The Influence of Vitamin D on Bone Health Across the Life Cycle

Vitamin D, Parathyroid Hormone, and Bone Mass in Adolescents

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ABSTRACT This article provides a review of the evidence identifying the factors related to vitamin D status in adolescents. The prevalence of vitamin D deficiency based on 25-hydroxyvitamin D [25(OH)D] of <25 nmol/L ranges from 0 to 32% depending on the season measured and the latitude of the population assessed. The factors that have been reported to affect serum 25(OH)D in adolescents include ethnicity, gender, puberty stage, parathyroid hormone (PTH), dietary vitamin D intake, and sun exposure. Vitamin D supplementation studies are limited to small populations and with supplementation focused on winter months when sunlight may be inadequate. The effects of vitamin D status and supplementation on bone assessment provide varied results. Differences in study design, modalities of bone assessment, and stage of puberty could contribute to disparate findings. Overall, the results from the available literature provide more questions than answers concerning the role of vitamin D in bone accrual in adolescents.

KEY WORDS: vitamin D, adolescents, bone density, bone accrual, parathyroid hormone

The Institute of Medicine released recommendations for vitamin D intake for adolescents in 1997 (1). Serum 25-hydroxyvitamin D [25(OH)D] as set as the criterion for determining vitamin D adequacy. Although during puberty, the metabolism of 25(OH)D to 1,25-dihydroxyvitamin D [1,25(OH)2D] increases, there are few studies that lend support to or refute this fact. Based on available studies, the deficiency level was set at <27 nmol/L (1). At the time of the report, there was a lack of data on vitamin D’s ability to maintain normal calcium metabolism or its effect on peak bone mass. Since the publication of this report there has been additional information to shed light on the relationship between intake, sunlight exposure, and deficiency of 25(OH)D in adolescents. This article provides an overview of factors related to serum vitamin D in adolescents.

Prevalence of serum 25(OH)D deficiency in adolescents

The production of 25(OH)D in the liver is dependent on vitamin D obtained from the diet and from exposure to ultraviolet light. Ultraviolet rays stimulate the conversion of pro-vitamin D in skin to vitamin D, making it available to the liver for hydroxylation to 25(OH)D. Thus, the circulating concentrations of 25(OH)D are considered to be reflective of the person’s total vitamin D exposure (2,3). Yet there is no consensus on the concentration of serum 25(OH)D that would yield the most benefit for bone health (4–6). The definition for vitamin D deficiency based on serum 25(OH)D varies between studies, with the majority consensus setting the level at 25 nmol/L (Table 1). The prevalence of 25(OH)D deficiency ranged from 0% to 32%, depending on the season measured and the latitude of the population under study. In those studies that reported higher cut-points for serum 25(OH)D insufficiency, the prevalence rates increased upward to 75% for some populations. Of the 3 studies that included boys and girls, 2 found a gender difference in the prevalence of vitamin D deficiency dependent upon the season in which they were measured. Decline in 25(OH)D stores from summer to winter have been well documented by numerous groups for adolescent males and females (7–13). In general, the prevalence of vitamin D deficiency was 5–14% higher for those assessed during the winter months compared with the summer months. Ethnic differences are prominent in the U.S.-based studies. African Americans have the highest prevalence, with progressively decreasing prevalence for Mexican Americans, Asians, and then Caucasians. In the third cycle of the National Health and Nutrition Examination Survey (NHANES III), northern latitudes were assessed in the summer and southern latitudes in the winter season. At first glance there ap-
peared to be a seasonal difference in 25(OH)D status; how-
however, the sample from the South contained a higher proportion
of African Americans and Mexican Americans. The apparent
seasonal difference could be explained by differences in ethnic
composition of the 2 regions. Because of differences in study
design, variability in different 25(OH)D assays (14), geo-
graphic latitude of the population under study, and the age
range, ethnicity, and gender of the sample makes comparing
studies difficult. However, these data underscore the impor-
tance of considering ethnic composition, gender, and regional
and seasonal differences in sample selection, and/or the anal-
ysis phase of research studies focusing on vitamin D status.

Effect of puberty on serum 25(OH)D

During puberty, the conversion of 25(OH)D to 1,25 dihy-
droxyvitamin D [1,25(OH)2-D] increases to meet the demands
of growth. A concomitant decrease in 25(OH)D stores has
been supported by some (11,15) but not all studies (16).
Aksnes and Aarskog (15) provide longitudinal data on 104
girls and boys as support for decreased serum 25(OH)D during
puberty. Lehtonen-Veromaa and colleagues (11) from Finland
provided support for declines in 25(OH)D during rapid growth
by classifying females with regard to the onset of menarche.
The authors reported that 2 yo r more prior to the onset of
menarche, serum 25(OH)D levels were 10 nmol/L higher than

### TABLE 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population</th>
<th>Age, y</th>
<th>Latitude</th>
<th>Deficiency; insufficiency cut-points</th>
<th>Overall prevalence</th>
<th>Season</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHANES III (7)</td>
<td>Random sample</td>
<td>12–19</td>
<td>25–45° N</td>
<td>25</td>
<td>1% W; 1% S</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Male, Females</td>
<td></td>
<td></td>
<td>37.5</td>
<td>5–12% W; 2–6% S</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>White, Black</td>
<td></td>
<td></td>
<td>50</td>
<td>13–29% W; 8–13% S</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Mexican Americans</td>
<td></td>
<td></td>
<td>62.5</td>
<td>25–47% W; 21–28% S</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Outila et al. (23)</td>
<td>178 Females</td>
<td>16–14</td>
<td>45° N</td>
<td>25</td>
<td>13.5% W</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td></td>
<td></td>
<td>40</td>
<td>61.8% W</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Du et al. (12)</td>
<td>Random sample</td>
<td>12–14</td>
<td>40° N</td>
<td>12.5</td>
<td>45.2% W</td>
<td>Yes</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>1248 Females</td>
<td></td>
<td></td>
<td></td>
<td>6.7% S</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Lehtonen-Veromaa et al. (11)</td>
<td>171 Females</td>
<td>9–15</td>
<td>60° N</td>
<td>20</td>
<td>14% W; 0% S</td>
<td>Yes</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td></td>
<td></td>
<td>20–37.5</td>
<td>75% W; 0% S</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Gordon et al. (10)</td>
<td>200 Females</td>
<td>11–18</td>
<td>42° N</td>
<td>20</td>
<td>4.6%</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>107 Males</td>
<td></td>
<td></td>
<td>37.5</td>
<td>24.1%</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td></td>
<td>White, Black</td>
<td></td>
<td></td>
<td>50</td>
<td>42%</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Hispanic, Asian</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>El-Hajj Fuleihan et al. (8)</td>
<td>164 Males</td>
<td>10–16</td>
<td>34° N</td>
<td>25</td>
<td>21% W; 4% S</td>
<td>Yes</td>
<td>Yes W</td>
<td>No S</td>
</tr>
<tr>
<td></td>
<td>182 Females</td>
<td></td>
<td></td>
<td>26–50</td>
<td>44% W; 35% S</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Cheng et al. (24)</td>
<td>193 Females</td>
<td>10–12</td>
<td>62° N</td>
<td>25</td>
<td>32% W</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>26–40</td>
<td>46% W</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

1 Participants were recruited from a convenience sample unless indicated otherwise; gender and ethnicity included in the study population.

2 Values below the selected cut-points were used to determine prevalence of 25(OH)D deficiency or insufficiency. These levels were established by each study.

3–5 Study reported a statistically significant influence of season (3), gender (4) or ethnicity (5) on prevalence estimates: yes, no, N/A (not applicable).

6 W, prevalence of 25(OH)D during winter months.

7 S, prevalence of 25(OH)D during summer months.

8 The prevalence estimates varied when calculated by gender and/or ethnicity.

Serum 25(OH)D within 2 y of menarche. Although the data
were not statistically compared by pubertal status and the
prepubertal groups were smaller than the older girls’ groups,
the data does provide substance for thought. In contrast,
cross-sectional data from NHANES III suggests the prevalence
of 25(OH)D deficiency for adolescent boys and girls ages 12 to
19 y old was lower than was reported for the other age groups
(7). The classification of chronological age from 12 to 19 y old
as an identifier for the pubertal years prevents NHANES III
data from refuting or supporting that 25(OH)D are compro-
mised during the rapid growth period. Longitudinal studies
underway or completed have the opportunity to provide in-
sight into the importance of 25(OH)D stores during a time
when demands for maximal height velocity and mineralization
are occurring.

Serum 25(OH)D and fractional absorption of calcium

Vitamin D demands during adolescence are a function of
dietary intake and growth velocity. The primary function of
vitamin D during puberty is to increase the absorption of
calcium to meet the demands of bone mineralization. Lee and
colleagues (17) reported a negative association between serum
25(OH)D and fractional absorption of calcium in 12 girls
between the ages of 9 to 17 y. The study was performed with
Chinese girls whose average calcium intake was 591 mg/d. In
VITAMIN D AND BONE ACCRUAL IN ADOLESCENTS

Contrast, Abrams and colleagues (18,19) did not find a correlation between serum 25(OH)D levels and fractional absorption in Caucasians, Mexican Americans, or African Americans. The average calcium intake in the children was between 821 and 1110 mg/d (19,20). In adults, serum 25(OH)D has been associated with fractional absorption of calcium (21). Thus, it is reasonable to pose a few questions: 1) Is the association dependent on adequacy of serum 25(OH)D or solely a function of dietary calcium intake, and, most importantly, 2) is the lower serum 25(OH)D reflective of the increased conversion of 25(OH)D to 1,25(OH)_{2}D to meet the demands for growth and mineralization of the skeleton?

Serum 25(OH)D and parathyroid hormone

The negative or curvilinear relationship between serum 25(OH)D and parathyroid hormone (PTH) during puberty has been shown in many cross-sectional studies (8,10,22,23). The focus of these efforts has been on defining the level of serum 25(OH)D that suppresses PTH. This inflection point is considered by some as the criteria for defining 25(OH)D deficiency (4,5). A graph of the relationship between serum PTH and 25(OH)D, published by Cheng et al. (24), is shown in Figure 1. The relationship reported by Cheng is very similar to that published by others (8,10,22,23). Examining the lower end of the reference range for serum 25(OH)D demonstrates much variability in PTH, with only a small sample number having above normal PTH levels. Further examination indicates that individuals are near the upper limit for normal PTH (65 nmol/L) across all 25(OH)D concentrations. The data should be scrutinized to identify those who have abnormal PTH, at low 25(OH)D concentrations, to evaluate those with high normal PTH regardless of 25(OH)D concentrations, and to determine the impact on bone accrual. Cross-sectional data can help to answer these questions, but only a longitudinal study can begin to untangle this complex and not well understood relationship during a period of rapid growth.

Serum 25(OH)D and bone assessment

The evaluation of the association between serum 25(OH)D and bone health during puberty, using bone assessment techniques, has shown varying results. Much of the variability between studies is due to differences in study design, sexual maturity of the sample studied, serum 25(OH)D concentrations defined as deficient, and bone assessment modality. Outila and colleagues (23) reported that females with serum 25(OH)D concentrations above 40 nmol/L had greater radial bone mineral density (BMD) (P < 0.05) and ulna BMD (P = 0.08). Using the same cut-points for serum 25(OH)D concentrations, Cheng and colleagues (24) clearly showed that a progressive increase in cortical BMD with increasing serum 25(OH)D concentrations at both the distal radius and the tibia shaft using peripheral quantitative computed tomography (pQCT). However, no differences based on serum 25(OH)D concentrations were found in the total femur, the lumbar spine, or whole body BMD as assessed by dual energy X-ray absorptiometry (DXA). Lehtonen-Veromaa’s data showed that the relationship between 25(OH)D status and BMD of femoral neck and spine was dependent on the length of time prior to the onset of menarche (25). These findings raise important questions that are not easily answered: 1) are these different findings due to differential growth patterns for the selected skeletal sites, and 2) are the different observations due to different bone assessment techniques? Answers to the questions can be obtained with the availability of pQCT in longitudinal studies.

Serum 25(OH)D and food intake

Gordon and colleagues (10) evaluated a multi-ethnic group of adolescents attending a medical clinic in Boston. They found that those who selected soft drinks were at higher risk for vitamin D deficiency, while the consumption of milk or cold cereal was protective against deficiency. This is the first multifactorial study that presents food selection as having a role in vitamin D deficiency. However, a discerning investigation is warranted to determine whether the 25(OH)D status was preserved due to the adequacy of calcium intake and/or vitamin D intake. It should be noted that milk and dairy products contain phosphorus, potassium, and magnesium, which are also beneficial for bone metabolism, and that may not be easily replicated by fortifying foods with vitamin D and calcium alone.

Vitamin D supplementation, serum 25(OH)D, and bone assessment

The effects of vitamin D supplementation on serum 25(OH)D has been extensively examined in adults (6). In contrast, there have been only a few studies investigating the effect in adolescents. Due to differences in populations, use of vitamin D-2 or cholecalciferol, the dosing regimen, and the duration of the study, the findings could be instructive for planning future studies. Guillemin and colleagues (13) evaluated the effect of vitamin D supplementation during the winter on serum 25(OH)D in white males in France. This study administered 2.5 mg (10,000 IU) cholecalciferol to participants at the end of September, November, and January. Serum 25(OH)D levels were the same at baseline and March for those receiving the supplements, while serum 25(OH)D levels fell 40 nmol/L for those individuals who did not receive supplements. PTH remained the same in the supplemented group and increased in the nontreated group. Bone assessments were not performed. Lehtonen-Veromaa and colleagues (26) made a baseline assessment of 171 females during the winter and summer months prior to starting a vitamin D supplementation study. The supplementation regimen included 10 μg of vitamin D-2 taken daily from October to February for 2 y; in addition, girls with <1000 mg of calcium intake were provided with daily supplements of 500 mg of calcium. At the end of the 2 y there was no increase in serum...
25(OH)D levels. For the 3rd y of the study the researchers increased the dose to 20 μg of vitamin D-2 daily. After 6 mo on the 20 μg dose, serum 25(OH)D concentrations were higher than those obtained during the winter baseline period, but did not reach concentrations observed during the summer months. There was a positive trend for a gain in spinal BMD (P = 0.01) and greater BMD at the femoral neck (P = 0.15) with greater vitamin D baseline stores. There were no results presented on the changes in bone area and bone mineral content, thus making it difficult to determine if differential growth was due to baseline bone size. As this study focused on the effect of vitamin D supplementation on vitamin D status, data were not provided on the effect of change in serum 25(OH)D in relation to bone status. Clearly, there is a need for more studies to evaluate the latter.

In summary, the paucity of research relating vitamin D nutrition to bone accrual in adolescents provides a wealth of opportunity for researchers to investigate the factors that impact serum 25(OH)D from the laboratory to population-based studies. The real challenge for performing free-living human studies is incorporating ethnicity, gender, sunlight exposure, diet, and stage of puberty into the study design. If the outcome measure is bone accrual, the studies should have a comprehensive assessment using DXA, pQCT, and other modalities that can provide information on the quality of bone mass. Calcium isotope studies may provide important information about the net effect on bone mineralization without the use of longitudinal studies.

LITERATURE CITED