Response to Vitamin D₃ Supplementation in Obese and Non-Obese Caucasian Adolescents

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Key Words

Vitamin D₃ • Obese adolescents • 25-Hydroxyvitamin D

Abstract

Background/Aims: Vitamin D deficiency is highly prevalent in obese children, and obese children tend to respond poorly to vitamin D supplementation. The objective of the study was to compare the response to vitamin D₃ supplementation (2,000 IU once daily for 12 weeks) between obese and non-obese Caucasian adolescents. **Methods:** The study design was open label non-randomized. It was carried out at a single center. Eighteen obese adolescents (aged 12–18 years) and the same number of age-, gender- and season-matched non-obese adolescents received vitamin D₃ (2,000 IU/day) orally for 12 weeks. Total serum 25-hydroxyvitamin D [25(OH)D], parathyroid hormone, calcium and phosphorus were measured at baseline and at the end of the 12-week period. **Results:** The mean baseline 25(OH)D level was higher in the non-obese compared to the obese subjects (mean 28.9 vs. 25.2 ng/ml; $p = 0.029$). The increment in 25(OH)D levels following vitamin D supplementation was significantly lower in the obese adolescents (mean change 5.8 vs. 9.8 ng/ml; $p = 0.019$). **Conclusions:** Higher doses of vitamin D are required to treat vitamin D deficiency in obese adolescents compared to their non-obese peers.

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Introduction

Vitamin D deficiency is common in children [1–4] and adults [5–8] and is significantly more prevalent in obese children [9–13]. A plausible explanation for the association of vitamin D deficiency and obesity is the sequestration of this lipid-soluble vitamin or degradation in the adipose tissue causing a lower bioavailability [9].

The recommended dietary intake of vitamin D for children was recently increased from 200 to 600 IU by several expert groups including the American Academy of Pediatrics and the Institute of Medicine [14–17]. While the guidelines by the Endocrine Society suggest a higher dose of vitamin D in obese adults [16], the pediatric guidelines do not recommend adjusting doses of vitamin D for prevention or treatment of vitamin D deficiency in obese children [14, 15, 17]. Limited studies in obese children and adults suggest that obese individuals tend to have a poor response to vitamin D supplementation [9, 10, 18]. A high-dose weekly vitamin D supplementation regimen (50,000 IU once a week for 6–8 weeks) in vitamin-D-deficient primarily Hispanic and African American adolescents was found to normalize 25-hydroxyvitamin D [25(OH)D] levels in only a minority of subjects [10, 19]. A study in preadolescent African American children also concluded that vitamin D₃ supplementation with

400 IU/day for 1 month was not effective in increasing the 25(OH)D levels in a majority of the subjects [18]. The objective of the study was to compare the response to vitamin D₃ between obese and non-obese Caucasian adolescents.

Methods

Subjects

Healthy adolescents, obese and non-obese, aged 12–18 years, were recruited through local advertisement. Subjects were considered obese if the body mass index (BMI) was $\geq$ 95th percentile for age and gender and non-obese if the BMI was between the 5th and 85th percentile for age and gender. The group of obese adolescents was part of a pilot double-blind placebo-controlled randomized clinical trial examining the effect of vitamin D₃ supplementation on insulin resistance and lipids. The non-obese adolescents were age, gender and season matched to the obese adolescents. The study was carried out between September 2008 and January 2011. Patients were evenly distributed throughout the four seasons. Exclusion criteria were: serum 25 (OH)D levels >80 ng/ml, serum calcium >10.8 mg/dl, serum phosphorus >5.5 mg/dl, pregnancy or nursing, current cancer, ongoing multivitamin supplementation, dietary calcium intake exceeding 1,500 mg/day, hepatic or renal disorders, type 1 or type 2 diabetes mellitus, ongoing use of insulin, metformin or oral hypoglycemic medications, and malabsorption disorders (celiac disease, cystic fibrosis and inflammatory bowel disease). The research protocol was approved by the Institutional Review Board of the Mayo Clinic, Rochester, Minn., USA. Informed consent and assent were obtained from participants and parents.

Study Design

The study design was an open-label non-randomized pre-post comparison of the effect of vitamin D supplementation in obese versus non-obese adolescents. All study participants received vitamin D₃ (cholecalciferol) 2,000 IU (1 capsule of 2,000 IU) daily for a period of 12 weeks. Compliance was assessed at the 12-week visit by counting the number of pills remaining in the pill bottle. All study participants received the same vitamin D₃ capsules compounded at the Mayo Clinic pharmacy. Baseline and post-treatment 25(OH)D, calcium, phosphorus and parathyroid hormone (PTH) levels were compared between non-obese and obese subjects.

Biochemical Measurements

Blood samples were drawn after at least 12 h of fasting. Blood tests were analyzed in the same laboratory at the Mayo Clinic. Measurement of 25(OH)D was performed using liquid chromatography tandem mass spectrometry. An internally developed and validated method in a single laboratory (Mayo Medical Laboratories) was used in order to assure uniform measurements. The total 25(OH) D concentration of each sample was calculated by summing the measured values of 25(OH)D₂ and 25(OH)D₃. This method has been shown to be accurate and precise, with excellent correlation between 25(OH)D₃ and 25(OH)D₂ measured by this method and high-pressure liquid chromatography with ultraviolet quantitation [20]. Vitamin D deficiency was defined as a

25(OH)D level of <20 ng/ml and vitamin D insufficiency as a 25(OH)D level of 20–29 ng/ml [21]. A 25(OH)D level of ≥ 30 ng/ml was considered as sufficient vitamin D status [21].

Calcium was measured by Photometric, O-Cresolphthalein assay (Roche Diagnostics, Indianapolis, Ind., USA), and phosphorus was measured by Photometric Ammonium Molybdate assay (Roche Diagnostics).

PTH was measured by a two-site chemiluminescent immunoassay on the Immulite automated immunoassay system (Diagnostic Products Corp., Los Angeles, Calif., USA).

Statistical Analysis

Age- and sex-specific BMI percentiles were determined using the 2000 Center for Disease Control growth charts [22]. Baseline data (age, weight, BMI and laboratory values) and changes following supplementation (before vs. after) were summarized using the mean $\pm$ SD and the median and range, separately for the two groups (non-obese vs. obese). The relationship between 25(OH)D levels and other variables was assessed graphically using scatter plots, and a smoothed line was generated using a cubic spline routine. Paired comparisons between the matched patients in the two groups were evaluated using the paired t test or Wilcoxon signed-rank test. All calculated p values were two-sided and p values <0.05 were considered statistically significant. Analyses were performed using the version 9.2 SAS software package (SAS Institute, Cary, N.C., USA).

Results

Clinical Characteristics

Twenty-seven obese adolescents (15 females, 12 males) who were recruited and randomized to receive vitamin D₃ in a separate study had their baseline laboratory studies drawn between 18 September 2008 and 9 July 2010; 20 obese adolescents completed the study. For each obese adolescent, 1 non-obese adolescent of the same gender, similar age (within 1.5 years) and enrolled in the same season was recruited (22 non-obese patients: 9 females and 13 males). Their baseline laboratory tests were drawn between 13 November 2009 and 6 October 2010. The study was completed by 18/22 non-obese adolescents. A total of 18 matched pairs for age, sex and season completed the study and were analyzed (table 1). All patients except 1 in the non-obese category were Caucasian. The ethnic distribution of the subjects in this study reflects that of the population seen in the community (Rochester, Minn., USA). The mean age $\pm$ SD was 15.2 ± 2 and 15.0 ± 2.3 years in the non-obese and the obese group, respectively. Each group comprised 10 males and 8 females. As expected, the BMI (20.3 ± 2.0 and 35.4 ± 7.5) and the BMI percentile for age and sex (52.7 ± 19.7 and 98.5 ± 1.0) were significantly different between the non-obese and obese groups.

Table 1. Baseline characteristics of the study subjects

	Non-obese (n = 18)	Obese (n = 18)
Gender		
Female	8 [44.4]	8 [44.4]
Male	10 [55.6]	10 [55.6]
Age at first visit, years		
Mean $\pm$ SD	15.2 $\pm$ 2.0	15.0 $\pm$ 2.3
Median	14.8 (12.4–18.6)	15.0 (11.8–18.6)
Baseline weight, kg		
Mean $\pm$ SD	57.7 $\pm$ 8.8	103.4 $\pm$ 25.3
Median	56.4 (45.5–81.8)	100.7 (64.6–148.8)
Baseline BMI		
Mean $\pm$ SD	20.3 (2.0)	35.4 (7.5)
Median	20.1 (16.5–25.1)	32.2 (25.6–53.3)
Baseline BMI, age- and sex-specific percentile		
Mean $\pm$ SD	52.7 (19.7)	98.5 (1.0)
Median	49.1 (4.8–83.6)	98.5 (96.7–99.8)

Figures in brackets are percentages and figures in parentheses are ranges.

Prevalence of Vitamin D Deficiency/Insufficiency

The prevalence of vitamin D deficiency or insufficiency (<30 ng/ml) was 78% in obese subjects and 61% in non-obese subjects. Three (17%) of the obese and 1 (6%) of the non-obese subjects were vitamin D deficient (<20 ng/ml). The mean baseline 25(OH)D level was higher in the non-obese compared to the obese subjects (mean 28.9 vs. 25.2; $p = 0.029$; table 2). There were no significant differences in serum calcium, phosphorus or PTH between the obese and non-obese groups.

Blood samples for 25(OH)D were obtained during fall (September–November) in 5 pairs (28%), during winter (December–February) in 2 pairs (11%), during spring (March–May) in 4 pairs (22%) and during summer (June–August) in 7 pairs (39%).

As to be expected, nearly half of the subjects (7/18 per group) were enrolled during the summer months when the subjects were off from school. Among the obese subjects, the mean 25OH(D) values were 24.0, 25.5, 25.7 and 25.5 ng/ml in winter, spring, summer and fall, whereas among the non-obese subjects, the mean 25OH(D) values were 24.5, 31.8, 33.4 and 20.3 ng/ml in winter, spring, summer and fall, respectively. Thus, based on this limited sample, it appears the seasonable variation is slightly more dramatic in the non-obese subjects. However, the seasonal variation needs to be interpreted with caution as there was a limited number of subjects per season.

Table 2. Baseline laboratory data from the study subjects

	Non-obese (n = 18)	Obese (n = 18)	p value
Baseline vitamin D, ng/ml			0.086
Mean $\pm$ SD	28.9 $\pm$ 8.2	25.2 $\pm$ 4.9	
Median	28.5 (7.9–44.0)	25.0 (15.0–32.0)	
Baseline calcium, mg/dl			0.25
Mean $\pm$ SD	9.8 $\pm$ 0.3	9.9 $\pm$ 0.3	
Median	9.8 (9.2–10.3)	9.8 (9.5–10.5)	
Baseline phosphorus, mg/dl			0.71
Mean $\pm$ SD	4.3 $\pm$ 0.7	4.2 $\pm$ 0.6	
Median	4.2 (3.1–5.5)	4.2 (3.2–5.3)	
Baseline PTH, pg/ml			0.96
Mean $\pm$ SD	32.3 $\pm$ 13.6	35.6 $\pm$ 25.9	
Median	29.5 (11.0–61.0)	28.0 (16.0–132.0)	

Figures in parentheses are ranges.
p values are based on the paired t test for all comparisons, except the Wilcoxon signed-rank test was utilized to evaluate baseline PTH.

Response to Supplementation with Vitamin D₃

The median duration between the two study visits was 94 and 95.5 days in the non-obese and obese groups, respectively. Over this time period, the mean change in weight was 1.0 and 2.1 kg in the non-obese and obese groups, respectively. Tables 1 and 2 delineate mean 25(OH)D levels at baseline and following supplementation with 2,000 IU vitamin D₃ daily for 12 weeks. The increment in 25(OH) D levels was significantly greater in the non-obese adolescents (mean change 9.8 vs. 5.8; $p = 0.019$; table 3; fig. 1). 25(OH)D levels normalized (>30 ng/ml) in 16/18 (89%) of the non-obese subjects but only in 9/18 (50%) of the obese subjects.

There was no clear relationship between the baseline level of 25(OH)D and the changes in 25(OH)D levels following vitamin D₃ supplementation for the obese and non-obese subjects. Additionally, the change in 25(OH) D did not correlate with body weight in either of the groups.

There were no significant differences between the change in levels of PTH and phosphorus after 12 weeks (table 3). The change in serum calcium levels, though statistically significant, did not appear to be of clinical significance (table 3).

Table 3. Change in laboratory data following supplementation

Change (12 weeks – baseline)	Non-obese (n = 18)	Obese (n = 18)	p value
25(OH)D, ng/ml			0.019
Mean $\pm$ SD	9.8 $\pm$ 7.13	5.8 $\pm$ 6.44	
Median	8.5 (–2.0 to 22.0)	5.0 (–5.0 to 21.0)	
Calcium, mg/dl			0.004
Mean $\pm$ SD	0.2 $\pm$ 0.27	0.0 $\pm$ 0.19	
Median	0.2 (–0.4 to 0.7)	0.0 (–0.4 to 0.3)	
Phosphorus, mg/dl			0.26
Mean $\pm$ SD	0.1 $\pm$ 0.61	–0.1 $\pm$ 0.36	
Median	0.2 (–1.0 to 1.3)	–0.1 (–0.6 to 0.7)	
PTH, pg/ml			0.10
Mean $\pm$ SD	0.1 $\pm$ 17.36	–11.2 $\pm$ 23.62	
Median	2.0 (–44.0 to 22.0)	–5.5 (–96.0 to 14.0)	

Figures in parentheses are ranges.

p values are based on the paired t test for all comparisons, except the Wilcoxon signed-rank test was utilized to evaluate baseline PTH.

Relationship between Compliance and Response to Vitamin D Supplementation

In the non-obese group, we were not able to determine compliance in 2 patients in the non-obese group and in 5 subjects in the obese group, as they did not bring the pill-box to the return visit at the end of the study.

Of the 16 non-obese subjects who did bring the pill box at the return visit, 10 had no pills left in the pill box, 2 had 3 pills left, 1 had 5 pills left, 1 had 7 pills left, 1 had 8 pills left and 1 had 17 pills remaining at the end of the study out of 12 weeks worth of pills (84 total). Of the 13 obese subjects who did bring the pill box at the return visit, 5 had no pills left in the pill box, 4 had 3 pills remaining, 1 had 5 pills remaining, 1 had 7 pills remaining, 1 had 12 pills remaining and 1 had 20 pills remaining at the end of the study. Among the patients who brought their pill box at the return visit, there was no statistically significant difference in the number of pills left between the obese and non-obese (Wilcoxon rank-sum test, $p = 0.31$). Based on the Spearman rank correlation coefficient, the correlation between the number of pills left and the change in 25(OH) D level was -0.30 , suggesting that patients with more pills remaining at the end of the study tended to have less of a change in the 25(OH) D level.

No adverse effects were reported during the course of the study by any of the study subjects.

Fig. 1. Increment in 25(OH)D levels following vitamin D₃ supplementation in study subjects (n = 18 for both groups).

Discussion

In this study, we compared the response to 3-month-long vitamin D₃ supplementation with 2,000 IU daily in obese and non-obese Caucasian adolescents. We found that the response to vitamin D supplementation with this dose of vitamin D was modest in both obese and non-obese children. More importantly, the response to vitamin D supplementation was approximately 1.7-fold lower in obese compared to non-obese adolescents. Despite using a dose of vitamin D that is 3.5 times the recommended dietary intake, we found that supplementation with 2,000 IU daily for 3 months only resulted in an increment in the 25(OH)D level by 5.8 ng/ml in obese adolescents. The increment in the 25(OH)D levels in the non-obese group was higher at 9.8 ng/ml and is similar to another study utilizing the same dose of vitamin D over a period of 8 weeks in children between the ages of 10 and 17 years [23]. The results of this study suggest that obese children and adolescents should be supplemented with doses of vitamin D that are approximately 2-fold higher than those used for non-obese children. To our knowledge, this is the first study that has examined the impact of obesity itself without any other confounding variables such as ethnicity, age, gender or season on the response to vitamin D₃ supplementation in Caucasian adolescents.

Our results of an almost 2-fold lower response to vitamin D₃ supplementation in Caucasian obese adolescents compared to non-obese adolescents are similar to those in a previous study of Caucasian obese and non-obese adults involving a single oral dose of 50,000 IU of vitamin D₂ [9]. We noted that oral administration of vitamin D₃ at a dose of 2,000 IU/day was able to normalize 25(OH)D levels in only half of the obese adolescents. Other investigators have also found poor response to vitamin D₂ or D₃ supplementation in African American [10, 19] and Hispanic obese adolescents [10]. In a retrospective medical record review, the weekly vitamin D supplementation regimen (50,000 IU once a week for 6–8 weeks) in vitamin-D-deficient primarily Hispanic and African American adolescents also normalized 25(OH)D in only a minority of subjects [10]. Ashraf et al. [19], in a prospective study of obese African American adolescents receiving ergocalciferol (vitamin D₂) 50,000 IU for 8 weeks, also noted that the serum 25(OH)D concentration increased to >20 ng/ml in only two thirds of subjects. The poor response to vitamin D supplementation in obese children and adolescents is likely secondary to a greater degree of sequestration of lipid-soluble vitamin D in the adipose tissue of obese adolescents as well as to potential differences in vitamin D metabolism in the obese state [24].

We did not find a correlation between baseline 25(OH)D level and increment in 25(OH)D level in obese adolescents. In contrast, a study on 6- to 10-year-old African American children receiving 400 IU of vitamin D₃ daily for 1 month suggested a different threshold level of 25(OH)D for an increase in 25(OH)D by >5 ng/ml in obese relative to non-obese children [18]. These differences may be secondary to differences in age and ethnicity of the subjects as well as to the dose and duration of vitamin D supplementation.

The strengths of our study include the prospective, pre-post comparison design of the study aimed at eliminating several confounding variables such as age, gender and season. The 25(OH)D levels were measured using the highly accurate liquid chromatography mass spectrophotometry in a nationally recognized laboratory. We used a dose of vitamin D that is recommended by several expert groups for treatment of vitamin D deficiency [14, 16] and is more than three times the recommended dietary intake. Another strength was the inclusion of only one ethnic group given the impact ethnic differences may have on vitamin D levels and metabolism [25]. Our study is limited by the small sample size and lack of assessment of vitamin D intake for the study subjects. We also did not

have information on sun exposure or sunscreen use by the study subjects. However, that we matched for season likely diminished the effect of sun exposure on vitamin D levels. While we did count remaining pills to measure compliance, several patients in both groups did not return their pill bottles, making it difficult to determine their degree of compliance. We did not measure bone turnover markers, and therefore, no conclusions can be drawn regarding impact of vitamin D supplementation on skeletal health in obese and non-obese children and adolescents.

We conclude that obese adolescents with vitamin D deficiency and insufficiency require doses that are at least 2-fold higher than those recommended for non-obese adolescents as has been recommended in the adult population. Longitudinal studies involving a larger number of children and adolescents from different ethnic groups are warranted. In these studies, treatment of patients with higher doses of vitamin D would clarify whether these doses not only increase serum vitamin D levels, but also improve skeletal health.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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