

Vitamin D Status and Parathyroid Hormone Levels in Girls With Central Precocious Puberty

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Abstract

The objective of this study was to analyze the vitamin D status and PTH levels in 6- to 8-years-old girls with central precocious puberty. A cross-sectional clinical and blood testing (calcium, phosphorus, 25(OH)D and PTH) were carried out in 78 girls with central precocious puberty (CPP group), aged 6.1-7.9 years. A control group was recruited (157 prepubertal girls, aged 6.1-8.2 years). The criteria of the US Endocrine Society were used for the definition of hypovitaminosis D. There were no significant differences in the vitamin D status between both groups. There were not significant differences in 25(OH)D levels between CPP (25.4 ± 8.6 ng/mL) and control groups (28.2 ± 7.4 ng/mL). In contrast, in CPP group PHT levels (44.8 ± 16.3 pg/mL) were higher ($p < 0.05$) with respect to control group (31.0 ± 11.9 ng/mL). In CPP group there was positive correlation ($p < 0.05$) between PTH levels and growth rate, bone age, basal estradiol, basal FSH, basal LH and LH peak.

Conclusion: Vitamin D status in 6- to 8-years-old girls with CPP is similar to that in prepubertal girls. PTH levels were significantly higher in girls with CPP, and could be considered as a pubertal characteristic and, in this case, of pubertal precocity.

Summary

“What is known”

- There is evidence that vitamin D has some effects on female fertility.
- There are hardly any studies on the relationship between vitamin D status and timing of puberty
- There are no reports on the relationship between PTH levels and precocious puberty.

“What is new”

- Vitamin D status in 6- to 8-years-old girls with CPP is similar to that in prepubertal girls.
- PTH levels in girls aged 6 to 8 years with CPP are increased in relation to control group
- Increase levels of PTH could be considered as a pubertal characteristic and, in this case, of pubertal precocity.

Introduction

Vitamin D is currently considered a pleiotropic hormone. The biological actions of vitamin D are mediated by a specific nuclear transcription factor located in the target cells, called vitamin D receptor (VDR). Vitamin D binds to nuclear VDR, which interacts with other transcription factors and modulates the transcriptional activity of vitamin D-sensitive genes that play an important role in bone and mineral metabolism, as well as in other biological functions (non-classical effects of vitamin D) [1, 2]. VDR is

distributed in most body cell and organs, including the skeleton and parathyroid glands, the immunity system (B and T lymphocytes, macrophages and monocytes), the endocrine system (pancreas, pituitary, and adrenal cortex), and the reproductive system (testicular tissue, sperm, prostate, ovaries, uterus, endometrium) [3]. The presence of VDR in both the pituitary gland and female reproductive tissue suggests that vitamin D could be involved in female fertility mechanisms as well as in the activation of the hypothalamic-pituitary-gonadal axis.

On the other hand, an inverse correlation between vitamin D and parathyroid hormone (PTH) levels has been reported by different authors [4–7]. In fact, relatively asynchronous variations in PTH take place simultaneously with seasonal variations in vitamin D, a fact that presumably would allow maintaining constant calcium levels throughout the year and within the precise limits necessary for the performance of its metabolic and neuroregulatory functions. [8]. However, it is noteworthy that several authors have highlighted how PTH levels, increase significantly in the age group of 8–10 years in girls, while, while they increase significantly in the age groups of 10–12 years in boys. Although these studies do not provide data on pubertal stage in the subjects, they do suggest the hypothesis of a relationship between the PTH level and the timing of puberty [9].

Observational studies have focused on a potential relationship among vitamin D deficiency and in vitro fertilization outcome, polycystic ovary syndrome and endometriosis [10, 11]. There are hardly any studies on the relationship between vitamin D status and the timing of puberty. Furthermore, although several authors have suggested a possible association between vitamin D deficiency and the risk of central precocious puberty or earlier menarche [12–14], other authors have not found any correlation between vitamin D status and central precocious puberty [15]. Curiously, there are no reports on the relationship between PTH levels and precocious puberty.

The objective of this study was to analyze the vitamin D status and PTH levels in 6- to 8-years-old girls with central precocious puberty. We compared the blood levels of 25-hydroxyvitamin D (25(OH)D) and PTH between girls with precocious puberty and prepubertal girls.

Materials And Methods

Participants

The present work is a cross-sectional study conducted in a sample of 78 girls, aged 6.0–7.9 years, diagnosed with idiopathic central precocious puberty (CPP group) (peak LH response to GnRH test > 5 IU/L), who followed a clinical examination and blood testing in the Pediatric Endocrinology Unit of the Navarra Hospital Complex (Pamplona, Spain) in the period January 2018–December 2020. All girls presented with Tanner stage 2 in breast development (appearance of the breast bud) and BMI SDS ranging from – 1.0 (15th percentile) to + 1.0 (85th percentile) (all those girls with overweight or obesity were excluded). The standardized protocol that was used for the GnRH test has been previously published [16].

In addition to that, these parameters (clinical examination and blood testing) were determined in a control group that consisted of 157 healthy prepubertal girls (with no signs of pubertal development: Tanner stage 1), aged 6.1–8.2 years, with BMI SDS ranging from – 1.0 (15th percentile) to + 1.0 (85th percentile). These participants came from external consultations of the different pediatric subspecialties.

All participants (CPP and control groups) included in the study were Caucasian individuals living in Navarra, Spain. Neither participant (sample patients and control group) had been previously diagnosed from any illness that could affect bone health or growth (chronic pathologies, nutritional or others endocrine problems), nor had received any medication (antiepileptic drugs or glucocorticoids), vitamin D or calcium supplements.

Adequate information of the proceedings and potential implications was delivered to the parents and/or legal guardians, and the corresponding consent was required prior to the inclusion in this study in all cases. The study was presented and approved after the evaluation of the Ethics Committee for Human Investigation at our institution (in line with the ethical standards stated in the Declaration of Helsinki 1964 and later amendments).

Clinical examination

The anthropometric measurements were taken according to a protocol that was previously published [17]. The information gathered from the participants included age, weight and height, body mass index (BMI), and bone age. Weight and height of every participant had been previously recorded by the pediatrician at the Primary Health Care Center (periodical health checkup), and enabled the calculation of growth rate (cm/year) 6–12 months before the current clinical evaluation. Weight and height measurements were taken in underwear and barefoot. An Año-Sayol scale was used for weight measurement (reading interval 0–120 kg and a precision of 100 g), and a Holtain wall stadiometer for height measurement (reading interval 60–210 cm and precision 0.1 cm). Subsequent calculations allowed the evaluation of BMI by means of the following formula: $\text{weight (kg)}/\text{height}^2 \text{ (m)}$. Bone age (BA) was calculated using RUS-TW2 method [18].

The SDS values for the BMI were estimated by applying the program Aplicación Nutricional, from the Spanish Society of pediatric gastroenterology, hepatology and nutrition (Sociedad Española de Gastroenterología, Hepatología y Nutrición Pediátrica, available at <https://www.gastroinf.es/nutritional/>). The graphics from Ferrández *et al.* (Centro Andrea Prader, Zaragoza 2002) were employed as reference charts [19].

Blood testing

Blood sample for biochemical determinations (calcium, phosphorus, 25(OH)D and PTH) was collected after overnight fasting in all individuals. Calcium and phosphorus plasma levels were measured by colorimetric methods using a COBAS 8000 analyzer (Roche Diagnostic, Mannheim, Germany). In addition, 25(OH)D levels were estimated by a high-specific chemiluminescence immunoassay (LIAISON

Assay, Diasorin, Dietzenbach, Germany), and PTH levels were determined by a highly specific solid-phase, two-site chemiluminescent enzyme-labeled immunometric assay using an Immulite analyzer (DPC Biermann, Bad Nauheim, Germany).

The distribution of individuals based on vitamin D plasma levels followed the criteria of the United States Endocrine Society [20, 21]. In this way, 25(OH)D serum levels lower than 20 ng/mL (< 50 nmol/L) corresponded to vitamin D deficiency, 25(OH)D levels between 20 and 29 ng/mL (50–75 nmol/L) to vitamin D insufficiency, and concentrations equal to or higher than 30 ng/mL (> 75 nmol/L) to vitamin D sufficiency.

Statistical analysis

The results are subsequently displayed as percentages (%) and means (M) with the corresponding standard deviation score (SDS). Chi-square test was used to compare percentages between CPP and control groups. Student's *t*-test was used to compare mean values in the variables recorded between CPP and control groups. ANOVA or Kruskal Wallis test (non-parametric test) were used to compare mean values in variables according to the season of the year or vitamin D status. Pearson's test was used to quantify the degree of linear association between quantitative variables in both groups. Statistical analyses were performed using the program Statistical Packages for the Social Sciences version 20.0 (Chicago, IL, USA). Statistical significance was accepted when *P*-value was < 0.05.

Results

In CPP group, 25(OH)D levels exceeded 30 ng/mL (Vitamin D sufficiency) in 27 patients (34.6%), varied from 20 to 29 ng/mL (Vitamin D insufficiency) in 39 (50%) and were lower than 20 ng/mL (Vitamin D deficiency) in 12 (15.4%). In control group, 58 participants (42.3%) exhibited vitamin D sufficiency, 63 (46%) were vitamin D insufficient and 16 (11.7%) vitamin D deficient. There were no significant differences in the prevalence of hypovitaminosis D between both groups (Chi-square test).

Table 1 displays and compares mean values for the clinical characteristics and biochemical determinations between CPP and control groups. The average values for growth rate and PTH were significantly higher ($p < 0.05$) in CPP group. There were no significant differences in age, BMI SDS, calcium, phosphate and 25(OH)D between both groups.

Table 1
Clinical and biochemical characteristics in CPP and control groups (M ± SDS)

Items	CPP group (n = 78)	Control group (n = 137)	P-value*
Age (years)	7.4 ± 0.5	7.5 ± 0.7	0.260
BMI SDS	0.33 ± 0.65	0.22 ± 0.75	0.356
Growth rate (cm/years)	7.2 ± 1.5	5.1 ± 0.4	0.001
Calcium (mg/dL)	9.9 ± 0.3	10.0 ± 0.3	0.192
Phosphorus (mg/dL)	4.8 ± 0.5	4.7 ± 0.5	0.231
PTH (pg/mL)	44.8 ± 16.3	31.0 ± 11.9	0.001
25(OH)D (ng/mL)	25.4 ± 8.6	28.2 ± 7.4	0.187
*Student's t-test			

Table 2 displays and compares the average values for biochemical characteristics whose determinations were made in the different seasons of the year between CPP and the control groups. There were not any statistically significant differences in mean values of calcium and phosphorous levels between CPP and control groups for each season. There were seasonal variations in 25(OH)D levels ($p < 0.05$) in both groups, and the highest 25(OH)D levels corresponded to summer (CPP group: 32.4 ± 8.4 ng/mL and control group: 36.3 ± 7.7 ng/mL). There were not any statistically significant differences in mean values of the 25(OH)D levels between CPP and control groups for each season. There were seasonal variations in PTH levels ($p < 0.05$) in both groups. The lowest PTH levels corresponded to summer (CPP group: 37.7 ± 14.9 pg/mL and control group: 23.6 ± 6.5 pg/mL) and reached a maximum value in autumn (CPP group: 50.2 ± 17.1 pg/mL and control group: 35.1 ± 12.9 pg/mL). In the CPP group, mean values for PHT levels were significantly higher ($p < 0.05$) in every season of the year with respect to the control group.

Table 2

Biochemical characteristic according to the season of the year in CPP and control groups (M ± SDS)

CPP group (n = 78)	Winter (n = 20)	Spring (n = 18)	Summer (n = 22)	Autumn (n = 18)	P- value*
Calcium (mg/dL)	9.9 ± 0.3	9.9 ± 0.3	10.0 ± 0.4	9.9 ± 0.2	0.785
Phosphorus (mg/dL)	4.7 ± 0.4	4.9 ± 0.3	4.7 ± 0.4	4.8 ± 0.5	0.284
25 (OH)D (ng/mL)	23.1 ± 7.0	23.7 ± 7.8	32.4 ± 8.4	23.0 ± 5.9	0.034
PTH (pg/mL)	48.8 ± 15.2#	47.3 ± 15.5#	37.7 ± 14.9#	50.2 ± 17.1#	0.009
Control group (n = 137)	Winter (n = 38)	Spring (n = 25)	Summer (n = 26)	Autumn (n = 38)	P- value*
Calcium (mg/dL)	10.1 ± 0.3	10.0 ± 0.2	10.0 ± 0.2	9.9 ± 0.4	0.358
Phosphorus (mg/dL)	4.6 ± 0.5	4.6 ± 0.3	4.6 ± 0.5	4.7 ± 0.5	0.608
25 (OH)D (ng/mL)	26.2 ± 6.7	26.0 ± 6.4	36.3 ± 7.7	26.5 ± 7.1	0.001
PTH (pg/mL)	29.4 ± 12.6#	30.5 ± 9.3#	23.6 ± 6.5#	35.1 ± 12.9#	0.003
*Kruskal Wallis test					
# (p < 0.05) between groups (Mann-Whitney's U-test)					

Table 3 shows and compares the mean values for biochemical determinations in accordance with to vitamin D status in PPC and control groups. No significant differences were found in calcium and phosphorus levels between different vitamin D status in both groups, and obviously 25(OH)D levels were significantly lower ($p < 0.01$) in deficiency and insufficiency vitamin D than sufficiency vitamin D in both groups. PTH levels were significantly higher ($p < 0.01$) in insufficiency and deficiency vitamin D than in sufficiency vitamin D in both groups. In addition, there were no significant differences in calcium, phosphorus, and 25(OH)D levels in each vitamin D status between the two groups. However, PTH levels were significantly higher ($p < 0.01$) for each vitamin D status in the CPP group with respect to the control group.

Table 3
Biochemical determinations according to vitamin D status in PPC and control groups (M ± SDS)

CPP group (n = 78)	Deficiency (n = 12)	Insufficiency (n = 39)	Sufficiency (n = 27)	p-values*
Calcium (mg/dL)	9.8 ± 0.3	9.9 ± 0.3	10.0 ± 0.3	0.232
Phosphorus(mg/dL)	4.9 ± 0.5	4.7 ± 0.4	4.7 ± 0.5	0.169
25 (OH)D (ng/mL)	14.9 ± 2.8	23.5 ± 3.0	36.7 ± 5.1	0.001
PTH (pg/mL)	59.5 ± 15.4#	47.1 ± 17.5#	36.2 ± 14.6#	0.001
Control group (n = 137)	Deficiency (n = 16)	Insufficiency (n = 63)	Sufficiency (n = 58)	p-values*
Calcium (mg/dL)	9.9 ± 0.4	10.1 ± 0.2	10.1 ± 0.3	0.726
Phosphorus(mg/dL)	4.8 ± 0.6	4.6 ± 0.6	4.6 ± 0.6	0.291
25 (OH)D (ng/mL)	15.8 ± 2.8	24.9 ± 2.6	35.1 ± 4.6	0.001
PTH (pg/mL)l)	33.9 ± 13.3#	33.8 ± 14.6#	27.3 ± 11.6#	0.001
*Kruskal-Wallis test.				
# (p < 0.05) between groups (Mann-Whitney´s U-test)				

Table 4 displays and compare the average values for clinical data and basal and stimulated serum concentrations of gonadotropins (LH and FSH) in accordance with vitamin D status in CPP group. There were not any statistically significant differences in age at onset, BMI SDS, growth rate, bone age, bone age advanced, basal estradiol, basal and stimulated LH and FSH between the different vitamin D status.

Table 4
Clinical data and concentrations of gonadotropin according to vitamin D status in PPC group (M ± SDS)

	Deficiency (n = 12)	Insufficiency (n = 39)	Sufficiency (n = 27)	p-values*
Age (years)	7.42 ± 0.60	7.40 ± 0.60	7.58 ± 0.43	0.571
BMI SDS	0.30 ± 0.67	0.29 ± 0.71	0.38 ± 0.68	0.665
Growth rate (cm/y)	7.16 ± 1.45	7.35 ± 1,31	7.19 ± 1.13	0.846
Bone age (years)	8.96 ± 0.87	9.04 ± 0.90	9.10 ± 0.80	0.722
BA-CA (years)	1.44 ± 0.75	1.64 ± 0.63	1.52 ± 0.70	0.668
Basal estradiol	26.33 ± 9.77	26.63 ± 8.44	26.40 ± 11.51	0.998
Basal LH (UI/L)	0.67 ± 0.38	0.56 ± 0.51	0.81 ± 0.62	0.760
LH peak (UI/L)	14.01 ± 6.55	13.22 ± 9.62	14.09 ± 7.67	0.962
Basal FSH (UI/L)	3.59 ± 0.94	3.06 ± 1.37	3.09 ± 1.67	0.698
FSH peak (UI/L)	19.31 ± 7.06	16.19 ± 4.26	18.76 ± 7.16	0.222
*Kruskal-Wallis test.				

There was a negative correlation ($P < 0.01$) between PTH and 25(OH)D levels in both CPP ($r = -0.345$) and control group ($r = -0.278$). In addition, in CPP group there was also a positive correlation ($p < 0.05$) between PTH levels and growth rate ($r = 0.285$), bone age ($r = 0.539$), basal estradiol ($r = 0.288$), basal FSH ($r = 0.284$), basal LH, ($r = 0.412$) and LH peak ($r = 0.378$). We did not find any significant correlation between 25(OH)D levels and puberty characteristics (BMI SDS, growth rate the year before puberty onset, BA, BA advance, basal estradiol, basal FSH, basal LH, FSH peak, and LH peak).

Discussion

This study highlights that vitamin D status in 6- to 8-years-old girls with CPP is similar to that in control group (prepubertal girls), whereas PTH levels were significantly higher in girls with CPP compared to those in control individuals. Furthermore, our data revealed that girls with CPP also maintain seasonal variations in 25(OH)D and PTH levels, as it occurs in the control group. It should be noted that this is the first report that simultaneously analyzes vitamin D status and PTH levels in girls with CPP.

Vitamin D and PTH are well known for their role in bone metabolism and calcium homeostasis. Their biological functions are widely complementary, contributing to the normal bone mass acquisition. The major physiologic function of vitamin D is to enhance the absorption of dietary calcium and phosphate, and to increase tubular reabsorption of calcium [1, 3]. On the other hand, under physiological conditions,

PTH promotes bone mineralization through the effect on osteoblasts. During hypovitaminosis D or hypocalcemic phases, PTH concentrations increase and the osteoclast becomes its main target cell in bone; in this way, it activates bone resorption. The two processes do not occur independently, and the increase in bone resorption is accompanied by stimulation of osteoblast activity via a series of paracrine and autocrine mechanisms that result in an increase in bone turnover [22]. In fact, PTH levels are currently used as the best markers of bone turnover [9]. In accordance to several authors [4, 6, 7, 23, 24], we found a negative correlation between PTH and 25(OH)D levels, and this would be consistent with the physiological feedback mechanism of vitamin D on PTH secretion.

In contrast to other studies, we found no association between vitamin D status and CPP characteristics (clinical data, and basal and stimulated gonadotropins). To a large extent, this disagreement is possibly due to methodological reasons, since the sample in this study was entirely made up of Caucasian girls and, furthermore, all those overweight/obese girls have been excluded (cutaneous pigmentation and overweight/obesity have been associated with hypovitaminosis D) [25–28]. On the other hand, we cannot define a vitamin D status in a concrete population without referring to seasonal variations since, as it occurred in this study, the maximum levels of 25(OH)D usually correspond to the summer period, being significantly lower in the rest of the seasons of the year [4, 8, 29]. In this case, there was sufficient homogeneity in the seasonal distribution among the participants included in this study (CPP and control groups). However, previous studies that evaluated a possible association between vitamin D status and timing of puberty in girls have several limitations, since they either did not refer to race or season of the year in which the sample was collected [12–14], or did not include a group control [15]. In other words, this study allows us to analyze the results obtained avoiding confounding factors.

There is evidence that vitamin D has some effects on female fertility. VDR has been shown to be expressed in ovarian cells, indicating a role in steroidogenesis of sex hormones [10, 11]. In addition, VDR and 1 α -hydroxylase are expressed in the endometrium, suggesting that it is an extra renal site of vitamin D synthesis and vitamin D action [30]. There are several studies that suggest that vitamin D status could contribute to hormonal dysregulation in patients with PCOS; and it is even pointed out that vitamin D supplementation may be useful to improve fertility and metabolic alterations in women with PCOS [31, 32]. Recent studies have reported that vitamin D is involved in ovarian steroidogenesis by modulating the expression of the 3 β -hydroxy steroid dehydrogenase enzymes [33]; therefore, it could be suggested that a situation of hypovitaminosis D could rather condition a deficiency of gonadal steroids and, consequently, a delayed puberty. In fact, experimental studies have revealed that peripubertal vitamin D sufficiency is important for an appropriate pubertal transition and maintenance of normal female reproductive physiology [34]. In this sense, it was expected that vitamin D status in girls with CPP were similar to that of the control group, as we found in this study. In addition, it should be remembered that we found no association between vitamin D status and CPP characteristics.

The main innovation of this study would be the fact that PTH concentrations in girls aged 6 to 8 years with CPP are increased in relation to control group. And, curiously, it should be noted that our finding that the PTH levels remained significantly increased throughout the year in the CPP group compared to the

control group, even with seasonal variations. In addition, it can be said that PTH levels were also significantly higher—independent of vitamin D status—in girls with CPP with respect to the control group. Our data support the hypothesis that the high levels of PTH found in girls with CPP do not represent, as it is commonly assumed, an increase secondary to hypovitaminosis D.

During growth, the shape and structure of bones are continuously modified and renovated by modeling and remodeling processes. Maintaining normal bone turnover is important to achieve optimal peak bone mass and to optimize growth. In fact, this apposition-reabsorption process involves a positive balance during childhood and adolescence until the maximum peak of bone mass is acquired in the third decade of life, then moving to a neutral balance [35]. PTH levels are currently considered the best available marker of bone turnover. It is interesting to note that (in childhood and adolescents with vitamin D with a D sufficiency) has been reported that PTH levels increase significantly in girls in the age group of 8–10 years, whereas in boys is significantly increased in the age groups of 10–12 years, leading to the hypothesis of a relationship between PTH level and pubertal and bone growth spurts [9]. That is, the increase of PTH levels in these age groups, and with a clear sexual dimorphism, could be considered as a physiological characteristic of the pubertal period and, in this case, of pubertal precocity. In fact, there was a strong correlation between PTH levels and bone age in CPP group. However, there is controversy regarding the relationship between vitamin D and bone turnover markers. In compliance with several studies [4, 6, 7, 23, 24], we found a negative correlation between the levels of PTH and 25(OH)D, and several authors have suggested that the Vitamin D deficiency could contribute through parathyroidism secondary to accelerated bone turnover. However, we found that PTH levels were also significantly higher, regardless of vitamin D status, in girls with CPP compared to the control group; therefore, this hypothesis seems unreliable.

In conclusion, our data showed that vitamin D status in 6- to 8-years-old girls with CPP is similar to that in prepubertal girls, and we did not find any correlation between vitamin D status and CPP characteristics. What is more, PTH levels were significantly higher in girls with CPP compared to those in control individuals, and could be considered as a physiological characteristic of the pubertal period and, in this case, of pubertal precocity.

Abbreviations

BA: Bone age

BMI: Body mass index

CA: Chronological age

CPP: Central precocious puberty

FSH: Follicle-stimulating hormone

GnRH: Gonadotropin hormone releasing hormone

LH: Luteinizing hormone

PTH: Parathyroid hormone

SDS: SD scores

VDR: Vitamin D receptor

25(OH)D: 25-hydroxyvitamin D

Declarations

Compliance with ethical statements

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Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article (none declared).

Ethical Approval

This study was approved by the Ethics Committee for Human Investigation of the Navarra Hospital Complex, Pamplona, Spain (code: 18/12) in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and later amendments.

Consent to participate

Parents and/or legal guardians were appropriately informed and gave written consent for the participation of the participants in this study in all cases.

Consent for publication

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Availability of data and material

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TDT and FGV participated in study design and data analysis, and wrote the first draft of the manuscript. LAM, PMG, MUM, and MMC participated in data collection and analysis. All authors participated in manuscript preparation and approved its final version.

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