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The relationship of pre-operative vitamin D and TSH levels with papillary thyroid cancer

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ABSTRACT

OBJECTIVE: Our goal in this study is to analyze the correlation between papillary thyroid cancer (PTC) with elevated thyroid-stimulating hormone (TSH) levels and deficiency of vitamin D.

METHODS: Patients who underwent thyroidectomy, also with available vitamin D test results preoperatively, were included in the study. The patients were separated into two different categories as having papillary thyroid carcinoma (Group 1), benign diseases (Group 2). According to the TSH (mUI/mL) level and vitamin D values, patients were categorized into four quarters.

RESULTS: Preoperatively, TSH level (mean±SD mUI/mL) was higher in Group 1 (2.04±1.55) compared to Group 2 (1.82±1.94) significantly (p=0.029). Preoperatively, vitamin D levels (mean±SD) were higher in Group 1 (15.88±10.88) than in Group 2 (12.94±10.26) significantly (p=0.011). There was no significant difference between Group 1 and Group 2 according to the vitamin D deficiency (65.5%, 72.8%; respectively (p=0.472)). When categorized with reference to pre-operative vitamin D levels, the proportion of patients in Group 2 and Category 1 was higher significantly (p=0.031).

CONCLUSION: Although the pre-operative TSH level was significantly higher in papillary thyroid carcinoma than benign thyroid diseases, the categorical distributions of the patients according to the TSH value were similar and the TSH values overlapped. Pre-operative mean vitamin D levels were similar in both PTC and benign thyroid disease groups so PTC was not associated with vitamin D deficiency.

Keywords: Papillary thyroid cancer; thyroid-stimulating hormone; vitamin D deficiency.

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A significant increase in the prevalence of both benign and malignant thyroid diseases has been observed, especially after the developments in neck imaging methods [1]. This increase attracts attention both in identification of thyroid nodules and as a result, of thyroid cancers [2].

The marked increase in the incidence of thyroid cancer for the last 3–4 decades is mainly due to the increase in papillary thyroid cancer (PTC). Although the detection of small thyroid tumors with advanced imaging methods contributes significantly to this increase in incidence, this increase cannot be explained only with this fact [2]. Because half of the total increase in PTC incidence is due to the tumors smaller than 1 cm in size, 30% is due to tumors of 1–2 cm and 20% to those of >2 cm [3].

Factors such as exposure to ionized radiation, family history, sex, and obesity known for thyroid cancer are not sufficient to explain this actual increase in incidence [2]. Like the relationship between exposure to flame retardants and PTC, there may still be many patient-related, environmental, and nutritional factors associated with thyroid cancer that remains unknown [2].

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In many observational studies, a relationship between PTC risk and high thyroid-stimulating hormone (TSH) levels was determined [4].

Vitamin D takes the main role in the management of bone mineralization, by coordinating calcium and phosphorus regulation. Although its name is "vitamin D," it is not really a vitamin and it is the precursor of calcitriol, a potent steroid hormone, also known as 1,25-dihydroxyvitamin D3.

Calcitriol regulates multiple signal pathways through nuclear vitamin D receptors (VDRs) and has a potential effect on cancer development and growth with its effect on proliferation, apoptosis, differentiation, inflammation, invasion, angiogenesis, and metastasis [5].

Nuclear VDRs have been found not only in bone and mineralization-related tissues but also in thyroid tissue and in some cancer cells such as breast, prostate, colorectal, and thyroid cancer [6–10].

Cancer cells express CYP21B1 and this enzyme is involved in hydroxylation of 25-hydroxy vitamin D. In addition, it is known that the increase in the production of calcitriol by local synthesis in cancer tissue increases the amount of 25-hydroxy vitamin D in serum.

In the previous studies, the relationship between many human cancers and vitamin D has been examined, and especially low vitamin D level was found to be correlated with colorectal, breast, and prostate cancer [11–13].

In addition, low vitamin D levels at the time of diagnosis were associated with low overall survival in breast cancer, colorectal cancer and lymphoma, and low disease-free survival in breast cancer and lymphoma [14]. Despite all, there are not many studies in the literature that evaluated the relationship between thyroid malignancies and vitamin D.

In the literature, however, the number of studies evaluating the relationship between vitamin D deficiency and thyroid cancer is limited, and the results these studies are inconsistent. Although some studies have reported a significant relationship between low serum vitamin D levels and thyroid cancer [15–19], other studies have reported no relationship [1, 20–23].

In this study, we aimed to evaluate the relationship between PTC and high TSH values and vitamin D deficiency.

Highlight key points

- In a limited number of studies, relationship between papillary thyroid cancer (PTC) and 25-OH-vitamin D3 (D vit) levels were evaluated.
- The relationship between thyroid carcinoma with vitamin D deficiency and TSH levels is still controversial.
- The aim of this study is to evaluate the correlation between PTC with elevated TSH levels and deficiency of vitamin D.
- No association was found between vitamin D deficiency and TSH values.

MATERIALS AND METHODS

Patients

The data of 505 patients operated for thyroid pathology at the Health Sciences University Şişli Etfal Training and Research Hospital between 2012 and 2017 were evaluated retrospectively. For this study, research permission was obtained from University of Health Sciences, Sisli Hamidiye Etfal Training and Research Hospital Ethics Committee on March 08, 2022, numbered 3444. All patients were informed about the use of pre-operative data in scientific studies and their consent was obtained. Patients who were operated for thyroid pathology and whose data could be accessed in regard to their post-operative pathology data and pre-operative thyroid function tests, biochemical data, and vitamin D tests, were included in the study.

Patients with cancers other than PTC, patients with hyperthyroidism, patients using antithyroid drugs, patients with simultaneous hyperparathyroidism, and patients receiving vitamin D therapy were excluded from the study.

Age, sex, pre-operative TSH, fT3, fT4, anti-TPO, anti-Tg, calcium (Ca), phosphorus (P), magnesium (Mg), alkaline phosphatase (ALP), vitamin D, and post-operative histopathological data of patients were collected.

Method

The present study was formed in accordance with STARD (Standards for Reporting of Diagnostic Accuracy Studies) criteria. Patients were divided into two groups as having PTC (Group 1) and benign pathologies (Group 2) according to the histopathological results of thyroid specimens.

According to the TSH level (1.94±1.74 mUI/mL) (min: 0.6-max: 13,38), patients were categorized into

Table 1. Demographic and biochemical properties of two groups

	Group 1 (n=119)	Group 2 (n= 103)	p
Age	46.8±13.8	48.1±12.5	0.428
Sex F/M	92/27	85/18	0.335
Preop vit D (ng/mL)	15.88±10.88	12.94±10.26	0.011
TSH (mU/L)	2.04±1.5	1.82±1.94	0.029
Preop fT3 (ng/L)	3.3 ±0.45	3.2±0.42	0.222
Preop fT4 (ng/L)	1.2±0.31	1.19±0.25	0.988
Preop PTH (pg/mL)	52.9±29.5	52.6±22.6	0.353
Preop Ca (mg/dL)	9.6±0.5	9.5±0.4	0.180
Preop P (mg/dL)	3.4±0.5	3.4±0.5	0.414
Preop Mg (mg/dL)	1.9±0.2	1.9±0.3	0.171
Preop ALP (U/L)	74±22	73±30	0.178
Preop anti-TPO n(±) (%) (IU/mL)	16/80 (16.7)	13/68 (16)	0.539
Preop anti-Tg n(±) (%) (IU/mL)	22/76 (22.4)	17/59 (22.4)	0.569
Chronic lymphocytic thyroiditis n (%)	56 (47.1)	41 (39.8)	0.230

F: Female; M: Male; Preop: Pre-operative; TSH: Thyroid-stimulating hormone; fT3: Free T3; fT4: Free T4; PTH: Parathyroid hormone; Ca: Calcium; P: Phosphorus; Mg: Magnesium; ALP: Alkaline phosphatase; anti-TPO: Anti-thyroid peroxidase; anti-Tg: Anti–thyroglobulin.

four quarters: Category 1 (≤0.71 mUI/mL), Category 2 (0.72–1.53 mUI/mL), Category 3 (1.54–2.49 mUI/mL), and Category 4 (≥2,5 mUI/mL).

Vitamin D (serum 25-hydroxy vitamin D3 [25-(OH) D3]) insufficiency was defined as the values between 21 and 29 ng/mL (525–725 nmol/liter) and vitamin D deficiency was defined as the value of <20 ng/mL (50 nmol/liter) [24].

Patients were divided into four 25% sections according to their pre-operative vitamin D values: Category 1 (≤6.42 ng/mL), Category 2 (6.43–10.38 ng/mL), Category 3 (10.39–22.29 ng/mL), and Category 4 (≥22.39 ng/mL).

Anti-TPO (0–35 IU/mL) was considered positive when it was >35 IU/mL and anti-Tg (0–40 IU/mL) was considered positive when it was >40 IU/mL.

Statistical Analysis

Chi-square tests and Mann–Whitney U-tests were used for comparisons between groups. P<0.05 was defined significant.

The correlation of serum vitamin D with age, antiTPO, antiTg, TSH, fT4, fT3 and presence of chronic thyroiditis was evaluated by Pearson Correlation test.

Statistical analysis of all data was performed using SPSS (the Statistical Packages for the Social Sciences, software, edition 21, SPSS Inc. Chicago, USA).

RESULTS

Two hundred and twenty-two out of 505 patients operated during the study period, with a mean age of 47.4±13.2 (17–83) were included in the study. One hundred and nineteen (female: 92, male: 27) of the patients were in Group 1, 103 (female: 85 male: 18) were in Group 2.

There was no significant difference between the groups in terms of age, sex, pre-operative Ca, P, PTH, ALP, pre-operative anti-Tg and anti-TPO positivity, and the presence of lymphocytic thyroiditis in the pathological examination of the thyroid (Table 1).

Pre-operative TSH level (mean±SD (median) mUI/mL) was significantly higher in Group 1 compared to Group 2 (2.04±1.5 vs. 1.82±1.94; p=0.029). Distribution rates of patients in Groups 1 and 2 according to TSH values were 17.9% and 33% in Category 1, 26.5% and 24.3% in Category 2, 29.1% and 19.4% in Category 3, and 26.5% and 23.3% in Category 4, respectively, with no significant difference between the groups (p=0.061) (Table 2).

Table 2. Distribution of TSH levels by quartiles

Quartiles	0–0.71 25%	0.72–1.53 50%	1.54–2.49 75%	≥2.5 100%	p score
TSH levels					0.061
Group 1, n=117	17.9	26.5	29.1	26.5	
Group 2, n=103	34 (33)	25 (24.3)	20 (19.4)	24 (23.3)	

TSH: Thyroid-stimulating hormone.

Table 3. Distribution of pre-operative vitamin D levels by quartiles

Quartiles	0–6.42 25%	6.43–10.38 50%	10.39–22.29 75%	≥22.30 100%	p score
Vitamin D					**0.031**
Group 1, n=119	16.8	26.9	28.6	27.7	
Group 2, n=103	34	23.3	21.4	21.4	

Pre-operative vitamin D levels were found to be significantly higher in Group 1 than in Group 2 (p=0.011). Number of patients with vitamin D deficiency, vitamin D insufficiency, and adequate vitamin D levels in Group 1 were 78 (65.5%), 26 (21.8%) and 15 (12.6%), and in Group 2, 75 (72.8%), 19 (18.4%), and 9 (8.7%), respectively. There was no significant difference between the groups in terms of vitamin D values (p=0.472).

When categorized according to pre-operative vitamin D values by quartiles, the distribution rates of patients in Group 1 and Group 2 were as follows: 16.8% and 33% in Category 1, 26.9% and 23.3% in Category 2, 28.6% and 21.4% in Category 3, and 27.7% and 21.4% in Category 4, and the rate of patients was significantly higher in Group 2, Category 1 (p=0.031). Vitamin D did not show any correlation with age (p=0.93), pre-operative TSH (p=0.522), pre-operative fT4 (p=0.616), pre-operative anti-TPO (p=0.864), pre-operative anti-Tg (p=0.974), and presence of lymphocytic thyroiditis (p=0.190) (Table 3).

DISCUSSION

Incidence of PTC is increasing worldwide [2]. Except for known risk factors for thyroid cancer, high TSH values and D vitamin deficiency are factors that have been evaluated in some studies in terms of risk and prognosis of thyroid cancer. The importance of both high TSH levels and vitamin D deficiency is that both factors are interchangeable with treatment.

In our study, pre-operative TSH level was significantly higher in the PTC group than in the benign thyroid diseases group (2.04±1.5 vs. 1.82±1.94; p=0.029, respectively). Distribution rates of patients in Groups 1 and 2 according to TSH values were 17.9% and 33% in Category 1, 26.5% and 24.3% in Category 2, 29.1% and 19.4% in Category 3, and 26.5% and 23.3% in Category 4, respectively, with no significant difference between groups (p=0.061). Therefore, although there is a difference in the TSH level, it is unlikely to use the TSH value to predict PTC as the TSH values of the two groups overlap.

Some studies have reported a relationship between high TSH levels and an increased risk of thyroid cancer. A non-linear positive relationship was detected between thyroid cancer diagnosis and serum TSH levels in the meta-analysis of McLeod et al. [4], and higher seum TSH levels were found to be associated with an increased risk of thyroid cancer. A non-linear relationship between TSH levels higher than 1.23 mUI/mL and cancer has been stated. In another study, high TSH level independent of age was found to correlate with the incidence of thyroid cancer [25].

In the study of Danilovic et al. [1], median TSH levels were shown to be higher in cases of malignancy, and 32% of patients with thyroid cancer had serum TSH levels of >2.4 mUI/mL (patients on the top quartile); this rate was higher than patients with benign thyroid disease (19.5%) (p<0.02). The risk of thyroid cancer was 2.4 times higher in patients with higher TSH values. Swan et al. [26] reported that TSH levels in patients with differentiated thyroid cancer were higher than patients with benign nodular disease, but this value was not an appropriate biomarker for thyroid cancer due to the small difference in median TSH values between the malignant and benign diseases and high level of overlapping of the values.

Despite this relationship, the relationship between thyroid carcinogenesis and cancer biology and TSH level is still not fully explained. In a recent study, high TSH levels were found to be associated with the progression of papillary microcarcinomas in active surveillance, and the cutoff value for progression was found as 2.5 mU/L [27].

The relationship between vitamin D deficiency and thyroid cancer is more controversial compared to the relationship with high TSH levels.

In our study, pre-operative vitamin D levels were significantly higher in patients with PTC than in patients with benign thyroid disease (15.88±10.88 ng/mL vs. 12.94±10.26 ng/mL, p=0.011). When the study group was divided into four 25% sections according to their pre-operative vitamin D values, the values were as follows: Category 1 (≤6.42 ng/mL), Category 2 (between 6.43 and 10.38 ng/mL), Category 3 (between 10.39 and 22.29 ng/mL), and Category 4 (≥22.39 ng/mL). Almost all patients up to the 3rd quartile were patients with D vitamin deficiency. Vitamin D deficiency is a common health problem not only in our country but globally [28].

When categorized according to pre-operative vitamin D values, the distribution rates of patients with PTC and benign thyroid disease in Group 1 and Group 2 were as follows: 16.8% and 33% in Category 1, 26.9% and 23.3% in Category 2, 28.6% and 21.4% in Category 3, and 27.7% and 21.4% in Category 4, and the rate of patients was significantly higher in the benign thyroid disease group, Category 1 (p=0.031). Although benign thyroid disease is seen at a higher rate in patients with very low vitamin D levels, these levels are not a feature that can make a significant contribution to the discrimination of patients. When these patients were evaluated in terms of vitamin D deficiency, this situation was common in both groups, and there was vitamin D deficiency in 78 (65.5%) of patients with PTC and in 75 (72.8%) of patients with benign thyroid disease; and the rates were similar (p=0.472). In addition, in our study, vitamin D did not show any correlation with age (p=0.93), pre-operative TSH (p=0.522), pre-operative fT4 (p=0.616), pre-operative anti-TPO (p=0.864), pre-operative anti-Tg (p=0.974), and presence of lymphocytic thyroiditis (p=0,190).

There are studies in the literature that examined the level of vitamin D and thyroid cancer risk and the results are incompatible.

Laney et al. [21] found vitamin D deficiency similar between patients with thyroid nodules and thyroid cancer, but at higher rates than the general population.

In other studies evaluating patients with benign thyroid disease and patients with thyroid cancer, no relationship was found between 25-OH vitamin D3 levels and the risk of thyroid cancer [1, 23].

Similarly, no relation was found between the prevalence of thyroid cancer and serum 25-OH vitamin D levels in euthyroid individuals without autoimmune thyroid disease [22].

However, in other studies, a significant relationship between vitamin D deficiency and differentiated thyroid cancer has been detected and patients with vitamin D deficiency have been reported to have a higher risk of thyroid malignancy [16, 18, 19]. Roskies et al. [16] found the relative risk to be 2 times higher than the patients with adequate vitamin D.

In the meta-analysis in which 14 case-controlled studies were evaluated, pre-operative serum 25-OH vitamin D3 levels were found lower in patients with thyroid cancer than in the control group, and the risk was found to be 30% higher in those with D vitamin deficiency (OR: 1.30, 95% CI 1.00–1.69, p=0.05) [29].

Although 25-OH vitaminD3 level is used as a marker to assess the status of vitamin D in the body, some studies have measured active hormone 1.25-OH vitamin D3.

In studies, although pre-operative 25-OH vitamin D3 levels were found to be similar between thyroid cancer patients and the control group, 1,25-OH vitamin D3 levels were lower in the thyroid cancer group [15, 17, 30].

Zhang et al. [31] detected 1,25-OH vitamin D3 levels lower in patients with PTC than in patients with nodular goiter, and claim that this may be a new potential biomarker.

The debate about the role of vitamin D deficiency in carcinogenesis continues not only in thyroid cancer but also in other cancers.

An inverse relationship was found between the pre-operative 25-OH vitamin D3 level and the risk of colorectal cancer in the Western European population [32]. In another larger study, a higher 25-OH vitamin D3 level in circulation was reported to be associated with a statistically significant lower risk of colorectal cancer in the entire population and women, but with a not statistically significant lower risk in men [12].

In breast cancer, while a meta-analysis stated that vitamin D supplementation in postmenopausal women did not decrease the incidence of breast cancer and vitamin D level was not associated with breast cancer risk [33]. In another meta-analysis in which prospective studies were evaluated, no relationship was found between blood 25-OH vitamin D level and breast cancer risk in premenopausal women, whereas in postmenopausal women, there was a nonlinear inverse relationship in the dose-response model and it was shown that breast cancer risk decreased with increasing vitamin D level [34].

In the meta-analysis of 50 studies evaluating blood vitamin D levels in breast cancer and 20 studies evaluating vitamin D intake, an inverse relationship was found between breast cancer [11]. In a large case–control study, prostate cancer risk was associated with both low (</= 19 nmol/l) and high (>/=80 nmol/l) serum vitamin D levels [13].

According to the latest international prospective study data, higher 25-OH vitamin D levels have been found to be associated with an increased risk of non-aggressive prostate cancer, but no association with aggressive disease [35].

Since our study was retrospective, there were no pre-operative vitamin D levels available in all patients; thus, only some of the patients operated during this period could be included in the study. Ignoring seasonal vitamin D changes in patients in the study can be considered as a limitation. However, in another study, although there was a significant seasonal difference between the summer and winter vitamin D3 levels in healthy individuals, vitamin D3 levels were seasonally similar in patients with PTC and follicular thyroid cancer [17].

Conclusion

There was no correlation between vitamin D deficiency and TSH levels in our study. Although the pre-operative TSH level was significantly higher in PTC than in benign thyroid diseases, the categorical distributions of the patients according to the TSH values were similar and the TSH values overlapped. Pre-operative mean vitamin D levels were lower in patients with benign thyroid disease than in patients with PTC, and although the rate of patients with benign thyroid disease was higher in the lowest quartile, vitamin D deficiency was high and similar in both PTC and benign thyroid disease groups, and PTC was not associated with vitamin D deficiency.

Ethics Committee Approval: The Sisli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 08.03.2022, number: 3444).

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