

Evaluation of Bone Density, Serum Total and Ionized Calcium, Alkaline Phosphatase and 25-hydroxy Vitamin D in Papillary Thyroid Carcinoma, and their Relationship with TSH Suppression by Levothyroxine

Abstract

Background: This study aimed to evaluate the situation of Bone Mineral Density (BMD), Z score, T score, serum level of corrected and ionized calcium, alkaline phosphatase and 25-hydroxy vitamin D in percutaneous transhepatic cholangiography (PTC) patients and correlation of these variants with thyroid stimulating hormone (TSH) suppression level by levothyroxine. **Materials and Methods:** Among the patients referred to Esfahan's endocrinology research center, 34 PTC patients (aged 20–50 years) with a history of thyroidectomy and conceived radioactive iodine and suppressive dose of levothyroxine were evaluated in this case–control study, and 38 healthy persons participated as the control group (matched by age and sex, body mass index). Bone density was evaluated with the DEXA method in four areas: Lumbar spine, femoral neck, and trochanter and distal of forearm. A reference laboratory assessed TSH, corrected and ionized calcium, Alkaline phosphatase (ALP) and 25OH vitamin D levels using fasting plasma and evaluated correlation of TSH level with variants by multivariate variance analysis. **Results:** There was no significant difference in bone density and laboratory data (unless TSH) between the groups. In the PTC group, there was no significant correlation between TSH and difference values of BMD, Z score or T score, corrected calcium (P value = 0.12), ionized calcium (P = 0.54), ALP (P = 0.22) and 25 OH vitamin D (P = 0.38). There was no significant correlation in the TSH subgroups with BMD. The TSH suppression level has no relation with the elevated prevalence of low BMD, hypocalcemia and vitamin D deficiency. Difference in odds ratio was not significant for osteopenia and osteoporosis between the TSH subgroups (TSH < 0.02, >0.02 and <0.1 and >0.1 mu/L). **Conclusion:** Suppressive therapy with levothyroxine cannot decrease BMD, Z score and T score in PTC patients.

Keywords: ALP, BMD, corrected calcium, DEXA, ionized calcium, PTC, T score, TSH, 25 OH vitamin D, Z score

Introduction

Papillary thyroid carcinoma includes about 80% of thyroid cancers. The patients are often 30–50 years old, among whom 70% are female. This malignancy has little effect on survival, with a 25-year survival of 95%,^[1,2] i.e., it had a good prognosis, the recurrence of the disease was not common and it has only been observed in 15% of patients (mostly during the first year) after their treatment.^[1] It often occurs locally in the thyroid bed or cervical lymph nodes. The recurrence or metastasis of this disease in distant regions is rare; in a follow-up of 20 years, only 4% of the patients experienced relapse of the disease. These are the patients who, in terms of recurrence, are placed into the moderate- or high-risk groups and, in case of multi-years'

follow-up of low-risk patients, it has been observed that recurrence had only occurred in <1% of the patients.^[2]

After diagnosis, patients with papillary thyroid cancer undergo total thyroidectomy and treatment with radioactive iodine.

All patients, after taking iodine, will be treated with high-dose levothyroxine (2 µg/kg/day) for TSH suppression to prevent tumor re-growth, so that TSH is initially kept in the range of <0.1 mu/L and that the drug will be taken until the end of life. But, the dose may differ in such a way that if there was no sign of recurrence in 6–12 months of follow-up and/or the patients were assigned

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Access this article online

Website: www.advbiores.net

DOI: 10.4103/2277-9175.211799

Quick Response Code:



How to cite this article: Kachui A, Tabatabaizadeh SM, Iraj B, Rezvanian H, Feizi A. Evaluation of Bone Density, Serum Total and Ionized Calcium, Alkaline Phosphatase and 25-hydroxy Vitamin D in Papillary Thyroid Carcinoma, and their Relationship with TSH Suppression by Levothyroxine. *Adv Biomed Res* 2017;6:94.

Received: August, 2014. **Accepted:** October, 2014.

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in the low-risk group, the high inhibitory dose should be reduced; this means that the serum TSH level should be kept within 0.1–0.5 mu/L in this situation.^[1] If there was no tumor recurrence in the second follow-up year, TSH will be increased to 0.5–2.5, such that the associated side-effects can be prevented. These complications resulted from the issue that the abundance of thyroid hormone causes bone resorption, which itself, in addition to osteopenia, may cause increased serum calcium. Hyperthyroidism-related hypocalcemia causes decreased serum PTH,^[1] which in turn causes low production of 1,25 (OH) vitamin D, reduces calcium and phosphorus absorption of the intestine as well as renal reabsorption and, consequently, the process of osteoporosis is accelerated. Also, similar to hyperthyroidism, the suppressive dose may, in addition to increase in ionized, total calcium and serum alkaline phosphatase, decrease BMD, especially in postmenopausal women.^[2] However, consumption of a suppressive dose for 10 years in premenopausal women had decreased BMD only about 9%, which was not significant, and was due to adequate estrogen in serum.^[3]

It should be noted that decrease in BMD is common in postmenopausal women and old men, but it can also be seen in middle-aged men and premenopausal women suffering from thyrotoxicosis, primary hyperparathyroidism, type 1 diabetes, malabsorption syndromes and severe vitamin D deficiency. Furthermore, the prolonged use of drugs such as glucocorticoid and phenytoin as well as high-dose levothyroxine can have a role in the development of osteoporosis. Low BMI (<20) is also a predisposing factor.^[4,5]

Although the effect of levothyroxine with inhibitory dose has been proven in menopausal women,^[6] different results have been reported on patients under 50 years, while some studies confirmed the effect on BMD and others did not show this result. On the other hand, 25-hydroxy vitamin D deficiency cannot be specified to them due to its elevated prevalence in all age groups, but determination of participants with deficiency is necessary because its treatment is effective in osteoporosis prophylaxis and treatment.^[7] Also, it is probable that the consumptive dose of radioactive iodine affects the level of TSH.

In fact, a suppressive dose of levothyroxine may affect the bone density and T-score, including lumbar spine, femoral neck, trochanter, distal of forearm, total and ionized calcium levels and alkaline phosphatase in menopausal women and older men, but this effect has not been proven in persons <50 years, and there is controversy. Also, ionized calcium levels of serum and its correlation with TSH suppression and bone density were not investigated which can be considered as a reason to design our study. This effect is expected to be more severe in cases of vitamin D deficiency. Thus, if the relationship between a high dose and the above variables is approved in cases where the risk of PTC recurrence is low, a minimum suppressive

dose of the drug will be recommended in order to prevent the complications of TSH inhibition, including heart complications such as heart failure and atrial fibrillation and bone complications such as osteoporosis, fractures and hypercalcemia.^[8] Therefore, this study aimed to determine the bone mineral density, total and ionized calcium, alkaline phosphatase and 25-hydroxy vitamin D serum in PTC patients <50 years, and their relationship with the inhibition of TSH by levothyroxine. If this correlation is confirmed, advise a decrease in the suppressive dose in low-risk cases.

Materials and Methods

Study design and participants

This is a case–control study, and subjects were selected among the outpatients with PTC cancer who had undergone thyroidectomy.

This study was conducted from April 2013 to March 2014 in Isfahan, Iran, in three clinic centers, i.e. Special Clinic of Al-Zahra Hospital, Isfahan Endocrine Research Center and Bone Densitometry Unit of Seyyed-Al-Shohada Hospital, all affiliated to the Isfahan University of Medical Sciences.

The inclusion criteria were: Male and female patients taking levothyroxine with an inhibitory dose of TSH for at least 6 months, age 20–50 years, no distant metastasis and no drug affecting the bone density (such as glucocorticoid, vitamin D, calcium and antiepileptic medications). Patients with low back pain (probably osteoarthritis of lumbar spine) due to its false-positive effect on bone density were excluded. As a control group, healthy relatives of patients who took no medications were included after BMI, sex and age matching. None of the participants in the two groups were nonsmokers. At least one person of the control group was selected as per patient simultaneously. Selection and data collection were carried out directly by an endocrinology resident. Because of the influence of old age and menopause on bone density, individuals over the age of 50 years were excluded from the study.

The minimum required sample size with respect to 95% confidence level, test power of 80, estimated standard deviation of BMD about 1.2 and minimum significant difference between the two groups was 0.8 and, by using the sample size formula for comparison of the two averages, it was estimated to be 30 subjects per group.

Written consent was obtained from all participants at the time of enrollment, followed by their primary characteristics including age, sex, height and weight, amount and duration of taking levothyroxine and cumulative dose of levothyroxine or received radioiodine were specified and recorded in a questionnaire. Requests were sent to the reference Endocrine laboratory center as well as the densitometry center of Seyyed-Al-Shohada in order to perform laboratory tests and evaluate bone density.

Procedures and variables assessment

A laboratory technician in the blood sampling unit collected the blood samples from referrals and a fasting sample (10 h fasting) with a volume of 4 cc was taken without the use of a tourniquet. Because there were no available facilities for testing 25-hydroxy vitamin D on the same day, a portion of the sample was kept frozen at -80°C . Total calcium serum level was determined by the Arsenazo method and ionized calcium was determined using the ISE device and the Arsenazo method. Also, TSH levels were determined by the ELISA method and with the use of an automatic Siemens device model: ADVIA center CP. The level of 25-hydroxy vitamin D serum was measured by the Eliza method and an IDS kit. All experiments were directly monitored by a laboratory expert. All reported calcium cases were corrected by fasting serum albumin.

An experienced expert working in densitometry performed bone measurement examinations on all cases at the Seyyed-Al-Shohada center. In this study, bone mineral density was measured by the highly sensitive Norland device and through the DEXA method in four regions of the lumbar spine (L2–L4), femoral neck, trochanter and distal forearm. The results, after adjustments for age, sex, BMI and race, were provided in BMD (g/cm^2), T-score and Z-score.

In order to increase the accuracy of the study, both laboratory and densitometry units had already received the required trainings. After preparing bone density test results and return of the patients to the research centers, their questionnaires were filled in and then at the end of the study patients with osteopenia and osteoporosis and/or 25-hydroxy vitamin D deficiency were prescribed calcium, vitamin D and levothyroxine with or without alendronate. 25 OH vitamin D serum levels in the range of 20–29.9 ng/mL were considered insufficient, 10–19.9 were considered as moderate deficiency and <10 was considered as severe deficiency.^[4,9] Moderate and severe deficiencies of this vitamin play a critical role in the development of osteopenia and osteoporosis.

In general, $-2.5 < \text{T-score} \leq -1$ of osteopenia, and less than or equal to -2.5 is regarded as osteoporosis. In this

research, Z-score was examined with respect to the age of the participants (equality T-score and Z-score in age <40 years), and values in the range of -1 to -2.5 were regarded as osteopenia while values less than or equal to -2.5 were regarded as osteoporosis.^[5,6]

Because the values of Z score, T score and BMD should be defined based on a healthy population of the same community, through consideration of previous studies, the BMD, Z score and T score of the patients and control group were evaluated according to healthy young adults of the same age in the region (reference or standard population), and SD range of ± 1 was considered as normal and lower values as abnormal.

In this study, personnel of the laboratory and center of bone densitometry were not aware of the health or disease situations of the participants of the study. Also, BMD was measured in one-third of the forearm to increase the sensitivity of osteoporosis detection.^[7,10]

Statistical analysis

The collected data were analyzed by using SPSS software version 22. Numerical variables were reported as mean and SD and nonnumerical variables as number and percentage. Comparison of the two groups was done using independent samples *t*-test in terms of numerical variables and Chi-square or Fisher's exact test (as appropriate) to evaluate the relationships between qualitative variables.

Results

A total of 47 patients and 55 healthy individuals were included in this study, among them 13 from the group of patients and 17 from the control group, due to do neither BMD nor laboratory tests, were excluded from the study. A total of 34 PTC patients and 38 healthy individuals completed the study. In Table 1, demographic and laboratory variables of the two groups of patients and controls are displayed according to gender segregation. According to the T-test, there was a significant difference in the TSH serum level of both groups of patients and controls ($P < 0.001$), but the difference between the serum

Table 1: Distribution of demographic and laboratory variables in both groups of patient and control according to gender segregation

Group Characteristics	Case group		Control group		P value		
	Female (25)	Male (9)	Female (28)	Male (10)	Female (53)	Male (19)	Total comparison of both the groups
Age (years)	49.7±38	65.6±7.33	18.8±2.36	13.8±2.33	06.0	08.0	41.0
Weight (kg)	1.16±3.69	7.15±1.76	35.11±79.65	34.11±75	0.06	870.	36.0
BMI (kg/m^2)	.85±827.	7.3±625.	14.5±63.26	74.2±4125.	450.	93.0	45.0
TSH ($\mu\text{u}/\text{L}$)	35.0±16.0	83.0±30.	23.1±871.	73.0±6.1	001.0<	03.0	001.0<
Total (corrected) calcium (mg/dL)	.670±9	4.0±66.9	56.0±4.9	21.0±5.9	0670.	31.0	017.0
Ionized calcium (mole/L)	21.0±131.	07.0±1.1	0.06±151.	21.0±21.1	750.	15.0	014.0
ALP (u/L)	6.58±4.197	4.66±7.202	59.41±5.187	7.55±7.247	49.0	140.	49.0
Vitamin D (ng/mL)	3.26±5.30	05.8±4.21	16.19±65.20	6.7±7.17	054.0	33.0	054.0

level of 25 OH vitamin D in the two groups was marginally meaningful ($P = 0.054$).

In Table 2, the frequency distribution of vitamin D serum level in both groups is shown. Based on this table, 25-hydroxy vitamin D deficiency was observed in 71% of the patients (65.2% women and 87.5% men), and the incidence of this deficiency was 91.7% in the control group (88.5% for women, 100% for men). Vitamin D deficiency was more common among men and, at the level of 10–19.9 ng/mL, there was a significant difference between women of both groups ($P < 0.02$). However, there was no relationship between serum vitamin D and TSH levels ($P < 0.09$). Also, we did not find a relation between daily doses of levothyroxine, accumulative dose and received radioactive iodine with BMD. Although a significant difference was found in the level of total and ionized calcium in both groups, no relationship between these two and the serum TSH level was observed ($P = 0.12$ and $P = 0.19$, respectively). Also, no relationship was observed between serum increased alkaline phosphatase level (that was seen in 10% of the cases) and TSH level.

The results are related to BMD, T score and Z score evaluation of the two participating groups in lumbar

spines (L2–L4), femoral neck, trochanter and distal of forearm [Table 3]. According to the BMD results, decrease in bone density was common and almost equal in the two groups. Therefore, a TSH suppressive dose of levothyroxine could not decrease BMD in PTC patients, but this correlation was meaningful in the trochanteric region ($P = 0.05$).

Table 4 shows the distribution of participants according to TSH and T-score level. In this study, there was no relationship between T-score of the lumbar spine and femoral neck with serum TSH level in the patients ($P = 0.33$ and 0.07 , respectively), but there was a significant relationship between T-score levels of trochanter with TSH values ($PV = 0.043$). Difference in odds ratio was not significant for osteopenia and osteoporosis between the TSH subgroups (TSH <0.02 , >0.02 , <0.1 and >0.1 mu/L).

The relationship between Z-score and TSH level was also examined in patients, and there was no significant relationship overall ($P < 0.07$). However, this relationship was marginally significant for the trochanteric region ($P = 0.055$).

Discussion

This case-control study on PTC patients of <50 years old aimed to evaluate the BMD, Z-score and T-score of bony

Table 2: Comparison of serum 25-hydroxy vitamin D level in both groups of patients and controls

*Vitamin D level ng/mL	Case group			Control group			P value		
	Female (23)	Male (8)	Total (31)	Female (26)	Male (10)	Total (36)	Female (49)	Male (18)	Total comparison of both groups
30 \geq	(.8%34) 11	(%12.5) 1	(19.2%) 9	(.5.11%) 3	0	(.38%) 3	0.550.	98.0	20.0
9/29-20	(1%26.) 6	(5.37%) 3	(29%) 9	(6.34%) 9	(50%) 5	(9 %38.) 14	0.630.	08.0	067.0
9/19-10	(7.21%) 5	(50%) 4	(29%) 9	(6.34%) 9	(30%) 3	(3 .33%) 12	0.020.	10.	054.0
10<	(4.17%) 1	0	(9.12%) 4	(2.19%) 5	(20%) 2	(8.29%) 7	0.750.	-	075.0

*Vitamin D level >30 ng/mL is defined as normal, 20-29.9 as mild deficiency, 10-19.9 as moderate deficiency and <10 as severe deficiency

Table 3: Comparison of BMD, T-score and Z-score in groups of patients and controls

Group	Case group		Control group		P value		
	Female	Male	Female	Male	Female	Male	Comparison of both groups
BMD g/cm²							
L2-L4	.140 \pm 99.0	15.0 \pm 98.0	.140 \pm 011.	13.0 \pm 10.1	64.0	83.0	64.0
Femoral neck	12.0 \pm 86.0	36.0 \pm 03.1	12.0 \pm 88.0	19.0 \pm 96.0	55.0	63.0	55.0
Trochanter	11.0 \pm 69.0	17.0 \pm 77.0	10.0 \pm 69.0	16.0 \pm 82.0	88.0	55.0	89.0
Distal forearm	120. \pm 37.0	12.0 \pm 47.0	11.0 \pm 37.0	08.0 \pm 47.0	930.	940.	930.
T score							
L2-L4	12.1 \pm 47.0-	17.1 \pm 74.1-	97.0 \pm 96.1-	99.0 \pm 65.1-	7.0	85.0	7.0
Femoral neck	07.1 \pm 77.0-	98.1 \pm 75.0-	02.1 \pm 51.0	33.1 \pm 84.0-	38.0	93.0	38.0
Trochanter	\pm 176.0-	44.1 \pm 2/1-	92.0 \pm 98.0-	04.1 \pm 03.1-	4.0	7.0	4.0
*Distal forearm	16/1 \pm 39.0-	-	02/1 \pm 35.0-	-	9.0	-	90.0
Z score							
L2-L4	15.1 \pm 75.1-	17.1 \pm 77.1-	99.0 \pm 71.1-	21.1 \pm 51.1-	88.0	65.0	88.0
Femoral neck	98.0 \pm 49.0-	47.1 \pm 76.0-	03.1 \pm 35.0-	28.1 \pm 91.0-	61.0	81.0	61.0
Trochanter	03.0 \pm 34.0-	40.1 \pm 85.0-	90.0 \pm 46.0-	27.1 \pm 59.0-	65.0	68.0	65.0
*Distal forearm	09.0 \pm 220.-	-	02.1 \pm 19.0-	-	930.	-	-

*T score and Z scores of the distal forearm were not measured in men

Table 4: Distribution of PTC patients according to various levels of T-score in the TSH groups

TSH (mu/l)	02/0<	1/0≤02/0>	49/0-1/0	5/0≥	Total cases	P value
T score	(5=n)	(18=n)	(4=n)	(3=n)	(30)	
L2–L4						
1- >	(20%) 1	(9.38%) 7	(25%) 1	(3.33%) 1	(3.33%) 10	0.33
1-≤ و 5.2->	(20%) 1	(4.44%) 8	(50%) 2	(7.66%) 2	(3.43%) 13	
5.2-≤	(%60) 3	(7.16%) 3	(25%) 1	0	(4.23%) 7	
Femoral neck						
1->	(40%) 2	(2.63%) 11	(25%) 1	(7.66%) 2	(3.53%) 16	0.07
1- و 5.2.≤	(40%) 2	(8/36%) 7	(75%) 3	(3/33%) 1	(4/43%) 13	
5.2 ≤	(20%) 1	0	0	0	(3.3%) 1	
Trochante						
1->	(20%) 1	(56%) 10	(75%) 3	(100%) 3	(7.56%) 17	0.043
1- و 5/2->	(60%) 3	(44%) 8	0	0	(7.36%) 11	
5/2-≤	(20%) 1	0	(25%) 1	0	(6.6%) 2	

levels of L2–L4, neck, thigh trochanter and distal forearm, and also evaluated the total and ionized calcium level, alkaline phosphatase, 25-hydroxine vitamin D serum and their relationship to the inhibition level of TSH. Daily levothyroxine dose in our patients was identical to some previously conducted studies, in which the inhibitory dose ranged from 1.9 to 2.8 µg/kg/day, and similar results were obtained in many cases. For example, Rosen *et al.*^[8,11] ruled out the effect of levothyroxine with a dose of 2.1 µg/kg/day on BMD of PTC patients under 50 years. Also, Sugitani proved that taking an inhibitory dose of 2.1 µg/kg/day over 6 years in PTC men and women under 50 years had no effect on BMD.^[12] Furthermore, Chen^[13] in a cross-sectional study on PTC patients under 50 years with 3 years' experience of a suppressive dose of 2 µg/kg/day found that TSH inhibition is not able to change T-score and calcium biochemical parameters, ALP and 25-hydroxy vitamin D serum. The results of the above three studies were to some extent different from ours, because medications could not reduce BMD in our patients, but there a relationship was observed between TSH level and BMD, Z-score and T-score of the trochanter region, the reason for which can be the higher inhibitory dose taken by our patients. Also, in a study carried out by Rita Schneider, an inhibitory dose for 4.5 years can lead to BMD in women's distal radius ($P < 0.01$).^[10] Also, the relationship between BMD decrease of left femoral neck and daily dose of levothyroxine was significant ($P < 0.05$), but no change was found in men's BMD, serum level of calcium, alkaline phosphatase and C-terminal telopeptide. The cumulative dose of levothyroxine was 350 mg for subjects of the study, and the average of TSH in both sexes was 0.04 and 0.05 mu/L, respectively. It seems that the difference between the above results and our findings is due to taking inhibitory agents for longer.

Also, Diamond^[14] in a study on 24 women at premenopausal and postmenopausal ages taking levothyroxine with a dose of 2.8 µg/kg/day found that BMD was obviously reduced in the neck, thigh and lumbar spine, and there was a significant relationship between cumulative dose of

medication and decrease in BMD. The reduction of BMD in the above regions in this study can be caused by higher inhibitory dose compared with our study; besides, the mean age of less than 50 patients was 47 years, which was higher than our mean age.

In our study, although there was a significant relationship between TSH level or inhibitory dose and osteopenia in the trochanter, there was no significant difference in the incidence of osteopenia or osteoporosis and various levels of TSH. This result is to some extent similar to that of Lee.^[15] In his study, he evaluated various levels of TSH on BMD and markers of bone turnover in PTC women with a mean age of 50 years taking inhibitory dose, and found no significant relationship between groups. In other words, no significant relationship was found in the incidence of osteoporosis and osteopenia in the femoral neck, trochanter and L2–L4 with various levels of TSH. This study, except for age and the absence of men, was approximately similar to our study in other respects, and the results in case of the odds of osteoporosis were consistent with our results. However, the risk of osteopenia or osteoporosis in long-term consumption and with high dose of levothyroxine should be taken into consideration because, in this situation, the inhibitory effect of TSH on osteoclasts is removed and their proliferation and differentiation is increased.^[16] In other words, levothyroxine has receptors on osteoclasts and, by stimulation, can increase their activity.^[17]

In a similar study conducted by Eftekhari *et al.*^[17] in Iran in the Tehran University, no relationship was found between TSH inhibition in 22 men and women less than 50 years with differentiated thyroid carcinoma and changes in BMD in L2–L4 and hip (25B). In addition, radioactive dose (131I) had no relationship with BMD level and, although the incidence of osteopenia and osteoporosis was similar to our study, it had no relationship with levothyroxine with 131I suppression. The mean level of TSH among patients and control subjects was 0.3 and 2.4 mu/L, respectively, and the mean lumbar BMD was 1.08 and 1.05 gr/m²,

respectively, with no significant difference in our patients. The problem of the above study is the shorter period of taking suppressive dose as well as no evaluation of the trochanter–femoral neck and distal forearm or markers of bone turnover (e.g., serum calcium) and vitamin D level. Therefore, our study is more complete and its results are more reliable. Because, in addition to the BMD evaluation of four regions and determination of total and ionized serum level of calcium as well as 25-hydroxine vitamin D and alkaline phosphatase serum, it also evaluates the relationship between the above variables and the inhibitory level of TSH. In this study, the relationship between cumulative dose of levothyroxine as well as the received 131I and BMD in four regions was evaluated, and only in the region of the distal forearm, did BMD have a significant relationship with cumulative dose ($P = 0.01$). Also, distal forearm BMD had a significant relationship with average time of levothyroxine intake (49.8 months) ($P = 0.04$).

Although most of the studies carried out so far have ruled out the effect of inhibitory TSH on density and markers of bone turnover, several multicenter studies with larger and more complete sample size are necessary to prove it decisively in the future.^[18,19]

Conclusion

In this study, we found that osteopenia and osteoporosis is not more common among PTC patients than among the whole population of the same age and sex. Also, vitamin D deficiency was slightly more common in the control group than in PTC patients, and long-term TSH inhibition by levothyroxine in these patients did not lead to a decrease in BMD. Although BMD, Z score and T score of the trochanter region are related to TSH, there was no significant difference in osteopenia or osteoporosis in various levels of TSH. However, hypocalcemia and increased alkaline phosphatase is more common among them, but there is no relationship with vitamin D, and low levels of vitamin D cannot affect the increase in BMD. Nevertheless, BMD and 25-hydroxy vitamin D serum should be evaluated in this group so that in cases with low bone mass or vitamin D deficiency, medical treatment can be instituted.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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