a gender difference in sensitivity to glucocorticoids.

We used dual energy x-ray absorptiometry (DXA), which bases its measurements on a two-dimensional projection of a three dimensional structure, and have focused on the assessment of areal BMD (aBMD is the ratio of BMC and bone area, expressed in units of grams per square centimeter), which is an important determinant of the risk of fracture in children [39], but it is affected by bone's size. Therefore

caution should be given in interpretation of aBMD results.

The number of patients investigated in this study was relatively limited; however, this was compensated for by the fact that the study population was very homogenous regarding

malignancy (all pre-B ALL), and treatment schedule.

Conclusion

Osteopenia in survivors of childhood ALL constitutes an important health risk. It is clear that changes in bone mass during childhood or adolescence significantly affect the bone health in adulthood. Therefore, patients and their families should be encouraged to take sufficient amount of calcium during chemotherapy and afterward.

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