DOI: 10.24287/1726-1708-2021-20-1-54-57

Received 19.12.2020
Accepted 02.02.2021

Bone changes during and after treatment of childhood acute lymphoblastic leukaemia

S. Ragab, B. Montaser, N. El-Ashmawy, M. El-Hawy

Menoufia University, Menoufia, Egypt

Correspondence:
Mahmoud Ahmed El-Hawy,
Pediatrics Department,
Faculty of Medicine, Menoufia University
Address: Shebin el Kom,
32511 Menoufia, Egypt
E-mail: mahmodelhawy18@yahoo.com

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, with a survival rate of 80%. Major complications of leukemia include osteoporosis that requires both a clinically significant fracture history and low bone mineral density (BMD). The present study aims to assess BMD among acute lymphoblastic leukemia patients and survivors using dual-energy x-ray absorptiometry and serum insulin growth factor binding protein 3. The study was approved by the Independent Ethics Committee and the Scientific Council of the Menoufia University, Egypt. Thirty patients with ALL and thirty survivors who were diagnosed with ALL but completely recovered were enrolled in this study. Sex and age matched normal controls while full history was taken. Patients and survivors were examined for anthropometric measurement. Laboratory including serum IGFBP3and dual-energy x-ray absorptiometry was done for all. It has been found out that patients and survivors showed a markedly lower BMD than normal population but no history of fracture was found in survivors. In this study, the prevalence of low BMD is 26/30 (86.6%) patients and 25/30 (83.3%) survivors. Also, there was a statistically significant decrease of DEXA scan measures in patients and survivors groups than the control group with a statistically significant decrease in both BMD and Z- score measures in patients and survivors groups than control group. Patients and long-term survivors of childhood ALL are at risk for morbidity associated with low BMD. They may benefit from interventions to optimize bone health as they age.

Ключевые слова: *acute lymphoblastic leukemia, osteoporosis, survivors, bone mineral density*

Ragab S., et al. Pediatric Hematology/Oncology and Immunopathology. 2021; 20 (1): 54–57.
DOI: 10.24287/1726-1708-2021-20-1-54-57

Acute lymphocytic leukemia (ALL) is an acute form of leukemia, characterized by the overproduction of immature white blood cells, known as lymphoblasts [1].

Lymphoblasts are overproduced in the bone marrow and continuously multiply, causing damage and death by inhibiting the production of normal cells in the bone marrow and by infiltrating to other organs. ALL is most common in children [1].

Osteoporosis is increasingly recognized as one of the major public health problems that occur throughout the world and have massive socioeconomic implications [2]. There are often no warning signs of osteoporosis until a fracture occurs. Many factors may contribute to the reduced bone mineral density (BMD), with advancing age, heredity and decreased weight-bearing activity being the most important. Additional factors include morbidity from other conditions that directly or indirectly lead to loss of bone [3].

Major skeletal complications of leukemia include osteoporosis. Osteoporosis was observed in all phases of the disease at diagnosis, during treatment, and throughout the post-treatment period for as long as 20 years [4].

Risk factors for the development of skeletal complications in ALL include poor nutrition, reduced mobility, impaired bone mineralization, older age at diagnosis and being of male gender [5].

Nutritional and behavioral factors may adversely impact bone health during treatment of ALL. Standard chemotherapy agents, including corticosteroids and methotrexate, have negative effects on bone failure to attain optimal bone mass during adolescence. This contributes to bone mineral deficits typically associated with aging, which may precipitate early onset osteoporosis during adulthood [6].

Thus, long-term survivors of childhood ALL are at risk for morbidity associated with low BMD. They may benefit from interventions to optimize bone health as they age.

MATERIALS AND METHODS

Thirty patients with ALL and receiving treatment and thirty survivors with ALL and completely recovered after completion of chemotherapy were carried out at the Pediatric Departments, Hematology and Oncology Unit and Clinical Pathology Department, Faculty of Medicine, Menoufia University.

Both groups have been compared with 30 control subjects. The control group was selected from comparable healthy control Egyptian children. All patients included in this study were subjected to complete history taking stressing on age, sex, dietetic history, duration of chemotherapy and cummulative dose of corticosteriods.

All groups were subjected to the following investigations. Firstly, laboratory; in which four milliliters (4 ml) of venous blood were withdrawn under complete aseptic conditions from each subject included in the study. 2ml was used for complete blood count. The rest of sample was left to clot for 30 minutes. Serum was separated by centrifugation at 1000 x g for 15 minutes. Another 2ml was used for chemistry (serum IGFBP3, calcium, phosphorus,alkaline phosphatase, kidney function tests, liver function tests). Hemolyzed samples were discarded, while repeated freezing and thawing were avoided.

BMD was measured in all groups using dual energy X-ray absorptiometry (DEXA). All DEXA measurements were performed with the same device, Lunar DPX- IQ apparatus (Lunar DPX-IQ, A+Medical Company, South Carolina, USA). The acquisition site was the lumbar spine (vertebrae L1–L4).

Because it is necessary to evaluate BMD in comparison with age-matched peers, the Z-score is evaluated using age- and sex-specific normative reference gathered on the DXA machine from the same manufacturer [7]. In this study, BMD values were expressed both in gms/cm2 and as a z-score. Z-score was assessed by the normal mean value for children and adolescents as follows: Z-score=patient BMD-mean BMD SD.

Low bone mineral content (BMC) or BMD is defined as a BMC or areal BMD Z-score that is less than or equal `to-2.0, adjusted for age, gender and body size as appropriate [8].

Informed consents were obtained from the parents of the children studied and the ethical committee in our medical school approved the study.

Statistical analysis

Data was collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 20. (SPSS, version 20; SPSS Inc., Chicago, Illinois, USA) The comparison between two groups with qualitative data was done using Chi-square test, ANOVA (Analysis of Variance) while the comparison between two independent groups regarding quantitative data with parametric distribution was done using Post Hoc test. Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group. The confidence interval was set to 95% and the margin of error accepted to 5%.

RESULTS

The present study included thirty patients of ALL receiving treatment with a mean age ranging from 4 to 16 years with mean 7.87±3.83 SD and thirty survivors who were diagnosed with ALL and completely recovered with a mean age ranging from 6 to 20 years with mean 12.37 ± 4.37SD. BMD and laboratory correlate osteoporosis require the presence of both a clinically significant fracture history and low BMC.

A reduced BMD defined as low z-score for age was detected in 20 (66.6%), 19 (63.3%) in patients and survivors and 6 (20%), 0 (0.0%) for osteoporosis in patients and survivors, respectively (*table 1*, *figure 1*). There was a statistically significant decrease of DEXA scan level and BMD measures in the patients and survivors group than the control group. Most of the patients and survivors have low Z-score while all the control group are normal.

Data shows that there was a statistically significant increase in serumIGFBP3 in the patients and survivors group than the control group than normal serum level (*table 2*, *figure 2*).

Reference for IGFBP3 level was described as increased more than the normal serum level (20–100 pg/ml).

DISCUSSION

The current study aimed to assess BMD in children diagnosed with ALL and who completely recovered using DEXA scan and its relation to serum IGFBP3 level in comparison with a matched group of thirty healthy children. Thirty patients with ALL and thirty survivors were recruited from Hematology and Oncology Clinic, Pediatric Department, Menoufia University.

Patients included 22 males and 8 females; their ages ranged between (4–16 years) who did not receive radiotherapy Mean ± SD (7.87 ± 3.83 yrs). Survivors were 16 males and 14 females. Their ages ranged from 6 to 20 years who did not receive radiotherapy Mean ± SD (12.37 ± 4.37 yrs).

The result shows that there was a statistically significant decrease of DEXA scan measures at the lumbar spine in survivors group than the control group with (*P*-value < 0.0001). The majority of the patients included and survivors had low BMD and low Z-score but survivors did not have osteoporosis as there was no history of fracture.

"Low bone mass for chronologic age" is the preferred terminology when either the BMC or the BMD Z-score is less than or equal to –2.0 Lewiecki et al. [9].

Muszynska-Roslan et al. [10] study the decrease in BMD in childhood ALL patients during therapy, who usually recover, returning to normal ranges, corresponding to the two years after the completion of treatment.

Like our results, Min Jae Kang et al. [11] show that survivors of ALL childhood and adolescent are at risk for osteoporosis (or low bone mass for chronologic age) during and after completion of therapy. At

Table 1
Comparison between study groups as regards DEXA Scan

Parameters	Patients (*n* = 30)		Survivors (*n* = 30)		Control (*n* = 30)		ANOVA test	*p*-value	Post hoctest
BMD, g/cm^2 Mean ± SD	0.55 ± 0.21		0.71 ± 0.23		0.84 ± 0.10		16.639	< 0.001 HS	P < S < C
Z Score of DEXA scan	**No**	**%**	**No**	**%**	**No**	**%**	**X^2 test**	***p* value**	
Normal Low z score for age Osteoporosis	4 20 6	3.3 6.6 0.0	11 19 0	36.7 63.3 0.0	30 0 0	100.0 0.0 0.0	56.41	< 0.001 HS	

Note. DEXA: dual-energy x-ray absorptiometry.

Table 2
Comparison between studied groups regarding Bone Markers (Serum Ca, Po4, ALP and IGFBP3)

Parameters	Patients (*n* = 30)	Survivors (*n* = 30)	Control (*n* = 30)	ANOVA test	*p*-value	Post hoctest
Serum Ca, mg/dl Range Mean ± SD	 6.8–11.0 9.4 ± 1.07	 7.9 – 11.3 9.3 ± 0.88	 9.4 – 11.5 9.8 ± 0.17	1.658	> 0.05 NS	–
Serum Po4 mg/dl Range Mean ± SD	 3.3–6.6 4.5 ± 0.81	 2.9–6.4 4.4 ± 0.76	 2.9–5.6 4.4 ± 0.74	0.404	 > 0.05 NS	–
Serum ALP, IU/L Range Mean ± SD	 111–400 176.3 ± 66.9	 51–220 143.4 ± 51.1	 38–90 66.4 ± 17.9	38.6	 < 0.001 HS	C < S < P
IGFBP3, pg/ml Range Mean ± SD	 900–1200 1061 ± 86.5	 300–601 409.6 ± 70.3	 23–80 47.9 ± 14.7	1872.6	< 0.001 HS	C < S < P

Note. NS – non significant (p-value > 0.05); HS – highly significant (p-value < 0.001); C – controls; P – patients; S – survivors; Ca – Calcium; Po4 – Phosphorus; ALP – Alkaline Phosphatase; IGFBP3 – Insulin growth factor binding protein 3

Figure 1
DEXA scan of studied group

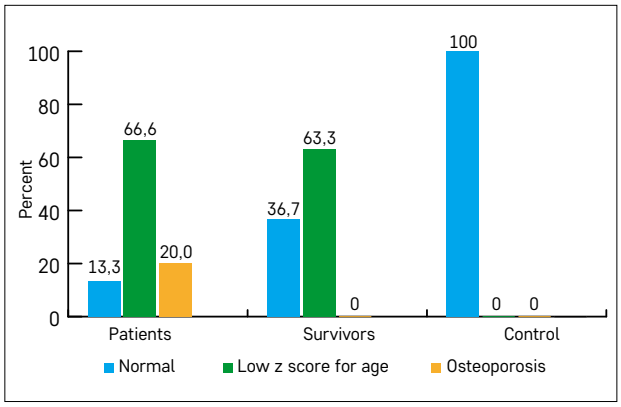
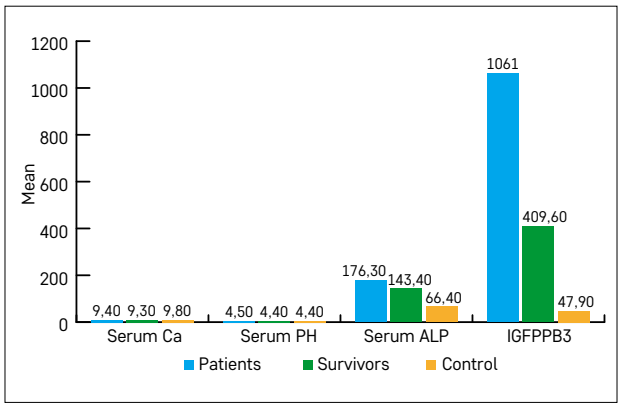


Figure 2
Serum Ca, Po4, ALP and IGFBP3 among studied groups



diagnosis, 10% to 20% of children with ALL exhibited reduced BMD at the lumbar spine. During therapy, additional bone mineral loss occurred, especially in early periods of intensified treatment, and approximately 50% of children had a reduction in BMD.

Kaste et al. [12] reported that ALL survivors had a median BMD Z-score of -0.78 standard deviations (SD), and 21% had abnormally low BMD, compared to 5% in normal populations after 15.9 years. Hoorweg-Nijman et al. [13] also concluded that bone development in patients cured of ALL is disturbed, resulting in a significantly reduced BMD. In a 24-year follow-up study, low BMD was found to be more prevalent (24%) than expected based on normative population data.

Contrary to this study and the previous studies, some reported normal BMD after cessation of ALL treatment. Van der Sluis et al. [14] reported that adult survivors of ALL whose treatment included cranial irradiation had reduced BMD, while those without cranial irradiation showed normal BMD.

An important finding in our study reveals that there was statistically significant increase serum IGFBP3 of patients and survivors group than control group than normal serum level with (*p*-value < 0.0001). Both groups had increased level of IGFBP3 > 80 pg/ml.

Similar to our result, NahidReisi et al. [15] included 33 of ALL survivors treated with chemotherapy compared with 33 matched age, sex, and pubertal stage of their healthy siblings.They found that the mean serum level of IGFBP3 in ALL survivors increased compared to the controls group.

The results of this study revealed that there was a statistically significant increase of serum parathor-

mone hormone in survivors group compared to the control group with (p-value < 0.0001).

Sebestyen et al. [16] reported the detection of defective bone integrity, associated with inadequate mineralization and abnormal architecture, would prompt the exploration of a role for bisphosphonates to enhance bone health and thereby minimize the risk of osteoporosis and debilitating/life-limiting fractures.

Pfeilschifter et al. [17] reported that chemotherapeutic agents, such as corticosteroids, methotrexate, and alkylating agents were well known to cause BMD deficits directly or indirectly. Corticosteroids inhibit new bone formation by decreasing osteoblastic activity, including osteocalcin production, and by directly increasing osteoclastic bone resorption.

CONCLUSION

A child with ALL may be cured. Still, the effects of treatment are life-long, and he or she is at risk of low bone density and osteoporosis.

We recommend that the patients and survivors of ALL be screened by regular follow up of serum Calcium, Phosphorus, and Alkaline phosphatase, and DEXA scan. Early detection of vitamin D deficiency with proper treatment by vitamin D supplementation should be done. Hypovitamin D is common among healthy children in our society, so enhancement of diet quality is necessary.

FUNDING
Not specified.

CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

References

1. Seiter K., Sarkodee-Adoo C., Talavera F., Sacher R.A., Besa E.C., eds. Acute Lymphoblastic Leukemia. Medscape Reference. WebMD. Retrieved 17 April 2014.
2. Lin J.T., Lane J.M. Osteoporosis: a review. Clin Orthop Relat Res 2004; 425: 126–34.
3. NIH Consensus Development Panel on Osteoporosis. Osteoporosis prevention, diagnosis, and therapy. JAMA 2001; 285: 785–95.
4. Haddy T.B., Adde M.A., McCalla J. Late effects in longterm survivors of high-grade non-Hodgkin's lymphomas. J Clin Oncol 1998; 16: 2070–9.
5. Kishi S., Griener J., Cheng C., Das S., Cook E.H., Pei D., et al. Homocysteine, pharmacogenetics, and neurotoxicity in children with leukemia. J Clin Oncol 2003; 21 (16): 3084–91.
6. Pui C.H., Sandlund J.T., Pei D. Improved outcome for children with acute lymphoblastic leukemia: results of Total Therapy Study XIIIB at St Jude Children's Research Hospital. Blood 2004; 104 (9): 2690–6.
7. ISCD Position Development Conference. Diagnosis of osteoporosis in men, premenopausal women, and children. J Clin Densitom 2004; 7: 17–26.
8. Frank R., Horacio P., Linda D.M., Raoul H.E., Richard C., Henderson C.M., et al. Fracture Prediction and the Definition of Osteoporosis in Children and Adolescents: The ISCD Pediatric Official Positions. J Clin Densitom 2007; 1: 22–8.
9. Lewiecki E.M., Baim S., Binkley N., Bilezikian J.P., Kendler D.L. Report of the International Society for Clinica Densitometry 2007 Adult Position Development Conference and Official Positions. South Med J 2008: 101: 735–9.
10. Muszynska-Roslan K., Panasiuk A., Latoch E., Krawczuk-Rybak M., Konstantynowicz J. Little evidence of a low bone mass in acute lymphoblastic leukemia survivors. J Clin Densitom 2012; 15: 108–15.
11. Kang M.J., Lim J.S. Bone mineral density deficits in childhood cancer survivors: Pathophysiology, prevalence, screening, and management. Korean J Pediatr 2013; 56 (2): 60–7.
12. Kaste S.C., Jones-Wallace D., Rose S.R., Boyett J.M., Lustig R.H., Rivera G.K., et al. Bone mineral decrements in survivors of childhood acute lymphoblastic leukemia: frequency of occurrence and risk factors for their development. Leukemia 2001; 15: 728–34.
13. Hoorweg-Nijman J.J.G., Kardos G., Roost J.C. Bone mineral density and markers of bone turnover in young adult survivors of childhood lymphoblastic leukemia. Clin Endocrinol 1999; 50: 237–44.
14. Van der Sluis I.M., van den Heuvel-Eibrink M.M., Hahlen K., Krenning E.P., de Muinck Keizer-Schrama S.M. Bone mineral density, body composition, and height in long-term survivors of acute lymphoblastic leukemia in childhood. Med Pediatr Oncol 2000; 35: 415–20.
15. Reisi N., Iravani P., Raeissi P., Kelishadi R. Vitamin D and Bone Minerals Status in the Long-term Survivors of Childhood Acute Lymphoblastic Leukemia. Int J Prev Med 2015; 6: 87.
16. Sebestyen J.F., Srivastava T., Alon U.S. Bisphosphonates use in children. Clin Pediatr (Phila) 2012; 51: 1011–24.
17. Pfeilschifter J., Diel I.J. Osteoporosis due to cancer treatment: pathogenesis and management. J Clin Oncol 2000; 18: 1570–93.