

DOI: 10.5152/eurasianjmed.2018.18196

Manuscript Type: Original Article

Title: Bone Loss in Pediatric Survivors of Acute Lymphoblastic Leukemia

Running Head: Bone Loss in ALL Survivors

Authors: Arzu Duygu Donmez, Pamir Isik, Semra Cetinkaya, Nese Yarali

Institutions:¹ Ankara Children's Hematology and Oncology Hospital, Ankara, Turkey

² Department of Pediatric Endocrinology, Dr. Sami Ulus Obstetrics and Gynecology, Children's Health and Disease Training and Research Hospital, Ankara, Turkey

Correspondence to: Arzu Duygu Donmez

Cite this article as: Donmez AD, Isik P, Cetinkaya S, Yarali N. Bone Loss in Pediatric Survivors of Acute Lymphoblastic Leukemia. Eurasian J Med 2018; DOI: 10.5152/eurasianjmed.2018.18196.

Abstract

Objective: Bone mineral density (BMD) in children may be negatively affected by acute lymphoblastic leukemia (ALL) or its treatment protocol. The aim of our study was to evaluate bone health by measuring BMD after ALL treatment.

Material and Methods: The age, anthropometric measurements, and lumbar spine BMDs were recorded in 39 pediatric survivors of ALL, with no history of relapse, secondary malignancy, or transplantation. The lumbar spine BMD was measured by dual energy x-ray absorptiometry. The BMD risk factors, pubertal status, age at diagnosis, risk category, the time interval from the completion of the chemotherapy, and cranial radiotherapy were investigated. Serum calcium,

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Donmez AD, Isik P, Cetinkaya S, Yarali N. Bone Loss in Pediatric Survivors of Acute Lymphoblastic Leukemia. Eurasian J Med 2018; DOI: 10.5152/eurasianjmed.2018.18196.

©Copyright 2018 by Atatürk University School of Medicine - Available online at www.eajm.org

phosphate, alkaline phosphates, magnesium, parathormone, and 25-hydroxy vitamin D levels were determined.

Results: The mean BMD value was calculated as 0.668 ± 0.176 g/cm². Osteopenia and osteoporosis were detected in nine patients (23.1%) and three patients (7.7%), respectively, according to previously published data of healthy age- and sex-related Turkish children's BMD values. The mean age at diagnosis of patients with ALL, having the Z-score above -1 was lower than in patients having bone defect (Z score <-1).

Conclusion: Early detection and intervention strategies to optimize bone health are essential in pediatric patients with ALL.

Keywords: *acute lymphoblastic leukaemia, bone mineral density, osteopenia, osteoporosis*

Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignant disorder in childhood. Since the survival is improved due to modern combined chemotherapy protocols today, long-term complications increase as a result of intensive therapy [1]. Osteopenia and osteoporosis are important but unnoticed problems that might appear due to disease itself and chemotherapeutical agents, most likely corticosteroids, methotrexate, and cranial radiotherapy. Dietary problems and decreased physical activity are additional factors that influence bone health [2,3]. The aim of our study was to evaluate the bone loss in ALL survivors who had received modified St. Jude Total XIII protocol [4].

Materials and Methods

Study population

Thirty-nine pediatric ALL survivors were enrolled into this cross-sectional study conducted in the year 2010. All patients had been treated according to a modified St. Jude Total XIII ALL protocol at the Pediatric Hematology Department of xxxxxxxxxxxxxxxxxxxx Hospital between the years 2000 and 2009. A total of 85 patients with ALL were treated during this period. Patients with relapsed

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Donmez AD, Isik P, Cetinkaya S, Yarali N. Bone Loss in Pediatric Survivors of Acute Lymphoblastic Leukemia. Eurasian J Med 2018; DOI: 10.5152/eurasianjmed.2018.18196.

©Copyright 2018 by Atatürk University School of Medicine - Available online at www.eajm.org

leukemia, secondary malignancy, and a history of transplantation were excluded. Patients who had any of the following features were accepted as high risk: age <1 year or >10 years; white blood cell (WBC) $\geq 25 \times 10^9/L$; DNA index <1.16 or >1.60; central nervous system (CNS) leukemia; and the existence of the t(9;22) or t(1;19) in a relationship with pre-B ALL. Low-risk patients received antimetabolite-based therapy including daily 6-mercaptopurine (6-MP) and weekly Methotrexate (MTX) for 3 weeks, alternating with a fourth week of daily prednisone and weekly vincristine. Weekly rotational combination of the chemotherapy and drug medication of the high-risk patients was the following: etoposide and cyclophosphamide, 6-MP and MTX, etoposide and cytarabine, prednisone and vincristine (with L-asparaginase for 7 doses), and MTX and cytarabine, and high-dose MTX and 6-MP every 8 weeks (the first 56-week period). Finally, high-risk patients received the similar remission induction therapy at the 32nd week as reinduction. All patients were treated for 120 weeks. All patients with the initial WBC $100 \times 10^9/L$, T-ALL with WBC $50 \times 10^9/L$, Ph+ ALL; patients with CNS leukemia at diagnosis were received craniospinal radiotherapy.

Informed consent was obtained from parents of the patients, and Ethical Committee approval was obtained from xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx.

Study protocol

On physical examination, height, weight, body mass index (BMI), and pubertal staging were evaluated. Height calculations were done by a Harpenden stadiometer. Weight and height values were calculated three times consequently, and the average values were recorded. The BMI was calculated by dividing the simple index of weight-for-height (in square and meter, respectively). Height, weight, and BMI values were analyzed according to Turkish children's standards [5]. The Greulich and Pyle Atlas was used as the methodology for bone age assessment [6]. According to the Tanner-Marshall staging, patients' pubertal stages were evaluated [7]. In laboratory analyses, serum calcium (Ca, 9.0–10.2 mg/dL), phosphorus (P, 2.0–6.6 mg/dL), magnesium (Mg, 0.7–0.96 mg/dl), alkaline phosphatase (ALP, 42–3823 u/L), parathormone (PTH; 19.2–119.4 pg/ml), and 25-hydroxy (OH) vitamin D levels (11.8–79.2 ng/mL) were noted. Ca, P, Mg, and ALP results were studied in an Beckman Coulter LX20 PRO autoanalyzer, and PTH was studied by the chemiluminescence method in an Immulite 2000 device. 25-OH-Vitamin D was studied by the radioimmunoassay method.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Donmez AD, Isik P, Cetinkaya S, Yarali N. Bone Loss in Pediatric Survivors of Acute Lymphoblastic Leukemia. Eurasian J Med 2018; DOI: 10.5152/eurasianjmed.2018.18196.

Bone densities of the patients were calculated on the lateral lumbar vertebrae via the Dual Energy X-Ray Absorptiometry (DXA) method (Hologic QDR-4000 [S/N 55530]). Bone mineral density was computed as the g/cm² unit. Z-scores were calculated according to the bone marrow density (BMD) values of healthy children by using the following formula:

$$\text{Z-score: } \frac{\text{Patients BMD value} - \text{Age related BMD}}{\text{Standard deviation}}$$

According to the definition by International Society of Clinical Densitometry from 2008, these patients having Z-scores below -2 SD, between -1 and -2 SD, and above -1 SD were accepted as low (osteoporosis), decreased (osteopenia), and normal respectively. Z-scores were classified as <-1 (pathological) and >-1 (normal) when statistical analyses were done [8]. While computing the Z-scores, the average BMD values of Turkish children, which had been determined in 345 healthy children by Goksen et al., were used [9].

Statistical analysis

For statistical analyses, the SPSS 15.0 program was used in definitive statistics as a numerical variables mean and standard deviation was used. The numerical percentage was used for comparison of two numerical groups, and the significance test of difference between two means (t-test) was used for categorical variables. For categorical variables, in-group comparisons chi-squared test (Yates correction or Fisher's exact chi-square) were used. The statistically significant level was accepted as p<0.05.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Donmez AD, Isik P, Cetinkaya S, Yarali N. Bone Loss in Pediatric Survivors of Acute Lymphoblastic Leukemia. Eurasian J Med 2018; DOI: 10.5152/eurasianjmed.2018.18196.

©Copyright 2018 by Atatürk University School of Medicine - Available online at www.eajm.org

Results

Twenty-one male (53.8%) and 18 female (46.2%) patients with the mean actual age of 11.3 ± 3.8 (range: 5.5–18) years were included into the study. Patients' weight, height, and BMI percentile values were compatible with values of healthy children, and 53.8% of patients were in the prepubertal stages. Eighteen patients (46.2%) were in the first 2-year, and 21 patients were in 2 years after the end of the chemotherapy.

The mean BMD value was calculated as 0.668 ± 0.176 g/cm². Thirty percent of our patients had bone deficit. Osteopenia was detected in 9 patients (23.1%), and osteoporosis was detected in 3 (7.7%). The BMD values of females and males were 0.659 ± 0.13 g/cm² and 0.674 ± 0.20 g/cm², respectively. Even though the pathological BMD levels were observed more frequently in males, a statistically significant difference was not determined between the gender and Z-score ($p>0.05$). The mean age at diagnosis of the patients was 6.6 ± 3.7 years (1.5–14 years). The age at diagnosis that had a normal Z-score was 5.7 ± 3.4 years, which was significantly lower than in those who had an abnormal Z-score (8.5 ± 3.7 years) ($p<0.05$). There was not any significant difference between the period after the chemotherapy discontinuation and Z-score ($p>0.05$).

According to patients' histories, 26 patients had not received vitamin D prophylaxis (66.7%) during infancy. Of the 26 patients who had not received vitamin D prophylaxis, Z-scores were above -1, between -1 and -2, and below -2 in 17 (65.4%), 6 (23.1%), and 3 (12.5%) patients, respectively. There was no any statistical significance between the Z-score and vitamin D prophylaxis intake in infancy ($p>0.05$).

The relationship between patients' pubertal status, disease risk category, craniospinal radiotherapy history, BMI, and bone age with Z-score is shown in Table 1. According to leukemia risk groups, 14 patients (35.9 %) were in low-risk, and 25 patients (64.1%) were in high-risk groups. There was no any statistically significant difference between the Z-score and leukemia risk groups detected. Although the disease risk status was not found to be significant, all 3 patients with osteoporosis were in the high-risk group. To evaluate the effect of puberty on BMD, patients were grouped as pubertal and prepubertal. Of the patients, 21 (53.8%) and 18 (46.2%) were in the prepubertal and pubertal period, respectively. Any statistically significant correlation was not noticed between the Z-scores of pubertal and prepubertal status of survivors.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Donmez AD, Isik P, Cetinkaya S, Yarali N. Bone Loss in Pediatric Survivors of Acute Lymphoblastic Leukemia. Eurasian J Med 2018; DOI: 10.5152/eurasianjmed.2018.18196.

Serum Ca, P, Mg, ALP, 25-OH-vitamin D, and PTH levels were analyzed, and each parameter was compared with the Z-score. The mean Ca was 9.6 ± 0.2 mg/dL (minimum–maximum: 9.0–10.2), mean P 4.7 ± 0.8 mg/dL (2.0–6.6), mean Mg 0.8 ± 0.06 mg/dl (0.7–0.96), mean ALP 195.5 ± 68.6 u/L (42–3823), mean 25-OH-vitamin D 33.4 ± 4.5 ng/dL (11.8–79.2), mean PTH 42.8 ± 22.1 (19.2–119.4) mg/dl. Vitamin D deficiency was found in 17% of the patients (n: 7), and severe deficiency in 1 patient. Secondary hyperparathyroidism was detected in 7.3% of patients (n=3). These biochemical parameters, 25-OH-vitamin D and PTH levels did not correlate with the Z-score.

Discussion

According to the International Clinical Densitometry Society definition, of our survivor ALL patients, 23.7% were osteopenic, and 7.7% were osteoporotic. Reduced BMD has been reported in 8%–23% of leukemia survivors who received chemotherapy prior to epiphyseal closure [10]. Although we did not evaluate the BMD before chemotherapy, Swiatkiewicz et al. reported that 30% of leukemia patients did have abnormal BMD values at diagnosis, and more than 70% of patients had abnormal BMD values after intensive chemotherapy prior to the maintenance treatment [11]. Leukemic cell infiltration to the spongy tissue of the bone, or the paracrine excretion of lymphokines and parathormone-related peptides, or parathormon excreted from leukemic cells or ectopically produced, might all explain the low BMD values at the diagnosis [11].

The bone size and BMD increase progressively through the childhood with rapid growth during puberty. Growth hormone, sex steroids, and several exogenous factors such as nutrition and exercise regulate bone growth and remodeling [12]. The mean age of our patients having the Z-score above -1 was younger than in patients with bone defect ($p < 0.05$). Halton et al. had analyzed the BMD values of 40 patients with ALL at 6-month intervals from the diagnosis, and they found that during the first 2 years of chemotherapy, the BMD values were decreased in patients whose age at diagnosis was above 11, but they were preserved in patients whose age at diagnosis was below 11 years [13]. In another study, patients older than 10 years at diagnosis had the lowest Z-scores for both girls and boys at the lumbar spine and femoral neck [14]. It was assumed that BMD is negatively affected by an increasing age, probably due to a rapid increase of bone turnover in adolescents and during puberty. Therefore, if bone growth in adolescents and puberty is affected, BMD is reduced quickly.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Donmez AD, Isik P, Cetinkaya S, Yarali N. Bone Loss in Pediatric Survivors of Acute Lymphoblastic Leukemia. Eurasian J Med 2018; DOI: 10.5152/eurasianjmed.2018.18196.

Nevertheless, many studies have not confirmed this relationship [15,16]. We also did not find any correlation between the Z-scores and the pubertal status.

The main therapeutic point according to risk groups was the doses of steroids and methotrexate. High-risk leukemia patients were applied an additional amount of prednisone and methotrexate. The exact mechanism of how methotrexate induces bone mineral loss is still unknown. It is suggested that in methotrexate-treated children, increased bone resorption and excretion can be the cause of increased excretion of the calcium rather than diminished bone formation. [17]. There are different types of mechanisms of glucocorticoid-induced osteoporosis; glucocorticoids prevent vitamin D to form the active metabolite 1.25-dihydroxy vitamin D. The impairment of the intestinal absorption of calcium is caused by disruption of this metabolite production. The inhibited expression of the vitamin D in the bone and production of osteocalcin, along with a decrease of the local production of several cytokines, are caused by glucocorticoid, which normally inhibits bone resorption. [18]. Although our high-risk group patients received more prednisone and methotrexate doses, there were no any significant differences detected between leukemia risk groups. Our study also demonstrated that craniospinal radiotherapy was not affected by the BMD of leukemia survivors. However, in another pediatric study regarding long-term effects of ALL treatment, the BMD values of patients that have received cranial radiotherapy were lower than in those who did not receive it [19]. In the study by Gurney et al. that evaluated the adult survivors of childhood ALL, it was stated that very low BMD was relatively unusual and that the BMD Z-scores tend to improve from adolescence to young adulthood. The primary predictor of suboptimal BMD in the aforementioned study was a high-dose cranial or craniospinal radiation exposure [20]. Defects in the hypothalamo-pituitary axes, growth hormone deficiency, and direct radiation effect on the bone may affect BMD.

Some of our patients presented with altered biochemical evidence of impaired bone health. Seven patients displayed vitamin D deficiency, and 3 of them with resulting secondary hyperparathyroidism. However, we did not find any significant correlation between the Z-score and Ca, P, ALP, Mg, PTH, and 25-OH-vitamin D levels in our study. Although a slight decrease in BMD has been found, Marinovic et al. reported that serum Ca, P, ALP, 25-OH-vitamin D, 1.25 dihydroxy vitamin D and PTH, and serum osteocalcin and bone ALP levels were normal both at the first evaluation and at the second evaluation, 1 year after the completion of chemotherapy [21].

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Donmez AD, Isik P, Cetinkaya S, Yarali N. Bone Loss in Pediatric Survivors of Acute Lymphoblastic Leukemia. Eurasian J Med 2018; DOI: 10.5152/eurasianjmed.2018.18196.

©Copyright 2018 by Atatürk University School of Medicine - Available online at www.eajm.org

Exercise combined with vitamin D and calcium supplementation in healthy children enhances bone mass [22]. Vitamin D and Ca supplementation along with promoted physical activity may ameliorate the bone mass loss in ALL patients. Some authors recommend vitamin D and biphosphonates treatment with low BMD. However, as the effects of biphosphonates on leukemia are not well known, this approach deserves marked caution [22, 23].

It is reported that the fracture prevalence is high in patients with ALL and survivors of all ages and is more common in young patients. A significant percentage of these fractures is asymptomatic and associated with a reduced BMD Z-score. Fractures can occur at any time of ALL treatment, frequently during maintenance or shortly after the treatment end [22]. Most significant impact of ALL is at the time of diagnosis and active phase of treatment with substantial recovery following completion of therapy [24].

In conclusion, osteopenia and osteoporosis are important, subtle complications of leukemia treatment. Early detection and intervention strategies to optimize bone health are essential. Thus, all of patients with ALL should be screened for BMD at the time of diagnosis and at various intervals, supportive treatments should be done, and follow-ups should be continued after treatment. Further prospective studies are needed for prevention and progression of osteopenia.

REFERENCES:

1. Oeffinger KC, Mertens AC, Sklar CA, et al. Childhood Cancer Survivor Study. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med.* 2006; 355:1572-1582
2. Inge M, Marry M. Osteoporosis in children with cancer. *Pediatr Blood Cancer* 2008; 50:474–478
3. Friedlaender GE, Tross RB, Doganis AC, et al. Effects of chemotherapeutic agents on bone. Short-term methotrexate and doxorubicin (adriamycin) treatment in a rat model. *J Bone Joint Surg,* 1984; 66-A: 602-607
4. Koc A, Aycicek A, Ozdemir ZC, et al. Outcome of modified St Jude total therapy 13A for childhood acute lymphoblastic leukemia in the southeast region of Turkey. *J Pediatr Hematol Oncol.* 2013 Jan;35(1):36-41
5. Neyzi O, Güröz H, Furman A, et al. Türk çocuklarında vücut ağırlığı, boy uzunluğu, baş çevresi ve vücut kitle indeksi referans değerleri. *Çocuk Sağlığı ve Hastalıkları Dergisi* 2008; 51:1-14

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Donmez AD, Isik P, Cetinkaya S, Yarali N. Bone Loss in Pediatric Survivors of Acute Lymphoblastic Leukemia. *Eurasian J Med* 2018; DOI: 10.5152/eurasianjmed.2018.18196.

6. Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist. The American Journal of the Medical Sciences.1959; 238(3), 393.
7. Tanner JM. Current advances in the study of physique. Photogrammetric anthropometry and an androgyny scale. Lancet. 1951; 1:574-579
8. Gordon CM, Bachrach LK, Carpenter TO, et al. Dual energy X-ray absorptiometry interpretation and reporting in children and adolescents: the 2007 ISCD Pediatric Official Positions. J Clin Densitom. 2008; 11:43-58
9. Goksen D, Darcan S, Coker M, et al. Bone mineral density of healthy Turkish children and adolescents. J Clin Densitom. 2006; 9:84-90
10. Kaste SC, Chesney RW, Hudson MM, et al. Bone mineral status during and after therapy of childhood cancer: An increasing population with multiple risk factors for impaired bone health. J Bone Miner Res.1999; 14: 2010-2014
11. Swiatkiewicz V, Wysocki M, Odrowaz-Sypniewska G, et al. Bone mass and bone mineral metabolism at diagnosis and after intensive treatment in children with acute lymphoblastic leukemia. Med Pediatr Oncol 2003; 41:578-580
12. Leonard MB, Elmi A, Mostoufi-Moab S, et al. Effects of sex, race and puberty on cortical bone and puberty on cortical bone and functional muscle bone unit in children, adolescent and young adults. J Clin Endocrinol Metab 2010; 95:1681-1689
13. Halton JM, Atkinson SA, Fraher L, et al. Altered mineral metabolism and bone mass in children during treatment for acute lymphoblastic leukemia. J Bone Miner Res 1996; 11: 1774–1783
14. Vitanza NA, Hogan LE, Zhang G, et al. The progression of bone mineral density abnormalities after chemotherapy for childhood acute lymphoblastic leukemia. J Pediatr Hematol Oncol 2015;37:356-361
15. Brennen BMD, Rahim A, Adams JA, et al. Reduced bone mineral density in young adults following cure of acute lymphoblastic leukemia in childhood. Br J Cancer 1999; 79:1859-1863
16. Le Meignen M, Auquier P, Barlogis V, et al. Bone mineral density in adult survivors of childhood acute leukemia: impact of hematopoietic stem cell transplantation and other treatment modalities. Blood. 2011;118(6):1481-9.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Donmez AD, Isik P, Cetinkaya S, Yarali N. Bone Loss in Pediatric Survivors of Acute Lymphoblastic Leukemia. Eurasian J Med 2018; DOI: 10.5152/eurasianjmed.2018.18196.

17. Nevinney HB, Krant MJ, Moore EW. Metabolic studies of the effects of methotrexate. *Metabolism* 1965; 14: 135–139
18. Joseph JC. Corticosteroid-induced osteoporosis. *Am J Hosp Pharm* 1994; 51: 188-197
19. Gilsanz V, Carlson ME, Roe TF, Ortega JA. Osteoporosis after cranial irradiation for acute lymphoblastic leukemia. *J Pediatr* 1990; 117:238-244
20. Gurney JG, Kaste SC, Liu W, et al. Bone mineral density among long-term survivors of childhood acute lymphoblastic leukemia: results from the St. Jude lifetime cohort study. *Pediatr Blood Cancer*. 2014; 61:1270-1276
21. Marinovic D, Dorgeret S, Lescoeur B, et al. Improvement in bone mineral density and body composition in survivors of childhood acute lymphoblastic leukemia: A 1-year prospective study. *Pediatrics* 2005; 116:102-107
22. Mostoufi-Moab S, Halton J. Bone morbidity in childhood leukemia: Epidemiology, mechanisms, diagnosis, and treatment. *Curr Osteoporos Rep* 2014;12: 300-312
23. Lethaby C, Wiernikowski J, Sala A, et al. Biphosphonate therapy for reduced bone mineral density during treatment of acute lymphoblastic leukemia in childhood and adolescence. *J Pediatr Hematol Oncol* 2007; 29:613-616
24. Mostoufi-Moab S, Brodsky J, Isaacoff EJ, et al. Longitudinal assessment of bone density and structure in childhood survivors of acute lymphoblastic leukemia without cranial radiation. *J Clin Endocrinol Metab* 2012; 97: 3584-3592

Table 1. Relationship between the Z-score and gender, treatment protocol, craniospinal radiotherapy, pubertal status, body mass index, age at diagnosis, and bone age of patients

--	--

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Donmez AD, Isik P, Cetinkaya S, Yarali N. Bone Loss in Pediatric Survivors of Acute Lymphoblastic Leukemia. *Eurasian J Med* 2018; DOI: 10.5152/eurasianjmed.2018.18196.

Patient (n=39)	Normal Z-score (n=27)	Abnormal Z-score (n=12)	p -value
Gender			
Female (18)	13 (72.2%)	5 (27.8%)	0.668
Male (21)	14 (66.7%)	7 (33.3%)	
Treatment protocol			
Low risk (14)	12 (85.7%)	2 (14.3%)	0.151
High risk (25)	15 (60%)	10 (40%)	
Radiotherapy			
Yes (14)	7 (50%)	7 (50%)	0.17
No (25)	20 (80%)	5 (20%)	
Puberty			
Prepubertal (21)	16 (76.2%)	5 (23.8%)	0.50
Pubertal (18)	11 (61.1%)	7 (38.9%)	
BMI (kg/m ²)	19.2±3.4	20.7±2.8	0.184
Age at diagnosis (year)	5.7±3.4	8.5±3.7	0.035
Bone age (year)	10.7±3.6	12.7±3.8	0.120

*difference between groups

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Donmez AD, Isik P, Cetinkaya S, Yarali N. Bone Loss in Pediatric Survivors of Acute Lymphoblastic Leukemia. Eurasian J Med 2018; DOI: 10.5152/eurasianjmed.2018.18196.

©Copyright 2018 by Atatürk University School of Medicine - Available online at www.eajm.org

UNCORRECTED

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Donmez AD, Isik P, Cetinkaya S, Yarali N. Bone Loss in Pediatric Survivors of Acute Lymphoblastic Leukemia. Eurasian J Med 2018; DOI: 10.5152/eurasianjmed.2018.18196.

©Copyright 2018 by Atatürk University School of Medicine - Available online at www.eajm.org

UNCORRECTED

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Donmez AD, Isik P, Cetinkaya S, Yarali N. Bone Loss in Pediatric Survivors of Acute Lymphoblastic Leukemia. Eurasian J Med 2018; DOI: 10.5152/eurasianjmed.2018.18196.

©Copyright 2018 by Atatürk University School of Medicine - Available online at www.eajm.org