25-Hydroxyvitamin D and functional outcomes in adolescents\textsuperscript{1–3}

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ABSTRACT
Vitamin D is essential for bone growth and development in children and adolescents. Adolescence is a crucial phase in bone development. Cross-sectional studies have shown a relation between vitamin D status and bone mineral density in adolescents. Long-term supplementation studies have supported the importance of vitamin D for bone health in adolescence. However, we need more studies on the optimal serum 25-hydroxyvitamin D concentration and the optimal vitamin D dosage for bone health in this age group. In addition, we need to evaluate the best way to increase vitamin D status in the general public from a public health point of view.

INTRODUCTION
Vitamin D is essential for bone growth and development in children and adolescents. Vitamin D deficiency leads to rickets, which is characterized by defective bone formation, in infants and children. In rickets, the mineralization of growth plate cartilage slows down, the bone formation rate increases, and new osteoid forms but does not mature because of the low mineralization rate. If rickets is diagnosed early, extensive vitamin D therapy can cure the disease, but if the deformities are severe and the growth plates have started to mature in puberty, no treatment for rickets is available. Vitamin D insufficiency can also have a negative effect on bone health in older infants and adolescents; several cross-sectional studies in this age group have shown a negative correlation between bone mineral density (BMC) and serum 25-hydroxyvitamin D [25(OH)D] concentrations. In this review, we discuss the relation between vitamin D status and bone health and the effect of vitamin D supplementation on bone in adolescents.

BONE ACCRUAL IN CHILDHOOD AND ADOLESCENCE
Adolescence is a crucial phase for bone development because it is the time when the most rapid bone accrual occurs. Bone accrual rates depend on age, growth rate, Tanner stage of puberty, and sex; studying the effect of different exposures on bone is therefore challenging.

Molgaard et al (3) found that peaks in the increase in bone area and bone mineral content (BMC) occurred at earlier ages in girls (12.3 y for bone area and 12.5 y for BMC) than in boys (13.4 y for bone area and 14.2 y for BMC). They also found that bone size increases before BMC does. Molgaard and colleagues calculated that the median annual bone calcium accretion rate in pubertal stage 3 was 220 mg/d in girls and 317 mg/d in boys. These results show that the time in adolescence is important when studying the effect of, for example, vitamin D on bone because the size of the observed effect will depend on whether the investigator is studying bone size or BMC. Furthermore, to achieve an average bone calcium accretion rate, adolescents need a high intestinal calcium absorption rate during puberty, and optimal calcium absorption requires an optimal vitamin D status.

VITAMIN D STATUS AND FUNCTIONAL OUTCOMES IN ADOLESCENTS
The serum parathyroid hormone (PTH) concentration is inversely associated with the 25(OH)D concentration in the elderly and in healthy adults, and low BMD is associated with low 25(OH)D concentrations. However, high serum PTH concentrations are associated with increased bone resorption (4–9). The inverse relation between serum PTH concentrations and BMC indicates that sustained high PTH concentrations could be deleterious to bone. In contrast, low serum PTH concentrations are deleterious to the skeleton because they lead to low bone turnover.

However, the situation might be somewhat different in adolescents, who apparently experience a physiologic increase in serum PTH concentrations, which their growing skeleton needs. Cioffi et al (10) found that serum PTH concentrations in healthy children were lower and had a narrower range than in adults. In girls, serum PTH concentrations increased after age 8 y and peaked between ages 10 and 14 y before decreasing slightly. In contrast, serum PTH values in boys increased consistently from ages 8 to 16 y.

Several studies have found an inverse association between serum PTH and 25(OH)D concentrations in adolescents and a positive association between serum 25(OH)D concentrations and BMD (11–18). Abrams et al (18) recently studied the relation between serum 25(OH)D and 1,25-dihydroxyvitamin D concentrations, serum PTH concentrations, and calcium absorption in young adolescents (50 girls and 50 boys with a mean age of…

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EFFECT OF VITAMIN D SUPPLEMENTATION ON SERUM 25-HYDROXYVITAMIN D CONCENTRATIONS AND BONE MINERAL DENSITY

A few vitamin D supplementation studies on the effect on serum 25(OH)D concentration and serum PTH concentration on BMD have focused on healthy children and adolescents (13, 16, 19–21). The vitamin D dosage and the intervention period in these studies varied. A French study gave 3 oral doses (end of September, end of November, end of January) of 2.5 mg (100 000 IU) of vitamin D₃ (40 μg, or 1600 IU, per day) to 54 boys aged 13–17 y. The investigators measured serum 25(OH)D concentration at several intervals during an 18-mo period. They found that the vitamin D₃ supplementation maintained serum 25(OH)D concentration at 55 nmol/L throughout the winter; in contrast, serum 25(OH)D concentrations decreased to 21 nmol/L in the placebo group (13). In a 1-y randomized controlled study in 179 girls aged 10–17 y in Lebanon (16), serum 25(OH)D concentrations reached 95 nmol/L with weekly vitamin D₃ supplementation equivalent to 50 μg vitamin D₃ (2000 IU) per day, but only 40 nmol/L with weekly vitamin D₃ supplementation equivalent to 5 μg vitamin D₃ (200 IU) per day, which did not differ from that of the placebo group.

In a 1-y randomized controlled study in Finland in 228 girls aged 12 y at Tanner’s stages 1 and 2, the investigators found that both 5 μg (200 IU) and 10 μg (400 IU) vitamin D₃ per day had a significant effect on serum 25(OH)D concentrations (20). At the end of the study, the mean 25(OH)D concentration was 45 nmol/L in the placebo group, 52 nmol/L in the group receiving 5 μg (200 IU) per day, and 60 nmol/L in the group receiving 10 μg (400 IU) per day.

The reason for the difference in results between the Lebanese and Finnish studies is not clear, but the difference might be due to the use of different assays—a commercial competitive protein binding assay and an HPLC-based assay, respectively—for measuring the serum 25(OH)D concentration. The difference could also be due to the fact that the Lebanese study administered vitamin D₃ orally once per week, and the Finnish study administered the supplement orally daily. Daily supplementation could have enhanced vitamin D adsorption or decreased the rate of catabolism.

What effect does vitamin D supplementation have on the skeleton? Cheng et al (21) did not find any beneficial effects on BMD of 5 μg (200 IU) per day of vitamin D₃ supplementation with or without calcium (1000 mg) in their vitamin D intervention study of 10–12–y-old Finnish girls. However, the number of subjects was low in all 4 intervention groups (38–49 girls per group; 32–39 girls per group with compliance higher than 50%) in this study, and this could explain why the authors found no effect of vitamin D supplementation on bone. In the 1-y controlled randomized trial in Lebanon, adolescent girls responded to weekly vitamin D supplementation equivalent to 50 μg vitamin D₃ (200 IU) per day by increasing total hip BMC when compared with the placebo, but weekly supplementation equivalent to 5 μg of vitamin D₃ (200 IU) per day did not have any effect on BMD or BMC (16). However, another 1-y randomized controlled study in Finland found that both 5 μg (200 IU) and 10 μg (400 IU) of vitamin D₃ per day increased BMC augmentation in a dose-dependent manner in both the femur and lumbar spine in participants who had consumed ≥80% of the vitamin D supplements (20). Compared with the placebo group, the retention in the femur region was 14.3% higher in the group that received 5 μg (200 IU) of vitamin D₃ and 17.2% higher in the group that received 10 μg (400 IU). The study found similar results in the lumbar vertebra, although only the highest dose increased BMC augmentation significantly in the entire group.

One of the differences between the 2 studies was that Viljakainen et al (20) studied a very narrow age range of girls and took their Tanner stage into account. By contrast, the age range of the girls in the Lebanon study (16) was much greater, and the investigators did not take Tanner stage into account in the same manner; they did not specify differences between Tanner groups (except for pre- and postmenarcheal) and did not take the transition from one Tanner stage to another into consideration in their analyses. After dividing the subjects by Tanner stage into early or late puberty, Viljakainen et al (20) also showed that the effect of vitamin D on BMC in the lumbar vertebra occurred in midpuberty but not in early puberty. Because spine growth accelerates at puberty (22), this could explain why girls in midpuberty responded more efficiently to vitamin D supplementation than did girls in early puberty.

In the elderly, researchers have emphasized the role of a combination of vitamin D and calcium in fracture prevention (4). However, only 2 studies in adolescents have addressed the effect of a combination of vitamin D and calcium on bone (19, 21). The first study (19) enrolled 71 white girls aged 12 y in Tanner stage 2 in a 1-y randomized study. They received 10 μg (400 IU) vitamin D and 800 mg calcium carbonate daily. The investigators showed that the combination therapy improved trabecular BMC and volumetric BMD acquisition compared with that in the unsupplemented placebo group. The study by Cheng et al (21) in Finland found no effect from 5 μg (200 IU) per day of vitamin D₃ supplementation with calcium (1000 mg) on bone variables in girls (36 girls in the intervention group and 31 in the placebo group), probably because of the small number of subjects.

CONCLUSIONS

Cross-sectional studies have shown a relation among serum 25(OH)D concentration, serum PTH concentration, and BMD in adolescents. Long-term randomized controlled intervention studies have shown that vitamin D₃ supplementation has a positive effect on BMD in adolescence; some of these studies found an effect with doses as small as 5 μg (200 IU) to 10 μg (400 IU) per day, or without supplemental calcium.

However, we still need research on adolescents in the following areas:

- The effect on bone of daily doses of, for example, 10–50 μg (400–4000 IU) vitamin D, because no studies to date have determined the optimal dose needed for bone health.
- Whether weekly or monthly oral supplements, which are easier to manage, are as effective as daily oral supplements.
• Whether the effect of vitamin D₃ supplementation on bone continues after adolescence.
• The effects on bone of combinations of vitamin D₃ and calcium supplementation.
• The role of vitamin D insufficiency in fractures.
• The best way to increase vitamin D status in the general population.

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