

Evaluation of Vitamin D3 levels and dietary management in patients with papillary thyroid cancer

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Keywords: Vitamin D

- Papillary thyroid cancer

- Supplementation

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Received:

16 June 2023

Accepted revised:

8 December 2023

Abstract

Objective: Vitamin D (VitD) plays various roles, promotes musculoskeletal health, maintains parathyroid hormone levels and supports the immune processes. Vitamin D deficiency is common among cancer patients including thyroid cancer. Since some data indicate that preoperative VitD levels in cancer patients correlate with the further prognosis of the disease. Therefore, it is worthwhile to investigate this in the most common cancer of the thyroid gland, papillary thyroid cancer (PTC). The aim of this study was to evaluate serum VitD levels in patients with PTC concerning age, gender, body mass index (BMI), cancer stage, thyroid hormone levels, thyroglobulin concentration and the efficiency of VitD3 supplementation in these patients.

Subjects and Methods: Our cross-sectional study included 105 patients, and 34 healthy subjects in the control group. After 12 weeks of VitD3 supplementation (insufficient patients received 1000IU/day, deficient patients 2000IU/day, severe deficient patient 5000IU/day) along with the lifestyle and dietary management, the response was evaluated according to the personal characteristics, levels of VitD, free thyroxine (FT4), free triiodothyronine (FT3) hormones and thyroglobulin (TG). **Results:** The responders whose median age was 61-year-old, were mostly women (94%), with BMI below 23.7kg/m², which indicates that most of the patients were normally nourished. Seventy percent (70%) of patients were in the first stage of PTC, 76% had a vitamin D deficiency, while musculoskeletal disorders were present in 30% patients. VitD supplementation improved serum VitD status, FT3 discretely elevated and the TG levels significantly decreased in our PTC patients.

Conclusion: It should be noted that VitD deficiency is presented in 70% of patients with PTC in our study sample. Dietary recommendation applied as lifestyle changes along with oral VitD3 supplementation, corrected VitD status to the recommended serum level. Although the data from our study is not sufficient to evaluate the VitD level as a prognostic factor for cancer, we have shown that it is necessary to examine its level along with an individual dietary approach for each patient with PTC.

Hell J Nucl Med 2023; 26(3): 194-200

Epub ahead of print: 14 December 2023

Published online: 28 December 2023

Introduction

Vitamin D (VitD) deficiency has been reported in various types of cancers and VitD levels have been recognized as a prognostic factor for breast, colon, and prostate cancer [1]. Based on the recent data, thyroid cancer is the fifth most common cancer in women. The focus of this study is on examining the role of VitD level as a prognostic factor in malignant thyroid disease. However, clinical data is sparse and inconsistent in the case of thyroid cancer. 25-hydroxyvitamin (25(OH)D) is the main circulating and stored form of VitD. Serum levels of 25(OH)D is considered the best marker representing whole body VitD status. The large sample study by Kim et al. (2017) [2], showed that pre-operative levels of 25(OH)D in serum are prognostic parameters primarily in women with thyroid cancer, therefore, patients with lower levels of VitD have a more aggressive disease. Another recent study reported that VitD deficiency may serve as a negative prognostic indicator in papillary thyroid cancer [3]. Other researchers have found no associations between serum 25(OH)D level or the percentage of VitD deficiency and the rate of diagnosis or stage of differentiated thyroid cancer [4-7].

Regarding the effects of VitD3 in various tissues and its absorption and activation, some indices point out that higher VitD3 level is followed by better thyroid hormone and substitution levels [8]. Although debated, proposed referent values for VitD deficiency is usually defined as a serum concentrate of 25(OH)D < 20ng/mL, VitD insufficiency from 21 to 29ng/mL, while severe lack was defined as < 10ng/mL [9]. In VitD deficient patients, the recommended range for oral VitD3 dose is between 1000 and 5000IU per day. The results of the study by Grant and Boucher (2020) [10] showed that improvement in VitD

status occurred after 10 weeks of supplementation. The metabolic processes of thyroid hormones depend on adequate diet; balanced in nutrients, rich in vitamins and minerals food sources maintaining good gastrointestinal function [11]. Therefore, it is necessary to provide dietary recommendations for patients with thyroid carcinoma.

Thus, the objective of this study is to evaluate VitD status and a response to VitD3 supplementation. Furthermore, the aim is to examine lifestyle diet changes in patients with papillary thyroid carcinoma (PTC) and to examine responses to treatment according to gender, age, different carcinoma stages and associated diseases.

Subjects and Methods

Patients

A total of 105 patients, median age 61 years (range 33-87) were examined in the period from January 2017 to December 2020 at the National Institute of Oncology and Radiology in Belgrade, Serbia. All patients underwent total thyroidectomy for well-differentiated histologically diagnosed thyroid cancer (papillary adenocarcinoma). Patients with parathyroid adenomas and those on therapy for rheumatic diseases were excluded. The control group consisted of 34 healthy individuals. The study was approved by the Institutional Review Board at this institution. Involved patients voluntarily provided the written informed consent to participate in this research.

Laboratory testing methods

Fresh sera from the participants was centrifugated at 3000 RPM for 15 minutes and used for analysis. Serum thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3) and total 25(OH) vitamin D (VitD) were determined by a quantitative enzymatic fluorescent assay on analyzers from the VIDAS family (MiniVidas and Vidas) by the original manufacturer's test from Biomerieux. The baseline testing was completed in late winter to facilitate the implementation of VitD3 supplementation in cases of deficiency. The principle of determination in these tests is the combination of sandwich method of enzyme immunoassay (in one or two steps) with final fluorescent detection (ELFA-Enzyme Linked Fluorescent Assay). Serum thyroglobulin (TG) was quantified with the original test on the ACCESS 2 immunochemical analyzer (manufactured by Beckman Coulter). The determination principle was based on the sandwich immunoenzymatically method in one step with the chemiluminescent substrate Lumi-Phos 530.

Vitamin D supplementation and lifestyle diet recommendation in PTC patients

Supplementation of VitD3 supplement used was in oil solution of cholecalciferol of 20,000IU/mL oral drops (concentration 0.5mg/mL total 10mL), for 12 weeks, 2-8 drops per day (insufficient patients 1000IJ/day, deficient patients 2000 IJ/day, severe deficient patient 5000IJ/day). In addition to the oral supplementation, all patients with diagnosed PTC

received a dietary recommendations for foods containing micronutrients: selenium, VitD3, zinc and iodine, and "FOD-MAP" diet to reduce the consumption of fermentable sugars and eliminate certain foods that cause hypersensitivity (Table 1). All patients were encouraged to take daily walks and sunbathe for at least 20 minutes. The effectiveness of VitD3 supplementation therapy and dietary approach in our PTC patients was monitored through hormonal tests (TSH, FT3, FT4) and TG levels after 12 weeks.

Table 1. Formed lifestyle factors recommendation for our PTC patients.

Dietary supplementation	Diet sources
Iodine	Seafood (e.g. seaweed, sardines, shrimps, salmon and tuna), animal products (yoghurt, cow's milk, eggs) fruits (cranberries and strawberries)
Selenium	Brazil nuts, oysters, tuna, sunflower seeds, most kinds of meat (pork, beef, lamb, turkey chicken), mushrooms
Zinc	Beef, chicken, tofu, pork, nuts, seeds, lentils, yogurt, oatmeal, and mushrooms.
Vitamin D	Fish (cod liver oil, wild fresh salmon, sardines) dairy products
Gluten-free diet	Grain
Gluten	Avoid: Wheat and related grains, such as barley, rye, and oat Eat: buckwheat, rice, corn, millet
FODMAP	Food carb groups avoid
Fructose	Fruits (including apples, mangos, pears, watermelon), honey, high-fructose corn syrup, agave
Lactose	Dairy (milk from cows, goats, or sheep), custard, yogurt, ice cream
Galactans	Legumes, such as beans (including baked beans), lentils, chickpeas, and soybeans
Polyols	Sugar alcohols and fruits that have pits or seeds, such as apples, apricots, avocados, cherries, figs, peaches, pears, or plums

(Continued)

FODMAP	Recommended food
Dairy	Almond milk, lactose-free milk, rice milk, coconut milk, lactose-free yogurt, and hard cheeses.
Vegetables	Lettuces, carrot, cucumber, chives, zucchini, baby ginger, olives, parsnips, potatoes, spring onions, and turnips
Fruits	Bananas, blueberries, cantaloupe, grapefruit, kiwi, lemon, lime, oranges, and strawberries.
Fish	salmon, tuna, and shrimp
Proteins	Beef, pork, chicken, fish (salmon, tuna, and shrimp) eggs, and tofu.
Fats	Oils, pumpkin seeds, butter, peanuts, and walnuts.
Nuts/seeds	Almonds, peanuts, pine nuts, and walnuts (limit to 10-15 each)
Grain	Oats, oat bran, rice bran, gluten-free pasta, quinoa, white rice, and corn flour.
Recommendation	
Supplementation Vitamin D	cholecalciferol oil solution 2-8 drops/day (from 1000-5000 IU daily). adjusted to blood level
Physical activity	20–30 minutes on average five times a week, preferably outdoors

Statistical methods

For normal distribution data testing, the Kolmogorov-Smirnov test was used. Descriptive methods (frequencies, percent, mean, median, standard deviation /SD/range) were used to summarize the data. Statistical significance level was set at $P < 0.05$. For data testing Wilcoxon signed rank test were used. Statistical analysis was performed with the program R (version 3.3.2 (2016-10-31) - "Sincere Pumpkin Patch"; Copyright (C) 2016 The R Foundation for Statistical Computing; Platform: x86_64-w64-mingw32/x64 (64-bit); downloaded: January 21, 2017).

Results

Clinical characteristics and VitD status of PTC patients enrolled in this study was presented in Table 2. We recruited 105 PTC patients with a median age of 61 (range 33-81) years. In the examined group, the majority of patients with PTC were females (90%), at the threshold of the seventh decade, with a median BMI of 23.7 kg/m^2 , indicating normal weight, and a

high percentage of associated diseases (e.g. 30% musculoskeletal disorders). Biomarker analyses revealed that 76% PTC patients had VitD deficiency. Table 3 shows the variables of the control group. Healthy subjects in control group with euthyroid status were mainly females (93%), in the fifth decade, with a median BMI of 24.2 kg/m^2 , however, biomarker analyses revealed that 57% of control subjects had VitD deficiency. As expected, compared to healthy subjects PTC patients have higher serum levels of TG and lower levels of FT4 and VitD3. The initial/baseline and post-supplementation levels of VitD and parameters such as FT4, FT3 and TG in the PTC group are presented in Table 4. Thyroid-stimulating hormone was suppressed according to the recommendations of the American Society of Clinical Oncology (ASCO), below the lower limit of standard values ($< 0.05 \mu\text{IU/mL}$) with the personalized dose of L-thyroxine medication. For the BMI reference range of 23 to 28 kg/m^2 , the ages 55 to 65 years, it is recommended that the 25(OH)D levels be above 30 ng/mL .

Table 2. Clinical characteristics and VitD status of study subjects.

Variables	PTC group n=105
Female/male (n)	95/10
Age (years)	61 (33-87)
BMI (kg/m^2)	23.7 (19-42.2)
Associated diseases (n%):	68 (65%)
Other cancer	13 (12%)
Musculoskeletal disorders	32 (30%)
Autoimmune, gastrointestinal, Mental and metabolic disorders	23 (22%)
Vitamin D $< 20 \text{ ng/mL}$: n (%)	77 (73%)

Table 3. Study parameters in control group.

Variable	Control group n=34
Gender (female) n (%)	31 (94%)
Age (years)	44.5 (35-65)
BMI (kg/m^2)	24.2 (19-26) Median
TSH ($\mu\text{IU/mL}$)	1.95
FT4 (pg/mL)	12.72
FT3 (pg/mL)	3.91
TG (ng/mL)	0.13
25 OHD (ng/mL)	35
Vitamin D $< 20 \text{ ng/mL}$ n (%)	20 (57%)

* Normal range values: BMI 23-28 kg/m^2 ; TSH (0-4 $\mu\text{IU/mL}$), FT3 (4-8.3 pmol/L), FT4 (10.6-19 pmol/L), TG (1.59-50.3 ng/mL), 25OHD $> 30 \text{ ng/mL}$

Table 4. Difference in test parameters, free fractions of thyroid hormones - FT3, FT4, TSH, TG and serum VitD levels in PTC group after VitD3 supplementation and diet treatment.

	Mean $\pm$ SD	Median (min-max)	P (Wilcoxon)
FT4 (pg/mL) PTC initial	18.23 $\pm$ 2.63	18.35 (12,81-23.79)	
After 12 weeks	17.74 $\pm$ 2.17	17.85 (12.15-24.0)	
Significance FT4 (FT4i > FT4t)			P<0.05
FT3 (pg/mL) PTC initial	3.86 $\pm$ 0.65	3.82 (2.1-5.74)	
After 12 weeks	4.18 $\pm$ 0.61	4.17 (2.4-5.57)	
Significance FT3 (FT3i < FT3t)			P<0.01
TG (ng/mL) PTC initial	0.72 $\pm$ 2.43	0.13 (0.01-20.4)	
After 12 weeks	0.45 $\pm$ 1.75	0.06 (0-12)	
Significance Tg (Tgi>Tgt)			P<0.01
25(OH)D (ng/mL) PTC initial	17.12 $\pm$ 7.3	15.75 (8-38)	
After 12 weeks	41.49 $\pm$ 17.78	38 (20-114)	
Significance 25 (OH)D (Di<Dt)			P<0.01

Normal range values: BMI je 23-28kg/m²; TSH (0-4μIU/mL), FT3 (4-8.3pmol/L), FT4 (10.6-19pmol/L), TG (1.59-50.3ng/mL), 25OHD 30ng/mL

Compared to basal levels, VitD3 supplementation along with dietary treatment led to a significant increase in serum 25(OH)D concentration ($P<0.01$), which reached the recommended level. There was also a discrete improvement in FT3 and a significant decrease in TG levels ($P<0.01$), in PTC patients. After 12 weeks of intervention, compared to the baseline, VitD3 supplementation resulted in increased serum 25 (OH)D levels from median values as 15.75 (8-38) ng/mL to 38 (20-114)ng/ml. No side effects were reported following the oral consumption of VitD3 supplements by participants throughout the study. Eight patients had several VitD deficiency and received VitD3 supplementation of 5000IJ per day. Due to the small number of patients, it was not appropriate to compare with patients on 2000IJ VitD3 treatment, although the increase in serum 25(OH)D levels was similar for both doses, more than 20ng/l, follow up 12 weeks. Eighteen insufficient patients received 1000IJ per day with the same response. Table 5 presents the response to therapy based on gender, age decades, associated diseases and cancer stages

among study patients.

Discrete differences were present in patients over the age of 50 in response to VitD3 supplementation. Since the patients were mostly in the first stage, and to a lesser extent in other cancer stages, it is difficult to compare these subgroups. Patients without comorbidities have a better response to VitD3 treatments compared to patients with associated diseases; the median serum 25(OH)D value increased from 16 to 40ng/mL and from 15 to 35ng/mL, respectively. In all PCT patients, supplementation successfully raised VitD levels to the recommended values.

Discussion

There is increasing evidence that VitD deficiency is associated with older age, sedentary lifestyle, winter period, inadequate nutrient intake, reduced absorption of nutrients in

Table 5. Response to therapy as analysis median values of initial VitD levels (Di) and after therapy (Dt) according to gender, age decades, cancer stages and associated diseases.

Variables	PTC group	Serum	
	n=105	Vitamin Di (ng/mL)	Vitamin Dt (ng/mL)
Female, n	95/105	16	38
Male, n	10/105	17	40
Age groups n (%)			
30-39 years	5 (5%)	16	53
40-49 years	14 (13%)	17	48
50-59 years	22 (21%)	18	43
60-69 years	46 (44%)	16	39
70-79 years	18 (17%)	13	37
Cancer stages n (%)			
I	73 (70%)	16	40
II	16 (15%)	15	38
III	3 (3%)	24	29
IV	13(12%)	17	33
Associated diseases n (%)	68 (65 %)	15	35
Without associated diseases		16	40

the intestines, impaired liver, kidney and skin health, with various metabolic and endocrine diseases and cancers of various origins [9-11]. In our study, the recommendation for a well-balanced diet rich in vitamins and minerals food sources (with a focus on selenium, VitD3, zinc and iodine) is a lifestyle with high impacts on the therapy outcome in the PCT patients. The dietary recommendation approach presented, along with VitD3 supplementation, proves to be useful and beneficial in improving hormone status, TG levels, and results in an effective increase in 25(OH)D concentration, meeting the recommended levels. The role of dietary minerals and VitD3 is now confirmed by previous evidence: iodine, iron and copper are involved in hormone syn-

thesis, selenium and zinc affect the conversion T4 to T3 and VitD3 as nutrient is a hormone that not only affects a bone metabolism but also various processes in different organ systems: muscle, gastrointestinal, skin, brain and neural, and the immune system [12-14]. Furthermore, thyroid diseases are accompanied with low levels of VitD. Sites for thyroid hormone receptors and VitD receptors are similar- therefore this new research highlights the importance of a VitD hormone-like system [15, 16]. VitD has many direct suppressive effects on immune cells, as evidenced by its protective effect against auto-immune disease. VitD can modify the immune microenvironment of the tumor [17]. Current research focuses on VitD status and VitD receptor (VDR) activa-

tion by VitD3 supplementation that may be used to augment immunotherapy designed to improve T cell function. Khadz Kou et al. (2006) [17] showed the expression of VDR and 1- α hydroxylase in PTC and normal thyroid tissue suggesting the endogenous production of calcitriol in the thyroid gland. In addition, lower VDR expression in PTC metastatic lymph nodes compared to primary PTC and normal thyroid tissue implied the possible role of VitD via its effects, such as inhibition of cell proliferation and promotion of cell differentiation.

Previously published studies are applicable in interpreting our results. Our results confirm the connection between thyroid carcinoma and VitD deficiency (76% PTC patients had VitD < 20 ng/mL). Notably, our healthy subjects presented low VitD levels in 57% of participants, that could be attributed to a sedentary lifestyle. Because the BMI standard range is average for the age groups of patients in our study, all patients were well-nourishing, and it is not possible to investigate the relationship between initial VitD levels and response to VitD3 therapy. However, our results confirmed lower levels of VitD in PTC patients older than 55 years. Patients were mostly in the first stage of thyroid cancer, and to a lesser extent in other stages, hence the comparison of these subgroups was not applicable. In PTC patients with two cancers, VitD levels were at the lower limit (unmeasurable). Stepien et al. (2010) [18] suggested that the 1,25(OH) $_2$ D $_3$ level is associated negatively with PTC and is correlated with clinical staging.

Studies on breast, lung, intestinal, and prostate cancer have shown VitD deficiency in patients, and implicated recommendations that VitD levels should be maintained at around 40 nmol/L during therapy [1]. After 12 weeks of supplementation, our PTC patients responded well hence, the mean presented serum VitD value was 41.49 ± 17.78 ng/mL. There is evidence that VitD could be a new, potential biomarker to identify PTC and nodular goiter [6].

Furthermore, thyroid supplementation has been monitored, which showed adequate TSH and FT4 levels with input of lower concentrations of TG concentration as marker of thyroid cancer. Free triiodothyronine level was shown to be approximately 10% below the trough level. In this study, increased levels of FT3 and decreased levels of FT4, along with increased levels of VitD, are in consensus with the study in which better serum VitD levels are accompanied by improved effect of hypothyroidism therapy [8, 16]. The improvement in serum FT3 levels reached the lower threshold of recommended values. Dietary nutrients (selenium and zinc) also contributed to the efficient conversion of the active form of thyroid hormones.

Effective VitD3 supplementation can be administered parenterally (via depot intramuscularly) and/or can optimize functioning of the organ systems responsible for its metabolism, including the gastrointestinal tract, renal and skeletal system. However, fat malabsorption, bile salt deficiency, loss of absorptive surface, liver and kidney failure, are conditions often associated with gastrointestinal disease, that affect VitD3 absorption. These conditions indicated the importance of increasing physical activity and staying outdoors on sunny days [9]. Testing the effect of VitD3 supplements at annual controls would contribute to the assess-

ment of the supplement dose necessary to maintain serum VitD concentration within the recommended reference range.

In vitro models of PTC cells have shown that VitD has anti-proliferative, and pro-apoptotic effects (by increasing the levels of the antimicrobial peptide, cathelicidin) [6, 19]. The tumor marker of well-differentiated PTC is thyroglobulin, and its increase indicates recurrence or prolonged disease. In our study, the decrease in thyroglobulin levels was paralleled with the increase in VitD levels. This result could be attributed to the immune effect of VitD. In the literature immunological effects of VitD have been demonstrated by in vitro activation of lymphocytes allergic reactions [20, 21].

Vitamin D contributes to boosting immunity and is associated with the restoration of intestinal bacterial flora. An imbalance in intestinal microflora can be caused by acute or chronic infections with bacteria, viruses, and parasites infections and allergic reactions to food, caused by inadequate nutrition, etc. [21, 22]. The combined use of VitD3 and probiotics in vivo studies allows for improvement of intestinal function and overall immune support. In our PTC study group, there is a significant proportion of autoimmune disorders (Hashimoto syndrome, Sysicca), metabolic syndrome, inflammatory bowel disease and patients positive on *Helicobacter pylori* (due to anamnestic and medical data). In this case, the use of probiotics must be considered, in addition to VitD3 supplementation and a special FODMAP diet regime that we implemented in our study. In cases where musculoskeletal disease was presented, various supplements and multidisciplinary treatment with individual modalities was expanded in the therapeutic approach. Future research will contribute to determining the optimal level of VitD3 supplementation, as well as to the creation of individual modalities of therapeutic recommendations to improve clinical outcomes.

In conclusion, the results of evaluation of VitD status in our thyroidectomy patients with PTC indicate VitD deficiency. This points out the necessity of nutritional assessment to control VitD status in patients with thyroid gland carcinoma. The presented dietary recommendation applied as lifestyle changes and oral VitD3 supplementation improved its VitD status to the recommended serum levels in our patients. An increased concentration of VitD in the serum led to a discrete improvement in the status of thyroid hormones and a decrease in the level of thyroglobulin. Clinical data is still insufficient to determine whether low circulating VitD can be considered a risk factor for cancers, but our results point to the importance of VitD testing in cancer patients and the need to develop more effective supplementation in PTC patients along with an individualized dietary approach in accordance with the defined nutritional guidelines.

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