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Original Paper

Assessment of Vitamin D Status and Response to Vitamin D3 in Obese and Non-Obese Iranian Children

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ABSTRACT

Background: Obesity seems to be a critical issue nowadays because of its high prevalence and its adverse effects on health. There is some evidence indicating the relationship between obesity and lower serum 25-hydroxyvitamin D [25(OH)D] concentration. The aim of the present study was to examine serum 25(OH)D status of obese and non-obese Iranian children and compare their therapeutic response with identical oral vitamin D3 treatment.

Methods: In a non-randomized clinical trial, serum 25(OH)D level of 45 obese and 45 non-obese Iranian children aged 2–14 years was measured. Those with serum 25(OH)D status <30 ng/ml (73 cases) were treated with one pearl of vitamin D3 (50 000 International Units) once a week for 6 weeks. Serum vitamin D was measured once more 2 weeks after treatment.

Results: The frequency of hypovitaminosis D was 43/45 (95.6%) in obese and 30/45 (66.7%) in non-obese children at baseline ($p < 0.001$). After treatment of 73 cases (43 obese, 30 non-obese), the above percentages were decreased to 24/43 (55.8%) and 1/30 (3.3%), respectively ($p < 0.001$).

Conclusion: Our study demonstrated a high frequency of vitamin D deficiency among Iranian children, particularly the obese ones. Moreover, low therapeutic response in the obese group is witnessed.

KEYWORDS: vitamin D, obesity, children, Iran.

INTRODUCTION

In recent decades, there have been reports suggesting high prevalence of hypovitaminosis D and its side effects [1–4]. It has been estimated that about 1 billion people worldwide are suffering from vitamin D deficiency or insufficiency [5, 6]. Additionally, the prevalence of inadequate vitamin D level is reported considerably higher in Middle-eastern countries. It could be the result of different factors such as cultural dress codes, less time spent outdoors and lower vitamin D intake [7].

Vitamin D plays an important role in children's bone health [2]. Its deficiency is responsible for secondary hyperparathyroidism and skeletal abnormalities such as rickets, osteopenia, osteoporosis and osteomalacia [3]. In recent years, a wide range of health problems such as cardiovascular diseases, hypertension, infections, autoimmune diseases and common cancers have been related to low vitamin D level [4, 8–14].

According to the World Health Organization's reports, obesity [Body Mass Index (BMI) $\geq$ 95th percentile] has recently become an epidemiologic problem because of its increasing prevalence [15, 16]. Since the late 1970s, the obesity rate has quadrupled among 6–11 year old children and tripled among 12–19 year old children [17–19]. There is evidence from previous studies, indicating the association between obesity and lower serum 25-hydroxyvitamin D [25(OH)D] level [20–28]. Furthermore, it has been suggested to treat obese children suffering from vitamin D deficiency with higher doses (two to three times higher) of vitamin D3 [29].

So far, no study has well documented the prevalence of vitamin D deficiency in obese Iranian children. Therefore, the authors developed a comprehensive study in this article to examine vitamin D status of obese and non-obese Iranian children and their therapeutic response to identical vitamin D3 therapy [50 000 International Units (IU) of vitamin D3 once a week for 6 weeks] [29].

MATERIALS AND METHODS

Study subjects

To perform the study, a group of 90 (45 obese, 45 non-obese) Iranian children aged 2–14 years were selected among those referred to Children's Medical Center of Tehran. Obese children were selected from endocrine clinics, while non-obese ones from vaccination and general clinics. It is important to note that in our clinical centre, obese children are generally referred to endocrine clinic. Exclusion criteria included usage of vitamin D, multivitamin supplements, anticonvulsants or systemic glucocorticoids, presence of chronic diseases, endocrine diseases causing obesity (Cushing syndrome, hypothyroidism, etc.) and BMI between 85th and 95th percentile (overweight) for age and gender. We excluded 2 children because of hypothyroidism and 22 because of mentioned BMI interval. Hence, the study specifically compares the non-obese group with the obese one.

The research was done during spring and summer over 2 years (2012–3). It was approved by the research ethic committee of Tehran University of Medical Sciences and was recorded at the IRCT Center (the code number 2012100210988N1). Informed parental consent and assent were obtained before sampling as well.

Study design

Study design was a non-randomized trial, comparing the prevalence of hypovitaminosis D and the therapeutic response with identical oral vitamin D3 in obese vs. non-obese children. Calculated sample size in each group was 45 (alpha-level 0.05, power 80%, difference 30%). The weight and height measurements were done using a Seca balance and stadiometer, respectively. The subjects were categorized as obese (BMI $\geq$ 95th percentile) or non-obese (5th $<$ BMI $<$ 85th percentile) considering age and gender-specific BMI [18].

Participants' skin colour was categorized as type 3 or 4 based on Pathak's classification [30]. Their pubertal maturity was assessed using the criteria of Tanner [31, 32].

Serum 25(OH)D, calcium, phosphorus, parathyroid hormone (PTH) and alkaline phosphate levels were measured before treatment and 2 weeks after treatment.

After the first blood sampling (done between 8 and 11 am), children with adequate vitamin D levels (17 cases) left the study and did not get the intervention, while those with serum 25(OH)D

levels < 30 ng/ml (73 cases) were treated by one pearl of vitamin D3 (50 000 IU) once a week for 6 weeks (D-Vitin, Zahravi, Iran) [29]. Families were reminded about their children's therapy every week.

The same dose of therapy was repeated in children who did not respond sufficiently to the first course.

Assessment of vitamin D and calcium intake

Parents filled out a validated food frequency questionnaire to assess their children's dietary intake of vitamin D and calcium. They also completed a questionnaire about the quantity and quality of their children's sun exposure, history of bone pain and fracture.

Biochemical measurements

Serum 25(OH)D quantification was done using the radioimmunoassay method by Immuno Diagnostic Systems Kits (IDS, Bold on, UK). The intra-assay and inter-assay coefficients of variation were 5.3% at the level of 15.6 ng/ml ($n = 10$) and 4.6% at the level of 16.2 ng/ml ($n = 11$), respectively. PTH was measured by Cobas e411 machine (Roche Diagnostics). The intra-assay and inter-assay coefficients of variation were <5% and 8%, respectively.

Vitamin D status

The following definitions for vitamin D status were used to classify the subjects: hypovitaminosis D, 25(OH)D levels <30 ng/ml; and vitamin D sufficiency, 25(OH)D levels ≥30 ng/ml [29].

Statistical analysis

Statistical analyses were carried out using SPSS, and results were represented as Mean ± SD. The means comparison between the groups were done using an independent *t*-test for continuous outcomes, while Fisher's exact and Chi-square were used for categorical outcomes. The Pearson correlation was applied to assess the relationship between baseline and post-treatment serum 25(OH)D level and BMI. To study the effects of independent variables (obesity, age group and sex) on serum 25(OH)D level change, a multiple linear regression was used. The significance level was set at $p \leq 0.05$ through the statistical analysis.

RESULTS

Clinical characteristics

The study enrolled 45 obese and 45 non-obese children aged 2–14 years matched for sex. Table 1 shows the characteristics (age, sex, height, weight, etc.) of the study participants. The mean weight and BMI measured significantly higher in the obese group ($p < 0.001$, Table 1). The mean height in non-obese children is lower than obese ones, which could be explained by higher mean age of the latter group. The majorities of subjects were tanner stage I and II and had type 3 skin colour. The cohorts were not significantly different in mean dietary intake of calcium and vitamin D, which were below the recommended dietary intakes. It should be noted that because of the short duration of sun exposure at inappropriate times of the day in all participants, we ignored its effect on serum 25(OH)D level [29].

Baseline laboratory data

At baseline, serum 25(OH)D level was significantly lower in the obese group, while alkaline phosphatase and PTH levels were significantly higher ($p < 0.05$). There were no remarkable differences between the obese and non-obese cohorts for calcium and phosphorus at baseline as well as no evidence of rickets (Table 2). The proportion of hypovitaminosis D was 43/45 (95.6%) obese vs. 30/45 (66.7%) non-obese ($p < 0.001$).

The proportion of hypovitaminosis D measured was 75% in obese children <6 years old, and 97.6% in the other age group ($p < 0.05$). In non-obese children, the proportion of low vitamin D level was not significantly different between the two age groups (63.6% vs. 69.6%, $p = 0.67$).

A similar analysis was done by dividing obese and non-obese groups based on gender, which was not significantly different in prevalence of low vitamin D level (100% in obese females vs. 90.5% in obese males, $p = 0.82$, and 70.8% in non-obese females vs. 61.9% in non-obese males, $p = 0.52$).

Post-therapy laboratory data

Following oral treatment of 73 cases (43 obese and 30 non-obese) with 300 000 IU of vitamin D3 during 6 weeks, serum 25(OH)D level was significantly lower in the obese group ($p < 0.001$). Furthermore,

Table 1. Baseline characteristics

Characteristics	Obese	Non-obese	*p*-value
Number of subjects	45	45	–
Age (years)	9.4 ± 2.1	7.4 ± 3.2	0.01
Gender (female/male)	24 / 21	24 / 21	1
Weight (kg)	54.5 ± 15.5	24.6 ± 9.8	<0.001
Height (cm)	142 ± 12.3	121 ± 21	<0.001
BMI (kg/m^2)	26.3 ± 3.8	15.9 ± 1.6	<0.001
Diet calcium (mg/dl)	822 ± 200.6	844 ± 141.4	0.53
Diet vitamin D (IU/day)	53.4 ± 13	54.4 ± 17.2	0.74
Tanner staging			
1	27	33	0.44
2	7	7	
3	9	5	
4	1	0	
5	1	0	
Skin colour type			
3	33	34	0.8
4	12	11	
History of bone pain (positive/negative)	8/37	4/41	0.21
History of bone fracture (positive/negative)	0/45	1/44	0.31

Table 2. Baseline laboratory data

Laboratory data	Obese	Non-obese	*p*-value
Calcium (mg/dl)	9.7 ± 0.4	9.7 ± 0.5	0.45
Phosphorus (mg/dl)	4.9 ± 0.6	5.2 ± 0.6	0.24
PTH (pg/ml)	34.3 ± 14	28.1 ± 12	0.02
25(OH)D (ng/ml)	11.9 ± 6	22.4 ± 16	<0.001
Alkaline phosphatase (IU/l)	700 ± 138	579 ± 126	<0.001

significant differences were observed between the obese and non-obese cohorts in post-treatment phosphorus, PTH and Alkaline phosphatase ($p = 0.02$, $p = 0.01$ and $p < 0.001$) (Table 3).

The proportion of hypovitaminosis D became 24/43 (55.8%) obese vs. 1/30 (3.3%) non-obese ($p < 0.001$). After treatment, the mean serum 25(OH)D level increased from 22.4 ± 16 ng/ml to 90.2 ± 39.4 ng/ml and from 11.9 ± 6 ng/ml to 43.5 ± 34.2 ng/ml in non-obese and obese groups, respectively (Tables 2 and 3).

We treated the above 25 cases (24 obese and 1 non-obese) for the second time with the same dose; however, serum 25(OH)D level was measured < 30 ng/ml in 7 obese cases. According to few non-responsive cases to first course of therapy (especially in the non-obese group), the comparative analysis was infeasible. It should be noted that 88% (15/17) of obese children who responded to the second course of therapy and 100% (7/7) of those who did not respond, had BMI >99th percentile for age and sex. Finally, we successfully treated the remaining seven cases with the third therapy course.

Correlations

Baseline and post-treatment serum 25(OH)D levels had significant negative correlations with BMI ($r = -0.39$, $p < 0.001$ and $r = -0.55$, $p < 0.001$, respectively).

Based on multiple linear regression analysis, the mean change of serum 25(OH)D level (before and after treatment) was 35.9 ng/ml lower in the obese group. The mean serum 25(OH)D level change in children <6 years old was 22 ng/ml higher than the older ones (Table 4). It should be noted that the subjects were divided into two age groups (first group <6 years old; second group ≥6 years old) to consider the effect of cultural dress code change because of the school uniform in both genders and hijab in girls. Therefore, in children >6 years old, the amount of body parts exposed to the sun is limited to face and hands. However, there was no such a limitation for children <6 years old.

DISCUSSION

In this non-randomized clinical trial, we examined vitamin D status in obese and non-obese Iranian children aged 2–14 years and their therapeutic response to 50 000 IU of vitamin D3 weekly, for 6 weeks.

Table 3. Post-therapy laboratory data

Laboratory data	Obese	Non-obese	*p*-value
Calcium (mg/dl)	9.8 ± 0.3	9.6 ± 0.5	0.51
Phosphorus (mg/dl)	4.8 ± 0.5	5.2 ± 0.6	0.02
PTH (pg/ml)	31.6 ± 19.7	22 ± 12.1	0.01
25(OH)D (ng/ml)	43.5 ± 34.2	90.2 ± 39.4	<0.001
Alkaline phosphatase (IU/l)	700 ± 138.6	579 ± 126.3	<0.001

Table 4. Effect of obesity, age group and gender on 25(OH)D status change

Variables	B[a]	SD	Beta	Significance
Constant	53.4	11.9	–	0
Obesity	−35.9	9.4	−0.42	0
Age group	−22	10.9	−0.22	0.048
Gender	−0.87	8.2	−0.1	0.916

[a]Y-intercept.

The proportion of hypovitaminosis D was 95.6% in obese vs. 66.7% in non-obese children. Therefore, a significantly higher prevalence of low serum vitamin D level was observed in the obese group compared with the non-obese one, which was independent of their dietary intake.

Studies have consistently shown the relationship between obesity and lower serum 25(OH)D level. For instance, a group of researchers in Italy examined 113 non-obese and 444 obese children. Their results indicated that 81.1% of the obese and 71.7% of the non-obese group were suffering from vitamin D levels <30 ng/ml [33]. In [34], a group of American researchers studied 87 non-obese and 411 obese subjects. The prevalence of vitamin D deficiency was reported 68% and 92% in each group, respectively. Such a difference can be explained by the storage of vitamin D in fat stores, which is higher in obese individuals [35].

Because of the increasing prevalence of obesity worldwide, this finding seems to become more important than before. Furthermore, we found that the treatment response to oral vitamin D3 was significantly different between the cohorts. As mentioned before, following treatment, the proportion of hypovitaminosis D became 55.8% in obese vs. 3.3% in non-obese children. It is also important to note that mean serum 25(OH)D level change was lower in obese children. Similar results were obtained by another group of researchers, who treated Hispanic and African American adolescents with the same dose of vitamin D3 (50 000 IU once a week, for 6 weeks) [36].

In [37], 18 obese and 18 non-obese adolescents were treated with vitamin D3 (2000 IU/day) orally for 12 weeks. The results revealed that the response to vitamin D supplementation was almost 2-fold lower in the obese group compared with the non-obese one.

In a study of obese and non-obese African American children, researchers treated subjects with 200 IU/day vitamin D3 for 1 month. The results illustrated that the treatment was more effective in the non-obese cohort [20]. Considering the above discussion, one can conclude that the poor therapeutic response to oral vitamin D3 in obese children is likely related to greater fat stores as well as different metabolism of 25(OH)D in obesity [35].

It should be noted that in our study, the mean dietary intake of vitamin D in all subjects was significantly lower than the recommended amounts (54.7 IU/day obese and 53.4 IU/day non-obese). This could be one of the main reasons for high vitamin D deficiency prevalence in our population.

Another remarkable observation was the negative correlation between BMI and baseline serum 25(OH)D level ($r = -0.39$, $p < 0.001$), as well as BMI and post-treatment serum 25(OH)D level ($r = -0.55$, $p < 0.001$). Similar results were reported by previous studies [2, 36–40].

To strengthen the study, we designed it as a clinical trial trying to eliminate confounding variables such as gender and season. We assessed subjects for daily vitamin D intake as well as the quality and quantity of sun exposure by a family filled-out validated questionnaire. We also used recommended treatment dose of vitamin D3 in children. However, our study is limited by its small sample size and not eliminating the confounding effect of age. Although, we reminded parents about their children's therapy every week, it was difficult to determine their compliance.

In conclusion, we observed that the response of obese children to standard dose of vitamin D3 was

significantly lower than that of non-obese children. Involving more participants in future studies would be beneficial to obtain the proper dose of vitamin D3 therapy in obese children. In addition, we suggest screening all obese children to treat vitamin D deficiency before its side effects happen.

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