The Effect of TSH Suppression on Vertebral Trabecular Bone Scores in Patients With Differentiated Thyroid Carcinoma

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Context: The effect of thyrotropin (TSH) suppressive therapy on trabecular bone scores (TBSs) is unclear.

Objective: The aim of this study was to investigate the effect of TSH suppression on vertebral TBSs of postmenopausal women with differentiated thyroid carcinoma (DTC).

Design, Setting, and Participants: We conducted a retrospective cohort study including 273 postmenopausal women with DTC who had received TSH suppressive therapy. Bone mineral density (BMD) and TBSs at the lumbar spine were analyzed using dual-energy X-ray absorptiometry (DXA).

Major Outcome Measure: The association between the parameters of TSH suppressive therapy and bone parameters was investigated.

Results: Study subjects showed upper-normal free thyroxine levels and suppressed TSH at DXA evaluation. The mean duration of TSH suppression was 4.4 $\pm$ 2.9 years. Serum free T4 and TSH were not independently associated with lumbar spine BMD or TBS levels. Duration of TSH suppression was negatively correlated with lumbar spine TBS levels, but not with BMD. Longer duration of TSH suppression was independently associated with lower lumbar spine TBSs after adjusting for age, body mass index (BMI), and BMD. Lumbar spine TBSs were significantly lower in patients whose duration of TSH suppression was $\geq$5 years compared with those whose duration was $<$3 years after adjusting for age, BMI, and BMD.

Conclusions: Longer duration of TSH suppression in postmenopausal DTC patients was associated with decreased vertebral bone strength by altering TBSs rather than BMD. TBSs should be considered when estimating vertebral bone fragility in postmenopausal DTC patients receiving long-term TSH suppressive therapy. **(*J Clin Endocrinol Metab* 102: 78–85, 2017)**

The incidence of differentiated thyroid carcinoma (DTC) has increased by >4% every decade for the last 30 years, and it is now the most frequent endocrine cancer (1). After the initial surgical treatment of DTC patients, thyrotropin (TSH) suppressive therapy using exogenous levothyroxine is recommended because of its inhibitory effect on the growth of any residual neoplastic tissue (1, 2). However, there is growing concern about the potential harmful effects of long-term TSH suppression related to prolonged patient survival after the initial treatment of DTC (1). In particular, it has been reported that exogenous subclinical thyrotoxicosis increased the risks of fracture and cardiovascular disease (1, 3–6). Therefore, the potential benefits and risks of TSH suppression

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 17 July 2016. Accepted 13 October 2016.
First Published Online 18 October 2016

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Abbreviations: ANOVA, analysis of variance; BMD, bone mineral density; BMI, body mass index; CTX, C-terminal telopeptide of type I collagen; DTC, differentiated thyroid carcinoma; DXA, dual-energy X-ray absorptiometry; KTA, Korean Thyroid Association; T4, thyroxine; TBS, trabecular bone score; TSH, thyrotropin.

should be considered carefully, and the 2015 American Thyroid Association management guideline (7) for DTC patients suggests less aggressive suppression of TSH than did the previous version.

Thyroid hormone regulates the initiation and duration of the bone remodeling cycle in the human skeleton (8, 9). Thyroid dysfunction alters the bone remodeling process, and in particular, thyrotoxicosis increases bone turnover and results in uncoupling of bone resorption and formation (10). Consequently, decreased bone mineral density (BMD) and an increased risk of fracture have been demonstrated in thyrotoxic patients (11). Moreover, recent population studies have reported that subclinical thyrotoxicosis or even higher thyroid status within the reference range also can cause deterioration of BMD and are associated with a higher risk of fracture (4, 12–16). However, there have been conflicting reports of the effect of exogenous TSH suppression on BMD in DTC patients (17–23). Therefore, the effect of TSH suppressive therapy on other bone parameters that reflect bone microarchitecture or geometry has received attention.

Bone strength is determined by composite aspects of bone mass, measured by BMD, and bone quality (24). One of the major parameters that reflects bone quality is bone microarchitecture (24). The trabecular bone score (TBS), which is determined by quantifying pixel gray-level variations on lumbar spine dual-energy X-ray absorptiometry (DXA) scans, was recently suggested as a parameter representing trabecular bone microarchitecture (25). Low TBS values indicate deteriorated trabecular bone microarchitecture and predict an increased vertebral fracture risk independently of lumbar spine BMD (25). A previous study reported that higher free thyroxine (T4) levels within the normal reference range are associated with deterioration of vertebral TBSs in postmenopausal women (26). However, the effect of TSH suppressive therapy on vertebral TBSs in DTC patients is still unclear. In this study, we conducted a retrospective cohort study including postmenopausal women with DTC who had received TSH suppressive therapy and evaluated the association between bone parameters, including BMD and TBSs, and the parameters of TSH suppressive therapy.

Methods

Subjects

Women aged ≥50 years at the time of DXA evaluation who were diagnosed with DTC or who had started follow-up of DTC at Seoul National University Bundang Hospital from June 2004 to May 2015 were eligible for the study. We included only postmenopausal women for the following reasons: (1) bone loss, especially in trabecular bone, is dramatically accelerated in the postmenopausal state, whereas bone turnover rate is suppressed by the higher level of estrogen present in the premenopausal state; (2) an impaired TBS is predominantly associated with osteoporotic fractures in postmenopausal women and older men, not in premenopausal women; and (3) the reference range for TBSs proposed by an international working group of TBS users applies only to postmenopausal women (27). Three hundred and twenty eligible patients had maintained TSH suppressive therapy with levothyroxine after thyroidectomy with or without radioactive iodine therapy. Their evaluations by DXA, which can provide both BMD and TBS data were performed between January 2015 and June 2016, during their TSH suppressive therapy. Forty-seven subjects who had history of exposure to alfacalcidol, calcitriol, bisphosphonate, oral contraceptives, menopausal hormone therapy, selective estrogen-receptor modulators, diuretics, lithium, or corticosteroids were excluded, and the remaining 273 women were included in this study. All included subjects had recovered from postoperative hypoparathyroidism and had no persistent DTC or active secondary malignancies and no history of liver or renal diseases, prior hyperthyroidism, hyper- or hypoparathyroidism (except transient postoperative hypoparathyroidism), malabsorption syndrome, or rheumatic disease. This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the Seoul National University Bundang Hospital.

Treatment and follow-up

All patients with DTC underwent treatment according to the Korean Thyroid Association (KTA) guidelines (28) for the initial treatment and long-term management of DTC. The KTA guidelines recommend a similar degree of TSH suppression to the American Thyroid Association guidelines (2) based on the risk group stratification. According to the KTA, serum TSH levels <0.1 mIU/L are recommended for patients with persistent disease; serum TSH levels of 0.1 to 0.5 mIU/L are recommended for patients free of disease, but who originally presented with high-risk disease; and a lower normal range (0.3 to 2.0 mIU/L) of serum TSH is recommended even for those patients at low risk of recurrence (28).

Anthropometric and biochemical parameters

We measured the height and weight of subjects in light clothing and without shoes to the nearest 0.1 cm and 0.1 kg, respectively. Body mass index (BMI) was calculated by determining the ratio between weight and the square of the height (expressed in kilograms per square meter). Serum levels of creatinine, calcium (corrected for albumin binding), ionized calcium, and phosphate were measured by automated standard laboratory methods (Hitachi 747; Hitachi, Tokyo, Japan). Serum 25-hydroxyvitamin D concentrations were measured using Diels–Alder derivatization and ultrahigh performance liquid chromatography–tandem mass spectrometry (Quattro Premier XE; Waters, Milford, MA). Serum intact parathyroid hormone was analyzed using a chemiluminescence assay (LIAISON; DiaSorin S.p.A., Saluggia, Italy). Serum C-terminal telopeptide of type I collagen (CTX) levels were measured with an electrochemiluminescence immunoassay (cobas; Roche, Indianapolis, IN). Concentrations of serum free T4 and TSH were measured by immunoradiometric assays (free T4: DiaSorin S.p.A.; TSH: OCPL07-TSH; CIS Bio International,

Gif-sur-Yvette, France). Free T4 had an analytical sensitivity of 0.05 ng/dL. TSH had an analytical sensitivity of 0.04 mIU/L and a functional assay sensitivity of 0.07 mIU/L. The reference ranges for free T4 and TSH were 0.89 to 1.79 ng/dL and 0.3 to 4.0 mIU/L, respectively.

Assessment of vertebral BMD and TBSs

BMD was measured at the lumbar vertebrae (L1-4) using DXA equipment (Discovery W; Hologic, Inc., Bedford, MA) according to the manufacturer's protocol. The normative database of BMD was Asian population data provided by manufacturer. TBSs were further analyzed from lumbar spine DXA scans using iNsight software (version 2.1; Med-Imaps, Pessac, France) on the same regions of interest as those used for lumbar spine BMD (29). The region of interest was automatically generated by the Hologic DXA system and adjusted by the technologist as necessary. The coefficient of variation of the TBSs and BMD calculated from 2 repeated measurements in 30 female subjects was 1.6% and 1.0%, respectively.

Data analysis

Values with normal distributions are expressed as mean ± standard deviation, and values with non-normal distribution are expressed as median and interquartile range. The value of serum TSH concentration was log-transformed in the statistical analyses because of its non-normal distribution. Other parameters showed normal distributions. A Pearson correlation coefficient was used to estimate the relationships between bone parameters and other parameters. Linear regression analysis was used to estimate multiple correlations between lumbar spine TBSs and other factors. One-way analysis of variance (ANOVA) and analysis of covariance tests were used for the comparison of bone and other parameters according to the duration of TSH suppression. Tukey B *post hoc* analysis was used in the 1-way ANOVA. All statistical analyses were performed using IBM SPSS Statistics (version 22; IBM Corp., Armonk, NY). Data with $P < 0.05$ were considered significant, and Bonferroni correction was used in multiple statistical tests.

Results

Subject characteristics

The clinical and biochemical characteristics of the subjects are shown in Table 1. The mean age of study subjects was 58.8 ± 6.9 years, and the mean duration of TSH suppression before the DXA evaluation was 4.2 ± 2.2 years. All subjects were on a stable dose of levothyroxine at the time of DXA evaluation (mean, 113.9 ± 24.7 μg/d; range, 50.0 to 200.0 μg/d). No subjects had evidence of persistent disease; low-, intermediate-, and high-risk disease was present in 59, 209, and 5 patients, respectively, at the time of diagnosis of DTC. The median (interquartile range) of the average serum TSH level during TSH suppressive therapy prior to DXA evaluation was 0.11 (0.64) mIU/L in the 59 patients with low-risk disease, 0.05 (0.14) mIU/L in the 209 patients with intermediate-risk disease, and 0.03 (0.10) mIU/L in the 5 patients with high-risk disease. Regarding parameters of calcium homeostasis, the mean serum total calcium and phosphate levels were 8.6 ± 0.5 and 4.0 ± 0.5 mg/dL, respectively.

Table 1. Subject Characteristics

	Value
Demographic and biochemical parameters	
Age, y	58.8 ± 6.9
BMI, kg/m^2	24.1 ± 3.3
Creatinine, mg/dL	0.7 ± 0.1
Total calcium, mg/dL	8.6 ± 0.5
Ionized calcium, mg/dL	1.15 ± 0.07
Phosphate, mg/dL	4.0 ± 0.5
25OHD, ng/mL	27.2 ± 10.0
PTH, pg/mL	20.5 ± 17.8
CTX, ng/mL	0.49 ± 0.22
Parameters of TSH suppression	
Dose of LT4, μg/d	
At DXA evaluation	113.9 ± 24.7
Average during TSH suppression	131.3 ± 14.4
Free T4, ng/dL	
At DXA evaluation	1.64 ± 0.24
Average during TSH suppression	1.76 ± 0.25
TSH, mIU/L	
At DXA evaluation	0.05 (0.23)
Average during TSH suppression	0.05 (0.17)
Duration of TSH suppression, y	4.2 ± 2.2
Bone parameters	
BMD (L1-4), g/cm^2	0.901 ± 0.131
TBS (L1-4)	1.314 ± 0.089

Data are expressed as mean ± standard deviation or median (interquartile range). All demographic and biochemical parameters were measured at DXA evaluation.

Abbreviations: 25OHD, 25-hydroxyvitamin D; LT4, levothyroxine; PTH, parathyroid hormone..

Correlation between bone and other clinical parameters

We evaluated the correlation between bone parameters, including lumbar spine BMD and TBSs, and other clinical parameters (Table 2). Age at the time of DXA evaluation was negatively correlated with both lumbar spine BMD and TBSs. BMI was positively correlated with lumbar spine BMD and negatively correlated with lumbar spine TBSs. The dose of levothyroxine was positively correlated with BMD, and average serum TSH levels during TSH suppression were negatively correlated with TBSs. The duration of TSH suppression was negatively correlated with lumbar spine TBSs, but not with BMD. The association between the dose of levothyroxine and BMD and the association between the duration of TSH suppression and TBSs were significant after Bonferroni correction for the multiple parameters of TSH suppression (7 tests), whereas the association between average serum TSH levels and TBSs was not significant after Bonferroni correction. Serum free T4 levels were not associated with BMD or TBSs.

Table 2. Correlation Between Bone and Other Clinical Parameters

	BMD (L1-4)		TBS (L1-4)	
	r Value	*P* Value	*r* Value	*P* Value
Demographic and biochemical parameters				
Age	−0.203	0.001[a]	−0.460	<0.001[a]
BMI	0.260	<0.001[a]	−0.127	0.035[a]
Creatinine	0.096	0.116	0.047	0.441
Total calcium	−0.085	0.165	−0.115	0.060
Ionized calcium	−0.072	0.277	−0.027	0.686
Phosphate	0.044	0.474	0.079	0.197
25OHD	−0.117	0.072	−0.073	0.259
PTH	−0.074	0.254	−0.028	0.663
CTX	−0.292	< 0.001[a]	−0.182	0.005[a]
Parameters of TSH suppression				
Dose of LT4				
At DXA evaluation	0.179	0.003[a,b]	0.083	0.175
Average during TSH suppression	0.202	0.001[a,b]	0.052	0.391
Free T4				
At DXA evaluation	−0.028	0.651	0.034	0.577
Average during TSH suppression	−0.067	0.267	−0.004	0.948
TSH[c]				
At DXA evaluation	0.002	0.968	−0.092	0.130
Average during TSH suppression	−0.037	0.545	−0.129	0.033[a]
Duration of TSH suppression	−0.081	0.181	−0.180	0.003[a,b]

All demographic and biochemical parameters were measured at DXA evaluation.

Abbreviations: 25OHD, 25-hydroxyvitamin D; LT4, levothyroxine; PTH, parathyroid hormone; *r*, Pearson correlation coefficient.

[a] $P < 0.05$.

[b] $P < 0.007$, statistically significant after Bonferroni correction for multiple parameters of TSH suppression (7 tests).

[c] Log-transformed variables were used in statistical analyses.

We performed multivariable analyses for the association between lumbar spine TBSs and the duration of TSH suppression. We adjusted for age and BMI, which were associated with lumbar spine TBSs in correlation analyses (Table 3, model 1). We also adjusted for lumbar spine BMD to show that the association between lumbar spine TBSs and the duration of TSH suppression was independent from BMD (Table 3, model 2). Longer duration of TSH suppression was independently associated with lower lumbar spine TBSs after adjusting for age, BMI, and BMD (Table 3). This independent association was statistically significant after Bonferroni correction. The associations between bone parameters and the dose of levothyroxine or average serum TSH levels during TSH suppression were not maintained after adjusting for BMI or the duration of TSH suppression, respectively (data not shown).

Bone and other clinical parameters according to the duration of TSH suppression

We compared bone and other clinical parameters according to the duration of TSH suppression using ANOVA (Table 4). Age, BMI, serum 25-hydroxyvitamin D, parathyroid hormone, and CTX did not differ with the duration of TSH suppression. Higher doses of levothyroxine, higher serum free T4 levels, and lower serum TSH levels were present in the subjects with shorter duration of TSH suppression. Lumbar spine TBSs decreased in the patients with longer duration of TSH suppression, whereas BMD did not significantly change with the duration of TSH suppression (Fig. 1). *Post hoc* analysis in ANOVA showed that lumbar spine TBSs differed between the patients whose duration of TSH suppression was ≥5 years and <3 years. Lumbar spine TBSs were significantly lower in patients whose duration of TSH suppression was ≥5 years compared with those whose duration was <3 years, after adjusting for age, BMI, and BMD (1.296 ± 0.078 vs 1.335 ± 0.092, respectively; $P = 0.032$).

Discussion

In this study, postmenopausal women with DTC receiving TSH suppressive therapy showed lower vertebral TBSs with increasing duration of TSH suppression, whereas no relevant deterioration of BMD was observed. This study demonstrates the effect of TSH suppressive therapy on the trabecular bone microarchitecture measured by the TBSs and shows an independent association between vertebral TBSs and the duration of TSH suppressive therapy in DTC patients. One previous cross-sectional study reported that high to normal free T4 levels

Table 3. Multivariable Linear Regression Analysis Of Associating Parameters With TBS

	Model 1		Model 2	
Clinical Parameters	**B**	***P* Value**	**B**	***P* Value**
Age	−0.006	<0.001[a]	−0.004	<0.001[a]
BMI	−0.002	0.275	−0.007	<0.001[a]
BMD (L1-4)			0.432	<0.001[a]
Duration of TSH suppression	−0.006	0.006[a,b]	−0.004	0.006[a,b]

The dependent variable was TBS (L1-4). Age, BMI, and duration of TSH suppression were included as independent variables in statistical models 1 and 2. BMD (L1-4) was included as an independent variable in model 2. All parameters were measured at DXA evaluation.

[a] $P < 0.05$.

[b] $P < 0.007$, statistically significant after Bonferroni correction for multiple parameters of TSH suppression (7 tests).

were negatively correlated with lumbar spine TBSs after adjusting for age, BMI, and BMD (26), and this association was consistent with previous reports of the skeletal toxicity of excessive thyroid hormone (30). However, our data showed that serum free T4 levels were not associated with lumbar spine TBSs; of the parameters of TSH suppressive therapy, only the duration of TSH suppression was independently associated with lumbar spine TBSs. This discrepant result can be explained by the different distribution of thyroid hormone levels in patients receiving TSH suppressive therapy compared with the general population. The dose of levothyroxine is adjusted to obtain the ideal target TSH levels in each patient; therefore, serum free T4 levels are adjusted to upper normal levels in most patients. In our study participants, the 95% confidence interval for mean free T4 levels at DXA evaluation was 1.62 to 1.67 ng/dL (average free T4 levels, 1.73 to 1.79 ng/dL), and this narrow distribution of free T4 levels might have been the cause of the lack of association between serum free T4 levels and lumbar spine TBSs. Generally, the initial dose of levothyroxine after surgery is determined by the patient's body weight and is adjusted to suppress adequately the serum TSH concentration. As the duration of follow-up increases, the potency of TSH suppression can be reduced after considering the risk stratification for disease recurrence. Because most DTC patients have a good prognosis, the dose of levothyroxine decreases and the serum TSH concentration increases with increasing duration of TSH suppression, as was the case for our study subjects. Therefore, in the clinical setting of long-term TSH suppressive therapy, only the duration of TSH suppression, which was not affected by other parameters, showed an independent association with vertebral TBSs. This clinical aspect of TSH suppressive therapy could also

Table 4. Bone and Other Clinical Parameters According to the Duration of TSH Suppression

	Duration of TSH Suppression				
	< 3 y (n = 62)	**3–5 y (n = 107)**	**≥5 y (n = 104)**	***P*[a]**	***P* Value for Trend[a]**
Demographic and biochemical parameters					
Age, y	57.9 ± 6.5	58.4 ± 6.9	59.7 ± 7.1	0.201	0.105
BMI, kg/m^2	24.0 ± 3.3	24.2 ± 3.3	24.1 ± 3.3	0.910	0.859
25OHD, ng/mL	26.2 ± 11.0	26.5 ± 9.9	27.9 ± 9.6	0.533	0.322
PTH, pg/mL	21.3 ± 25.5	22.0 ± 15.0	18.9 ± 12.2	0.456	0.413
CTX, ng/mL	0.52 ± 0.25	0.50 ± 0.23	0.46 ± 0.18	0.256	0.105
Parameters of TSH suppression					
Dose of LT4, μg/d					
At DXA evaluation	128.2 ± 22.6	113.6 ± 24.3	105.7 ± 22.7	<0.001[b]	<0.001[b]
Average during TSH suppression	139.5 ± 11.8	130.5 ± 14.2	127.1 ± 14.1	<0.001[b]	<0.001[b]
Free T4, ng/dL					
At DXA evaluation	1.78 ± 0.21	1.64 ± 0.23	1.56 ± 0.22	<0.001[b]	<0.001[b]
Average during TSH suppression	1.90 ± 0.21	1.77 ± 0.22	1.67 ± 0.26	<0.001[b]	<0.001[b]
TSH, mIU/L[c]					
At DXA evaluation	0.03 (0.05)	0.03 (0.16)	0.13 (0.68)	<0.001[b]	<0.001[b]
Average during TSH suppression	0.03 (0.10)	0.05 (0.15)	0.10 (0.23)	0.002[b]	0.001[b]
Bone parameters					
BMD (L1-4), g/cm^2	0.922 ± 0.140	0.901 ± 0.127	0.889 ± 0.130	0.282	0.112
TBS (L1-4)	1.335 ± 0.092	1.320 ± 0.094	1.296 ± 0.078	0.015[b]	0.006[b]

Data are expressed as mean ± standard deviation, median (interquartile range), or as otherwise indicated. All parameters were measured at DXA evaluation.

Abbreviations: 25OHD, 25-hydroxyvitamin D; LT4, levothyroxine; PTH, parathyroid hormone; *r*, Pearson correlation coefficient.

[a] Derived from ANOVA.

[b] $P < 0.05$.

[c] Log-transformed variables were used in statistical analyses.

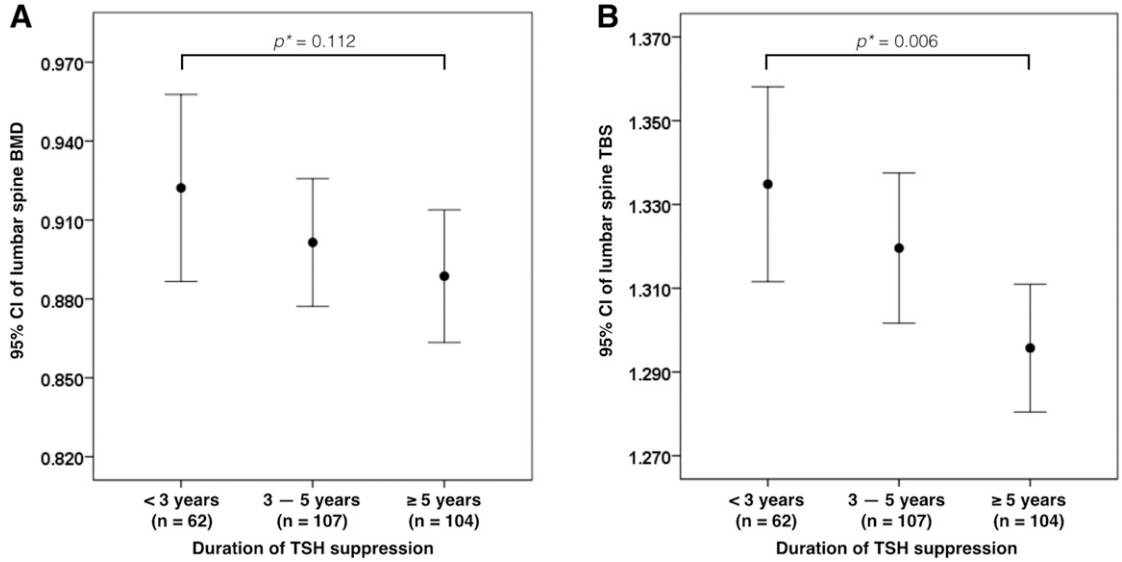

Figure 1. Ninety-five percent confidence interval (CI) of (A) lumbar spine BMD and (B) TBSs according to the duration of TSH suppression in postmenopausal DTC patients (n = 273). **P* value from linear-trend ANOVA.

explain the positive correlation between the dose of levothyroxine and lumbar spine BMD (Table 2). In our data, BMI was highly correlated both with the dose of levothyroxine (dose at DXA evaluation, $r = 0.296$, $P < 0.001$; average dose, $r = 0.316$, $P < 0.001$) and lumbar spine BMD ($r = 0.260$, $P < 0.001$), and the association between BMD and the dose of levothyroxine disappeared after adjusting for BMI (data not shown). Therefore, a positive correlation between BMI and the dose of levothyroxine might have resulted in the unexpected positive correlation between the dose of levothyroxine and lumbar spine BMD in the univariate correlation analyses. The negative correlation between average serum TSH levels and lumbar spine TBSs (Table 2) could also be explained by the positive correlation between average serum TSH levels and the duration of TSH suppression (log-transformed average TSH levels, $r = 0.202$, $P = 0.001$). The association between serum TSH levels and TBSs also disappeared after adjusting for the duration of TSH suppression (data not shown).

A noteworthy result of this study is the difference between the association of lumbar BMD and TBSs with the duration of TSH suppression. Only TBSs, not BMD, decreased with increasing duration of TSH suppression. The skeletal toxicity of excessive thyroid hormone is well established. Triiodothyronine is an important regulator of osteoblast differentiation and increases bone turnover through stimulating osteoclasts (30). In addition, it has been proposed that TSH has direct effects via the TSH receptor found on osteoblast and osteoclast precursors and potential protective effects on bone by enhancing osteoblast differentiation while suppressing osteoclast differentiation (31–34). Moreover, TSH predominantly affects trabecular bone microarchitecture (32). Considering these effects of thyroid hormones and TSH on bone, TSH suppression using excessive levothyroxine in DTC patients might result in bone loss (35). However, there have been conflicting reports of the effect of exogenous TSH suppressive therapy on BMD in DTC patients (17–23). Our data showing reduced lumbar spine TBSs and unaltered BMD with long-term TSH suppression suggest that the TBS is a more sensitive parameter than BMD to assess vertebral bone strength in DTC patients receiving TSH suppressive therapy. As previously mentioned, long-term TSH suppressive therapy in DTC patients causes clinically controlled and modifiable iatrogenic subclinical thyrotoxicosis. Although this controlled long-term subclinical thyrotoxicosis did not significantly reduce vertebral BMD, increased bone turnover caused by excessive thyroid hormone and reduced TSH might result in an alteration in vertebral trabecular bone microarchitecture occurring before substantial bone loss.

This study has some important clinical implications. Currently, available guidelines for long-term treatment of DTC after initial treatment suggest no ideal or maximal duration of TSH suppressive therapy. Our data demonstrating reduced lumbar spine TBSs in DTC patients whose duration of TSH suppression was ≥5 years have added to the clinical evidence for estimating potential benefits and risks of long-term TSH suppressive therapy in DTC patients. Considering that ≥1.350 is proposed as the value of the TBS for normal microarchitecture (27), our data showing a mean TBS of 1.296 in the patients whose duration of TSH suppression was ≥5 years suggests that long-term TSH suppression degrades vertebral bone microarchitecture.

The potential limitations of this study include the absence of control subjects. The ideal controls with which to compare bone parameters for our study subjects are age-matched subjects who have maintained levothyroxine replacement without TSH suppression after thyroidectomy because of benign disease. However, we could not secure enough TBSs and BMD data for such subjects, and only the analyses in DTC patients were available. Thus, although this study showed that longer duration of TSH suppression independently altered vertebral TBSs without changing BMD in postmenopausal DTC patients, our findings cannot determine that this alteration of vertebral TBSs was entirely because of TSH suppression: it could be the result of the thyroidectomy and the use of levothyroxine. In addition, menopausal bone loss also could contribute to our results because we did not assess accurate menopausal durations in each study subject. However, CTX, the bone turnover marker, at DXA evaluation was not correlated with age ($r = 0.05$, $P = 0.445$) but with free T4 ($r = 0.281$, $P < 0.001$) and TSH ($r = -0.305$, $P < 0.001$) in our data. These results postulate that bone turnover is affected by TSH suppression rather than menopausal effects in this study population. Another limitation is the lack of data on fragility fractures during TSH suppressive therapy. We assessed lateral spine X-rays to evaluate vertebral fractures, but the rate of vertebral fractures in the study subjects was too low (<10%) to give sufficient power to investigate the association between lumbar spine TBSs and vertebral fractures. Moreover, we could not confirm that the fractures had occurred during TSH suppression after thyroidectomy because we obtained the lateral X-rays only once, at the time of DXA evaluation.

In conclusion, longer duration of TSH suppression in postmenopausal DTC patients was associated with decreased vertebral bone strength by altering TBSs rather than BMD. This deteriorative effect on vertebral TBSs was observed in the patients whose duration of TSH suppression was ≥5 years, despite their unaltered BMD. Our results suggest that long-term TSH suppression may result in the alteration of trabecular bone microarchitecture in postmenopausal DTC patients. TBSs should be considered when estimating the potential risk of vertebral bone fragility in postmenopausal DTC patients receiving long-term TSH suppressive therapy.

Acknowledgments

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Author contributions: J.H.M. and K.M.K. designed the study. J.H.M., K.M.K., T.J.O., S.H.C., S.L., Y.J.P., D.J.P., and H.C.J. contributed data interpretation and manuscript review. J.H.M., K.M.K., and Y.J.P. collected the data. J.H.M. and K.M.K. drafted the manuscript. All authors agreed on the final content of the manuscript.

Disclosure Summary: The authors have nothing to disclose.

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