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The effect of serum 25-hydroxy vitamin D levels on malignancy in exophytic thyroid nodules

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ABSTRACT

Aim: The increase in the incidence of thyroid cancer brings about research of new risk factors. In this study, we aimed to investigate the effect of vitamin D status on malignancy in exophytic nodules.

Material and Method: Two hundred and sixteen patients with exophytic thyroid nodules were included in the study. All patients' thyroid nodule ultrasonographic features, fine needle aspiration biopsy cytology results, rate of surgery and surgery histopathological results were recorded. Vitamin D levels were analyzed and patients were divided into two groups as vitamin D sufficient groups (vitamin D≥20 ng/ml) and vitamin D deficient group (vitamin D<20 ng/ml).

Results: Malignancy rate was significantly higher in the vitamin D deficient group (%19 vs %8.7; p=0.03). There were no significant difference between two groups in terms of demographic characteristics and ultrasonographic features including diameter, hypoechoic nature, having irregular border and microcalcifications.

Conclusion: In exophytic nodules, vitamin D deficiency increases malignancy risk. Determining vitamin D levels may be useful in patients with exophytic nodules.

Keywords: Thyroid nodule, thyroid malignancy, exophytic nodule, vitamin D

INTRODUCTION

Thyroid cancer is the most common malignant tumor in the endocrine system with a rising incidence worldwide over the past decades (1). The factors increasing the risk of thyroid cancer include exposure to radiation to the head and neck, sex, age, iodine deficiency or excess, and family history of thyroid cancer (2,3). Although there are many studies on risk factors and mechanisms in thyroid cancer to date, the number of studies on new risk factors that will explain the dramatic increase in recent years are rather new. Lately, one of the most important potential risk factors suggested by researchers is vitamin D deficiency (4-8).

Epidemiological studies point to a relationship between vitamin D deficiency and cancer risk and alterations in vitamin D levels are involved in the growth regulation of tumours (9,10). The association between vitamin D deficiency and breast, colon, prostate, and pancreatic cancers has been reported (9). In recent years, the number of studies investigating the relationship between thyroid cancer and vitamin D has increased. The data obtained show that low vitamin D is associated with an increased risk of thyroid cancer (11).

Ultrasonographic findings considered as signs for malignancy in a thyroid nodule include the presence of microcalcification, interrupted margin calcification, hypoechogenicity, irregular margin, taller than wide shape and intra-nodular vascularization (2,12-18). In addition, the presence of pathological lymphadenopathy (LAP) and ultrasonographic findings of extrathyroidal extension are considered as signs of malignancy (2,19,20). In recent years, studies on ultrasonographic findings that increase the risk of malignancy have been increasing. There are studies showing an increased risk of malignancy in exophytic nodules (21-23). Exophytic nodule is identified as a nodule that makes a prominent angle with the adjacent thyroid capsule or a nodule that sticks out of the normal thyroid boundary/outline (24).

In this study, we aimed to determine the effect of vitamin D levels on malignancy in exophytic thyroid nodules.

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MATERIAL AND METHOD

All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Ethics approval has been taken from the Dışkapı Yıldırım Beyazıt Training and Research Ethics Committee (Date: 22.07.2019, Decision No:68/11)

Subjects

Two hundred and sixteen patients with exophytic nodules were included in this retrospective cross sectional study. All patients were followed up in the Endocrinology outpatient clinic of Diskapi Yildirim Beyazit Training and Research Hospital between January 2017 and May 2022. Patients with chronic kidney diseases and patients with a previous history of thyroidectomy and radiotherapy to the head and neck region were also excluded from the study.

Laboratory

TSH and vitamin D levels were noted. Vitamin D cut-off level defining deficiency was 20 ng/ml.

Imaging, Fine Needle Aspiration Biopsy (FNAB) and Surgery

Thyroid ultrasonography (US) and thyroid fine needle aspiration biopsies were performed by Endocrinology and Metabolic Diseases specialists. Hitachi (Hitachi, Japan; EUB 7000) US device with 13 MHz linear probe was used for thyroid US evaluation. Thyroid parenchymal heterogeneity, number of nodules, nodule dimensions (width, depth, and height), nodule properties and localization within the thyroid gland were recorded for each patient. Nodules disrupting the natural course of the thyroid capsule border outward by forming a prominent angle were defined as exophytic nodules.

Thyroid FNAB was US-guided and done by experienced endocrinology specialists. The nodules to be biopsied were decided by following the European Thyroid Association (ETA) guidelines. Patients with malignancy or suspected malignancy cytopathology results underwent surgical treatment.

Cytopathology and Histopathology

Bethesda classification system was used for the cytological diagnoses. The results were reported as benign, atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasm/suspicious for follicular neoplasm (FN), suspicious for malignancy and malignant. Patients with non-diagnostic cytology results underwent repeated FNAB after 3 months and adequate biopsy results were considered valid in repeated biopsies. Non-diagnostic results were not included in the study.

Post-operative histopathological results were classified as benign and malignant according to the WHO thyroid cancer classification. In malignant nodules, tumor type, size and histopathological features were documented.

Statistical Analysis

Normal distribution of the variables were determined via visual (histograms, probability plots) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk's test). The Mann-Whitney U test was performed to compare non-normally distributed numeric variables. The Chi-square test or Fisher's exact test (when Chi-square test assumptions do not hold due to low expected cell counts) was used to compare the proportions in different groups. The continuity correction was used when the expected count was between 5 and 25. Medians and 25-75% quartile ranges were given for non-parametric parameters. Numbers and percentages were given for categorical variables. A p-value less than 0.05 was considered statistically significant.

RESULTS

As demonstrated in demographic characteristics shown in **Table 1**, there was no difference between two groups in terms of age, sex and TSH levels (normal value range: 0.27-4.2 mIU/L). Ultrasonographic features including diameter, hypoechoic nodule ratio, nodules that have irregular borders and microcalcifications did not reveal any statistically significant difference between two groups. Cytology results are given in **Table 2**. Suspicious for malignancy and malignancy cytology result ratios were higher in the vitamin D deficient group but the results did not reach a statistically significant level (p=0.12). Surgery ratio and histopathological results are given in Table 3. The ratio of the patients who underwent surgery was similar in both groups (p=0,05). Malignancy rate in the vitamin D deficient group was significantly higher (p=0,03). All malignant nodules histopathological results were reported as thyroid papillary carcinoma.

Table 1. Demographic and ultrasonographic characteristics of the patients

	Vitamin D Sufficient Group (n=69)	Vitamin D Deficient Group (n=147)	p value
Age (years)	50.12 (47.58-52.66)	51.39 (48.10-54.68)	0.20
Female. n (%)	62 (89.9)	121 (82.3)	0.15
TSH. mIU/L	1.61 (1.01-2.72)	1.72 (1.11-2.58)	0.11
Ultrasonograpic Features			
Diameter (mm)	17 (12-21)	15 (11-21)	0.06
Hypoechoic nodule n (%)	16 (23.2)	32 (21.8)	0.81
Irregular border n (%)	2 (2.9)	12 (8.2)	0.14
Microcalcification n (%)	3 (4.3)	9 (6.1)	0.59

TSH: Thyroid stimulating hormone

Table 2. Cytology results of the patients

	Vitamin D Sufficient Group (n=69)	Vitamin D Deficient Group (n=147)	P value
Cytology			0.12
Benign, n (%)	56 (81.2)	118 (80.3)	
AUS/FLUS	9 (13)	11(7.5)	
FN/suspicious of FN, n (%)	1 (1.4)	0 (0)	
Suspicious of malignancy, n (%)	1 (1.4)	11 (7.5)	
Malignant, n (%)	2(2.9)	7 (4.8)	

AUS/FLUS: atypia of undetermined significance/follicular lesion of undetermined significance; FN: follicular neoplasm

Table 3. Surgery ratio and malignancy rate of the patients

	Vitamin D Sufficient Group (n=69)	Vitamin D Deficient Group (n=147)	P value
Surgery n (%)	6 (8.7)	28 (19)	0.05
Malignancy (+) n (%)	3 (4.3)	21 (14.3)	0.03

DISCUSSION

In our study, we found that vitamin D deficiency increases the risk for malignancy in patients with exophytic nodules. The signaling role of vitamin D deficiency in the pathogenesis of breast, colon, prostate, and pancreatic cancers has been suggested in literature (9). However, such pathways are not clear for thyroid cancer yet. Several studies showed that the potential antineoplastic effects of vitamin D may include apoptosis (25), paused cell cycle (7,26), inhibited proliferation, promoted differentiation (26,27) and reduced inflammatory response (28). Despite all these data, the role of vitamin D deficiency in carcinogenesis remains controversial. Although many studies have suggested that higher serum vitamin D levels might protect against thyroid cancer (5, 6, 11,29,30), some other studies did not indicate the same results (4, 31-35). In this study, cytology results did not reach a statistically significant level but looking at the statistically significant histopathological results data, our study suggests that vitamin D deficiency increases the risk of malignancy. With further studies in the future, as the data on this subject increases, the importance of the role of vitamin D may become more clearer.

In our study, the malignancy rate in exophytic nodules was found as 11.1% which is higher than the malignancy prevalance (5% for women and 1% for men) indicated by guidelines (2). The incidence of thyroid cancer has been increasing in recent years. Current risk factors have become insufficient to explain this rise. Therefore, in recent years, new risk factors in thyroid cancer have been the subject of researchers. One of the most important evaluation methods in thyroid nodules is thyroid US. Among the thyroid US findings, the features that increase the risk of malignancy are well defined in literature. However, studies on possible additional criteria have been increasing lately. The examination of exophytic nodules is one of these new research areas. Our study supports that the risk of malignancy increases in exophytic nodules. We think that the importance of exophytic nodules will increase as more studies and data are published on this subject.

This study has its limitations as it had a retrospective design, not all histopathological features were recorded and long-term follow-ups have not been evaluated. Also, increasing the number of cases may lead to more statistically significant results including cytology. However, we think that the results of this study will contribute to the literature since there is a considerably growing attention on this subject.

CONCLUSION

Vitamin D deficiency in exophytic nodules increases the risk of malignancy. When evaluating thyroid nodules, it will be useful to assess these two features in addition to the existing risk factors. With the increase in studies on this subject, vitamin d deficiency in exophytic nodules may take place in the literature as a modifiable risk factor.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Dışkapı Yıldırım Beyazıt Training and Research Hospital, Noninvasive Clinical Ethics Committee (Date:22.07.2019, Decision No: 68/11).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version

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