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Vitamin D deficiency in healthy adolescents aged 12–17 years in Kirikkale, Turkey

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ABSTRACT

Objective: This study was performed to determine the prevalence of vitamin D deficiency and associated factors in apparently-healthy adolescents in the Central Anatolia region of Turkey where nutritional rickets is common.

Materials and Methods: This prospective cohort study was performed in the Kirikkale province of Central Anatolia, Turkey. Adolescents aged 1 to 17 years old with no health complaints were enrolled between February 2012 and February 2013. Adolescents younger than 12 and older than 17 age, those with chronic diseases, and those using any medications known to affect vitamin D metabolism were excluded. A total of 358 adolescents, consisting of 235 (65.5%) girls and 123 (34.5%) boys with an average age of 14.6 ± 1.58 years, were included in this study. Serum concentrations of 25-hydroxy vitamin D [25(OH)D] and other bone mineralization markers were measured in the summer and winter.

Results: In blood samples, phosphorus (P), alkaline phosphatase (ALP), bone-ALP (B-ALP), parathyroid hormone (PTH), and 25(OH)D levels were considerably lower in female adolescents than in male adolescents. The rate of vitamin D deficiency was higher in girls than in boys. B-ALP level was compared to Vitamin D level in each season; there was no significant relation in winter, but vitamin D level decreased with increasing B-ALP level in summer. B-ALP level was compared to vitamin D level according to sex; there was no significant relation in male adolescents, but vitamin D level decreased while B-ALP level increased in female adolescents.

Conclusion: This study showed that vitamin D deficiency or inadequacy is very common among adolescents, particularly in females in Central Anatolia region of Turkey.

Key words: 25-hydroxy vitamin D, Adolescent rickets, Vitamin D inadequacy, Subclinical vitamin D deficiency, Vitamin D insufficiency

INTRODUCTION

Vitamin D plays a pivotal role as a hormone together with parathyroid hormone (PTH) in regulating calcium (Ca) and phosphorus (P) levels, and therefore, ensuring optimal bone mineralization and metabolic and neuromuscular functions (1, 2). Rickets is the most important result of vitamin D deficiency in children. However, without clinical symptoms of rickets, inadequate vitamin D level is defined by serum 25-hydroxy vitamin D3 (25(OH)D) levels in laboratory tests. The prevalence of vitamin D insufficiency (hypovitaminosis D) or subclinical vitamin D deficiency is estimated to be higher than previously thought, and its incidence is increasing both in Turkey and worldwide (3–8). In vitamin D insufficiency, 25(OH)D levels decrease first, followed by a reduction of intestinal Ca and P absorption. Parathormone and active vitamin D maintain serum Ca levels within the normal range, and clinical and biochemical findings become more apparent during this process. Ultimately, it becomes impossible to maintain Ca equilibrium in vitamin D insufficiency despite PTH and active vitamin D production, with adverse effects on bone metabolism (9).

Vitamin D receptors are present in many tissues, and active vitamin D is synthesized by exposure of the skin to sufficient sunlight. Vitamin D deficiency is a risk factor for the development of several cancers (breast, ovarian, colon, prostate), autoimmune diseases (multiple sclerosis, type 1 and type 2 diabetes mellitus), hyperproliferative skin diseases (psoriasis), hypertension, and infectious diseases. Therefore, maintaining normal vitamin D levels is becoming increasingly important to ensure optimal bone health and prevent chronic diseases (10).

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The present study was performed to determine the prevalence of vitamin D insufficiency in healthy-appearing adolescents, to identify factors involved in vitamin D deficiency, and to demonstrate the effects on bone health in our region where subclinical vitamin D insufficiency is relatively common. This report will provide information about vitamin D insufficiency and/or deficiency to parents and adolescents to prevent vitamin D insufficiency; it will also emphasize the significance of nutrition, sunlight exposure, and physical activity for protection against the effects of vitamin D insufficiency, aid in developing health policy to address vitamin D deficiency, and highlight the need for vitamin D supplementation in high risk subjects.

MATERIAL and METHODs

Adolescents aged 12–17 years old without chronic disorders or on medications and attending primary and secondary schools in the central Anatolian city of Kirikkale, Turkey, were enrolled in this study via a screening study conducted between February 2012 and February 2013. The study was conducted in four phases:

1) identification of the study group;
2) obtaining blood samples and a questionnaire;
3) evaluation of serum samples; and
4) statistical analysis.

Based on the survey data provided by Kirikkale Census Bureau, the population contained 30000 adolescents aged 12–17 years old at the time of the study. Given an estimated vitamin D deficiency incidence rate of 1.67%–19% (7), sample-size calculation indicated that it was necessary to enroll 250–450 adolescents (n=284) in the study. All subjects were selected randomly from different schools and underwent physical examination in the schools according to the study plan. The Tanner staging system was used for the assessment of puberty.

A questionnaire regarding sociodemographic characteristics, dietary habits, sunlight exposure, drug usage, chronic diseases, and physical activity of the subjects was developed. All subjects who agreed to complete the questionnaire after discussing it with their parents/guardians were included in the study. The ethical committee of our institution approved the study (10.05.2012, No: 12/32), and all subjects provided written informed consent. Adolescents using vitamin D and Ca preparations, anticonvulsant agents, corticosteroids, heparin, and estrogen derivatives, which may affect bone metabolism, and those with chronic liver, kidney, endocrine, or gastrointestinal diseases were excluded from the study.

Blood samples were drawn from all subjects into vacuum tubes and EDTA tubes after an overnight fast for biochemical evaluation. Sera were obtained by centrifugation at 3780 rpm for 7 minutes. Serum samples were analyzed at the Biochemistry and Paediatric Metabolism Laboratory of Kirikkale University Medical Faculty, to assess the levels of Ca, P, ALP, B-ALP, vitamin D, and PTH.

Serum calcium levels were assessed using the O-cresolphthalein method, and the results are given as mg/dL. Normal serum total Ca level was defined as 8.8–10.4 mg/dL (37).

Serum phosphorous levels were assessed using the phosphomolybdenum complex method. Normal serum total P level was defined as 2.9–5.4 mg/dL (37).

Serum alkaline phosphatase levels were assessed using the p-nitrophenylphosphate (P-NPP) kinetic method, and the results were given as U/L (37). Normal ALP levels were evaluated according to the age and sex. Bone-specific alkaline phosphatase levels were assessed by enzyme-linked immunosorbent assay (ELISA) using a commercial kit (39).

To evaluate serum 25(OH)D levels, 2 cc of venous blood samples were added to EDTA tubes, centrifuged for 5 minutes at 5000 rpm, and the resulting plasma samples were examined by high performance liquid chromatography (HPLC).

Serum PTH levels were assessed using a chemiluminescent (immunoassay) method, and the results were given as pg/mL. Normal serum PTH level was defined as 12–65 pg/mL.

Statistical analyses were performed using SPSS version 20.0. Quantitative variables are expressed as means±standard deviation (SD), while qualitative variables are expressed as percentages. Independent samples, t-test, and chi-square test were used for comparisons, as appropriate. Spearman's correlation test was used to assess correlations between parameters. In all analyses, $p<0.05$ was taken to indicate statistical significance.

RESULTs

A total of 358 subjects from six different schools met the inclusion criteria and completed the study. The study population consisted of 235 (65.6%) girls and 123 (34.4%) boys with a mean age of 14.6±1.58 years, ranging from 12 to 17 years. The ratio of girls/boys was 1.9.

Biochemical values relevant to our investigation are shown in **Table 1**.

Table 1. Biochemical values (mean±SD)

	Whole group n=358	Girls n=235	Boys n=123	*p*-value boys vs. girls
Ca	9.96±0.389 mg/dL	9.968±0.386	9.966±0.376	>0.05
P	3.94±0.663 mg/dL	3.816±0.614	4.198±0.683	>0.05
ALP	147.23±89.328 U/L	111.62±58.29	215.26±98.6	>0.05
B-ALP	64.38±46.11 µg/L	46.706±34.27	98.00±47.26	>0.05
25(OH)D	20.86±10.97 ng/mL	19.88±11.04	22.987±10.509	>0.05
PTH	48.62±24.04 pg/mL	46.0.88±19.64	53.524±30.318	>0.05

Ca, calcium; P, phosphorus; ALP, alkaline phosphatase; B-ALP, bone alkaline phosphatase; PTH, parathormone.

Mean levels of Ca, P, ALP, B-ALP, PTH, and 25(OH)D3 were significantly lower in adolescent girls than in adolescent boys (p<0.05) (**Table 2**).

The prevalence of vitamin D insufficiency, defined according to the accepted vitamin D levels in Europe, was high in our population and was more common among girls than boys (41).

- Deficiency: serum 25(OH)D3 level BELOW 10 ng/mL
- Inadequate: serum 25(OH)D3 level BETWEEN 10 and 25 ng/mL
- Adequate: serum 25(OH)D3 level ABOVE 25 ng/mL (**Table 2**)

The USA Institute of Medicine (IOM) adjusts the following guidelines for serum 25(OH)D levels (42) (**Table 3**).

- Deficiency: serum 25(OH)D3 level BELOW 20 ng/mL
- Inadequate: serum 25(OH)D3 level BETWEEN 20-30ng/mL
- Adequate serum 25(OH)D3 level ABOVE 30 ng/mL

Vitamin D levels were lower in adolescents 12–14 years old than in those 15–17 years old although the difference was not significant (p>0.05) (**Table 4**).

Assessment of the relationship between sex and physical activity indicated that the number of adolescents who did not participate in sporting activities was higher in girls than in boys (60.7% vs. 24.4%, respectively). Adolescents with lower levels of physical activity showed reduced vitamin D levels. There was a non-significant difference in serum vitamin D levels related to physical activity between boys and girls.

A positive correlation was found between mean Ca level and household income (**Table 5**).

Ca levels were higher in adolescents whose mothers were employed than in those whose mothers did not work outside the home (p>0.05).

B-ALP levels were compared with seasonal vitamin D levels, and the results indicated that there was no significant relation in winter, while there was an increase in B-ALP levels with decreasing vitamin D levels in summer. B-ALP levels were compared to vitamin D levels in both sexes, and the results indicated that there was a significant increase in B-ALP levels with decreasing vitamin D levels in adolescent girls, while there was no significant relation in adolescent boys (**Table 6**).

Season, age, parental educational status, mother's employment status, socioeconomic status, dietary habits, pubertal stage, mode of dressing in girls, physical activity, duration of sun exposure, and body mass index had no effect on vitamin D level. No associations were detected between vitamin D levels and those of Ca, P, ALP, or PTH.

Table 2. Accepted vitamin D levels according to the Ministry of Health, Turkey (31-33, 38)

	Group n (%)	Girls n (%)	Boys n (%)	*p*-value boys vs. girls
Deficiency: <10 ng/mL	46 (12.8%)	37 (15.7%)	9 (7.3%)	>0.05
Inadequate: 10–25 ng/mL	204 (57%)	131 (55.7%)	73 (59.3%)	>0.05
Adequate: >25 ng/mL	108 (30.2%)	67 (28.5%)	41 (33.3%)	>0.05

Table 3. Accepted 25(OH)D serum levels according to USA IOM guidelines (40)

	Group n (%)	Girls n (%)	Boys n (%)	*p*-value boys vs. girls
Deficiency: <20 ng/mL	183 (51.1%)	137 (58.3%)	46 (37.4%)	>0.05
Inadequate: 20–30 ng/mL	112 (31.3%)	60 (25.5%)	52 (42.3%)	>0.05
Adequate: >30 ng/mL	63 (17.6%)	38 (16.2%)	25 (20.3%)	>0.05

Table 4. Comparison of Vitamin D levels according to age

Age (year)	Mean±SD (ng/mL)	Minimum (ng/mL)	Maximum (ng/mL)	*p*-value
12 (n=44)	19.85±9.78	3.76	57.57	p>0.05
13 (n=52)	19.78±9.41	8.64	44.99	p>0.05
14 (n=72)	21.14±11.30	4.20	63.04	p>0.05
15 (n=71)	20.30±10.41	3.53	48.07	p>0.05
16 (n=66)	20.91±13.02	4.68	76.15	p>0.05
17 (n=49)	23.23±10.93	4.91	57.40	p>0.05

Table 5. Income classes and mean serum Ca levels (mean±SD)

Income class (TL/month*)	Group Ca (mg/dL)	Minimum Ca (mg/dL)	Maximum Ca (mg/dL)	*p*-value
High (213)	9.993±0.356	8.90	11.00	>0.05
Medium (117)	9.956±0.417	9.19	11.50	>0.05
Low (28)	9.802±0.468	8.14	10.61	>0.05

Table 6. Relationship between gonadal for B-ALP and vitamin D levels

B-ALP	Group B-ALP	Minimum	Maximum	*p*-value
Girls (235)	20.08±11.47	4.20	76.15	**<0.05**
Boys (123)	22.63±10.73	15.65	63.04	>0.05

DISCUSSION

Adolescence is a critical period for bone health in adulthood. In this period, the risk of vitamin D insufficiency is increased due to accelerated bone development. Vitamin D deficiency and/or insufficiency are important health issues that affect not only infants but also +adolescents (30). There is still no absolute consensus as to what a normal range for 25(OH)vit D. However, recently, are being agreed that by most experts/scientists, vitamin D deficiency should be defined as a 25(OH)D of <20 ng/mL. Vitamin D insufficiency is now accepted as a 25(OH)D of 21-29 ng/mL. Thus, despite the lack of rickets in both developed and developing countries, the high incidence rates of vitamin D deficiency and/or inadequate vitamin D levels in the adolescent period have attracted a great deal of attention (7).

There have been few studies in Turkey regarding vitamin D levels in adolescents. In a study performed in Van province, Acar et al. reported a rate of vitamin D insufficiency of 52.4% among adolescents (11). Hatun et al. reported inadequate levels of vitamin D and vitamin D deficiency in 43% and 21.3% of 89 adolescent girls, respectively (12). In a study by Budak et al., vitamin D level was found to be <16 ng/mL in the majority of 69 female university students in a reproductive age (13). Demirçeken et al. reported a 13-year-old adolescent with rickets who presented with hypocalcemic tetanus due to vitamin D deficiency caused by limited sunlight exposure (14). In our study, the rates of inadequate vitamin D level and vitamin D deficiency were 57% and 12.8% among the adolescents in Kirikkale. One of the latest studies conducted by Karagüzel et al. on vitamin D status in Turkey showed that the proportion of vitamin D deficiency (<20 ng/mL) in adolescents was 82%, and girls had lower 25(OH)D levels than boys in northeastern Turkey (24). Vitamin D level above 25 ng/mL (normal) was seen in 30.2% of the subjects. Based on the European vitamin D level classification, vitamin D deficiency (or)(<20 ng/mL) and vitamin D insufficiency (20–30 ng/mL) were seen at rates of 51.1% and 31.3%, respectively, in the adolescents from Kirikkale. Vitamin D level was >30 ng/mL (normal) in 17.6% of the adolescents included in the present study.

Nutritional rickets is more common in boys during infancy (15), while the risk is higher for girls during adolescence (3). In previous studies, the rate of vitamin D deficiency was higher in adult women than in adult men (34,35). Narchive et al. reported that 95.2% of patients diagnosed with adolescent rickets in Saudi Arabia were girls (16), while Rajeswari et al. reported that all patients diagnosed with symptomatic rickets in India were girls (17). Moussavive et al. reported vitamin D deficiency rates of 72.1% in girls and 18.3% in boys, indicating a fourfold higher incidence of vitamin D deficiency in girls (18). In our study, the mean vitamin D level was 19.7±11.03 ng/mL in adolescent girls, while that in adolescent boys was 22.9±10.5 ng/mL (p<0.05). Conversely, Chapuy et al. reported that age and sex had no effect on serum 25(OH)D levels in a study performed in 1596 volunteers from nine geographic regions in France (19). Our study showed no significant association between age and vitamin D level in adolescence. However, vitamin D insufficiency and deficiency were more common in adolescents at 12–13 years old, when puberty is accelerated.

This finding emphasized the importance of diagnosis and treatment of inadequate vitamin D level and/or deficiency in the early adolescent period in terms of bone development during subsequent years.

Therefore, it is recommended to initiate prophylaxis in the early period of adolescence due to the effects of vitamin D on subsequent life.

In a study in Izmir, Ölmez et al. reported that vitamin D levels were low in adolescents whose parents have low educational status (13). Bener et al. (20) found no associations between vitamin D level and parental educational status, employment status, or occupation in a study comparing cases with vitamin D deficiency to those with normal vitamin D levels. Our study found no significant associations between parental educational status and inadequate, deficient, or normal vitamin D levels (p>0.05).

In the present study, Ca levels were significantly higher in adolescents whose mothers were employed compared to those not working outside the home (p<0.05), suggesting higher awareness regarding nutrition among employed mothers. In addition, we speculated that the children of these mothers may be playing outside more frequently and, expose to the sun light more. Narchi et al. (16) reported that risk factors for rickets included insufficient intake of Ca (490 mg/day) and vitamin D (2.8 µg/day) from foods, as well as consumption of carbonated beverages with high P contents. In our study, no significant associations were found between adolescents' dietary habits and vitamin D deficiency, insufficiency, or normal vitamin D levels (p>0.05).

A previous study indicated an association between socioeconomic status and vitamin D level in adolescents, with low socioeconomic status being a significant risk factor for vitamin D deficiency (21). In our study, however, there was no significant association between income and vitamin D deficiency (p>0.05). Similarly, Hatun et al. also reported that socioeconomic status had no effect on vitamin D levels (12).

However, Ca levels were significantly increased in adolescents from households with higher income levels (p<0.05). This finding suggests that increased income also increases consumption of calcium-rich foods.

Narchi et al. (16) reported that the daily duration of sunlight exposure was less than 60 minutes in all 21 cases diagnosed with adolescent rickets and less than 30 minutes in three-quarters of these cases. In our study, there were no significant associations between the duration of sunlight exposure and vitamin D deficiency and/or insufficiency (p>0.05).

In our study, no significant association was detected between physical activity and vitamin D level (p>0.05). However, adolescent boys showed a significantly higher rate of participation in sports activities than girls (p<0.05). This suggests that adolescent girls with limited physical activity are at higher risk of vitamin D deficiency and/or insufficiency. In a study performed in a population of 89 girls aged 13–17 years old, Hatun et al. found that vitamin D levels were lower in girls who dressed conservatively due to religious and traditional demands. The authors found inadequate vitamin D levels in 70% of these girls and vitamin D deficiency in 30% of girls who dressed conservatively, and that vitamin D levels were significantly lower in girls who dressed conservatively compared to those who dressed more liberally (12). Ergür et al. reported lower vitamin D levels in infants of mothers who dressed conservatively (23). These studies emphasize the influences of clothing and sunlight on vitamin D levels. Acar et al. reported that vitamin D levels were lower in girls who dressed conservatively, but there was no significant association between clothing style and incidence of adolescent rickets (11). In our study population, 94.5% of adolescent girls dressed liberally whereas 5.5% dressed conservatively. There was no significant relation between clothing style and vitamin D levels in our study (p>0.05). However, this may have been due to bias caused by the lower number of adolescents who dressed conservatively.

Narchive et al. reported that all of 21 cases with adolescent rickets were in Tanner II and IV pubertal stage (16). However, we found no significant association between the pubertal stage and vitamin D in the present study (p>0.05).

Low Ca and high ALP levels are anticipated in classical nutritional rickets (15). However, 25(OH)D, Ca, P, and ALP levels were measured in a study of 193 cases, but low Ca and P levels as well as high ALP levels were not detected in any of the subjects with inadequate vitamin D levels (11). The authors suggested that 25(OH)D level should be determined in patients with risk factors who are thought to have vitamin D deficiency or insufficiency clinically even if their serum Ca, P, and ALP levels are normal (25). In another study, no changes were detected in serum Ca, P, and ALP levels in relation to vitamin D deficiency and inadequacy (20). Moreover, in another study, PTH levels remained within the normal range in adolescents with insufficient vitamin D stores at the end of winter, suggesting a distinct mechanism for maintaining normal PTH levels (26). In our study, no significant associations were detected between vitamin D level and Ca, P, ALP, or PTH.

In adults with normal liver function, 50% of total ALP originates from bones, while B-ALP accounts for 90% of total ALP in children and adolescents due to accelerated bone mineralization (27). Therefore, it is recommended to determine B-ALP for the assessment of bone turnover. However, a study performed on 382 children indicated that B-ALP levels were normal in 92% of children despite the detection of vitamin D levels <20 ng/mL in 25% of the children (28). Similarly, no significant association was detected between vitamin D level and B-ALP (p>0.05) in our study. However, the mean B-ALP level was found to be significantly higher in adolescent girls with vitamin D deficiency and/or inadequacy in winter (p<0.05). Abdullah et al. (29) suggested that there were no clinical findings of rickets in adolescents with rickets and that the most common complaint was a pain in the lower extremities. In our study, there were musculoskeletal complaints in 7% of cases, with the remaining 93% of the adolescents in the study showing no musculoskeletal complaints. Thus, there was no significant association between vitamin D levels and musculoskeletal complaints (p>0.05).

In conclusion, vitamin D deficiency and inadequate vitamin D levels were detected in 37 (15.7%) and 131 (55.7%) of 235 girls and in 9 (7.3%) and 73 (59.3%) of 123 boys included in this study, respectively, according to the criteria of the Turkish Republic Ministry of Health despite the subtropical climate and abundant sunlight in our country. Using the European vitamin D limits in our study, we found vitamin D deficiency and inadequate vitamin D levels in 60 (25.5%) and 137 (58.3%) of the girls and in 46 (37.4%) and 52 (42.3%) of the boys, respectively, indicating that low vitamin D status is a serious problem in Turkey. Results suggest that vitamin D intervention, which is a safe and non-invasive treatment, may exert a potential benefit in reducing the severity of COVID-19 infection (43). Vitamin D deficiency or inadequate vitamin D levels may increase the incidence of intrauterine growth retardation, premature birth, and congenital rickets at the time of birth. In addition, given the positive effects in reducing the risks of multiple sclerosis, hypertension, type 1 and 2 diabetes, asthma, and colon, prostate, breast, and ovarian cancer, it is becoming increasingly clear that sufficient levels of vitamin D in childhood and adolescence are essential for health.

CONCLUSION

When assessing vitamin D, geographic location, climate, lifestyle, and dietary habits should be determined, and vitamin D supplementation should be planned according to the results. This approach will prevent unnecessary diagnosis and treatment as well as vitamin D intoxication. Our results indicated that it is appropriate to use prophylactic vitamin D dosages determined according to the conditions in Turkey. Information about inadequate and/or deficient vitamin D levels should be provided to parents and adolescents to prevent vitamin D insufficiency. This important health issue can be ameliorated by emphasizing the significance of proper nutrition, sunlight exposure, and physical activity for protection against vitamin D insufficiency. It is necessary to develop a health policy to address vitamin D deficiency and to emphasis the need for vitamin D supplementation in adolescents.

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