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Differences in Response to Conventional Vitamin D Therapy among Obese and Normal Weight Children and Adolescents in Qazvin, Iran

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Abstract

Background

Vitamin D (Vit D) deficiency is one of the major nutritional deficiencies in children. Obesity has inverse association with vitamin D levels. The aim of this study was to determine the differences in response to conventional treatment for Vit D deficiency and insufficiency in obese and normal weight children and adolescents.

Materials and Methods: This nested case control study was conducted in 69 obese children and 133 normal weight matched control suffering from Vit D insufficiency or deficiency. Vit D deficiency was defined as serum 25(OH) D3 <10 ng/mL and Vit D insufficiency was defined as 11< 25(OH) D3 <30 ng/mL. Conventional treatment with 300,000-600,000 IU of vitamin D_3 was administered intramuscularly over one day for both groups. The participants were followed up after three month. 25 (OH) D3 was measured at baseline and after the follow up period. Data were analyzed using SPSS version 22.0.

Results: At baseline, mean Vit D level was 13.5 ng/mL in obese and 14.5 ng/mL in normal weight children (P>0.05). After follow up, mean Vit D level became 29.6 ng/mL in obese and 33 ng/mL in normal weight children (P<0.05). 39.8% of normal weight group still had Vit D insufficiency, while 50.7% of obese group had Vit D insufficiency or deficiency and the difference was borderline significant (P= 0.064).

Conclusion

Therapeutic response in obese children was less than normal weight children. It seems that treatment with higher doses of Vit D or longer period is necessary in obese children of the present study.

Key Words: Adolescents, Children, Obesity, Vitamin D deficiency.

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1- INTRODUCTION

Vitamin D (Vit D) deficiency is one of the most important nutritional issues in children (1). Although this problem has been greatly solved in the developed countries, rickets is still an intractable problem in the developing countries (2).
The prevalence of Vit D deficiency in the world is much higher than that of rickets; for example, one out of each seven adolescents has Vit D deficiency in the USA (3). In Turkey that has growing prevalence of obesity, the prevalence of hypovitaminose D has been reported as 65% including 12% Vit D deficiency and 53% Vit D insufficiency (4). In a study conducted on the age range of 20-64 years in Tehran- Iran, the severe, moderate, and mild Vit D deficiency were estimated as 9.5%, 57.6% and 14.2%, respectively (5).

Vit D role is not limited to osteogenesis. Since Vit D receptors are extensively distributed in different tissues such as bone and adipose tissue, Vit D deficiency leaves severe outcomes on bone and non-bone tissues (6). Vit D plays an important role in the metabolism of bones, adipogenesis and prevention of diseases such as osteoporosis, cancer, heart failure, diabetes mellitus and immune diseases (7-9). Some studies even indicated that Vit D deficiency is associated with hypertension, psychiatric illnesses such as schizophrenia and depression, sudden death, and death following heart failure (10-12). Also, there is an association between Vit D deficiency and pulmonary dysfunction, wheezing, and pneumonia (13).

On the other hand, a specific relationship also exists between children's body weight and Vit D level. Different studies showed a reverse relationship between the obesity and the level of 25-hydroxy vitamin D [25 OH (D3)] (14-17). Obesity is considered as an epidemic problem in the USA. About 32% of children and adolescents, and 66% of young adults are obese (18). It is reported that the prevalence of obesity has increased significantly within recent two or three decades and is about 40% in some communities. Hypertension, dyslipidemia, insulin resistance, fatty liver disease and psychosocial disorders are some impacts of obesity on health (19). Considering the importance of Vit D in musculoskeletal development and fat mass in children, and its common deficiency all around the world, the aim of the present study was to determine the differences in response to conventional treatment for Vit D deficiency and insufficiency in obese and normal weight children and adolescents in a nested case control design.

2- MATERIALS AND METHODS

2-1. Study design and population

This nested case control study was conducted in 69 obese and 138 normal weight children and adolescents (4-14 years old) with hypovitaminose D, referred for treatment to the Endocrine clinic of Children Hospital in Qazvin city, Iran, during spring 2013.

2-2. Methods

The normal weight group was matched for age and gender with obese group. Obesity was defined as body mass index (BMI) higher than 95th percentile for age and gender while normal weight was defined as BMI between 5th and 85th percentile for age and gender (20). Vit D deficiency was defined as 25 (OH) D3 <10 ng/mL and 10<25 (OH) D3<29 ng/mL was considered as Vit D insufficiency. Conventional treatment (stoss therapy) with 300,000-600,000 IU of vitamin D_3 was administered intramuscularly as 1-2 doses over one day for both groups (21). The participants were followed up after three months. The 25 (OH) D3 level was evaluated in the participants after the follow up period and the results were compared between the groups.

2-3. Measuring tools

Age was calculated in days, months and years, based on the birthday. The standing height was measured with a wall mounted stadiometer seca nearest 1 mm, without shoes. The weight was also measured using Seca scale (Vogel and Halke, Hamburg, Germany), nearest 100 grams. The BMI was calculated as weight in kilograms per height in squared meters.

2-4. Laboratory measurements

Thyroid stimulating hormone (TSH) and Thyroxine (T4) level were measured to exclude hypothyroidism. Alkaline phosphatase (ALP), phosphorus (P), calcium (Ca), parathyroid hormone (PTH), and 25 (OH) D3 were measured in a single laboratory. TSH was measured using Electrochemiluminescene (ECL) (Roche, Germany). Intra and inter assay coefficients of variation (CVs) were ≤ 8.6 and ≤8.7, respectively. A Hitachi 917 autoanalyzer with Arsenozo III and reagent (Parsazmun Company, Iran), was used to measure Ca; Mean intra- and interassay CVs were ≤1.7 and 2.0, respectively.

A Hitachi 917 autoanalyzer with UV/VIS Photometric test and reagent (Parsazmun Company), was used to measure P; intra- and inter-assay coefficients of variation (CVs) were ≤1.6 and ≤2.2, respectively. A Hitachi 917 autoanalyzer with DGKC and reagent (Parsazmun Company), was used to measure ALP; Mean intra and inter assay CVs were <1.5 and <1.6, respectively. PTH was measured using Electrochemiluminescene (ECL) (Roche, Germany). Intra and inter assay coefficients of variation (CVs) were ≤ 2.7 and ≤6.5, respectively. 25 (OH) D3 was measured using ELISA (Euroimmune, Germany). Intra and inter assay CVs were 4.4 and <8.2, respectively.

2-5. Ethical consideration

The ethics committee of Qazvin University of Medical Sciences approved the study protocol. Written informed consent was obtained from both parents and participants.

2-6. Inclusion and exclusion criteria

Inclusion criterion was diagnosis of Vit D deficiency or insufficiency without underlying disease. Children with chronic liver and renal diseases, hypothyroidism, cancer, malabsorption and those who were under corticosteroid therapy, treatment with antiepileptic drugs or multi-vitamins were excluded from the study.

2-7. Data Analyses

Data were described as mean ± standard deviation (SD) or number (percent) where appropriate. Categorical variables were analyzed by Chi square test. T-test was used for analysis of quantitative variables. P-values less than 0.05 were considered as statistically significant. All of the analyses were performed using the SPSS software, version 19.0 software.

3- RESULTS

Totally, 207 children with hypovitaminose D were enrolled in the study. In the normal weight and obese groups, 37.6% and 40.6% of the participants were male, respectively (P: 0.396). All subjects in the obese group completed the study. Five subjects (3.62 %) in the normal weight group were lost to follow up due to long delay for visit after treatment. Demographic and biochemical characteristics of the participants at baseline are shown in **Table.1**.

There was a significant difference regarding the mean BMI between the groups (P=0.001). Mean PTH (P= 0.009) and ALP (P= 0.017) levels in the obese group were significantly higher than the normal weight group. Biochemical characteristics of the participants after the follow up period are shown in **Table.2**.

After three month, the mean 25 (OH) D3 level in the normal weight and obese groups was increased; while PTH (P=

0.006) and ALP (P <0.001) levels were decreased but their difference was still statistically significant between the two groups. The Vit D status in both groups at baseline and after the follow up period has been shown in **Table.3**.

39.8% of normal weight group still had Vit D insufficiency, while 50.7% of obese group had Vit D insufficiency or deficiency. Response to the treatment was better in normal weight group compared to the obese group with borderline significance. After follow up period in normal weight group, out of 92 subjects with Vit D insufficiency, 21.7% had still Vit D insufficiency and out of 41 participants with Vit D deficiency, only 19.5% were found normal, but all of them responded to the treatment. In the obese group, out of 42 participants with insufficiency, 26.2% did not respond to the treatment and out of 27 participants with Vit D deficiency, 11.1% were found normal and 7.4% did not respond to the treatment.

The mean Vit D level at baseline was 15.9 and 13 ng/mL in males and females, respectively. After the follow up period, the mean Vit D levels was 33.5 and 30.8 ng/mL in males and females, respectively and also, the difference was not significant.

Table-1: Demographic and biochemical characteristics of the study subjects at baseline

Variable	Normal weight	Obese	P-value
Age (year)	9.7±2.8	9.3±2.3	0.257
Body Mass Index (Kg/m^2)	16.3±1.9	25.7±3.4	0.001
Serum Calcium (mg/dL)	9.5±0.5	9.6±0.5	0.175
Serum Phosphorus (mg/dL)	4.9±0.6	5±0.6	0.205
ALP (IU/L)	623.1±199.1	683.5±151.6	0.017
PTH (pg/mL)	34.3±13.5	39.9±15.5	0.009
25 (OH) D (ng/ml)	14.5±7.2	13.5±7.2	0.369
TSH (IU/dL)	2.7±1.4	3±1.4	0.298
T4 (nmol/dL)	107±21.7	109.9±23.3	0.373

Data are presented as mean± standard deviation (SD).

Table-2: Biochemical characteristics of the study subjects three months after conventional Vit D therapy

Variable	Normal weight	Obese	P-value
Serum Calcium (mg/dL)	9.5±0.48	9.6±0.46	0.176
Serum Phosphorus (mg/dL)	4.8±0.5	4.9±0.5	0.397
ALP (IU/L)	527.1±142.8	660.2±127.7	<0.001
PTH (pg/mL)	32.9±12.2	38.2±13.3	0.006
25 (OH) D (ng/ml)	33.0±8.5	29.6±8.6	0.007

Data are presented as mean± standard deviation (SD).

Table-3: Vitamin D status of the study subjects at baseline and three months after conventional Vit D therapy

Group	Vitamin D status					P-value*
	At baseline		Three months after conventional treatment			
	Insufficiency	Deficiency	Normal	Insufficiency	Deficiency	
Normal weight	92 (69.2)	41 (30.8)	80 (60.2)	53 (39.8)	0	0.064
Obese	42 (60.9)	27 (39.1)	34 (49.3)	33 (47.8)	2 (2.9)	

Data are presented as number (percent); * Comparing Vitamin D status after conventional Vit D therapy between obese and non-obese children and adolescents by Chi-square test.

4- DISCUSSION

There was an insignificant difference regarding the levels of Ca and P between the obese and normal weight children in the present study which was compatible with the results reported by some other studies. Rajakumar et al., found no significant difference between the levels of Ca and P in the obese and non-obese children with Vit D deficiency (22). Also, Arunabh et al., studied 410 healthy females with the age range of 20-80 years and reported no significant difference regarding the levels of Ca and P between the obese and non-obese cases; results of their study is consistent with those of the current study (14).

The compensatory increase of PTH in blood, responding to the hypovitaminose D, preserves the level of blood Ca, even in the patients with prolonged Vit D deficiency and rickets. The hypocalcemia occurs only in severe conditions. The means PTH level was significantly different between the two groups in the present study; while in the study by Rajakumar et al., the PTH level in the obese and non-obese subjects with Vit D deficiency was statistically insignificant (22). According to the study by Alamzadeh et al., in the USA, people with Vit D deficiency had higher weights and higher PTH level (16). Parikh et al., obtained similar results about the level of PTH in adolescents; accordingly, in such patients the level of Vit D and PTH were higher and lower than those of non-obese ones, respectively (15). But these two mentioned studies did not compare the level of PTH in the obese and non-obese subjects with the same Vit D level. PTH is one of the functional indices of Vit D. Higher levels of PTH in the obese subjects is associated with decreased function of Vit D compared with non-obese subjects with the same Vit D level. In the present study, the mean ALP in the children with obesity was higher than normal weight children. It has been reported that the ALP level has direct relationship with obesity. In Conroy et al.'s study in obese children, the mean ALP reduced about 10% after treatment with leptin for weight loss, compared to that of the control group (23).

In the present study, the mean 25 (OH) D3 was significantly higher in the normal weight group, compared to the obese group, after the follow up period. Also, the response rate to conventional Vit D therapy in the normal weight group was higher than the obese group. Various studies compared the response to Vit D therapy in the obese and non-obese patients with Vit D deficiency. In the study by Rajkumar et al., 21 obese and 20 non-obese children were compared before and after the treatment with Vit D (22); there

was no significant difference regarding the response to treatment between the obese and non-obese subjects (22) which is incompatible with the results of the present study. The difference in the type of treatment may be considered as one of the reasons for such incompatibility. The treatment in the mentioned study was the oral drops of Vit D (400 U/day), for one month and in the present study an intramuscular injections of Vit D (300,000-600000 IU) was applied. The ethnic differences between the participants of the studies and the few number of studies conducted on this topic also lead to find different results.

On the other hand, in the study by Rajakumar et al., some differences were found between the obese and non-obese groups. These differences were at the threshold level of responding to treatment between the groups. In the obese and non-obese groups, the responding thresholds were lower than 20 and 30ng/mL, respectively (22). No similar differences were observed between the groups of the present study. It should be considered that in the Rajakumar et al. study the cut point for Vit D insufficiency and deficiency were 20 and 30ng/mL, respectively; while these cut points were 10 and 30ng/mL in the present study.

In the present study, the mean Vit D level in males was higher than females at baseline, which can be associated with the higher levels of fat mass in the females and more importantly, differences in females clothing and less exposure to sunlight in the countries like Iran, that is because of cultural and religious believes. After completing the treatment, the mean Vit D level was higher in males than females, but the difference was statistically insignificant. On the other hand, there was no difference regarding the response to treatment between the groups; while the Vit D level was lower in females than males, at baseline and after the follow up period. Season of Vit D sampling, physical activity and sun exposure of children are the important points in Vit D evaluation. In a study among 477 children and adolescents aged 9-18 years in Fars province- Iran during 2011, Vit D level had negative and significant correlation with BMI, pubertal status, and fat mass index; but it had positive and significant correlation with sun exposure (24).

In addition, age, sun exposure, physical activity, pubertal status, and fat mass index were independent predictors of Vit D concentration in Saki et al. study (24). In another study, total fat percent and fat mass index had a negative correlation with serum concentration of 25(OH) D3 in 8–18 years old patients with type 1 diabetes in Iran (25). In the present study, the participants were selected from similar location, family status, and residence to match their conditions; so sun exposure, dairy intake, and physical activity were not evaluated.

4-1. Limitations of the study

The present study had some limitations. Sun exposure, dairy intake, and physical activity were not evaluated. More longitudinal studies with larger sample size and longer follow up period are necessary to determine the differences in response to vitamin D therapy in obese and normal weight children and adolescents

5- CONCLUSION

Therapeutic response to conventional Vit D therapy in obese children was less than normal weight children. It seems that treatment with higher doses of Vit D or longer period is necessary in obese children of the present study. Bone turnover markers (PTH and ALP level) in the obese children and adolescents were significantly higher than normal weight children and adolescents even with the same level of Vit D.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENT

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