Preoperative Low 25-hydroxyvitamin D Level Is Associated With Poor Prognosis of Papillary Thyroid Cancer

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Preoperative low 25-hydroxyvitamin D level is associated with poor prognosis of papillary thyroid cancer

Munire Abuduwaili¹, Zhichao Xing¹, Yuan Fe¹, Baoying Xia¹, Jingqiang Zhu¹, Anping Su^{1, 2}

Abstract

Purpose: To evaluate the relationship between preoperative 25-hydroxyvitamin D (25[OH]D) level and poor prognosis factors of papillary thyroid cancer. **Methods:** A total of 1198 patients diagnosed of papillary thyroid cancer were analyzed retrospectively. Patients were categorized into vitamin D deficiency (VDD) group and normal group according to preoperative 25(OH)D <20 ng/mL and 25(OH)D ≥20 ng/mL. Differences of demographic data and clinicopathological characteristics were analyzed between two groups. Linear and logistic regression analysis to determine the effect of 25(OH)D on the established poor prognosis factors of papillary thyroid cancer were also applied. **Results:** We observed a negative linear correlation between 25(OH)D levels and tumor size and an independent relationship between VDD and lymph node metastasis in central area. Additionally, there was a significant correlation between preoperative 25(OH)D and thyroid-stimulating hormone (TSH) levels. **Conclusions:** 25(OH)D level significantly associated with certain poor prognosis factors of papillary thyroid cancer. Assessing and supplementing vitamin D may be an important addition to preoperative management of patients with papillary thyroid cancer.

Keywords: 25-hydroxyvitamin D, Papillary thyroid cancer, Prognosis, Lymph node metastasis

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The authors have no conflicts of interest to declare that are relevant to the content of this article.

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Not applicable

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Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Zhichao Xing, Baoying Xia and Munire Abuduwaili. The first draft of the manuscript was written by Munire Abuduwaili and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

Ethical approval was waived by the local Ethics Committee of West China Hospital, Sichuan University, in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

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Introduction

Vitamin D is a group of compounds, regulating the absorption of calcium, phosphates, and magnesium is its classic function. Additional function of vitamin D is to regulate the cellular life cycle and angiogenesis by certain signaling pathways. Numerous studies have demonstrated that vitamin D deficiency was related to various diseases including metabolic syndrome, hypertension, cardiovascular diseases and cancer.[1, 2] Besides, Vitamin D and its metabolites had been found to participate in the development and progression of cancers. In breast, colon, and prostate carcinoma, vitamin D have been recommended as a prognostic indicator[3, 4].

Thyroid cancer is the most popular malignant tumor in endocrine-system, with incidence varying from 0.5 to 1.5%. Prognostic factors of thyroid cancer that have been established before including age, invasive pathological subtypes, tumor size, lymphovascular invasion, extra-capsular spread, and lymph nodal metastases[5]. Compared with these factors that can't be intervened before operation, it is more essential to determine the high-risk prognostic features that are easily modifiable. A relationship between vitamin D and thyroid diseases was highlighted recently. Low status of 25(OH) D was found to significantly relate to autoimmune thyroid diseases (AITD) and thyroid cancer. While the etiology is not clear, it may be related to inflammatory processes [6, 7, 8, 9, 10, 11, 12] However, a definitive correlation between vitamin D deficiency and poor prognosis in papillary thyroid carcinoma has never been demonstrated in a large number of patients.

Our study aimed to evaluate the relationship between preoperative 25(OH)D level and poor prognosis factors in papillary thyroid cancer, and to determine if vitamin D deficiency is able to predict poor prognosis of papillary thyroid carcinoma.

1. Material and Methods

In this study, we enrolled 1198 patients diagnosed as papillary thyroid cancer between June 2016 and Nov 2019 at the Department of Thyroid Surgery of West China Hospital. Clinicopathological characteristics, prognostic features and demographic data were retrospectively collected. Our research had been waived by the medical ethics committee of the institution.

At least unilateral lobectomy of thyroid and excision of thyroid isthmus was performed on all patients. Therapeutic neck dissection was performed only in cases that lymph node metastasis was confirmed by preoperative fine-needle aspiration biopsy (FNAB) or intraoperative pathologic section. Tumor size, confirmed by histopathology reports of patients, was defined as the greatest cancer diameter. AJCC/TNM stag system was applied in this study [13].

Serum 25(OH)D concentrations were measured the day before surgery. VDD was defined by 25(OH)D<20 ng/mL[14]. Patients were categorized into VDD group and normal group according to preoperative 25(OH)D <20 ng/mL and 25(OH)D $\geq$ 20 ng/mL .

2. Statistical Analysis

We used SPSS 23.0 to process data and considered p-values <0.05 as statistically significant. Categorical variables were presented as absolute. Pearson's χ^2 -test was used to examine the differences of categorical variables. Continuous variables were presented as median values because non-normal distribution. Differences of continuous variables were examined using Mann-Whitney U test. Spearman rank correlation test and Kendall's tau correlation test was used to determine the correlations between age, sex, BMI, TgAb, Tg, TSH and 25(OH)D levels. Simple linear regression analysis was performed to demonstrate the correlation between tumor size and 25(OH)D level. We also applied univariate logistic regression analysis to determine the effect of VDD on the poor prognosis factors of papillary thyroid cancer. Multivariate logistic regression analysis for various prognostic factors in relation to VDD was also used to determine independent influencing factors.

3. Results

A total of 1198 patients were involved in the present analysis. The characteristics and comparison of the patients separated into two groups based on 25(OH)D level are noted in Table 1. Patients with VDD had higher TSH level than patients in normal group (2.87(1.97-3.96) VS 2.61(1.65-3.94)), $P = 0.028$). The median age of patients with VDD was 39, compared to 47 in patients without VDD ($p = 0.00$). The proportion of females in VDD group was lower than normal group (76.33%vs 62.30%, $p = 0.00$). There was no significant difference between the two groups for BMI (body mass index), TgAb and Tg levels.

Table 1: Demographic of patients with papillary thyroid cancer

	VDD group	Normal group	P
Age (years)	39(31-48)	47(37-53.75)	0
Female	616(76.33%)	243(62.30%)	0
BMI (kg/m ²)	22.72(20.56-25.29)	23.36(21.56-25.39)	0.184
TSH (mU/L)	2.87(1.97-3.96)	2.61(1.65-3.94)	0.028
TgAb (IU/mL)	15.73(10.26-119.90)	13.09(10-42.28)	0.31
Tg (μ g/L)	13.56(5.66-29.68)	12.07(6.74-25.42)	0.521

Abbreviations: BMI = body mass index; TSH = thyroid-stimulating hormone; TgAb: anti-thyroglobulin antibodies; Tg: Thyroglobulin.

Clinicopathological characteristics among the two groups were analyzed (Table2). Histopathological features associated with poor prognosis were also documented. Positive results of multifocality, tumor size ≥ 1 cm, presence of extra-thyroid invasion, capsular invasion, BRAF mutation, stratification of the risk of recurrence and other characteristics did not significantly differ between the two groups. Diagnosis of lymph nodes metastasis and central lymph node metastasis between the two groups showed significant differences ($P < 0.05$). Cancer stages also showed significant differences among the two groups ($P = 0.035$). The median of tumor size was different between the two groups, but the differences were not statistically significant (9 vs 8, $p = 0.10$).

Simple linear regression analysis was performed to demonstrate the correlation between tumor size and 25(OH)D level. As shown in Fig1, tumor size increased with decreased 25(OH)D level (Fig.1). The correlation was significant following adjustment for age, sex, BMI and TSH ($r = -0.067$, $p = 0.049$).

Correlations of 25(OH)D level with age, sex, BMI, TgAb, Tg and TSH levels were analyzed used Spearman rank correlation test and Kendall's tau correlation test (Table 3). According to the preoperative laboratory examination results, increasing 25(OH)D was significantly associated with decreasing TSH and increasing age ($OR = -0.078$ $P = 0.007$; $OR = 0.175$ $P = 0$; respectively). However, postoperative 25(OH)D level did not correlate with TSH level examined after operation. Besides, there was a significant sexual distinction in 25(OH)D level.

Table 2: Clinicopathological characteristics according to groups of 25-Hydroxyvitamin D levels

	VDD group	Normal group	P
Tumor size (mm)	9(6-15)	8(6-11.75)	0.1
Tumor size > 1 cm	201	80	0.093
Multiplicity	21	9	0.76
Capsular invasion	506	234	0.367
Extrathyroidal invasion	137	66	0.982
Lymph node metastasis	516	222	0.019
Central	311	123	0.018
Lateral	205	99	0.995
Multinodular goiter	358	160	0.275
Hashimoto's thyroiditis	118	54	0.72
Risk of recurrence			0.63
Low	349	179	
Intermediate	324	146	
High	134	66	
Radioactive iodine therapy	338	153	0.382
TNM			
T1a/T1b/T2/T3a/T3b/T4	463/157/38/12/65/72	239/70/12/3/26/40	0.425
N0/N1a/N1b	291/311/205	168/124/99	0.036
M1	6	7	0.101
Stage I / II / III-IV	732/57/18	337/45/9	0.035
BRAFV600E mutation	149	81	0.353

Table 3: Correlations of 25-Hydroxyvitamin D levels with sex, age, BMI, TgAb, Tg and TSH levels

	Before operation		After operation	
	OR	P	OR	P
Sex	-0.131	0	-0.999	0
Age	0.175	0	0.171	0
BMI	0.045	0.132	-0.011	0.749
TSH	-0.078	0.007	0.023	0.483
TgAb	-0.006	0.848	-0.004	0.896
Tg	-0.028	0.462	0.036	0.29

Table 4: Univariate logistic regression analysis of the effect of vitamin D deficiency on the aggressiveness of papillary thyroid cancer

	P	OR	CI
T3/4			
Model 1	0.746	1.053	0.769-1.44
Model 2	0.39	1.162	0.825-1.64
Lymph node metastasis			
Model 1	0.019	1.342	1.049-1.72
Model 2	0.077	1.263	0.975-1.64
Lymph node metastasis in central area			
Model 1	0.018	0.735	0.569-0.95
Model 2	0.04	1.317	1.012-1.72
Stage 3/4			
Model 1	0.836	0.918	0.408-2.065
Model 2	0.261	1.863	0.629-5.52
Extrathyroidal invasion			
Model 1	0.982	1.004	0.727-1.38
Model 2	0.734	1.062	0.752-1.50

Model 1 showed unadjusted ORs; Model 2 was adjusted for sex, age, BMI and TSH.

Table 5: Multivariate logistic regression analysis for various prognostic factors in relation to vitamin D deficiency

	P	OR	CI
Male	0	0.483	0.349-0.669
Age (years)	0	0.959	0.947-0.972
TSH (mU/L)	0.062	0.97	0.939-1.002
Tumor size (mm)	0.016	1.022	1.004-1.041
Central lymph node metastasis	0.026	1.428	1.043-1.954

Fig 1 Simple linear regression analysis between tumor size (mm) and 25-Hydroxyvitamin D (ng/mL)

4. Discussion

Papillary thyroid cancer is often an indolent disease, but it can become much more aggressive in its advanced stages. The 5-year survival rate of stage 1 and 2 thyroid papillary carcinoma is close to 100%, while that of stage 4 thyroid papillary carcinoma decreased to 51% [15]. Increasing tumor size, lymph node metastasis and extra-thyroid invasion have been found as poor prognostic factors for papillary thyroid cancer [16, 17]

Vitamin D and its metabolites were found to be capable of regulating cell differentiation and proliferation of normal and malignant cells [18]. The relationship between vitamin D level and thyroid disease has been highlighted recently. It was first observed in 2010 that impaired vitamin D metabolism implicated in thyroid follicular cell oncogenesis by Stepien, Tomasz et al [19]. They found a significant decrease in circulating 1-25 (OH) 2 D 3 concentrations in patients with different TNM stage and histological subtypes. These findings were supported by several studies performed subsequently [7, 8, 9].

However, the exact mechanisms have not been known yet. The promotion actions of vitamin D deficiency on immunological reaction might be the mechanism

involved. Thyroid cancer often shows inflammatory cell infiltration [20, 21, 22], inflammatory cells possess pro-tumorigenic potential, the oncoprotein can trigger the pro-inflammatory process in turns [23]. Therefore, the inflammatory process may provide a potential explanation for the underlying association between low vitamin D status and advanced papillary thyroid cancer.

In this study, we observed a negative linear correlation between tumor size and 25(OH)D level, tumor size increased with decreased 25(OH)D level. Besides, we found that VDD was significantly correlated with increased tumor size and central lymph node metastasis, independent of age, sex, BMI and TSH. The results of our study indicated that VDD was an independent risk factor for advanced papillary thyroid cancer.

Similar conclusions had been reached by Kim, Ji Ryang et al [24]. They reported that patients with tumor size ≥ 1 cm ($p = 0.041$) or lymph node metastasis had a significantly lower preoperative 25(OH) D level ($p = 0.043$), and there was a linear correlation between preoperative vitamin D levels and tumor size. But the study was only performed on 548 female patients, and the absence of male patients could lead to different outcomes. Another retrospective study involved 820 cases of papillary thyroid cancer further analyzed the relationship between vitamin D quartiles and poor prognostic factors including extra-thyroid invasion, lymph node metastasis, advanced cancer stage (stage III or IV) and recurrence risk. But they failed to demonstrate a significant association between 25(OH)D level and thyroid cancer [25]. Sulibhavi, Anita et al [26] had identified that vitamin D deficiency correlated with thyroid cancer stage, but only limited to those who documented Vitamin D deficiency, and the laboratory values examined before surgery did not show a significant correlation. There had been another article reported similar results and the different distribution of vitamin D levels in benign and malignant thyroid tumors [19]. However, the number of patients involved in the study was too small to draw strong conclusions.

An additional finding in our study was that preoperative 25(OH)D level was significantly correlated with preoperative TSH, but this relationship was not significant after surgery. Q, Zhang et al [27] had the same conclusions, while others had conflicting results [28]. In a cross-sectional cohort study, increased TSH level was found to association with the risk of cancer in thyroid nodules and had an impact on prognosis. However, no correlation was found between 25(OH)D level and thyroid carcinoma, or TSH level [29]. Therefore, in our study, TSH was also listed as a potential confounding factor in regression analysis.

There were some experimental evidence supported the claim that vitamin D reduces the risk of cancer incidence and death [4, 30]. A recent study evaluated whether vitamin D receptor can be used as a cancer treatment target for poorly differentiated thyroid cancer. They found promising results, although it depended on the specific genotype of the vitamin D receptor[31]. Another case has been reported in which vitamin D3 (cholecalciferol) being used as a therapeutic measure to halt progression of advanced cases of thyroid cancer [32].

In conclusion, 25(OH)D level was significantly associated with certain poor prognosis factors of papillary thyroid cancer. Assessing and supplementing vitamin D may be an important addition to preoperative management of patients with papillary thyroid cancer. Further prospective investigations on vitamin D supplementation for patients with papillary thyroid cancer before surgery using larger cohorts are need.

Declarations:

Funding and Conflicts of interests

The authors did not receive support from any organization for the submitted work. The authors have no relevant financial or non-financial interests to disclose.

Ethics approval

Ethical approval was waived by the local Ethics Committee of West China Hospital, Sichuan University, in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

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