Research Article

Serum Vitamin D Deficiency and Its Association with Idiopathic Central Precocious Puberty in Iranian Girls: A Case-Control Study

Masoume Aliabadi[1, 2], Mohammadreza Azadi Pourghahestani[3], Mitra Nourbakhsh[1], Maryam Razzaghy-Aza[3], Mona Nourbakhsh[3*]

[1] *Department of Clinical Biochemistry, School of Medicine, Iran University of Medical Sciences, Tehran, Iran*
[2] *Student Research Committee, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran*
[3] *Hazrat Aliasghar Children's Hospital, School of Medicine, Iran University of Medical Sciences, Tehran, Iran*

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[*] **Corresponding Author:**

Mona Nourbakhsh
Department of Pediatric Endocrinology, Hazrat Aliasghar Children's Hospital, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
Email: nourbakhsh.m@iums.ac.ir

ABSTRACT

Objectives: Precocious puberty is a significant pediatric endocrine disorder with potential long-term physical and psychosocial consequences, including short stature, obesity, and increased risk of certain malignancies. Vitamin D (vitD) has been proposed to play a role in reproductive maturation. However, the evidence regarding its association with precocious puberty remains inconsistent across populations. This study aimed to investigate the relationship between serum vitD levels and idiopathic central precocious puberty (ICPP) in Iranian girls.

Methods: This case-control study included 81 girls diagnosed with central precocious puberty and 51 healthy girls as controls. Demographic, anthropometric, and laboratory data (including age, weight, height, and serum levels of estradiol, LH, FSH, TSH, T4, and 25-hydroxyvitamin D) were extracted from clinical records. BMI z-scores, weight-for-age z-scores, and weight-for-height z-scores were calculated using standardized tools. Serum vitD levels were compared between groups, and correlations with anthropometric and biochemical parameters were assessed using appropriate statistical tests.

Results: Median serum vitD levels were significantly lower in the case group than in controls (27.05 vs. 41.00 ng/mL; $P = 0.0006$). BMI z-score and weight-for-age z-score were significantly higher in girls with precocious puberty ($P < 0.0001$). Cases showed a larger discrepancy between bone age and chronological age ($P < 0.0001$). Serum vitD showed significant inverse correlations with BMI z-score ($r = -0.236$, $P = 0.035$) and weight-for-height z-score ($r=-0.605$, $P=0.028$), and a significant positive correlation with T4 ($r = 0.317$, $P = 0.010$). No significant correlations were observed between vitD and reproductive hormones, including estradiol, LH, or FSH.

Conclusion: Serum vitD levels are significantly lower in Iranian girls with ICPP compared to healthy controls. These findings suggest that vitD may influence pubertal development; therefore, routine assessment of vitD status in girls presenting with precocious puberty may be clinically warranted, particularly in populations with a high background prevalence of deficiency.

Keywords: 25-hydroxyvitamin D, Case-control study, Girls, Idiopathic central precocious puberty, Iran, Vitamin D deficiency

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Introduction

Puberty is a complex biological process involving the maturation of the hypothalamic-pituitary-gonadal (HPG) axis, culminating in the development of secondary sexual characteristics and reproductive capacity. The timing of pubertal onset is determined by an interplay of genetic, nutritional, metabolic, and environmental factors. In girls, puberty is considered normal when it begins between the ages of 8 and 13. Epidemiological data from the past two decades indicate a secular trend toward earlier pubertal onset in both genders, a shift that has prompted considerable research into its underlying determinants (1, 2).

Central precocious puberty (CPP) is defined as the premature activation of pulsatile gonadotropin-releasing hormone (GnRH) secretion in girls before age 8, leading to early breast development, accelerated linear growth, and advanced bone age. The idiopathic form (ICPP) accounts for approximately 90% of cases in girls, with no identifiable organic cause (3, 4). From a clinical standpoint, CPP carries significant long-term consequences. Premature epiphyseal fusion results in reduced adult height, while prolonged estrogen exposure during early breast development has been associated with increased risks of obesity, type 2 diabetes, and hormone-sensitive malignancies in adulthood (5, 6). Psychosocial sequelae, including behavioral difficulties and early engagement in risky behaviors, have also been reported (7).

Vitamin D (vitD) is a fat-soluble secosteroid obtained primarily through cutaneous synthesis upon ultraviolet B exposure and, to a lesser extent, through dietary intake. Following hepatic and renal hydroxylation, its active metabolite (1,25-dihydroxyvitamin D) exerts biological effects through the vitD receptor (VDR), which is expressed in virtually all nucleated cells, including those of the ovaries and pituitary gland (8). A serum 25-hydroxyvitamin D concentration below 20 ng/mL is widely regarded as indicative of deficiency (9). VitD deficiency is estimated to affect approximately one billion individuals worldwide and carries a disproportionately high burden in Middle Eastern populations, particularly among schoolchildren and during winter months (10).

Beyond its established role in calcium homeostasis and skeletal metabolism, accumulating evidence points to a broader influence of vitD on reproductive function. VDRs are expressed along the hypothalamic-pituitary axis, including in GnRH-producing neurons, suggesting a direct modulatory role in the neuroendocrine regulation of puberty (11, 12). Two principal mechanisms have been proposed. First, vitD deficiency has been associated with elevated pre-ovulatory LH levels, and reduced pre-ovulatory LH has been linked to decreased GnRH neuronal density (12). Second, VDRs may modulate GnRH neuronal activity through calcium signaling pathways, given that GnRH neurons express L-type calcium channels that are regulated by vitD (11). At the molecular level, animal studies have demonstrated a correlation between serum vitD levels and aromatase gene expression in rats (13, 14), while VDR gene polymorphisms in humans have been associated with earlier age at menarche (15). Epidemiological data further support this relationship. A prospective cohort study of 242 healthy girls aged 5-12 years, followed over 30 months, reported that vitD-deficient girls had twice the risk of early menarche compared to those with sufficient levels (16). Moreover, female gender and pubertal status have been identified as independent negative predictors of vitD levels (17), raising the possibility of a bidirectional relationship between vitD status and pubertal progression.

Despite these findings, the literature remains inconsistent. Studies from South Korea and China have reported lower vitD levels in girls with CPP and a significant inverse association between vitD levels and pubertal timing (18, 19). In contrast, reports from France and Spain found no significant difference in vitD levels between affected girls and healthy controls (20, 21). These discrepancies likely reflect the differences in geographic latitude, sunlight exposure, dietary habits, ethnicity, and study design, underscoring the importance of population-specific investigations.

Given the high prevalence of vitD deficiency in Iran and the limited data available in this population, the present study was conducted to investigate the association between serum 25-hydroxyvitamin D levels and ICPP in Iranian girls, and to examine its relationship with anthropometric and hormonal parameters.

Methods

Study Design and Setting: This case-control study was conducted using clinical records from the private endocrinology practice of Dr. Maryam Razaghi Azar. Data were collected retrospectively from the medical records of patients evaluated for precocious puberty alongside records of healthy girls attending the same practice for routine follow-up during the same period.

Participants: The case group comprised 81 girls with a confirmed diagnosis of idiopathic central precocious puberty (ICPP). Diagnosis was established by the attending physician based on the following criteria: onset of breast development before age 8, elevated basal or GnRH-stimulated luteinizing hormone (LH) levels with an increased LH-to-follicle-stimulating hormone (FSH) ratio, and a significant advance in bone age beyond chronological age. The control group consisted of 51 healthy girls with no evidence of premature pubertal development, recruited from the same clinic during the same period.

Girls were excluded from the case group if they had any identifiable secondary cause of precocious puberty, including central nervous system tumors, cushing's

syndrome, or genetic syndromes such as Turner syndrome, Down syndrome, or McCune-Albright syndrome. Additional exclusion criteria applied to both groups were: current or recent vitD supplementation, ongoing treatment with calcium supplements or medications known to affect vitD metabolism, and incomplete medical records.

Data Collection: Data were extracted from medical records at the time of first presentation and initial diagnosis. The following variables were recorded for each participant. Anthropometric indices included age at diagnosis, age at pubertal onset, bone age, pubertal stage, height, and weight. Pubertal staging was assessed according to the Tanner breast development scale. Tanner pubic hair staging was not used as the primary criterion, as it may be influenced by adrenarche independently of gonadotropin activation and could therefore misrepresent the true pubertal stage.

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. BMI-for-age z-scores were calculated using the PediTools online calculator (https://peditools.org/growthpedi), based on 2022 CDC growth charts for 2 to 20 years (22). Weight-for-age and height-for-age z-scores were also calculated and used for analysis.

The biochemical parameters were measured from fasting blood samples as part of routine clinical assessment at the time of diagnosis. They included serum concentrations of 25-hydroxyvitamin D, thyroid-stimulating hormone (TSH), and thyroxine (T4), measured by chemiluminescent methods on an Abbott Architect analyzer. VitD status was classified according to the Endocrine Society guidelines: deficiency was defined as a serum level below 20 ng/mL, insufficiency as 20-29 ng/mL, and sufficiency as 30 ng/mL or above. Calcium and phosphate were measured by colorimetric methods using an autoanalyzer.

Statistical Analysis

Data were analyzed using MedCalc® Statistical Software version 23.4.5; MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2025. The normality of continuous variables was assessed using the Shapiro-Wilk test. As most continuous variables were non-normally distributed, between-group comparisons were performed using the Mann-Whitney U test, and results were reported as median (interquartile range). For normally distributed variables, the independent-samples t-test was applied, and the results were reported as mean ± standard deviation (SD). To account for the significant age difference between the study groups, multivariable binary logistic regression analysis was performed with CPP status as the dependent variable and serum vitamin D, age, and BMI z-score as independent variables. Categorical variables were compared using the chi-square test. Correlations between serum vitD and other parameters were assessed using Spearman's rank correlation coefficient. A P-value of less than 0.05 was considered statistically significant.

Table 1. Demographic and anthropometric characteristics of the case and control groups.

Variable	Case Group (n = 81)	Control Group (n = 51)	P-value
Age (months)	94.00 (83.00-101.00)	107.00 (94.50-124.00)	< 0.0001
BMI (kg/m²)	18.55 (16.36-19.92)	17.02 (15.89-18.23)	0.006
BMI z-score	1.11 (0.25-1.56)	0.28 (−0.42-0.80)	< 0.0001
Weight-for-age z-score	0.99 (0.07-1.80)	−0.17 (−0.81-0.40)	< 0.0001
Height (cm)	130.00 (125.00-134.00)	131.00 (124.00-139.25)	0.587
Height-for-age z-score	0.63 (-0.12 - 1.35)	-0.55 (-1.18 - 0.33)	< 0.0001
BA−CA (months)	15.00 (5.00-27.00) n = 77	−6.50 (−13.25-2.25) n = 24	< 0.0001
Vitamin D (ng/mL)	27.05 (18.90-37.30)	41.00 (26.02-57.88)	0.0006
T4 (µg/dL)	8.52 (7.35-10.12) n = 65	8.90 (8.05-10.13) n = 23	0.497
TSH (µIU/mL)	2.80 (1.80-3.75) n = 73	3.27 (1.71-4.08) n = 23	0.309
Calcium (mg/dL)	9.92 ± 0.44	9.71 ± 0.37	0.048
Phosphate (mg/dL)	5.19 ± 0.57	4.99 ± 0.58	0.106

Data are expressed as median (interquartile range) or mean ± SD.
P-values are from Mann-Whitney U test or independent-samples t-test, as appropriate.
BA: bone age; CA: chronological age; BA-CA: The difference between BA and CA.

Results

Participant Characteristics

A total of 132 girls were included in the study, comprising 81 girls in the case group and 51 girls in the control group. The median age of all participants was 94 months in the case group and 107 months in the control group; this difference was statistically significant ($P < 0.0001$). Demographic and anthropometric characteristics of both groups are summarized in Table 1. BMI z-score and weight-for-age z-score were significantly higher in the case group than in the control group ($P < 0.0001$ for both), indicating greater adiposity among girls with precocious puberty. The height z-score was also significantly higher in cases than in controls. The difference between bone age and chronological age was significantly greater in the case group than in controls, consistent with the accelerated skeletal maturation characteristic of CPP (Table 1).

Laboratory Findings

Serum concentrations of calcium, phosphate, TSH, and T4 were compared between the two groups (Table 1). No statistically significant differences were observed between the groups for any of these biochemical parameters. Median serum 25-hydroxyvitamin D concentration was significantly lower in the case group compared to controls (27.05 (18.90-37.30) ng/mL vs. 41.00 (26.02-57.88) ng/mL, $P = 0.0006$), as illustrated in Figure 1.

To account for the significant age difference between the study groups, a multivariable logistic regression analysis was performed including serum vitamin D, age, and BMI z-score. Lower serum vitamin D remained independently associated with CPP after adjustment for age and BMI z-score (adjusted OR = 0.953, 95% CI 0.929–0.978, $P = 0.0002$). Age (adjusted OR = 0.956, 95% CI 0.935–0.978, $P = 0.0001$) and BMI z-score (adjusted OR = 2.217, 95% CI 1.384–3.551, $P = 0.0009$) were also independently associated with CPP.

Correlations Between VitD and Study Parameters

Spearman correlation analyses were performed to examine the relationship between serum vitD levels and anthropometric and biochemical parameters within the case group. Serum vitD showed a significant inverse correlation with BMI z-score and weight-for-age z-score, indicating that greater adiposity was associated

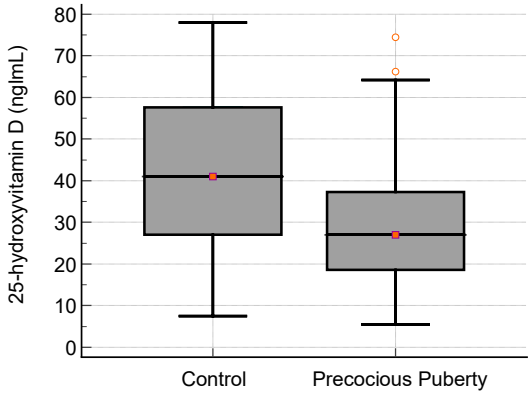

Figure 1. Comparison of vitamin D levels (median and interquartile range) in subjects with precocious puberty and control subjects.

Table 2. Correlation between serum vitD levels and anthropometric and laboratory parameters (case group).

Variable	Correlation coefficient	P-value
BMI z-score	−0.236	0.035
Weight-for-age z-score	−0.220	0.050
Weight-for-height z-score	−0.605	0.028
T4 (µg/dL)	0.317	0.010
TSH (µIU/mL)	0.048	0.685
BA−CA discrepancy	−0.131	0.257
Ca (mg/dL)	0.175	0.099
Phosphate (mg/dL)	-0.206	0.061

BA: bone age; CA: chronological age; BA-CA: The difference between BA and CA.

with lower vitD levels. The bone age-chronological age discrepancy was not significantly correlated with vitD levels. Full correlation data are presented in Table 2.

A significant positive correlation was observed between vitD and T4; however, no significant correlations were found between serum vitD and TSH, Ca, and Phosphate levels.

Discussion

The present study demonstrated that serum 25-hydroxyvitamin D levels were significantly lower in Iranian girls with ICPP compared to healthy controls. Girls in the case group also exhibited significantly higher BMI z-scores and weight-for-age z-scores, as well as a greater discrepancy between bone age and chronological age. Serum vitD showed significant inverse correlations with BMI z-score and weight-for-height z-score, and a significant positive correlation with T4.

These findings are consistent with several prior reports. Lee et al. (2014) found that 70% of South Korean girls with precocious puberty had vitD deficiency compared to 43% of controls (18), and Rafati et al. (2018) similarly reported a higher prevalence of deficiency in affected girls (23). A prospective cohort study by Villamor et al. (2011) found that vitD-deficient girls had twice the risk of early menarche over a 30-month follow-up period (16), while Zhang et al. (2018) identified a significant inverse association between vitD status and idiopathic precocious puberty (19). In contrast, Dura-Trave and Gallinas-Victoriano (2022) and de Bruin et al. (2017) found no significant difference in vitD levels between girls with CPP and healthy controls (20, 21). These inconsistencies likely reflect differences in geographic latitude, seasonal variation in sun exposure, dietary habits, and study design, all of which exert considerable influence on population-level vitD status. The high background prevalence of vitD deficiency in Iran, documented at 76.22% in a national survey of children (24), further underscores the relevance of these findings to the study population.

The significantly higher BMI z-scores in the case group merit careful consideration when interpreting the vitD findings. As a fat-soluble compound, vitD undergoes volumetric dilution in adipose tissue, which reduces its circulating bioavailability (25), and the significant inverse correlations between serum vitD and both BMI z-score and weight-for-height z-score observed in this study are consistent with this mechanism. However, adiposity alone is unlikely to fully account for the observed differences, given that VDRs are expressed in GnRH-producing neurons of the hypothalamus and along the pituitary axis. Proposed mechanisms include vitD-mediated regulation of GnRH neuronal density and pulsatile secretion (12), as well as modulation of L-type calcium channels expressed on GnRH neurons (11). At the molecular level, vitD has been shown to influence aromatase gene expression in animal models (13, 14), and VDR gene polymorphisms have been associated with earlier menarche in humans (15). Furthermore, the significant positive correlation between vitD and T4 observed in this study is consistent with emerging evidence linking vitD status to thyroid hormone metabolism (26), though the mechanistic basis of this relationship warrants further investigation.

Several limitations of this study should be acknowledged. The retrospective design and the lack of information on the season of sample collection represent potential sources of bias, given the known seasonal variation in vitamin D levels. Additionally, dietary vitD intake, physical activity, and time spent outdoors were not recorded and could not be accounted for in the analysis.

Conclusion

The present study demonstrates that serum 25-hydroxyvitamin D levels are significantly lower in girls with ICPP compared with healthy controls, accompanied by greater adiposity and more pronounced bone age advancement in the affected group. Although the retrospective design precludes causal inference, the observed associations suggest that vitD may play a modulatory role in pubertal timing. These findings support routine assessment of vitD status in girls presenting with precocious puberty, particularly in populations with a high prevalence of deficiency. Prospective randomized controlled trials are needed to determine whether vitD deficiency correction can influence pubertal progression and to clarify the nature of this relationship.

Conflict of Interest

The authors declare that they have no conflict of interest

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