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Is There Any Threshold for Vitamin D That Elevates Parathyroid Hormone

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Abstract

Objective: To evaluate vitamin D status in relation to serum levels for parathyroid hormone (PTH) and corrected calcium among endocrine outpatients. **Methods:** A total of 760 patients (mean(SD) age: 40.0(12.6) years, 94.6% were females) admitted to our endocrinology outpatient clinic were included and evaluated with respect to patient demographics, serum levels for 25-hydroxyvitamin D (25(OH) D, ng/mL), PTH (pg/mL) and corrected calcium (mg/dL) as well as the vitamin D status. **Results:** Vitamin D deficiency was determined in 65.0% and elevated PTH levels in 20.3% of patients. iPTH levels were significantly higher in females than in males (58.9(40.4) vs. 45.1(26.2) pg/mL, p = 0.031) and in summer than in winter cases (63.9(47.7) vs. 54.2(32.8) pg/mL, p = 0.002), whereas no difference was found in serum levels for 25(OH) D, corrected calcium and phosphate with respect to gender and season. Significantly higher levels for iPTH were noted in vitamin D deficient patients (60.7(43.9) pg/mL) than in normal (51.1(33.4) pg/mL) and vitamin D insufficient (57.1(26.0) pg/mL) cases (p = 0.03). iPTH levels were correlated positively with age (r = 0.116, p = 0.001) and negatively with corrected calcium (r = −0.097, p = 0.008), P (r = −0.224, p = 0.000) and 25(OH) D (r = −0.134, p = 0.000), whereas no correlation was noted between 25(OH) D and corrected calcium levels. **Conclusion:** Our findings indicated that vitamin D deficiency in 65.0%, whereas PTH elevation only in 20.3% of endocrine outpatients, despite the significantly negative correlation of PTH to 25(OH) D and significantly higher levels of PTH among vitamin D deficient cases than in vitamin D insufficient and sufficient cases. Gender's and seasonal differences had influence on serum levels for PTH but not on either 25(OH) D or corrected calcium, and no correlation was evident between 25(OH) D and corrected calcium levels.

Keywords

Vitamin D Deficiency, Parathyroid Hormone, Calcium, 25(OH) D Testing

1. Introduction

Vitamin D is an essential fat-soluble vitamin that affects nearly every organ system, and thereby, vitamin D deficiency has been associated not only with bone diseases such as rickets, osteoporosis and osteomalacia, but also with the risk of metabolic syndrome, diabetes, autoimmune diseases, cardiovascular disease, chronic kidney disease and certain types of cancers [1]-[8].

Owing to greater awareness within the medical community regarding the importance of poor vitamin D status as a public health problem affecting almost every second person worldwide [2] [9] [10] [11], the interest in the biology of vitamin D and vitamin D deficiency and thereby the demand for vitamin D testing has increased dramatically in the last 2 decades [12] [13] [14].

The serum level of 25-hydroxyvitamin D (25(OH) D) is considered to be a reliable indicator of the vitamin D status of an individual [15], and albeit there is no consensus on a cut-off level of vitamin D for defining vitamin D status categories, it has been widely accepted that circulating 25(OH) D concentrations of <30 ng/mL to indicate vitamin D insufficiency and levels < 20 ng/mL to be indicative of vitamin D deficiency [16]. Accordingly, it has been estimated that 40% to 100% of elderly US and European non-hospitalized men and women and an estimated one billion people worldwide, to be either vitamin D deficient or insufficient [2] [17].

The plasma (or serum) 25(OH) D is currently the best indicator for vitamin D status as a measure of the circulating concentration of serum 25(OH) D, which reflects vitamin D from all sources including cutaneous synthesis, diet and supplements [2] [18]. However, given that it requires advanced technical equipment, not all investigators may have the resources to assay 25(OH) D and thus the clinical decision on vitamin D deficiency has been based on evaluation of serum levels for calcium, phosphate and parathyroid hormone (PTH) [19]. Therefore, the present study was designed to evaluate vitamin D status in relation to serum levels for PTH and corrected calcium among endocrine outpatients.

2. Materials and Methods

2.1. Study Population

A total of 760 patients (mean age: 40.0 (standard deviation (SD) =12.6; range: 15.0 - 86.0) years, 94.6% were females) admitted to Clinic of Endocrinology at Kayseri Training and Research Hospital were included in this study. Patients with exposure to sunlight for more than 30 minutes during summer months (Mar-Sep) and less than 30 minutes during winter months (Sep-Mar) were included, while patients with renal dysfunction, hyper- or hypo-parathyroidism or

malabsorption and patients under calcium replacement therapy were excluded from the study.

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the institutional ethics committee.

2.2. Assessments

Data on patient demographics, serum levels for 25(OH) D (ng/mL), PTH (pg/mL) and corrected calcium (mg/dL) were recorded. Vitamin D status of patients were categorized according to the published criteria based on serum levels for 25(OH) D as adequate vitamin D (≥30 ng/ml), vitamin D insufficiency (20 - 29 ng/ml) and vitamin D deficiency (<20 ng/ml) [20].

Seasonal variation in 25(OH) D (ng/mL), PTH (pg/mL) and corrected calcium (mg/dL) levels, the alteration in PTH (pg/mL) and corrected calcium (mg/dL) levels with respect to vitamin D status and the correlation between 25(OH) D (ng/mL), PTH (pg/mL) and corrected calcium (mg/dL) levels were determined in both genders.

2.3. Blood Biochemistry

Patient's venous serum and plasma specimens with addition of the ethylenediaminetetraacetic acid (EDTA) to be used in biochemistry and hormone analyzes are taken between 0.8 - 0.10 in the morning after 12 hours fasting. All laboratory test parameters, except iPTH, were measured within 3 hours. iPTH plasma samples stored −80˚C until final analysis.

Insulin and iPTH levels were measured in an autoanalyzer (Beckman Coulter Unicel DXI 800, Brea, California, USA) with original commercial original kit, controls and calibrators of the same lot number; using the the paramagnetic particle and chemiluminescence immunoanalysis method for the quantitative determination. For insulin analysis, the total correlation coefficient (CV) was detected as 5.6% at 0.15 μIU/mL concentrations, 4.0% at 0.30 μIU/mL concentrations, 4.5% at 0.93 μIU/mL concentrations, 3.5% at 12.90 μIU/ml concentrations, 3.3% at 37.40 μIU/mL concentration and 3.1% at 99.30 μIU/mL concentrations. In human plasma samples coefficients of variation for iPTH test was detected to be 2.6% within the study at 12.1 (1.3) pg/ml (pmol/L) concentration, 5.8% between the study, 1.6% within the study at 144 (15.3) pg/ml (pmol/L) concentration, 3.2% between the study, 2.2% within the study at 1439 (152.5) pg/ml (pmol/L) and 2.8% between the study.

Serum intact PTH was measured from venous blood samples using a solid-phase two-site chemiluminescent enzyme-labeled immunometric assay with a reference range of 12 - 88 pg/mL.

Plasma levels of vitamin D of patient cohorts were measured at the Department of Clinical Biochemistry of Kayseri Education and Research Hospital CentralLaboratory. Samples were analyzed by a high-performance liquid chromato-

graph (HPLC) method using the Immuchrom HPLC system (Immuchrom GmbH, Heppenheim, Germany) and Immuchrom vitamin D3 controls and kit (Immuchrom GmbH, Heppenheim, Germany).

500 µL plasma sample from EDTA was purified from proteins and 50 µL of the cleaned supernatant was applied into instrument. The flow rate of the methanol water mixture used as the mobile phase was 1.1 mL/minute. An UV detector was used during the analysis. Vitamin D levels were detected as 2.6% at 56.5 nmol/L concentration and 1.5% at 104.8 nmol/L concentration. Inter-assay values were measured as 4.0% at 54.1 nmol concentration and 3.6% at 105.4 nmol concentration [1].

Serum calcium, phosphorus were measured colorimetrically. Serum albumin levels were measured by immunoturbidimetric assay. Corrected calcium (adjusted calcium) levels were determined via using formulae "corrected calcium (mg/dL) = measured total calcium (mg/dL) + 0.8 (4.0 - serum albumin [g/dL])", where 4.0 represents the average albumin level in g/dL.

2.4. Statistical Analysis

Statistical analysis was made using computer software (SPSS version 16.0, SPSS Inc. Chicago, IL, USA). Chi-square test for the comparison of categorical data and student-t-test was used for the analysis of numerical data. The relation between 25OH (D), corrected calcium and PTH was evaluated with Pearson correlation analysis. Data were expressed as "mean (SD)", and percent (%) where appropriate. $p < 0.05$ was considered statistically significant.

3. Results

3.1. Patient Characteristics and Laboratory Findings

Vitamin D levels were normal in 20.4% of patients, while 14.6% and 65.0% of patients were determined to be vitamin D insufficient and deficient, respectively. PTH levels were determined to be elevated in 20.3% of patients, similarly in winter (19.9%) and summer (20.8%) months (Table 1). Age and biochemical variables with respect to gender can be seen in Table 2. Mean age of males vs females (46.1(15.4) vs. 39.7(12.4) years, $p = 0.013$) was found. Moreover, mean ages of summer cases vs winter cases(43.8(13.4) vs. 37.4(11.4) years, $p = 0.0001$) were significantly older. iPTH levels were significantly higher in females than in males (58.9(40.4) vs. 45.1(26.2) pg/mL, $p = 0.031$) and in summer than in winter cases (63.9(47.7) vs. 54.2(32.8) pg/mL, $p = 0.002$), particularly for females ($p = 0.001$). Calcium levels were significantly higher in summer compared with winter cases (9.6(1.8) vs. 9.4(0.5) mg/dL, $p = 0.048$), particularly for females ($p = 0.048$). No difference was noted in serum levels for 25(OH) D, corrected calcium and phosphate with respect to gender and season (Table 2).

3.2. Age, Biochemical Variables and Seasonal Distribution with Respect to Vitamin D Status

Significantly higher levels for iPTH were noted in vitamin D deficient patients

Table 1. Patient characteristics and categories with respect to season, vitamin D status and PTH level.

Age (year), mean(SD, min-max)		40(12.6, 15 - 86)
Gender		
Female (n-%)		719 - 94.6
Male (n-%)		41 - 5.4
Season		
Winter months	Total (n-%)	448 - 58.9
	Female (n-%)	428 - 95.5
	Male (n-%)	20 - 4.5
Summer months	Total (n-%)	312 - 41.1
	Female (n-%)	291 - 93.3)
	Male (n-%)	21 - 6.7
Vitamin D status		
Normal (≥30 ng/ml) (n-%)		155 - 20.4
Vitamin D insufficiency (20 - 29 ng/ml) (n-%)		111 - 14.6
Vitamin D deficiency (<20 ng/ml) (n-%)		494 - 65.0
PTH levels		
Normal	Total (n - %)	606 - 79.7
	Winter (n - %)	359 - 80.1
	Summer (n - %)	247 - 79.2
Elevated	Total (n - %)	154 - 20.3
	Winter (n - %)	89 - 19.9
	Summer (n - %)	65 - 20.8

Table 2. Age and biochemical variables with respect to gender and season.

	Total (n = 760)	Female (n = 719)	Male (n = 41)	p value
Age (year)	40(12.6)	39.7(12.4)	46.1(15.4)	0.013
Ca(mg/dL)	9.5(1.2)	9.5(1.2)	9.5(0.7)	0.829
Corrected Ca (mg/dL)	9.7(0.5)	9.7(0.5)	9.8(0.8)	0.387
Phosphate (mg/dL)	3.5(0.6)	3.5(0.6)	3.6(0.6)	0.249
iPTH (pg/mL)	58.2(39.9)	58.9(40.4)	45.1(26.2)	0.031
25(OH) D (ng/mL)	20.4(17.2)	20.2(17.1)	24.7(18.5)	0.103

	Total			Females			Males		
	Winter (n = 448)	Summer (n = 312)	p value	Winter (n = 428)	Summer (n = 291)	p value	Winter (n = 20)	Summer (n = 21)	p value
Age (year)	37.4(11.4)	43.8(13.4)	0.0001	37.3(11.2)	43.1(13.2)	0.0001	39.5(14.7)	52.3(13.7)	0.006
Ca(mg/dL)	9.4(0.5)	9.6(1.8)	0.048	9.4(0.5)	9.6(1.9)	0.048	9.6(0.8)	9.5(0.7)	0.752
Corrected Ca (mg/dL)	9.7(0.5)	9.7(0.6)	0.055	9.7(0.5)	9.7(0.6)	0.082	10.0(0.8)	9.7(0.8)	0.239
Phosphate (mg/dL)	3.5(0.5)	3.5(0.6)	0.593	3.5(0.6)	3.5(0.6)	0.759	3.6(0.6)	3.7(0.6)	0.458
iPTH (pg/mL)	54.2(32.8)	63.9(47.7)	0.002	54.6(32.9)	65.3(48.8)	0.001	45.5(30.8)	44.8(21.7)	0.927
25(OH) D (ng/mL)	21.3(17.5)	19.2(16.7)	0.110	21.1(17.4)	18.8(16.5)	0.084	24.8(19.4)	24.5(18.0)	0.963

Data are shown as mean (SD). Ca: calcium; PTH: parathyroid hormone; 25(OH) D: 25-hydroxyvitamin D.

Table 3. Age, biochemical variables and seasonal distribution with respect to vitamin D status.

	Vitamin D status			p value
	Normal (≥30 ng/ml)	Vitamin D insufficiency (20 - 29 ng/ml)	Vitamin D deficiency (<20 ng/ml)	
	Mean(SD)	Mean(SD)	Mean(SD)	
Age	38.8(13.5)	40.5(13.9)	40.3(12.0)	0.432
Ca (mg/dL)	9.4(0.5)	9.7(2.9)	9.5(0.6)	0.066
Corrected Ca (mg/dL)	9.7(0.5)	9.7(0.6)	9.7(0.5)	0.989
Phosphate (mg/dL)	3.5(0.5)	3.5(0.6)	3.5(0.6)	0.886
iPTH (pg/mL)	51.1(33.4)	57.1(26.0)	60.7(43.9)	0.03
25(OH) D (ng/mL)	48.8(15.8)	24.4(2.6)	10.6(4.7)	0.0001
Winter cases (n-%)	93(20.8)	76(17.0)	279(62.3)	0.065
Summer cases (n-%)	62(19.9)	35(11.2)	215(68.9)	0.063

Ca: calcium; PTH: parathyroid hormone; 25(OH) D: 25-hydroxyvitamin D.

Table 4. Correlation between biochemical variables.

		Age	Corrected Ca	Phosphate	iPTH	25(OH) D	Ca
Age	r		−0.013	0.014	0.116	−0.039	0.033
	p		0.726	0.705	0.001	0.285	0.361
Corrected Ca	r	−0.013		−0.027	−0.097	0.005	0.390
	p	0.726		0.459	0.008	0.882	<0.001
Phosphate	r	0.014	−0.027		−0.224	0.011	−0.062
	p	0.705	0.459		<0.001	0.753	0.088
iPTH	r	0.116	−0.097	−0.224		−0.134	−0.033
	p	0.001	0.008	<0.001		<0.001	0.364
25(OH) D	r	−0.039	0.005	0.011	−0.134		−0.019
	p	0.285	0.882	0.753	<0.001		0.601
Ca	r	0.033	0.390	−0.062	−0.033	−0.019	
	p	0.361	<0.001	0.088	0.364	0.601	

Ca: calcium; PTH: parathyroid hormone; 25(OH) D: 25-hydroxyvitamin D; Pearson correlation analysis. Correlation is significant at 0.05 level (2-tailed).

(60.7(43.9) pg/mL) than in normal (51.1(33.4) pg/mL) and vitamin D insufficient (57.1(26.0) pg/mL) cases (p = 0.03), whereas no difference was noted in vitamin D status with respect to age, corrected calcium levels, and seasonal change (Table 3).

3.3. Correlation between Biochemical Variables

iPTH levels were correlated positively with age (r = 0.116, p = 0.001) and negatively with corrected calcium (r = −0.097, p = 0.008), P (r = −0.224, p = 0.000) and 25(OH) D (r = −0.134, p = 0.000), whereas no correlation was noted between 25(OH) D and corrected calcium levels (Table 4).

4. Discussion

Our findings in a cohort of endocrine outpatients indicated that vitamin D deficiency was clearly prevalent as noted in 65.0% of patients with no alteration in vitamin D status, 25(OH) D levels and corrected calcium levels with respect to gender and season. Increased levels for PTH were noted in females than in males and in vitamin D deficient than in normal and vitamin D insufficient patients. Negative correlation of PTH levels both to 25(OH) D and corrected calcium was noted, while no correlation was evident between 25(OH) D and corrected calcium levels.

High prevalence of vitamin D deficiency in our study population is in agreement with the consistently reported high prevalence of vitamin D deficiency in different populations worldwide even in areas that receive ample sunlight [14] [21] [22] [23] [24]. Also, evaluation of vitamin D status via a population-based survey of households in the Aegean region of Turkey indicated that 74.9% of the subjects had 25(OH) D deficiency (<20 ng/mL) [25].

In a retrospective study to analyze the biochemical results stored in the database of a pathology laboratory, it was reported that 33% of 3745 men and 40% of 6754 women were vitamin D deficient to some degree (25[OH] D ≤ 50 nmol/L) along with a significant negative association between PTH and 25(OH) D, while a significant positive association between calcium and 25(OH) D levels [12]. Supporting data from past studies, PTH levels were higher in vitamin D deficient than in vitamin D insufficient patients along with a negative correlation between 25(OH) D and PTH in the present study [12] [17] [26] [27] [28].

However, despite 65.0% prevalence of vitamin D deficiency and the negative correlation between 25(OH) D and PTH levels, PTH levels were within normal range in majority of our patients with identification of elevated PTH levels only in 20.3%. Alike to our findings, data from ambulatory patients of an outpatient clinic in Poland revealed 84.4% of subjects to be vitamin D deficient (25(OH) D < 20 ng/mL), while 21% of subjects had elevated serum PTH concentration (*i.e.* >62 pg/mL) along with a negative correlation between PTH and 25(OH) D concentrations [26].

Indeed, data from some studies indicated an association between vitamin D deficiency and elevated PTH levels [12] [29] [30] [31] [32] leading consideration of the theoretical plateau in PTH as 25(OH) D increases to be used as a determinant in establishing the adequacy of vitamin D status [33]. However it should be noted that while 25(OH) D and PTH levels are inversely related, less than half of the patients with a low vitamin D level have been confirmed to have an elevated PTH, and, in most of these patients, the PTH does not immediately normalize with correction of the vitamin D [27] [34]. Likewise, blunted parathyroid hormone response to vitamin D deficiency was reported in a past study conducted with premenopausal women along with no difference between serum PTH levels of the subjects with and without vitamin D deficiency [35]. Hence, our findings support that PTH has a limited role in defining vitamin D status in individual patients and in guiding vitamin D therapy in clinical practice [34].

In contrast to data from past studies indicated that season of blood withdrawal was a significant predictor of vitamin D status, with identification of lower median 25(OH) D levels during winter and spring [36] [37] [38], seasonal alteration had no influence on 25(OH) D levels as well as corrected calcium levels in our study population, whereas serum PTH levels were higher in summer cases, especially among females. Lack of the effect of seasonal difference on serum vitamin D levels was also reported in a past study in stroke patients which revealed similar levels for vitamin D levels between the cases in summer (Apr-Sep) and winter (Oct-Mar) [39].

While no data are available to indicate whether seasonal variation in 25(OH) D is good, bad or neutral for health, vitamin D deficiency (<30 nmol/L) in summer has been of concern, as this implies a much lower level is likely in winter, and should certainly prompt treatment and checking of the winter level [40]. In this regard, our findings may emphasize the insufficient exposure to sunlight even in summer months during which sun exposure is more effective in promoting vitamin D activation as well as its storage for an optimal vitamin D status during the remaining months of the year [36].

Higher levels of PTH in summer than in winter months among females in the present study is contradictory to the higher winter-time than summer-time prevalence of secondary hyperparathyroidism shown in past studies [12] [41] [42]. Given that absence of seasonal variation of 25(OH) D levels in our cohort, our findings seem to emphasize the influence of confounding variables, such as weight status, calcium intake and calcium absorption on elevation in PTH levels [17] [27] [36] [43].

Likewise, lack of a gender influence on 25(OH) D levels in the present cohort seems also contradictory to previous reports indicated that females had significantly lower mean 25(OH) D levels and thereby were more likely to be vitamin D deficient than men [12] [25] [44] [45] [46] [47]. Indeed, likely to be influenced by the cultural attitudes towards sun exposure and concealing clothes [48] [49], the role of gender in the determination of vitamin D status has not yet been clarified and lack of a gender influence on vitamin D status was also reported in other studies [36] [50] [51] [52].

In a retrospective study to analyze the biochemical results stored in the database of a pathology laboratory, it was reported that 33% of 3745 men and 40% of 6754 women were vitamin D deficient to some degree (25[OH] D ≤ 50 nmol/L) along with a significant negative association between PTH and 25(OH) D and a significant positive association between calcium and 25(OH) D levels [12].

PTH levels but not corrected calcium levels were correlated with 25(OH) D in the present study, whereas it should be noted that, while not correlated directly with 25(OH) D levels, corrected Ca levels were negatively correlated with PTH levels and in contrast to Ca levels, this relationship was free from the season effect.

Although, serum 25(OH) D levels have been widely accepted as the best indicator of a person's short-term vitamin D status not all investigators have the re-

sources to assay 25(OH) D [53].

In this regard, given the increased demand for 25(OH) D testing in the clinical practice [12] as the fastest growing Medicare item that increased exponentially over the past 15 years [40], our findings indicate that PTH levels rather than corrected Ca levels more accurately reflect vitamin D status in case of unavailability of 25(OH) D testing, provided that gender and seasonal variations are considered. Nevertheless, it should be kept in mind that, given the discrepancy between the rates of vitamin D deficiency and elevated PHT within a study population, PTH has been considered to have a limited role in either defining vitamin D status in individual patients or guiding vitamin D therapy in clinical practice [34].

Although, the potential benefits of improving a population's vitamin D status would be substantial given the high burden of vitamin D deficiency, lack of clear evidence-based guidelines regarding the long-term management of incidentally detected cases as well as differentiating clinically significant cases from an incidental biochemical finding have been considered to be the major clinical challenges [54]. Given the growing interest and demand for 25(OH) D testing, further investigation on identification of subpopulations that are mostly affected by vitamin D deficiency seems to be helpful in more appropriate and targeted allocation of scarce healthcare resources and services [12].

Certain limitations to this study should be considered. No data are available on body mass index, physical activity and diet characteristics in the study population despite their well-known effect on serum 25(OH) D levels. Also, while likely to contribute to the changes in the serum PTH responses to changes in serum 25(OH) D levels, no data are available considering the weight status as well as dietary calcium intake in our patients. Accordingly, lack of data on these confounding factors seems to be the major limitation which otherwise would extend the knowledge achieved in the current study. Nevertheless, despite these certain limitations, given the paucity of the solid information available on this area, our findings represent a valuable contribution to the literature.

The relationship between the serum levels of 25(OH) D and maximal suppression of PTH has been assessed in a few studies. Results from one investigation show that serum 25(OH) D needs to be higher than 31 ng/mL to suppress PTH in normal weight adult populations [55]. Lotito, *et al.* found that, lower doses of vitamin D along with calcium can also significantly suppress PTH in the meta-analysis [56].

In conclusion, our findings indicated that vitamin D deficiency in 65.0%, whereas PTH elevation only in 20.3% of endocrine outpatients, despite the significant negative correlation of PTH to 25(OH) D and significantly higher levels of PTH among vitamin D deficient cases than in vitamin D insufficient and sufficient cases. Gender and seasonal difference had influence on serum levels for PTH but not on either 25(OH) D or corrected calcium, and no correlation was evident between 25(OH) D and corrected calcium levels. Accordingly, while our findings support that 25(OH) D testing is the best indicator of a person's vitamin

D status, given that not all investigators have the resources to assay 25(OH) D, PTH levels rather than corrected calcium levels may more accurately reflect vitamin D status with consideration of gender and seasonal variations.

Conflict of Interest

There is no conflict of interest for all authors.

This article does not contain any studies animals performed by any of the authors.

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the institutional ethics committee.

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