Lower Vitamin D Status in Patients with Differentiated Thyroid Carcinoma

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Thyroid cancer (TC) has become the most rapidly increasing type of cancer representing 1-1.5% of all cancers diagnosed annually probably due to intensive screening. It is estimated that the death rate of TC has slowly increased from 0.49 to 0.51/100.000 in the last 10 years and 53.990 new cases will be diagnosed in 2018 in the United States. Therefore, efforts are being made in order to stop the increasing incidence and genetic alterations are thoroughly studied. One of the most recent incriminated factors in TC etiology and physiopathology is vitamin D deficiency. Besides the well-known role in bone metabolism, vitamin D has extra-skeletal effects exerted through the vitamin D receptor (VDR) and has been shown to interfere with many cellular functions such as inhibiting cell proliferation, stimulating differentiation and malignant cell apoptosis in different types of cancer. Cross-sectional, retrospective study which included 114 patients (71 with confirmed thyroid cancer and 43 patients in the control group with benign pathology). Preoperative levels of 25(OH)vitamin D, PTH, biochemical and thyroid panel were measured. The histopathologic features were analyzed. Mean values of vitamin D was 16.31 ± 7.14 ng/mL with lower levels in patients with thyroid cancer (14.95 ± 5.91 ng/mL) in comparison to patients with benign thyroid pathology (18.55 ± 8.41 ng/mL), with a p value of 0.008. Majority of the cases were papillary thyroid cancer (97.18%) in stage 3 (45.07%). Vitamin D levels also correlated negatively with TNM staging. The necessity of further studies is a reality in order to establish if vitamin D deficiency is a possible risk factor for thyroid cancer and its correction can be considered an additional therapy.

Keywords: thyroid cancer, vitamin D, 25-hydroxyvitamin D

Differentiated thyroid carcinoma (DTC) is considered to be the most frequent endocrine malignancy [1]. Papillary and follicular thyroid carcinoma account for 80–84% and 6-10% of all thyroid carcinomas, respectively [8, 9]. Differentiated thyroid carcinoma represents the majority of all thyroid cancer types, and it is usually curable by surgery and radioiodine ablation, associated with the treatment of the underlying hyperthyroidism or hypothyroidism [10]. In many cases, for the patients undergoing surgery, the perioperative management is complicated, especially related to endotracheal intubation, but also for patients with underlying comorbidities [11-13]. Studies show that 4 cases/million of TC are refractory to radioiodine therapy, life expectancy in these patients being 3-6 years with a 10-year survival rate of 10% [4]. The physiopathology of TC is still incompletely understood and it is unclear if besides genetic and environmental causes, other factors such as vitamin D deficiency are involved [14-16]. Anterior cervical irradiation during childhood and genetic mutations such as BRAF V600E, RAS and its association with BRAF or TERT, PAX8/PPARγ, the association between RET and NTRK have been shown to increase mortality, invasive phenotype, and the progression of DTC [17-21]. Vitamin D is a hormone with skeletal and extra-skeletal actions, mainly through the vitamin D receptor (VDR) [22, 23]. Vitamin D deficiency measured through its main circulating compound, 25-OH-vitamin D (levels < 20 ng/mL) and insufficiency (levels 20-30 ng/mL) affects almost 1 billion people worldwide, leading to various complications which requires specific management [24-26]. These people who develop bone fragility with a high prevalence of complicated bone fractures may require special ostheo-synthesis techniques [27, 28]. Vitamin D has been known for its classic role in bone health and calcium homeostasis but the physiological function of 1,25-dihydroxyvitamin D suggests a possible role in preventing carcinogenesis in different tissues (prostate, colon, breast, kidney, thyroid) [29, 30]. In case of patients with different forms of renal disease, the activation of vitamin D is affected leading to its insufficiency [31, 32]. Vitamin D through its active form, $1,25(OH)_2D$ promotes cell differentiation and is a potent inhibitor of malignant cell proliferation by stimulating their apoptosis and activation of antiangiogenic proteins thus increasing sensibility to chemotherapy [5,6,25,33].The anti-carcinogenic effects are exercised through molecular mechanism by blocking cellular cycle and inhibiting growth factors and also genetic alterations. The correlations between vitamin D deficiency and thyroid cancer are still incompletely understood but some studies proved that TC patients have significantly lower levels of vitamin D by comparison to healthy individuals suggesting that vitamin D deficiency is a possible modifiable risk factor for TC. Low levels of vitamin D were correlated with tumor size and negative prognosis (lymph node metastasis and progression to stage III/IV) [34-36]. Vitamin D receptor gene polymorphisms were also incriminated in TC, some offering protection (alleles AA and FF of ApaI and FokI) and others associated with the occurrence of distant metastases and aggressive forms of TC (AA alleles of BsmI and TT genotype of ApaI) [37, 38].

The purpose of this study is to examine any association between vitamin D levels and thyroid cancer.

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Experimental part

Materials and methods

We conducted a cross-sectional, retrospective study in a Tertiary Endocrine Center, East Europe (a single center experience) in the C.I. Parhon National Institute of Endocrinology which includes 114 patients divided into two groups: the first group includes 71 patients who underwent total thyroidectomy for thyroid cancer (TC group) and the second group includes 43 patients with total thyroidectomy for a benign thyroid pathology (control group or non-TC group). Serum levels of vitamin D were evaluated before thyroidectomy in both groups. Biochemical, thyroid hormonal panel and histopathological features were also evaluated. Serum concentrations of 25(OH)D, parathormon and TSH receptor antibodies were obtained using electrochemiluminescence (ECLIA) on a Cobas e601-roche Diagnostics Gmbh using Roche kits with measurements limits of 4-100 ng/mL for 25(OH)D and 1.2-5000 pg/mL for parathormon. We established the following limits: 25(OH)D deficiency < 10 ng/mL, insufficiency between 10-30 ng/mL, normal levels between 30-100 ng/mL and toxicity > 100 ng/mL. Biochemical tests were made on the Cobas c501 device using spectrophotometry. Thyroid panel values (TSH, fT4, T3, TPO antibodies) were measured using chemiluminescence (CMIA) on a Architect I2000 device and Immulite for TPO antibodies.

The study was performed according to the ethical principles originating from the Helsinki declaration. Each patient signed a written consent and their personal information is strictly confidential. The study is approved by the Ethical Committee of the National Institute. Statistical analysis was made using Microsoft Office Excel 2010 functions and t-student test, Spearman Correlation test and IBM SPSS software.

Results and discussions

The study included a total of 114 patients: 71 with thyroid cancer (62.28%) and 43 without thyroid malignancy (37.72%). In both groups female sex was more frequent, the cohort study included a total of 8 (7.02%) male patients and 106 (92.98%) female patients distributed like this: the thyroid cancer group had 4 men (5.63%) and 67 women (94.37%) and the control group had 4 (9.30%) male patients and 39 female patients (90.70%), respectively.

Out of the total of 114 patients, 27 (23.68%) were from rural environment and 87 (76.31%) from urban environment (table 1).

Regarding age distribution, in the TC group the majority of patients included were in the 51-60 category representing 30.98% (fig. 1) by comparison to the control group where most patients were in the 61-70 years category (fig. 2). Also, in the TC the mean age was 49.76 years ± 13.61 SD and in the non-TC group mean age was 59.18 years ± 9.42 SD (*p-value = 0.000116*).

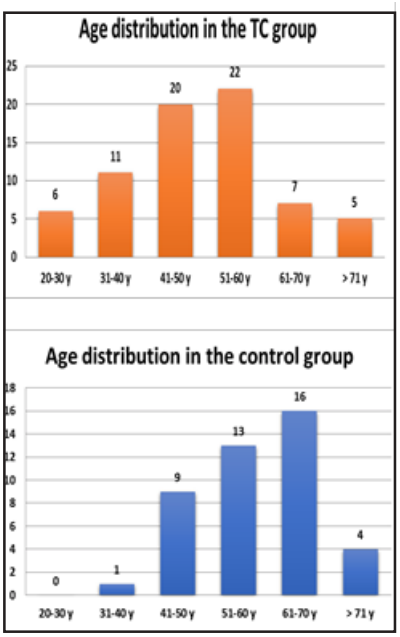

Fig. 1. Age distribution in the TC group

Fig. 2. Age distribution in the non-TC group

Study of the phosphor-calcic metabolism (table 2) revealed significantly higher level of serum calcium in patients from the non-TC group with a mean value of 9.41 ± 0.75 mg/dL in comparison to the TC group with a mean value of 9.16 ± 0.53 mg/dL (p value = 0.043). The phosphorus level was also lower in the control group (3.43 ± 0.64 mg/dL versus 3.54 ± 0.54 mg/dL in the thyroid cancer group) but without a statistical significance.

Levels of alkaline phosphatase were lower in the cancer group compared to the control group with a p value of 0.013. Parathyroid hormone was higher in the TC group with a mean value of 61.36 ± 32.27 pg/mL and of 53.11 ±

Table 1

PATIENTS DISTRIBUTION ACCORDING TO SEX, ENVIRONMENT AND ENDEMIC AREAS

Patients	Sex		Rural	Urban	Endemic	Non-endemic
	F	M				
Cohort study	106 (92.98%)	8 (7.02%)	27 (23.68%)	87 (76.31%)	99 (86.84%)	15 (13.16%)
TC group	67 (94.37%)	4 (5.63%)	17 (23.94%)	54 (76.05%)	63 (88.73%)	8 (11.26%)
Control group	39 (90.70%)	4 (9.30%)	10 (23.25%)	33 (76.75%)	36 (83.72%)	7 (16.28%)

Parameter	Total (n=114) Mean value ± SD	Cancer (n=71) Mean value ± SD	Control (n=43) Mean value ± SD	*p value*
Calcium mg/dL	9.26 ± 0.63	9.16 ± 0.53	9.41 ± 0.75	*0.043*
Phosphorus mg/dL	3.49 ± 0.58	3.54 ± 0.54	3.43 ± 0.64	*0.351*
Alkaline phosphatase U/L	75.70 ± 35.35	65.08 ± 16.46	84.99 ± 44.10	*0.013*
PTH pg/mL	56.93 ± 34.19	61.36 ± 32.27	53.11 ± 35.77	*0.328*
25(OH)D ng/mL	16.31 ±7.14	14.95 ± 5.91	18.55 ±8.41	*0.008*
TSH uUI/mL	1.77 ± 1.96	1.69 ± 1.39	2 ± 2.61	*0.670*
fT4 pmol/L	16.38 ±11.17	13.93 ± 3.34	19.29 ±15.73	*0.021*
T3 ng/dL	152.02±135.18	113.68 ± 28.11	181.70 ± 173.79	*0.063*
TPO-Ab UI/mL positivity	23/60 (38.33%)	10/32 (31.25%)	13/28 (46.42%)	*0.109*

Table 2

BASELINE CHARACTERISTICS DIVIDED BY THE TWO GROUPS

* SD=standard deviation

35.77 pg/mL in the non-cancer group (*p = 0.328*).

The overall mean serum 25(OH)D level was 16.31 ± 7.14 ng/mL with significantly lower levels in the thyroid cancer patients with a mean of 14.95 ± 5.91 ng/mL compared to the control group in which mean value was 18.55 ± 8.41 ng/mL (p value = 0.008) (fig. 3). Considering vitamin D deficiency as being 25(OH)D < 10 ng/mL, the prevalence of its deficiency was: 19 patients (26.76%) in the cancer group and 8 patients (18.60%) in the control group. In the thyroid cancer group, vitamin D insufficiency represented 70.42% (50 patients) and 67.44% (29 patients) in the control group. Only 2 patients had normal 25(OH)D levels (> 30 ng/mL) and 6 patients from the control group. Thyroid function was similar in the two groups, the only significant difference being fT4 levels with a mean of 13.93 ± 3.34 pmol/L in the cancer group and 19.29 ± 15.73 in the control one (*p value = 0.021*).

According to histopathological report the cohort study included 69 patients with papillary carcinoma (97.18%) and 2 patients with follicular carcinoma (2.81%). After TNM classification, in the thyroid cancer group were 2 patients with **T4**(T4a-N1b-M0-Gx and T4b-N1b-M0-G1) representing 2.81%, 32 patients with **T3**-N(x/0/a/b)-M0-G(x/1) (45.07%), 10 patients with **T2**-N(x/0)-M0-G(x/1) (14.08%) and 27 patients in the **T1**(a/b)-N(x/0/1a/1b)-M(0/1)-G(x/1) category representing 38.04%. Levels of 25(OH) vitamin D varied by cancer stage, mean value in stage 1 being 13.31± 4.97 ng/mL. In stage 2 values were higher (17.21 ± 6.23 ng/mL) and in stage 3 were lower with a mean of 16.28 ± 5.83 ng/mL. In stage 4 levels of vitamin D were significantly lower (4.46 ± 0.94 ng/mL). Therefore, 25(OH) vitamin D levels correlated negatively with TNM staging (*r = -0.23, p = 0.004*). Out of the 71 patients with TC, 39 (54.92%) had multifocal tumors, 41 (57.74%) has extrathyroidal invasion, 12 (16.9%) had lymphatic invasion and 10 (14.08%) had cervical lymph node metastasis but none had distant metastasis. e resected primary tumors were 1.68 ± 1.50 cm in size. In the control group there were 15 patients (34.88%) had follicular adenoma, 19 (44.18%) had multinodular goiter, 7 (16.27%) had Graves' disease and 2 had chronic autoimmune thyroiditis (4.67%). Vitamin D levels were higher in patients with follicular adenoma (20.88 ± 8.7 ng/mL) by comparison to multinodular goiter patients (16.6 ± 8.02 ng/mL) and patients with Graves' disease (19.55 ± 9.69 ng/mL) and Hashimoto thyroiditis (15.3 ± 3.81 ng/mL).

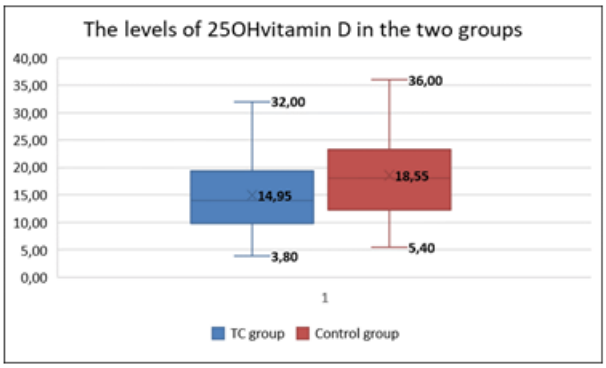

Fig. 3. Vitamin D levels in both groups

In this study the serum 25(OH)D levels were significantly lower in the thyroid cancer group by comparison to the control group. Also, vitamin D levels correlated negatively with TNM staging. Several clinical studies demonstrated lower levels of 25(OH)D in patients with thyroid cancer, especially levels under < 37.5 nmol/L [30]. Tumor size was also associated with vitamin D levels [29]. Kim et al showed that patients with tumors > 1 cm or metastasis had significantly lower vitamin D levels and that values < 46.2 nmol/L had higher risk of advanced stage thyroid carcinoma and metastasis [35, 36]. Other authors revealed that certain vitamin D receptor gene polymorphism such as AA and FF haplotypes of the ApaI polymorphism offer protection against follicular carcinoma and TT genotype of ApaI can increase predisposition to more aggressive types of differentiated thyroid carcinoma being positive in patients with stages 3-4 [37, 38]. Several other studies denied the association between vitamin D status and increasing prevalence of thyroid cancer and lymphoid tumors, as well as their worse prognosis and aggressiveness [39, 40, 41].

Molecular studies demonstrated that vitamin D and especially its active metabolite 1,25-dihydroxyvitamin D has important antitumoral effects mainly through its anti-proliferative, pro-apoptotic and pro-differentiate effects over the tumoral cells [42, 43]. These actions are exercised through effects on the cell cycle regulation by inhibition of growth factors such as insulin-like growth factor 1 (IGF1) and epidermal growth factor (EGF) and stimulation of growth inhibitors such as transforming growth factor-β (TGF-β). Calcitriol stimulates the apoptosis of malignant cells by repressing survival proteins (BCL-2, telomerase, reverse transcriptase) and activation of antiangiogenic and pro-apoptotic proteins (BAX). It inhibits malignant cell proliferation by modulation of kinase pathways such as Wnt/ âcatenin, MAPK5, ERK. The anti-inflammatory effect are due to blocking prostaglandin synthesis with suppression of COX 2 and NF-kB signaling [44-46].

Due to the continuous increasing incidence of thyroid cancer, besides the well-known risk factors such as cervical irradiation and genetic alterations (BRAF, RAS mutations, PAX8-PPARã rearrangements), studies demonstrated that 1,25(OH)2D has antitumoral effects in thyroid cancer cells. The active form of vitamin D inhibits cell proliferation mainly by blocking the actions of proto-oncogenes (c-Myc) and activation of fibronectin therefore increasing cell adhesion [44-48].

This study has some limitations. First of all the sample size is small, for data confirmation we will continue to enroll patients and secondly, seasonal variations of vitamin D may influence the end results.

Conclusions

In conclusion, low vitamin D levels were more frequently found in patients with thyroid cancer versus patients with benign thyroid pathology and also correlated with the aggressiveness of the disease and cancer staging. However because of the small sample size, additional randomized are needed in order to establish if vitamin D deficiency can be considered a risk factor for thyroid cancer and thus its supplementation can be considered as additional therapy.

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