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Vitamin D and Bone Minerals Status in the Long-term Survivors of Childhood Acute Lymphoblastic Leukemia

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ABSTRACT

Background: Low vitamin D and diminished bone minerals with the potential for fractures are one of the nonapparent late effects of acute lymphoblastic leukemia (ALL). Chemotherapy and radiation were known as two important risk factors. We evaluated these late effects in ALL survivors who were treated with chemotherapy or chemo plus cranial radiation therapy.

Methods: In a case–control study, 33 of ALL survivors who were treated with chemotherapy (Group A), and 33 subjects who were treated with chemoplus cranial radiation (Group B) were compared against 33 matched age, sex, and pubertal stage of their healthy siblings (Group C). Standard anthropometric data were collected as well as Tanner staging for puberty, number of fractures since treatment, serum calcium (Ca), phosphorus (P), magnesium (Mg), alkaline phosphatase, parathyroid hormone, and 25-hydroxyvitamin D (25(OH) D). The independent *t*-test, one-way ANOVA, Chi-square test, and Tukey's test were used to analyze the data.

Results: The findings indicated that the mean serum levels of 25(OH) D in ALL survivors (i.e. Groups A and B) with age mean score of 11.2 years and 12.3 years, average treatment length: 3.25 years and average time after treatment completion: 4 years, was lower compared to the controls group (12.94 ± 6.69, 14.6 ± 8.1, 20.16 ± 10.83, respectively, $P < 0.001$) but no significant difference was observed between Group A and B in this regard ($P > 0.05$). Other clinical and laboratory parameters had no significant differences between the survivors and control. Vitamin D deficiency (<20 ng/ml) was observed in 27% of group A and 24% of group B and vitamin D insufficiency (20–30 ng/ml) in 72.7% and 69.6% survivors of Group A and B and 48.5% of controls group ($P = 0.003$).

Conclusions: ALL treatment is associated with the increase in prevalence of vitamin D insufficiency in the childhood ALL survivors and since the low vitamin D level potentially increases the risk of low bone density, subsequent malignancies, and cardiovascular disease in the survivors, close follow-up of such patients are highly recommended to prevent the stated complications.

Keywords: Acute lymphoblastic leukemia, bone minerals, long-term survivors, vitamin D insufficiency

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common malignancy in childhood.[1] The advances in diagnostic and therapeutic methods have led to increase the 5-year survival of childhood ALL patients to more than 80% and about two-thirds of patients reached adulthood.[2-4]

Improved survival of childhood leukemia is a success but is associated with increase the late effects.[5,6] Some of the late effects are more recognized, but little is known about the vitamin D status and bone minerals.[2] Vitamin D status may be the effect on adverse medical outcomes of childhood cancer and increase the risk of osteoporosis, cardiovascular disease, and subsequent malignancies in survivors of childhood malignancies.[7,8] In addition may be associated with higher cancer risk,[9] inferior relapse-free survival,[10] cancer mortality rate[11] and worse prognosis[12] in adult patients.

In survivors of childhood ALL low sun exposure, nutritional deficiencies, decrease physical activity, systemic or intrathecal (IT) methotrexate, long-term glucocorticoid therapy, and radiation are known as potential risk factors for impaired 25-hydroxyvitamin D (25(OH) D) status and bone metabolism.[7,13-18] Hypocalcemia, hypomagnesemia, hypovitaminose D, and decreased matrix mineralization were seen during and after chemotherapy[1,13,19] Abnormalities in bone minerals and bone density were also reported after radiation therapy.[2,20]

Bioactive form of vitamin D (1,25(OH) D) helps the absorption and regulation of calcium, magnesium, and phosphorous.[12,21] Regulation of bone matrix proteins, stimulation of differentiation of osteoclasts, and induction of the expression of osteocalcin are the effects of vitamin D on bone but the most important effect of vitamin D on bone "is to provide the proper balance of calcium and phosphorous to support bone mineralization."[21] The major inducer of synthesis of 1,25(OH) D is parathormone. This hormone associated with alkaline phosphatase (Alk P) and vitamin D is the most important predictors of bone mass changes.[21,22]

Corticosteroids can decrease intestinal absorption of calcium and vitamin D, and can decrease activity and lifespan of osteoblasts, and also can increase bone resorption (due to decrease intestinal Ca absorption) and urinary excretion of calcium.[2,23] Bone changes usually occurred in the first 6 months after starting of oral steroid. Low dose of oral prednisone (≥5 mg daily) for more than 3 months was associated with risk of bone fracture and 30–50% of all patients treated with glucocorticoids continuously over 6 months would develop low bone mass or fractures.[23,24] van der Sluis IM *et al*. reported that ALL patients had a six-fold higher fracture rate than healthy controls.[25] Methotrexate is the other antineoplastic drug which can effect on bone metabolism. This drug has similar and occasionally synergic effects with glucocorticoid.[24]

Although in the past, studies established that ALL patients are at risk of bone and mineral abnormalities[1,5,13-15,17-20] but there are limited studies about this in ALL survivors and at time of present study, based on our knowledge, there was no study that to compare bone minerals and vitamin D status in childhood ALL survivors who were treated with different type of treatment (chemotherapy alone or chemotherapy plus radiation therapy) so we decided to evaluate and compare these conditions in long-term survivors of childhood ALL.

METHODS

A case–control study was performed on survivors of childhood ALL who were treated at the Isfahan University of Medical Sciences' Children's Cancer Centers (Syed Al-Shohada and Al-Zahra Hospitals) during 2012. The Isfahan Province is located in the central part of Iran. In this study, two groups of survivors of childhood ALL-one treated with chemotherapy alone, and the other with a combination of chemotherapy and cranial radiation (the so-called Group A and B) were compared against their healthy siblings. Research Council and Ethics Committee of School of Medicine approved this study (ethical and study project number: 392082).

The statistical population was survivors of childhood ALL (n = 127) who were coming to the center for periodic follow-up during 2012. To select the sample, the inclusion criteria were having a past history of childhood ALL, age more than 3 years (because the mean length of treatment is 3 years), and completion of treatment. The exclusion criteria were having history of ALL relapse, past history of mental retardation and Down syndrome (due to possible decreased physical activity), physical disability, extracranial radiation, bone disease (Osteogenesis Imperfecta), consumption of any substances or drug that may affect bone mass after completion of treatment (calcium, corticosteroid, vitamin D, etc.). Thirteen of the survivors excluded from the study for the following reasons: Down syndrome (3 cases), mental retardation (1 case), physical disability (1 case) and extracranial radiation (3 cases), ALL relapse (5 cases). From the remaining survivors, two groups of subjects (i.e. Group A and B) with 33 subjects within each were selected to be to be included in this research. Group A consisted of the survivors of childhood ALL who were treated with chemotherapy (including prednisolone 40 mg/m^2 for 4 weeks induction, dexamethasone 10 mg/m^2 or prednisolone 40 mg/m^2 for 3 weeks re-induction and then 9 days tapering and 40 mg/m^2 prednisolone for 5 days monthly as pulses during maintenance therapy and minimum 16 times IT MTX (age <1 year: 6 mg, age 1–1.9 years: 8 mg, age 2–2.9 years: 10 mg, age more than 3 years: 12 mg) during treatment,[26] and Group B treated with chemotherapy

similar to group A and 1800 rad cranial radiation. Thirty-three of voluntary healthy siblings of survivors were matched by age, sex, and pubertal stage to be included in the control group (Group C).

A written informed consent was obtained from the parents who agreed with the participation of their children in this study.

Data collection

The data were collected via questionnaire and medical chart. The data were collected from parents of the investigated children and recorded in the questionnaire. The measured items were age at diagnosis of ALL, the time interval after the completion of treatment and duration of treatment for Group A and B and history of bone fractures for three groups were collected by data in medical patient's charts and questions from parents and recorded in questionnaires. Height and weight were measured for all subjects, and body mass index (BMI) was calculated as the weight in the kilogram divided by height in square meters. Pubertal stage also was assessed by the physician according to the tanner staging.[27]

Biochemical and hormonal studies

Five milliliter of fasting venous blood was taken from participants and was centrifuged after 15 min incubation at room temperature. Serum biochemistries (Ca, P, Mg, and albumin [Alb]) and serum Alk P (as marker of bone remodeling) and calciotropic hormones (25(OH) D and parathyroid hormone [PTH]) were measured using standard methods and when available, laboratory specific age and sex matches' reference data were used. For any of cases that had hypoalbuminemia (normal range of Alb was 3.5–5.2 [g/dl]), adjusted serum calcium was calculated using the following formula:

$$\text{Adjusted Ca} = \text{Serum Ca} + 0.8 \times (\text{Normal Alb} - \text{Patient Alb})$$

Serum Ca, P, and total Alk *P* levels were measured using photometric methods (Calcium CPC, Phosphate UV and Alk *P* DGKC Kit, Pars Azmoun Co., Tehran, Iran). The sensitivity of assays mentioned was 0.2 mg/dl, 0.7 mg/dl, and 3 U/L, respectively. Intra and inter assay CV% for calcium, *P* and total Alk *P* of the samples were 1.4, 2.7, 1.9, 3.1, and 1.1, 1.8, respectively. Mg was measured using photometric methods with 0.2 sensitivity (Takbio System Co., Spain). Alb was measured using Pars Azmoun kit with 0.1 sensitivity (Pars Azmoun Co., Tehran, Iran). Serum level of 25(OH) D was measured using the Chemiluminescent Immunoassay (CLIA) method (25(OH) D CLIA kit, Diasorin, Stillwater, MN, USA); the kit expected range was 4-150 ng/ml. The lowest reportable value was 4.0 ng/ml based on an inter-assay precision that approximates 20% CV (functional sensitivity). Vitamin D level <20 ng/ml: Deficient (<10 ng/ml: Sever deficient), 20–30 ng/ml: Insufficient and >30 ng/ml: Normal.[28,29] Sera PTH level was determined using a CLIA kit (Diasorin, USA).

Statistical analysis

The data were analyzed using one-way ANOVA, independent *t*-test, Tukey's test, and Chi-square test SPSS: V. 17.0. Chicago: SPSS Inc. Age at diagnosis, duration of treatment and time interval after completion of treatment were compared using an independent *t*-test. Age, weight, height, BMI, and the markers of bone turnover were compared using the one-way ANOVA test. Bone fractures numbers and pubertal stages, and vitamin D deficiency among the investigated groups was also compared using the Chi-square test.

The one-way ANOVA was also utilized to compare the mean differences of serum level Ca, P, Mg, Alk P, PTH, and 25(OH) D between the three investigated groups. The Post-hoc comparisons were done using the Tuley's test.

RESULTS

The finding of the present study revealed that the age mean score for Group A, B, and C was 11.2 years, 12.3 years, and 11.2 years, respectively, and 60.6% of Group A, 63.6% of Group B, and 60.6% of Group C were male. Male to female ratio (M/F) was 2/1, average length of treatment was 3.25 years, and average time after completion of treatment was 4 years (range: 1–15.5 years) [Table 1].

No significant difference between age, age at diagnosis, duration of treatment and time interval after completion of treatment, height, weight, BMI of survivors, and subjects in the control group was observed.

In regard to the pubertal stage, overall, 42 participants were in Stage 1 of puberty, 13 participants in Stage 2, 5 participants in Stage 3, 10 participants in Stage 4, and 29 of them were in Stage 5 of puberty, and pubertal stage distribution between 3 groups showed no significant difference ($P = 0.38$).

In regard to the bone fractures history after the beginning of treatment, 3 subjects in Group A and 2 subjects in Group B (1 subject during and 4 subjects after treatment, more in forearm) and none in Group C showed to have history of bone fractures, and no significant differences were observed between the three groups ($P = 0.65$).

Table 2 represents mean and standard deviation of serum biochemical and hormonal analysis of bone mineral metabolism for Group A, B, and C.

The findings of the present study indicated that there was no significant difference between serum Ca, P, Mg and Alb levels of the three groups ($P = 0.24$). The Tukey's test findings showed a significant difference between Alk P of the survivors groups (A and B) versus control group

Table 1: Demographic and anthropometric characteristics of participants of Groups A, B, and C

Characteristics	Group A (*n*=33)	Group B (*n*=33)	Group C (*n*=33)	*P*
Male/female	20/33	21/33	20/33	0.95
Age (years)	11.2±4.7	12.3±4.8	11.2±4.1	0.51
Age at diagnosis (years)	5.1±3.8	6.6±3.8	-	0.07
Height (cm)	138.6±24.6	143.9±26.2	144.3±19.5	0.55
Weight (kg)	39.0±21.4	32.7±20.5	37.4±16.5	0.51
BMI (kg/m^2)	18.6±4.0	17.1±3.9	17.4±4.5	0.52
Duration of treatment (years)	3.3±0.5	3.5±0.7	-	0.70
Time interval after completion of treatment (years)	3.7±2.4	4.5±4.1	-	0.67

BMI=Body mass index

Table 2: Mean and SD of serum biochemical and hormonal studies of bone mineral metabolism in Group A, B, and C

Bone mineral	Group A	Group B	Group C	*P*
	Chemotherapy alone	Chemo+cranial radiation therapy	Control	Group A, B, C
Ca (mg/dl)	9.8±0.36	9.7±0.39	9.8±0.38	0.24
P (mg/dl)	4.2±0.69	4.3±0.81	4.1±0.61	0.58
Mg (mg/dl)	2.1±0.22	2.1±0.29	2.2±0.22	0.40
Alb (g/dl)	4.5±0.27	4.4±0.40	4.5±0.64	0.67
Alk *P* (IU/L)	498.9±195	483.3±245.5	402.3±148.5	0.026
PTH (pg/ml)	39.6±33.3	32.5±16.6	27.9±24.8	0.040
25(OH) D (ng/ml)	12.94±6.69	14.6±8.1	20.16±10.83	0.003

Ca=Calcium, *P*=Phosphorus, Mg=Magnesium, Alk *P*=Alkaline phosphatase, PTH=Parathyroid hormone, Alb=Albumin, 25(OH) D=25-hydroxyvitamin D, SD=Standard deviation

($P < 0.05$), but no significant difference was observed between Group A and B ($P > 0.05$). The same statistics hold true for the serum level of PTH and serum level of 25(OH) D of the stated groups.

Vitamin D deficiency (<20 ng/ml) was observed in 27% of group A and 24% of group B and vitamin D insufficiency (20–30 ng/ml) in 72.7% and 69.6% survivors of Group A and B and 48.5% of control group. These differences were significant among the investigated groups ($P = 0.003$).

DISCUSSION

The findings of the present study indicated that prevalence of 25(OH) D insufficiency in childhood ALL survivors was high (70%) and more than their healthy siblings, and treatment type (chemotherapy or chemo plus cranial radiation [1800 cGy]) had no differential effect on such prevalence.

Sinha *et al.*[8] also in an outpatient-based cross-sectional study of 61 children with a history of cancer (median age 11.1 years; range 1.5–24.4 years) and 60 control subjects (median age 8.4 years; range 0.2–18.0 years) showed that "vitamin D deficiency (<10 ng/ml]) was more common among children with malignant disease than the control group (21.3% vs. 3.3%; $P = 0.013$)" and "suboptimal vitamin D (<20 ng/mL) was noticeable in 62% of cases". Halton *et al.*[19] in a prospective longitudinal cohort study that measured bone mass and biochemical mineral status of 40 subjects of childhood ALL (27 male, 13 female, aged 0.3–17.0 years) during 2 years of chemotherapy reported that plasma 1,25-dihydroxyvitamin D remained to be subnormal for more than 70% of the children. In a 25(OH) D testing, Choudhary *et al.*[7] also revealed that the prevalence of 25(OH) D insufficiency (<20 ng/mL) was high for (29%) of the 484 cancer survivors (brain tumors [23.6%], neuroblastoma [21%], and leukemia [17.6%], mean age = 12.3 years).

In our study, the prevalence of vitamin D insufficiency was also common in controls group (48.5%) and was compatible with the prevalence of 25(OH) D insufficiency in the general healthy children and adolescents (14–49%).[7]

Other studies' findings being done in the city of Isfahan (central part of Iran)[28] reported a "high prevalence of vitamin D deficiency in 513 healthy children living in this city (25(OH) D was <20 ng/mL in 3%, and <33 ng/mL in 26% of subjects)." Moussavi *et al.*[29] also indicated that up to 70% of the adolescent girls in Isfahan's high schools had 25(OH) D levels below 20 ng/ml.

Rabbani *et al.*[30] in a cross-sectional study with 963 students (424 boys and 539 girls) aged 7–18 years that were selected by random sampling in Tehran (Capital of Iran) revealed that 53.6% of girls and 11.3% of boys had vitamin D insufficiency (serum 25(OH) D <20 ng/ml).

The findings of the present study indicated that approximately 8% of the ALL survivors had long bones fractures which more involved the forearm.

Our findings support the findings of the te Winkel *et al*.[31] te Winkel *et al*.[31] in a prospective study who conducted on 69 newly diagnosed ALL patients with a mean age of 7.4 years that were treated according to the dexamethasone-based protocol of the Dutch Childhood Oncology Group (ALL9) revealed that 9 patients had a fracture during therapy (n = 5) or within 1 year after completion of treatment (n = 4). Some researchers believe that children treated for ALL, because of widely used corticosteroids in the treatment have a high incidence of bone fractures[32] and "fracture rate is 6 times higher in ALL survivors compared to the healthy matched group counterpart."[25] Halton *et al*.[19] also reported that bone fractures occurred in 39% of investigated subjects (n = 40) during the treatment.

In the present study, there was no significant difference between age, sex, age at diagnosis, duration of treatment and time interval after completion of treatment and BMI of survivors of Group A and B. Our findings are compatible with Simmons *et al*.[33] and Choudhary *et al*.[7] findings that reported "there was not enough evidence to suggest treatment type, gender, years since diagnosis or BMI were associated with low serum 25(OH) D levels."

The findings of the present study revealed that there was no significant difference between the vitamin D levels, and bone minerals of the radiotherapy and chemotherapy-treated survivors, although Choudhary *et al*.[7] contended that cranial radiation is not a risk factor for 25(OH) D insufficiency yet more, and larger studies are needed to determine the role of radiation therapy on bone minerals and vitamin D.

It should be noted that some of the positional factors that may affect vitamin D status in ALL patients directly or indirectly is nutritional status, level of physical activities, and sun exposure. Nutritional status is an important factor which can ameliorate secondary effects of ALL and its treatment on vitamin D metabolism.[33] In general, low percentage of children and adolescents in the world take enough recommended daily dose of calcium and vitamin D. In healthy US adolescent population vitamin D deficiency and insufficiency have been estimated 9% and 61%, respectively.[34] In urban areas of Iran, moderate to severe vitamin D deficiency for age <50 years have been observed in 47.2% of males and 54.2% of females.[35] In Isfahan Province, this statistics for adults were 26.9% and 43.5%, respectively.[36] Physical inactivity and sun exposure are the other factors that may effect on bone metabolism and vitamin D levels which we did not evaluate in this study.

CONCLUSIONS

Acute lymphoblastic leukemia treatment is associated with the increase in prevalence of vitamin D insufficiency in the childhood ALL survivors and since the low vitamin D level potentially increases the risk of low bone density, subsequent malignancies and cardiovascular disease in the survivors, close follow-up of such patients are highly recommended to prevent the stated complications.

Limitations

Inability to accurately determine the dietary status of the ALL survivors, levels of their sun exposure and physical activities during of disease and after completion of their treatment was one of the main limitations of the present study. Small sample size was also another limitation in this research.

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REFERENCES

1. Mandel K, Atkinson S, Barr RD, Pencharz P. Skeletal morbidity in childhood acute lymphoblastic leukemia. J Clin Oncol 2004;22:1215-21.
2. Arikoski P, Komulainen J, Riikonen P, Jurvelin JS, Voutilainen R, Kröger H. Reduced bone density at completion of chemotherapy for a malignancy. Arch Dis Child 1999;80:143-8.
3. Williams JM, Davis KS. Central nervous system prophylactic treatment for childhood leukemia: Neuropsychological outcome studies. Cancer Treat Rev 1986;13:113-27.
4. Allen JC. The effects of cancer therapy on the nervous system. J Pediatr 1978;93:903-9.
5. Nysom K, Holm K, Michaelsen KF, Hertz H, Müller J, Mølgaard C. Bone mass after treatment for acute lymphoblastic leukemia in childhood. J Clin Oncol 1998;16:3752-60.
6. Nahid R, Leila K. Comparison of intelligence quotient in children surviving leukemia who received different prophylactic central nervous system treatments. Adv Biomed Res 2012;1:83.
7. Choudhary A, Chou J, Heller G, Sklar C. Prevalence of vitamin D insufficiency in survivors of childhood cancer. Pediatr Blood Cancer 2013;60:1237-9.
8. Sinha A, Avery P, Turner S, Bailey S, Cheetham T. Vitamin D status in paediatric patients with cancer. Pediatr Blood Cancer 2011;57:594-8.
9. Shanafelt TD, Drake MT, Maurer MJ, Allmer C, Rabe KG, Slager SL, *et al*. Vitamin D insufficiency and prognosis in chronic lymphocytic leukemia. Blood 2011;117:1492-8.
10. Lee HJ, Muindi JR, Tan W, Hu Q, Wang D, Liu S, *et al*. Low 25(OH) vitamin D3 levels are associated with adverse outcome in newly diagnosed, intensively treated adult acute myeloid leukemia. Cancer 2014;120:521-9.
11. Lappe J M, Travers-Gustafson D, Davies KM, Recker RR, and Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: Results of a randomized trial 1,2. Am J Clin Nutr 2007; 85:1586-91.
12. Molica S, Digiesi G, Antenucci A, Levato L, Mirabelli R, Molica M, *et al*. Vitamin D insuffi ciency predicts time to fi rst treatment (TFT) in early chronic lymphocytic leukemia (CLL). Leuk Res 2012;36:443-7.
13. 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.
14. Warner JT, Evans WD, Webb DK, Bell W, Gregory JW. Relative osteopenia after treatment for acute lymphoblastic leukemia. Pediatr Res 1999;45:544-51.

15. Wasilewski-Masker K, Kaste SC, Hudson MM, Esiashvili N, Mattano LA, Meacham LR. Bone mineral density deficits in survivors of childhood cancer: Long-term follow-up guidelines and review of the literature. Pediatrics 2008;121:e705-13.
16. Kelly J, Damron T, Grant W, Anker C, Holdridge S, Shaw S, *et al.* Cross-sectional study of bone mineral density in adult survivors of solid pediatric cancers. J Pediatr Hematol Oncol 2005;27:248-53.
17. Kelly KM, Thornton JC, Hughes D, Osunkwo I, Weiner M, Wang J, *et al.* Total body bone measurements: A cross-sectional study in children with acute lymphoblastic leukemia during and following completion of therapy. Pediatr Blood Cancer 2009;52:33-8.
18. van der Sluis IM, van den Heuvel-Eibrink MM, Hählen K, Krenning EP, de Muinck Keizer-Schrama SM. Bone mineral density, body composition, and height in long-term survivors of acute lymphoblastic leukemia in childhood. Med Pediatr Oncol 2000;35:415-20.
19. 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;11:1774-83.
20. 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;15:728-34.
21. How KL, Hazewinkel HA, Mol JA. Dietary vitamin D dependence of cat and dog due to inadequate cutaneous synthesis of vitamin D. Gen Comp Endocrinol 1994;96:12-8.
22. El-Hajj Fuleihan G, Muwakkit S, Arabi A, Daouk LE, Ghalayini T, Chaiban J, *et al.* Predictors of bone loss in childhood hematologic malignancies: A prospective study. Osteoporos Int 2012;23:665-74.
23. Osteoporosis and Steroid Medications, What's Effects do Steroids Have on Bone? Department of Health. Information for a Healthy New York. New York States. Available from: http://www.health.ny.gov/diseases/conditions/osteoporosis/osteoporosis_and_steroids.htm. [Last accessed on 2015 Feb 03].
24. Bianchi ML. Glucorticoids and bone: Some general remarks and some special observations in pediatric patients. Calcif Tissue Int 2002;70:384-90.
25. 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;141:204-10.
26. Lanzkowsky P. Treatment of newly diagnosed acute lymphoblastic leukemia. In: Manual of Pediatric Hematology Oncology. 5th ed. USA: Academic Press; 2011. p. 535-40.
27. Tanner JM. Puberty and the Tanner Stages. Available from: http://www.childgrowthfoundation.org. [Last accessed on ???].
28. Ardestani PM, Salek M, Keshteli AH, Nejadnik H, Amini M, Hosseini SM, *et al.* Vitamin D status of 6- to 7-year-old children living in Isfahan, Iran. Endokrynol Pol 2010;61:377-82.
29. Moussavi M, Heidarpour R, Aminorroaya A, Pournaghshband Z, Amini M. Prevalence of vitamin D deficiency in Isfahani high school students in 2004. Horm Res 2005;64:144-8.
30. Rabbani A, Alavian SM, Motlagh ME, Ashtiani MT, Ardalan G, Salavati A, *et al.* Vitamin D insufficiency among children and adolescents living in Tehran, Iran. J Trop Pediatr 2009;55:189-91.
31. te Winkel ML, van Beek RD, de Muinck Keizer-Schrama SM, Uitterlinden AG, Hop WC, Pieters R, *et al.* Pharmacogenetic risk factors for altered bone mineral density and body composition in pediatric acute lymphoblastic leukemia. Haematologica 2010;95:752-9.
32. Strauss AJ, Su JT, Dalton VM, Gelber RD, Sallan SE, Silverman LB. Bony morbidity in children treated for acute lymphoblastic leukemia. J Clin Oncol 2001;19:3066-72.
33. Simmons JH, Chow EJ, Koehler E, Esbenshade A, Smith LA, Sanders J, *et al.* Significant 25-hydroxyvitamin D deficiency in child and adolescent survivors of acute lymphoblastic leukemia: Treatment with chemotherapy compared with allogeneic stem cell transplant. Pediatr Blood Cancer 2011;56:1114-9.
34. Kumar J, Muntner P, Kaskel FJ, Hailpern SM, Melamed ML. Prevalence and associations of 25-hydroxyvitamin D deficiency in US children: NHANES 2001-2004. Pediatrics 2009;124:e362-70.
35. Heshmat E, Mohammad K, Majdzadeh SR. Vitamin D deficiency in IRAN: A multi-center study among different urban areas. Iran J Public Health 2008 37:72-78.
36. Hovsepian S, Amini M, Aminorroaya A, Amini P, Iraj B. Prevalence of vitamin D deficiency among adult population of Isfahan City, Iran. J Health Popul Nutr 2011;29:149-55.

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