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Comparison of vitamin D levels in euthyroidindividuals with and without thyroid nodule

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Abstract

Thyroid nodules are frequently observed in the thyroid gland, with a malignancy rate of less than 5%. The etiology of nodule formation remains unclear, and various hypotheses have been proposed. Vitamin D, known to influence cell turnover, may also play a role in the development of thyroid nodules. This study aims to investigate the association between vitamin D deficiency and thyroid nodule formation. Blood samples were collected from individuals categorized into two groups based on the presence of thyroid nodules. 100 patients with thyroid nodules detected by ultrasonography and 100 individuals with no thyroid nodules were included in the study. The 25-hydroxyvitamin D [25(OH)D3] levels were measured in a single session. The mean 25(OH)D3 levels were 15.39±9.1 ng/ml in the patient group and 13.33±7.1 ng/ml in the control group. Vitamin D deficiency was identified in 72% of the patient group and 82% of the control group. No significant correlation was found between 25(OH)D3 levels and the presence of thyroid nodules. Further research is needed to elucidate this relationship.

Keywords: Thyroid cancer, vitamin D deficiency, nodule

Introduction

Thyroid nodules usually occur with hyperplasia and/or hypertrophy of thyrocytes and can be distinguished from the thyroid parenchyma by ultrasonography and palpation. Thyroid nodules are very common, and their prevalence varies between 20–76% with high-resolution ultrasonography [1,2]. It is of clinical importance due to the possibility of cancer. It is likely that genetic and some environmental factors play a role in thyroid oncogenesis. However, it is not yet clear how thyroid nodules develop. It is also unknown why nodules can be solitary or multiple [3].

Vitamin D has important effects on calcium metabolism in the human body. Studies conducted in recent years have shown the presence of vitamin D receptors (VDR) in approximately 30 different tissues in the human body, and it has been understood that vitamin D has many different functions through these receptors, from cell differentiation [4]. Meanwhile, due to the antiproliferative effects of vitamin D on cells, it is well known that deficiency of this vitamin may be a risk factor in the development of more than 20 cancers, especially thyroid cancer, colon, prostate, ovarian, breast, and esophageal cancers [5-10].

Considering that vitamin D deficiency may be a risk factor for some cancers and thyroid nodules are considered precancerous lesions, we thought that this situation may also affect the development of nodules. For this purpose, 100 patients with thyroid nodules detected by ultrasonography and 100 individuals with no thyroid nodules were included in the study. It was investigated whether there was a relationship among vitamin D levels and the presence of thyroid nodules. In addition, it was also evaluated whether there is a correlation between vitamin D level and thyroid gland volume, nodule volume and the number of nodules.

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Material and Methods

Individuals who applied to the endocrinology clinic between May and November 2013 and were diagnosed with thyroid nodule on ultrasonography (USG) were included in the study. A total of 200 individuals were considered in two groups. All 200 people were euthyroid. It was aimed to compare the 25-hydroxyvitamin D [25(OH)D3] levels of the two groups. This thesis study was carried out with the approval of Necmettin Erbakan University Meram Medical Faculty 'Non-Interventional Ethics Committee' dated 10.10.2012 and protocol number 2012/54.

The control group was planned to be 100 people, and the patient group was to be 100 people. Blood samples were taken from each patient into potassium EDTA tubes to run 25(OH)D3 and centrifuged in the 'NF 400' brand centrifuge device at 3000 rpm for 10 minutes. The plasma samples were preserved in the 'Haier' brand cooler at -80 degrees Celsius. Vitamin D levels of both groups were studied at Meram Medical Faculty Hospital Biochemistry Laboratory with project number 131518004, financed by Necmettin Erbakan University Scientific Research Projects Unit. During outpatient clinic controls, thyroid stimulating hormone (TSH), serum-free T3 (fT3), free T4 (fT4), thyroid microsomal antibody (TMAB), antithyroglobulin (AntiTG), phosphorus (P), calcium (Ca), alkaline phosphatase (ALP), and parathorman (PTH) were collected.

Each patient's age, gender, daily sunbathing time (<30 min, 30-60 min, 60-120 min, and >120 min), clothing style (open or closed clothing), sunscreen use and the months in which blood samples were taken were recorded. Patients meeting any of the exclusion criteria listed below were excluded from the study. The study was conducted prospectively.

Exclusion Criteria

1. Those who use vitamin D preparations,
2. Those who use drugs that affect vitamin D metabolism (glucocorticoids, antiepileptics),
3. Those with calcium metabolism disorders,
4. Those with chronic kidney failure,
5. Those with chronic liver disease,
6. Patients who are bedridden due to any disease,
7. Those who are not between the ages of 18-65,
8. Pregnant or breastfeeding women,
9. Those diagnosed with chronic granulomatous disease,
10. Patients with nephrotic syndrome,
11. Obese people,
12. Those with thyroid dysfunction,
13. Those who do not consent.

Thyroid USG was performed on all patients using the GE Medical Systems LOGIQ P5 device with an 11L probe. The patient was placed supine, and the neck was extended. The structure of the thyroid tissue and the being of nodules were examined, and the volumes of the right and left lobes of the thyroid gland were measured in three dimensions, and their volumes were calculated. The formula anteroposterior diameter x Lateral diameter x Longitudinal diameter /0.5' was used in volume measurements [11]. The structure (solid, cystic, mixed), echogenicity, anterior-posterior, transverse, and longitudinal diameters of the detected thyroid nodules were measured, and their volumes were calculated and recorded. When a thyroid nodule was detected, a fine needle aspiration biopsy was performed with a 22 gauge, 2.8 cm long needle and a 10 cc syringe, as indicated. The same specialist performed all USGs.

Electrochemiluminescence immunoassay and spectrophotometric methods were used for all in vitro analyses. 25(OH)D3 level was studied with the 'Tandem Gold LC-MS/MS' (liquid chromatography-mass spectrometry) analyzer on a Zivak brand device. The reference range and unit of the studied parameters are stated in Table 1. The reference range and units of the parameters were specified according to the data from Meram Medical Faculty Hospital Biochemistry Laboratory (Table 1). Vitamin D status according to serum 25(OH)D3 level was evaluated as four categories (<10 ng/ml: Severe Vitamin D deficiency, 10-20 ng/ml: Vitamin D insufficiency, 20-30 ng/ml: Vitamin D deficiency, >30 ng/ml: sufficient) [12].

Table 1. The reference range and unit of the studied parameters

Parameters	The reference range	Unit
TSH	0.34-5.6	µIU/ml
fT3	2.5-3.9	Pg/ml
fT4	0.61-1.12	ng/dl
TMAB	0-9: negative, >9: positive	IU/ml
AntiTG	0-40: negative, >40: positive	IU/ml
Ca	8.4-10.2	mg/dl
P	2.3-4.7	mg/dl
ALP	>20 age, man: 40-150 >15 age, women: 40-150	u/l
PTH	12-88	pg/ml

*TSH: thyroid stimulating hormone, fT3: serum-free T3, fT4: serum free T4, TMAB: thyroid microsomal antibody, AntiTG: antithyroglobulin, P: phosphorus, Ca: calcium, ALP: alkaline phosphatase, PTH: parathorman

Statistical Analysis

SPSS 18.0 computer program was used for statistical evaluation. Descriptive findings are shown as mean and standard deviation in continuous data and as numbers and percentages in categorical data. Student-t-test was used for comparisons between groups. The chi-square test was used to compare categorical data. The relationship between the variables was examined with Pearson correlation. ANOVA test was used for multiple group comparisons. $P<0.05$ was accepted as the significance level for all comparisons.

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Results

The patient and control groups consisted of 100 individulas separately. 88 of the patient group and 86 of the other group consisted of women. The mean ages of the patient and control groups were 44.4±10.9 (20–65) and 33.3±10.05 (18–61), respectively.

The patient group's mean 25(OH)D3 was 15.39±9.1 ng/ml, and that of the control group was 13.33±7.1 ng/ml. Based on the threshold value >30 ng/ml for an adequate 25(OH)D3 level, an adequate level of 25(OH)D3 was detected in only 11% of the patient group and 6% of the other group (Table 2). As the two groups were compared, the average calcium level was higher in the patient group (p=0.036), while the average phosphorus level was also higher in the control group (p=0.043). TSH level was lower in the patient group (p=0.05). When ft3 and ft4 levels were compared, these values were higher in the patient group (p=0.026) (Table 3).

Table 2. Vitamin D status according to 25(OH)D3 level and 25(OH)D3 level of groups

Vitamin D deficiency or sufficiency according to serum 25(OH)D3 level	25(OH)D3 (ng/ml)	Patient group (n=100)		Control group (n=100)	
		n	%	n	%
Severe deficiency	<10	35	35	44	44
Vitamin D deficiency	10-20	37	37	38	38
Vitamin D insufficiency	20-30	17	17	12	12
Sufficient	>30	11	11	6	6

*25(OH)D3: Vitamin D

Table 3. Comparison of laboratory values of the groups

Parameters	Patient group (n=100)	Control group (n=100)	P value
25(OH)D3 (ng/ml)	15.39±9.1	13.33±7.1	Not significant
Ca+2 (mg/dL)	9.33±0.4	9.19±0.4	0.036
P+3 (mg/dL)	3.58±0.4	3.75±0.6	0.043
ALP (u/L)	69.92±19.4	70.15±58.0	Not significant
PTH (pg/mL)	49.53±26.4	51.57±35.7	Not significant
TSH (µIU/ml)	1.58±1.1	1.89±0.9	0.050
fT3 (pg/mL)	3.13±0.3	3.09±0.4	Not significant
fT4 (ng/mL)	0.85±0.1	0.80±0.1	0.026

* 25(OH)D3: Vitamin D, Ca: calcium, P: phosphorus, ALP: alkaline phosphatase, PTH: parathorman, TSH: thyroid stimulating hormone, fT3: Serum-free T3, fT4: Serum free T4

When 25(OH)D3 levels were compared by gender in both groups, the average 25(OH)D3 level was detected to be higher in the male gender (p<0.001). When 25(OH)D3 levels were compared in both groups according to clothing style, the average 25(OH) D3 level was found to be higher in those with light clothing, and this was statistically significant (p<0.001). When sunscreen use and 25(OH)D3 were compared in both groups, no difference was detected between those who used and those who did not.

25(OH)D3 levels, age, thyroid volume of two groups; No statistically significant correlation was detected when compared with nodule volume and number of nodules in the patient group.

When the echogenicity of the thyroid gland parenchyma was examined, it was seen that 35.1% of the patient group and 25% of the other group were heterogeneous. The groups were similar in terms of anti-TG and TMAB positivity. Thyroid volume was 17.8±15.7 cm^3 in the patient group, and 8.4±3.7 cm^3 in the other group. This dissmilarity was significant (p<0.001).

72 patients in the patient group had solitary nodules, and 28 had multinodules. The number of patients with thyroid nodules who underwent biopsy was 81. Biopsy was performed on 2 nodules in 17 of these patients and from 3 nodules in 8 patients. The biopsy results of these patients were insufficient material in 4 patients

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(4.9%), benign cytology in 72 patients (88.9%), suspicious for malignancy in 4 patients (4.9%), and malignant cytology in 1 patient (1.1%).

Operations were planned for a total of 8 patients who had pressure symptoms and whose biopsy results were reported as malignant or suspicious of malignancy. Postoperative pathology results of 5 patients (62.5%) were reported as benign, and 3 (37.5%) were reported as malignant (thyroid papillary carcinoma).

The postoperative pathology result of 1 of 4 patients with insufficient biopsy results was reported as malignant. Postoperative pathology results of the other 3 patients were not available. Cytology results were reported as benign findings in all patients taking biopsies from the second and third nodules. The cancer rate was calculated as 3.70% in 81 patients who underwent biopsy.

Discussion

Our study found no significant difference when vitamin D levels were compared in the individuals with thyroid nodules and the other group. Likewise, no correlation was detected among vitamin D level and age, gender, number of nodules, thyroid gland volume and nodule volume. In this study, 25(OH)D3 levels were lower in women in both groups. Moreover, adequate vitamin D levels were very low in the patient and control groups (11% and 6%, respectively). This may be explained by the fact that women are more numerous in both groups, mostly adopt a closed-dress style, and therefore cannot sunbathe adequately. Similarly, the low vitamin D level in both groups may have made it difficult to evaluate its relationship with thyroid nodules.

Studies conducted in recent years claim that vitamin D deficiency may be a risk factor about thyroid cancer [13-16]. In their retrospective research, Roskies and colleagues discussed patients who were operated on with suspicion of thyroid cancer. They divided these patients into two groups, vitamin D deficient and vitamin D sufficient, by their preoperative 25(OH)D3 level. When the postoperative pathology results of the patients were examined, differentiated thyroid cancer was detected in 75% (9/12) of the vitamin D-deficient group. In comparison, differentiated thyroid cancer was detected in 37.5% (33/88) of the vitamin D-sufficient group. Based on this study, they claimed that this vitamin deficiency may be a correctable risk factor about developing thyroid cancer [10]. Yet, this study was conducted retrospectively, and no control group in the study was healthy or did not have thyroid disease. Laney and colleagues compared the 25(OH)D3 levels of 42 patients with thyroid nodules, 45 patients diagnosed with thyroid cancer in remission, and 24 patients with active thyroid cancer. They did not detect any difference between the groups in terms of 25(OH)D3 levels. However, vitamin D levels were lower in all three groups compared to the normal population [17]. Yet, in this study, the existing groups were not compared with the healthy control group without thyroid nodules or thyroid disease. In our study, 100 euthyroid individuals with thyroid nodules and 100 healthy euthyroid individuals without thyroid nodules were included. No statistically significant difference was detected when the 25(OH)D3 levels of the groups were compared. However, considering 30 ng/ml as the threshold value, vitamin D deficiency was detected in 89% of the patient group and 94% of the control group. Although this rate of 89% suggests that vitamin D deficiency may have a role in developing thyroid nodules, the high rate of vitamin D deficiency in the control group prevents the findings from being interpreted this way. Since both thyroid nodule development and vitamin D deficiency are affected by many factors, the significant difference we expected may not have been detected.

A handful of studies have been conducted on comparing vitamin D deficiency with thyroid gland volume. Again, there is no published study on the relationship between vitamin D deficiency and the presence of thyroid nodules or nodule volüme [18]. In the research managed by Yasuda et al., they compared the 25(OH) D3 levels and thyroid volume of 26 new-onset Graves patients and 48 euthyroid, antiTPO, and antiTg antibody negative control groups. Both groups consisted entirely of women. 25(OH)D3 level was lower in the patient group. The average 25(OH)D3 level of the patient group was 14.4±4.9 ng/ml, while that of the control group was 17.1±4.1 ng/ml ($p<0.05$). At the same time, 25(OH)D3 level and thyroid volume were negatively correlated. While the average thyroid volume of the patient group was 36.5±19.4 cm^3, the average thyroid volume of the control group was 15.5±8.2 cm^3 ($p<0.001$) [19]. In our study, the average thyroid volume of the patient group was higher and no negative correlation was detected between thyroid volume and 25(OH) D3 level. This was probably related to both groups' low 25(OH) D3 levels. The higher thyroid volume of the patient group was associated with nodules.

The weak points of our study are that it was single-centered, conducted in a region where Vitamin D deficiency is common, that the majority of the patient and the other groups were women, and that the Vitamin D level was very low in the groups.

Conclusion

As a result, no relationship was detected between vitamin D level and nodular thyroid disease in this study. The volunteers in the study lived in a single region of Türkiye, and their vitamin D levels were lower than those of other studies [20]. This may be due to the sociocultural structure and geographical location of Konya province. Further studies should be conducted to determine whether vitamin D deficiency plays a role in the development of thyroid nodules.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

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Ethical Approval
This thesis study was carried out with the approval of Necmettin Erbakan University Meram Medical Faculty 'Non-Interventional Ethics Committee' dated 10.10.2012 and protocol number 2012/54.

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