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Low Vitamin D Status Among Obese Adolescents: Prevalence and Response to Treatment

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A B S T R A C T

Purpose: To explore the prevalence of low vitamin D status among obese adolescents and to examine the effect of current management of low vitamin D status in these patients.
Methods: A retrospective chart review of obese adolescents who had been screened for vitamin D status by serum total 25-hydroxyvitamin D (25(OH)D) level. Vitamin D deficiency was defined as 25(OH)D level of $<$20 ng/mL, vitamin D insufficiency as 25(OH)D level of 20–30 ng/mL, and vitamin D sufficiency as 25(OH)D level of $>$30 ng/mL. Adolescents with vitamin D deficiency were treated with 50,000 IU of vitamin D once a week for 6–8 weeks, whereas adolescents with vitamin D insufficiency were treated with 800 IU of vitamin D daily for 3 months. Repeat 25(OH)D was obtained after treatment.
Results: The prevalence rate of low vitamin D status among 68 obese adolescents (53% females, 47% males, age: 17 ± 1 years, body mass index: 38 ± 1 kg/m^2, Hispanic: 45%, African American: 40%, Caucasian: 15%) was 100% in females and 91% in males. Mean (±SE) 25(OH)D level was significantly higher in summer (20 ± 8 ng/mL) than in spring (14 ± 4 ng/mL, $p < .02$), and significantly lower in winter (15 ± 7 ng/mL) than in fall (25 ± 15 ng/mL, $p < .05$). Although there was a significant ($p < .00001$) increase in mean 25(OH)D after the initial course of treatment with vitamin D, 25(OH)D levels normalized in only 28% of the participants. Repeat courses with the same dosage in the other 72% did not significantly change their low vitamin D status.
Conclusions: Increased surveillance and possibly higher vitamin D doses are warranted for obese adolescents whose total 25(OH)D levels do not normalize after the initial course of treatment.

The epidemic of obesity among adolescents, which has been recognized and reported regularly during the past 10–15 years, is worsening. The prevalence of obesity among adolescents in the United States increased by 10% between 2003 and 2007, with a current (2007) prevalence rate of 16.4% among those aged 10–17 years [1]. This increased prevalence of obesity among adolescents may lead to increased risk of diabetes, hypertension, and cardiovascular disease, as well as to increased risk of cancer [2]. Some of these obesity-related health consequences have been associated with vitamin D deficiency or insufficiency [3–9], and recent reports have suggested that vitamin D supplementation may reduce these risks [10,11].

Serum levels of total 25-hydroxyvitamin D (25(OH)D) of $<$20 ng/mL have been associated with decreased pancreatic B-cell function, and insulin sensitivity was as much as 60% higher in individuals with serum 25(OH)D levels of 30 ng/mL versus those with levels of 10 ng/mL [3]. A serum 25(OH)D concentration of $\leq$15 ng/mL has been suggested to be the threshold for negative effects of vitamin D deficiency on insulin sensitivity in obese

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female African American adolescents [12]. These studies indicate a role for vitamin D in promoting adequate pancreatic B-cell function and adequate peripheral insulin sensitivity, and thus a possible role in the prevention of diabetes mellitus. Higher levels of 25(OH)D have also been associated with decreased blood pressure [6]. Men with deficient and insufficient vitamin D levels have a higher risk for developing prostate, colon, and esophageal cancer, among other cancers [8]. In women, the risk of breast cancer was significantly inversely associated with vitamin D intake [9], the protective effect of vitamin D was independent of dietary calcium intake [9], and vitamin D significantly reduced the risk of breast cancer, with calcium having no significant effect [10]. A meta-analysis of several studies in adults revealed that increasing vitamin D intake to a mean daily dose of 528 IU/d reduced the risk of all-cause mortality over a mean of 5.7 years by 7% [13].

Total body vitamin D stores can be assessed by measuring the serum concentration of total 25(OH)D. Although there has been an intense debate as to the optimal serum 25(OH)D concentrations for acquisition and maintenance of bone mass, it is believed that a serum 25(OH)D level of 32 ng/mL (80 nmol/L) is needed for optimal calcium absorption efficiency and for optimal suppression of serum parathyroid hormone concentrations [14]. Thus, it is recommended that clinicians strive to maintain 25(OH)D concentrations above 32 ng/mL (80 nmol/L) in their patients, in an attempt to maximize bone health.

Although obesity in adolescents is not associated with a decrease in bone mass [15], low vitamin D status may increase the risk for diabetes mellitus, hypertension, cardiovascular diseases, and certain types of cancer, which have been associated with obesity [3–9]. In addition, a recent report in adolescent girls indicates that vitamin D status is significantly associated with muscle power and force [16], and therefore, vitamin D deficiency or insufficiency may interfere with the obese adolescent's ability to increase physical activity. Thus, since 2007, the attending physicians in our Division of Adolescent Medicine in Providence, RI, have incorporated screening for vitamin D status, in addition to screening for lipid abnormalities, in obese adolescents.

In the present study, we explored the prevalence of low vitamin D status among obese adolescents as well as examined the effect of current management of low vitamin D status in these patients.

Methods

Study population

We conducted a retrospective chart review of male and female adolescents who suffered from obesity and who had been screened for vitamin D status and lipid abnormalities between May 2007 and May 2010. The patients were seen at the adolescent clinic of an urban children's hospital (Hasbro Children's Hospital, Providence, RI). Body mass index (BMI, kg/m^2) was calculated, and only those with a BMI of >95% were included in this study. The study was approved by the Rhode Island Hospital Institutional Review Board.

Measurement of lipid profile and total 25(OH)D level

Measurements of lipid profile (after 12 hours of fasting) and of total 25(OH)D level were conducted at the Rhode Island Lifespan Laboratory, Providence, RI. Serum cholesterol, triglyceride, and high-density lipoprotein cholesterol (HDL-C) concentrations were measured by a colorimetric method using the Synchron system (Beckman Coulter Inc., Fullerton, CA). Serum low-density lipoprotein cholesterol (LDL-C) concentrations were calculated as total cholesterol minus TG/5 minus HDL-C. HDL-C levels of <35 mg/dL, LDL-C levels of >130 mg/dL, and triglyceride levels of >150 mg/dL were considered abnormal, based on American Heart Association guidelines [17].

Total 25(OH)D level was measured using the chemiluminescence assay (DiaSorin; Diasorin Inc., Stillwater, MN) system. 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 20–30 ng/mL [18]. A 25(OH)D level of >30 ng/mL was considered as sufficient vitamin D status [18].

Treatment of patients with low vitamin D status

Patients with vitamin D deficiency were treated with one tablet of vitamin D (50,000 IU) once a week for 6–8 weeks [19,20]. Patients with vitamin D insufficiency were treated with two tablets of vitamin D (400 IU) daily for 3 months [19,20]. The patients were also counseled regarding sources of vitamin D and were encouraged to increase consumption of dairy products and seafood, which contain vitamin D. A repeat blood sample for the measurement of total 25(OH)D level was obtained after completion of treatment. Patients who continued to exhibit deficient or insufficient vitamin D levels received an additional course of treatment, and their 25(OH)D levels were rechecked after completion of treatment.

Statistical methods

Comparisons between and within groups were performed using repeated-measures analysis of variance and Student's two-tailed *t*-test for unpaired data, and χ^2 analysis, as appropriate. Multiple regression analysis was used to examine associations of patients' 25(OH)D levels with regard to age, gender, ethnic group, season of the year, and lipid profile. A type I error of <.05 was considered significant. For descriptive data, results are expressed as the mean ± standard error of the mean.

Results

Participants' characteristics

A total of 68 obese adolescents (females: 36 [53%]; males: 32 [47%]) with a mean age of 17 ± 1 years (range, 11–27 years) and BMI of 38 ± 1 kg/m^2 were included in the study. Ethnic distribution was composed of Hispanic (31, 45%), African American (27, 40%), and Caucasian (10, 15%) patients. The ethnic distribution of the adolescents in the study reflects that of the population seen at this adolescent clinic (Hasbro Children's Hospital, Providence, RI).

Participants' lipid profile

Among the participants, 22 (32%; 13 boys and nine girls) exhibited lipid abnormalities. The most common lipid abnormality in these patients was isolated low HDL-C (nine patients, 41%), followed by isolated high triglyceride (six patients, 27%), combined low HDL-C and high triglyceride (three patients, 14%), combined high LDL-C and high triglyceride (two patients, 9%),

combined low HDL-C and high LDL-C (one patient, 4.5%), and isolated high LDL-C (one patient, 4.5%).

Prevalence of vitamin D deficiency/insufficiency

The prevalence of low vitamin D status was 100% in obese girls and 91% in obese boys. About 72% of the females were vitamin D deficient and 28% were vitamin D insufficient, whereas 69% of the males were vitamin D deficient, 22% were vitamin D insufficient, and 9% had sufficient vitamin D status. Mean (±SE) 25(OH)D level of all 68 participants was 18 ± 1 ng/mL. Mean (±SE) 25(OH)D levels in Caucasian participants was slightly higher (21 ± 3 ng/mL) than the mean in African American (18 ± 1 ng/mL) and in Hispanic (17 ± 2 ng/mL) participants, but this difference did not reach statistical significance. There were no significant associations between 25(OH)D levels, age, and lipid abnormalities.

Blood samples for 25(OH)D were obtained during fall (September–November) in 11 patients (16%), during winter (December–February) in 17 patients (25%), during spring (March–May) in 21 patients (31%), and during summer (June–August) in 19 patients (28%). The highest concentration of 25(OH)D was during fall (mean ± SE: 25 ± 15 ng/mL), and there were no statistically significant differences between these 25(OH)D levels and mean (±SE) 25(OH)D levels during the summer (20 ± 8 ng/mL). The lowest concentration of 25(OH)D was during spring (mean ± SE: 14 ± 4 ng/mL), and there were no statistically significant differences between these 25(OH)D levels and mean (±SE) 25(OH)D levels during the winter (15 ± 7 ng/mL). However, mean (±SE) 25(OH)D level was significantly higher in the summer than in the spring ($p < .02$), and significantly lower in the winter than in the fall ($p < .05$).

Response to treatment with vitamin D

Figure 1 delineates the mean (±SE) 25(OH)D levels of study participants. Of the 65 participants with either vitamin D deficiency or insufficiency who had received treatment, 43 (51% girls and 49% boys; 21 Hispanics, 17 African Americans, five Caucasians) had a repeat (second) measurement of their 25(OH)D levels after completion of treatment (5 ± 1 months after first measurement). After this initial course of treatment, there was a significant increase in mean (±SE) 25(OH)D levels (16 ± 1 ng/mL before treatment vs. 23 ± 1 ng/mL after treatment, $p < .000\,01$).

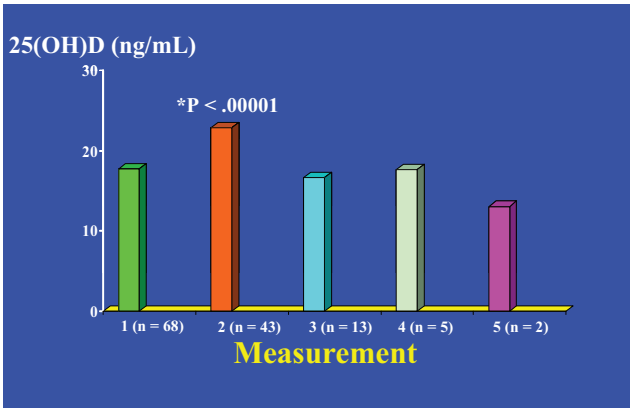

Figure 1. Mean 25(OH)D levels at baseline and during treatment with vitamin D. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article. *Statistically significant increase compared with levels before treatment.

However, serum 25(OH)D levels normalized in only 12 patients (28% of participants; eight girls and four boys; four Caucasians, four Hispanics, four African Americans). The repeat 25(OH)D measurements were obtained during fall in five patients, during winter in two, during spring in two, and during summer in three. Significantly more Caucasian adolescents (80%) normalized their 25(OH)D levels after initial course of treatment as compared with 24% of African American adolescents ($p < .05$) and 19% of Hispanic adolescents ($p = .02$). Mean (±SE) second 25(OH)D level was significantly higher in Caucasian adolescents (34 ± 4 ng/mL) as compared with mean 25(OH)D level in African American adolescents (22 ± 2 ng/mL, $p < .05$) and in Hispanic adolescents (21 ± 2 ng/mL, $p < .02$).

The other 31 patients (72% of participants; 17 boys and 14 girls; one Caucasian, 17 Hispanics, 13 African Americans) who continued to exhibit deficient or insufficient vitamin D levels received an additional course of treatment, and 13 of these participants (42%) had a repeat (third) measurement of their 25(OH)D levels (6 ± 1 months after second measurement). In all 13 patients, 25(OH)D levels did not normalize and they continued to exhibit deficient or insufficient vitamin D levels (mean [±SE] 25(OH)D level of 18 ± 2 ng/mL before second treatment vs. 17 ± 2 ng/mL after treatment, nonsignificant). Five of these participants underwent a third course of treatment (mean [±SE] 25(OH)D level of 19 ± 2 ng/mL before third treatment vs. 18 ± 3 ng/mL after third treatment, nonsignificant), and two underwent a fourth treatment (mean [±SE] 25(OH)D level of 12 ± 1 ng/mL before fourth treatment vs. 13 ± 5 ng/mL after fourth treatment, nonsignificant), which did not change their low vitamin D status. Response to treatment was not affected by age, gender, or season of the year.

Changes in weight and BMI during treatment with vitamin D

There were no significant changes in body weight or BMI during the first course of treatment with vitamin D (n = 43, weight: 233 ± 9 lbs, BMI: 39 ± 1 kg/m^2 before first treatment vs. weight: 233 ± 8 lbs, BMI: 39 ± 1 kg/m^2 after first treatment), second course (n = 13, weight: 255 ± 20 lbs, BMI: 41 ± 3 kg/m^2 before second treatment vs. weight: 257 ± 18 lbs, BMI: 41 ± 3 kg/m^2 after second treatment), third course (n = 5, weight: 259 ± 40 lbs, BMI: 41 ± 6 kg/m^2 before third treatment vs. weight: 260 ± 41 lbs, BMI: 41 ± 6 kg/m^2 after third treatment), and fourth course (n = 2, weight: 336 ± 80 lbs, BMI: 55 ± 6 kg/m^2 before fourth treatment vs. weight: 339 ± 81 lbs, BMI: 55 ± 6 kg/m^2 after fourth treatment).

Discussion

The present study reports a very high prevalence of low vitamin D status among obese adolescents, both in girls (100%) and in boys (91%). The prevalence of low vitamin D status among obese adolescents in the present study is greater than the previously reported prevalence in this age group in general [21], and among obese adolescents in particular [22,23].

Vitamin D is fat-soluble and, thus, is incorporated into the body fat. For a normal-weight individual, this ability to store vitamin D in body fat provides a source of vitamin D for the body during winter when there is not enough sunlight to

produce vitamin D in the skin [18]. However, for obese patients with a high BMI, the body fat sequesters the vitamin D, making it less bioavailable to the body [24]. A study by Cheng et al underscored the importance of adipose tissue, particularly visceral adiposity, as a correlate of vitamin D status, above and beyond body size [25].

In addition to body fat, ethnicity and the season of the year may affect vitamin D status [22]. Vitamin D deficiency and insufficiency among adolescents have been reported particularly in African American adolescents and during winter [26,27]. Although ethnicity did not have a significant effect on the baseline 25(OH)D levels of our study participants, it did affect response to vitamin D treatment, with significantly more Caucasian adolescents than Hispanic or African adolescents normalizing their 25(OH)D levels after initial course of treatment. Baseline mean 25(OH)D level was significantly higher in the summer than in the spring, and significantly lower in the winter than in the fall. Mean 25(OH)D level during winter and spring was within the deficient range, whereas mean 25(OH)D level during summer and fall was within the insufficient range. Because baseline and subsequent measurements of 25(OH)D were spread across the seasons, there was no significant effect of season of testing on response to treatment with vitamin D.

In the present study, only 28% of adolescents normalized their 25(OH)D levels after one course of treatment with the recommended dose for vitamin D deficiency and insufficiency, whereas the other 72% failed to normalize their 25(OH)D levels even with repeat treatments with the recommended dose. Wortsman et al reported that when obese adults were placed in a tanning bed and exposed to the same amount of ultraviolet B radiation as normal-weight healthy adults, they were able to raise their blood levels of vitamin D to only about 45% of the levels attained by normal-weight adults [24]. A similar observation was made when these obese adults ingested 50,000 IU of vitamin D_2 [24]. Prospective studies are warranted to explore whether obese adolescents who do not respond to one course of the recommended treatment for vitamin D deficiency and insufficiency require repeat course(s) of treatment with at least twice the amount of vitamin D as normal-weight individuals to normalize their blood levels of 25(OH)D to more than 30 ng/mL.

In human beings, the main source of vitamin D is from cutaneous synthesis through a process initiated by ultraviolet radiation of the skin. Small amounts are also derived from dietary sources including oily fish, eggs, and fortified foods such as dairy products and breakfast cereals. It is possible that the association between obesity and low vitamin D status is indirect, arising from obese individuals having fewer outdoor activities than lean individuals, and therefore, less sun exposure. Similarly, it is possible that obese individuals do not consume enough vitamin D-containing foods.

Our study is limited by the lack of nutritional evaluation of vitamin D intake. In addition, we could not assess compliance with vitamin D treatment in this study, because medication diaries or pill counts were not used owing to the retrospective nature of the study. Furthermore, we did not estimate the duration of participants' sunshine exposure nor did we inquire about the use of sunscreens, which are known to reduce cutaneous vitamin D synthesis. Finally, given the retrospective nature of this study, we do not have exact information on the various vitamin D preparations that the patients had received from pharmacies or on the manufacturers of these preparations. Patients with vitamin D deficiency might have received ergocalciferol (vitamin D_2), which is the only high-dose calciferol available in the U.S. market, whereas patients with vitamin D insufficiency may have taken ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3). However, although an earlier study in male volunteers reported that vitamin D_2 potency was less than one-third of that of vitamin D_3 [28], a more recent study reported that both were equally effective [29].

Recently, the Institute of Medicine recommended 600 IU/d of vitamin D as dietary allowance for adolescents [30], with an upper level of safe intake of vitamin D set at 4,000 IU/d [30]. Others believe that adolescents require a higher daily intake of vitamin D. Weaver and Fleet estimated that to achieve an appropriate serum 25(OH)D concentration of 32 ng/mL (80 nmol/L) in female adolescents aged 12–19 years, it is necessary to consume 1,063 IU of vitamin D per day [14]. Holick recommends intake of 1,500–2,000 IU of vitamin D/day in an attempt to sustain vitamin D sufficiency in teenagers and adults [31]. Because the current mean (±SE) vitamin D intake from food and dietary supplements containing vitamin D in adolescents (14–18 years) in the United States is 210 ± 9.2 IU/d in females and 310 ± 16 IU/d in males [32], it seems that many adolescents will require specific vitamin D supplements to achieve the recommended daily allowance of vitamin D. In the present study, we did not examine which dose of vitamin D supplementation is most appropriate for maintenance of normal 25(OH)D levels in obese adolescents, after treatment of vitamin D deficiency and insufficiency. Thus, studies are warranted to examine whether the current recommended allowance of 600 IU/d of vitamin D will be able to sustain normal 25(OH)D concentrations in obese adolescents, or whether they require a higher daily supplementation dose.

Our study used a cut-off 25(OH)D level of 30 ng/mL for sufficient vitamin D status, as recommended by Holick [18]. It is important to note that the recent report by the Institute of Medicine recommended a cut-off of 20 ng/mL 25(OH)D level for sufficient vitamin D status in a healthy population [30]. It remains to be determined in future studies whether certain conditions, such as obesity, require a higher cut-off of 25(OH)D level in an attempt to prevent risks of adverse health consequences.

Lipid abnormalities were observed in about one-third of participants in the present study. Isolated low HDL-C was the most common lipid abnormality among these obese adolescents with lipid abnormalities, similar to findings reported by a previous study [33]. However, although an earlier study found a significant association between vitamin D insufficiency and decreased HDL-C in obese children and adolescents [22], we did not find such an association in our study.

There are some experimental data to suggest that vitamin D deficiency could promote weight gain and greater adiposity. Moderate to severe vitamin D deficiency leads to elevated levels of parathyroid hormone, which may promote calcium influx into adipocytes and enhance lipogenesis [34]. Depletion of vitamin D stores may also lead to excess differentiation of preadipocytes to adipocytes [35]. These studies raised the possibility that treatment of low vitamin D status would lead to less adiposity and to weight loss. However, similar to a previous report in obese adults [36], there was no effect of vitamin D treatment on body weight or BMI in the present study.

In summary, the present study reports high prevalence of low vitamin D status among obese adolescents, and calls for increased surveillance of obese adolescents whose blood total 25(OH)D levels do not normalize after initial course of treatment.

Prospective studies are needed to evaluate whether normalizing vitamin D levels in obese adolescents will lower the health risks associated with obesity.

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