High Prevalence of Radiological Vertebral Fractures in Women on Thyroid-Stimulating Hormone–Suppressive Therapy for Thyroid Carcinoma

Gherardo Mazziotti,[1] Anna Maria Formenti,[2] Stefano Frara,[3] Roberto Olivetti,[1] Giuseppe Banfi,[4,5] Maurizio Memo,[2] Roberto Maroldi,[6] Raffaele Giubbini,[7] and Andrea Giustina[3]

[1]Endocrine Unit, Azienda Socio-Sanitaria Territoriale, 46100 Mantua, Italy; [2]Department of Molecular and Translational Medicine, University of Brescia, 25121 Brescia, Italy; [3]Department of Endocrinology, Vita-Salute San Raffaele University, 20132 Milan, Italy; [4]Department of Biochemistry, Vita-Salute San Raffaele University, 20132 Milan, Italy; [5]Laboratory of Experimental Biochemistry and Molecular Biology, I.R.C.C.S. Istituto Ortopedico Galeazzi, 20161 Milan, Italy; [6]Department of Radiology, University of Brescia, 25121 Brescia, Italy; and [7]Department of Nuclear Medicine, University of Brescia, 25121 Brescia, Italy

Context: Bone loss and nonvertebral fractures have been reported in patients with differentiated thyroid carcinoma (DTC) undergoing thyroid-stimulating hormone (TSH) suppressive therapy. Radiological vertebral fractures (VFs) are an early and clinically crucial marker of bone fragility.

Objective and Design: A cross-sectional study to evaluate the prevalence and determinants of radiological VFs in women receiving L-thyroxine (L-T4) therapy for DTC.

Patients and Interventions: A total of 179 consecutive women (median age, 59 years; n = 178 postmenopausal) who had undergone thyroidectomy for DTC and were currently receiving L-T4 were evaluated for radiological VFs and bone mineral density (BMD). There were three TSH target levels [<0.5 mU/L, group 1 (n = 83); 0.5 to 1.0 mU/L, group 2 (n = 50); >1.0 mU/L, group 3 (n = 46)].

Results: VFs were found in 51 patients (28.5%), with significantly ($P < 0.001$) higher prevalence in group 1 (44.6%) as compared with group 2 (24.0%) and group 3 (4.3%). VF prevalence was not significantly different among patients in group 1 with normal BMD, osteopenia, or osteoporosis, whereas in groups 2 and 3, VFs were more frequent in patients with osteoporosis than in those with either osteopenia or normal BMD. In the whole population, VFs were significantly and independently associated with TSH level <1.0 mU/L; densitometric diagnosis of osteoporosis at lumbar spine, femoral neck, or total hip; age of patients; and duration of L-T4 therapy.

Conclusion: The prevalence of VFs was high in women with DTC who were undergoing long-term, suppressive L-T4 therapy. (***J Clin Endocrinol Metab*** **103: 956–964, 2018)**

Thyroid hormones have physiological stimulatory effects on bone remodeling and bone mineralization, and normal euthyroid status during childhood and adolescence is required for acquisition of peak bone mass (1). However, when thyroid hormone levels increase, bone remodeling is excessively stimulated, with consequent bone loss, decrease in bone mineral density (BMD), and increase in fracture risk (2). Interestingly, an increased risk of fragility fractures has been reported even in patients exposed to mild excess of thyroid hormones, because it occurs during over-replacement of primary and central hypothyroidism (3–5).

Differentiated thyroid cancer (DTC) arising from thyroid follicular epithelial cells accounts for the vast

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

Received 8 September 2017. Accepted 1 November 2017.
First Published Online 7 November 2017

Abbreviations: BMD, bone mineral density; DTC, differentiated thyroid carcinoma; DXA, dual-energy X-ray absorptiometry; FT4, free thyroxine; Ha, anterior vertebral height; Hm, middle vertebral height; Hp, posterior vertebral height; L-T4, L-thyroxine; RAI, radioactive iodine; TSH, thyroid-stimulating hormone; VF, vertebral fracture.

majority of thyroid cancers. Papillary thyroid cancer is found in about 85% of cases, compared with about 12% in cases with follicular histology, including conventional and oncocytic (Hürthle cell) carcinomas; and <3% being poorly differentiated tumors (6). DTC expresses TSH receptor on the cell membrane and TSH stimulates cell growth rate (7). Suppression of TSH by supraphysiologic doses of L-thyroxine (L-T4) is commonly used to treat patients with DTC with the aim of decreasing the recurrence risk (8–10). However, the consequent, chronic subclinical hyperthyroidism may be responsible for undesired effects, such as atrial fibrillation, major cardiovascular events, and osteoporosis (11).

Several studies and meta-analyses have reported an association between subclinical thyroid hormone excess and risk of fractures, mainly in postmenopausal women (4, 12–18). However, most of the data on fracture risk in these patients with subclinical hyperthyroidism were based on a retrospective historical assessment of the prevalence of clinical fractures, whereas data on vertebral fractures (VFs) are scanty (12). Indeed, VFs are the most common complication of osteoporosis (19) and are associated with decreased survival (20) and impaired quality of life (21). Moreover, in patients with DTC who may have secondary localization at the bone level, the finding of a VF raises the issue of differential diagnosis between osteoporosis and bone metastasis (22). Because only about one-third of VFs are clinically recognized (19), the radiological and morphometric approach has emerged as the method of choice for evaluating the true prevalence and incidence of these fractures in population and clinical studies (23). To our knowledge, this approach has not been used to investigate the VF risk in patients with DTC who are receiving TSH suppressive therapy.

In this cross-sectional study, we evaluated the prevalence and determinants of radiological VFs in patients with DTC who were undergoing L-T4 therapy with different serum TSH target levels.

Study population and protocol

A total of 179 women (median age, 59 years; range, 42 to 82 years) attending outpatient endocrine clinics in the period from 2012 to 2017 were consecutively enrolled in this cross-sectional study (Supplemental Table 1). All but one of the women were postmenopausal. The inclusion criteria were as follows: (1) female sex, (2) histological diagnosis of DTC, (3) treatment with L-T4 for at least 1 year before study entry, (4) serum TSH values stable since the time of first tumor restaging after thyroid surgery with or without radioactive iodine (RAI) therapy, and (5) availability to be studied for BMD and VFs. The following were the exclusion criteria: (1) bone metastases, (2) treatment with drugs that could cause secondary osteoporosis (24), and (3) treatment with anti-osteoporotic drugs (except for calcium and vitamin D). The clinical data were collected from a questionnaire administered at the study entry and from the information available in the clinical files. Staging of DTC was assessed according to American Joint Committee on Cancer criteria TNM system (10).

At the study entry, 144 of 179 patients were receiving treatment with vitamin D3 (combined with calcium in 75 patients), and serum 25-hydroxyvitamin D was measured in each patient within 3 months before the enrollment. Information on family history of osteoporosis and fractures was collected for each patient.

L-T4 treatment was performed according to clinical judgment and international guidelines available at the time of patient evaluation in the endocrine clinics (9, 10). During the follow-up after surgery and RAI therapy, serum TSH and free thyroxine (FT4) values were measured every 4 to 6 months for the first 5 years and then, for patients with longer follow-up, every 12 months. For the purpose of the study, we considered the last available biochemical data before the study entry. Based on serum TSH values during L-T4 therapy, patients were subdivided in three groups: group 1 (n = 83 cases; TSH values <0.5 mU/L), group 2 (n = 50 cases; TSH values between 0.5 and 1.0 mU/L), group 3 (n = 46 cases; TSH values >1.0 mU/L). Per inclusion criteria, all patients had stable TSH values within each group for the whole period of follow-up. The primary end point was the evaluation of VFs in patients with suppressed TSH values (group 1) as compared with those with higher serum TSH values (groups 2 and 3). The secondary end points were evaluation of the relationship between VFs and duration of L-T4 therapy, and of the relationship between VFs and BMD at different skeletal sites.

The protocol was approved by local ethics committee and the patients gave the informed consent to the study.

Assessment of VFs and BMD

VFs were assessed by a quantitative morphometric approach using spine radiographs (25). Using a translucent digitizer and a cursor, six points were marked on each vertebral body to describe the vertebral shape. Anterior (Ha), middle (Hm), and posterior (Hp) vertebral heights were measured and height ratios (Hp/Hm, Hp/Ha, Hm/Ha) were calculated for each vertebral body from T5 to L4; the fractures were defined as mild, moderate, or severe on the basis of a height ratio decrease of 20% to 25%, 26% to 40%, and >40%, respectively. The analyses were performed by three experienced physicians (G.M., A.M.F., and S.F.). The intraobserver and interobserver coefficients of variation

were between 1% and 4% and 3% and 6%, respectively, in relation to the skeletal site (lumbar vs thoracic) and severity (mild vs severe) of VFs.

BMD was measured by dual-energy X-ray absorptiometry (DXA) at the total hip, femoral neck, and lumbar spine (QDR-4500W; Hologic, Waltham, MA). DXA results were expressed as a T-score comparing the results with those obtained in a sex-matched white population at the peak of bone mass (26). A T-score ≤ -2.5 standard deviations at either skeletal site was defined as osteoporosis, whereas osteopenia was defined as a T-score between -1.0 and -2.5 standard deviations. Lumbar vertebrae affected by artifacts or involved by fractures were excluded from the BMD analysis. The coefficients of variation in the DXA measurements for BMD, bone mineral content, and area were 0.614%, 2.981%, and 2.89%, respectively.

Biochemical assays

Fasting blood samples were collected for measurement of serum FT4 and TSH. Serum concentrations of TSH (reference range, 0.35 to 4.2 mIU/L; analytical sensitivity 0.004 mIU/L; intra- and interassay coefficients of variation, 2.5% and 5.7%, respectively) and of FT4 (reference range, 8.0 to 18.0 pg/mL analytical sensitivity 1.0 pg/mL; intra-assay and interassay coefficients of variation, 2.4% and 6.8%, respectively) were measured using a fully automated Architect i2000 analyzer (Abbott Diagnostics, Abbott Park, IL) based on chemiluminescent magnetic immunoassay. Serum 25-hydroxyvitamin D was measured by RIA (DiaSorin, Saluggia, Italy). The sensitivity of the test was 1.5 ng/mL and the intra-assay coefficient of variation ranged from 8.6% to 12.5%. Hypovitaminosis D was defined as values of 25-hydroxyvitamin D <30 ng/mL.

Statistical analysis

Data were presented as median and range, unless otherwise stated. χ^2 (or Fisher exact test, when necessary), Kruskall-Wallis, and Mann-Whitney nonparametric tests were used to compare categorical and quantitative data. Multivariate logistic regression was implemented to evaluate relationship between covariates and VFs in the whole population of enrolled patients. $P < 0.05$ was considered statistically significant.

Results

Whole population

Clinical characteristics

Clinical characteristics of the patients are listed in Supplemental Table 1. Papillary thyroid carcinoma was the most frequent tumor histotype (57%) and most patients had an intrathyroidal tumor without invasion of extraglandular structures (T1-T2, 78.8%) and/or without lymph node localization (N0, 85.5%) and distant metastases (M0, 96.0%). The median duration of L-T4 therapy was 5.0 years (range, 1 to 45 years) and the median L-T4 dose at the time of study entry was 100 μg/d (range, 50 to 175 μg/d; Supplemental Table 1).

Osteopenia and osteoporosis were found in 88 (49.2%) and 52 (29.1%) patients, respectively. Fifty-one patients (28.5%) had VFs, which were moderate to severe in 20 patients (11.2%) and/or multiple in 15 patients (8.4%)(Supplemental Table 1).

Determinants of VFs

Patients with fractures had received RAI therapy more frequently; had lower serum TSH and higher serum FT4 values; were treated with a higher daily dose of L-T4 and for a longer time; had lower BMD T-score at the lumbar spine and femoral neck, and more frequently had osteopenia and osteoporosis, as compared with patients who did not have fractures (Table 1). Moreover, patients with fractures were less frequently treated with vitamin D3 plus calcium and more frequently treated with vitamin D alone, as compared with patients without VFs (Table 1). Stratifying the patients for tertiles of duration of L-T4 therapy, prevalence of VFs increased significantly after 6 years of therapy (Fig. 1).

Multivariate logistic regression analysis showed that VFs were significantly and independently associated with TSH levels <1.0 mU/L, densitometric diagnosis of osteoporosis at either skeletal site (lumbar spine, femoral neck, or total hip), age, and duration of L-T4 therapy (Table 2).

Groups stratified based on TSH values

Clinical characteristics

Patients in group 1 had more advanced TNM stage of DTC, had received more frequent RAI therapy, were treated with a higher daily dose of L-T4 and for a longer period of time, and had higher serum FT4 values than patients in groups 2 and 3 (Supplemental Table 2). Moreover, patients in groups 1 and 2 were significantly younger than patients in group 3 (Supplemental Table 2).

Patients in group 1 had a lower BMD T-score at the femoral neck and total hip as compared with patients in groups 2 and 3, without a statistically significant difference in lumbar spine BMD T-score (Supplemental Table 2). The prevalence of osteoporosis was higher in group-1 patients than those in groups 2 and 3, and there were no significant differences between groups 2 and 3 (Supplemental Table 2).

Table 1. Demographic and Clinical Features of Women With VFs as Compared With Those Who Did Not Have VFs

	No VF	VF	*P* Value[a]
Patients, No.	128	51	
Age, y	60 (42–79)	63 (47–82)	0.159
RAI therapy, No. (%)	83 (64.8)	49 (96.1)	<0.001
Duration of L-T4 therapy, y	5 (1–26)	6 (1–45)	0.006
L-T4 dose, μg/d	100 (50–175)	125 (50–175)	0.02
Serum TSH, mU/L	0.80 (0.005–1.60)	0.15 (0.004–1.20)	<0.001
Serum FT4, pg/mL	11.0 (8.50–16.8)	13.0 (9.00–17.00)	<0.001
Serum 25OH-vitamin D, ng/mL	27 (7–54)	30 (11–46)	0.43
Treatment of hypovitaminosis D, No. (%)			0.01
No therapy	24 (18.8)	11 (21.6)	
Vitamin D3 alone	42 (32.8)	27 (52.9)	
Vitamin D3 plus calcium	62 (48.4)	13 (25.5)	
Family history of osteoporosis or fractures, No. (%)	56 (43.8)	29 (56.9)	0.11
LS BMD T-score	−1.10 (−3.60 to +2.80)	−1.90 (−3.40 to +2.30)	0.001
FN BMD T-score	−1.00 (−3.40 to +2.30)	−1.55 (−2.70 to +1.00)	0.02
TH BMD T-score	−0.90 (−2.90 to +3.40)	−0.50 (−2.20 to +0.20)	0.99
BMD categories, No. (%)			<0.001
Normal	34 (26.6)	5 (9.8)	
Osteopenia	68 (53.1)	20 (39.2)	
Osteoporosis	26 (20.3)	26 (51.0)	

Data are given as median (range) unless otherwise indicated.

Abbreviations: 25OH-vitamin D, 25-hydroxyvitamin D; FN, femoral neck; LS, lumbar spine; TH, total hip.

[a]Comparisons were performed by nonparametric tests.

Determinants of VFs

Patients in group 1 had a higher prevalence of total (44.6%), moderate/severe (18.1%), and multiple (14.5%) VFs as compared with patients in groups 2 and 3 (Fig. 2). Moreover, patients in group 2 had a higher prevalence of total VFs than patients in group 3 (24.0% vs 4.3%; $P = 0.008$; Fig. 2). The differences in total VFs among the three groups were statistically significant regardless of BMD values (Fig. 3). Moreover, in group 1, the prevalence of total VFs was not significantly different ($P = 0.13$) among patients with normal BMD (30.8%), osteopenia (37.1%), or osteoporosis (57.1%), whereas VFs were more frequent in patients with osteoporosis (62.5%) than with either osteopenia (18.8%) or normal BMD (10.0%) in group 2 ($P = 0.02$; Fig. 3). In the presence of osteoporosis, the prevalence of VFs was not significantly different between groups 1 and 2 (57.1% vs 62.5%; $P = 0.78$; Fig. 3).

No significant differences in prevalence of VFs were found among FT4 tertiles within each TSH group (Fig. 4).

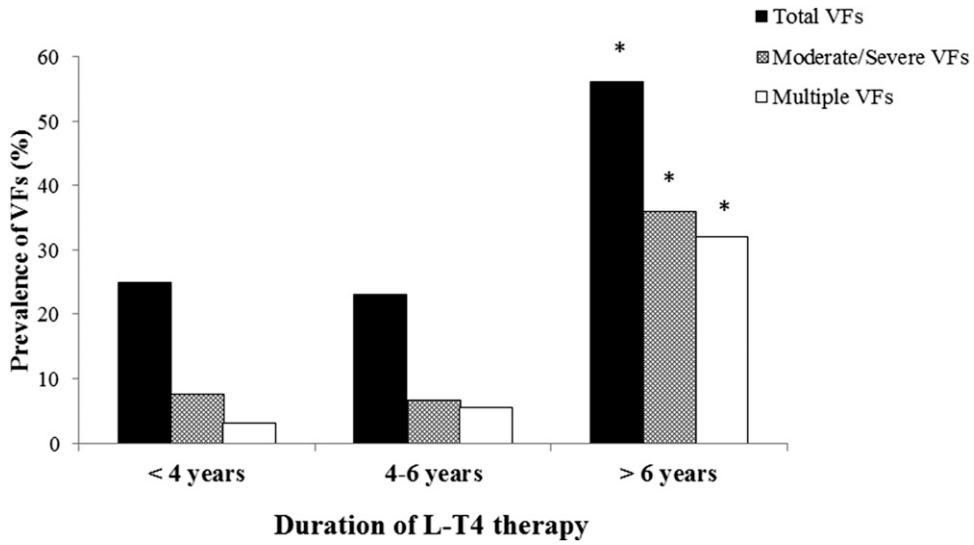

Figure 1. Prevalence of VFs in 179 women with DTC who were stratified for tertiles of duration of L-thyroxine (L-T4) therapy.*$P < 0.05$ for third tertile vs first and second tertiles.

Table 2. Results of Multivariate Logistic Regression Analysis, Using Total VFs as the Dependent Variable

	Odds Ratio	95% CI	*P* Value
Age	1.08	1.02–1.14	0.01
Osteoporosis	3.64	1.01–13.25	0.05
L-T4 dose	0.97	0.96–1.01	0.06
Duration of L-T4 therapy	1.12	1.02–1.23	0.02
TSH <0.5 mU/L	25.04	2.62–238.88	0.005
TSH 0.5–1.0 mU/L	10.38	1.67–64.45	0.01
Serum FT4 value	0.99	0.77–1.26	0.92
RAI therapy	3.35	0.59–18.97	0.17
Treatment with vitamin D3 plus calcium	0.65	0.42–1.02	0.06

Abbreviation: CI, confidence interval.

Discussion

In this cross-sectional study, radiological VFs were found in about one-third of women with DTC who were undergoing postsurgical L-T4 therapy and correlated with duration of treatment, degree of TSH suppression, and age of patients. Interestingly, VFs were found even in patients with normal BMD, mainly when the TSH level was <0.5 mU/L.

The effects of thyroid hormone on bone metabolism are well established, ranging from impaired skeletal development in childhood hypothyroidism to an increased risk for osteoporosis in hyperthyroidism (27). The pathogenesis of bone damage due to thyroid hormone excess is multifactorial, including shortening of the bone remodeling cycle and acceleration of bone turnover (1). Indeed, thyroid hormones indirectly promote osteoclast formation and activation by inducing the expression of cytokines, prostaglandins, and the receptor activator of nuclear factor-κ B ligand (28). Moreover, there is experimental evidence that TSH may exert direct effects on bone turnover with a specific inhibitory effect on bone resorption (29, 30). Therefore, effects on bone metabolism that were previously ascribed solely to high thyroid hormone levels could also be attributed to suppressed TSH levels (31). It has been hypothesized that low TSH values may contribute to bone loss in patients with hyperthyroidism, especially when the thyroid hormone excess is mild, such as in subclinical hyperthyroidism characterized by a low or undetectable concentration of serum TSH with free triiodothyronine and FT4 levels within laboratory reference ranges (32).

Exogenous subclinical hyperthyroidism is therapeutically induced by supraphysiologic doses of L-T4 in patients with DTC after thyroidectomy and RAI therapy to prevent tumor recurrence and eventually improve patient survival (9, 10). Several studies have reported an increase in bone turnover and decrease in BMD due to TSH suppressive therapy, especially in postmenopausal women and older men (11). Data on fractures in this clinical setting are scanty and produced by retrospective historical and questionnaire-based studies mostly focused on nonvertebral fractures (13–18). The effect of TSH suppressive therapy on VFs is still largely unknown because previous studies only looked at clinical VFs (14, 15), which represent a minority of the vertebral osteoporotic events, in heterogeneous populations including patients with exogenous and endogenous subclinical hyperthyroidism (12). It is noteworthy that VFs, even if mild, single, and asymptomatic, are always a hallmark of skeletal fragility predisposing patients to develop incident fragility fractures (33–36). Therefore, a radiological and morphometric analysis is mandatory to identify patients with VFs (23).

This was a clinical study evaluating the prevalence and determinants of radiological VFs in patients receiving chronic L-T4 therapy for DTC. When TSH was suppressed due to supraphysiologic dose of L-T4, VFs were

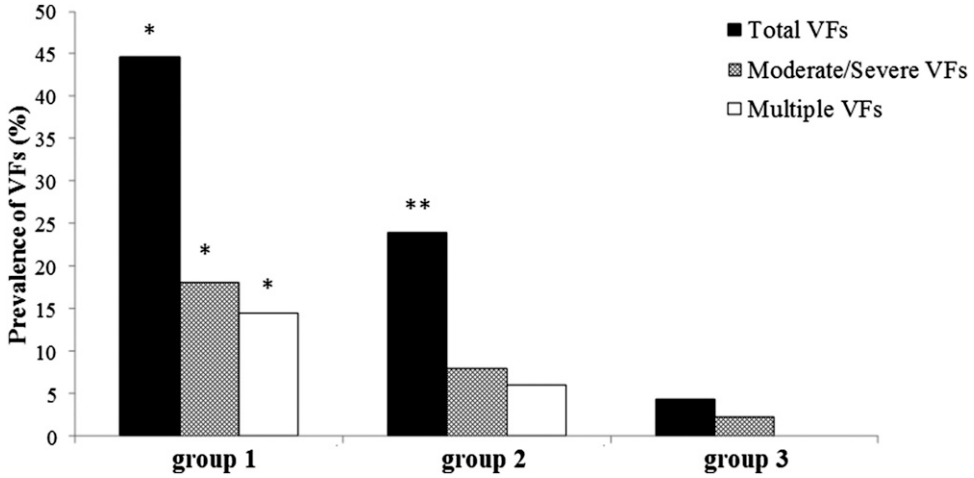

Figure 2. Prevalence of total, moderate/severe, and multiple VFs in patients stratified for serum TSH values (<0.5 mU/L, group 1; 0.5 to 1.0 mU/L, group 2; >1.0 mU/L, group 3).*$P < 0.05$ vs groups 2 and 3; **$P < 0.05$ vs group 3.

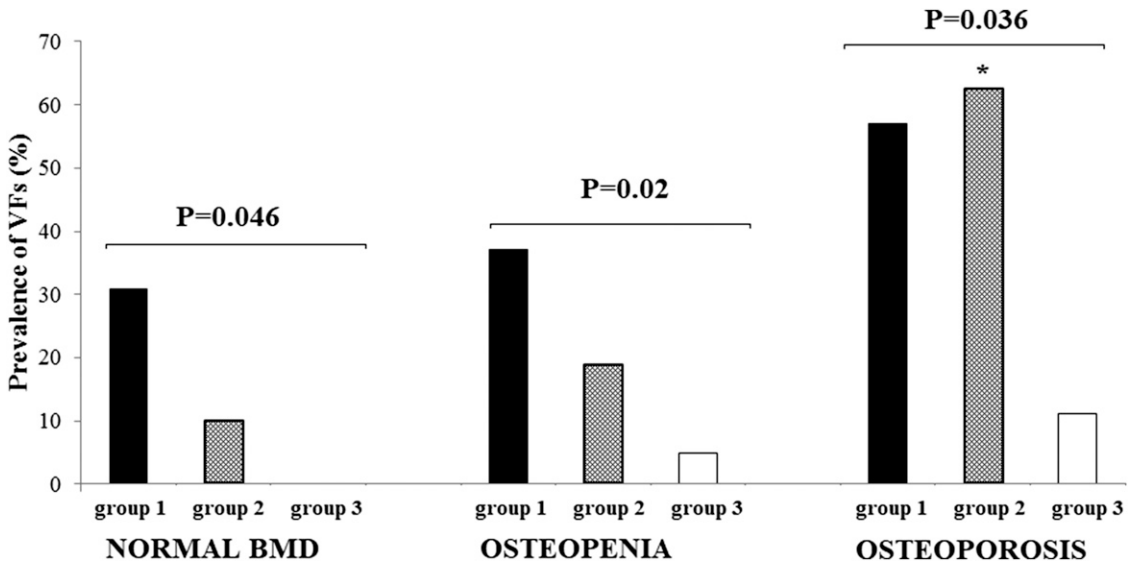

Figure 3. Prevalence of VFs in patients stratified for BMD categories (*i.e.*, normal BMD, osteopenia, and osteoporosis) and TSH values, as described in the text and the Fig. 2 legend. *$P < 0.05$ vs osteopenia and normal BMD.

found in about 40% of cases. This prevalence was comparable and even higher than that reported in other well-known forms of secondary osteoporosis (37–39), providing additional evidence that exogenous subclinical hyperthyroidism may cause skeletal fragility and fractures. Interestingly, VFs were moderate to severe in approximately one-half on patients who had fractures and multiple in approximately one-third, suggesting that these fractures may be also clinically relevant for their potential impact on quality of life and survival (20, 21). When TSH values were between 0.5 and 1.0 mU/L, about 25% of the women developed VFs, and the VF prevalence increased to >50% in the presence of densitometric diagnosis of osteoporosis. Interestingly, in these women, as well as in those with suppressed TSH values, the prevalence of VFs was not influenced by serum FT4 values. These results are in agreement with previous observations in untreated, euthyroid, postmenopausal women with low-normal TSH values and concomitant low BMD (40), consistent with the hypothesis that low TSH levels *per se*, regardless of thyroid function or L-T4 therapy, may influence skeletal health and risk of fractures.

In several forms of drug-induced osteoporosis, fragility fractures are an early complication of the treatment (24, 41–43). In this series of patients with DTC who were undergoing L-T4 suppressive therapy, prevalence of VFs increased significantly only after 5 years of treatment. This finding is in agreement with results of a previous

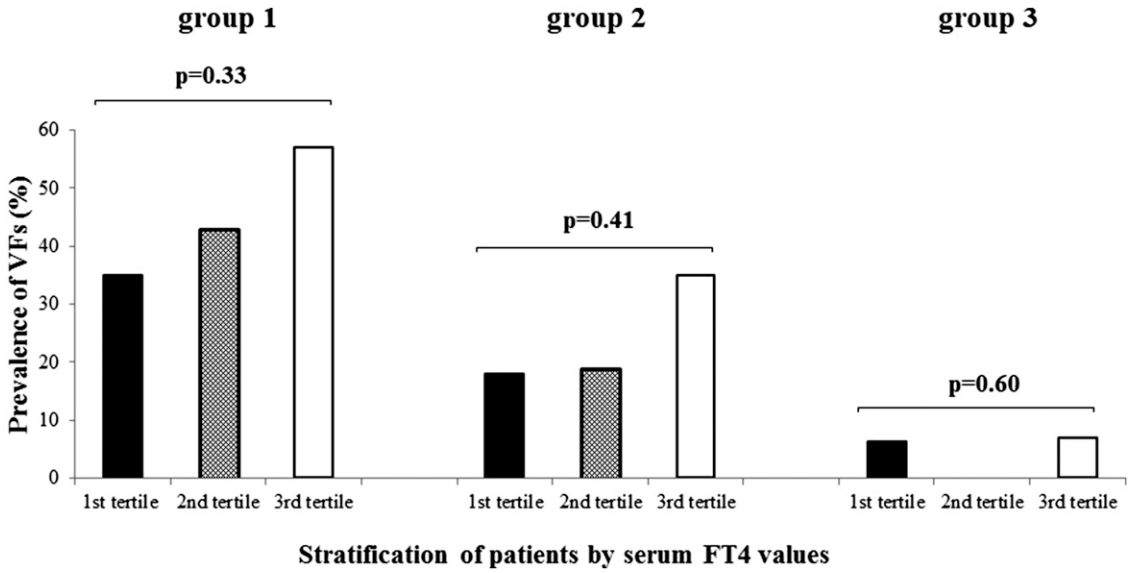

Figure 4. Prevalence of VFs in patients stratified for serum FT4 values within each therapeutic group defined in the text and the Fig. 2 legend.

population-based study in which a strong association was found between hip fracture and long-standing exposure to low TSH values (44). And the finding is reassuring about the skeletal safety of L-T4 suppressive therapy when used for a few years after thyroidectomy and RAI therapy in patients with DTC who have an intermediate risk of recurrence (10).

Previous studies did not clarify whether BMD could be a reliable marker of skeletal fragility in patients with DTC. In our patients, densitometric diagnosis of osteoporosis was an independent predictor of VFs, as demonstrated in women with postmenopausal osteoporosis (45). However, VFs also frequently occurred in patients with normal BMD, mainly when TSH was suppressed as an effect of L-T4 therapy. This finding is consistent with the concept that the skeletal damage induced by altered bone turnover caused by subclinical hyperthyroidism may not be always detected by DXA scan (46). This already has been demonstrated in other forms of secondary osteoporosis in which bone quality is generally affected more than bone quantity (41, 42, 47). The mechanisms responsible for the impairment in bone quality caused by subclinical hyperthyroidism are unknown. We could speculate that, whereas thyroid hormone excess causes predominantly an increase in bone resorption, suppressed TSH values may also inhibit bone formation (48), determining an uncoupled bone turnover responsible for a severe deterioration of bone microstructure that cannot be completely captured by DXA (48, 49). Previous studies have reported that TSH suppressive therapy may cause abnormalities in trabecular bone microstructure, as detected by trabecular bone score measurement (49) and peripheral high-resolution quantitative computed tomography (50); the current study demonstrated the actualization of this, thus far, theoretical risk.

These previous findings, along with the results of our study, may raise concerns and uncertainty in choosing the L-T4 dose and TSH targets in patients with DTC patients. The current guidelines suggest using DXA measurement of BMD to guide therapeutic-decision-making and stratify the fracture risk(10). Our study findings confirm that patients with osteoporosis are at high risk of VFs, but they also provide evidence that even patients with normal BMD may experience fracture when exposed to long-term suppression of TSH values.

The prevention and treatment of bone loss induced by thyroid hormone excess is still a matter of controversy, because the effects of bisphosphonates on BMD were shown to be variable (51, 52) and data on fractures are still lacking (53). Our study did not address this specific issue, because women treated with bone-active drugs were not enrolled. However, we found lower prevalence of VFs in women treated with vitamin D3 plus calcium as compared with either those treated with vitamin D3 alone or those who were untreated, which is consistent with the concept that vitamin D in combination with calcium may be more effective than vitamin D alone in preventing fractures (54).

There are some limitations to our study to be acknowledged and discussed. The cross-sectional design did not allow us to determine the onset of VFs during L-T4 therapy, as well as subsequent VF risk after decreasing L-T4 doses. However, the results deriving from the association analysis suggest that VFs may not be an early complication of L-T4 therapy and reduction of the L-T4 dose restoring TSH levels to >1 mU/L may normalize the fracture risk. The assignment of patients to different L-T4 regimens (*i.e.*, TSH suppressive vs replacement therapies) was not randomized but based on clinical judgment and current guidelines (9, 10), and this approach allowed us to provide information on fracture risk induced by L-T4 therapy in real-life clinical practice. Another concern is that TSH measured on a single occasion may not reflect the overall suppression of TSH over time. To partly address this shortcoming, we enrolled patients with stable L-T4 therapy and TSH values during the years after thyroid surgery and RAI therapy. Finally, we did not enroll a sex- and age-matched group of patients without diagnosis of thyroid cancer for comparison with our study groups. However, we have previously demonstrated that in 263 postmenopausal women with hormone receptor-positive early breast cancer, the prevalence of VFs was only 18.9% in aromatase inhibitor-naive patients and increased to 31.2% only in those assessed during aromatase inhibitor therapy; these data apparently are lower than those reported here for women with DTC who were receiving TSH suppressive therapy (42)

The aforementioned limitations notwithstanding, the results of this study may provide some practical insights into the management of DTC. In current guidelines, DXA BMD is the only skeletal parameter considered among the factors influencing the indication of the optimal TSH target levels during L-T4 therapy (10, 55). Conversely, our study supports the importance of a first-line morphometric evaluation of VFs in all patients in whom a TSH-suppressive regimen is started, because VFs can occur even when BMD is normal. Moreover, the current guidelines recommend maintaining TSH values at the lowest end of the normal range when the risk of DTC recurrence is low (10). In this regard, concerns may arise from our study about the potential risk of VFs when TSH values are between 0.5 and 1.0 mU/L in patients with DTC who have a densitometric diagnosis of osteoporosis. Therefore, before opting for a moderate suppression of

TSH in patients at low risk for DTC, based on our results, a second-line morphometric study is recommended when DXA BMD results indicate a patient is in the osteoporotic range. Finally, based on the high prevalence of VFs, morphometric evaluation should also be considered the method of choice for the evaluation of skeletal health during the follow-up of patients with DTC who are undergoing long-term suppressive TSH treatment.

In conclusion, the results of study showed, in women with DTC who were undergoing long-term suppressive L-T4 therapy, a high prevalence of VFs, likely due to an impairment of bone quality. Vertebral morphometry at baseline and during follow-up should be performed in patients with DTC whose TSH levels are suppressed.

Acknowledgments

Financial Support: This work was partially supported by the Glucocorticoid-Induced Osteoporosis Skeletal Endocrinology Group.

Correspondence and Reprint Requests: Andrea Giustina, MD, Endocrinology Department, Vita-Salute San Raffaele University, Via Olgettina 60, 20132 Milano, Italy. E-mail: giustina.andrea@hsr.it.

Disclosure Summary: The authors have nothing to disclose.

References

1. Murphy E, Williams GR. The thyroid and the skeleton. *Clin Endocrinol (Oxf)*. 2004;**61**(3):285–298.
2. Vestergaard P, Mosekilde L. Hyperthyroidism, bone mineral, and fracture risk–a meta-analysis. *Thyroid*. 2003;**13**(6):585–593.
3. Abrahamsen B, Jørgensen HL, Laulund AS, Nybo M, Bauer DC, Brix TH, Hegedüs L. The excess risk of major osteoporotic fractures in hypothyroidism is driven by cumulative hyperthyroid as opposed to hypothyroid time: an observational register-based time-resolved cohort analysis. *J Bone Miner Res*. 2015;**30**(5):898–905.
4. Ko YJ, Kim JY, Lee J, Song HJ, Kim JY, Choi NK, Park BJ. Levothyroxine dose and fracture risk according to the osteoporosis status in elderly women. *J Prev Med Public Health*. 2014;**47**(1):36–46.
5. Mazziotti G, Mormando M, Cristiano A, Bianchi A, Porcelli T, Giampietro A, Maffezzoni F, Serra V, De Marinis L, Giustina A. Association between l-thyroxine treatment, GH deficiency, and radiological vertebral fractures in patients with adult-onset hypopituitarism. *Eur J Endocrinol*. 2014;**170**(6):893–899.
6. Asa SL. The evolution of differentiated thyroid cancer. *Pathology*. 2017;**49**(3):229–237.
7. Carayon P, Thomas-Morvan C, Castanas E, Tubiana M. Human thyroid cancer: membrane thyrotropin binding and adenylate cyclase activity. *J Clin Endocrinol Metab*. 1980;**51**(4):915–920.
8. Brabant G. Thyrotropin suppressive therapy in thyroid carcinoma: what are the targets? *J Clin Endocrinol Metab*. 2008;**93**(4):1167–1169.
9. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM; American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer [published correction appears in Thyroid. 2010;20(8):942]. *Thyroid*. 2009;**19**(11):1167–1214.
10. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016;**26**(1):1–133.
11. Biondi B, Cooper DS. Benefits of thyrotropin suppression versus the risks of adverse effects in differentiated thyroid cancer. *Thyroid*. 2010;**20**(2):135–146.
12. Bauer DC, Ettinger B, Nevitt MC, Stone KL; Study of Osteoporotic Fractures Research Group. Risk for fracture in women with low serum levels of thyroid-stimulating hormone. *Ann Intern Med*. 2001;**134**(7):561–568.
13. Lee JS, Buzková P, Fink HA, Vu J, Carbone L, Chen Z, Cauley J, Bauer DC, Cappola AR, Robbins J. Subclinical thyroid dysfunction and incident hip fracture in older adults. *Arch Intern Med*. 2010;**170**(21):1876–1883.
14. Blum MR, Bauer DC, Collet TH, Fink HA, Cappola AR, da Costa BR, Wirth CD, Peeters RP, Åsvold BO, den Elzen WP, Luben RN, Imaizumi M, Bremner AP, Gogakos A, Eastell R, Kearney PM, Strotmeyer ES, Wallace ER, Hoff M, Ceresini G, Rivadeneira F, Uitterlinden AG, Stott DJ, Westendorp RG, Khaw KT, Langhammer A, Ferrucci L, Gussekloo J, Williams GR, Walsh JP, Jüni P, Aujesky D, Rodondi N; Thyroid Studies Collaboration. Subclinical thyroid dysfunction and fracture risk: a meta-analysis. *JAMA*. 2015;**313**(20):2055–2065.
15. Flynn RW, Bonellie SR, Jung RT, MacDonald TM, Morris AD, Leese GP. Serum thyroid-stimulating hormone concentration and morbidity from cardiovascular disease and fractures in patients on long-term thyroxine therapy. *J Clin Endocrinol Metab*. 2010;**95**(1):186–193.
16. Wirth CD, Blum MR, da Costa BR, Baumgartner C, Collet TH, Medici M, Peeters RP, Aujesky D, Bauer DC, Rodondi N. Subclinical thyroid dysfunction and the risk for fractures: a systematic review and meta-analysis. *Ann Intern Med*. 2014;**161**(3):189–199.
17. Yan Z, Huang H, Li J, Wang J. Relationship between subclinical thyroid dysfunction and the risk of fracture: a meta-analysis of prospective cohort studies. *Osteoporos Int*. 2016;**27**(1):115–125.
18. Yang R, Yao L, Fang Y, Sun J, Guo T, Yang K, Tian L. The relationship between subclinical thyroid dysfunction and the risk of fracture or low bone mineral density: a systematic review and meta-analysis of cohort studies [published online ahead of print March 29, 2017]. *J Bone Miner Metab*.
19. Cooper C, Atkinson EJ, O'Fallon WM, Melton LJ III. Incidence of clinically diagnosed vertebral fractures: a population-based study in Rochester, Minnesota, 1985-1989. *J Bone Miner Res*. 1992;**7**(2):221–227.
20. Jalava T, Sarna S, Pylkkänen L, Mawer B, Kanis JA, Selby P, Davies M, Adams J, Francis RM, Robinson J, McCloskey E. Association between vertebral fracture and increased mortality in osteoporotic patients. *J Bone Miner Res*. 2003;**18**(7):1254–1260.
21. Nevitt MC, Ettinger B, Black DM, Stone K, Jamal SA, Ensrud K, Segal M, Genant HK, Cummings SR. The association of radiographically detected vertebral fractures with back pain and function: a prospective study. *Ann Intern Med*. 1998;**128**(10):793–800.
22. Takigawa T, Tanaka M, Sugimoto Y, Tetsunaga T, Nishida K, Ozaki T. Discrimination between malignant and benign vertebral fractures using magnetic resonance imaging. *Asian Spine J*. 2017;**11**(3):478–483.
23. Griffith JF, Genant HK. New advances in imaging osteoporosis and its complications. *Endocrine*. 2012;**42**(1):39–51.
24. Mazziotti G, Canalis E, Giustina A. Drug-induced osteoporosis: mechanisms and clinical implications. *Am J Med*. 2010;**123**(10):877–884.
25. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res*. 1993;**8**(9):1137–1148.

26. Schousboe JT, Shepherd JA, Bilezikian JP, Baim S. Executive summary of the 2013 International Society for Clinical Densitometry Position Development Conference on bone densitometry. *J Clin Densitom*. 2013;**16**(4):455–466.
27. Greenspan SL, Greenspan FS. The effect of thyroid hormone on skeletal integrity. *Ann Intern Med*. 1999;**130**(9):750–758.
28. Giusti M, Cecoli F, Fazzuoli L, De Franchis V, Ceresola E, Ferone D, Mussap M, Minuto F. Serum osteoprotegerin and soluble receptor activator of nuclear factor kappaB ligand levels in patients with a history of differentiated thyroid carcinoma: a case-controlled cohort study. *Metabolism*. 2007;**56**(5):699–707.
29. Abe E, Marians RC, Yu W, Wu XB, Ando T, Li Y, Iqbal J, Eldeiry L, Rajendren G, Blair HC, Davies TF, Zaidi M. TSH is a negative regulator of skeletal remodeling. *Cell*. 2003;**115**(2):151–162.
30. Mazziotti G, Sorvillo F, Piscopo M, Cioffi M, Pilla P, Biondi B, Iorio S, Giustina A, Amato G, Carella C. Recombinant human TSH modulates in vivo C-telopeptides of type-1 collagen and bone alkaline phosphatase, but not osteoprotegerin production in postmenopausal women monitored for differentiated thyroid carcinoma. *J Bone Miner Res*. 2005;**20**(3):480–486.
31. Bassett JH, Williams GR. Critical role of the hypothalamic-pituitary-thyroid axis in bone. *Bone*. 2008;**43**(3):418–426.
32. Baliram R, Sun L, Cao J, Li J, Latif R, Huber AK, Yuen T, Blair HC, Zaidi M, Davies TF. Hyperthyroid-associated osteoporosis is exacerbated by the loss of TSH signaling. *J Clin Invest*. 2012;**122**(10):3737–3741.
33. Lindsay R, Pack S, Li Z. Longitudinal progression of fracture prevalence through a population of postmenopausal women with osteoporosis. *Osteoporos Int*. 2005;**16**(3):306–312.
34. Mazziotti G, Bianchi A, Porcelli T, Mormando M, Maffezzoni F, Cristiano A, Giampietro A, De Marinis L, Giustina A. Vertebral fractures in patients with acromegaly: a 3-year prospective study. *J Clin Endocrinol Metab*. 2013;**98**(8):3402–3410.
35. Johansson H, Odén A, McCloskey EV, Kanis JA. Mild morphometric vertebral fractures predict vertebral fractures but not non-vertebral fractures. *Osteoporos Int*. 2014;**25**(1):235–241.
36. Mazziotti G, Doga M, Frara S, Maffezzoni F, Porcelli T, Cerri L, Maroldi R, Giustina A. Incidence of morphometric vertebral fractures in adult patients with growth hormone deficiency. *Endocrine*. 2016;**52**(1):103–110.
37. Angeli A, Guglielmi G, Dovio A, Capelli G, de Feo D, Giannini S, Giorgino R, Moro L, Giustina A. High prevalence of asymptomatic vertebral fractures in post-menopausal women receiving chronic glucocorticoid therapy: a cross-sectional outpatient study. *Bone*. 2006;**39**(2):253–259.
38. Mazziotti G, Bianchi A, Bonadonna S, Nuzzo M, Cimino V, Fusco A, De Marinis L, Giustina A. Increased prevalence of radiological spinal deformities in adult patients with GH deficiency: influence of GH replacement therapy. *J Bone Miner Res*. 2006;**21**(4):520–528.
39. Mazziotti G, Mancini T, Mormando M, De Menis E, Bianchi A, Doga M, Porcelli T, Vescovi PP, De Marinis L, Giustina A. High prevalence of radiological vertebral fractures in women with prolactin-secreting pituitary adenomas. *Pituitary*. 2011;**14**(4):299–306.
40. Mazziotti G, Porcelli T, Patelli I, Vescovi PP, Giustina A. Serum TSH values and risk of vertebral fractures in euthyroid postmenopausal women with low bone mineral density. *Bone*. 2010;**46**(3):747–751.
41. Mazziotti G, Formenti AM, Adler RA, Bilezikian JP, Grossman A, Sbardella E, Minisola S, Giustina A. Glucocorticoid-induced osteoporosis: pathophysiological role of GH/IGF-I and PTH/VITAMIN D axes, treatment options and guidelines. *Endocrine*. 2016;**54**(3):603–611.
42. Pedersini R, Monteverdi S, Mazziotti G, Amoroso V, Roca E, Maffezzoni F, Vassalli L, Rodella F, Formenti AM, Frara S, Maroldi R, Berruti A, Simoncini E, Giustina A. Morphometric vertebral fractures in breast cancer patients treated with adjuvant aromatase inhibitor therapy: A cross-sectional study. *Bone*. 2017;**97**:147–152.
43. Mancini T, Mazziotti G, Doga M, Carpinteri R, Simetovic N, Vescovi PP, Giustina A. Vertebral fractures in males with type 2 diabetes treated with rosiglitazone. *Bone*. 2009;**45**(4):784–788.
44. Abrahamsen B, Jørgensen HL, Laulund AS, Nybo M, Brix TH, Hegedüs L. Low serum thyrotropin level and duration of suppression as a predictor of major osteoporotic fractures-the OPENTHYRO register cohort. *J Bone Miner Res*. 2014;**29**(9):2040–2050.
45. Mazziotti G, Bilezikian J, Canalis E, Cocchi D, Giustina A. New understanding and treatments for osteoporosis. *Endocrine*. 2012;**41**(1):58–69.
46. Waring AC, Harrison S, Fink HA, Samuels MH, Cawthon PM, Zmuda JM, Orwoll ES, Bauer DC; Osteoporotic Fractures in Men (MrOS) Study. A prospective study of thyroid function, bone loss, and fractures in older men: the MrOS study. *J Bone Miner Res*. 2013;**28**(3):472–479.
47. Mazziotti G, Biagioli E, Maffezzoni F, Spinello M, Serra V, Maroldi R, Floriani I, Giustina A. Bone turnover, bone mineral density, and fracture risk in acromegaly: a meta-analysis. *J Clin Endocrinol Metab*. 2015;**100**(2):384–394.
48. Sampath TK, Simic P, Sendak R, Draca N, Bowe AE, O'Brien S, Schiavi SC, McPherson JM, Vukicevic S. Thyroid-stimulating hormone restores bone volume, microarchitecture, and strength in aged ovariectomized rats. *J Bone Miner Res*. 2007;**22**(6):849–859.
49. Moon JH, Kim KM, Oh TJ, Choi SH, Lim S, Park YJ, Park DJ, Jang HC. the effect of TSH suppression on vertebral trabecular bone scores in patients with differentiated thyroid carcinoma. *J Clin Endocrinol Metab*. 2017;**102**(1):78–85.
50. Tournis S, Antoniou JD, Liakou CG, Christodoulou J, Papakitsou E, Galanos A, Makris K, Marketos H, Nikopoulou S, Tzavara I, Triantafyllopoulos IK, Dontas I, Papaioannou N, Lyritis GP, Alevizaki M. Volumetric bone mineral density and bone geometry assessed by peripheral quantitative computed tomography in women with differentiated thyroid cancer under TSH suppression. *Clin Endocrinol (Oxf)*. 2015;**82**(2):197–204.
51. Williams GR. Is prophylactic anti-resorptive therapy required in thyroid cancer patients receiving TSH-suppressive treatment with thyroxine? *J Endocrinol Invest*. 2014;**37**(8):775–779.
52. Panebianco P, Rosso D, Destro G, Scarpinato RA, Tropea S, Rizzo A, Russo MS, Motta M, Di Stefano F, Mazzarella R, Maugeri D. Use of disphosphonates in the treatment of osteoporosis in thyroidectomized patients on levothyroxin replacement therapy. *Arch Gerontol Geriatr*. 1997;**25**(2):219–225.
53. Panico A, Lupoli GA, Fonderico F, Marciello F, Martinelli A, Assante R, Lupoli G. Osteoporosis and thyrotropin-suppressive therapy: reduced effectiveness of alendronate. *Thyroid*. 2009;**19**(5):437–442.
54. Avenell A, Mak JC, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. *Cochrane Database Syst Rev*. 2014;**14**(4):CD000227.
55. Wang LY, Smith AW, Palmer FL, Tuttle RM, Mahrous A, Nixon IJ, Patel SG, Ganly I, Fagin JA, Boucai L. Thyrotropin suppression increases the risk of osteoporosis without decreasing recurrence in ATA low- and intermediate-risk patients with differentiated thyroid carcinoma. *Thyroid*. 2015;**25**(3):300–307.