The effect of suppressive thyroxine therapy in nodular goiter in postmenopausal women and 2 year's bone mineral density change

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Abstract. The efficacy of thyroxine suppressive therapy in reducing nodular growth and its effect to bone mineral density (BMD) in postmenopausal women is still debated. This study aimed to evaluate the therapeutic effect of thyroxine and its influence on BMD. Postmenopausal women with nodular or multinodular goiter during 2013–2015 at Chang Gung Memorial Hospital were enrolled and retrospectively traced back to the first date of visit or treatment. Ninety-four eligible patients were enrolled, of whom 45 were thyroxine-treated (LT-4 group) and 49 were treatment-naïve (control group). Data, including volume of nodules, were analyzed retrospectively. BMD was measured in each LT-4 group patient since the year of enrollment. Nodular volumes were reduced in both LT-4 (from 4.89 ± 4.46 to 4.10 ± 4.57 mL, $p = 0.033$) and control group (3.48 ± 4.36 to 3.09 ± 2.88 mL, $p = 0.239$) at initial 2-year follow-up. Nodular volume in LT-4 group increased insignificantly (from 4.89 ± 4.46 to 4.91 ± 5.40 mL, $p = 0.711$) at the end of 7-year follow-up. The best cut-off predictive nodular volume that may have responded to thyroxine is 2.6 mL (AUC, 0.740; sensitivity, 0.750; specificity, 0.733) during first 2 year. Lumbar spine, total hip and femoral neck BMD were not significantly changed during 2 year's thyroxine suppression therapy. In conclusion, thyroxine suppressive therapy in postmenopausal women had significant reduction in nodule volume at initial 2 years of treatment, especially in volume larger than 2.6 mL. Prolonged thyroxine treatment did not benefit nodular size reduction and may affect BMD minimally in postmenopausal women.

Key words: Thyroxine, Multinodular goiter, Bone mineral density

THYROID NODULAR GOITER has an increasing trend worldwide with prevalence ranging from 19% to 68% and higher frequency in older adults, especially in women [1]. The prevalence of goiter has been estimated to be 25% in Taiwan, with 19.4% in males and 33.6% in females.

The therapeutic effect of thyroxine on thyroid nodular goiter has been well studied, but with mixed results in the effectiveness of reducing the volume of thyroid nodules. Responsiveness to suppression of thyroid stimulating hormone (TSH) as a way to reduce nodular size was satisfactory in several studies [2–4], but not in all studies

[5–8]. The conflicting data on outcomes may be due to differences in gender, age, duration of therapy, suppressed or non-suppressed TSH levels, initial nodule size, nodule characteristics, the definition of responder or non-responder, and whether the patient was menopausal or not [9].

Aside from the therapeutic effect of thyroxine, possible adverse effects of thyroxine are worrisome, including increased risk of atrial fibrillation (Af) and cardiovascular disease in older adults with low TSH levels [10–14]. The action of thyroid hormone on the human skeleton has also been reviewed [15, 16], and low TSH level was proposed as a direct negative regulator of bone turnover [16]. For example, Surks *et al.* [17] reported an association between bone mineral density (BMD) loss and subclinical hyperthyroidism. Although some studies found that thyroxine treatment had a minimal effect on bone loss [18, 19], it is worth noting that women are known to have decreased BMD on aging, which accelerates after

Submitted Mar. 28, 2018; Accepted Jul. 13, 2018 as EJ18-0125
Released online in J-STAGE as advance publication Aug. 30, 2018
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menopause. Aging is also noted for increased risk of osteoporosis-related fracture and associated co-morbidity and mortality [20].

The objective of this study was to evaluate the therapeutic effect of thyroxine in postmenopausal women with thyroid nodule goiter and the possible effect of thyroxine on changes in BMD. Results may provide useful clinical information for the clinician managing thyroid nodules, especially in postmenopausal women.

Material and Methods

Patients and study design

Postmenopausal women with nodular or multinodular goiter seen during the period from 2013 to 2015 at the outpatient department of Chang Gung Memorial Hospital (CGMH), Taipei, Taiwan were included in the study. The records of enrolled women were retrospectively reviewed back to the date of the first visit for the condition. Taipei is a metropolitan and non-endemic area for goiter in Taiwan. Postmenopausal women were identified and enrolled who either received thyroxine (Aspen Pharmacare, Germany and GlaxoSmithKline Pharmaceuticals, United Kingdom) treatment (LT-4 group) or not (Control group) during the study period.

In LT-4 group, thyroxine was started before the time of enrollment and was traced back to the year 2001 in the earliest record. In control group, the size of nodules was traced back to the year 2002 in the earliest record and the observation period was 5 years. In all subjects in both groups, the goiters were identified before enrollment in the study, and the baseline of the control and LT-4 group was the time point when the nodules were found. The dose of thyroxine was adjusted and maintained at the minimal dose to keep the thyroid hormone (T4) level within the normal range, and TSH below the lowest normal limit reference range ($<0.35 \mu\text{IU/mL}$), but above the lowest detectable limit ($>0.008 \mu\text{IU/mL}$) to avoid thyrotoxicosis. Postmenopausal status was defined by the cut-off point of age 50 [21, 22], or according to the patients' medical chart record.

The study protocol was reviewed and approved by the Ethics Committee on Research and The Institutional Review Board of CGMH.

Selection criteria

The following inclusion criteria were used: (a) single or multiple thyroid nodules diagnosed by ultrasonography (US); (b) diagnosis of benign lesion from fine needle

aspiration cytology (FNAC) according to the Bethesda's criteria [23]; (c) US characteristics of a solid nodule with less than 50% of cystic components; (d) normal thyroid function without previous thyroid hormone and/or anti-thyroid drug treatment. The exclusion criteria were: (a) US characteristics of cystic component $>90\%$ [24]; (b) confirmed or suspected of malignancy and/or neoplasm; (c) history or current hyperthyroidism and/or hypothyroidism under treatment, and (d) history of neck irradiation. Patients who treated or ever treated with the human monoclonal antibody to the receptor activator of nuclear factor-kappa B ligand (RANKL), selective estrogen-receptor modulator (SERM), and bisphosphonate for osteoporosis were also excluded. Accordingly, while 77 patients were initially included in LT-4 group, 17 pre- and perimenopause subjects, 4 with previous hypothyroidism, 2 with previous hyperthyroidism, 2 with pure cystic component, 2 with suspicion of follicular neoplasm, and 5 with non-suppressible TSH level were excluded, leaving a total of 45 patients in LT-4 group. Similarly, 2 out of 51 patients in control group were excluded due to premenopausal status (Fig. 1). All of the nodules were carefully examined to fit the inclusion criteria, and all of the nodules were measured carefully after the assurance the same lesion during follow-up. Meanwhile, 32 patients who received at least 2 consecutive BMD tests during thyroxine suppression therapy in LT-4 group were analyzed for change of BMD. The baseline BMD in the study was the first time when participants were enrolled and the time point may allocate at several years after LT-4 administration.

Measurements

Ultrasound examination was performed with a commercially available real-time instrument (Hitachi Avius and Aloka alpha 5 with a high resolution 7.5 MHz linear probe; Hitachi, Japan) capable of visualizing solid lesions down to 3 mm size and with a theoretical axial resolution of less than 1 mm. In both L-T4 and control groups, US examinations were performed at 6–12 months intervals after the first visit. The timeframe of US follow-up was determined by a routine schedule or *pro re nata* according to physician's judgment.

US characteristics of the nodules were divided into solid, or mixed type (pure cystic lesions were excluded). As a rule, measurements of the nodules were taken as longitudinal (D1), transverse (D2) and depth (D3). The nodule volume was calculated according to the ellipsoid formula:

Fig. 1 Flowchart of participants

Volume (mL) = D1 (cm) × D2 (cm) × D3 (cm) × $\pi/6$ [25]

FNAC was done by a 23 or 25-gauge needle, as previously reported [23].

Bone mineral density

BMD was measured using a dual-energy X-ray absorption (DXA) fan-beam bone densitometer (Lunar Prodigy; GE Health-care Bio-Sciences, Piscataway, NJ, USA) at the lumbar 1–4 levels of the posterior-anterior spine, femoral neck, and total hip. Coefficient of variation was less than 1% in all centers where the densitometries were performed. The T-score, calculated using bone density data from the reference range of a healthy Caucasian female population [26].

Laboratory tests

Serum thyroglobulin (Tg) was detected by chemiluminescence immunoassay (CLIA) using immunoassay systems (Beckman Coulter, Inc. Brea, CA 92821, USA). Anti-thyroid peroxidase antibody (anti-TPO Ab) was checked by chemiluminescence microparticle immunoassay (CMIA) with the Architect i2000 system (Abbott Laboratories Diagnostics Division, IL, USA). T4 and TSH were examined using CLIA methodology on the Advia Centaur XPi system (Siemens, Germany). Roche e602 modular immunoassay analyzer (Elecsys, Roche Diagnostics, Mannheim, Germany) was used to detect

anti-Tg and anti-TSH receptor Abs. The reference range for T4, TSH and Tg were 4.8–12.5 $\mu\text{g/dL}$, 0.35–5.50 $\mu\text{IU/mL}$ and <25 ng/mL, respectively. The normal range for anti-Tg Ab, anti-TPO Ab and anti-TSH receptor Ab were <115 IU/mL, <5.6 IU/mL, and <1.75 IU/L, respectively. The hormone measurements and clinical evaluations were repeated in the follow-up period.

Statistical analysis

All statistical analyses were performed using the Statistical Product and Service Solutions (SPSS, version 20, IBM Corp., New York, USA). Differences in age, body weight, body mass index (BMI), TSH, T4, and Tg were compared between groups by Mann-Whitney *U* test, and autoimmune antibodies such as anti-Tg Ab and anti-TPO Ab, anti-TSH Ab were compared between groups by Fisher's exact test. Comparisons between baseline and annual nodule volumes were performed by Wilcoxon signed-rank test. Receiver operating characteristic (ROC) curve was performed to determine the cut-off point for best specificity and sensitivity. The best discrimination point of initial thyroid nodule volume was determined by Youden index [27]. Paired student *t*-test was used to evaluate changes in BMD after serial DXA measurement. A *p* value of less than 0.05 was established as statistical significance.

Table 1 Demographic, clinical and biochemical data of postmenopausal patients

	Baseline Control	LT-4	<i>p</i> value	After suppressive thyroxine LT-4	<i>p</i> value
<i>n</i>	49	45		45	
Age at study entry (years)	63.3 ± 7.3	60.6 ± 8.4	0.123		
Height (cm)	155.2 ± 6.3	157.7 ± 5.0	0.041*		
Weight (kg)	59.0 ± 10.1	57.8 ± 7.2	0.843		
Body mass index (kg/m ²)	24.2 ± 4.4	23.2 ± 2.8	0.765		
Anti-TPO (positive), <i>n</i> (%)	5 (10.2%)	6 (13.3%)	0.753		
Anti-TSHR (positive), <i>n</i> (%)	0 (0%)	1 (2.2%)	0.479		
Anti-Tg (positive), <i>n</i> (%)	2 (4.1%)	4 (8.9%)	0.421		
TSH (μIU/mL)	1.31 ± 0.67	1.11 ± 0.48	0.565	0.13 ± 0.15	<0.001*
Tg (ng/mL)	14.6 ± 10.3	79.5 ± 122.4	0.001*	32.0 ± 51.9	0.006*
T4 (μg/dL)	8.3 ± 1.6	10.6 ± 9.1	0.827	10.9 ± 2.2	0.023*
Nodule volume (mL)	3.48 ± 4.36	4.89 ± 4.46	0.066		
Thyroxine dose (μg/day)				104.9 ± 19.0	
Thyroxine dose (μg/kg/day)				1.8 ± 0.4	
Duration of thyroxine therapy (months)				91.2 ± 44.7	

Continuous variables are presented as mean and standard deviation (mean ± SD). Nonparametric Mann–Whitney *U* test was used for continuous variables. Fisher's exact test was used for nominal variables.

* Significant difference, defined by *p* value <0.05.

Abbreviations: anti-TPO Ab, anti-thyroid peroxidase antibody; anti-TSHR, anti-thyroid stimulating hormone receptor antibody; anti-Tg Ab, anti-thyroglobulin antibody; T4, Thyroid hormone thyroxine.

Results

All participants were euthyroid and postmenopausal when enrolled. The mean age was 63.3 ± 7.3 years in control group and 60.6 ± 8.4 years in LT-4 group (*p* = 0.123, Table 1). BMI was similar between the two groups (24.2 ± 4.4 kg/m² in control group and 23.2 ± 2.8 kg/m² in LT-4 group, *p* = 0.843). The baseline TSH level was 1.31 ± 0.67 and 1.11 ± 0.48 μIU/mL (*p* = 0.565) in control and LT-4 groups, respectively. The baseline T4 level was 8.3 ± 1.6 μg/dL in control group and 10.6 ± 9.1 μg/dL in the LT4 group (*p* = 0.827). Tg level was significantly lower in control group than in LT-4 group (14.6 ± 10.3 vs. 79.5 ± 122.4 ng/mL, *p* = 0.001). The mean nodule size of control group and LT-4 group was 3.48 ± 4.36 mL and 4.89 ± 4.46 mL, respectively (*p* = 0.06). The average body weight (BW)-adjusted thyroxine dose was 1.8 μg/kg/day in LT-4 group. The post-treatment TSH values in LT-4 group were maintained in the range of 0.08 to 0.35 μIU/mL (mean = 0.13 ± 0.15 μIU/mL). Additionally, the T4 level was increased (10.9 ± 2.2

μg/dL, *p* = 0.023) and the Tg level was decreased (32.0 ± 51.9 ng/mL, *p* = 0.006) significantly after thyroxine treatment (Table 1).

Nodule size

Fig. 2 shows a trend of reduction of thyroid nodule volume in control group after initial 2-year follow-up but no further volume decreases were shown after 5 years. A similar condition was observed in LT-4 group but the reduced volume was more obvious in the initial 2 years (Δvolume change = −0.39 ± 2.95 mL in control group vs. −0.90 ± 3.98 mL in LT-4 group, *p* = 0.304). Changes in nodule volume were not significantly different at 2-year and 5-year follow-up between the two groups (Fig. 2).

In LT-4 group, a gradual volume reduction was observed as early as 1 year (3.98 ± 3.38 mL, *p* = 0.174) and was more statistically significant in 2 years (4.10 ± 4.57 mL, *p* = 0.033) when compared with baseline values (4.89 ± 4.46 mL) (Table 2). However, the nodule volume increased insignificantly later during 7-year follow-up (4.91 ± 5.40 mL, *p* = 0.711) and 9-year

Fig. 2 Thyroid nodule volumes at baseline (White columns), during 2-year (Red columns) and 5-year follow-up (Black columns) in control and L-T4 group.

Each column indicates mean values; bars represent standard deviations. *N* equals numbers of participants.

Nonparametric Mann-Whitney *U* test was used for continuous variables between the two groups and Wilcoxon signed rank test was used for related continuous variables in different time interval.

* Significant difference, defined by *p* value < 0.05.

Table 2 Thyroid nodule volumes at baseline and during follow-up in LT-4 group

	<i>n</i>	Range	mean ± SD	median	<i>p</i> value
Baseline	45	(0.18–17.76)	4.89 ± 4.46	3.14	
1 year	32	(0.23–13.31)	3.98 ± 3.38	2.96	0.172
2 years	43	(0.23–27.41)	4.10 ± 4.57	2.82	0.033*
3.5 years	26	(0.04–19.09)	4.57 ± 5.13	2.24	0.200
5 years	34	(0.17–27.04)	4.29 ± 5.27	2.61	0.197
7 years	18	(0.23–19.75)	4.91 ± 5.40	3.74	0.711
9 years	8	(0.31–21.43)	6.06 ± 7.03	3.63	0.208

Continuous variables are presented as mean and standard deviation (mean ± SD). Nonparametric Wilcoxon Signed Rank test was used for repeated measurement.

* Significant difference, defined by *p* value < 0.05.

follow-up (6.06 ± 7.03 mL, *p* = 0.208). In LT-4 group, the best value for predicting the reduction of nodule volume was observed in 21 patients (84.0%) during 2-year follow-up when the initial nodule volume was greater than 2.6 mL (AUC = 0.740, sensitivity: 0.750, specificity: 0.733, 95% CI (0.580–0.901), *p* = 0.010) (Fig. 3).

Bone mineral density

The initial BMD was evaluated by DXA in patients of LT-4 group at the age of 66.9 ± 9.0 years after an average thyroxine treatment duration of 61.9 ± 9.6 months. During the 2-year follow-up interval of BMD measurements, TSH levels in these patients were suppressed and maintained around 0.11 ± 0.1 μ IU/mL. Changes in BMD during the 2-year follow-up showed no remarkable differences in lumbar spine (from 0.989 ± 0.134 to 0.981 ± 0.135 g/cm², *p* = 0.460), total hip (from 0.806 ± 0.091 to 0.810 ± 0.094 g/cm², *p* = 0.474) and femoral neck (from 0.742 ± 0.090 to 0.750 ± 0.083 g/cm², *p* = 0.204) (Table 3).

Discussion

The natural course of thyroid goiter is not fully understood. In a series of observational studies, thyroid nodules were estimated to have grown from 15% to 69% during 5 years [28, 29]. Such a wide range of variation was attributed to different definitions of volume increments and small sample size in those studies. For example, while an annual growth of 4.5% was reported in a cross-sectional study [30], only 15.4% of growth in nod-

Fig. 3 ROC curve analysis was performed by SPSS to determine the best discrimination point of initial nodule volume and reduction of volume after 2-years' thyroxine treatment.

The best discrimination points of initial thyroid nodule volume determined by Youden index was located at 2.6 mL with a sensitivity of 0.750 and a specificity of 0.733. Area under ROC curve was 0.740; p value = 0.010, 95% CI (0.580–0.901).

Abbreviation: ROC = receiver operating characteristic.

Table 3 BMD changes in LT-4 group

	Baseline ($n = 32$)	2-yr follow-up ($n = 32$)	p value
BMD (g/cm²)			
Lumbar spine	0.989 ± 0.134	0.981 ± 0.135	0.460
Total hip	0.806 ± 0.091	0.810 ± 0.094	0.474
Femoral neck	0.742 ± 0.090	0.750 ± 0.083	0.204
T-score			
Lumbar spine	−1.595 ± 1.121	−1.662 ± 1.124	0.460
Total hip	−1.620 ± 0.758	−1.581 ± 0.785	0.475
Femoral neck	−1.985 ± 0.749	−1.937 ± 0.696	0.315

Continuous variables are presented as mean and standard deviation (mean ± SD).

p values were determined using the paired t test.

* Significant difference, defined by p value < 0.05.

Abbreviation: BMD, bone mineral density.

ular size >0.2 mL was found in patients who were younger than 60 years old in a 5 year prospective, multi-

center, observation study [31]. As reported in other studies [8, 32], Taiwan was at one time an endemic area for goiter but, since 1958, the prevalence of goiter was remarkably reduced after iodine supplementation [33], which may correlate with the slow growing nodules found in postmenopausal women without thyroxine treatment in the present study.

The efficacy of thyroxine suppression on thyroid nodules has been controversial and is still under debate. Patients in the current study were treated by different clinicians, with various strategies for managing thyroid nodules. Treatment decisions were made after discussion with the patients. This may be the reason why the nodule volume in control group was smaller, as patients with smaller nodules are more willing to undergo observation rather than initial medical treatment. Although Gharib *et al.* [7] claimed a reduction of 10%–20% nodule volume after 3 to 21 months thyroxine treatment, a meta-analysis by Castro and colleagues [34] reported a statistically insignificant reduction of nodule volume of more than 50% after suppressive thyroid hormone therapy for more than 6 months. Results of the present study were also contradictory since a volume reduction in the treatment group in a 2-year follow-up period was still statistically insignificant compared to results for control group.

Regarding the length of thyroxine treatment, other investigators reported a >50% nodule volume reduction using short-term thyroxine treatment of 18 months in one study vs. 12 months in another [9, 35]. During mean follow-up of 4 to 4.9 years, the efficacy of thyroxine treatment was not sustained in study subjects with both suppressive and non-suppressive clinical conditions [8, 28, 36]. Results of the present study are in agreement with those findings since a gradual nodule volume reduction nadir was found at the initial 2-year follow-up in both the treatment and control groups. However, at the end of 7-year and 9-year follow-up, the nodule size was even larger than that of the initial nodules. Thus, a duration of more than 2 years of thyroxine suppressive treatment appears to have no benefit in controlling nodule size.

Costante *et al.* [8] found that nodules with a smaller size (<1.5 mL) had a better response rate after one year of thyroxine suppressive treatment in postmenopausal women. Similarly, La Rosa *et al.* [2] also reported a higher frequency of positive response to thyroxine in patients with nodule volume <5 mL. In contrast, the present study found better responsiveness to thyroxine treatment in patients with larger thyroid nodules (>2.6

mL). Some discrepancies between the Costante study and results of the present study may help to explain the differences in response rates. The Costante study, for example, included younger (aged 45–54) postmenopausal women, iodine status (mild to moderate iodine deficiency in contrast to iodine sufficient), and the exclusion of larger nodule volumes (>12 mL). In contrast, patients in the present study were relatively older (mean age 60.6 ± 8.4 years) with larger nodules (11.1% of patients had initial nodule volume larger than 12 mL). Also, the typical iodine status in Taiwan is mild deficiency in women older than 45 years [37].

Since 1995, with the arrival of the ageing era, more than 20 million women were estimated to have osteoporosis worldwide [38]. The risk of fracture and associated mortality and mobility is high (40%–50%) in people aged 50 and older with osteoporosis [39]. Since thyrotoxicosis, lack of estrogen and female gender are risk factors associated with osteoporosis [40, 41], the possibility of aggravating bone loss is a major concern. In the present study, minimal changes in BMD were observed in postmenopausal women under thyroxine treatment for two years even though other investigators have reported cortical bone loss in short and long term follow-up [18, 19, 42]. These inconsistencies in short-term thyroxine treatment might be due to the age-range of the participants since BMD loss is accelerated in the late perimenopausal and first postmenopausal years [43, 44]. Even with the neutral findings in the present study, serial BMD evaluations may be needed in postmenopausal women under long-term suppressive thyroxine treatment to avoid possible unwanted outcomes.

Another important issue is the influence of thyroid hormone on the cardiovascular system. Prior studies have shown that when the TSH level was <0.10 mIU/L (subclinical hyperthyroidism) the risk of heart failure and Af are increased [45, 46]. However, other study has reported an unclear association of cardiovascular risk in patients with subclinical hyperthyroidism when TSH levels are between 0.10 and 0.44 mIU/L [47]. The average TSH level of our participants during suppressive treatment was 0.13 ± 0.15 μ IU/mL. Furthermore, no patient experienced congestive heart failure or Af during follow-

up. Nevertheless, caution is needed in the management of benign thyroid nodules, and for longer-term thyroxine treatment, the risk of congestive heart failure and Af should be taken into account.

The present study has several limitations. First, the study is retrospective, which precludes inferences of causality, and only a small number of participants were enrolled from a single medical center with unavoidable missing data. Second, it is possible that observation rather than treatment is the shared decision made by both physicians and patients with smaller thyroid nodules, which may explain why the initial nodule size was smaller in control group. Third, the baseline data of BMD and biomarkers of bone turnover were not collected from patients before thyroxine treatment. Additionally, long-term effects of thyroxine treatment on BMD were not studied.

Conclusions

In conclusion, the present study demonstrates that thyroxine suppression therapy successfully reduces the volume of thyroid nodules in postmenopausal women in the initial two years of treatment, especially in nodules with larger volume (>2.6 mL). Prolonged treatment for longer than two years does not improve the nodular size in this patient population. No significant BMD loss is observed during the initial two-year period.

Acknowledgments

This research was supported by Chang Gung Memorial Hospital (CORPG3F0811). This study is based in part on data from the Chang Gung Research Database provided by the Chang Gung Memorial Hospital.

Disclosure

None of the authors have any potential conflicts of interest associated with this research. No specific grants from any funding agency in the public, commercial or not-for-profit sector were received to support this study.

References

1. Morganti S, Ceda G, Saccani M, Milli B, Ugolotti D, *et al.* (2005) Thyroid disease in the elderly: sex-related differences in clinical expression. *J Endocrinol Invest* 28: 101–104.

2. La Rosa GL, Lupo L, Giuffrida D, Gullo D, Vigneri R, *et al.* (1995) Levothyroxine and potassium iodide are both effective in treating benign solitary solid cold nodules of the thyroid. *Ann Intern Med* 122: 1–8.
3. Lima N, Knobel M, Cavaliere H, Szejnszajd C, Tomimori E, *et al.* (1997) Levothyroxine suppressive therapy is partially effective in treating patients with benign, solid thyroid nodules and multinodular goiters. *Thyroid* 7: 691–697.
4. Zelmanovitz Fv, Genro S, Gross JL (1998) Suppressive therapy with levothyroxine for solitary thyroid nodules: a double-blind controlled clinical study and cumulative meta-analyses. *J Clin Endocrinol Metab* 83: 3881–3885.
5. Gharib H, James EM, Charboneau JW, Naessens JM, Offord KP, *et al.* (1987) Suppressive therapy with levothyroxine for solitary thyroid nodules. *N Engl J Med* 317: 70–75.
6. Mainini E, Martinelli I, Morandi G, Villa S, Stefani I, *et al.* (1995) Levothyroxine suppressive therapy for solitary thyroid nodule. *J Endocrinol Invest* 18: 796–799.
7. Gharib H, Mazzaferri EL (1998) Thyroxine suppressive therapy in patients with nodular thyroid disease. *Ann Intern Med* 128: 386–394.
8. Costante G, Crocetti U, Schifino E, Ludovico O, Capula C, *et al.* (2004) Slow growth of benign thyroid nodules after menopause: no need for long-term thyroxine suppressive therapy in post-menopausal women. *J Endocrinol Invest* 27: 31–36.
9. Cesareo R, Iozzino M, Isgro MA, Annunziata F, Di Stasio E (2010) Short term effects of levothyroxine treatment in thyroid multinodular disease. *Endocr J* 57: 803–809.
10. Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, *et al.* (1994) Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med* 331: 1249–1252.
11. Uzzan B, Campos J, Cucherat M, Nony P, Boissel JP, *et al.* (1996) Effects on bone mass of long term treatment with thyroid hormones: a meta-analysis. *J Clin Endocrinol Metab* 81: 4278–4289.
12. Gencer B, Collet TH, Virgini V, Auer R, Rodondi N (2013) Subclinical thyroid dysfunction and cardiovascular outcomes among prospective cohort studies. *Endocr Metab Immune Disord Drug Targets* 13: 4–12.
13. Blum MR, Bauer DC, Collet TH, Fink HA, Cappola AR, *et al.* (2015) Subclinical thyroid dysfunction and fracture risk: a meta-analysis. *JAMA* 313: 2055–2065.
14. Lee SJ, Kim KM, Lee EY, Song MK, Kang DR, *et al.* (2016) Low normal TSH levels are associated with impaired BMD and hip geometry in the elderly. *Aging Dis* 7: 734–743.
15. Bassett JD, Williams GR (2003) The molecular actions of thyroid hormone in bone. *Trends Endocrinol Metab* 14: 356–364.
16. Gogakos AI, Bassett JD, Williams GR (2010) Thyroid and bone. *Arch Biochem Biophys* 503: 129–136.
17. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, *et al.* (2004) Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA* 291: 228–238.
18. Müller CG, Bayley TA, Harrison JE, Tsang R (1995) Possible limited bone loss with suppressive thyroxine therapy is unlikely to have clinical relevance. *Thyroid* 5: 81–87.
19. Appetecchia M (2005) Effects on bone mineral density by treatment of benign nodular goiter with mildly suppressive doses of L-thyroxine in a cohort women study. *Horm Res* 64: 293–298.
20. Riggs BL, Melton LJ 3rd (1995) The worldwide problem of osteoporosis: insights afforded by epidemiology. *Bone* 17: S505–S511.
21. Chow S, Huang C, Lee Y (1997) Demographic characteristics and medical aspects of menopausal women in Taiwan. *J Formos Med Assoc* 96: 806–811.
22. Chen SC, Lo TC, Chang JH, Kuo HW (2014) Variations in aging, gender, menopause, and obesity and their effects on hypertension in Taiwan. *Int J Hypertens* 2014: 515297.
23. Cibas ES, Ali SZ (2009) The Bethesda system for reporting thyroid cytopathology. *Am J Clin Pathol* 132: 658–665.
24. Andrioli M, Carzaniga C, Persani L (2013) Standardized ultrasound report for thyroid nodules: the endocrinologist's viewpoint. *Eur Thyroid J* 2: 37–48.
25. Gallo M, Pesenti M, Valcavi R (2003) Ultrasound thyroid nodule measurements: the “gold standard” and its limitations in clinical decision making. *Endocr Pract* 9: 194–199.
26. Kanis J, Glüer CC (2000) An update on the diagnosis and assessment of osteoporosis with densitometry. *Osteoporos Int* 11: 192–202.
27. Youden WJ (1950) Index for rating diagnostic tests. *Cancer* 3: 32–35.
28. Quadbeck B, Pruellage J, Roggenbuck U, Hirche H, Janssen OE, *et al.* (2002) Long-term follow-up of thyroid nodule growth. *Exp Clin Endocrinol Diabetes* 110: 348–354.
29. Alexander EK, Hurwitz S, Heering JP, Benson CB, Frates MC, *et al.* (2003) Natural history of benign solid and cystic thyroid nodules. *Ann Intern Med* 138: 315–318.
30. Berghout A, Wiersinga WM, Smits NJ, Touber JL (1990) Interrelationships between age, thyroid volume, thyroid nodularity, and thyroid function in patients with sporadic nontoxic goiter. *Am J Med* 89: 602–608.
31. Durante C, Costante G, Lucisano G, Bruno R, Meringolo D, *et al.* (2015) The natural history of benign thyroid nodules. *JAMA* 313: 926–935.
32. Kuma K, Matsuzuka F, Yokozawa T, Miyauchi A, Sugawara M (1994) Fate of untreated benign thyroid nod-

- ules: results of long-term follow-up. *World J Surg* 18: 495–498.
33. Chen K, Lin CC, Wu HY, Sun C, Chen C, *et al.* (1964) Pilot project on endemic goiter prevention with iodized salt in Hsinchu County, Taiwan, China. *Memoirs Coll Med Nat Taiwan Univ* 10: 73–92 (In Chinese).
 34. Castro MR, Caraballo PJ, Morris JC (2002) Effectiveness of thyroid hormone suppressive therapy in benign solitary thyroid nodules: a meta-analysis. *J Clin Endocrinol Metab* 87: 4154–4159.
 35. Wemeau JL, Caron P, Schvartz C, Schlienger JL, Orgiazzi J, *et al.* (2002) Effects of thyroid-stimulating hormone suppression with levothyroxine in reducing the volume of solitary thyroid nodules and improving extranodular non-palpable changes: a randomized, double-blind, placebo-controlled trial by the French Thyroid Research Group. *J Clin Endocrinol Metab* 87: 4928–4934.
 36. Puzziello A, Carrano M, Angrisani E, Marotta V, Faggiano A, *et al.* (2014) Evolution of benign thyroid nodules under levothyroxine non-suppressive therapy. *J Endocrinol Invest* 37: 1181–1186.
 37. Tang KT, Wang FF, Pan WH, Lin JD, Won GS, *et al.* (2016) Iodine status of adults in Taiwan 2005–2008, 5 years after the cessation of mandatory salt iodization. *J Formos Med Assoc* 115: 645–651.
 38. Melton LJ 3rd (1995) Perspectives: how many women have osteoporosis now? *J Bone Miner Res* 10: 175–177.
 39. Johnell O, Kanis J (2005) Epidemiology of osteoporotic fractures. *Osteoporos Int* 16 Suppl 2: S3–S7.
 40. Fraser SA, Smith DA, Anderson JB, Wilson GM (1971) Osteoporosis and fractures following thyrotoxicosis. *Lancet* 297: 981–983.
 41. Riggs BL, Khosla S, Melton LJ 3rd (1998) A unitary model for involutional osteoporosis: estrogen deficiency causes both type I and type II osteoporosis in postmenopausal women and contributes to bone loss in aging men. *J Bone Miner Res* 13: 763–773.
 42. Guo CY, Weetman AP, Eastell R (1997) Longitudinal changes of bone mineral density and bone turnover in postmenopausal women on thyroxine. *Clin Endocrinol (Oxf)* 46: 301–307.
 43. Finkelstein JS, Brockwell SE, Mehta V, Greendale GA, Sowers MR, *et al.* (2008) Bone mineral density changes during the menopause transition in a multiethnic cohort of women. *J Clin Endocrinol Metab* 93: 861–868.
 44. De Rosa G, Testa A, Giacomini D, Carrozza C, Astazi P, *et al.* (1997) Prospective study of bone loss in pre- and post-menopausal women on L-thyroxine therapy for non-toxic goitre. *Clin Endocrinol (Oxf)* 47: 529–535.
 45. Gencer B, Collet T-H, Virgini V, Bauer DC, Gussekloo J, *et al.* (2012) Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from six prospective cohorts. *Circulation* 126: 1040–1049.
 46. Collet T-H, Gussekloo J, Bauer DC, den Elzen WP, Cappola AR, *et al.* (2012) Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. *Arch Intern Med* 172: 799–809.
 47. Donangelo I, Suh SY (2017) Subclinical hyperthyroidism: when to consider treatment. *Am Fam Physician* 95: 710–716.