

The optimal dose of vitamin D in growing girls during academic years: a randomized trial

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Aim: Prevalence of vitamin D deficiency is remarkable during childhood and adolescence throughout the world. Sufficient intake of vitamin D contributes to a number of health outcomes. The aim of this study was to specify the optimal dose of vitamin D in growing girls in a Muslim country during an academic year.

Materials and methods: This randomized clinical trial study was carried out in Yazd in the center of Iran in 2007; 120 junior high school girls (aged 12-15 years) were randomly divided into 4 groups. Sixty students in groups I and II were treated for vitamin D deficiency with 300,000 IU vitamin D₃ and then randomly received 50,000 U/monthly or 100,000IU/3 months vitamin D₃; 60 other students in groups III and IV received 50,000 IU/3 months and 100,000/3 months from the beginning of the academic year. Medication continued for the entire academic year; 1 month after the last dose, serum 25(OH)D levels were measured.

Results: The mean level of 25 (OH) D was 29.7 ± 4.60 ng/mL in group I and 30 ± 5.61 ng/mL in group II. Mean serum levels of 25 (OH) D were 15.2 ± 6 ng/mL and 23 ± 6.8 ng/mL for groups III and IV, respectively.

Conclusion: Neither doses of about 800 IU/day nor 1000 IU/day are sufficient to maintain 25(OH)D in optimal level (> 20 ng/mL) for all, but after the treatment of deficiency, intakes of about 1000 IU/day or 2000 IU/day of vitamin D maintained optimal level in all of the students.

Key words: Vitamin D, girl, bolus therapy, 25OH vitamin D

Introduction

Vitamin D is an essential hormone for growth and development of bones in children and strong skeletal structure in adults (1). In vitamin D deficiency, only 10%-15% of calcium of normal diet is absorbed. This amount increases to 40% in the presence of adequate vitamin D (2,3). Moreover, epidemiologic studies show vitamin D deficiency increases the risk of important diseases like malignancy, cardiovascular disease, hypertension, stroke, diabetes, multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease (4). Many studies in recent years have demonstrated that vitamin D deficiency could exist in children and young adults without any obvious sign or symptoms (5-12). Girls particularly are more prone to vitamin D deficiency because of their less exposure to the sun and also their limited outdoor activities (5). Since about 35% of bone mass is acquired during 4 years around puberty (13) it seems rational to pay special attention to this age group. Diagnosis, treatment, and prevention of vitamin D deficiency in adolescents could, therefore, be very important for their future health (14). In Iran, primary evaluation demonstrated a high percentage of vitamin D deficiency in different age groups and in various locations especially in winter (15-19).

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There are different ways to receive sufficient vitamin D: either enough exposure to sunshine or consumption of supplements separately or in combination with fortified foods. Considering the importance of puberty, in some countries (e.g. France and Argentina) in which foods are not fortified, vitamin D supplements are offered to the girls in bolus doses every few months (18,20-22). Currently recommended intakes of vitamin D are 200-400 IU/day for young adults. These recommendations are not sufficient to reach the optimal 25(OH)D concentration in most of the population. For the majority of endpoints, an advantageous serum concentration of 25(OH)D is 30 ng/mL (4). The recommended dose of vitamin D for serum 25(OH)D level of 30 ng/mL in 50% of subjects is 1000 IU/day and for 88% of them is 4000 IU/day (23,24).

Results of several studies supported that intake of vitamin D 4000-10000 IU/day for adults and 2000 IU/day for children over the age of 1 is safe and sufficient (23,25).

Studies have investigated the required daily dose of vitamin D for adults (26,27); however, further studies are needed to evaluate the best dose of vitamin D for optimal 25(OH)D concentrations in healthy growing children and adolescents.

In view of the high prevalence of vitamin D deficiency among girls in Yazd (28) this study was designed to determine the adequate amount of vitamin D to maintain a level more than 20 ng/mL through academic years. Yazd is one the sunniest provinces in the country and the Middle East, and, therefore, this study could reveal the minimum requirement of vitamin D in other areas with less sunshine than our region.

Methods

This study was conducted as a randomised clinical trial on the female students at junior high school (aged 12-15 years) in Yazd during autumn and winter 2007. A total sample size of 120 subjects was calculated based on a previous study (20), considering CI = 95%, study power of 80%, SD1 = 4.4 ng/mL, SD2 = 4.6 ng/mL and minimal clinical differences ($d = 3.3$ ng/mL) with loss to follow up of 20%. The students were all healthy without any history of endocrine,

bone, liver, kidney, gastrointestinal, and metabolic diseases. None of the students had been consuming any vitamin D supplements. Students were chosen randomly and after an explanatory session to describe the details of experiment to the parents and students, their consents were taken. Students were then arbitrarily divided into 4 groups: 60 in group I and II who treated as vitamin D deficiency with 300,000 vitamin D3 and then randomly received 50,000 IU each month (about 2000 IU/day) or 100,000 IU/3 months (about 1000 IU/day), 30 in group III received 50,000 IU/3 months (400 IU/day), and 30 in group IV received 100,000 IU/3 months (about 1000/day). A questionnaire was filled face to face for each student. Height, weight, and the stage of their puberty (Tanner stage) were then assessed. Vitamin D3 was given as a pearl (50,000 units, Alhavi Company Iran) to groups. The second and complementary doses (identical to dose one) were given at the intervals up to the end of the academic year. An information pack on side effects of vitamin D along with a questionnaire was provided for participants to fill if any of side effects occurred within 2 weeks of taking doses. After 2 weeks all the questionnaires were collected. One month after taking the final dose, a 3-5 mL blood sample was taken and assessed for 25(OH)D. The blood samples were transferred to the laboratory where they were centrifuged and frozen at -20°C . Chemiluminescence immunoassay (DiaSorin, LIAISON® 25 OH Vitamin D assay) was used to measure 25(OH)D (as a main indicator of vitamin D). SPSS was used to analyse the data where statistical descriptive and analytic tests like mean (SD), t-test, and Mann-Whitney were applied. $P < 0.05$ was considered as the significant level of differences.

Results

One hundred and twenty students were enrolled in this study. Two students in group I and 7 students in group II were eliminated because of their changing school or not using the right dose. In the 2 groups who were treated first as deficient, the mean levels of 25(OH)D were 29.7 ± 4.60 ng/mL in the 50,000 IU group and 30 ± 5.61 ng/mL in the 100,000 IU group. There were no significant differences in serum level means (P value = 0.75 t-test). The range of serum 25(OH)D level in the 1000 IU/day group was 20.34-

36.23 ng/mL and while it was 20.43-47.88 in the 2000 IU/day group. All the students who received vitamin D had serum level of > 20 ng/mL. Serum 25(OH)D levels in 53.5% of 2000 IU/day group and 43.5% of 1000 IU/day group were > 30 ng/mL. The Table shows the vitamin levels at the end of the academic year.

In the other 2 groups mean serum levels of 25(OH)D were 15.2 ± 6 ng/mL and 23 ± 6.8 ng/mL for groups III and IV, respectively. Differences between means in groups III and IV were significant ($PV = 0.0000$). The range of serum 25(OH)D level in group III was 7-27 ng/mL while it was 13.4-37.5 in group IV. Neither dosage produced serum levels of 25(OH)D above 20 ng/mL in all cases, but in group IV all had levels of 25(OH) more than 12 ng/mL and 55% more than 20 ng/mL. In group III only 13% had levels of 25(OH) more than 20 ng/mL. All these doses were safe for all of the students although some complained about headaches and nausea for which none of them needed any medical care.

Discussion

In this study we evaluated the effect of 4 oral vitamin D bolus doses on 25(OH)D level in junior high school girls in Yazd (with its geographical location of 30°N). The required serum 25(OH)D level is the point which avoids serum parathyroid hormone (PTH) elevation. Several studies estimated this point to be between 8 and 35 ng/mL, but for most of the population, 25(OH)D level of 20 ng/mL or even higher is considered appropriate (29).

Intake of vitamin D 1600 IU/day to maintain serum 25(OH)D concentrations > 32 ng/mL in 97.5% of the 20- to 40-year-old adults was suggested by Cashman et al. (26), but Heaney et al. recommended 5000 IU/day for this purpose (25). Although the exact optimal consumption dose of daily vitamin D is not determined, 2000 units/day has been suggested to be safe for adolescents (31). In a study carried out in French adolescents aged 10-15 years, 100,000 units of vitamin D every 3 months during winter were able to raise their serum level of vitamin D above 20 ng/mL with decreasing parathyroid hormone levels. This study is similar to our study regarding the duration and the age of participants (30). In our study, after 9 months, 36% of students who received vitamin D 2000 IU/day had serum 25(OH)D concentrations > 32 ng/mL. It seems that a greater requirement of vitamin D in adolescent girls or severe initial deficiencies in this region could be reasons for these differences.

Conclusion

Results of this study show that in the area with high prevalence of vitamin D deficiency (more than 50%), the recommended dose of neither 400 IU/day nor 800 IU/day is sufficient to maintain optimal level in all. However, after treatment of deficiency with 300,000 IU of vitamin D, both doses of 1000 or 2000 IU/day would maintain serum 25(OH)D concentrations > 20 ng/mL in all of the samples during academic years. If we consider level more than 30 ng/mL as the ideal level our study revealed higher doses than what we use should be recommend.

Table. The distribution of 25 OH vitamin D among treated groups at the end of the academic year.

100,000 unit/ 3 months Group IV (n: 30)	50,000 unit/ 3 months Group III (n: 30)	300,000 IU + 100, 1000/ 3 months Group II (n: 23)	300,000 IU + 50,000/months Group I (n: 28)	Groups Level 25OH-VITD
0%	13.5%	zero	zero	Severe deficiency (25(OH)D<10)
45%	7%	zero	zero	Deficiency 25(OH)D=10-20
35.5%	10.8%	57%	47%	Adequate 25(OH)D=20-30
19.5%	2.7%	43%	53%	Ideal 25(OH)D=30-100

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