Original Article

Effect of 1/25 $(OH)_2$-Vitamine D on Bone Mineral Density in Childhood Acute Leukemia

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Abstract

Background

Bone mineral density (BMD) may have occurred following treatment of Acute lymphoblastic Leukemia (ALL). 25-hydroxyvitamin D has been insufficiency described in these patients. In this Randomized Control Trial (RCT), we assessed the effectiveness of oral vitamin D administration after one year of treatment to protect bone density.

Materials and Methods

Twenty-four survivors of ALL patients (17 males and 7 females), who had completed their treatment with oral vitamin D supplement, at least 1 yr previously, and Twenty-five (20 males and 5 females) control group were examined with dual energy x-ray absorptiometry of the total body and L2–L4 vertebrae and neck of femur.

Result

Average of BMD (g/cm^2) was significantly increased in oral vitamin D supplemented children (p=0.038) but average of Z-score decreased (p=0.006). Osteoporosis in this group was 4.2% and in lortnoc group, 40.9%.

Conclusion

Oral vitamin D supplementation to ALL children during 1 year did not show impact on Z-score and BMD (g/cm^2). On the other hand, osteoporosis decreased in this group.

Keywords

Leukemia, Vitamin D, Bone Density

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Introduction

As a result of using modern treatment protocols, the prognosis of acute lymphoblastic leukemia (ALL) in childhood has dramatically improved over the past 30 years, reaching cure rates of at least 80%. Hence, the long-term complications of their disease and treatment have become increasingly important (1). Patients treated for ALL, the most common childhood cancer, are at particular risk of impaired bone mass accretion, because the peak age of disease onset corresponds to a period of rapid growth and bone mass accumulation. Adults treated for ALL in childhood have shown significant reduction in bone mineral density (BMD) (2). A decrease in BMD by 1SD is associated with a 1.5- to 3-fold increase in the relative risk of fracture(3). Cancer and cancer treatments can affect BMD through several mechanisms. Illness itself may result in reduced BMD because of prolonged immobilization, altered diet, and elevated immune cytokines (4,8). Contemporary cancer treatment regimens, include antimetabolite drugs, alkylating agents, glucocorticoids and cranial radiation can reduce BMD. ALL treatments have several side effects such as sex hormone deficit, growth hormone deficit, changes in insulin-like growth factor and its ligand proteins (insulin-like growth factor binding proteins), and alterations in vitamin D metabolism (9,13). 1,25(OH) vitamin D promotes enterocyte differentiation and the intestinal absorption of calcium and phosphorus, thereby enhancing bone mineralization. ALL patients have calcitriol deficit, because of tumoral necrosis factor-related citoquines (14, 15). Dual energy x-ray absorptiometry (DXA) measures areal bone mineral density, providing an estimate of bone mass at a specific site. Results must be interpreted using age and gender-specific standards (Z-scores) and not adult standards (T-scores)(16).

In this study we used oral vitamine D to administered bone mineral mass accretion in childhood survivors of ALL, who had completed their treatment.

Materials and Methods

This is a Randomized Control Trial (RCT) study. Statistical society of this research contains all Leukemic children who referred to cooperate doctor's office and samples selected from 90-91(2011-2012), after 1 year's induction remission chemotherapy .

Exclusion criteria were: Consent of parents for participating, lack of infect to a disease which influenced bone metabolism (e.g. chronic disease, bone disease), lack of diagnosis of growth hormone deficiency or treated with growth hormone and also no consumption of Calcium or Vitamin D supplement during the past 6 months. Among the patients, those who had one exclusion criteria were removed from our study, and the remaining patients were randomly divided into two groups. First, level of 25 (OH) D of serum in all patients were measured till we could determine status of level of vitamin D. Then group 1 were treated by oral vitamin D supplement with dose of 50000 units weekly during 12 months and group 2 received placebo during this time. In our study, we needed patient's level of vitamin D and other factors in 2 time points (in first and when 12 months ended) which in both times they were introduced to one laboratory for all experiments. Measuring of serum 25(OH) D with ELISA method by 5nmol/lit sensitivity (equal with 2ng/lit) and 100 percent specificity by Fax Stat 2100 Device manufactured by awareness Company of United States America. Bone Mineral Density of Lumbar Vertebral (L_2-L_4) and neck of femur were assessed after 12 months follow up by DXA.

Statistical Analysis

After gathering data they were analyzed by Statistical Package for the Social Sciences,

SPSS 11.5 for Windows with using of Descriptive Statistics and based on Chi-Square,T-test and Fisher.

Results

Results of this study showed that between 49 participated patients in group one consist of 70.8% male and 29.2% female and in group two, 80% male and 20% were female. Average of age was 7.34±4.1, which there was no significant difference between both patients. Average of the amount of Calcium in group 1 was 9.481and in group 2, 9.279. Also average of the amount of Phosphor in group 1 was 4.7 and in group 2, 4.525. As a result, there was no significant difference between 2 groups for amount of Calcium and Phosphor. (P_{ca}=0/139, P_P=0/370). raey eno retfA average of amount of vitamin D_3 in group 1 was 94.21± 57.18 and in group 2 was 93.76±55.98, p =0.979. There is estimated that 5% of the normal population has diminished BMD; thus, 95% of the normal population has BMD *z* scores above -1.645 SDs (17). We considered a BMD value of 1.645 SDs below the mean (5th percentile) or lower to be abnormal. However, our results showed significant different in amount of BMD in 2 groups with p=0.038. Average of Z-score in group 1 was -1.116±0.853 and in group 2, -1.963±1.114. Osteopenia in group 1 was 58.3% and in group 2, 45.5%, Osteoporosis in group 1, 4.2% and in group 2, 40.9%. In group 1, 37.5% and in group 2, 13.6% of patients had normal none status and there was significant difference between two groups and group 1 had better none status than group 2.

Table 1.Variation between BMD AND Z-score in group 1 and group 2(p-value=0.006)

	Group 1 Mean±SD	**Group 2** Mean±SD	**Total** Mean±SD	**p-value**
BMD(g/cm^3)	0.521±0.112	0.448±0.111	0.489±0.119	0.038
Z-Score	-1.116±0.853	-1.963±1.114	-1.549±1.068	0.006

T-test exact

Table 2.Variation between Osteopenia and Osteoporosis and normal status in group 1 and group 2(p-value= 0.007)

	Group1	**Group2**
Osteopenia	14(%58/3)	10(%45/5)
Osteoporosis	1(%4/2)	9(%40/9)
Normal	9(%37/5)	3(%13/6)

Discussion

The majority of children with acute lymphoblastic leukemia (ALL) will now survive to adulthood. The prevalence and risk factors for long-term treatment sequelae have increased. Decreased bone mineral density (BMD), which can lead to fractures, has been recognized in acute lymphoblastic leukemia (ALL) patients. A reduction in BMD may abound with bone strength and increase the risk of fragility fractures in adult survivors and even in childhood(18). Radiographic evidence of osteopenia was reported by *Atkinson* and Halton et al (12, 15) as an initial finding in 13% of ALL patients. Achievement of normal BMD largely genetically determined (19). But it may also be modified by such factors as cranial irradiation (14, 20) chemotherapy, nutritional status and physical activity levels(21,22). Alterations in vitamin D

metabolism are one of the several side effects of ALL treatments.

In our study, the placebo group had lower plasmatic calcitriol after 12 months. This is similar to a prospective longitudinal cohort study, Halton et al described in 40 children submitted to an ALL therapeutic protocol, interestingly 70% of them had subnormal calcitriol levels (15), and Atkinson described in a group of 66 children at diagnosis of ALL, 70% of the children had low plasmatic calcitriol (12). We evaluated oral vitamin D effect on BMD, according to the literature reported evidence that suggests deficit of this vitamin in the children with ALL. Our investigation did not prove a significant benefit on BMD (g/cm^2) and Z-score in the vitamin D supplement ALL children. This result concur the findings of Paulina et al, concurred with who described that One-year calcitriol administered to recently diagnose ALL children did not show benefit on BMD (g/cm^2) but they observed a positive effect of calcitriol in a subset of patients whose baseline lumbar BMD was lower (24). A possible explanation to our observation could be explained because the age of the children. It is well known that with the pubertal spurt starts a period of exponential bone accretion. This pubertal period may be dramatically affected with any deleterious factor to bone metabolism. Decreased bone mineral density (BMD), which can lead to fractures, deformity has also been recognized in acute lymphoblastic leukemia (ALL) patients (24). *Rogalsky et al*. reported the fractures in 25% of children with acute leukemia, 12% pathological, and 13% following trauma, during the course of their disease (20). In the study of Atkinson at the end of 2-year chemotherapy, 39% of them had fractures and 83% had radiographic evidence of osteopenia(12). In our study osteoporosis was low in patients who had completed their treatment with oral vitamin D supplement than group 2 and normal bone status increased. In conclusion, oral vitamin D supplementation to ALL children during 1 year enhances did not show impact on Z-score and BMD (g/cm^2). ALL children who received oral vitamin D supplementation showed a decrease osteoporosis. In the last group Calcium and Phosphor levels had increased.

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Conflict of Interest

The authors have no conflict of interest.

References

1-Schrappe M, Reiter A, Ludwig WD, Harbott J, Zimmermann M, Hiddemann W,et al. Improved outcome in childhood acute lymphoblastic leukemia despite reduced use of anthracyclines and cranial radiotherapy: results of trial ALL-BFM 90.German-Austrian-Swiss ALL-BFM Study Group. Blood. 2000;95(11):3310-22.

2-Brennan BM, Rahim A, Adams JA, Eden OB, Shalet SM. Reduced bone mineral density in young adults following cure of acute lymphoblastic leukaemia in childhood. Br J Cancer. 1999 Apr;79(11-12):1859-63.

3-Melton LJ 3rd, Chrischilles EA, Cooper C, Lane AW, Riggs BL. Perspective. How many women have osteoporosis? J Bone Miner Res. 1992 ;7(9):1005-10.

4-Friedlaender GE, Tross RB, Doganis AC, Kirkwood JM, Baron R. Effects of chemotherapeutic agents on bone. I. Short-term methotrexate and doxorubicin (adriamycin) treatment in a rat model. J Bone Joint Surg Am. 1984 ;66(4):602-7.

5-BaylinkDJ. Glucocorticoid-induced osteoporosis. N Engl J Med 1983; 309:306-308.

6-Silverman FN. The skeletal lesions in leukemia; clinical and roentgenographic observations in 103 infants and children, with a review of the literature. Am J Roentgenol Radium Ther. 1948 ;59(6):819-44.

7-Samuda GM, Cheng MY, Yeung CY. Back pain and vertebral compression: an uncommon presentation of childhood acute lymphoblastic leukemia. J Pediatr Orthop. 1987;7(2):175-8.

8-Tillmann V, Darlington AS, Eiser C, Bishop NJ, Davies HA. 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. 2002;17(6):1073-80.

9-van der Sluis IM, van den Heuvel-Eibrink MM, Hählen K, Krenning EP, de Muinck Keizer-Schrama SM. Altered bone mineral density and body composition, and increased fracture risk in childhood acute lymphoblastic leukemia. J Pediatr. 2002;141(2):204-10.
10-Fischer G S, Neira L L, Ferreiro M M, Torres C MT, Giadrosich R V, Milinarsky T A, et al. [Bone mineral density in leukemic children after completing one month of chemotherapy]. Rev Med Chil. 2005;133(1):71-6.
11-Davies JH, Evans BA, Jenney ME, Gregory JW. Skeletal morbidity in childhood acute lymphoblastic leukaemia. Clin Endocrinol (Oxf). 2005;63(1):1-9.
12-Atkinson SA, Halton JM, Bradley C, Wu B, Barr RD. Bone and mineral abnormalities in childhood acute lymphoblastic leukemia: influence of disease, drugs and nutrition. Int J Cancer Suppl. 1998;11:35-9.
13-Arikoski P, Komulainen J, Voutilainen R, Riikonen P, Parviainen M, Tapanainen P, et al. Reduced bone mineral density in long-term survivors of childhood acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 1998;20(3):234-40.
14-Halton JM, Atkinson SA, Fraher L, Webber CE, Cockshott WP, Tam C, et al. Mineral homeostasis and bone mass at diagnosis in children with acute lymphoblastic leukemia. J Pediatr. 1995;126(4):557-64.
15-Halton JM, Atkinson SA, Fraher L, Webber C, Gill GJ, Dawson S, et al.Altered mineral metabolism and bone mass in children during treatment for acute lymphoblastic leukemia. J Bone Miner Res. 1996;11(11):1774-83.
16-Kaste SC. Skeletal toxicities of treatment in children with cancer. Pediatr Blood Cancer. 2008;50(2 Suppl):469-73; discussion 486.
17.Kaste SC, Jones-Wallace D, Rose SR, Boyett JM, Lustig RH, Rivera GK, et al. Bone mineral decrements in survivors of childhood acute lymphoblastic leukemia: frequency of occurrence and risk factors for their development. Leukemia. 2001;15(5):728-34.
18-Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ. 1996 ;312(7041):1254-9.
19.Warner JT, Evans WD, Webb DK, Bell W, Gregory JW. Relative osteopenia after treatment for acute lymphoblastic leukemia. Pediatr Res. 1999;45(4 Pt1):544-51.
20-Atkinson SA, Fraher L, Gundberg CM, Andrew M, Pai M, Barr RD. Mineral homeostasis and bone mass in children treated for acute lymphoblastic leukemia. J Pediatr. 1989;114(5):793-800.
21-Masera G, Carnelli V, Ferrari M, Recchia M, Bellini F. Prognostic significance of radiological bone involvement in childhood acute lymphoblastic leukaemia. Arch Dis Child. 1977;52(7):530-3.
22-Pui C-H, Evans WE. Acute lymphoblastic leukemia. N Engl J Med 1998; 339:605-615.
24- Díaz PR, Neira LC, Fischer SG, Teresa Torres MC, Milinarsky AT, Giadrosich VR, et al. Effect of 1,25(OH)2-vitamin D on bone mass in children with acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2008;30(1):15-9.
23-Söker M, Devecioğlu C, Gürkan F, Haspolat K. Spontaneous humerus fracture and osteoporosis: an unusual initial presentation of acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2000;22(4):358-60.
24-Rogalsky RJ, Black GB, Reed MH. Orthopaedic manifestations of leukemia in children. J Bone Joint Surg Am. 1986 Apr;68(4):494-501.