



Original Research

Low Vitamin D Status is Not Associated with the Aggressive Pathological Features of Papillary Thyroid Cancer

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Abstract

Objectives: In the present study, we investigated the effects of Vitamin D (vit D) deficiency on aggressiveness of papillary thyroid cancer (PTC).

Methods: Patients with PTC confirmed with pathological examination, whom were operated by a single surgeon between 2012 and 2017, were included in the study. The data of the patients were analyzed retrospectively. Cancers other than PTC, patients with hyperthyroidism and/or using antithyroid drugs were excluded from the study. The patients were classified as four quartiles according to serum Vit D levels; category 1 (<7.1 ng/mL), category 2 (7.2–11.8 ng/mL), category 3 (11.9–23.4 ng/mL) and category 4 (>23.5 ng/mL).

Results: A total of 133 patients (103 female, 30 male) with mean age of 46.4±13.6 (17–82) years were included in the study. There was no significant difference between the categories in terms of preoperative Vit D values according to the evaluated tumor aggressiveness characteristics. It was determined that the presence of tumor with a size above 1 cm and T3/4 tumor were not affected by Vit D level. There was no significant difference between Vit D categories regarding the characteristics of aggressiveness such as multicentricity, lymphovascular invasion, central, and lateral metastases.

Conclusion: According to our results, serum Vit D levels are not associated with the aggressive tumor characteristics of PTC.

Keywords: Papillary thyroid cancer, Tumor aggressiveness, Vitamin D

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Vitamin D (Vit D) is a steroid pro-hormone required for many metabolic regulations in the body, especially for bone mineralization and calcium-phosphate homeostasis.^[1] In the body, it is found as either 25(OH)D₃ (the storage form) or as 1α, 25(OH)₂D₃ (the active form). Vit D is one of the first vits described, and its first proven effects are on Ca-P balance. Studies in recent years explain the extraskeletal effects of Vit D and its relationship with some malignancies, in ad-

dition to its effects on bone mineralization and metabolite balance. It has been shown that low Vit D levels may increase cancer development such as colon, breast, and prostate cancers, and Vit D deficiency is associated with an increased incidence of advanced cancer stage, recurrence and lymph node metastasis in these cancers. It has been reported in current publications that Vit D shows its anti-cancer effects due to its anti-inflammatory and anti-prolif-

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erative properties, inducing apoptosis, inhibiting invasion, and angiogenesis.^[2]

It has been supported by the strongest evidence that Vit D deficiency causes an increased risk of colorectal cancer, and its close relationship with breast and prostate cancers has also been established. Investigation of the effect of Vit D in bladder and ovarian cancers continues with current studies.^[3]

Thyroid cancer is the most common endocrine organ cancer and its incidence has been increasing for the past three decades.^[4] The development of diagnostic methods day by day has a great role in the increased incidence of thyroid cancer. Therefore, it is important to evaluate the possible risks for the prognosis of thyroid cancer, the incidence of which is gradually increasing.

Vit D deficiency is common worldwide and in our country. Since the day it was identified, Vit D deficiency is a global health problem and has been described as the pandemic of the era.^[5] It is ironic that a vit deficiency, which can easily be eliminated with replacement therapy, changes the course of any malignancy, and in our study, we investigated the effects of Vit D deficiency on aggressiveness of papillary thyroid cancer (PTC).

Methods

Prior to the study, the permission of the local ethics committee (Date: 29/09/2019, Number: 1854) was obtained. Our study was conducted in accordance with the Declaration of Helsinki. Patients who were operated by a single surgeon at between 2012 and 2017 and who had PTC confirmed with pathological examination, were included in the study. Patient data and pathology reports were analyzed retrospectively. Cancers other than PTC, patients with hyperparathyroidism, patients with hyperthyroidism and/or patients using antithyroid drugs were excluded from the study.

The most reliable way to measure Vit D level is stated to check 25(OH)D levels today, thus, we used serum 25(OH)D level in our study.^[6,7] Vit D deficiency is defined as serum 25(OH)D being less than 20 ng/ml (50 nmol/l), and vit D insufficiency is defined as serum 25(OH)D to be between 21 and 29 ng/ml (50–75 nmol/l).^[8] In our study, since most of our patients had Vit D deficiency or insufficiency, patients were divided into four different groups and catego-

ries determined according to multinomial logistic regression analysis. The patients were classified as four quartiles according to serum Vit D levels; category 1 (<7.1 ng/mL), category 2 (7.2–11.8 ng/mL), category 3 (11.9–23.4 ng/mL) and category 4 (>23.5 ng/mL). Vit D quartiles were statistically divided into different groups considering the number of patients and their Vit D levels.

The effect of Vit D on tumor aggressiveness of PTC was evaluated in patients in this study. According to the 2015 American Thyroid Association (ATA) guidelines, PTC tumor aggressiveness features have been identified as male gender, over 55 years of age, tumor size of above 1 cm, T3/4 tumor, multicentricity, lymphovascular invasion, presence of lymph node metastasis, central and lateral metastases.^[9] These parameters were compared in accordance to serum Vit D (ng/mL) values. Patients in these four categories were analyzed based on PTC aggressiveness.

Statistical Analysis

Statistical analysis was performed with IBM SPSS for Windows version 15.0 (SPSS Inc, Chicago, IL, USA). For descriptive statistics, numbers and percentages for categorical variables were calculated, and mean, standard deviation, minimum and maximum values were calculated for numerical variables. Since numerical variables did not meet the normal distribution condition, two group comparisons were made using the Mann-Whitney U test. Rates in groups were compared with Chi-square analysis. Factors determining numerical variables were investigated by Linear Regression Analysis. Statistical alpha significance level was accepted as $p < 0.05$.

Results

A total of 133 patients (103 female, 30 male) were included in the study. The mean age of the patients was 46.4 ± 13.6 (17–82) years. There was no significant difference between the categories in terms of preoperative Vit D values according to the evaluated tumor aggressiveness characteristics.

When categorized according to Vit D values, the female gender ratio in categories 1, 2, 3, 4 was 31.1%, 21.4%, 22.3%, 25.2%, and male gender ratio was 6.9%, 34.5%, 34.5%, 24.1%, respectively. The female ratio was significantly higher in category 1 ($p = 0.044$) (Table 1).

Table 1. Distribution of preoperative vitamin D level by gender and categories (Pearson Chi-square test)

Characteristic	Category 1 (<7.1 ng/mL) (%)	Category 2 (7.2–11.8 ng/mL) (%)	Category 3 (11.9–23.4 ng/mL) (%)	Category 4 (>23.5 ng/mL) (%)	p*
Female	31.1	21.4	22.3	25.2	0.044
Male	6.9	34.5	34.5	24.1	

Preoperative vit D levels were not different when all patients were grouped with reference age of 55. In groups created according to tumor size and stage, it was determined that the presence of tumor with a size above 1 cm and the presence of T3/4 tumor were not affected by vit D level. When multicentricity, presence of lymphovascular invasion, presence of lymph node metastasis, central metastasis, and lateral metastasis, which are among the aggressiveness characteristics of PTC, were evaluated, there was no statistically significant difference in terms of patient ratios according to Vit D levels and Vit D categories (Table 2).

Based on the group with the lowest vit D level in our study (category 1), it was planned to interpret whether the tumor's aggressiveness characteristics of patients in this category differ from those in the other categories. In the multinomial logistic regression analysis, taking the category 1 (Vit D <7.1 ng/mL) as the reference group, when the relative estimated risk ratios of other categories in terms of tumor aggressiveness characteristics were evaluated compared to category 1, no significant feature was detected.

Discussion

In our study, it was determined that most of the patients operated for PTC were within the vit D insufficiency or deficiency limits. In category 1 (Vit D <7.1 ng/mL), it was determined that the majority of the patients were female with statistical significance and this was an expected result considering that vit D deficiency was more common in women. Although the opposite is expected, it was found that the level of Vit D and tumor aggressiveness were not significantly different in patients over the age of 55, who may develop osteopenia dependent on the age, compared to those under the age of 55.

No statistically significant results were found when PTC aggressiveness characteristics, based on 2015 ATA guidelines, were examined for each separate vit D category. Failure to find a significant result can be associated with the frequent

occurrence of vit D deficiency and insufficiency in our country.^[10] vit D deficiency is one of the most common Vit deficiencies in Turkey. Although the number of controlled studies related to this subject is quite low, for example, in a study conducted in 391 adults over 20 years of age in the Aegean region, Vit D deficiency was found to be 74.9%. It has been determined that there may be some differences between the arrival angle of the sun rays, the type of clothing and the months that the measurement is made. Vit D deficiency in women was found to be significantly higher than in men.^[11]

There are conflicting results in publications claiming that serum vit D level neither affects or not both prognosis and clinicopathological features in PTC. Considering that vit D has anti-inflammatory and anti-proliferative effects, publications claiming its impact on the course and aggressiveness of PTC should not be ignored.

Jonklaas et al.,^[12] who investigated whether deficiency of elements such as selenium as well as vit D level also had an effect on PTC, did not find a significant correlation on PTC aggressiveness. This study with 65 patients concludes that the study should be expanded with larger case series. Our study was designed retrospectively and the characteristics of patients with PTC such as recurrence, lymph node metastasis, and survival in the postoperative period could not be compared with Vit D levels. In Ahn et al.'s study^[13] with 795 patients in 2016, they evaluated the relationship between vit D levels and PTC aggressiveness, and these patients were followed up with a median follow-up period of 35 months in the postoperative period. Considering the seasonal differences in Vit D levels, they divided the patients into four groups. In this study, there was no significant difference between groups according to Vit D level in terms of extrathyroidal invasion, lateral lymph node metastasis, tumor size, and recurrence. Although the number of cases was less than this study in our own study, similar results are noticeable as a result of detailed statistical analysis.

Table 2. Comparison of vitamin D levels regarding the papillary thyroid cancer aggressiveness characteristics (Mann-Whitney U test)

Characteristics of aggressiveness	Aggressive characteristics (+) Vit D (ng/mL)	Aggressive characteristics (-) Vit D (ng/mL)	p*
Above 55	18.31±13.67	15.31±11.21	0.297
Female	15.95±12.3	16.4±10.5	0.261
T >1 cm	14.66±8.84	16.64±16.25	0.875
T3/4 tumor	13.25±11.5	15.87±11.55	0.504
Multicentricity	15.62±11.47	15.34±11.11	0.909
Lymphovascular invasion	15.48±11.55	15.46±11.18	0.819
Central metastasis	15.38±11.35	15.41±11.24	0.985
Lateral metastasis	15.66±9.43	15.42±11.44	0.607

Considering that most of our patients (77.44%) were female and Vit D deficiency is observed more in women in our country, the groups may be thought to consist of similar populations in terms of Vit D level.^[11] Therefore, no difference detected in tumor size, lymph node metastasis or extrathyroidal metastasis can be explained by the fact that Vit D deficiency is a very common Vit deficiency. In some studies, Vit D deficiency was found to be effective in the prognosis of the cancer type in cancer types that are more equally distributed in terms of sex, such as colorectal cancer.^[14] Thyroid cancer is the most common in endocrine cancers and considering that Vit D deficiency is seen more frequently in women, it is not expected to find different results in terms of the role of vit D in the prognosis of PTC.

Thyroid cancer has an increasing prevalence. And the known risk factors include a history of radiation to the neck region, familial history of thyroid cancer, and having a previous thyroid cancer, and it is actually a type of cancer that may have unknown risk factors. There are also studies showing that Vit D deficiency adversely affects PTC development and prognosis.^[15,16] In a meta-analysis published in 2019, other thyroid cancers, including PTC, were also included in the study. As a result of the analysis of 14 studies, they stated that vit D deficiency was 30% effective in the development of all thyroid cancers, but postoperative Vit D deficiency did not show a significant difference in terms of thyroid cancer prognosis in patients who underwent total thyroidectomy. Although it is assumed that meta-analysis groups are highly heterogeneous and not only PTC is included, the researchers stated that the preoperative Vit D level was effective in the development of thyroid cancer.^[15]

In their large case series with 548 female patients operated for PTC, Kim et al.^[16] reported that vit D deficiency was closely associated with poor clinicopathological features in terms of tumor size, stage, both central and lateral lymph node metastasis, and extrathyroidal metastasis. In some experimental studies, Vit D has been shown to affect inflammatory cells and gain pro-tumorigenic properties. The researchers, therefore, highlighted the hypothesis that oncoproteins are associated with poor clinicopathological features by increasing the expression of oncoproteins in PTC.

If other types of cancers other than thyroid cancer are evaluated, Vit D deficiency which is common has created a research area for the researchers. In breast cancer, Vit D deficiency has been detected to have a significant effect on both tumor aggressiveness characteristics, Ki-67, and p53 positivity, and tumor stage and lymph node metastasis. Vit D deficiency was found to have a negative effect on both disease-free survival and overall survival.^[17] At this stage, the researchers explained that Vit D shows its anti-cancer

effects with its effect on the proteins that regulate proliferation and by providing the communication of the cells with their microenvironments. They suggested that cells tend to proliferate uncontrollably in case of D Vit deficiency, as regulation of apoptosis is provided by the inhibition of differentiation of cells by binding to the Vit D receptor.

In 2019, Ferrer-Mayorga et al.^[18] published the mechanism of action of vit D on colon cancer. In summary, they explained the beneficial effects of Vit D on colon cancer with many complex cellular control mechanisms. Vit D has been explained to be protective for colon cancer by reducing cell proliferation with down-regulation of cyclin-dependent kinases, increasing apoptosis by inducing pro-apoptotic genes, and by reducing Vascular endothelial growth factor to inhibit angiogenesis and invasion. For this reason, Vit D deficiency has been reported to be a bad prognostic factor in colon cancer, since all these protective pathways cannot function adequately on colon cancer in Vit D deficiency.

Although the effect of Vit D on cancer types such as breast, colon, prostate has been almost explained, our knowledge of the effects on thyroid cancer is scarce. Active Vit D is thought to bind directly to the Vit D receptor in the cell and to indirectly affect the cell cycle by interacting with other transcriptional factors. In some publications, active Vit D has been shown to induce apoptosis and inhibit anti-apoptotic proteins. Therefore, it can be thought to prevent tumor development. However, more prospective case-control studies are needed to understand the effects of Vit D on PTC with these reported effects in limited studies. Although it has not been proven yet, it should be noted that Vit D deficiency may be important in terms of PTC prognosis.

The limitations of our study are that it has a retrospective design, not all histopathological features have been recorded in some patients, and long-term follow-ups have not been evaluated. It was not specified whether the extracapsular spread was minimal or extensive, as it was not mentioned in the pathology reports. And all the aggressive pathological features of PTC could not be included in the study. However, we think that the results of this study will contribute significantly to the literature since there are limited studies on this subject in the literature.

As a result; PTC is the most common type of endocrine cancer and we have little information about the factors affecting its course. In our study, male gender, being over 55 years of age, presence of tumor above 1 cm in size, T3/4 tumor, multicentricity, lymphovascular invasion, presence of lymph node metastasis, central metastasis, and lateral metastasis, which are of aggressiveness characteristics of PTC, were evaluated according to serum D Vit level.

Conclusion

According to our results in our patient series, serum Vit D levels are not associated with aggressive tumor characteristics in PTC. In order to evaluate this, case-controlled studies with a larger number of cases and prospective extended studies are needed.

Disclosures

Ethics Committee Approval: Şişli Hamidiye Etfal Training and Research Hospital Local Ethics Committee (Date: 29/09/2019, Number: 1854).

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Conflict of Interest: None declared.

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