Vitamin D status affects serum parathyroid hormone concentrations during winter in female adolescents: associations with forearm bone mineral density[1–3]

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ABSTRACT

Background: Vitamin D deficiency leads to secondary hyperparathyroidism, which has a negative effect on bone metabolism in the elderly. Puberty is an important time of bone metabolism and growth. The effect of serum 25-hydroxyvitamin D [25(OH)D] concentrations on parathyroid hormone concentrations and bone mineral density (BMD) has not been well studied cross-sectionally in adolescents.

Objective: We studied the effect of vitamin D status on serum intact parathyroid hormone (iPTH) concentrations and bone metabolism in adolescents.

Design: One hundred seventy-eight healthy female adolescents (aged 14–16 y) volunteered for this study, which was conducted in Finland (Helsinki, 60°N) during the winter. Forearm BMD at radial and ulnar sites was measured by dual energy X-ray absorptiometry. The determinants of different variables were studied by use of regression models.

Results: On the basis of the relation between serum 25(OH)D and iPTH concentrations, serum 25(OH)D concentrations $>\approx 40$ nmol/L were needed to keep serum iPTH concentrations low. One hundred ten subjects (61.8%) had serum 25(OH)D concentrations ≤ 40 nmol/L. Twenty-four subjects (13.5%) were considered vitamin D deficient when the serum 25(OH)D concentration of 25 nmol/L was used as a cutoff. Subjects with serum 25(OH)D concentrations ≤ 40 nmol/L had low mean forearm BMD values at both the radial ($P = 0.04$) and ulnar ($P = 0.08$) sites.

Conclusion: A large percentage of adolescent females have low vitamin D status during the winter in Finland, which seems to have negative effects on bone health. *Am J Clin Nutr* 2001;74:206–10.

KEY WORDS Vitamin D, serum parathyroid hormone concentrations, 25-hydroxyvitamin D, adolescent females, bone metabolism, bone mineral density, Finland

INTRODUCTION

At northern latitudes, mean serum 25-hydroxyvitamin D [25(OH)D] concentrations in humans vary significantly with the seasons. High serum concentrations in the summer and low concentrations in the winter have been observed in young and old persons, reflecting the amount of exposure to the sun (1, 2). In Finland, where there is practically no ultraviolet light from October to February, dietary vitamin D is important for maintaining a healthy vitamin D status throughout the year (3). In Finland, fish and margarine fortified with vitamin D (0.07 μg/1 g) supply 70–80% of the population's daily dietary vitamin D intake (2, 4). Milk is not as an important source of dietary vitamin D because nonfat milk and milk with 1% fat are only slightly fortified with vitamin D (0.0008 μg/1 g). Thus, because the dietary sources of vitamin D are scarce, a low vitamin D status might be expected during the winter months. A study in the early 1980s showed that during the winter, 20 of 85 (23.5%) 11–17-y-old Finnish adolescents had serum 25(OH)D concentrations <12.5 nmol/L (5). In addition, a recent study by Lehtonen-Veromaa et al (6) showed that 25 of 185 (13.4%) 9–15-y-old girls had serum 25(OH)D concentrations <20 nmol/L in the winter.

Mild vitamin D deficiency leads to secondary hyperparathyroidism in postmenopausal women and in the elderly, which has negative effects on calcium and bone metabolism. In these groups, low serum 25(OH)D and elevated serum intact parathyroid hormone (iPTH) concentrations are associated with low bone mineral density (BMD; 7, 8). In addition, increased vitamin D intake was shown to suppress the seasonal variations of serum 25(OH)D and iPTH concentrations in the elderly (9, 10). The relation between serum 25(OH)D and iPTH concentrations has not been studied much in adolescents, but earlier studies conducted with children (11) and growing male adolescents (12) found an association between serum 25(OH)D and iPTH concentrations.

On the basis of reference values, the cutoff for vitamin D deficiency in children, adolescents, and adults is generally set at 25 nmol/L (13, 14). Recently, attention has focused on choosing an appropriate serum 25(OH)D concentration that would indicate

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TABLE 1
Characteristics of the study group[1]

	Value
Age (y)	15.3 ± 0.6
Height (cm)	165 ± 6
Weight (kg)	55 ± 8
BMI (kg/m^2)	20 ± 2
Serum 25(OH)D (nmol/L)	39 ± 14
Serum iPTH (ng/L)	30 ± 14
Dietary intake	
Vitamin D (μg/d)	4.3 ± 2.8
Calcium (mg/d)	1216 ± 591
Height velocity (cm/y)	2.3 ± 2.0
Sampling time	0838 (±32 min)
Exercise (min/d)	76 ± 37
Postmenarche (mo)	35 ± 15
Users of vitamin supplements (%)[2]	27
Smokers	
(%)	16
(cigarettes/d)	4 ± 3
Users of alcohol[3]	
(%)	46
(g/d)	4.3 ± 4.8
Sunlight exposure (%)[4]	34

[1] $\bar{x}$ ± SD; n = 178; PTH, intact parathyroid hormone.
[2] During previous 3 mo.
[3] During previous month.
[4] Sunlight exposure in sunny areas abroad during previous 3 mo.

a suitable vitamin D status, based on the relation of serum 25(OH)D to iPTH concentrations. Adolescence is a crucial period for bone health, but few studies have analyzed closely the associations between serum 25(OH)D and iPTH concentrations among adolescents, or the effects of vitamin D status on the growing skeleton, with the exception of florid rickets. PTH is known to be an important regulator of bone metabolism, but the effect of serum iPTH concentrations on BMD also has not been studied much in adolescents (15, 16). In addition to serum 25(OH)D concentrations, other factors such as growth hormone and calcium intake may affect serum iPTH concentrations.

This study was conducted in Finland during the winter season (February through March) when serum 25(OH)D concentrations are lowest. We identified the prevalence of low serum 25(OH)D and high serum iPTH concentrations in 178 females aged 14–16 y, and studied the relation between serum 25(OH)D and iPTH concentrations in this age group. Because vitamin D status and serum iPTH concentrations affect BMD in the aging skeleton, we also tried to determine whether such concentrations have an effect on BMD in growing adolescents. In addition, various determinants of serum 25(OH)D and iPTH concentrations and forearm BMD were evaluated in regression models.

SUBJECTS AND METHODS

Subject selection

The study was conducted in the Helsinki area of Finland (60°N) during the months of February through March, 1997. Subjects were recruited from the upper levels of comprehensive schools. Data were obtained from 178 healthy female adolescents (aged 14–16 y) who were not taking any medication and who had no medical conditions that would affect vitamin D and calcium metabolism. Eight of the 178 females were premenarcheal and 8 were taking oral contraceptives. Informed consent was obtained from the subjects and their families before the study began. The study was approved by the Committee of Human Studies at The University of Helsinki, Department of Applied Chemistry and Microbiology, Finland.

Laboratory measurements

Blood samples were drawn between 0745 and 1000 from subjects after they had fasted. Serum samples were stored at –20°C until analyzed. The serum 25(OH)D concentration was measured by radioimmunoassay (Incstar Corporation, Stillwater, MN). The intra- and interassay CVs were 10.1% and 14.9%, respectively. On the basis of studies conducted with children and adolescents, the limit for vitamin D deficiency was set at 25 nmol/L (13, 14). Serum iPTH concentrations were measured by use of an immunoradiometric method (Incstar Corporation) with a reference range of 10–55 ng/L. Intra- and interassay CVs for serum iPTH were 2.6% and 5.9%, respectively.

Nutrient intakes and measurement of forearm bone mineral density

The dietary vitamin D and calcium intakes from the past month were estimated by use of food-frequency questionnaires (FFQ), which included pictures of portion sizes that were used previously in other dietary studies of young adults (17). Approximately 50 food items containing calcium or vitamin D were included in the FFQ. When the FFQs were returned, a nutritionist checked the FFQs together with the subject. Forearm BMD (g/cm^2) at distal radial and ulnar sites was measured with a DTX-200 Osteometer with 0.7% precision (Meditech Inc, Hawthorne, CA). The quality control of measurements was ensured daily by use of phantoms provided by the manufacturers.

Other background data

A self-reported questionnaire was used to collect information on subjects' daily habits. Subjects were required to report their weight, height, yearly height velocity, physical activity, smoking habits, alcohol intake during the previous month, use of supplements, and the amount of sunlight exposure when in places abroad during the previous 3 mo. Physical activity was calculated from subject responses in regard to hours spent on school exercise and leisure activities. A nutritionist checked each questionnaire with the subject.

Statistics

Variables were checked for normality and natural logarithm (ln) transformations were used to determine serum 25(OH)D and iPTH concentrations, dietary calcium, and vitamin D intake. Characteristics of the study group are shown in **Table 1**. The association between serum 25(OH)D and iPTH concentrations was analyzed by both linear and nonlinear regression models. The determinants of serum 25(OH)D and iPTH concentrations and forearm BMD were also analyzed in the regression models. On the basis of the relation between serum 25(OH)D and iPTH concentrations, the effects of low serum 25(OH)D and elevated serum iPTH concentrations on forearm BMD were studied by Mann-Whitney U test. Statistical analyses were performed with the use of BMDP software (18).

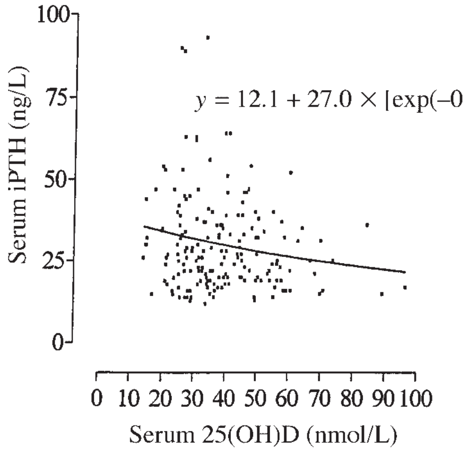

FIGURE 1. Association between serum 25-hydroxyvitamin D [25(OH)D] and intact parathyroid hormone (iPTH) concentrations in a nonlinear analysis of the study group ($n = 178$).

RESULTS

Serum 25(OH)D and iPTH concentrations

Vitamin D deficiency, based on the reference range and defined as a serum 25(OH)D concentration ≤25 nmol/L, was observed in 24 of 178 subjects (13.5%; $\bar{x}$ ± SD: 21 ± 4 nmol/L; range: 14–25 nmol/L). Elevated serum iPTH concentrations, defined as a serum iPTH concentration >55 ng/L, was observed in 9 of 178 subjects (5.1%; $\bar{x}$ ± SD: 72 ± 15 ng/L; range: 56–93 ng/L).

In linear regression analysis, a 1 unit increase in serum 25(OH)D concentration on the ln scale decreased serum iPTH concentrations by 0.198 units ($P = 0.02$). In addition to the linear model, a nonlinear regression model was fitted between serum 25(OH)D and iPTH concentrations (**Figure 1**). Among the subjects with adequate calcium intake, the relation between serum 25(OH)D and iPTH concentrations did not plateau. Thus, depending on a mean serum iPTH concentration of ≈30 ng/L, the subjects were divided into 2 groups. From the equation it can be calculated that in the study group, the mean serum iPTH concentration of ≈30 ng/L was reached at serum 25(OH)D concentrations >≈40 nmol/L [29.6 ng/L = 12.1 ng/L + 27.0 × exp(−0.011 × 39.5 nmol/L)]. In our study group, 110 subjects (61.8%; $\bar{x}$ ± SD: 30 ± 7; range: 14–40 nmol/L) had serum 25(OH)D concentrations ≤40 nmol/L.

To analyze the determinants of serum 25(OH)D concentrations, the following variables were tested in the regression model: age, body mass index (BMI), exposure to sun in places abroad, use of vitamin D–containing supplements, dietary vitamin D intake, smoking, alcohol consumption, and exercise. In the study group, sunlight exposure ($P < 0.001$), the use of vitamin D supplements ($P < 0.001$), and dietary vitamin D intake ($P = 0.33$) on the ln scale increased the serum 25(OH)D concentration on the ln scale by 0.202, 0.181, and 0.039 units, respectively. The following variables were tested when analyzing the determinants of serum iPTH concentration: age, BMI, dietary calcium intake, serum 25(OH)D concentration, height velocity, sampling time, smoking, alcohol consumption, and exercise. An increase in 1 unit of sampling time ($P = 0.02$) and in serum 25(OH)D concentration on the ln scale ($P = 0.05$) decreased the serum iPTH concentration on the ln scale by 0.138 and 0.170 units. A 1 unit increase in height velocity ($P = 0.01$) increased the serum iPTH concentration on the ln scale by 0.044 units.

Determinants of forearm bone mineral density

Simple linear regression analysis showed no significant associations between serum 25(OH)D concentration and forearm BMD (distal radius and ulna; **Table 2**). Serum iPTH concentrations also did not correlate with measured BMDs. However, regression analysis, including serum 25(OH)D and iPTH concentrations with background variables and lifestyle factors (ie, age, BMI, calcium intake, exercise, smoking, and alcohol consumption), revealed that in the forearm, background variables, including BMI and height velocity, were the strongest determinants of BMD in these growing adolescents. The daily exercise rate also significantly predicted forearm BMD at the radial site. Tested variables explained 37% ($P_{\text{model}} < 0.001$) and 34% ($P_{\text{model}} < 0.001$) of the variance in radial and ulnar BMDs.

Although BMI and yearly mean height velocity appeared to be the strongest determinants of BMD, further analyses revealed

TABLE 2
Correlation between variables reflecting bone mineral density (BMD) and serum 25-hydroxyvitamin D [25(OH)D] concentration, serum intact parathyroid hormone (iPTH) concentration, and serum 25(OH)D and iPTH concentrations in the same regression model with background variables and lifestyle factors

	BMD (ulna; g/cm^2)			BMD (radius; g/cm^2)		
	r	β	P	r	β	P
Serum 25(OH)D (nmol/L)[1]	0.09	0.005	0.59	0.09	0.013	0.25
Serum iPTH (ng/L)[1]	0.06	−0.006	0.47	0.09	−0.011	0.26
Regression model	0.34[2]	—	<0.001	0.37[2]	—	<0.001
BMI (kg/m^2)	—	0.007	<0.001	—	0.008	<0.001
Age (y)	—	−0.002	0.77	—	0.007	0.27
Height velocity (cm/y)	—	−0.009	<0.001	—	−0.011	<0.001
Dietary calcium (mg/d)[1]	—	−0.001	0.88	—	0.007	0.29
Serum 25(OH)D (nmol/L)[1]	—	−0.001	0.95	—	0.005	0.62
Serum iPTH (ng/L)[1]	—	0.004	0.60	—	0.003	0.73
Exercise (every 20 min/d)	—	0.002	0.14	—	0.004	0.04
Smoking (cigarettes/d)	—	−0.002	0.30	—	−0.001	0.77
Alcohol (every 5 g/d)	—	−0.004	0.33	—	−0.003	0.51

[1] Ln.

[2] Model r^2.

TABLE 3
Differences in forearm bone mineral density (BMD) measurements and in background variables in the subjects divided into 2 categories according to serum 25(OH)D concentration and serum intact parathyroid hormone (iPTH) concentration

	Serum 25(OH)D concentration (nmol/L)			Serum iPTH concentration (ng/L)[1]		
	≤40 (*n* = 110)	>40 (*n* = 68)	*P*	≤30 (*n* = 108)	>30 (*n* = 70)	*P*
BMD						
Ulnar (g/cm^2)	0.343 ± 0.047[2]	0.351 ± 0.043	0.08	0.348 ± 0.048	0.342 ± 0.042	0.38
Adjusted[3]	—	—	—	0.349 ± 0.046	0.342 ± 0.046	0.35
Radial (g/cm^2)	0.419 ± 0.054	0.434 ± 0.053	0.04	0.428 ± 0.055	0.420 ± 0.053	0.34
Adjusted[3]	—	—	—	0.428 ± 0.054	0.419 ± 0.054	0.28
Background variable						
Age (y)	15.3 ± 0.5	15.4 ± 0.5	0.10	15.3 ± 0.6	15.3 ± 0.6	0.92
BMI (kg/m^2)	22 ± 2	22 ± 2	0.99	22 ± 3	22 ± 2	0.32
Serum iPTH (ng/L)	31 ± 16	28 ± 11	0.41	21 ± 5	43 ± 14	<0.001
Serum 25(OH)D (nmol/L)	30 ± 7	54 ± 11	<0.001	40 ± 15	37 ± 14	0.24
Dietary calcium (mg/d)	1217 ± 631	1214 ± 525	0.46	1205 ± 566	1234 ± 632	0.86
Height velocity (cm/y)	2.4 ± 2.1	2.2 ± 1.7	0.74	2.2 ± 1.8	2.6 ± 2.2	0.25
Exercise (min/d)	73 ± 35	81 ± 41	0.20	72 ± 37	83 ± 38	0.03

[1] Mann-Whitney *U* test.

[2] $\bar{x}$ ± SD.

[3] Adjusted for exercise.

that, on the basis of the relation between serum 25(OH)D and iPTH concentrations, serum 25(OH)D concentrations ≤40 nmol/L were or tended to be associated with low forearm BMD (**Table 3**); however, serum iPTH concentrations did not significantly predict BMD.

DISCUSSION

Puberty is an extremely important time of life for bone growth; however, no previous cross-sectional study has analyzed closely the distribution of the serum 25(OH)D concentration and its connection to serum iPTH concentrations and BMDs in adolescents. In earlier studies, young, adult, and elderly Finnish populations were shown to have low vitamin D status during the winter months (2, 5, 6, 19). Studies by Ala-Houhala et al (5) and Lamberg-Allardt et al (3) showed that serum 25(OH)D concentrations are significantly lower in 11–17-y-old Finnish adolescents than in children <10 y of age. Regardless of the mean serum 25(OH)D concentrations being within the normal range, the present study showed that a low vitamin D status is common among adolescents during the winter season in southern Finland; an average of 14% of the females had serum 25(OH)D concentrations <25 nmol/L. In earlier studies, low serum 25(OH)D concentrations during winter were found in Finnish adolescents (5, 6) and in French adolescents [aged 10–17 y; 24.5% of 53 subjects had serum 25(OH)D concentrations <15 nmol/L] (20) and in French adolescent males [aged 14–16 y; 50% of 28 subjects had serum 25(OH)D concentrations <15 nmol/L] (12). However, because there might be large variability in the serum 25(OH)D assays between laboratories, the results are not always comparable (21). In the present study, although subjects with high dietary vitamin D intakes tended to have high serum 25(OH)D concentrations, vitamin D consumption became less of a contributing factor to vitamin D status when supplement consumption and sunlight exposure were increased, which confirms the results of earlier studies (22–25).

Only a few studies have addressed serum iPTH concentrations during adolescence (12, 15, 26). Our results suggest that during puberty, height velocity is positively associated with serum iPTH concentrations, which corresponds with earlier findings (16, 26). Serum iPTH concentrations >55 ng/L were found in 5% of subjects, regardless of low serum 25(OH)D concentrations. However, note that reference ranges are set for adults, not for growing adolescents. Guillemant et al (12) showed in a group of 14–16-y-old French adolescent males that despite low vitamin D status during the winter [50% of 28 subjects had serum 25(OH)D concentrations <15 nmol/L], the mean serum iPTH concentration remained within the normal range. They suggested that compared with adulthood, adolescence is a time when different physiologic mechanisms regulate the secretion of PTH (12). Our study showed that a reduction in the serum 25(OH)D concentration does not always lead to a rise in the serum iPTH concentration, even though we found higher serum iPTH concentrations in subjects with low serum 25(OH)D concentrations and a strong negative correlation between variables. In adults, it was suggested that a stable plateau for serum iPTH concentrations could be reached at serum 25(OH)D concentrations >≈75 nmol/L (27, 28). In our study, the nonlinear curve between serum 25(OH)D and iPTH concentrations did not plateau. One explanation could be that, on average, serum 25(OH)D concentrations were low and within a narrow range [all serum 25(OH)D values were <100 nmol/L]. However, the mean serum iPTH concentration in subjects during the winter season was ≈30 ng/L. On the basis of the nonlinear curve, serum iPTH concentrations of 30 ng/L can be reached at serum 25(OH)D concentrations >≈40 nmol/L. Interestingly, an earlier study also confirmed that the threshold for vitamin D deficiency in children (aged 7–10 y) may be somewhere between 30 and 50 nmol/L (29). Thus, our results indicate that a large percentage of adolescents have low vitamin D status during the winter and that the cutoff generally used for adequate serum 25(OH)D concentrations (>25 nmol/L) is too low to maintain an appropriate serum iPTH concentration during the winter, at least at higher latitudes.

In the present study, exercise correlated positively with distal radial BMD and tended to be associated with ulnar BMD, which further supports the earlier findings of positive effects of exercise on the growing skeleton (30). Also, high forearm distal radial and ulnar BMDs were found in subjects with high BMI and low height velocity, which suggests that peak bone mass is achieved after the adolescent growth spurt. Although BMI, exercise, and height velocity appeared to be the strongest determinants of BMD, low BMD values were found in subjects with serum 25(OH)D concentrations ≤40 nmol/L. Thus, our results suggest that to keep bone turnover in balance throughout the year and to reach the maximal peak bone mass during puberty, serum 25(OH)D concentrations should be >40 nmol/L all year long. However, during adolescence, other factors, such as growth hormone, affect calcium and bone metabolism, and thus, the effect of vitamin D status on the development of the skeleton should be studied further.

In the present study, an average of ≈14% of 178 adolescent Finnish females had serum 25(OH)D concentrations <25 nmol/L during the winter. If the relation between serum 25(OH)D and serum iPTH concentrations was used as an indicator of vitamin D sufficiency, ≈60% of the females would have had serum 25(OH)D concentrations <40 nmol/L. Although serum 25(OH)D and serum iPTH concentrations correlated inversely, secondary hyperparathyroidism was uncommon. The effect of a low vitamin D status on the growing skeleton has not been studied before, and our results show that in growing females, low vitamin D status (≤40 nmol/L) is negatively associated with forearm radial BMD and tends to be associated with ulnar BMD. However, the effects of low vitamin D status on the growing skeleton should be further evaluated in an intervention study.

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