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Serum vitamin D levels in girls with central precocious puberty

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ABSTRACT

Precocious puberty can cause several adverse effects on final growth and social behavior in girls. Recent studies showed that low serum level of vitamin D might be associated with precocious puberty. The aim of this research was to investigate the association between serum vitamin D level and central precocious puberty in girls. Girls with central precocious puberty under the age of eight were enrolled in the study. Subjects with brain tumor, inherent adrenal hyperplasia, or thyroid dysfunction were excluded from the study. Age, weight, height, serum level of vitamin D, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, free thyroxin (FT_4), bone age, thyroid-stimulating hormone (TSH), and Tanner stages were determined for all the subjects. Healthy girls with no precocious puberty were considered as the control group. Finally, 58 girls (28 with central precocious puberty and 30 healthy) were included in the study. The average levels of serum vitamin D were 12.9 ± 7.8 ng/mL and 15.2±5.9 ng/mL in the case and control groups, respectively (P = 0.02). We found that 37% of girls with precocious puberty were in Tanner stage 2 and 63% in stage 3. The serum vitamin D level had considerable relationship with chronological-bone age difference (P < 0.01). Vitamin D deficiency was more common in girls with central precocious puberty than those with normal sexual maturation. Insufficiency and deficiency of vitamin D were more common in girls who were evaluated in this study in comparison with other studies.

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Introduction

Vitamin D deficiency is the most common nutritional disorder in the world (1). It is estimated that one billion people have vitamin D deficiency or insufficiency worldwide. This subject is a global health problem in people of all ages, especially those who live in the Middle East (1, 2).

Vitamin D plays a key role in bone metabolism, and it is important for the maintenance of calcium homeostasis by intestinal calcium absorption and renal reabsorption (3). Vitamin D receptor (VDR) is expressed in almost all body cells, including ovaries and human pituitary gland (4, 5). This has led researchers to extensively study vitamin D as a potential effective factor in the pathogenesis of a number of non-skeletal diseases, including infectious and autoimmune diseases, obesity, cancer, and fertility (6).

Some studies reported that serum level of vitamin D is related to the timing of menarche and precocious puberty in children (1, 2, 8, 9). One study in Korea demonstrated a significant increase in the incidence of central precocious puberty among children over the period of 2004–2010, particularly among girls (10). Central precocious puberty is caused by early maturation of the hypothalamic-pituitary-gonadal axis and is characterized by sequential maturation of breasts and pubic hair in girls. Early onset of puberty can cause several problems in girls. The early growth spurt can be initially associated with tall stature, but rapid bone maturation can cause linear growth to cease too early and ultimately, result in short stature.

Recent studies reported that vitamin D status is associated with the timing of menarche, and vitamin D modulates reproductive function in women (11-13). Precocious puberty can bring about several adverse effects on growth and social behavior in girls due to the early appearance of breasts or menses in girls and increased libido in boys, causing emotional distress in some of them (14, 15). Few studies have been carried out on this issue, especially in Iran. The purpose of this study was to determine the relationship between serum level of vitamin D with the age of onset and stages of puberty in girls with central precocious puberty symptoms.

Materials and Methods

This cross-sectional, case-control study was conducted from October 2015 to October 2016 on 30 girls suffering from idiopathic central precocious puberty in Bagheban medical center affiliated to Mazandaran University of Medical Sciences, in Sari, Iran. Also, 30 healthy girls with normal sexual maturity were recruited as the control group. Patients' characteristics including age, weight,

height, serum vitamin D (25OHD), bone age, and puberty stage were ordered and documented. Serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), estradiol, and free thyroxin (FT_4) were evaluated and patients with lab test abnormalities were excluded. Based on inclusion criteria, girls younger than 8 years of age with symptoms of puberty who referred to a pediatric endocrinologist with the diagnosis of central precocious puberty were investigated. Tanner method was used to assess pubertal status.

The enzyme-linked immunosorbent assay method (by monobind kit manufactured by Monobind Inc. Company, Lake Forest, CA 92630 USA) was used to determine serum level of vitamin D, and the samples of all the patients were evaluated in a laboratory. Various vitamin D states were considered as follows: sufficient vitamin D state: at least 30 ng/mL; vitamin D insufficiency: less than 30 ng/mL; and vitamin D deficiency: less than 10 ng/mL (16).

SPSS version 20 was used to analyze the collected data using Chi–square test for qualitative variables and independent samples t–test was run to compare quantitative variables between the two groups. Results are described as mean±standard deviation (SD), and P-value less than 0.05 was considered significant.

Results

Overall, 60 girls were participated in the study (30 with central precocious puberty and 30 as control). Two subjects in the case group were excluded due to receiving vitamin D supplements. The demographic characteristics of the patients are shown in Table 1. The mean ages of the case and control groups were 7.1 ± 1.3 and 6.9 ± 1.2 years, respectively, and there was no significant difference between the two groups ($P = 0.47$).

The mean weights in the case and control groups were 26.9 ± 6.9 and 22.8±5.9 kg, showing a statistically significant difference ($P = 0.01$).

Although the mean height and body mass index (BMI) of the girls in the case group were higher than those in the control group, these differences were not statistically significant ($P = 0.09$, and $P = 0.1$, respectively). The mean level of serum vitamin D in the case group was 12.9±7.8 ng/mL and in control group, it was 15.2 ± 5.9 ng/mL, indicating a statistically significant difference (P=0.02). Also, the case group had more subjects with deficiency of vitamin D than the control group. The majority of the girls in the two groups had serum vitamin D level < 30 ng/mL (96.5% and 93.3% in the case and control groups, respectively; Table 2). Totally, only three subjects in the two groups had sufficient serum vitamin D concentrations (>30 ng/mL), while 24% of them were deficient (<10 ng/mL; tables 3 and 4).

The means of chronological age and bone age in all the girls with precocious puberty were 7.1±1.6 and 8.6±1.1 years, respectively, which were significantly different ($P < 0.01$). On the other hand, bone age in 82.1% of the patients was higher than their chronological age and 70% of them had serum vitamin D concentrations less than 20 ng/mL. Based on Tanner scale, all the girls in the case group were in stages 2 or 3, 11 (37%) were in stage 2 of puberty, and 17 (63%) in stage 3. Means of chronological age and bone age in girls with stage 2 and 3 were significantly different ($P < 0.001$, $P < 0.01$, respectively; Table 5). The serum vitamin D level had a significant relationship with chronological-bone age ($P = 0.02$; Table 6). There was a significant relationship between chronological age and bone age in girls with central precocious puberty ($P < 0.01$; Table 7).

Discussion

The results of the current study showed a significant difference in the mean of serum vitamin D concentration between the case and control groups ($P = 0.02$). The number of girls with precocious puberty and severe vitamin D deficiency (serum levels <10 ng/ml) was more than controls (32.1% vs. 16.7%, respectively).

Table 1 Demographic characteristics of the patients in the two study groups

Parameters (Mean±SD)	Case (n=28)	Control (n=30)	P-value
Age (year)	7.1±1.3	6.9±1.2	0.47
Weight (kg)	26.9±6.9	22.8±5.9	0.01
Height (cm)	125.6±9.1	121.1±11.5	0.09
BMI*	16.9±2.2	15.7±4.3	0.1
Serum Vitamin D Conc.(ng/mL)	12.9±7.8	15.2±5.9	0.02

*BMI: body mass index

Table 2 Serum vitamin D level in the case and control groups

Vitamin D levels (ng/mL)	Case no. (%)	Control no. (%)	P-value
<10	9 (32.1)	5 (16.6)	0.27
10.1-20	12 (42.9)	17 (56.7)	
20.1-29.9	6 (21.4)	6 (20)	
≥30	1 (3.6)	2 (6.7)	

Table 3 Serum vitamin D level in different age ranges of all subjects (case and control groups)

		Serum vitamin D level (ng/mL)				P-value
Age (y)		<10	10.1-20	20.1-29.9	>30	
	<6	3	6	3	0	0.45
	6.01-7	2	6	4	2	
	7.01-8	4	9	4	0	
	>8	5	8	1	1	
No (%)		14 (24)	29 (50)	12 (21)	3 (5)	

Table 4 Serum vitamin D level and puberty stage in the case group

Vit D levels (ng/mL) Puberty stage	<5	5.1-10	10.1-20	20.1-29.9	>30	P-value
2	2	1	5	3	0	0.52
3	1	5	7	3	1	
Total	3	6	12	6	1	

Table 5 Mean chronological and bone ages in different puberty stages in the case group

Puberty stage	Chronological age (y) (Mean±SD)(lowest-highest)	Bone age (y) (Mean±SD)(lowest-highest)	P-value
2	6.4±1.2 (4.8-8.1)	7.8±1.3 (6-10)	<0.001
3	7.9±0.9 (5.6-9.3)	9.1±1.6 (6.5-11)	<0.01

Table 6 The relationship between serum vitamin D level and chronological-bone age difference

		Serum vitamin D level (ng/mL)				
		<10	10.1-20	20.1-29.9	≥30	P-value
Chronological-bone age difference (y)	Bone age>age	5	11	6	1	0.02
	Bone age=age	1	0	0	0	
	Bone age<age	3	1	0	0	

Table7 The relationship between chronological age and bone age

		Chronological age (y)				P-value
Bone age (y)		<6	6.01-7	7.01-8	>8	
	<7	2	2	0	0	<0.01
	7.01-8	1	3	5	0	
	8.01-10	0	1	3	4	
	>10	0	0	2	4	

Vitamin D insufficiency and deficiency were more common in our study in comparison to other reports. Vitamin D levels in 96.4% and 93.3% of the subjects in the case and control groups were lower than 30 ng/mL, showing the high prevalence of hypovitaminosis D in our study population and probably in this area of Iran.

Torkaman et al. evaluated the serum level of vitamin D of Iranian children younger and older than 2 years (17). In that report, 76.22% of children with a mean age of 5.09 ± 2.82 yr had vitamin D deficiency, and 23.78%, with a mean age of 2.58±1.88 yr had normal vitamin D levels (P = 0.001). The mean level of vitamin D was 29.71 ± 14.42 ng/mL in 30.8% of patients aged up to 2 years and 17.11 ± 14.02 ng/mL in 69.2% of patients older than 2 years.

A systematic review and meta-analysis by Tabrizi et al. exhibited the prevalence of vitamin D deficiency among male, female, and pregnant women (45.64%, 61.90%, and 60.45%, respectively) (18).

Vitamin D deficiency is a global public health problem in all age groups, particularly in those from the Middle East (19). Even in a sun-rich country, hypovitaminosis D is common in school children, more so in the winter. Girls, especially those with a lower socioeconomic status, are at particular risk. Vitamin D insufficiency may be prevalent in many other countries where supplementation of milk with vitamin D is not mandatory (20). Lee et al. stated that vitamin D deficiency was seen in 43.3% of Korean girls, 50% had vitamin D insufficiency, and 6.7% had sufficient serum vitamin D (defined as serum 25[OH]D > 30 ng/mL) (21).

In the present study, there was a significant association between more advanced bone age and lower serum level of vitamin D in comparison with chronological age (P = 0.02). In the case group, 37% of the patients were in stage 2 of puberty and 63% were in stage 3 based on Tanner scale. Regarding the statistical analysis and the comparison of the two groups, vitamin D deficiency was more frequent in girls with higher Tanner stage of puberty.

The first menstrual period, menarche, is one of the most significant milestones in a woman's life. The age at menarche is an important anthropological variantm which may influence the overall duration of tissue estrogen exposure and affect woman's health in later life (22). Our study is the first report on the association between serum vitamin D level and stage of puberty in girls with central precocious puberty in Iran. There have been a few similar studies in other countries that show similar results with our study.

The study of Lee et al. showed that the level of vitamin D was significantly lower in girls with central precocious puberty compared to a normal control group. There was a significant difference in the mean serum 25(OH)D concentration between the precocious puberty group and the control group (17.1 ± 4.5 ng/mL vs. 21.2 ± 5.0 ng/mL; P<0.05). Forty-two of the 60 girls with central precocious puberty (70%) had vitamin D deficiency (defined as serum 25OHD < 20 ng/mL) and 18 (30%) had vitamin D insufficiency. Also, within the central precocious puberty group, advanced Tanner stage was more frequently observed in the vitamin D deficiency subgroup (21).

Endocrine Society journal published its findings about the effects of vitamin D on precocious puberty in girls and stated that precocious puberty significantly raises the probability of severe vitamin D deficiencies (23). Serum 25OHD levels in girls with central precocious puberty were found to be lower than in girls with normal puberty (13.28 ± 4.04 vs 11.29 ± 3.77 ng/mL; p < 0.05) and prevalence of severe vitamin D deficiency was significantly higher in central precocious puberty group than in the normal group (21.3 vs 44.1%; p < 0.05).

Villamor et al. reported that after 30 months of follow up of 5-12 years old girls, the probability of early menarche in girls with lower serum vitamin D level was two times higher than in girls with sufficient vitamin (11). This study showed the relationship between serum level of vitamin D and the time of starting the first menstruation; 57% of girls in the vitamin D deficient group reached menarche during follow-up compared with 23% of girls in the vitamin D-sufficient group (P = 0.001). The estimated mean (±SE) ages at menarche in the same groups were 11.8 ± 0.2 y and 12.6 ± 0.2 y, respectively (P < 0.001). The study of Aypak et al. showed that gender and puberty were independent predictors of vitamin D status. Female gender and puberty were all negatively associated with 25(OH)D (24). Similarly, Zhao et al. demonstrated idiopathic central precocious puberty (ICPP) group had significantly lower serum 25-hydroxyvitamin D (25[OH]D) levels than the control group. Furthermore, a nonlinear relationship was found between serum 25(OH)D and ICPP. The ICPP subjects with 25(OH)D deficiency had a higher BMI than the subjects from the two other subgroups. Correlation analysis showed that vitamin D level is correlated with BMI and some metabolic parameters in the ICPP group (25).

Contrary to the results of our study and others, a recent study by Duhil de Bénazé et al. found no correlation between vitamin D status and the characteristics of central precocious puberty. Overall, patients had a satisfactory vitamin D status and the mean 25(OH)D serum concentration was 27.6 ± 17.3 ng/mL (26).

In our study, the mean bone age in the case group was significantly higher than the chronological age (P<0.01), which shows more quick growth toward healthy children in the same age. The mean weight in the case group was 26.9 ± 6.9 kg and in the control group it was 22.8 ± 5.9 kg, showing a significant difference (P = 0.01). Although the mean height and BMI of girls in the case group were higher than those in the control group, these differences were not significant (P = 0.09, P = 0.1, respectively). Normally, height growth occurs with a delay relative to weight gain. The prevalence of vitamin D

deficiency in Neyestani et al. study was higher in girls than boys and serum levels of 25(OH)D were inversely correlated with BMI (r =-0.092, *P* = 0.002) (27).

Conclusion

The results of this study indicated that vitamin D deficiency was more common in girls with central precocious puberty than those with normal sexual maturation. Based on the results of available studies, we assume that a low level of vitamin D plays an important role in early puberty in girls. Identifying girls with vitamin D deficiency and proper vitamin D supplementation can prevent precocious puberty.

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Conflict of Interest

The authors declare no conflict of interest.

Authors' contributions

Mohammadreza Rafati; study concept and design, supervision of whole study, critical revision of the manuscript. Daniel Zamanfar; diagnosis and entry of patients to the study, revision of the manuscript. Seyedeh-Nesa Rezaeian Shiadeh; acquisition of data, drafting of the manuscript. Fatemeh Faramarzi; participated in literature bibliography, drafting of the manuscript. Mohsen Aarabi; statistical analysis. Hamid Rayati Damavandi; enrolling the patients to the study. All authors read and approved the final manuscript.

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