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The effect of vitamin D supplementation on bone mineral density in patients with differentiated thyroid cancer

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Abstract

It has demonstrated that there is a connection between chronic TSH suppressive treatment and the reduction of bone mineral density (BMD) or the development of osteoporosis in patients with differentiated thyroid cancer (DTC). The aim of the study was to determine the effect of vitamin D3 supplementation on BMD and the development of osteoporosis in patients with DTC. Two hundred four (204) patients with a diagnosis of DTC were included. All patients received thyroid hormone replacement therapy along with vitamin D (5000IU/day). Data including age, gender, body mass index, smoking, menopausal status, family history of osteoporosis, and postoperative duration were collected. The serum levels of TSH, calcium, 25-OH-vitamin D, and parathyroid hormone measurements and BMD by using dual-energy X-ray absorptiometry were performed on whole patients. The mean age of patients was 56.20±9.31 years. With osteoporosis, 22 of the patients were female (10.8%) and 1 was male (0.5%). Twenty one (21) females with OP were postmenopausal state. There was a statistically significant difference between osteoporosis and age, menopausal status, and family history of osteoporosis, but not for the other factors. Although there was no statistically significant difference between osteoporosis and the levels of TSH and vitamin D, most patients with osteoporosis had TSH<0.5 mIU/mL (n=18) and vitamin D<30 ng/mL (n=16). Age and family history of osteoporosis were identified as independent predictive factors for developing osteoporosis. Vitamin D may be considered as a supplemental and supportive treatment in patients with thyroid cancer for preventing cancer recurrence and osteoporosis.

Keywords: differentiated thyroid cancer, TSH suppressive therapy, osteoporosis, vitamin D

1. Introduction

Thyroid cancer is the most common endocrine malignant neoplasia (1). The traditional treatment for thyroid cancer is thyroidectomy with or without radioactive iodine ablation, followed by thyrotropin (TSH) suppression to prevent tumor recurrence (2). Although the survival rates increase with this treatment, long-term TSH suppressive therapy causes chronic subclinical hyperthyroidism (defined as suppressed TSH levels in the presence of normal free T4 levels), resulting in bone loss and osteoporosis due to stimulating bone resorption via extreme thyroid hormone and lack of TSH-mediated osteoclast suppression (3).

Vitamin D has a potential role in thyroid disorders such as autoimmune thyroid diseases (e.g. Hashimoto's thyroiditis, Graves' disease) and thyroid cancers. It acts on cancer cells via multiple signaling pathways, including inhibition of cellular proliferation, induction of differentiation, enhancement of apoptosis, and, reduction of inflammation, angiogenesis, and metastasis. Vitamin D deficiency has been implicated in the pathogenesis of thyroid cancers (4,5,6), therefore, vitamin D may be considered as a therapeutic tool for thyroid cancers. Moreover, it may also prohibit bone loss and osteoporosis associated with thyroid cancer therapy via the regulating function of bone and calcium homeostasis.

Previous studies have demonstrated that there is a connection between chronic TSH suppressive treatment and the reduction of bone mineral density (BMD) or the development of osteoporosis (7,8,9,10,11,12). We aimed that bone loss and osteoporosis may be prevented by using vitamin D in addition to the standard treatment. Therefore, the goal of the study is to determine the effect of vitamin D supplementation on BMD and the development of osteoporosis in patients with differentiated thyroid cancer (DTC).

2. Material and Methods

This prospective study was conducted at Kocaeli Government Hospital, Kocaeli, Turkey, between June 2020 and December 2020. Written informed consent was obtained from all patients.

We included 204 patients (172 female, 32 male) with a diagnosis of DTC followed up at the Department of Nuclear Medicine who received thyroid hormone replacement therapy in this study. Some studies have indicated that vitamin D supplementation for 12 weeks or longer is required for serum 25(OH)D levels to reach adequate levels (13,14). Therefore, the patients also utilized vitamin D (5000 IU/ day) for 6 months. Data including age, gender, body mass index (BMI), smoking, menopausal status, family history of osteoporosis, and postoperative duration were collected. The serum levels of TSH, calcium (Ca), 25-hydroxyvitamin D (25OHD), and

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parathyroid hormone (PTH) measurements were performed on whole patients. TSH suppressive therapy consists of the LT4 administration to suppress serum TSH levels, maintaining normal levels of serum-free T4 (FT4) and free T3 (FT3) (15). The dose of levothyroxine (LT4) was titrated by the level of TSH according to the guidelines of the American Thyroid Association. Patients with a previous history of osteoporosis and taking medication (such as bisphosphonates, calcium, and vitamin D supplements) for this were excluded from the study. Mean serum TSH levels were calculated from at least two serum TSH measurements per year. Vitamin D deficiency was defined as <20 ng/mL, insufficiency was defined as 21-29 ng/mL, and sufficiency was described as >30 ng/mL. The level of serum Ca was determined to be normal at 8.6–10.6 mg/dL, with hypocalcemia at less than 8.6 mg/dL and hypercalcemia at more than 10.6 mg/dL. The range of PTH level was 15-68 ng/L. Moreover, all patients underwent BMD of the femoral neck and lumbar vertebrae (L1-L4) by using dual-energy X-ray absorptiometry (DEXA). The presence of osteoporosis was accepted as T scores ≤ -2.5.

2.1. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY). The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the assumption of normality. Numerical variables were presented as mean±standard deviation and median (25th-75th percentile). Categorical variables were summarized as counts (percentages). Differences between groups were determined by independent-sample *t*-test for numerical variables with normal distribution and by Mann-Whitney U test for numerical variables without normal distribution. Relationships between categorical variables were evaluated using the Chi-square test, Fisher's exact test, and Fisher-Freeman-Halton exact test. Binary logistic regression was used to determine the cause-effect relationship between the dependent variable and the independent variables. The goodness of fit for logistic regression models was performed by the Hosmer-Lemeshow test. The likelihood-ratio statistic was used to compare the estimated models. Pearson Correlation analysis was used for the correlation between numerically measured and normally distributed variables, and Spearman Correlation analysis was used for the others. P-value < 0.05 was considered as statistically significant.

3. Results

The demographic characteristics of patients including age, gender, BMI, smoking, menopausal status, family history of osteoporosis, and duration of surgery are presented in Table 1. The mean age of patients was 56.20±9.31 years. Of all patients, 84.3% were female (*n*=172) and 15.7% were male (*n*=32). The mean BMI of patients was 30.34±5.00. Of all patients, 65.7% were non-smokers (*n*=134), 15.7% were smokers (*n*=32) and 18.6% had previously smoked and quit (*n*=38). While 60.3% of the women were in the postmenopausal period (*n*=123), 39.7% were in the premenopausal period (*n*=81). Of the patients, 16.7% had a family history of osteoporosis (*n*=34) and 83.3% had no family history of osteoporosis (*n*=170). The mean postoperative duration of patients was 6.69±4.69 years.

Table 1. Demographic and clinical characteristics of the patients

Variables	n (204)
Age (year)	56.20±9.31
Gender	
Female	84.3% (172)
Male	15.7% (32)
Body mass index (BMI)	30.34±5.00
Smoking	
Smoker	15.7% (32)
Non-smoker	65.7% (134)
Previously smoker and quit	18.6% (38)
Menopausal state	
Premenopausal	39.7% (81)
Postmenopausal	60.3% (123)
Family history of osteoporosis	
Yes	16.7% (34)
No	83.3% (170)
Postoperative duration (year)	6.69±4.69
Mean level of TSH (mIU/mL)	0.29±0.49
TSH < 0.1	38.2% (78)
TSH 0.1-0.5	46.1% (94)
TSH 0.5-1	11.8% (24)
TSH > 1	3.9% (8)
Mean level of PTH (ng//L) (15-68)	64.95±27.03
PTH 15-68	65.7% (134)
PTH > 68	34.3% (70)
Mean level of Ca (mg/dL) (8.6-10.6)	9.51±0.43
Ca < 8.6	2% (4)
Ca 8.6-10.6	98% (200)
Mean level of vitamin D (ng/mL)	27.67±11.01
Vitamin D < 20	22.5% (46)
Vitamin D 20-30	39.7% (81)
Vitamin D > 30	37.8% (77)

All values are expressed as mean±standard deviation, number and percentage

The various mean levels measured were: TSH, 0.29±0.49 mIU/mL; PTH, 64.95±27.03 ng/L; Ca was 9.51±0.43 mg/dL; and vitamin D, 27.67±11.01 ng/mL. The level of PTH was 15-68 ng/L in 65.7% (*n*=134) and >68 ng/L in 34.3% (*n*=70) of patients. The level of vitamin D was <20 ng/mL in 22.5% (*n*=46), 20-30 ng/mL in 39.7% (*n*=81), and >30 ng/mL in 37.8% (*n*=77) of patients. The level of Ca was < 8.6 mg/dL in 2% (*n*=4) and 8.6-10.6 mg/dL in 98% (*n*=200) of patients. Twenty-three (11.3%) patients had osteoporosis: one of them

was male (0.5%) and the others were female (10.8%). Twenty one (21) females with OP were postmenopausal state. The L1-L4 T score was ≤ -2.5 in 7.4% of the patients (*n*=15) and the femoral neck T score was ≤ -2.5 in 6.9% of the patients (*n*=14); both T scores were ≤ -2.5 in 2.9% of the patients (*n*=6) who were women. The patients were divided into four groups according to their TSH levels: Group 1: 78 patients (38.2%) with TSH < 0.1 mIU/mL; Group 2: 94 patients (46.1%) with TSH 0.1-0.5 mIU/mL; Group 3: 24 patients (11.8%) with TSH 0.5-1.0 mIU/mL; and Group 4: 8 patients (39.%) with TSH > 1 mIU/mL.

Table 2. The findings of patients with osteoporosis

Variables	Osteoporosis (n=23)	Non-osteoporosis (n=181)	*P value
Age (year)	61.17±9.91	55.56±9.07	0.006
Gender			
Female	10.8% (22)	73.5% (150)	0.137
Male	0.5% (1)	15.2% (31)	
Body mass index (BMI)	28.68±4.51	30.55±5.03	0.122
Smoking			
Smoker	1.5% (3)	14.2% (29)	0.408
Non-smoker	8.8% (18)	56.9% (116)	
Previously smoker and quit	1% (2)	17.6% (36)	
Menopausal state			
Premenopausal	2% (4)	37.7% (77)	0.020
Postmenopausal	9.3% (19)	51% (104)	
Family history of osteoporosis			
Yes	4.4% (9)	12.3% (25)	0.005
No	6.9% (14)	76.5% (156)	
Postoperative duration (year)	6.13±4.93	6.76±4.67	0.505
Mean level of TSH (mIU/mL)	0.34±0.39	0.29±0.51	
TSH < 0.1	3.4% (7)	34.8% (71)	
TSH 0.1-0.5	5.4% (11)	41.7% (85)	0.551
TSH 0.5-1	1.5% (3)	9.8% (20)	
TSH > 1	1% (2)	2.9% (6)	
Mean level of PTH (ng//L) (15-68)	73.22±28.42	63.90±26.75	
PTH 15-68	5.9% (12)	59.8% (122)	0.224
PTH > 68	5.4% (11)	28.9% (59)	
Mean level of Ca (mg/dL) (8.6-10.6)	9.61±0.34	9.49±0.44	
Ca < 8.6	0% (0)	2% (4)	0.231
Ca 8.6-10.6	11.3% (23)	86.8% (177)	
Mean level of vitamin D (ng/mL)	26.07±8.65	27.88±11.27	
Vitamin D < 20	2.9% (6)	19.6% (40)	0.750
Vitamin D 20-30	4.9% (10)	35.3% (72)	
Vitamin D > 30	3.4% (7)	33.8% (69)	

All values are expressed as mean±standard deviation, number and percentage. *p<0.05, significant difference

The demographic and clinical characteristics of patients with and without osteoporosis are presented in Table 2. There was a statistically significant difference between osteoporosis and age, menopausal status, and family history of osteoporosis, but not for the other factors (Table 2). The sensitivity, selectivity, and accuracy rate of the logistic regression model selection method was found to be 87.7%. Age and family history of osteoporosis were identified as independent predictive factors for developing osteoporosis (Table 3). A statistically significant relationship was found between L1-L4 T score and age, BMI, and duration of surgery. Also, a statistically significant relationship was found between the femoral neck T score and only age (Tables 4 and 5).

Table 3. Independent predictive factors of developing osteoporosis (OP)

Variables	B (Odds ratio)	P value	95% CI for B (CI: Confidence interval)
Age	1,117	<0,001	1,051-1,188
Family history of OP	2,472	0,001	1,421-4,298

Table 4. Correlation between L1-L4 T score and age and calcium

Variables		Age	Calcium
L1-L4 T score	Pearson Correlation (r)	**-0,270***	0,012
	Sig. (2-tailed) (p)	<0,001	0,863

*Correlation is significant. p<0.05, significant difference

Table 5. Correlation between osteoporosis and age, duration of surgery, BMI, PTH, TSH, vitamin D and calcium

Variables	L1-L4 T score		Femoral neck T score	
	r	p	r	p
Age	-	-	**-0,389***	<0,001
Postoperative duration	**-0,166***	0,018	-0,081	0,250
Body mass index (BMI)	**0,181***	0,009	0,048	0,495
The level of PTH	-0,053	0,454	-0,115	0,102
The level of TSH	0,016	0,815	-0,094	0,183
The level of vitamin D	0,016	0,822	0,004	0,957
The level of Ca	-	-	-0,001	0,990

r: Spearman Correlation Coefficient,*Correlation is significant. p<0.05, significant difference

4. Discussion

The suppression of TSH by exogenous levothyroxine has an important place in the prognosis of thyroid cancer owing to the expression of TSH receptors on the tumor cell membrane and the stimulation of cell growth rate by TSH. The main goal of TSH suppressive therapy is to obtain lower levels of TSH in order to decrease cancer recurrence. On the other hand, long-term TSH suppressive therapy and associated subclinical hyperthyroidism are related to an increased risk of fractures (7,8,9,10,11,12,16,17). Apart from the function of regulating bone and calcium metabolism, vitamin D also has an important role in arranging cell proliferation, differentiation, and apoptosis, and in coordinating the improvement of the immune system (5). Considering the impaired vitamin D signal in thyroid cancers (4,5,6), we aimed that bone loss and osteoporosis may be prevented with vitamin D supplementation in addition to the standard treatment. According to our study, we found that 23 patients (22 females and 1 male) had osteoporosis and there was a statistically significant difference between osteoporosis and age, menopausal status, and family history of osteoporosis, but not for the other factors. Although there was no statistically significant difference between osteoporosis and the levels of TSH and vitamin D, most patients with osteoporosis had TSH<0.5 mIU/mL (n=18) and vitamin D<30 ng/mL (n=16). As a result of the study, even though vitamin D replacement does not seem to prevent the development of osteoporosis caused by TSH suppressive therapy, the failure to achieve this effect may be due to the inability to reach the targeted vitamin D level despite replacement therapy. Well-designed randomized clinical trials are needed to determine the efficacy of vitamin D. Moreover, we analyzed additional risk factors for developing osteoporosis and determined age and family history of osteoporosis as independent predictive factors.

Tournis et al. investigated the effect of TSH suppressive therapy on skeletal integrity using peripheral quantitative computed tomography (pQCT) at the radius and tibia in pre- and postmenopausal women with DTC and controls. They found that levothyroxine suppressive therapy leads to significant trabecular bone loss only in postmenopausal women and mainly at non-weight-bearing sites such as the radius, but not cortical bone. They explained this finding, with higher 25OHD levels leading to lower PTH and parathyroid dysfunction following thyroidectomy in patients with DTC (16). Moon et al. examined the effect of TSH suppression on bone geometry in the hip area of pre-and postmenopausal women with DTC. They remarked that the suppression of TSH in postmenopausal DTC patients was related to decreased bone strength by the altered bone geometry rather than BMD in the hip region, particularly at the femoral neck (17). Kim et al. demonstrated no detrimental effect of suppressive levothyroxine therapy in women with DTC regardless of their estrogen status and found a protective effect in women with postoperative hypoparathyroidism (18). Lin et al. compared the risk of osteoporosis and osteoporotic fracture among 9398 thyroid cancer patients with levothyroxine use, those without levothyroxine use, and propensity-score-matched controls. They found that thyroid cancer patients receiving levothyroxine have a higher risk of osteoporosis. They also reported that long-term levothyroxine use and high cumulative levothyroxine dose were significantly related to an increased risk of osteoporosis in thyroid cancer patients after subsequent thyroidectomy (19). In a meta-analysis, Yoon et al reported

that chronic TSH suppressive therapy caused lower BMD of the spine and total hip in postmenopausal women (but not in premenopausal women and men) with DTC. They identified postmenopausal women with DTC receiving TSH suppressive therapy as a risk group for bone loss and stated that menopause is also an important risk factor in the formation of osteoporosis (11). In another meta-analysis, Wang et al evaluated the effect of TSH suppressive therapy on BMD in patients with DTC. They found that TSH suppressive therapy in patients with DTC mainly reduces the proximal femur BMD. They attributed this to the fact that cancellous bone is dominant in the lumbar spine whereas cortical bone is dominant in the femur, and the osteoclast activity of cortical bone is higher than that of cancellous bone (20). In our study, there was no statistically significant relationship between TSH values and both L1-L4 T scores and the femoral neck T score. However, the TSH level was <0.5 mIU/mL in most patients with osteoporosis. It seems that further studies are needed to evaluate it in this respect. Moreover, Soydal et al identified the risk factors for the development of osteoporosis in patients receiving TSH suppressive therapy for DTC. They reported that postmenopausal women, men, and patients with a family history of receiving TSH suppressive therapy tend to develop osteoporosis (12). In our study, the independent predictive factors contributing to the development of osteoporosis in patients who received TSH suppressive therapy were age and family history of osteoporosis.

Although Kim et al. proved that low but normal TSH values are related to low BMD in healthy euthyroid women (21), several other studies have shown no effect of TSH on BMD in euthyroid women (15,22,23). Arnautovic-Halimic et al. suggested that although the physiological variations of TSH are an early marker for the emergence of osteoporosis, understanding the effects of thyroid hormone on bone tissue is a major challenge. They also stated that further studies are needed to determine the cut-off value of serum TSH, which is a risk factor for bone loss (24). The main effect of thyroid hormone on the skeleton is the shortening of the bone remodeling cycle by regulating osteoblast differentiation and stimulating osteoclasts, resulting in increased bone turnover and a general loss of mineralized bone. Moreover, TSH displays a direct protective effect on bones by increasing osteoblast differentiation and reducing bone resorption via stimulating osteoprotegerin, which is a soluble receptor for receptor activation for nuclear factor-kB ligand (RANKL) and inhibits osteoclasts by preventing interaction of RANKL with its receptor RANK. Bone loss in patients with DTC may be caused by both the direct effect of thyroid hormones and the inability to maintain the protective effect of TSH (11,16,17,18). However, the possible side effects of TSH suppressive therapy on bone metabolism continue to be controversial (10). This indicates that the increased incidence of osteoporosis in patients with thyroid cancer is associated not only with iatrogenic hyperthyroidism but also with a variety of other factors, such as age, gender, and bone health of the patient, a family history of osteoporosis, menopausal status, the presence of preoperative hyperthyroidism, calcium intake, vitamin D status, residual parathyroid function and medications (9,12,16). Therefore, it has been suggested that TSH suppressive therapy should be individualized according to the risk group of thyroid cancer and the risk factors associated with the patient in terms of the development of osteoporosis, making sure that patients with risk factors are followed carefully (8,12,25). We also agree with this idea.

Although there is no consensus on the optimal TSH concentration to reduce tumor recurrence and the risk of osteoporosis due to exogenous subclinical hyperthyroidism, it seems that a TSH level of around 0.9 or 1 mIU/L is ideal for preventing the risk of osteoporosis, even if the risk of cancer recurrence remains unaltered. Interestingly, the lower level of TSH (between 0.5 and 0.7 mIU/L or ≤0.4 mIU/L) enhances the risk of osteoporosis (7,8). Although we found no significant correlation between mean serum TSH levels and the presence of osteoporosis, most patients with osteoporosis had TSH<0.5 mIU/mL (n = 18). However, this may be due to the small sample size.

The American Thyroid Association and the European Thyroid Association advocate setting treatment goals based on the risk grade of tumor recurrence in DTC patients (20). Despite contradictory results in existing studies regarding the effect of TSH suppressive therapy on bone in patients with thyroid cancer, postmenopausal women are at risk for developing osteoporosis (8). The possible mechanism of exogenous hyperthyroidism is to induce bone turnover and shorten the bone remodeling cycle through the TSH receptor on osteoblast and osteoclast precursors, thereby resulting in bone loss and a decline of BMD (11). The absence of estrogen at menopause causes the release and production of RANKL, which activates the proliferation of osteoclasts. This impact could be increased by subclinical hyperthyroidism related to TSH suppressive therapy (10). However, there is no firm recommendation for monitoring TSH levels to prevent accelerated bone turnover (18). This is not only explained by the negative impact of TSH suppressive therapy on the bone but may also be due to several factors, such as genetic determinants, age, gender, nutrition, particularly calcium and vitamin D intake, delayed puberty, physical activity, a wide variety of intercurrent illnesses and social factors (i.e. low family income), that affect the ability to reach optimal peak bone mass (20,26). Moreover, postmenopausal women undergoing chronic TSH suppressive therapy with levothyroxine are at risk of bone loss, especially if osteopenia or osteoporosis is already present, whereas there is no adverse effect on BMD in premenopausal women and men (25,26). In our study, we also detected more osteoporosis in postmenopausal women with DTC. In a review, Brancatella et al. proposed that bone health should be evaluated via BMD and/or QCT in postmenopausal women under chronic TSH

suppressive therapy or in those patients planning to be treated for several years (more than 3-5 years) and repeated every 2 years thereafter. They also stated that adequate calcium intake and vitamin D supplementation should be considered when planning antiresorptive therapy in order to prevent bone loss in selected cases (increased risk of fracture or significant decline of BMD/QCT during therapy) (25).

Hypocalcemia is one of the most common complications after thyroidectomy because of unplanned parathyroidectomy or parathyroid gland devascularization. Therefore, routine oral calcium and vitamin D supplements have been proposed to prevent the development of symptomatic hypocalcemia owing to postsurgical hypoparathyroidism after thyroidectomy (27,28). A meta-analysis evaluating the effectiveness of routine calcium supplementation with or without vitamin D in preventing hypocalcemia post-thyroidectomy demonstrated that calcium plus vitamin D was more influential than calcium alone, even if only calcium supplementation is effective (29). Another meta-analysis and systematic review proposed that the combination of vitamin D or metabolites with calcium is the most effective strategy. Postoperative PTH levels have a high sensitivity and specificity for predicting hypocalcemia. There is no consensus on the dosage and duration of use of these supplementation treatments, therefore, calcium and/or vitamin D supplementation may be determined using the postoperative PTH level (28). None of the patients in our study had hypoparathyroidism. Therefore, they received only vitamin D supplementation but not calcium supplementation.

The active form of vitamin D (1,25(OH)2D) exposes its biological effects by binding to the vitamin D receptor (VDR). Thyroid and thyroid cancer cells have VDRs (4). There is an interaction between vitamin D signaling and nuclear receptor ligands in cancer cells. Subsequently, vitamin D signaling increases the expression of its target genes (6). The anti-tumoral mechanisms of vitamin D can be listed as follows: (a) inhibition of cell proliferation by modulating the intracellular kinase pathways, such as p38, MAPK, ERK and PI3K, repressing the proto-oncogene *MYC, inhibiting* the high telomerase activity characteristic of human cancer cells by decreasing telomerase reverse transcriptase (*TERT*) mRNA expression, inhibiting mitogenic signaling by growth factors such as insulin-like growth factor 1 (IGF-1) and epidermal growth factor (EGF), increasing the expression of growth inhibitors such as transforming growth factor-β (TGF-β), expressing the cyclin-dependent kinase (CDK) inhibitors p21 and p27, and reducing CDK activity, thereby leading to dephosphorylation of the retinoblastoma (Rb) protein and G0/G1 cell cycle arrest; (b) apoptosis by inhibiting anti-apoptotic proteins (BCL-2 and BCL-X_L) and inducing the expression of pro-apoptotic proteins (BAX, BAK and BAD) and caspase activation ; (c) activation of differentiation by regulating β-catenin, JUN N-terminal kinase, PI3K and nuclear factor-κB (NF-κB) signaling pathways and the activity of transcription factors such as activator protein 1 complex and CCAAT/enhancer-binding protein (C/EBP); (d) suppression of inflammation via inhibiting prostaglandin synthesis (by suppressing cyclooxygenase 2 expression), prostaglandin signaling (by upregulating the expression of catabolic enzyme and repressing the expression of prostaglandin receptors), p38 stress kinase signaling and subsequently the production of pro-inflammatory cytokines and NF-κB signaling; and e) prevention of invasion and metastasis by adjusting the expression of the plasminogen activator system and matrix metalloproteinases (MMPs), raising the expression of E-cadherin (a tumor suppressor gene that is inversely related to the metastatic potential) and inhibiting angiogenesis by suppressing the expression of vascular endothelial growth factor (VEGF) (5). Moreover, it has been suggested that vitamin D deficiency may be a potential risk factor for thyroid cancer, and it can be thought that higher concentrations of vitamin D may have a protective effect against thyroid cancer and decrease the risk of thyroid cancer (30,31).

It is known that the main function of vitamin D is to maintain healthy bones by arranging calcium homeostasis. Moreover, osteoblasts are among the cells expressing VDR; in this way, active vitamin D can affect human osteoblast growth and differentiation, stimulating bone formation and mineralization. Active vitamin D also inhibits differentiation into mature osteoclasts by suppressing c-Fos protein (which is the product of the RANK/RANKL signaling pathway) in bone marrow macrophages via VDR. Additionally, calcium is well known to be necessary for healthy bone development and plays a very important role in bone remodeling. In the bone deposition process, bone is formed by calcium and phosphate ions binding to create hydroxyapatite crystals. Vitamin D is also able to increase the absorption of gastrointestinal calcium into the bone (32). Kung et al. have shown that thyroxine suppressive therapy is related to bone loss in postmenopausal women and can be prevented even with calcium supplements alone (33). Moreover, vitamin D and calcium supplementation can reduce accelerated bone loss in patients after menopause, with an increase in bone mineralization and a decrease in remodeling (18). Liu et al suggested that supplementation with vitamin D and calcium should be in addition to the basic drug administration in order to delay the osteoporosis process in the treatment of patients with hyperthyroidism combined with osteoporosis (34). Although there was no statistically significant difference between osteoporosis and both Ca and vitamin D levels, most patients with osteoporosis had vitamin D <30 ng/mL (n=16), and all patients with osteoporosis had normal serum levels of Ca (n=23). Therefore, we think that vitamin D in addition to the standard treatment may contribute to the prevention of osteoporosis and cancer recurrence.

On the other hand, some limitations of the present study include a small sample size; no control group; no menopausal duration; the absence of serum levels of free T3 and T4; the lack of data with serum levels of 25(OH)D before vitamin D

supplementation; the lack of serum and urine bone turnover markers; no evaluation of the long-term consequences of TSH suppressive therapy on bone metabolism. Further studies with larger sample sizes and control groups are needed to investigate the effect of vitamin D supplementation in addition to TSH suppressive therapy on BMD.

Although there are controversies regarding the detrimental effect of TSH suppressive therapy on BMD, vitamin D may be considered a supplemental and supportive treatment

Conflict of interest

The authors declared no conflict of interest.

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None to declare.

Authors' contributions

Concept: E.Y., Design: E.Y., Data Collection or Processing: E.Y., G.T., Analysis or Interpretation: E.Y., Literature Search: E.Y., Writing: E.Y.

Ethical Statement

The study protocol was approved by the Ethical Committee of Derince Training and Research Hospital, Kocaeli, Türkiye (Trial registration: DEAH GOKAEK 2020/128).

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