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ORIGINAL PAPER

Inverse correlation between high body mass index and response to cholecalciferol treatment in children with vitamin D deficiency

Sahar Masoumi-Moghaddam[1], Samar Masoumi-Moghaddam[2], Seyed Alinaghi Kazemi[1], Saeideh Mazloomzadeh[3], Ahmad Jalilvand[1], Ziba Molaei[1, 4]

[1]Department of Paediatrics, Mousavi Hospital, Zanjan University of Medical Sciences, Zanjan, Iran
[2]Alfred Hospital, Central Clinical School, Monash University, Melbourne, Australia
[3]Department of Epidemiology and Statistics, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran
[4]Metabolic Disease Research Centre, Zanjan University of Medical Sciences, Zanjan, Iran

ABSTRACT

Aim of the study: An inverse correlation between excessive body weight and response to cholecalciferol in vitamin D deficiency (VDD) has been reported but no adjusted or conventional dose and treatment period has universally been recommended by the paediatric guidelines for obese children. In this study, we explored the efficacy of vitamin D supplementation in treatment of children with VDD based on their body mass index (BMI) and different levels of initial serum 25(OH)D.

Material and methods: In a single-centre, prospective, open label non-randomized trial in 255 subjects, baseline serum 25(OH)D was measured and different doses of oral D3 prescribed accordingly. Serum D_3 was measured at the end of the treatment period. All statistical analyses were conducted using the statistical package SPSS and p values less than 0.05 considered statistically significant.

Results: The response rate to vitamin D supplementation was associated with the patients' BMI characteristics. 25(OH)D levels normalized in 97.7% and 92.7% of the non-obese and obese subjects, respectively. In subjects with BMI ≥ 85th percentile, there was a lower increase in vitamin D levels after treatment than those with a BMI < 85th percentile. Evaluating the efficacy of the therapeutic dosage of cholecalciferol as per different categories of vitamin D levels, we observed the highest increase in the level of serum D_3 in the severely deficient D_3 category of both obese and non-obese groups.

Conclusions: There is an inverse correlation between high Body Mass Index and response to treatment with vitamin D supplementation, suggesting a higher dose of vitamin D for the optimal treatment of vitamin D deficiency in obese children.

KEY WORDS:

body mass index, children, cholecalciferol, vitamin D deficiency.

INTRODUCTION

Vitamin D deficiency (VDD) is a common problem worldwide with a markedly higher prevalence in the Middle East [1]. This is explained in part by limited sun exposure as a result of cultural practices and dress codes, skin colour, climate, genetic disposition, and insufficiently revisited regulation and guidelines for prevention and treatment of VDD [2]. As a major public health problem across all life stages with deleterious immediate and latent health consequences, VDD does not spare the paediatric age group [3, 4].

ADDRESS FOR CORRESPONDENCE:

Ziba Molaei, Department of Paediatrics, Mousavi Hospital, Zanjan University of Medical Sciences, Zanjan, Iran, e-mail: zmolaei@zums.ac.ir

An inverse association has been reported between hypovitaminosis D and obesity, likely due to the increased degradation of vitamin D_3 in the adipose tissue of obese individuals, hence its decreased bioavailability [5, 6]. However, obese people do not necessarily experience lower levels of serum vitamin D. Compensatory hyperparathyroidism and obesity-induced changes in bone metabolism were demonstrated to raise the level of vitamin D and/or its derivatives in a small number of obese subjects [7, 8]. The association between vitamin D insufficiency and obesity has been extensively investigated in adults, resulting in recommendation of higher dose of vitamin D for treatment of VDD in obese adults [9]. However, overweight children seem to receive inadequate attention. There are no universally recommended treatment protocols or widely-used paediatric guidelines with adjustments considered for the treatment of VDD in obese children.

Limited studies have suggested higher doses of vitamin D for the treatment of obese children with VDD. In a study on African-American children, it was revealed that vitamin D_3 supplementation with 400 IU per day for one month did not increase its serum level [10]. In another study on African-American adolescents, usage of 50,000 IU vitamin D supplementation, once a week for 6-8 weeks was found to be effective only in non-obese individuals [11, 12]. The aim of the present study was to assess the response to vitamin D_3 supplementation in children with VDD based on their BMI.

MATERIAL AND METHODS

PARTICIPANTS

After reviewing the medical records of 2500 children referred to the paediatric clinic from Jan 2019 to September 2020, 550 cases aged 2-10 years with known serum vitamin D test results entered the study through subsequent consultation at the Paediatric Endocrine Clinic. Age- and sex-specific BMI percentiles were determined from the 2000 Center for Disease Control (CDC) growth charts. Serum levels of 25-hydroxyvitamin D [25(OH)D] were measured at the reference laboratory using a CDI kit. Subjects were considered non-obese if BMI was between the 5th and 84th percentile, overweight if BMI fell between 85 to 94 percentiles, and obese if BMI equates or exceeds 95th percentile for age and gender. Hereafter, any subject with BMI ≥ 85th percentile is referred to as obese. The study was carried out between October 2019 and September 2020. Patients were evenly distributed throughout the four seasons. Exclusion criteria were: ongoing multivitamin supplementation; dietary calcium intake exceeding 1500 mg/day; use of an anticonvulsant; systemic glucocorticoid or vitamin D supplements; presence of signs of puberty; hepatic, renal, endocrine or hypothalamic disease; malabsorptive disorder; disorder of bone or calcium metabolism; cancer or genetic disorder that predisposes to obesity. Research protocol was approved by the Institutional Review Board (reference number: 1395.233 ZUMS.REC). Written informed consents and assents were obtained from the parents or guardians of the children who served as subjects of the investigation. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration.

STUDY DESIGN

This study was a prospective open label non-randomized pre-post comparison of the efficacy of vitamin D supplementation in children based on their BMI. Sufficient vitamin D status was defined as 25(OH) D level of ≥ 30 ng/ml, whereas VDD was considered 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. Children with serum vitamin D levels of < 10 ng/ml, 10-19 ng/ml and 20-29 ng/ml were prescribed in total 12, 10, and 6 pearls of vitamin D_3 (Zahravi Pharmaceutical), respectively, to take one pearl (50,000 IU) per week.

All subjects received the same compounded vitamin D_3 tablets, and compliance was assessed at regular follow-ups by counting the number of pills remaining in the pill bottle. The level of 25(OH)D was retested by the same laboratory two weeks after completion of the treatment.

STATISTICAL ANALYSIS

All statistical analyses were conducted using the statistical package SPSS, version 22 (SPSS Inc., USA). Descriptive analysis was used to describe the data either as mean ± standard deviation (SD) for quantitative variables or frequency (percentage) for categorical variables. Chi square test, independent *t*-test and Mann-Whitney U test were performed for comparing the actual difference between variables. All calculated *p*-values were two-sided, with p values less than 0.05 considered statistically significant.

RESULTS

550 children consisting of 56.2% girls and 43.8% boys were recruited and divided into two study groups as per the settings criteria: 75.3% non-obese with a BMI < 85th and 24.7% obese with BMI ≥ 85th percentile. With an average age of 7 years in total, the mean (±SD) age was 6.49 ±2.65 and 7.40 ±2.19 years in the obese and non-obese groups, respectively. While 121 children (22.0%) were found to have normal or high levels of vitamin D, 78% of individuals (45.1% female and 32.9% male) were initially diagnosed with VDD or insufficiency, among whom 22.7% were obese. The overall

TABLE 1. Baseline characteristics of initial 550 participants

Characteristics/Categorization	Patients number (%)	Obese	Non-obese	*P*-value
Age (years)				
2-10 years	550	6.49 ±2.65	7.40 ±2.19	< 0.0001
Sex				
Male	241 (43.8)	45 (18.7%)	196 (81.3%)	0.004
Female	309 (56.2)	91 (29.4%)	218 (70.6%)	
Season				
Spring	131 (23.8)	31 (23.7%)	100 (76.3%)	0.649
Summer	174 (31.6)	45 (25.9%)	129 (74.1%)	
Autumn	110 (20.0)	31 (28.2%)	79 (71.8%)	
Winter	135 (24.5)	29 (21.5%)	106 (78.5%)	
Vitamin D status				
< 10 ng/ml	57 (10.4)	15 (26.3%)	42 (73.68%)	< 0.0001
10-19.9 ng/ml	188 (34.2)	59 (31.3%)	129 (68.62%)	
20-29.9 ng/ml	184 (33.5)	51 (27.7%)	133 (72.28%)	
30-99.9 ng/ml	112 (20.4)	11 (9.82%)	101 (90.18%)	
≥100 ng/ml	9 (1.6)	0	9 (100%)	

Values are presented as mean ±SD

TABLE 2. Baseline characteristics in 255 vitamin D-deficient, compliant participants

Characteristics/categorization	Patients number (%)	Obese	Non-obese	*P*-value
Age (years)				
2-10 years	255	7.40 ±2.18	6.65 ±2.54	0.013
Sex				
Male	99 (38.8)	44 (35.8%)	55 (41.7%)	0.369
Female	156 (61.2)	79 (64.2%)	77 (58.3%)	
Season				
Spring	57 (22.4)	29 (50.9%)	28 (49.1%)	0.802
Summer	82 (32.2)	37 (45.1%)	45 (54.9%)	
Autumn	57 (22.4)	30 (52.6%)	27 (47.4%)	
Winter	59 (23.1)	27 (45.8%)	32 (54.2%)	
Vitamin D status				
< 10 ng/ml	34 (13.3)	15 (12.2%)	19 (14.4%)	0.542
10-19.9 ng/ml	109 (42.7)	57 (46.3%)	52 (39.4%)	
20-29.9 ng/ml	112 (43.9)	51 (41.5%)	61 (46.2%)	

Values are presented as mean ±SD

prevalence of VDD and insufficiency (< 30 ng/ml) was 78% with 22.72% in obese subjects and 55.27% in non-obese subjects. 74 (13.45%) of the obese subjects and 171 (31.1%) of the non-obese subjects were vitamin D deficient (< 20 ng/ml). Table 1 shows the baseline characteristics of these 550 candidates.

Patients with vitamin D levels greater than 30 ng/ml and those found to be non-compliant with their medication or follow-ups were excluded and the study continued with 255 patients. Of these, 51.8% and 48.2% were non-obese and obese, respectively. The mean baseline 25 (OH) D level was higher in the non-obese subjects compared to the obese subjects (mean, 26.82 ±1.07 vs. 20.15 ±0.82, $p = 0.001$). 41.5% of obese subjects and 46.2% of non-obese subjects had vitamin D level in the 20-29.9 ng/ml range. 72 (58.5%) of the obese subjects and 71 (53.8%) of the non-obese subjects were vitamin D deficient (< 20 ng/ml). As shown in Table 2, the distribution of sex, season and initial levels of vitamin D in the obese and non-obese groups was not statistically different.

TABLE 3. The correlation of baseline vitamin D with patients' characteristics

Categorization	< 10 ng/ml	10-19.9 ng/ml	20-29.9 ng/ml	*P*-value
Sex				0.26
Male	9 (26.5)	43 (39.3)	47 (42.0)	
Female	25 (73.5)	66 (60.6)	65 (58.0)	
BMI				0.53
< 85th percentile	19 (55.9)	52 (47.7)	61 (54.5)	
≥ 85th percentile	15 (44.1)	57 (52.3)	51 (45.5)	

Values are presented as mean ±SD

Considering the correlation of baseline vitamin D with patients' characteristics (Table 3), no significant difference in the mean serum level of vitamin D was found between boys and girls prior to the treatment (p-value = 0.22). Among those with severe VDD (< 10 ng/ml), girls comprised the majority (73.5%) when compared to boys (26.5%). The correlation between the initial level of vitamin D and children's BMI was found insignificant (p = 0.74).

Following the treatment, all cases demonstrated a marked increase in their serum levels of vitamin D, irrespective of their BMI and initial vitamin D grouping (the mean pre-treatment level: 18.20 ±6.6 ng/ml vs. post-treatment level: 59.90 ±23.0 ng/ml, p < 0.0001). Nevertheless, in only 89.4% of children the improved level of vitamin D fell within the normal range. 25(OH)D levels normalized (> 30 ng/ml) in 129 (97.7%) of the non-obese subjects, compared to 114 (92.7%) of the obese subjects. Serum vitamin D remained below the normal range in 4.7% of subjects, consisting of 3 (25%) of the non-obese and 9 (75%) of the obese subjects. Toxic levels of vitamin D (> 100 ng/ml) were recorded in 5.8% of treated children, among whom one child was obese and 14 children were in the non-obese group. Of these 14 children, 9 had an initial vitamin D level between 20 and 30ng/ml, 2 had it between 10 and 20 ng/ml, and 3 had it below 10 ng/ml. The mean level of vitamin D after treatment was not statistically different between boys and girls (p-value: 0.36). Moreover, no correlation between different categories of post-treatment vitamin D levels and gender was indicated (p-value: 0.48).

Contrary to the insignificant correlation of the initial level of vitamin D and BMI, the effectiveness of response to vitamin D supplementation was found to be affected by the patients' BMI characteristics. Following the completion of treatment, the mean serum level of vitamin D was 69.3 ±25.3 ng/dl and 49.8 ±14.6 ng/ml in the BMI < 85th and ≥ 85th percentile groups, respectively (p < 0.001) showing a lower increase in the post-treatment vitamin D levels in the obese group (Table 4).

TABLE 4. Pre- and post-treatment serum vitamin D according to the BMI

Categorization	Serum vitamin D level		*P*-value
	Pre-treatment	Post-treatment	
< 85th percentile			< 0.001
<10 ng/ml	7.5 ±1.5	63.5 ±30.2	
10-19.9 ng/ml	15.3 ±3.1	64.5 ±25.3	
20-29.9 ng/ml	24.2 ±2.7	75.3 ±22.7	
≥ 85th percentile			< 0.001
< 10 ng/ml	7.3 ±2.2	44.4 ±24.9	
10-19.9 ng/ml	17.3 ±2.7	47.3 ±12.7	
20-29.9 ng/ml	29.9 ±2.0	54.1 ±11.8	

Values are presented as mean ±SD

DISCUSSION

In this study, we compared response to cholecalciferol treatment in obese and non-obese Caucasian middle-eastern children aged 2-10 years who were diagnosed with VDD. While the overall response to vitamin D supplementation was acceptable in the studied subjects with 89.4% of them showing a normalized vitamin D level, the overall response to treatment was approximately 1.4-fold lower in obese group as compared to the non-obese one. This finding is in line with a previous study demonstrating an inverse correlation between BMI and either peak serum vitamin D_2 or D_3 concentrations following a single oral dose of 50,000 IU of vitamin D_2 or UV-B irradiation in adolescence, likely due to the decreased bioavailability of vitamin D_3 as a result of its deposition in body fat compartments [8]. Poor response to vitamin D_2 or D_3 supplementation has also been reported in other studies. Castaneda *et al.* showed that the increment in 25(OH)D levels following vitamin D supplementation was significantly lower in the obese adolescents, thus higher doses of vitamin D are required to treat VDD in obese adolescents than in their non-obese peers [13]. A negative correlation between vitamin D levels and BMI, BMI percentiles, waist and hip circumference was also reported by Bellone *et al.* in children [14]. Moreover, body mass index has been shown to have a significant effect on serum 25-(OH)D levels, as well as the dose of vitamin D_3 in white [15] and African-American menopausal women [16]. Gallagher *et al.* showed that treating obese and non-obese individuals with the same dosage of vitamin D_3 resulted in a lower response rate in obese subjects. In

accordance with this, a retrospective study of vitamin D deficient Hispanic and African American adolescents who were treated with weekly vitamin D supplementation (50,000 IU for 6-8 weeks) demonstrated that only a subset of subjects could reach normalized 25(OH)D. They thus suggested that increased surveillance and possibly higher vitamin D doses are warranted for obese adolescents [12]. A similar observation was made by Ashraf *et al*. when they prospectively studied obese African American female adolescents receiving ergocalciferol (vitamin D_2) 50,000 IU for 8 weeks. The increment of the serum 25(OH)D concentration was noted in only two thirds of the participants [11]. In another study by Mazahery *et al*. in premenopausal Middle-Eastern women, lower body fat percentage as well as a larger dose appeared to be significantly influencing a better response to oral vitamin D supplementation [17]. They reported that one unit decrease in body fat (%) resulted in a 0.7 nmol/l increase in serum-25(OH)D. Chung et al studied an eight-week course of vitamin D replacement (2,000 IU/day) and reported normalization in 61.9% and 47.6% of normal-weight and overweight children, respectively, without a statistically significant difference in the mean serum 25(OH)D levels following treatment in those groups [18]. Although the exact mechanism for a poorer response is yet unknown, this might be secondary to difference in vitamin D metabolism in obese group or a possible greater degree of sequestration of lipid-soluble vitamin D in the adipose tissue [19].

In our study, participants were instituted with three different doses of vitamin D_3 as per their initial serum vitamin D concentrations. With a desirable response rate in the entire cohort, the toxic serum levels of vitamin D were observed in 15 children, consisting of only one obese case who received a total of 6 pearls. The majority of non-obese children (9 out of 14) with toxic serum levels of D_3 were found to be prescribed the minimum dosage (6 pearls) of vitamin D. "Considering both the lower response rate and toxicity rate in obese children, it seems sensible that higher doses of vitamin D would be required for the treatment of obese children. The total amount of vitamin D received by our patients ranged from a minimum of 300,000 (6 pearl, each 50,000) to a maximum of 600,000 UI (12 pearl, each 50,000 UI). To the best of our knowledge, this is the first report of such treatment adjustments where high dosage of oral vitamin D are prescribed for different time periods based on the initial serum level of vitamin D and consideration of the possible toxicity ensuing".

In a similar study, Motlaghzadeh *et al.* prescribed the whole cohort with 6 pearls of vitamin D3 in total (50000 IU/week for 6 weeks) but the normalization rate of 25(OH)D3, in particular in obese children was lower than that in our study [20]. When Gabi *et al.* commenced obese patients on an intramuscular vitamin D_3 of 300,000 to 600,000 units, only 35% got normal level of vitamin D [21]. Rajakumar *et al*. treated vitamin D_3 deficient subjects with 400 units of vitamin D_3 daily for 1 month but this was found inadequate [10]. A 24-week treatment with weekly vitamin D_2 50,000 IU by Samaranayake *et al.* was also reported inadequate as the mean vitamin D levels did not rise above the deficiency cut-off value of 20 ng/ml [22].

The Institute of Medicine (IOM) recommended dietary allowance for vitamin D is 600 IU daily for healthy population aged 1-18 years in order to maintain the recommended level for serum 25(OH)D (≥ 50 nmol/l). However, there is disagreement between recommendations of the American Academy of Pediatrics (AAP) and Endocrine Society guidelines who recommend lower and higher dosage than that of 600 IU for the same age group, respectively [23]. When it comes to deficiency, while the AAP recommends 5,000 IU per day, the Endocrine Society guidelines recommend 50,000 IU weekly of vitamin D for at least 6 weeks or until serum concentrations of 25(OH)D are above 50 nmol/l. Although these dosages are found to be well tolerated, there is no evidence if the maintenance dosage can be similar in nonobese and obese as the obese are approximately half as efficient in using vitamin D compared to their non-obese counterparts. In light of the above, a separate set of guidelines for obese adolescents is warranted [23].

Although the relationship between obesity and vitamin D status is clear in the adult population, there is no consensus on the literature regarding a higher frequency of vitamin D deficiency in children and adolescents with obesity. In our study, the correlation between the primary level of vitamin D and children's BMI was found insignificant. According to previous studies, the prevalence of VDD seems to be related to obesity level and BMI, being expected to be higher in overweight and obese children [24]. However, in our study, 22.7% of cases diagnosed with hypovitaminosis D were obese and the rest were children with normal BMI. While some studies have indicated a higher prevalence of VDD in obese children [14, 25, 26], others describe this linkage insignificant. Rajakumar *et al.* reported that while VDD occurred in 57% obese vs. 40% non-obese subjects who were matched for age, sex, skin colour, and pubertal maturation, the difference was not statistically significant [10]. A study by Dura-Trave et al found that 25(OH)D levels in children with obesity were inversely associated with body fat content, and this association was stronger than that between 25(OH)D and BMI or body weight [27]. They indicated that obesity increases the prevalence of suboptimal vitamin D status, and a BMI status reduction in children with obesity may be required to at least stabilize vitamin D status. In a meta-analysis study, the relative risk for the association between VDD and obesity in children was lower compared to in adults (1.41 vs. 3.43) [28]. However, high heterogeneity was seen in all studies with regard to the different cut-off points for 25(OH)D defi-

ciency, the severity of obesity and multifactorial aetiology of hypovitaminosis D as possible confounding factors in the analysis.

In the current study, treatment-response effects were different between obese and non-obese groups with regard to different threshold levels of serum 25(OH)D ranging from severely deficient to just insufficient levels. Evaluating the efficacy of the therapeutic dosages of prescribed cholecalciferol as per different categories of vitamin D levels, the difference was more prominent in the severely deficient as well as insufficient vitamin D patients. The highest increase in the level of serum vitamin D_3 after treatment was seen in the severely deficient D_3 category of both obese and non-obese group. The association between treatment response and basal 25(OH)D thresholding in obese group was consistent with a previous study reporting that treatment was effective in the obese cohort for those with basal 25(OH)D ≤ 20 ng/ml [10]. In the present study, among the children who had serum vitamin D levels of < 10 ng/ml and received weekly D_3 50,000 IU for a period of 12 weeks, the non-obese cases showed 8.5-fold increment in the 25(OH)D levels but the change was only 6-fold in the obese group (1.4-fold lower in the obese group). The raise in the serum 25(OH)D_3 level following the treatment with 6 pearls of vitamin D_3 50,000 IU was 1.3-fold lower in the obese group as cases in the < 85th percentile reached a 3.1-fold increase in their serum vitamin D level versus an only 1.8-fold increase in the ≥ 85th group. These findings suggest that the efficacy of cholecalciferol treatment is correlated with the BMI and partly with the severity of hypovitaminosis D in the 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, gender or season, on response to different doses of vitamin D_3 supplementation in Caucasian Middle Eastern children. We conclude that the threshold levels of primary serum 25(OH)D associates with response to vitamin D therapy in obese and non-obese children, potentially due to differences in the metabolism of 25(OH)D and a greater degree of sequestration of vitamin D in the body fat deposits of obese children. However, further assessment is warranted in a larger cohort.

Evaluating the association of primary vitamin D level and gender, no significant difference in prevalence was observed between girls and boys with regard to the mean serum 25(OH)D. This was in accordance with Gordon *et al*. findings in which the prevalence of VDD was 26.0% vs. 20.6 in girls and boys, respectively [25]. Inclusion of serum D_3 level thresholding, however, resulted in girls to be defined as the majority of severe vitamin D deficient cases in our study. This was consistent with some previous studies reporting girls to have higher prevalence of VDD than boys [29, 30]. Studying 68 obese adolescents, Harel *et al*. reported that the prevalence of low vitamin D status was 100% in obese girls and 91% in obese boys. About 72% of the females were vitamin deficient and 28% were vitamin insufficient, whereas 69% of the males were vitamin D deficient, 22% were vitamin D insufficient, and 9% had sufficient vitamin D status [12]. Variation in physical activity and cultural differences, including difference in clothing style and coverage among boys and girls may partly justify this difference.

CONCLUSIONS

In this study, we observed that the response of vitamin-D deficient obese children to the recommended high-dose intermittent vitamin D therapy as per the Endocrine Society guidelines was significantly lower than that of non-obese individuals. In addition, stratification of obese and non-obese patients with VDD based on different cut-offs of initial serum vitamin D showed different response rates in the cohort. Determination of the proper dosage of vitamin D in children with VDD according to their initial serum levels of D3 and BMI is warranted in a larger study.

DISCLOSURE

The authors declare no conflict of interest.

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