The role of vitamin D deficiency in parathyroid hormone levels

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Aim: Vitamin D deficiency is an important cause of secondary hyperparathyroidism. We aimed to investigate the effect of vitamin D levels on parathyroid hormone (PTH) levels.

Materials and methods: We retrospectively chose 2226 patients who were admitted to our hospital's general internal medicine department for various reasons and had both PTH and vitamin D tests on the same day.

Results: It was found that 22.3% of the patients had high levels of PTH and 92% of them had secondary hyperparathyroidism. The average vitamin D level was 16.4 ng/mL. The vitamin D levels of 64% of the patients were below 20 ng/mL (n = 1417), and those of the rest of the patients were above 20 ng/mL (n = 809). Of the patients with vitamin D deficiency (≤20 ng/mL), 74.7% had normal levels of PTH. Furthermore, 27.2% of patients with high levels of PTH (n = 135) received further evaluation using imaging modalities (parathyroid ultrasonography and scintigraphy), and 66.6% had normal findings (n = 90).

Conclusion: Although PTH levels rise in the case of vitamin D deficiency, most of the patients had normal levels of PTH, and there were no pathological findings in the imaging studies of most of the patients with high PTH levels.

Key words: Vitamin D deficiency, high parathyroid hormone levels, secondary hyperparathyroidism

1. Introduction

Hyperparathyroidism is a clinical entity that occurs in the case of increased parathyroid hormone (PTH) secretion from parathyroid glands. It has long been thought to be a rare disease; however, today we know that it is the most common cause of diagnosed cases of hypercalcemia (1). Hyperparathyroidism was first described as a disease of bones. Further studies have shown, however, that it has a wide spectrum of symptoms. Secondary hyperparathyroidism is observed when there is another cause that decreases serum ionized Ca levels, which stimulates the parathyroid glands constantly and increases serum PTH levels (2). Vitamin D deficiency is a major cause of hyperparathyroidism. Vitamin D synthesis in the skin with the effect of UV-B rays is dependent on many factors. Geographical location, season of the year, melanin density of the skin, sunblock application, clothing habits, age, and food are all factors that affect vitamin D synthesis in the skin (3,4).

There is no consensus on the optimal vitamin D level or vitamin D deficiency levels (5–7). In a study conducted on adults over 49 years old, Malabanan et al. found that in order to reach desired levels of PTH, vitamin D levels

should be above 20 ng/mL (8). Other studies contend that when vitamin D levels are above 28 ng/mL, PTH levels range between minimum levels (9–11). Some other studies, on the other hand, suggest that vitamin D, even when it is below 37 ng/mL, has some effect on PTH levels (12).

In this study, we aimed to investigate the threshold vitamin D level for secondary hyperparathyroidism in patients who were admitted to the General Internal Medicine Outpatient Clinic of Hacettepe University.

2. Materials and methods

We retrospectively evaluated 2226 patients who were admitted to our internal medicine clinic between the years 2000 and 2011, who were between 18 and 75 years of age, and who had a vitamin D test and a PTH test on the same day. We received the data from the Department of Information Processing at Hacettepe University. We also recorded the patients' date of birth; age; age at the time of diagnosis; month when the tests were done; creatinine, Ca, P, alkaline phosphatase (ALP), and ionized Ca levels; and 24-h Ca excretion levels. We also obtained the imaging results of patients with high levels of PTH from our data collecting system.

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We considered PTH of 9.5–75 pg/mL, vitamin D of ≥20 ng/mL, serum calcium of 8.4–10.2 mg/dL, phosphorus of 2.7–4.5 mg/dL, ALP of 35–104 U/L, creatinine of 0.5–0.9 mg/dL, ionized Ca of 1.12–1.32 mmol/L, and 24-h urinary Ca excretion of 100–300 mg/24 h as normal level ranges in our study.

Exclusion criteria were chronic kidney disease, celiac disease, malabsorption, inflammatory bowel diseases, malignant disease history, age over 75, and not having PTH and vitamin D tests on the same day.

We received the approval of Hacettepe University's Ethical Council before the study.

2.1. Statistics
Statistical analysis was done by using SPSS 18. The distribution of the variables was evaluated by visual techniques (histogram and probability graphics) and analytic techniques (Kolmogorov–Smirnov/Shapiro–Wilk tests, variation coefficient, skewness, and kurtosis tests).

Descriptive analyses were done for the normally distributed variables using mean and standard deviation. For variables that are normally not distributed (PTH, vitamin D, 24-h urinary Ca excretion), median and min–max values were used for analyses. Categorical data were expressed as percentages. Normally distributed numerical variables in 2 groups were compared using the independent samples t-test, whereas numerical variables that are normally not distributed were compared using the Mann–Whitney U test. ANOVA was used for normally distributed numerical values when comparing more than 2 groups. Tukey and Tamhane tests were used in post-hoc analysis, i.e. after checking the homogeneities of the variances. The Kruskal–Wallis test was used for numerical variables lacking normal distribution when comparing more than 2 groups. Statistically significant results were reevaluated among themselves in pairs using the Mann–Whitney U test, and the results were interpreted after the application of the Bonferroni correction. For variables with and without normal distribution, the Pearson and Spearman correlation tests were used, respectively. P < 0.05 was considered statistically significant.

3. Results
Out of 2226 patients, 1840 were women (82.6%) and 386 were men (17.4%). The mean age of the women was 50.21 ± 10.12 years, while that of the men was 52.71 ± 10.11. Detailed demographical information can be found in Table 1.

We divided our patients into 2 groups: patients with low (<20 ng/mL) vitamin D levels and those with normal (≥20 ng/mL) vitamin D levels. However, since there is no consensus on the optimal vitamin D level, we further divided the patients into 4 groups for statistical analysis.

We divided the patients into 4 groups according to vitamin D levels: <10 ng/mL, 10–20 ng/mL, 20–30 ng/mL, and >30 ng/mL. No statistical significance was detected regarding the ages of the patients (P = 0.394). Although vitamin D levels were not significantly different between the age groups (P = 0.143), PTH levels were higher in older age groups (P < 0.01) (Table 1).

The mean vitamin D level was 17.6 ng/mL in women and 21.2 ng/mL in men. The difference was statistically significant (P < 0.01) (Table 1).

Patients were divided into 2 groups with respect to their PTH levels: normal (<75 pg/mL) and high (≥75 pg/mL) (Table 2). Normal PTH levels were found in 76.7%

Table 1. Demographic information of the study group.

Number of patients (n = 2226)		Primary hyperparathyroidism = 45 (2%)	
Female	1840 (82.6%)	Secondary hyperparathyroidism = 456 (20.3%)	
Male	386 (17.4%)	Chronic renal disease = 14 (0.6%)	
		Vitamin D deficiency = 442 (19.7%)	
Average age = 51.99 ± 11.41 years			
Female	50.21 ± 10.12	Mean vitamin D level = 16.4 (1.2–94)	
Male	52.71 ± 10.11	Male	17.670 (P < 0.01)
		Female	21.230 (P < 0.01)
PTH average = 51.8 (0.2–2500)		0–10 ng/mL	462 (20.7%)
<75	1725 (76.7%)	10.1–20 ng/mL	955 (42.9%)
≥75	501 (22.3%)	20.1–30 ng/mL	542 (24.3%)
		>30.1	267 (12.1%)

PTH: Parathyroid hormone.

Table 2. Comparison of groups according to PTH levels.

	PTH (pg/mL)	Mean	P-value
VitD	<75	19.2 ± 10.8	<0.01
	≥75	15.6 ± 9.4	
Age	<75	51.66 ± 11.2	0.011
	≥75	53.13 ± 11.9	
Cre	<75	0.7382 ± 0.20	0.062
	≥75	0.7692 ± 0.35	
Ca	<75	9.295 ± 0.65	0.007
	≥75	9.389 ± 0.77	
Ionized Ca	<75	1.102 ± 0.13	0.002
	≥75	1.185 ± 0.26	
24-h urine	<75	135.2 ± 52.4	<0.01
	≥75	256.4 ± 63.8	
P	<75	3.750 ± 0.45	0.001
	≥75	3.673 ± 0.46	
ALP	<75	74.35 ± 20.6	0.009
	≥75	77.45 ± 24.1	

VitD: vitamin D, Cre: creatinine, Ca: calcium, P: phosphorus, ALP: alkaline phosphatase.

of the patients (n = 1725), and high PTH levels in 22.3% (n = 501). In patients with normal PTH levels, the mean vitamin D level was 19.2 ng/mL, whereas in patients with high levels of PTH the mean vitamin D level was 15.6 ng/mL, and the difference was statistically significant (P < 0.01).

Statistically significant differences were present in the low and high PTH groups with respect to age (P = 0.011), Ca (P = 0.007), ionized Ca (P = 0.002), P (P = 0.002), ALP (P = 0.001), and 24-h urine Ca (P < 0.01) levels. On the other hand, no difference was detected in creatinine levels (P = 0.062).

When we divided the patients into 2 groups according to vitamin D levels (normal (≥20 ng/mL) and low (<20 ng/mL)), 64% had low vitamin D levels (n = 1417) and 36% had normal vitamin D levels (n = 809). Only 26.4% of the group with low vitamin D levels had high PTH levels (n = 374); 73.6% of the patients had PTH levels of less than 75 pg/mL, and this difference was statistically significant (Table 3).

Of the patients with high PTH levels, 27.2% had imaging such as parathyroid ultrasound and scintigraphy (n = 135). Of these, 66.6% had normal findings (n = 90), 20.6% had adenoma (n = 27), and 12.6% had hyperplasia (n = 17).

Table 3. Comparison between PTH and vitamin D levels.

	Vitamin D <20 ng/mL	Vitamin D ≥20 ng/mL	N
PTH <75 pg/mL	1043 (73.6%)	682 (84.3%)	1725
PTH ≥75 pg/mL	374 (26.4%)	127 (15.7%)	501
	1417 (64%)	809 (36%)	2226

PTH: Parathyroid hormone.

4. Discussion

PTH and vitamin D have a very complex relationship. Increased Ca and vitamin D levels have a negative feedback effect on PTH levels. Although no effects of vitamin D on PTH levels have been observed in in vivo studies, there are studies that suggest a link between the suppression of PTH secretion and increased levels of $1,25(OH)_2D_3$ (13–15).

In order to prevent secondary hyperparathyroidism, increased bone turnover, and bone mineral loss, the minimum vitamin D level is described as 20 ng/mL, and any level below 20 ng/mL is described as vitamin D deficiency. In levels over 30 ng/mL of vitamin D, maximum Ca absorption is obtained; for this reason, vitamin D levels between 20 and 30 ng/mL are described as suboptimal (16–20).

Vitamin D deficiency has been associated with increased risk of osteopenia, osteoporosis, hypertension, cardiovascular disease, infectious diseases, many cancers, autoimmune diseases, and other diseases. In recent years, studies have focused on determining the optimal level of vitamin D (3,16,21–23). Since there is no consensus among authorities about the optimal vitamin D level, we first divided our patients into 2 groups (those having low (<20 ng/mL) and those having normal (≥20 ng/mL) levels), and then into 4 groups (<10 ng/mL, 10–20 ng/mL, 20–30 ng/mL, and >30 ng/mL), conducting statistical analyses in both cases. Of the patients, 64% had vitamin D levels lower than 20 ng/mL, and almost 88% had levels lower than 30 ng/mL.

Vitamin D deficiency is commonly seen in women living far from the Equator (3,16,24,25). Holick showed that geographical location, season, and time of exposure to the sun affect vitamin D synthesis (4). In our study, the average vitamin D level of patients who were diagnosed with secondary hyperparathyroidism was 16.4 ng/mL. Since Ankara is located in a region with long winters, clothing habits may have caused this result. The low vitamin D levels might be explained by most of our patients being women, as in our study the vitamin D levels of women were significantly lower than those of men.

We found statistically significant increasing PTH levels with age. However, among patients with vitamin D levels below 20 ng/mL, only 26.4% had PTH levels of ≥75 pg/mL. This was an unexpected finding. There might be reasons for this other than ethnic and genetic differences. Studies have shown that vitamin D levels may vary according to season, and PTH levels are negatively correlated with vitamin D levels (26). In our study, we found the lowest vitamin D levels in April and the highest vitamin D levels in October, and the difference was statistically significant. On the other hand, we did not find any negative correlation in PTH levels between months. Most of the patients with vitamin D deficiency had normal PTH levels, which might explain the lack of a correlation between month and PTH levels.

Imaging techniques are frequently used in patients with high PTH levels. Parathyroid ultrasonography and scintigraphy are the most commonly used imaging modalities. In our study, 27.2% of patients (n = 135) with high PTH levels received imaging. Most of the patients (66.6%; n = 90) had normal findings. This brings up the question of imaging in patients with high PTH levels. However, we did not group the patients with high levels of PTH and investigate the PTH levels of patients with pathological imaging.

Our study's limitations include the lack of information on comorbidities and lifestyles that may affect vitamin D levels, such as vitamin D usage, clothing, sun exposure, and vitamin D-related drug use. Additionally, this study is retrospective, and as such, further prospective studies with larger patient groups are warranted for verifying our results.

We found that most of the patients with vitamin D deficiency had normal PTH levels, and most of the patients with high levels of PTH had normal imaging results. In order to determine the normal ranges of PTH levels, more studies need to be conducted in our geographical region. Vitamin D replacement in patients with vitamin D deficiency might also preclude high PTH levels, hence preventing unnecessary imaging.

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