Journal of Disease Markers

Open Access

Austin Publishing Group

Research Article

Vitamin D and Thyroid Nodules in an Eastern Region of Turkey

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Received: December 04, 2018; **Accepted:** January 22, 2019; **Published:** January 29, 2019

Abstract

Objective: There are reported associations between Vitamin D and some cancers, but the relationship in thyroid cancer has not been fully evaluated. The aim of this study is evaluate the relationship between Vitamin D levels and ultrasonographical data and cytological features of the nodules obtained by biopsy and after surgery in an eastern region of Turkey.

Methods: The records of 225 patients who underwent fine needle aspiration biopsy were included in the research. Thyroid hormone, and Vitamin D levels, ultrasonograpical parameters and biopsy and surgery results of the individuals were recorded. We seeked a relationship between Vitamin D levels and also results of the nodules obtained with ultrasonography, biopsy and surgery.

Results: There were no relationship between Vitamin D and ultrasonographical characteristics, fine needle aspiration biopsy and also histopathological surgery results.

Conclusions: Our results showed that there were no relationship between Vitamin D and ultrasonographical characteristics, biopsy and surgery results. However although size of our group was small, we found that if the patient had a large nodule and deficient Vitamin D levels, their cytological results might be malign. So we reached a conclusion that in such patients although biopsy reveals a benign result, the procedure must be repeated.

Keywords: Thyroid nodules; Vit D

Introduction

Thyroid nodule is a common pathology. After the detection of a thyroid nodule, it is important to determine the nature of it and plan how to treat and follow it up. Prevalence of the nodules in the general population is around 4-10% [1,2], but by autopsy surveys the rates increases by 37 to 57% [3]. In radiological surveys using thyroid ultrasonograpy (USG), 20-76% of adults were found to have thyroid nodules [4]. Incidence of the nodules markedly increases in iodine deficient regions as in our country. Although higher prevalence of thyroid nodules were expected in our country where serious or moderate iodine deficiency were seen in last decades, in Turkey according to different screening studies, sonographic prevalence of the nodules in people aged 18-65 years was 23.5%, it was 37.4 after 65 years [5,6]. Despite its relative frequency, studies have shown that only 5-15% of thyroid nodules demonstrate histologically proven malignancy [7,8] and thyroid cancer comprises 0.5-1% of all malignancies in adults and accounts for 3% of childhood cancers [8,9]. Although the rate seems low, the early diagnosis of these cancers is very important because of their slow progression and patients longevity due to early treatment. After detection, thyroid nodule should be evaluated with USG. Numerous studies have attempted to define ultrasound features that may predict benignity and malignity [10-12]. For cytological interpretation, fine needle aspiration biopsy (FNAB) is an established diagnostic modality in the evaluation of thyroid nodules.

The essential role of Vitamin D(Vit D) in bone and calcium metabolism is well known [13]. Besides, it is clear that Vit D has additional physiological functions. There are studies about vitamin D deficiency being a risk factor for hypertension [14,15], type 1 and 2 diabetes mellitus [16,17], cardiovascular disease [18], and various cancers [19-22]. However the association between Vit D levels and thyroid cancer is unknown.

In our study we aimed to compare Vit D levels and ultrasonographical and the cytological results of the patients exposed to FNAB and surgery, and find if Vit D levels affect them.

Methods

Patients

This retrospective study was approved by our university board. Informed consent was not required. A total of 225 patients with thyroid nodules aged from 17-83 years [189 female (84%), 36 male (16%)] who admitted to outpatient Clinics of Endocrinolojy and Metabolism and also Internal Medicine of Kafkas University from October 2012 to October 2014 and had thyroid USG and FNAB were included in this study. Subjects without complete informations or taking medications that affected their thyroid function, such as oral contraceptives, oestrogen, glucocorticoids and iodine and women having doubt of pregnancy were excluded.

Laboratory measurements

Free triiodothyronin (fT_3), free thyroxin (fT_4), thyroid stimulating hormone (TSH), Vitamin D3(25(OH)D, thyroid autoantibodies; thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody

Citation: Atalay E, Kurt GK, Gursoy G, Sisman P, Erdogdu HI, Tur K, et al. Vitamin D and Thyroid Nodules in an Eastern Region of Turkey. J Dis Markers. 2019; 4(1): 1037.

Table 1: USG characteristics of the nodules.

			Vit D						p
			Deficient		Insufficient		Normal		
	n	%	n	%	n	%	n	%	
Number Single	88	39.1	26	29.6	31	35.2	31	35.2	0.209
Multi	137	60.9	48	35	44	32.1	45	32.9	
Structure Solid	111	49.3	60	54	31	27.9	20	18.1	0.632
Cystic	8	3.6	4	50	0	0	4	50	
Mixed	106	47.1	24	22.6	44	41.5	38	35.9	
Tall Positive	115	51.1	37	32.2	37	32.2	41	35.6	0.09
configuration Negative	110	48.9	39	35.5	36	32.7	35	31.8	
Ecogenity Isoechoic	89	39.7	27	30.3	30	33.7	32	36	0.078
Hyperechoic	11	4.9	4	36.4	4	36.4	3	27.2	
Hypoechoic	64	28.6	18	28.1	26	40.6	20	31.3	
Mixed	39	17.3	11	28.2	13	33.3	15	38.5	
Unknown	22	9.7	6	27.3	9	40.9	7	31.8	
Calcification None	169	75.1	61	36.1	58	34.3	50	29.6	0.394
Rough	32	14.2	9	28.1	11	34.4	12	37.5	
Micro	24	10.7	8	33.3	9	37.5	7	29.2	
Vascularity None	188	83.6	64	30.03	56	29.8	68	36.2	0.705
Peripheral	18	8	7	8.9	5	27.8	6	33.3	
Intranodular	19	8.4	6	31.6	5	26.3	8	42.1	
Boundary Regular	192	85.4	69	35.9	77	40.1	46	24	0.34
Irregular	33	14.6	9	27.3	11	33.3	13	33.4	
Halo sign Negative	223	99.1	82	36.8	72	32.3	69	30.9	0.93
Positive	2	0.9	1	50	0	0	1	50	
Total	225	100	172	76.4	27	12	26	11.6	

(TgAb) levels of the patients were noted. FT_3,fT_4, TSH concentrations were determined by Access immunoassay method using Beckman Coulter DX1600 device. TPOAb and TgAb were examined by chemoluminessant immunoassy method using Cobas 4001 device.

Euthyroidism was defined as the absence of hypo and hyperthyroidism. Hypothyroidism was defined as the presence of TSH levels ≥ 5.0uIU/ml and fT4 levels ≤ 0.8ng/dl, hyperthyroidism was defined as the presence of TSH levels ≤ 035uIU/ml and fT4 levels ≥ 1,9ng/dl. Reference ranges of the parameters were as follows TSH: 0.34-5.6 µIU/ml, fT3: 2.5-3.9 pg/ml, fT4: 0.6-1.1 ng/ml, TPOAb: >34IU/ml positive, TgAb: >IU/ml115 positive, Vit D <20IU/ml: deficient, 20-30 IU/ml : insufficient, 30-100 IU/ml: normal.

The presence of thyroid nodule(s) and size of the thyroid gland were determined by thyroid ultrasonography. As every patient with a thyroid nodule is a candidate for FNAB, in our Clinic of Endocrinology and Metabolism section one doctor performed FNABs with the guide of USG. If surgical decision was taken, it was performed in our Clinic of General Surgery.

USG

Toshiba brand Apliox6 model using 12 MHz ultrasound probe was utilized in this study. The patient was placed in the supine position without a pillow with his or her neck in extension. Structure and size of thyroid tissue and presence of nodule were examined. The paranchimal structure (solid, cystic or mixed), size, location, number, shape, boundaries, acoustic halo, echo intensity, echo uniformity of the nodules were recorded. Three dimentions of the nodule was measured and the largest diameter was determined. Echogenity of the nodule was named as iso, hypo and hyperechoic according to thyroid tissue. Calcifications were classified as rough and micro. In Doppler examination vascularisation was evaluated and classified as intranodular and peripheral.

Specific ultrasonography features of a nodule that raise suspicion for malignity was accepted as follows: solidity, tall configuration (the anterioposterior diameter of the nodule is greater than its transvers diameter), markedly hypoechoic, microcalcifications, intranodular vasculatity, irregular margin, no halo. One of these USG features was accepted as suspicious.

FNAB

After the patient was placed in supine position, a pillow was put under the shoulders, their neck was brought to maximum extantion. The neck region was cleaered with iodine. No anesthetical agent was used. Aspiration was performed with an 10 cc enjector mounted 22G needle once or if it was necessary more. Biopsy material were evaluated in Clinic of Pathology. Preperations were examined with

Table 2: Ultrasonographical images and Vit D levels.

		Vit D						Total	
		Deficient		Insufficient		Normal			
		N	%	N	%	N	%	N	%
Ultrasonograpy	Suspicious 56.40%	90	52.3	17	63	20	76.9	127	56.4
	Benign 34.6%	82	47.7	10	37	6	23.1	98	43.6
Total		172	100	27	100	26	100	225	100

Vit D: Vitamin D.

Table 3: Evaluation of Vit D levels and FNAB results.

		Vit D						Total	
		Deficient		Insufficient		Normal			
		N	%	N	%	N	%	N	%
FNAB	Non-diagnostic	36	64.3	9	16.1	11	19.6	56	24.9
	Benign	113	82.5	13	9.5	11	8	137	60.8
	Atipia of undetermined significance	16	88.8	1	5.6	1	5.6	18	8
	Follicular neoplasm or suspicious for follicular neoplasm	4	66.7	2	33.3	0	0	6	2.7
	Suspicious for malignancy/malignant	3	37.5	2	25	3	37.5	8	3.6
Total		172	100	27	100	26	100	225	100

Vit D: Vitamin D.

light microscopy after they were stained with May-Grunwald-Giemsa, Hemotoxylin and eosin and covered with coating material. The occurence of at least 6 follicule groups consisting at least 10 cells without artifacts were accepted as qualification criteria. The cytological diagnosis was given according to Bethesda system. The cytology results were stratified into following 6 cathegories: non-diagnostic, benign, atipia of undetermined significance, follicular neoplasm or suspicious for follicular neoplasm, suspicious for malignancy and malignant. In malign group suspicious for malignancy and malign cathegories were included. In benign group non-diagnostic, benign, atipia of undetermined significance and follicular neoplasm or suspicious for follicular neoplasm cathegories were included.

Statistical analysis

Calculations were performed using SPSS version PASW 18. Descriptive value on the numerical measurements obtained in this study were determined as mean, standard deviation, median, minimum, maximum, and the descriptive statitics of categorical variables were determined as number and percentage. The relationship between cathegorical variables have been studied with Pearson-Qui Square and Fisher Exact Qui Square, Fisher-Freeman Halton tests. Shapiro Wik test was used for determining whether the numerical values were normally dsitributed. We compared the groups (consisting of two cathegories) in terms of the mean of numerical variables by Student t test and in terms of the median of them by Mann Whitney U test. One way ANOVA and Kruskall Wallis tests were used to compare the mean of numerical variables of the groups (consisting of more than two cathegories). In order to compare the methods used in the study with biopsy which is regarded as a gold standard, sensitivity, selectivity, positive predictive value and negative predictive value rates were analysed. The relationship between numarical variables were investigated by Sperman and Pearson correlation analysis. Zero point zero five was taken for statistical significance level and a p value of < 0.05 was considered as statistically significant.

Results

A total of 225 thyroid nodules were noted for the study. Thirty six patients (16%) were male and 189 were female (84%). Female-male ratio of the nodules were 5.2. The avarage age of female was 48.9 ± 12.7 and male was 53.6 ± 11.1, total age was 49.6 ± 12.6. The mean age was significanly higher in men than women (p 0.039).

In terms of thyroid hormone status our patients were mostly euthyroid (79.0%). Hypothyroidy rate was 20.0% and hyperthyroidy 1.0%. The rate of the patients with POAb positivity was 22.9% and TgAb positivity 22.3%.

Vit D results of the patients were as follows:

- 172 (76.4%) deficient,
- 27 (12.0%) insufficient,
- 26 (11.6%) normal.

The avarage level of Vit D were 16.1 ± 7.6. In males the level was 16.2 ± 8.2 and in females 14.4 ± 4.9. There was no relationship between ages and Vit D levels of the patients.

When Vit D levels were deficient, insufficient and normal, there was no correlation between thyroid hormone levels. The size of thyroid nodules were between 5-61 mm (19.5 ± 10.3), in 14 cases the size of the nodules were > 4cm and in others the size were 0.5-1.5cm. As Vit D levels decreased, thyroid nodule sizes significantly increased (p:0.02, r:- 0.299).

In Table 1 USG characteristics of the nodules and Vit D levels were presented. When Vit D levels and characteristics of the nodules were evaluated, we did not find significant difference in Vit D levels (Deficient, insufficient and normal) of the patients and the number, the structure, echogenity, calcification, vascularity, boundaries and

Table 4: Surgical histopathological and Vit D results.

		Vit D						Total	
		Deficient		Insufficient		Normal			
		N	%	N	%	N	%	N	%
Histopathological results	Benign	8	53.3	4	26.7	3	20	15	60
	Benign 34.6%	6	60	3	30	1	10	10	40
Total		14	100	7	100	4	100	25	100

Vit D: Vitamin D.

Table 5: The comparison between FNAB and histopathological surgery results.

		Vit D						Total	
		Deficient		Insufficient		Normal			
		N	%	N	%	N	%	N	%
FNAB	Non-diagnostic	1	10	1	6.7	2	8	1	10
	Benign	1	10	14	93.3	15	60	1	10
	Atipia of undetermined significance	1	10	0	0	1	4	1	10
	Follicular neoplasm or suspicious for follicular neoplasm	0	0	0	0	0	0	0	0
	Suspicious for malignancy/ malignant	7	70	0	0	7	28	7	70
Total		10	100	15	100	25	100	10	100

FNAB: Fine Needle Aspiration Biopsy.

halo sign of the nodules.

Nodules having one of those features, which were solidity, tall configuration, markedly hypoechoic, microcalcifications, intranodular vasculatity, irregular margin, no halo were listed as suspicious. Evaluation of Vit D levels and ultrasonographical results as suspicious and benign were presented in Table 2.

It was ultrasosnographically determined that 98 (43.6%) cases were benign and 127 (56.4%)were suspicious. In deficient group 52.3% patients had suspicious and 47.7% had benign USG features. Thirty seven percent nodules in insufficient group had benign USG signs and 63% of this group had suspicious signs. In the group where normal Vit D levels were encountered, 23.1% had benign, 76.9% had susopicious USG characteristics. When the relationship between Vit D levels and malign-benign USG features were examined no relationship was found.

FNAB was performed to all patients participated in the study. During and after the procedure there were no complications. FNAB results were as follows:

56 (24.9%)	non-diagnostic
137 (60.8%)	benign
18 (8.0%)	atipia of undetermined significance
6 (2.7%)	follicular neoplasm or suspicious for follicular neoplasm
4 (1.8%)	suspicious for malignancy
4 (1.8%)	malignant

When the patients in follicular neoplasm or suspicious for follicular neoplasm and suspicious for malignancy groups were included in the malignant group, the malignity rates became 3.5%. Malignity rates were 3.2% (6/189) in women and 5.6% (2/36) in men.

When we evaluated FNAB and Vit D levels, there was not difference between FNAB and Vit D results according to their levels as deficient, insufficient or normal. Evaluation of Vit D levels and FNAB results were presented in Table 3.

Considering the histopathological surgery results of the patients, it was seen that 25 patients(11.1%) out of 225 were operated. When we examined the histopathological surgery results we found that 10 of them (10/225) (4.44%) were found malign and 15 of them (15/225) (6.66%) were found benign. All of the nodules diagnosed as histopathologically malign were papillary carcinomas.

When we evaluated surgical histopathology results and Vit D levels we did not find any difference in terms of malignancy (Table 4).

When we revised FNAB results of patients participating in the study and their histopathological surgery results (Table 5), we observed that 1 case whose FNAB results were undiagnosed, were malign. According to Bethesda classification a case with benign result and a case with atipia of undetermined significance were diagnosed as papillary carcinomas. Seven cases whose histopathological result was malignant were also diagnosed as malign with FNAB. Fifteen FNAB results detected as benign, were found to be benign after surgery. Seven malign cases according to FNAB results were operated but one case chose to be treated in another center. We found that 3 cases with benign FNAB results were recommended surgery for their sizes of the nodules.

Discussion

Skin exposure and dietary intake are the two sources of VitD. Its metabolic activity depends on activation through hdroxylation of the 25 followed by the 1 position of this molecule by cytochromes P450s, the final product is active $1,25(OH)_2D3$. The action of Vit D occurs

through its binding to Vit D receptor (VDR) in the nucleus. Then VDR forms a heterodimer with retinoid-X receptors and binds Vit D response elements(VDRE) on chromatin resulting in the regulation of the expression of some target cells. Binding of VDRE with VDR affects gene transcription. Besides being involved in mineral metabolism VDR regulates some metabolic processes, like immune response and cancer signalling.

Thyroid cancer (TC) is the most common endocrine malignancy worldwide. Besides risk factors such as exposure to ionizing radiation, chemical genotoxins and obesity, lack of protective factors, like Vit D deficiency have been implicated in TC increased incidence [23-25].

Low levels of Vit D are measured all over the world, and its determined rate is 59.4-65.0 % [26,27]. In almost all studies, with normal Turkish individuals, Vit D levels were found to be below normal limits [28,29]. The season when the study was performed, genetical variations, our clothing style, limited intake of food high in Vit D, lack of outdoor physical activity due to the season must be considered as the reason of hypovitaminosis D in our country. In another study of ours we found 14.3ng/mL Vit D levels in normal individuals [30]. In our study the avarage level of Vit D were 16.1 ± 7.6. In Hekimsoy's study the mean serum 25(OH)D concentration was 16.9±13.09 ng/mL, with 74.9% of the subjects having 25(OH)D deficiency (<20ng/mL), 13.8% having insufficiency (20-29.99 ng/mL), and 11.3% of the subjects having sufficient 25(OH)D (≥30 ng/mL) levels. The present study determined similar results with 76.4% of the patients being deficient, 12.0% being insufficient and 11.6% being sufficient in terms of Vit D status. Levels were lower in women than in men (14.4 ± 4.9. vs 16.2 ± 8.2 ng/mL, respectively). These results were consistent with Hekimsoy's study (15.25 ± 11.53 ng/mL vs 20.70 ± 15.50 ng/mL, respectively) [31].

Studies have shown associations between Vit D deficiency and breast [20], colon [21] and prostate cancers [22]. However the relationship between Vit D levels and thyroid cancer is unknown. In experimental studies using cell lines or preclinical models to assess Vit D effect on thyroid cancer, overexpression of Cyp24A1 mRNA, VDR and also CYP27B1 [32-36] was shown. Antiproliferative effect of Vit D on thyroid cancer was also determined [37-39]. In some clinical studies protective effect [40-47] and in some no effect of VitD was found on thyroid cancer [48-52]. In limited number of studies Vit D was determined to be an increasing risk for thyroid cancer [53,54].

Solar irradiation which is the primary source of Vit D, can be estimated by the lattitude. Although our country is in a lattitude that benefits from high solar irradiation, Vit D deficiency is highly prevalent in Turkey. Our clothing style, skin type, limited intake of food high in Vit D, lack of outdoor physical activity must be considered as the reason of hypovitaminosis D. Morover, genetic determinants has effect on host intrinsic pathways such as polymorphic cytochromes P 450s responsible for the activation of Vit D, and can impact VitD interaction vit VDR [32,38]. Downstream pathways in VDR are also subject to wide genetic variability among populations [55,56]. These genetic variations were also shown to be critical determinants for the potential preventive properties of Vit D in TC. An inverse relationship was determined between TC incidence and lattitude [41,42]. In a country like ours which has a low lattitude but low Vit D levels we seeked studies about genetic variations in our population, but we were not able to find such studies. In a study held with nonwestern immigrants searching the Vit D status in Europe, found that Vit D levels was low in the Turkish groups in Europe [57]. Although this result may be explained by covering clothes, in the study group there was Turkish unveiled adult women. We cannot show the genetical effects on these result.

By wondering if there is a relationship between Vit D and TC in Turkey, we not only seeked a correlation with surgery results of thyroid nodules but also the results of USG and FNAB of the nodules and Vit D levels.

We classified our Vit D levels as deficient, insufficient and normal. When Vit D levels and characteristics of the nodules were evaluated, we did not find significant difference in Vit D levels of the patients and the characteristics of the nodules. After we listed our nodules having one of those features, which were solidity, tall configuration, markedly hypoechoic, microcalcifications, intranodular vasculatity, irregular margin, no halo as suspicious, no relationship between Vit D levels and malign-benign USG features was found. Then we classified our FNAB results according to Bethesda classidfications. There was also no relationship between Vit D levels and malign-benign FNAB results. We determined the same result with Vit D levels and histopathological surgery results.

Our results showed that there were no relationship between Vitamin D and USG characteristics, FNAB and also histopathological surgery results. However, when we examined our results retrospectively we found that a very small number of cases who were found malign with surgery were found benign by biopsy. These cases were in suspicious cathegory ultrasonographically, and also above 2.5 cm in size. All of those 3 cases had Vit D levels below 20IU/ml. We admit that our number of cases were very small, but we think that when patients with nodules have low Vit D levels and have large nodules must to be held cautiously and although FNAB reveals a benign result the procedure had to be repeated.

Acknowledgements

We thank the patients.

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Citation: Atalay E, Kurt GK, Gursoy G, Sısman P, Erdogdu HI, Tur K, et al. Vıtamın D and Thyroıd Nodules in an Eastern Regıon of Turkey. J Dis Markers. 2019; 4(1): 1037.