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).

Ultrasoundographic findings considered as signs for malignancy in a thyroid nodule include the presence of microcalcification, interrupted margin calcification, hypoechoogenicity, 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.
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   |
| Ultrasonographic 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
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