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Effects of TSH Suppressive Therapy On Bone Mineral Density (BMD) and Bone Turnover Markers (BTMs) in Patients with Differentiated Thyroid Cancer in Northeast China: A Prospective Controlled Cohort Study

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Abstract

Purpose

This study aimed to evaluate the effects of thyroid-stimulating hormone (TSH) suppressive therapy on bone mineral density (BMD) and bone turnover markers (BTMs) in differentiated thyroid cancer (DTC) patients after postoperative 1-2 years in Northeast China.

Methods

Five male, sixteen premenopausal, and eight postmenopausal female DTC patients receiving TSH suppressive therapy after thyroidectomy were enrolled. Patients were matched with healthy controls in a ratio of 1:2. All participants completed postoperative 1-year follow-up, and postmenopausal women completed 2-year follow-up. We measured BMD of the lumbar spine (LS), femoral neck (FN), and total hip (TH) using dual-energy X-ray absorptiometry (DXA). Bone formation marker P1NP and bone resorption marker β-CTX were also evaluated. Fracture risks were assessed by FRAX.

Results

There was no difference in BMD and BTMs between DTC patients and controls in the male group at 1-year follow-up. In the premenopausal women, the LS-BMD, FN-BMD, and TH-BMD in DTC patients were all higher than those in controls, but only FN-BMD showed a significant difference. The change rate of P1NP showed a significant difference between DTC patients and controls, while no difference was found in the β-CTX level. In the postmenopausal women, no difference in BMD and BTMs were observed between DTC patients and controls at the 1-year and 2-year follow-up.

Conclusion

Our study indicated that postoperative 1-year TSH suppressive therapy did not show detrimental effects on BMD and BTMs in men, premenopausal, and postmenopausal DTC patients. The 2-year postoperative TSH suppressive therapy did not lead to additional loss of bone mass in postmenopausal DTC patients.

Introduction

Differentiated thyroid cancer (DTC) is a common endocrine malignant tumor in the head and neck. In recent years, the incidence of thyroid cancer has increased rapidly and substantially in many countries, but the prognosis of DTC is favorable and the mortality is still stable [1]. After regular surgical resection of the tumor, thyroid-stimulating hormone (TSH) suppressive therapy using exogenous levothyroxine (LT4) to maintain a low level of TSH is recommended in the management of DTC, to inhibit residual tumor cell growth and decrease the risk of tumor recurrence and metastasis [2]. However, long-term administration of supraphysiological doses of LT4 which induces a state of subclinical hyperthyroidism could have potential adverse effects on the skeletal system [3]. A meta-analysis demonstrated that subclinical hyperthyroidism was associated with an increased risk of hip and other fractures, particularly among those with TSH levels of less than 0.1 mIU/L [4]. Given the high incidence and low mortality of DTC, the administration duration of LT4 can be long and the deleterious effects on skeletal health cannot be ignored. However, the effects of TSH suppressive therapy on bone mineral density (BMD) and bone turnover markers (BTMs) are not conclusive and the existing studies yield conflicting results.

Up to date, few prospective longitudinal studies [5-9] have been reported and the studies in mainland China are limited [10, 11]. To the best of our knowledge, no prospective cohort study has been conducted in China. This prospective controlled cohort study aimed to evaluate BMD and BTMs in male, premenopausal female and postmenopausal female DTC patients receiving TSH suppressive therapy at postoperative 1 year in northeast China. Postoperative 2-year follow-up was conducted in postmenopausal female DTC patients.

Materials And Methods

Patients and selection criteria

The study population consisted of patients who underwent operation for DTC from 2012 to 2014 at the First Affiliated Hospital of China Medical University. The following inclusion criteria were used: (1) patients who were diagnosed with DTC underwent total or subtotal thyroidectomy; (2) BMD was tested and serum sample was obtained before operation; (3) TSH suppressive therapy using LT4 was conducted immediately after thyroidectomy, the goal of TSH suppressive level was less than 0.5 mIU/L. The exclusion criteria included: (1) recurrence and distant metastasis; (2) parathyroid injury presented with abnormal serum calcium, phosphate, and parathyroid hormone due to thyroidectomy; (3) showing symptoms of thyrotoxicosis and forced to stop TSH suppressive therapy; (4) use of drugs affecting bone metabolism, including estrogen/progestin, bisphosphonate or glucocorticoids; (5) patients who spontaneously interrupted TSH suppressive therapy; (6) patients whose TSH level did not meet the suppression goal during follow-up; (7) patients who refused to measure BMD at follow-up.

Accordingly, while 65 DTC patients were initially included, 1 with use of glucocorticoid, 2 with thyrotoxicosis, 3 with spontaneously interruption of TSH suppressive therapy and 30 with refusion of BMD measurement were excluded. Finally, a total of 29 DTC patients who met the inclusion criteria were enrolled and completed the 1-year follow-up. There were five men, sixteen premenopausal women and eight postmenopausal women. The eight

postmenopausal women completed 2-year follow-up. The set of controls was drawn from a cohort of euthyroid community population who were matched for age, gender, and BMI. Patients were matched with healthy controls at a ratio of 1:2 (Fig. 1). Postmenopausal female controls were also matched for menopausal time. The baseline time for DTC patients was within one week before the operation. Measurements of BMD and BTMs were performed for all DTC patients and respective controls at baseline and 1-year follow-up. BMD and BTMs were measured for postmenopausal DTC patients and controls at 2-year follow-up. Calcium and/or vitamin D supplement, smoking, alcohol use, exercises, and sleeping during the follow-up period were investigated by a questionnaire. In this study, all participants decided whether to use calcium and/or vitamin D supplement according to their own wishes. Participants who exercised for more than 30 minutes at least three times a week were considered to have regular exercise. The sleeping evaluation consists of sleep quality and sleep duration. The sleep quality is defined by the number of insomnia days per month. Less than or equal to 3 days is considered as good sleep quality, and more than 3 days is considered as poor.

This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of China Medical University. All the participants signed informed consent prior to enrollment.

Laboratory assessments

The serum samples were obtained before 9 a.m. after overnight fasting and immediately frozen at −80 °C until they were analyzed. Serum TSH, free thyroxine (FT4), procollagen type I N-terminal propeptide (P1NP), and C-terminal telopeptide of type I collagen (β-CTX) were measured using an electrochemiluminescence immunoassay on a Cobas Elecsys 601 (Roche Diagnostics, Roche Ltd., Basel, Switzerland). Serum 25-hydroxyvitamin D [25(OH)D] levels were measured by liquid chromatography-mass spectrometry (LC-MS/MS) method on SCIEX QTRAP 4500 mass spectrometer. Quality control analyses were performed before, during and after testing according to the manufacturer's instructions. The reference ranges were provided by the manufacturer. The reference ranges of TSH and FT4 were 0.27-4.20 mIU/L and 12-22 pmol/L. The reference ranges of P1NP were 15.13-58.59 ng/ml for premenopausal women and men, 20.25-76.31 ng/ml for postmenopausal women. The reference ranges of β-CTX were less than 0.573 ng/ml for premenopausal women and men, less than 1.008 ng/ml for postmenopausal women. The intra- and inter-assay coefficients of variation (CVs) for TSH were 1.1-3.0 % and 3.2-7.2 %, for FT4 were 1.1-4.3 % and 2.6-8.4 %，for P1NP were 1.4-3.2 % and 1.9-3.7%, for β-CTX were 1.2-4.7 % and 1.5-5.7 %, for 25(OH)D were 1.7-6.4 % and 2.2-7.8%.

Assessment of BMD

BMD was measured at the lumbar spine (L1-L4, LS-BMD), the femoral neck (FN-BMD), and the total hip (TH-BMD) using dual-energy X-ray absorptiometry (DXA) (Medix DR, Medilink, France) equipment at baseline and follow-up. All measurements were performed according to the manufacturer's manual on the same machine using the same software and scan speed by a single well-trained technologist throughout the study. A daily quality assurance scan was conducted by scanning a spine phantom. Measurement precision error expressed as coefficient of variation (CV) values for the BMD measurements at the lumbar spine, the femoral neck, and the total hip was 0.52 %, 0.66 %, and 0.73 %, respectively. The normative data of BMD was Chinese population data provided by the manufacturer (Chinese Male/Female Rachis/Femur from DMS normality curves 2003/2004). BMD values were expressed as absolute values (g/cm^2), T-score, and Z-score. T-scores which represent the number of standard deviations an actual BMD deviates from the peak BMD of the young-adult population were used for men and postmenopausal women, while Z-scores which represent the number of standard deviations an actual BMD deviates from the expected BMD of the same age, gender, and ethnicity were used for premenopausal women. According to the Chinese society of osteoporosis and bone mineral research (CSOBMR) criterion, men and postmenopausal women were diagnosed as osteoporosis (T-score ≤-2.5 SD), osteopenia (-2.5 SD＜T-score ＜-1.0 SD), and normal BMD (T-score ≥-1.0 SD); premenopausal women were diagnosed as osteopenia (Z-score≤ −2.0 SD) and normal BMD (Z-score＞-2.0 SD) [12].

Assessment of fracture risk (FRAX)

The 10-year probability of hip fracture (HF) and major osteoporotic fracture (MOF) risks (expressed as a percentage) was calculated by FRAX on country-specific (China) data on the website (https://www.sheffield.ac.uk/FRAX/tool.aspx?country=2). For premenopausal women whose age was less than 40 years old, the age was set at 40 in the calculation. All fracture risk factors included in FRAX (age, BMI, previous fracture, parental history of hip fracture, glucocorticoid therapy, smoking, alcohol intake, rheumatoid arthritis, and secondary causes of osteoporosis) were assessed, together with the FN-BMD data.

Statistical analysis

The SPSS 23.0 was used in the statistical processing of the results. Data with a normal distribution are expressed as mean ± standard deviation (Mean ± SD), while with non-normal distribution are expressed as medians (interquartile range) (IQR). The change rates of BMD and BTMs from baseline were calculated using the formula: Change rate = (follow-up value-baseline value)/ baseline value (%). Student's t tests, non-parametric Mann-Whitney *U* tests, or Chi-squared tests were used to analyze the differences between DTC patients and controls according to the characteristic of the data. Paired t-tests or Wilcoxon tests were performed to compare indexes at baseline and follow-up depending on the data characteristics. Pearson correlation or Spearman correlation was adopted for correlation analysis. Multivariate regression analysis was performed in overall participants to detect the associations between bone-related outcome (BMD and BTMs) and TSH or FT4 level at the 1-year follow-up assessment adjusting for age, gender, and BMI. A P value < 0.05 was regarded as statistically significant. All tests were two-tailed.

Results

Baseline characteristics

A total of 29 patients (5 men, 16 premenopausal women, and 8 postmenopausal women) with DTC were included in this study. The features of the study cohort are shown in Table 1. The age and BMI of the controls were similar with those of the DTC patients in each subgroup. The mean menopausal duration of postmenopausal patients was 55.6±41.9 months, which was similar with the controls (52.7±47.5 months, *P*=0.884). The number of patients receiving total vs. subtotal thyroidectomy was 2:3, 7:9, and 2:6 in the male, premenopausal, and postmenopausal group, respectively. The DTC patients and controls of each subgroup were similar in the number of smoking subjects during the follow-up. The number of subjects using alcohol was similar between DTC patients and controls in the male group. All the female participants were non-drinkers. The number of individuals using calcium and/or vitamin D supplement did not differ between DTC patients and controls in the premenopausal and postmenopausal groups. No significant differences were observed in BMD at any site and the *β*-CTX level between DTC patients and respective controls at baseline in each subgroup. In the male and postmenopausal groups, there was no difference in the P1NP level, but the P1NP level in DTC patients was lower than controls in the premenopausal group. The MOF and HF in male controls (MOF: 2.4±0.8; HF: 0.7±0.5) were higher than those in the male DTC patients (MOF: 1.7±0.3, *P*=0.027; HF: 0.3±0.2, *P*=0.045). A slight elevation in MOF was observed in premenopausal controls [1.4 (1.2; 1.6)] compared with that in DTC patients [1.2 (1.1; 1.4), *P*=0.047). No differences were detected in exercise and sleep quality between DTC patients and controls in each subgroup. Only in the premenopausal group, a significant difference was observed in the sleep time. The number of subjects with a sleep duration less than 7 hours in premenopausal controls was significantly higher than that in DTC patients (*P*=0.018) (Supplemental Table 1).

Men

In men, the TSH level in DTC patients [0.34 (0.11; 0.43) mIU/L] at 1-year follow-up was significantly lower than that in controls [1.90 (1.26; 2.84) mIU/L, *P*=0.001]. The FT4 level in DTC patients was higher than that in controls, however, this did not reach a statistical difference. No significant differences were detected between DTC patients and controls with regard to LS-BMD, FN-BMD, TH-BMD, *β*-CTX, and P1NP. In controls, the LS-BMD showed a significant decrease (*P*=0.006) in follow-up compared to baseline. In terms of change rates of the parameters, there was a significant difference in the change rate of LS-BMD between DTC patients and controls (0.96±2.03 vs. -3.44±2.95 %, *P*=0.011) (Table 2 and Fig. 2). The MOF and HF in controls were significantly higher than those in DTC patients.

Premenopausal women

In premenopausal women, there were significant differences in the TSH level and FT4 level between DTC patients and controls (both P□0.001) at the 1-year follow-up. The LS-BMD, FN-BMD, and TH-BMD in DTC patients were all higher than those in controls, but only FN-BMD showed a significant difference [0.882 (0.781; 0.964) vs. 0.783 (0.747; 0.867) g/cm^2, *P*=0.026) (Table 2 and Fig. 2). The P1NP level at follow-up in DTC patients was significantly lower than that in controls (*P*=0.023), but it was significantly higher than the baseline P1NP level within the DTC patients (*P*=0.003) with a median change rate of 26.25 %. The *β*-CTX level was similar between DTC patients and controls. In controls, there were significant reductions in the BMD at all sites (*P*□0.001 for LS-BMD, *P*=0.001 for FN-BMD, and *P*=0.002 for TH-BMD) and a significant increase in the MOF (*P*=0.009) and HF (*P*=0.018) after 1-year follow-up. Regarding change rates from baseline, significant differences were observed in the LS-BMD (0.21±3.96 vs. -3.40±3.41 %, *P*=0.002), the FN-BMD [0.23 (-2.32; 2.95) vs. -3.73 (-7.53; 0.63) %, *P*=0.019], and the P1NP level [26.25 (5.94; 60.87) vs. -0.56 (-16.42; 22.36) %, *P*=0.003] between DTC patients and controls. The MOF and HF in controls were significantly higher than those in DTC patients.

Postmenopausal women

In postmenopausal women, the TSH level in DTC patients was lower compared to controls at both 1-year (0.22±0.14 vs. 2.31±1.06 mIU/L, *P*□0.001) and 2-year (0.18±0.13 vs. 2.42±1.02 mIU/L, *P*□0.001) follow-up. The FT4 level in DTC patients was significantly higher than that in controls. No significant differences were found in BMD at any site, BTMs (P1NP and *β*-CTX), and fracture risk (MOF and HF) between DTC patients and controls, either at 1-year or 2-year follow-up timepoint (Table 2, Table 3, and Fig. 2). In DTC patients, there was a significant difference in the *β*-CTX level between follow-ups and baseline (*P*=0.036 for 1-year, *P*=0.008 for 2-year), with median change rates from baseline by -46.14 % at 1-year and -51.06% at 2-year follow-up. However, the *β*-CTX level in controls at 1-year follow-up was significantly higher than the baseline (*P*=0.015), with a median change rate of 14.73 %. There was no difference in the *β*-CTX level between 2-year follow-up and baseline in controls. In DTC patients, the LS-BMD at 2-year follow-up was significantly lower than that at baseline (*P*=0.019). In controls, the LS-BMD at both follow-up (both *P*□0.001) and the FN-BMD at 2-year follow-up (*P*=0.012) were significantly lower than those at baseline. In terms of change rates from baseline, significant differences between DTC patients and controls were shown in LS-BMD (-1.30±3.87 vs. -6.17±4.24, *P*=0.012) and *β*-CTX [-46.14 (-53.15; 3.46) vs. 14.73 (1.11; 33.13), *P*=0.011] at 1-year follow-up. There were significant differences between DTC patients and controls in LS-BMD [-2.97 (-4.75; -1.88) vs. -12.33 (-13.03; -9.28), *P*=0.001], FN-BMD [-1.50 (-4.92; 2.19) vs. -8.60 (-15.02; -4.02), *P*=0.011], TH-BMD [-3.38 (-4.84; 2.33) vs. -7.01 (-9.33; -2.21), *P*=0.038], and *β*-CTX [-46.14 (-51.06 (-68.97; -42.86)) vs. 4.95 (-2.32; 28.06), *P*=0.005] at 2-year follow-up. In DTC patients, the MOF at both follow-ups were higher than the baseline (*P*=0.017 for 1-year, *P*=0.018 for 2-year). In controls, the MOF and HF at 2-year follow-up were higher than the baseline (*P*=0.005 for MOF, *P*=0.007 for HF).

Correlations

Correlation analyses between bone-related parameters (BMD and BTMs) and the TSH or FT4 level at the 1-year follow-up assessment were performed in overall participants. Moreover, associations between BMD and BTMs were also explored (Table 4). LS-BMD was negatively correlated with age (r=-0.416, P<0.001), P1NP (r=-0.336, P=0.001), and β-CTX (r=-0.374, P<0.001). FN-BMD was positively correlated with BMI (r=0.326, P=0.002) and FT4 (r=0.290, P=0.006), negatively correlated with TSH (r=-0.245, P=0.022) and P1NP (r=-0.218, P=0.043). TH-BMD was positively correlated with BMI (r=0.329, P=0.002) and FT4 (r=0.268, P=0.012), negatively correlated with TSH (r=-0.223, P=0.038). No association was found between BTMs and TSH or FT4. β-CTX was positively correlated with age (r=0.617, P<0.001) and BMI (r=0.329, P=0.002). Multivariate regression analysis was further carried out, parameters with a P value less than 0.2 in the correlation analysis were tested in the multivariate regression model adjusting for age, gender, and BMI (Table 5). The results showed that P1NP was independently associated with LS-BMD (B=-0.202, P=0.002). The associations between TSH and FN-BMD or TH-BMD were not maintained in the multivariate analysis. However, FT4 was still significantly positively correlated with both FN-BMD (B=0.251, P=0.014) and TH-BMD (B=0.276, P=0.005). In addition, P1NP and β-CTX were found to be independently negative predictors for FN-BMD.

Discussion

The effects of TSH suppressive therapy on bone cannot be ignored because of the favorable prognosis and long survival of DTC patients [13]. However, there is no consensus about the effects of TSH suppressive therapy on BMD and fracture risk on account of heterogeneous study design (cross-sectional and longitudinal study), selected population, TSH suppressive level and duration, choice of outcome parameters, and so on. Here, we carried out a prospective cohort study that stratified the patients into three groups according to gender and menopausal status. DXA, as a gold standard for the diagnosis of osteoporosis, was used for the measurement of BMD in our study [14]. P1NP (bone formative marker) and β-CTX (bone resorptive marker) were used to evaluate BTMs, and they were recommended as reference BTMs by the International Osteoporosis Foundation (IOF) [15].

The effect of TSH suppressive therapy on BMD is the most controversial in postmenopausal women. In our study, there were no differences between postmenopausal DTC patients and controls in either BMD or BTMs both at 1-year and 2-year follow-up. The fracture risks calculated by FRAX were also similar between the two groups. These results suggested that short-term postoperative TSH suppressive therapy might not result in a deleterious effect on postmenopausal women. Consist with our results, Pei Zhang et al. reported that although postmenopausal women with 2-year postoperative TSH suppressive therapy (TSH<0.3 μIU/mL) showed a 1.9 % reduction in the LS-BMD, there was no significant difference in the LS-BMD between patients with TSH suppressive therapy (TSH<0.3 μIU/mL) and non-suppressed TSH patients (TSH>0.3 μIU/mL) after postoperative 6, 12, and 24 months [10]. In another 2-year longitudinal study including 23 postmenopausal patients with TSH suppressive therapy, no significant difference was observed in BMD at either baseline or follow-up compared with healthy controls [16].A recent meta-analysis including 17 cross-sectional studies reported that postmenopausal DTC patients receiving TSH suppressive therapy showed a significant decrease in LS-BMD, and a similar trend was seen in TH-BMD [17]. A large randomized controlled prospective cohort study by Sugitani et al. compared the T-score of the lumbar spine in 120 women receiving TSH suppressive therapy with those who did not receive TSH suppressive therapy. Those receiving TSH suppressive therapy had a significant deterioration of lumbar BMD from 1 year postoperatively, of which significant decreases in T-score within 1 year were seen in patients over 50 years old. The confounders such as menopause status, dietary calcium, vitamin D intake, physical exercise, and smoking were not evaluated in this study [6]. A retrospective cohort study including 273 postmenopausal women reported that a longer duration of TSH suppressive therapy was associated with decreased TBS rather than BMD [18]. Taken together, the results of TSH suppressive therapy on BMD in postmenopausal women are conflicting, but it is generally believed that TSH suppressive therapy has a negative effect on BMD. In this study, we failed to find an additional loss of BMD in postmenopausal DTC patients compared with controls, which might be related to the small sample size and short follow-up duration. Studies with a longer follow-up duration and a larger population are warranted. In premenopausal women, the FN-BMD in the DTC group was significantly higher than that in the control group at postoperative 1-year follow-up, a similar trend was observed in LS-BMD and TH-BMD. Therefore, our study suggested that TSH suppressive therapy had no adverse effects on BMD in premenopausal women. Two meta-analyses consistently reported FN-BMD and LS-BMD were significantly higher in patients with TSH suppressive therapy than in the control group [17, 19]. The safety of TSH suppressive therapy in premenopausal women might contribute to the protective role of estrogen. In our study, there was no significant difference in BMD between the male DTC patients and controls, which was in accordance with the results observed in previous studies. The majority of studies have shown that TSH suppressive therapy is safe in men [20]. Karner et al. conducted a 1-year cohort study of 9 men who had received TSH suppressive therapy for 8 years, and only mild bone loss was found in the distal radius. However, this study lacked a control group [5]. Another prospective cohort study which included the largest male sample size (n=28) showed LT4 therapy did not impair the BMD of patients compared with controls. The mean duration of LT4 therapy was 5.9 years and the mean follow-up duration was 1.1 years [7].

Up to date, only 2 studies evaluated risk fracture assessed by FRAX [21, 22]. Our results showed that, in postmenopausal women, MOF and HF were similar between DTC patients and controls, but in premenopausal women and men, MOF and HF in DTC patients were generally lower than those in the control group. These results suggested that postoperative 1-year TSH suppressive therapy did not increase the risk of fracture in patients on TSH suppressive therapy. A large population-based study revealed that both high and low dosage of levothyroxine treatment was associated with a higher risk for fractures in a J-shaped dose-dependent manner in post-thyroidectomy patients [23]. Another large cohort study also showed that DTC

patients receiving levothyroxine have a higher risk of osteoporosis and osteoporotic fracture [24]. However, no fracture events were observed in overall participants during the period of the follow-up in this study, which might be limited to the small sample size and the short follow-up period.

LS-BMD in the male and postmenopausal controls, BMD at all sites in premenopausal controls significantly decreased at the 1-year follow-up compared to the baseline, while no significant change was observed within DTC patients. The male and premenopausal controls had a higher risk of fracture than DTC patients, which might partially account for their reduction of BMD. We further investigated lifestyles consisting of sleep and exercise between DTC patients and controls, only in the premenopausal women group, there was a significant difference in sleep time between the two groups. The number of subjects with sleep duration less than 7 hours was significantly higher in the premenopausal controls than the DTC patients (40.6 % vs. 6.3 %). A previous study showed decreased sleep duration closely associated with lower BMD, especially in middle-aged and elderly women [25]. Patients with cancer are usually told to rest and exercise properly, take a balanced diet, and avoid fatigue when they leave the hospital. Due to the possible negative effects of TSH suppressive therapy on bone, patients with DTC are also recommended to eat foods rich in calcium and ensure adequate sun exposure. Thus, DTC patients might adopt a healthier lifestyle compared to controls, which might be beneficial for bone health. Further researches can be carried out to explore whether lifestyle intervention can increase the BMD and reduce fracture risk of patients with long-term TSH suppressive therapy.

BTMs did not differ between male DTC patients and controls at baseline and at 1-year follow-up. At baseline, P1NP in premenopausal DTC patients was significantly lower than that in controls, the same was true at 1-year follow-up. However, P1NP was significantly increased at 1-year follow-up compared to baseline within the premenopausal DTC group. In vitro studies have demonstrated that thyroid hormone enhances expression and synthesis of the osteoblast differentiation markers collagen I, osteocalcin, and ALP in osteoblasts [26, 27]. The increased P1NP level might result from the action of mildly excess thyroid hormone. On the other hand, estrogen may provide some protection against bone loss and counteracts the resorptive effects of excess thyroid hormones in premenopausal patients with levothyroxine therapy [28]. The change of BTMs might provide an explanation for the higher BMD observed in premenopausal DTC patients than controls in this study, as well as in the above-mentioned meta-analyses [17, 19]. The change of β-CTX was significantly different between postmenopausal DTC patients and controls, with a reduction in DTC patients and an increase in controls. One possible explanation for the reduction of β-CTX is the aforementioned healthier lifestyle adopted by cancer patients. A longitudinal study by Schneider et al. including 28 men and 46 women with a 7.2-year TSH suppressive duration showed that both bone formation (PICP) and resorption (ICTP) serum markers generally decreased in DTC patients and healthy controls after 1.1-year follow-up, moreover, female DTC patients had significantly greater ICTP decreases than controls [7]. A cross-sectional study by Tournis et al. found that β-CTX in postmenopausal DTC patients was significantly higher than that in the control group, but no difference in P1NP. No difference in BTMs was found in premenopausal women [29]. Another cross-sectional study by Heijckmann reported ICTP levels were significantly higher in DTC patients than that in age-matched controls, PINP levels were not different [30]. In the research by Duan Bin Hong et al., the ALP, CTX-1, and P1NP of premenopausal DTC patients were significantly higher than that of the control group [11]. An early cross-sectional study by Kung et al. found that on thyroxine treatment for a mean period of 12.2 years, bone formation index (ALP, osteocalcin) and bone resorption index (urinary hydroxyproline) in postmenopausal DTC patients were higher than those in the control group [31]. Taken together, previous studies showed inconsistent results of BTMs, longitudinal studies with a longer duration of follow-up are necessary. In the multivariate regression analysis, P1NP and β-CTX were found to be negatively associated with FN-BMD. Therefore, FN-BMD might be more sensitive to the changes in BTMs.

The key strength of this study is that it is a prospective controlled cohort study and the data of this field in China was scarce. Both BMD and BTMs were evaluated in our study. Our study has several limitations. First, the sample size in each group was small. To avoid the difference between groups caused by sampling error, age, gender, and BMI were carefully matched between groups in our study. Second, the duration of follow-up was short and prolonged follow-up should be further investigated. Third, some factors associated with bone health were not thoroughly investigated, such as demographic characteristics (education, income), dietary habits, and so on.

In conclusion, our prospective controlled cohort study indicated that postoperative 1-year TSH suppressive therapy did not have detrimental effects on BMD and BTMs in men, premenopausal, and postmenopausal DTC patients. The postoperative 2-year TSH suppressive therapy did not lead to additional loss of bone mass in postmenopausal DTC patients.

Declarations

Statements and Declarations

The authors declare no competing interests.

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Author contributions

Y.L., Z.S., W.T., and H.Z. contributed to the study conception and design. Y.W., L.Z., M.L., and H.W. performed the study. S.W., L.H., Y.L., and F.Z. performed data analysis and interpretation. S.W. wrote the manuscript. Y.L. and Z.S. revised the manuscript. All authors have read and approved the

final version of the manuscript.

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Tables

Table 1 Baseline characteristics of the study groups

[#] Normal BMD/ osteopenia for premenopausal women. n, Number of subjects.

Table 2 BMD and BTMs in DTC patients and controls at postoperative 1-year follow-up

Parameters	Men			Premenopausal women			Postmenopausal women		
	DTC Patients (n=5)	Controls (n=10)	*P* value	DTC Patients (n=16)	Controls (n=32)	*P* value	DTC Patients (n=8)	Controls (n=16)	*P* value
Age (years)	50.6±7.0	50.5±5.2	0.975	28.5 (26.0; 41.0)	33.5 (25.0; 44.0)	0.767	52.6±3.6	53.6±4.4	0.607
BMI (kg/m^2)	25.0±1.7	24.4±1.7	0.581	23.2±3.2	22.7±3.3	0.673	25.3±3.3	25.1±2.9	0.891
Total vs. subtotal thyroidectomy n	2:3	-	-	7:9	-	-	2:6	-	-
Daily LT4 doses (g)	105.0±19.0	-	-	100.0 (90.6; 121.9)	-	-	100.0 (81.3; 109.4)	-	-
Daily LT4 doses/weight (g/kg)	1.41 (1.16; 1.58)	-	-	1.68±0.36	-	-	1.48±0.34	-	-
Smoking n (%)	2 (40.0)	7 (70.0)	0.329	0 (0)	2 (6.3)	0.546	0 (0)	1 (6.3)	1.000
Alcohol n (%)	2 (40.0)	5 (50.0)	1.000	0 (0)	0 (0)	-	0 (0)	0 (0)	-
Calcium and/or vitamin D supplement n (%)	0 (0)	0 (0)	-	4 (25.0)	2 (6.3)	0.086	6 (75.0)	7 (43.8)	0.211
25(OH)D (ng/ml)	13.9±3.1	14.4±2.9	0.729	12.1±3.4	13.6±4.5	0.239	13.8±5.0	15.4±4.80	0.429
P1NP (ng/ml)	31.7±10.7	44.9±16.0	0.121	29.3±11.0	49.1±15.8	***0.001***	53.7±28.9	56.6±16.8	0.755
β-CTX (ng/ml)	0.401±0.129	0.404±0.216	0.979	0.308 (0.119; 0.434)	0.216 (0.161; 0.284)	0.309	0.760±0.479	0.470±0.146	0.134
LS-BMD (g/cm^2)	0.995±0.192	0.999±0.156	0.963	1.102±0.138	1.063±0.092	0.245	0.930±0.097	0.924±0.137	0.915
FN-BMD (g/cm^2)	0.897±0.100	0.823±0.096	0.185	0.859 (0.798; 0.954)	0.835 (0.785; 0.894)	0.304	0.828±0.111	0.800±0.093	0.523
TH-BMD (g/cm^2)	1.022±0.110	0.913±0.098	0.073	0.950 (0.860; 1.032)	0.902 (0.844; 0.968)	0.129	0.910±0.125	0.858±0.110	0.307
FRAX (%)									
MOF	1.7±0.3	2.4±0.8	***0.027***	1.2 (1.1; 1.4)	1.4 (1.2; 1.6)	***0.047***	2.2 (2.0; 2.4)	2.3 (1.8; 3.7)	0.569
HF	0.3±0.2	0.7±0.5	***0.045***	0.1 (0.0; 0.1)	0.1 (0.1; 0.2)	0.120	0.2 (0.1; 0.5)	0.2 (0.1; 0.5)	0.653
Normal BMD/ osteopenia/ osteoporosis# n	3/1/1	6/3/1	0.832	16/0	32/0	-	5/3/0	8/7/1	0.603

Parameters	Men			Premenopausal women			Postmenopausal women		
	DTC Patients (n=5)	Controls (n=10)	*P* value	DTC Patients (n=16)	Controls (n=32)	*P* value	DTC Patients (n=8)	Controls (n=16)	*P* value
TSH (mIU/L)	0.34 (0.11; 0.43)	1.90 (1.26; 2.84)	***0.001***	0.09 (0.03; 0.27)	1.89 (1.40; 2.62)	***<0.001***	0.22±0.14	2.31±1.06	***<0.001***
FT4 (pmol/L)	20.1±3.9	16.2±1.8	0.088	21.1±2.4	16.1±2.0	***<0.001***	19.1±2.7	16.8±2.1	***0.031***
P1NP (ng/ml)	41.9±11.3	51.4±18.3	0.307	**32.5 (24.8; 50.1)** [b]	47.6 (39.0; 55.5)	***0.023***	62.6±27.4	60.8±15.7	0.863
β-CTX (ng/ml)	0.328 (0.212; 0.465)	0.337 (0.275; 0.432)	0.594	0.234 (0.138; 0.301)	0.200 (0.144; 0.295)	0.735	**0.468 (0.288; 0.582)** [a]	**0.488 (0.417; 0.692)** [a]	0.320
LS-BMD (g/cm^2)	1.002±0.179	**0.964±0.145** [b]	0.665	1.104±0.139	**1.026±0.088** [c]	0.053	0.917±0.093	**0.866±0.127** [c]	0.327
FN-BMD (g/cm^2)	0.903±0.099	0.831±0.187	0.439	0.882 (0.781; 0.964)	**0.783 (0.747; 0.867)** [b]	***0.026***	0.813±0.118	0.786±0.100	0.566
TH-BMD (g/cm^2)	1.010±0.107	0.916±0.098	0.114	0.979 (0.870; 1.028)	**0.887 (0.842; 0.922)** [b]	0.060	0.902±0.124	0.853±0.095	0.288
Change from baseline (%)									
P1NP	10.60 (-9.82-143.48)	4.11 (-2.73-31.57)	0.371	26.25 (5.94; 60.87)	-0.56 (-16.42; 22.36)	***0.003***	36.08±85.10	9.47±13.79	0.408
β-CTX	-33.11 (-40.20-36.49)	-9.32 (-18.80-38.07)	0.129	-15.16 (-40.39; 21.68)	5.09 (-35.27; 38.26)	0.382	-46.14 (-53.15; 3.46)	14.73 (1.11; 33.13)	***0.011***
LS-BMD	0.96±2.03	-3.44±2.95	***0.011***	0.21±3.96	-3.40±3.41	***0.002***	-1.30±3.87	-6.17±4.24	***0.012***
FN-BMD	0.73±4.43	0.24±11.96	0.932	0.23 (-2.32; 2.95)	-3.74 (-7.53; 0.63)	***0.019***	-2.25 (-4.83; 1.46)	-4.00 (-10.44; 0.72)	0.350
TH-BMD	-1.61 (-4.43-2.40)	-1.02 (-1.43-2.20)	0.371	-0.04±5.27	-1.89±2.82	0.204	-0.58 (-3.86; 3.37)	-4.16 (-6.00; 0.74)	0.320
FRAX (%)									
MOF	1.7±0.2	2.8±1.2	***0.020***	1.2±0.2	**1.5±0.4** [b]	***0.009***	**2.3 (2.1-2.7)** [a]	2.6 (2.1-3.4)	0.452
HF	0.2±0.1	0.9±0.8	***0.027***	0.05 (0.0-0.2)	**0.2 (0.1-0.3)** [a]	***0.015***	0.3±0.3	0.5±0.4	0.361
Normal BMD/ osteopenia/ osteoporosis [#] n	4/0/1	6/3/1	0.239	16/0	32/0	-	4/4/0	6/8/2	0.152

[#] Normal BMD/ osteopenia for premenopausal women. n, Number of subjects.

[a] $P<0.05$, [b] $P<0.01$, and [c] $P<0.001$ compared to baseline by paired t-test or Wilcoxon test.

Table 3 BMD and BTMs in postmenopausal female DTC patients and controls at postoperative 2-year follow-up

Parameters	DTC Patients (n=8)	Controls (n=16)	*P* value
TSH (IU/L)	0.18±0.13	2.42±1.02	***0.001***
FT4 (pmol/L)	21.9±2.2	17.0±1.9	***0.001***
P1NP (ng/ml)	54.4±31.4	60.2±14.0	0.634
β-CTX (ng/ml)	**0.357±0.289** [b]	0.498±0.162	0.136
LS-BMD (g/cm^2)	**0.901±0.078** [a]	**0.827±0.114** [c]	0.113
FN-BMD (g/cm^2)	0.813±0.099	**0.741±0.092** [a]	0.094
TH-BMD (g/cm^2)	0.896±0.120	0.822±0.096	0.115
Change from baseline (%)			
P1NP	8.31±50.00	10.89±25.30	0.867
β-CTX	-51.06 (-68.97; -42.86)	4.95 (-2.32; 28.06)	***0.005***
LS-BMD	-2.97 (-4.75; -1.88)	-12.33 (-13.03; -9.28)	***0.001***
FN-BMD	-1.50 (-4.92; 2.19)	-8.60 (-15.02; -4.02)	***0.011***
TH-BMD	-3.38 (-4.84; 2.33)	-7.01 (-9.33; -2.21)	***0.038***
P1NP	8.31±50.00	10.89±25.30	0.867
β-CTX	-51.06 (-68.97; -42.86)	4.95 (-2.32; 28.06)	***0.005***
FRAX (%)			
MOF	**2.5 (2.3-2.8)** [a]	**3.1 (2.4-3.9)** [b]	0.136
HF	0.3±0.2	**0.7±0.6** [b]	0.088
Normal BMD/ osteopenia/ osteoporosis n	4/4/0	5/7/4	0.152

n, Number of subjects.

[a] *P*0.05, [b] *P*0.01, and [c] *P*0.001 compared to baseline by paired t-test or Wilcoxon test.

Table 4 Correlation between bone-related parameters and other parameters at postoperative 1-year follow-up assessment

	LS-BMD		FN-BMD		TH-BMD		P1NP		*β*-CTX	
	r	*P*-value	*r*	*P*-value	*r*	*P*-value	*r*	*P*-value	*r*	*P*-value
Age	**-0.416**	**0.001**	-0.062	0.568	-0.033	0.759	0.124	0.252	**0.617**	**0.000**
BMI	0.055	0.613	**0.326**	**0.002**	**0.329**	**0.002**	0.084	0.441	**0.329**	**0.002**
TSH	-0.195	0.071	**-0.245**	**0.022**	**-0.223**	**0.038**	0.207	0.055	0.069	0.523
FT4	0.174	0.107	**0.290**	**0.006**	**0.268**	**0.012**	-0.139	0.199	-0.013	0.904
P1NP	**-0.336**	**0.001**	**-0.218**	**0.043**	-0.191	0.077				
β-CTX	**-0.374**	**0.001**	-0.160	0.140	-0.081	0.455				

Table 5 Multivariate regression analysis of associated parameters with bone-related parameters

	Beta	95% CI	*P*-value
LS-BMD			
TSH	-0.133	-0.034; 0.005	0.154
FT4	0.142	-0.002; 0.015	0.136
P1NP	-0.202	-0.003; 0.000	**0.035**
β-CTX	-0.187	-0.308; 0.030	0.105
FN-BMD			
TSH	-0.148	-0.031; 0.005	0.147
FT4	0.251	0.002; 0.018	**0.014**
P1NP	-0.214	-0.003; 0.000	**0.041**
β-CTX	-0.252	-0.313; -0.003	**0.045**
TH-BMD			
TSH	-0.171	-0.030; 0.002	0.084
FT4	0.276	0.003; 0.017	**0.005**
P1NP	-0.166	-0.002; 0.000	0.102
P1NP			
TSH	0.130	-1.212; 5.101	0.224
FT4	-0.086	-2.008; 0.864	0.430

Beta, Standardized regression coefficients. All models were adjusted for age, gender, and BMI.

Figures

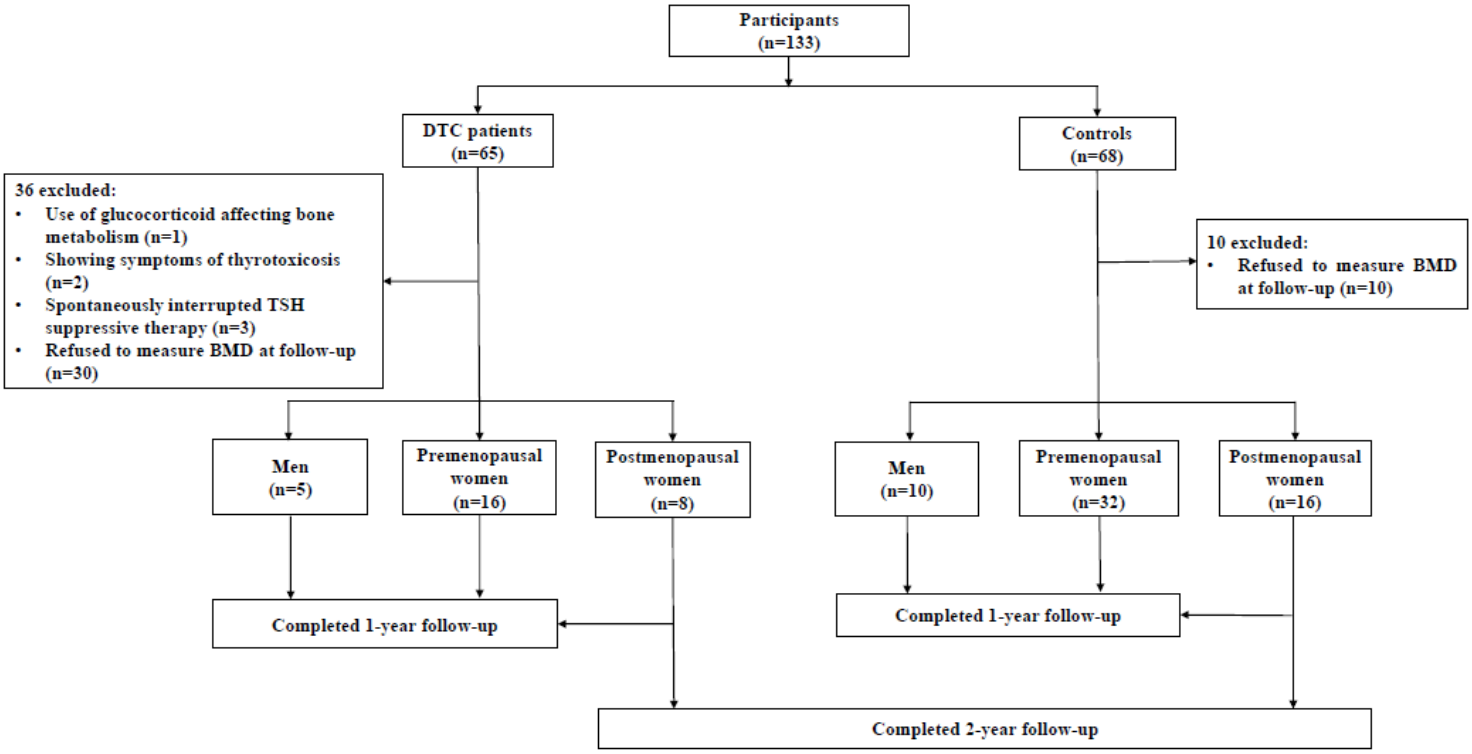

Figure 1

Study enrollment diagram

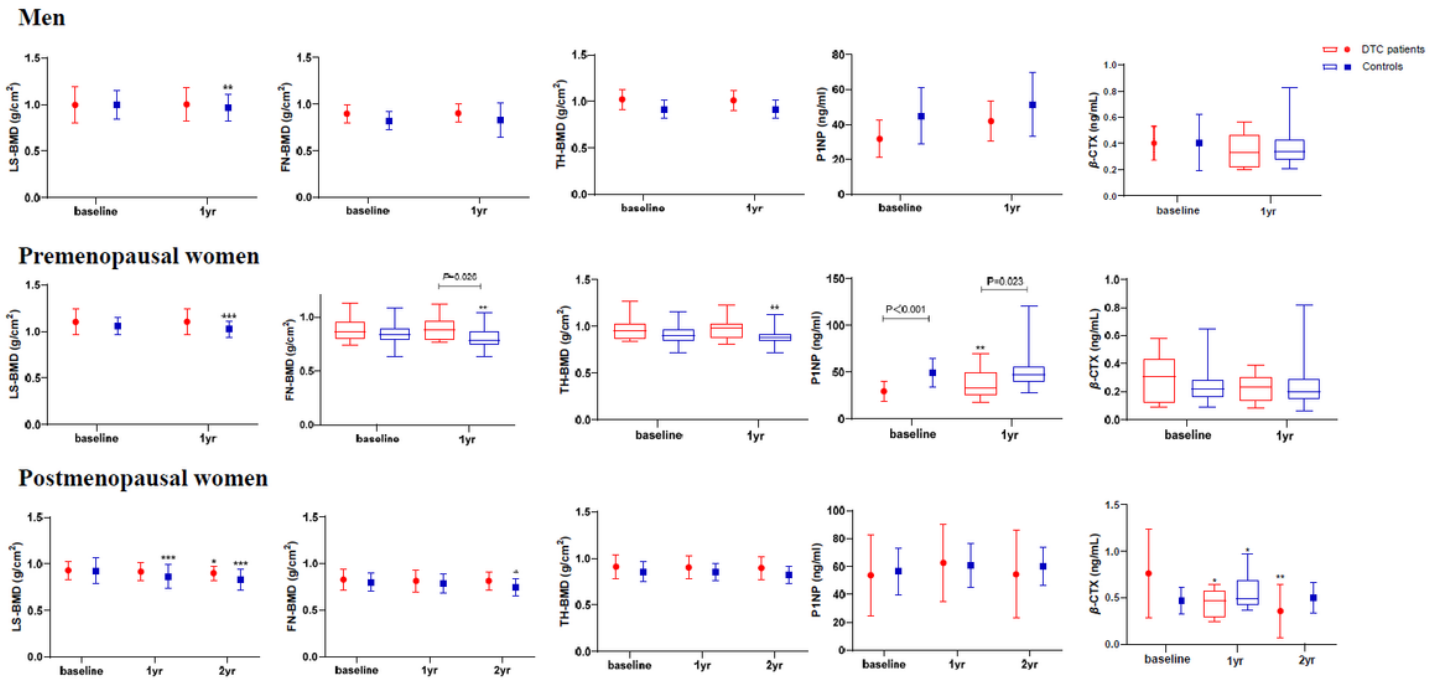

Figure 2

Bone mineral density (BMD) and bone turnover markers (BTMs) in differentiated thyroid cancer (DTC) patients and controls *P < 0. 05, **P < 0. 01, and ***P < 0. 001 compared with baseline by paired t-test or Wilcoxon test.

Supplementary Files

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- SupplementalTable1.docx