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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. Recently studies showed that low serum vitamin D levels might be associated with precocious puberty. The aim of this research was to investigate the association between serum vitamin D levels and central precocious puberty in girls. Girls with central precocious puberty under the age of 8 were enrolled into the study. Subjects with brain tumor, inherent adrenal hyperplasia and thyroid dysfunction were excluded from the study. Age, weight, height, serum level of vitamin D concentration, LH, FSH, Estradiol, FT_4, bone age, TSH and tanner stages were determined for all subjects. The healthy girls with no precocious puberty were considered as control group. Finally 58 girls (28 with central precocious puberty and 30 in control group) were enrolled to the study. The average of serum vitamin D levels were 12.9 ± 7.8 ng/mL and 15.2±5.9 ng/mL in case and control groups respectively, (P = 0.02). The thirty seven percent of girls with 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 of 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 world health problem in people of all ages, especially those who live in the Middle East (1,2). It plays a key role in bone metabolism, being 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 ovary and human pituitary gland (4,5). This led the researchers to extensive study on vitamin D as apotential effective factor in the pathogenesis of a number of nonskeletal diseases, including infectious and autoimmune diseases, obesity, cancer and fertility (6). Some studies reported that serum levels of vitamin D are related to the timing of menarcheand precocious puberty in children (1,2, 8-9). One study in Korea demonstrates a significant increase in the incidence of central precocious puberty (CPP) among children over the period of 2004–2010, particularly among girls (10). CPP 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 initially associated with tall stature, but rapid bone maturation can cause linear growth to cease too early and it is resulted ultimate short stature. Recent studies reported that vitamin D status was associated with the timing of menarche and vitamin D modulates reproductive function in women (11-13). Precocious puberty can cause several adverse effects on growth and social behavior in girls due to the early appearance of breasts or menses, as well as, increased libido in boys can cause emotional distress in some of them (14,15). Similar studies have been carried out few, and a similar study has not been found in Iran. The purpose of this study was to determine the relationship between serum levels of vitamin D with the age of the beginning and stages of puberty in girls with central precocious puberty symptoms.

Materials and Method

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 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 level of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), estradiol, and free thyroxin (FT_4) were evaluated and patients with lab test abnormality were excluded. Based on inclusion criteria, the girls younger than 8 years old with symptoms of pubertywho referred to the pediatric endocrinologist with 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 vitaminD level and the samples of all patients were determined in a solely laboratory. Various vitamin D states were considered as following: sufficient vitamin D state, at least 30 ng/mL; vitamin D insufficiency less than 30 ng/mL; andvitamin D deficiency less than 10 ng/mL (16). $SPSS_{20}$ software was used to analyze the collected data using chi–square test for qualitative variables and independent sample t–test was used to compare quantitative variables between two groups. Results are described as mean±standard deviation (SD) and P-value<0.05 was considered as a significant difference.

Results

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

The mean weight in the case group was 26.9 ± 6.9 kg and in the control group was 22.8±5.9 kg with statistically significant difference ($P = 0.01$).

Although the mean height and body mass index of the girls in the case group were higher than the control group, these differences were not statistically meaningful between two groups ($P = 0.09$, and $P = 0.1$, respectively). The average of serum vitamin D level in case group was 12.9±7.8 ng/mL and in control group was 15.2 ± 5.9 ng/mL, with statistically significant difference (P=0.02). Also case group had more subjects with deficiency of vitamin D than control. The majority of girls in two groups had serum vitamin D level < 30 ng/mL (96.5% and 93.3% in case and control group respectively (Table 2). Totally only three subjects of 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 and bone ages in all girls with precocious puberty were 7.1±1.6 and 8.6±1.1 years respectively, which had significantly difference ($P < 0.01$). At the other hand, bone ages in 82.1% of patients were higher than chronological ages and 70% of them had serum vitamin D concentrations less than 20ng/mL. Based on tanner scale, all of girls in case group were in 2 or 3 stages, 11 (37%) were in stage 2 of puberty and 17 (63%) in stage 3. Means of chronological and bone ages in girls with stage 2 and 3 with meaningfully differences ($P < 0.001$, $P < 0.01$, respectively) were shown in table 5. The serum vitamin D level had considerable relationship with chronological-bone age difference ($P = 0.02$) (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 there was a significant difference between the mean of serum vitamin D concentration in case and control groups ($P = 0.02$). Girls with precocious puberty and severe vitamin D deficiency (serum levels <10 ng/ml) were more than controls (32.1% vs. 16.7% respectively).

Table 1 Demographic characteristics of the patients in 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 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 range of all subjects (case and control groups)

		Serum vitamin D level (ng/mL)				P-value
		<10	10.1-20	20.1-29.9	>30	
Age (y)	<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 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 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
		<6	6.01-7	7.01-8	>8	
Bone age (y)	<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 girls who were evaluated in comparison to other reports. Vitamin D levels in 96.4 and 93.3% of subjects in case and control groups were lower than 30 ng/mL and this showed the prevalence of hypovitaminosis D is very high in our study population and probably in this area of Iran.

Torkaman et al were evaluated the serum vitamin D levels of Iranian children younger and older than 2 years (17). In this report, 76.22% 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% patients up to 2 years and 17.11 ± 14.02 ng/mL in 69.2% patients older than 2 years. A systematic review and meta-analysis by Tabrizi et al, the prevalence of vitamin D deficiency among male, female, and pregnant women was estimated to be 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 sunny country, hypovitaminosis D is common in schoolchildren, 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 25OHD > 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% patients were in stage 2 of puberty and 63% were in stage 3 based on tanner scales. Regarding the statistical analysis and the comparison of 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 variant which may influence the overall duration of tissue estrogen exposure and then affect woman'shealth in later life (22). Our study is the first report about the association between serum vitamin D levels with stage of puberty in girls with CPP in Iran. There were 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 CPP compared to normal control group. There was a significant difference in the mean serum 25OHD 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 CPP (70%) had vitamin D deficiency (defined as serum 25OHD < 20 ng/mL) and 18 (30%) had vitamin D insufficiency. Also within the CPP 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 the precocious puberty girls and stated precocious puberty significantly had more probability of severe vitamin D deficiencies (23). Serum 25OHD levels in girls with CPP 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 CPP group than that of normal group (21.3 vs 44.1 %, p < 0.05).

Villamor et al. reported that after 30 months of followed up the 5-12 years old girls; the probability of early menarche in girls with lower serum vitamin D level is two times higher than girls with sufficient vitamin (11). This study showed the relationship between serum levels 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 body mass index (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 was found no correlation between vitamin D status and the characteristics of central precocious puberty. Overall, the 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 of bone age in case group was significantly higher than their chronological age (P<0.01) which shows more quick growth toward the healthy children in the same age. The mean weight for case group was 26.9 ± 6.9 kg and for the control group was 22.8 ± 5.9 kg that the means difference between two groups was statistically significant (P = 0.01). Although the mean height and BMI of girls in the case group were higher than the control group, this differences were not statistically meaningful between two groups (P = 0.09, P = 0.1, respectively). Usually 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 inversely correlated with body mass index (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 guess that a low level of vitamin D plays an important role to accelerate early puberty in girls. Identifying girls with vitamin D deficiency and proper vitamin D supplementation can prevent precocious puberty.

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Conflicts 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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