

Benign nodules of the thyroid gland and 25-hydroxy-vitamin D levels in euthyroid patients

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BACKGROUND: The presence of nodules in the thyroid gland is common in iodine-deficient areas of the world. Recently, vitamin D levels were found to be lower than normal and sometimes deficient in malignant nodules of the thyroid.

OBJECTIVE: Evaluate the relationship between the serum vitamin D levels and benign thyroid nodules in euthyroid patients.

DESIGN: Cross-sectional.

SETTING: Tertiary care center in Turkey.

PATIENTS AND METHODS: Patients referred to the general surgery outpatient clinic and diagnosed with thyroid nodules were the study group. The control group consisted of healthy individuals without thyroid nodules. Age, BMI, thyroid ultrasonography, serum 25-hydroxy-vitamin D, free T3, free T4, thyroid stimulating hormone, calcium, magnesium, phosphorous, total protein, albumin, glucose, creatinine levels and glomerular filtration rate (GFR) were compared between groups.

MAIN OUTCOME MEASURE: Serum 25-hydroxy-vitamin D levels and size of the thyroid nodules.

SAMPLE SIZE AND CHARACTERISTICS: Of 849 individuals, 453 were patients with thyroid nodules and 396 were healthy individuals.

RESULTS: The mean serum vitamin D levels of patients with thyroid nodules were significantly lower than controls ($P < .001$). Serum vitamin D levels along with serum total protein levels and eGFR were independent variables associated with the presence of a thyroid nodule ($P < .001$, $p = .005$ and $P = .017$, respectively).

CONCLUSION: These findings suggest vitamin D deficiency might be one of the pathophysiologic factors in development of thyroid nodules.

LIMITATION: Single-center and possible information bias.

CONFLICTS OF INTEREST: None.

The prevalence of nodules in the thyroid gland, a common condition in iodine-deficient regions of the world, is on the rise.¹ Among endocrine diseases thyroid gland nodules are more often encountered than other conditions and are at least 4 times more frequent in women than in men.² Although the increase in thyroid nodule incidence has been attributed to factors like age, gender and iodine deficiency,^{3,4} recent research has demonstrated that serum thyroid stimulating hormone (TSH) levels, genetic factors, obesity, insulin resistance and metabolic syndrome have contributions in the process of nodule development in the thyroid gland.⁵ Of these factors, TSH is the major responsible mitotic factor and therefore due to serum TSH elevations, nodules are detected in more than half of the population that live in an iodine-deficient environment and consume an iodine-deficient diet.^{6,7} Additionally, it has been suggested that nutritional deficiencies, exposure to various toxic agents, changes in eating habits, lifestyle and environmental pollution might be contributing factors for the increase in incidence of thyroid nodules.⁸

Ultrasonography (USG) is the most sensitive diagnostic tool in detection and treatment of thyroid gland nodules.⁹ Early detection of thyroid nodules is essential since they possess a potential for malignant transformation with a probability of 7-15% and USG is the preferred tool for diagnosis.^{7,10} 25-hydroxy-vitamin D is a lipid-soluble precursor of steroid hormones and plays a part in calcium, phosphorus and bone mineralization.^{11,12} Besides, vitamin D is a major part of many cellular processes like reproduction, transformation, apoptosis, inflammation, angiogenesis and invasion. Vitamin D prevents cellular reproduction and metastasis by regulating the mRNA coding of malignant cells,¹³ but it is hard to identify any relationship between thyroid nodules and vitamin D deficiency. However, vitamin D might play a critical prognostic role in papillary thyroid cancer.¹⁴ Lower than normal serum 25-hydroxyvitamin D levels have been shown to be associated with increasing thyroid cancer risk.^{2,15}

In a retrospective cohort study vitamin D levels in patients with thyroid cancer were deficient.¹⁶ A recent meta-analysis found that vitamin D deficiency might be a risk factor for thyroid cancer.¹⁷ In another study, vitamin D was significantly lower in both thyroid nodules and in thyroid cancer compared to the healthy population.¹⁸ Additionally, thyroid nodules are less frequent in populations with normal vitamin D levels.¹⁹ Despite the relatively vast medical literature derived from observational studies relating vitamin D and thyroid autoimmunity and cancer, the effects of vitamin D supplementation on these conditions need further study.²⁰

Many studies have reported a negative relationship between vitamin D levels and severity of disease as well as mortality rates during the COVID-19 pandemic.²¹ The rapid increase in thyroid nodule incidence parallels a decrease in vitamin D levels in society. The aim of this study was to evaluate the serum vitamin D levels in euthyroid patients with thyroid nodules.

PATIENTS AND METHODS

This cross-sectional study was conducted in Niğde Ömer Halisdemir University Training and Research Hospital, Niğde, Turkey, between 3 January 2016 to 3 January 2020. The study protocol was approved by the university ethics committee (26 November 2020-2020/66) and was conducted according to the Helsinki declaration.

Patients referred to the general surgery outpatient clinic and diagnosed as having thyroid nodules constituted the study group. The control group consisted of healthy individuals without thyroid nodules. Using the electronic database of our hospital, we collected data on serum vitamin D levels along with other laboratory parameters at the time of thyroid USG, which was within the 6 months prior to the physical examination. Thyroid USG results were recorded for each patient. Individuals younger than 18 and older than 80 years, patients with hypothyroidism, hyperthyroidism, Hashimoto thyroiditis, previous thyroid surgery, thyroid malignancy, parathyroid adenoma and previous gastrointestinal surgery were excluded. Individuals between 18-80 years old with thyroid nodules who did not use vitamin D supplements and who did not have previous thyroid surgery or additional thyroid disease were included in the study. The height and weight of each subject and the presence of any treatment for thyroid disease or previous thyroid surgery were noted for each patient. The presence of any nodules in the thyroid gland, the characteristics of the nodule (cystic, solid, solitary, multiple, benign, malignant), the size of the nodule and the presence of thyroiditis were obtained by USG. In patients with a suspicion of malignancy from the USG, fine needle aspiration biopsy had been performed. Only patients with benign pathological findings were included in the analysis. The control group consisted of patients referred with thyroid symptoms who had no thyroid nodules either on physical examination or on thyroid USG. For both groups 25-hydroxy-vitamin D levels, free T3, free T4, TSH, calcium, magnesium, phosphorus, total protein, albumin, glucose, creatinine and glomerular filtration rate were recorded.

The descriptive statistics are expressed as mean and standard deviation for continuous variables and

as percent and range for categorical variables. The descriptive characteristics were compared with either the t test or Mann-Whitney U test where appropriate for the distribution of the data. The categorical variables were compared with Pearson χ^2 test or the Fisher Exact test as appropriate. The Pearson correlation test was used to test the relationship between continuous variables. In order to determine any independent parameters associated with the binary dependent variable, the presence of thyroid nodule, multiple logistic regression was used. For statistical analysis IBM SPSS Statistics 22 version (Armonk, New York, United States: IBM Corp) was used. *P* values $<.05$ was accepted as statistically significant. A post hoc power analysis was performed by using G*Power 3.1^{22,23} to test the difference between the two independent group means using a two-tailed test with a high effect size ($d=0.99$) and an alpha of .05. A sample size of 453 in the nodule group and a sample size of 396 in the control group were adequate to detect the difference of serum D vitamin levels between euthyroid patients with and without thyroid nodules (the power was over 80%, the scientifically acceptable value).

RESULTS

We retrieved 849 patient records (453 in the nodule group and 396 in the control group) from the electronic medical records. There were no statistically significant differences in gender and age between the groups, but BMI was greater in the nodule group ($P=.001$) (Table 1). Gender distribution and BMI were similar among patients with different nodule types (Table 2). Patients with solitary nodules were significantly younger than patients with multiple nodules ($P=.03$), while mean age was similar between patients with cystic nodules and solid nodules ($P=.506$). The mean (SD) diameter of the nodule in the study group was 1.33 (1.02) centimeters. Although the mean diameter of the nodule was significantly higher in patients with multiple nodules than in patients with solitary nodules ($P=.0001$), the diameter was similar in patients with cystic and solid nodules. There was no detectable correlation between the diameter of the nodule and the vitamin D levels ($p=.561$; $r=0.027$) (Figure 1). In the nodule group the mean level of vitamin D, serum total protein and the estimated GFR differed between groups (Table 3). The effect size in the vitamin D level difference was almost twice the standard deviation. In the logistic regression model vitamin D levels, serum total protein levels and eGFR of the patients were independently associated with the presence of a thyroid nodule ($P<.001$, $P=.005$ and $P=.017$, respectively) (Table 4).

DISCUSSION

In this study we compared the serum vitamin D levels of euthyroid patients with nodules with individuals without thyroid nodules. The gender and age distributions were balanced in both groups. Serum vitamin D levels of patients with thyroid nodules were significantly lower than in patients without nodules. Serum vitamin D levels along with serum total protein levels and eGFR were independent variables associated with the presence of a thyroid nodule. Additionally, BMI, GFR and serum total protein levels were higher in the thyroid nodule group.

In limited number of studies, serum vitamin D levels of patients with thyroid nodules were lower than normal values.^{19,24} There are various studies reporting decreased serum vitamin D levels in patients with malignant masses.^{25,26} In a recent study about thyroid masses, the authors reported lower levels of vitamin D in patients with nodules in comparison with controls.¹⁸ It is important to note that in the same study serum vitamin D levels were not different in patients with malignant or benign masses of the thyroid.¹⁸

In vitro and animal studies have demonstrated that vitamin D has preventive effects on malignant masses by provoking cellular differentiation and inhibiting proliferation and invasion.²⁷ In vitro studies found that vitamin D binds to the vitamin D receptor gene (VDR) and regulates the genes responsible for cellular proliferation.²⁸ In thyroid nodules, by binding VDR receptors, vitamin D affects the expression of single nucleotide polymorphism and might result in regulation in cellular functions and morphology of thyrocyte.²⁹ There are a few studies reporting that vitamin D physiologically affects growth and function of thyroid follicular cells. The mechanism underlying these effects is the inhibition of cAMP production which provides TSH activation, the principal contributor in growth of thyroid nodules.^{30,31} Kim et al reported a negative correlation between vitamin D levels and the diameter of the nodule by demonstrating lower vitamin D levels in larger nodules.³² The findings of the present study are consistent with previous results as vitamin D levels were significantly lower

Table 1. Gender distribution and general characteristics of study groups.

	Nodule (n=453)	Control (n=396)	P value
Women	416 (54)	354 (46)	.222
Men	37 (46.8)	42 (53.2)	
Age (years)	46.4 (12.6)	46.2 (15.2)	.896
BMI (kg/m ²)	26.9 (3.9)	26 (4.2)	.001

Data are number (%) or mean (SD).

Table 2. Gender distribution and general characteristic of subgroups of the nodule group.

	Solitary	Multiple	P value	Cystic	Solid	P value
Women	102 (24.5)	314 (75.5)	.694	33 (7.9)	383 (92.1)	.581
Men	8 (21.6)	29 (78.4)		2 (5.4)	35 (94.6)	
Age	44.1 (13.4)	47.1 (12.2)	.03	45 (15.4)	46.5 (12.3)	.506
BMI	26.4 (4.6)	27.1 (3.6)	.133	26.8 (6.7)	26.9 (3.6)	.921
Diameter	1 (0.8)	1.4 (1.1)	.0001	1.25 (0.9)	1.33 (1.02)	.656

Data are number (%) for gender and mean (S) for age, BMI and nodule diameter.

Table 3. Laboratory values of the study groups.

	Nodule (n=453)	Control (n=396)	P	Cohen's d
Vitamin D (ug/L)	12 (5.2)	26.1 (10.6)	.0001	1.945
Calcium (mg/dL)	9.5 (0.5)	9.5 (1)	.415	
Phosphorus (mg/dL)	3.4 (0.6)	3.5 (0.6)	.227	
Magnesium (mg/dL)	2.0 (0.4)	2.0 (0.2)	.709	
Protein (g/L)	7.1 (0.5)	7.2 (0.5)	.005	0.2
Albumin	4.3 (0.36)	4.3(0.4)	.211	
Thyroid stimulating hormone (mIU/L)	2.2 (1.3)	2.2 (1.3)	.714	
T3	3.3 (0.5)	3.3 (0.5)	.908	
T4	1.2 (0.2)	1.2 (0.3)	.485	
Glucose (mg/dL)	102.6 (29.3)	99.5 (31.1)	.144	
Creatinine (mg/dL)	0.8 (0.6)	0.8 (0.2)	.187	
Estimated glomerular filtration rate (mL/min)	89.6 (19.5)	95.6 (19.7)	.0001	0.3

Data are mean (standard deviation)

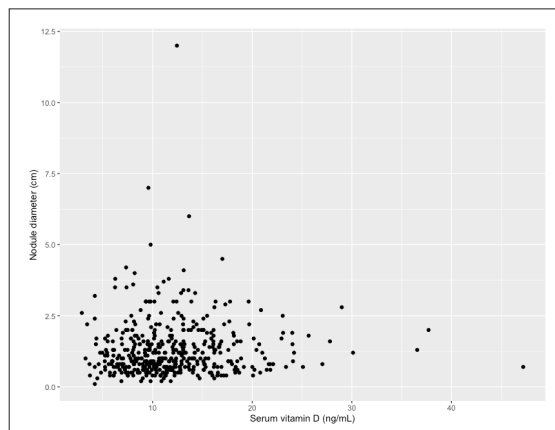


Figure 1. Serum vitamin D by diameter of thyroid nodule (n=453).

in patients with thyroid nodules. Additionally, these results demonstrated that deficient serum vitamin D levels were one of the independent factors associated with the presence of thyroid nodules.

TSH is the major factor in the process of nodule development in the thyroid gland.⁶ Two case control studies demonstrated that vitamin D levels were significantly lower in patients with high serum TSH levels.^{33,34} On the other hand, some studies were not able to demonstrate a relationship between serum vitamin D and TSH levels.^{35,36} In the present study serum TSH levels were higher, yet not statistically significant, in the thyroid nodule group. This is probably due to the fact that our study population constituted euthyroid patients.

Recent studies indicate a positive relationship between renal function and thyroid nodules, especially nodules showing characteristics of hypothyroidism.³⁷

Table 4. Multivariate logistic regression with dependent variable presence of thyroid nodule in euthyroid patients (n=277).^a

	β coefficient	P value	Odds ratio	95% CI of odds ratio	
				Lower	Upper
Age (years)	-0.017	.393	0.983	0.946	1.022
BMI (kg/m ²)	0.055	.391	1.057	0.932	1.199
Gender	0.49	.459	1.632	0.446	5.97
Vitamin D (ug/L)	-0.311	<.0001	0.733	0.681	0.789
Calcium (mg/dL)	0.503	.242	1.653	0.712	3.841
Phosphorus (mg/dL)	-0.443	.186	0.642	0.333	1.238
Magnesium (mg/dL)	0.867	.427	2.38	0.28	20.216
Protein (g/L)	-1.406	.005	0.245	0.091	0.661
Albumin	0.324	.629	1.383	0.371	5.152
Glucose (mg/dL)	0.003	.675	1.003	0.99	1.015
Creatinine (mg/dL)	-0.492	.16	0.611	0.308	1.215
Estimated glomerular filtration rate (mL/min)	-0.036	.017	0.965	0.936	0.994

^aMissing cases, 572. Model summary measures: deviance 170.575, Nagelkerke R2 0.702

Korean scientists concluded that there is a positive correlation between vitamin D levels and GFR in their study investigating 4948 individuals.³⁸ Accordingly, our results revealed that eGFR was one of the independent parameters associated with the presence of thyroid nodules.

In addition to the recognition of female gender and high BMI as independent risk factors for development of thyroid nodules in clinical trials,³⁹⁻⁴¹ Vitamin D levels were significantly lower in these patients.⁴² The serum protein levels were also low in individuals with low vitamin D levels.¹³ Our results are consistent with previous literature in this aspect.

The main limitation of this study is that it is from a single center. Information bias, as a result of missing or illegible data and/or errors in data collection, may be present. Another limitation is that the hormonal status of women was not evaluated. Female hormones may affect vitamin D status. Another limiting factor might be

the fact that vitamin D levels of the control group were near the lower border in the present study. The strength of this study is that it is the first study performed on vitamin D for benign thyroid nodules and the sample size was relatively large.

In conclusion, serum vitamin D levels were significantly lower in patients with thyroid nodules than in healthy individuals. Moreover, although nodule diameter was not significantly correlated with vitamin D levels, vitamin D deficiency was a significant factor for the presence of thyroid nodules. These findings raise the question whether vitamin D deficiency might be one of the pathophysiologic factors in development and growth of thyroid nodules. Vitamin D, which has protective effects in many conditions including the current COVID-19 pandemic, might be used for protection against thyroid nodule development and growth. The results of this study should be validated by other large scale studies.

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