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TSH-suppressive therapy can reduce bone mineral density in patients with differentiated thyroid carcinoma: a meta-analysis

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Abstract. – OBJECTIVE: To evaluate the effect of TSH-suppressive therapy on the bone mineral density in patients with differentiated thyroid carcinoma (DTC).

MATERIALS AND METHODS: The cross-sectional, cohort, prospective controlled, and case-control studies on the bone mineral density change in patients with DTC after TSH-suppressive therapy from databases were searched, including PubMed, Embase, and Cochrane library databases. The effect of TSH-suppressive therapy on bone mineral density of lumbar, femoral neck, femoral greater trochanter, and Ward triangle was analyzed. Data from the database establishment to January 2019 were all reviewed. Meta-analysis was performed with RevMan 5.3 software after two reviewers independently screened the date. The categorical variables were expressed as odds ratios, while the numerical variables were expressed as mean differences. Based on the heterogeneity of the study, a comprehensive analysis was performed by using fixed or random effect models.

RESULTS: A total of 11 studies involving 434 patients with differentiated thyroid cancer were included. No significant difference in the bone mineral density of lumbar indications between the experimental and control groups was observed (MD=0.00, 95% CI=-0.03-0.03, *p*=0.96). The bone mineral density of the femoral neck indications (MD=-0.01, 95% CI=-0.04-0.03, p=0.70). A significant difference between experimental and control groups in the bone mineral density of femoral trochanter indications was observed (MD=-0.11, 95% CI=-0.14-0.07, *p*<0.00001). The bone mineral density of Ward's triangle indications (MD=-0.06, 95% CI=-0.11-0.01, *p*=0.02).

CONCLUSIONS: TSH-suppressive therapy in patients with DTC mainly reduces the proximal femur bone mineral density.

Key Words:
TSH-suppressive therapy, Bone mineral density, Differentiated thyroid carcinoma, Meta-analysis.

Introduction

Thyroid cancer is a malignant tumor of the thyroid gland[1]. The causes of the disease are mainly manifested in many aspects, such as sex hormone action, radiation, family factors, and so on[2]. In general, thyroid cancer includes differentiated and undifferentiated types. In differentiated thyroid carcinoma (DTC), follicular thyroid carcinoma and papillary thyroid carcinoma can also be refined[3]. DTC is more common in middle-aged women and children. Incidence of men and women 1:2-3. In about 10% of cases, the first sign is enlarged lymph nodes in the neck. The clinical feature is a single and hard thyroid nodule. B-ultrasound scanner showed that the nodules were > 1 cm in diameter and solid, which could be clearly distinguished from the peripheral tissues. The radionuclide scan showed "cold nodules". The thyroid cancer based on a polynodular goiter presents as a single prominent, large, and rigid nodule distinguished from the surrounding tissue[4].

In recent years, the incidence of DTC has been increasing significantly[5]. At present, the main treatment methods of the disease are surgery, postoperative ^{131}I treatment, and TSH-suppressive therapy[6]. Most DTC progresses slowly and has a good prognosis. About 90% of patients can

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survive for more than 15 years after treatment[7]. Conventional TSH can maintain the normal physiological needs after the operation; however, the inhibitory dose leaves patients with subclinical hyperthyroidism[7]. Reports[8] have shown that subclinical hyperthyroidism increases the risk of fractures and cardiovascular disease. At present, many studies have reported the effect of TSH-suppressive therapy on bone mineral density; however, the sample size of each work is small, and the results of the effect on bone mineral density are different. Therefore, the conclusions are of a limited reference value. We used a meta-analysis to systematically evaluate whether TSH-suppressive therapy has a negative effect on bone mineral density to provide a theoretical basis for clinical practice.

Materials and Methods

Search Strategy

Two reviewers independently searched PubMed, Embase, and Cochrane Library databases. The retrieval time is from the establishment of each journal to January 2019. The search words were: "differentiated thyroid gland carcinoma", "DTC", "TSH-suppressive therapy", "thyroxine suppressive therapy", "levothyroxine therapy", and "bone mineral density". The keyword and subject term were used to search literatures, while the language was set as English.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) cross-sectional studies, cohort studies, prospective controlled studies, and case-control studies on TSH-suppressive therapy; (2) inhibition group was DTC patients receiving TSH-suppressive therapy, while control group was healthy people matching the age, gender, weight, and menstrual status of patients in the inhibition group; (3) age of the patient was older than 18 years old; (4) time of TSH-suppressive therapy was provided; (5) TSH level of the patients reached the inhibition target; (6) the corresponding research data were provided.

Exclusion criteria: (1) republished studies; (2) literature without access to abstracts or full texts; (3) the data were unable to achieve; (4) non-monotherapy research; (5) cases of diseases were related to bone metabolism; (6) there were other cases at risk of osteoporosis; (7) patients use glucocorticoids or other drugs that may affect bone metabolism.

Data Extraction and Quality Assessment

Two reviewers selected literature independently. In case of disagreement and inability to decide after the discussion, the third reviewer would decide. Data were extracted, including study author, gender, region, number of participants, mean age, duration of medication, and outcome measures.

We evaluated the quality of each research using the Newcastle Ottawa scale (NOS). When disagreements arise, they are determined by a third reviewer. The full score of NOS score was 9, and the evaluation included selection, comparability, and exposure factors of the case-control study between groups. Reports with a score of more than 6 are of high quality.

Outcome Indicators

The results included in this study are were as follows: (1) lumbar vertebra bone density; (2) femoral neck bone density; (3) femoral trochanter bone density; (4) Ward triangle bone density.

Statistical Analysis

We used RevMan 5.3 statistical software (London, UK) to make a statistical analysis of the data. The counted data were analyzed by odd ratio (OR), while the measured ones were analyzed by mean difference (MD). We used a chi-square test to determine whether there was heterogeneity among the results of various studies. If there was no statistical heterogeneity ($p>0.10$, $I^2\leq 50\%$), the fixed-effect model was used for analysis. On the contrary, when there was statistical heterogeneity, a random effect model analysis was adopted after excluding the influence of significant heterogeneity. $p<0.05$ indicated a statistically significant difference.

Results

Study Selection and Study Characteristics

We initially included 1680 literatures after searching the databases. After reading titles, abstracts and the full text, 11 articles[9-19] were finally included. The screening process is shown in Figure 1. Among them, Schneider's et al[12] included male and female studies, which were divided into two parts to reduce the heterogeneity of results and facilitate subgroup analysis. Baseline characteristics of the included reports are shown in Table I. The quality assessments of various works

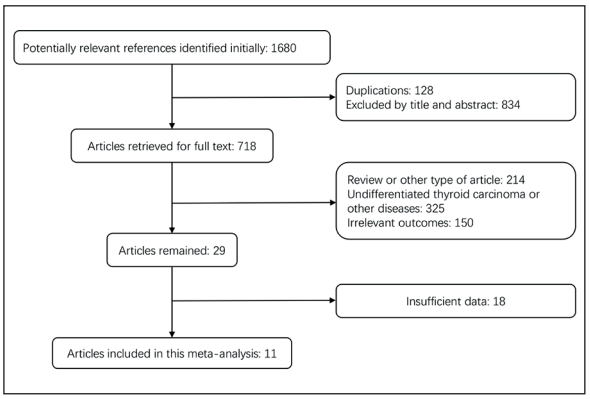

Figure 1. Study flow and selection diagram.

are shown in Table II. Results showed that the quality of all the reports was more than 6 points, indicating that the included researches were all of high quality.

Results of Meta-Analysis

Lumbar Vertebrae Bone Mineral Density

Nine studies[9-14,16,18,19] reported lumbar vertebra bone density levels in 392 DTC patients. There was a statistical heterogeneity among the researches (p<0.00001, I^2=73%). Therefore, the random effect model was selected for analysis. Subgroup analysis showed that there was no statistically significant difference in the lumbar vertebra bone mineral density between postmenopausal female (MD=-0.03, 95% CI=-0.09-0.02, p=0.25), premenopausal female (MD=0.02, 95% CI=-0.00-0.05, p=0.07), and male DTC patients (MD=0.03, 95% CI=-0.02-0.08, p=0.27) and control group after the TSH-suppressive therapy (Figure 2).

Femoral Neck Bone Mineral Density

Seven studies[9,11,13-15,17,18] reported bone mineral density levels of the femoral neck in 248 DTC patients. There was statistical heterogeneity among studies (p=0.003, I^2=70%). Therefore, we used the random effect model for analysis. Results showed that there was no statistically significant difference in lumbar vertebra bone density between DTC patients and control group after the TSH-suppressive therapy (MD=-0.01, 95% CI=-0.04-0.03, p<0.70; Figure 3A) Heterogeneity was significantly reduced by subgroup analysis (p=0.15, I^2=35%). Therefore, the fixed-effect model was used for analysis. Results showed that there was no statistically significant difference in the femoral neck bone mineral density between postmenopausal women (MD=-0.03, 95% CI=-0.07-0.01, p=0.10), premenopausal women (MD=0.01, 95% CI=-0.01-0.03, p=0.24), and men (MD=0.01, 95% CI=-0.03-0.04, p=0.76), as well as control group (Figure 3B).

Femoral Trochanter Bone Mineral Density

Two works[9,14] reported bone mineral density levels of the greater trochanter of the femur in a total of 135 DTC patients. There was no significant heterogeneity between studies (p=0.28, I^2=13%). Therefore, we adopted a fixed-effect model for analysis. The results of the meta-analysis showed that the bone mineral density of the femoral trochanter was lower in inhibition group than

Table I. Baseline characteristics of included studies.

Study	Region	No. of patients	Mean age (years old)	Length of medication use (years)	TSH (mU/L)
Eftekhari et al[19] 2008	Iran	66	51.7 ± 7.3	14.9 ± 2.1	< 0.30
Giannini et al[10] 1994	Italy	25	49.7 ± 2.1	7.6 ± 0.9	< 0.10
Hawkins et al[16] 1994	Spain	21	59.6 ± 7.5	5	0.30 ± 0.40
Kung et al[9] 1993	China	34	62.0 ± 8.0	12.2 ± 6.6	< 0.05
Mendonca et al[17] 2016	Brazil	17	27.4 ± 6.4	14.2 ± 7.2	0.16 ± 0.22
Muller et al[15] 1995	Canada	25	47.0 ± 3.0	10.0 ± 1.4	0.08 ± 0.01
Reverter et al[13] 2005	Spain	88	51.0 ± 12.0	12.0 ± 5.0	0.03 ± 0.03
Reverter et al[11] 2010	Germany	33	56.0 ± 14.0	2.0-3.0	< 0.10
Sajjinanont et al[18] 2005	Thailand	22	38.0 ± 7.3	7.0 ± 3.4	< 0.10
Schneider et al[12] 2012 (1)	Germany	46	39.2 ± 7.7	4.9 ± 5.2	0.05 ± 0.20
Schneider et al[12] 2012 (2)	Germany	28	40.8 ± 8.0	5.9 ± 5.1	0.04 ± 0.07
Toivonen et al[14] 1998	Finland	29	27.0-71.0	9.0-11.0	< 0.05

Table II. NOS scores of included studies.

Study	Selection	Comparability	Exposure	Total
Eftekhari et al[19] 2008	4	2	3	9
Giannini et al[10] 1994	4	2	2	8
Hawkins et al[16] 1994	4	2	2	8
Kung et al[9] 1993	4	1	2	7
Mendonca et al[17] 2016	4	2	3	9
Muller et al[15] 1995	4	1	3	8
Reverter et al[13] 2005	4	2	3	9
Reverter et al[11] 2010	4	2	3	9
Sajjinanont et al[18] 2005	4	2	2	8
Schneider et al[12] 2012	4	1	3	8
Toivonen et al[14] 1998	4	2	2	8

in control group. Also, the difference was statistically significant (MD=-0.11, 95% CI=-0.14-0.07, p<0.00001; Figure 4).

Ward's Triangle Bone Mineral Density

Two studies[9,14] reported bone mineral density levels in Ward's triangle, involving 135 patients with DTC. There was no statistical heterogeneity between studies (p=0.49, I^2= 0%). Therefore, we used the fixed-effect model for analysis. The results of the meta-analysis showed that the level of bone mineral density in Ward's triangle of patients in inhibition group was lower than that in control group. Also, the difference was statistically significant (MD=-0.06, 95% CI=-0.11-0.01, p=0.02; Figure 5).

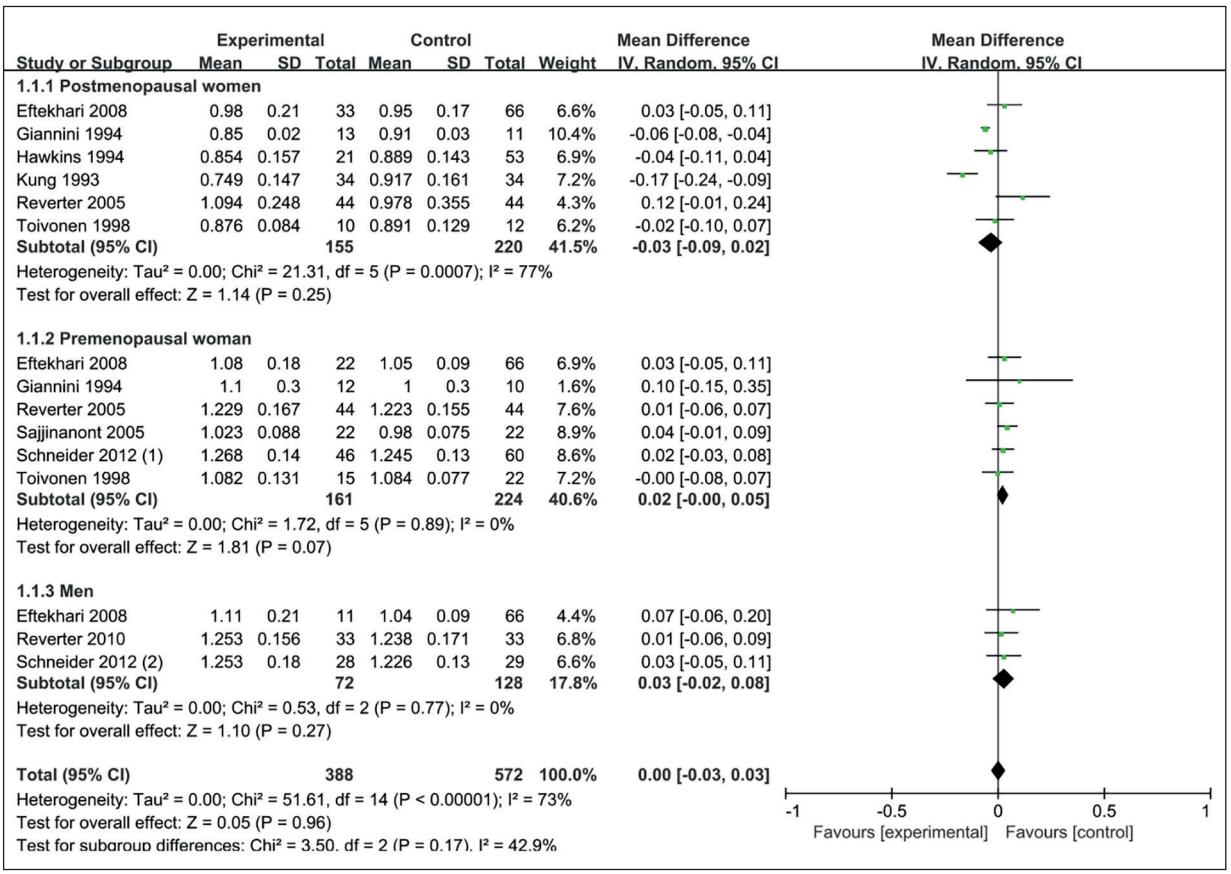

Figure 2. Forest plot for comparison of lumbar vertebrae bone mineral density between two groups.

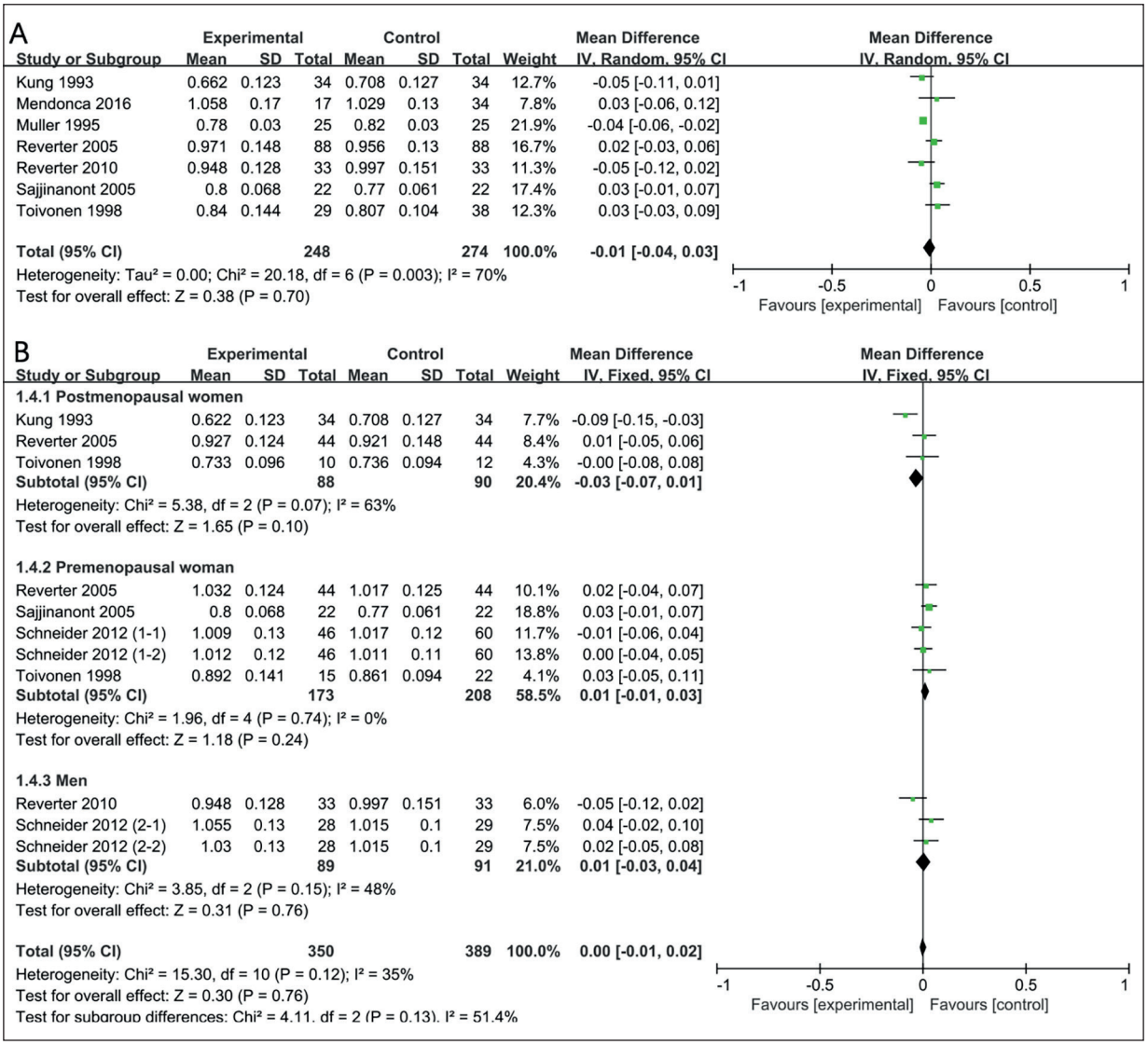

Figure 3. Forest plot for comparison of femoral neck bone mineral density between two groups. **A,** Overall results of meta-analysis; **B,** Results of subgroup analysis.

Discussion

TSH-suppressive therapy refers to the use of levothyroxine to make TSH at a low level or even undetectable[20]. On the one hand, TSH can supplement the thyroid hormone lacking in patients; on the other hand, TSH at a low level has an inhibitory effect on tumor cells, thereby

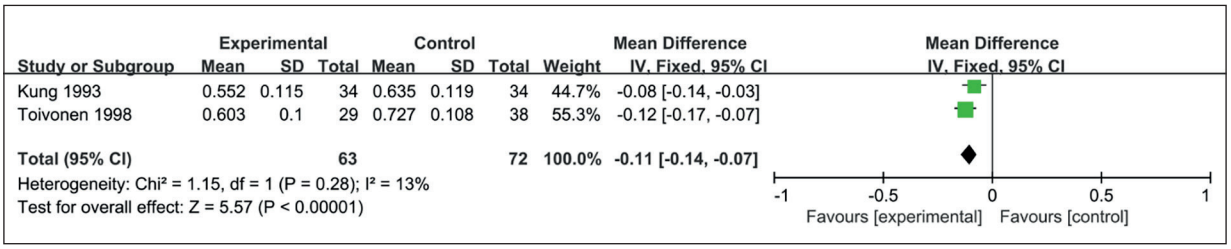

Figure 4. Forest plot for comparison of femoral trochanter bone mineral density between two groups.

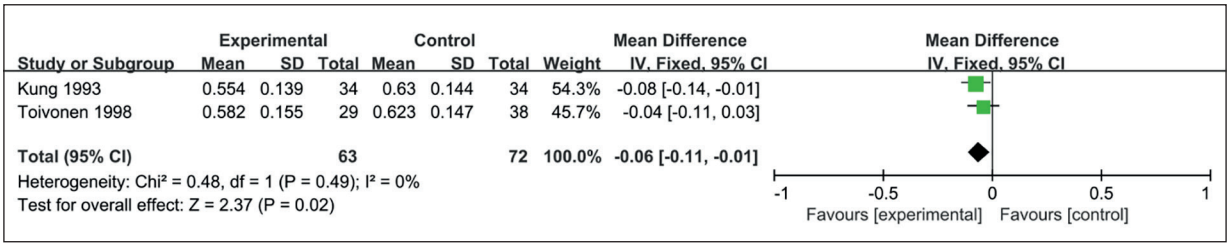

Figure 5. Forest plot for comparison of Ward's triangle bone mineral density between two groups.

reducing the recurrence rate and mortality of the disease[21]. Its therapeutic value for DTC has been proved. In recent years, the concept of TSH-suppressive therapy has changed, and no consensus has been reached on the clinical guidelines for TSH-suppressive therapy and its degree of inhibition. The American Thyroid Association and the European Thyroid Association advocate setting treatment goals based on the risk grade of tumor recurrence in DTC patients[22]. In 2015, the American Thyroid Association recommended that the TSH of high-risk patients should be controlled at <0.1 mU/L. Also, the TSH of low-risk patients should be controlled at the lower limit of the normal reference range (0.1-0.5 mU/L) or maintained at the lower limit of the normal reference range (0.5-2.0 mU/L) according to their triglyceride level[23]. After the dual-risk assessment, it is recommended to control the TSH of patients with high-risk recurrence at <0.1 mU/L, regardless of the risk of TSH-suppressive therapy. The long-term use of levothyroxine beyond the physiological requirements will make thyroid function in a subclinical state of hyperthyroidism, and its potential adverse reactions have been concerned[24]. Osteoporosis is characterized by decreased bone mass and destruction of the fine structure of bone tissue, which leads to an increased bone brittleness and fracture risk. In addition to age, gender, calcium, and vitamin D, parathyroid function and other factors affecting bone mineral density, as well as hyperthyroidism are also some of the common risk factors for osteoporosis[25]. However, whether subclinical hyperthyroidism caused by levothyroxine will cause bone loss and the occurrence of osteoporosis has not been clearly determined[26]. In this study, 434 cases of DTC patients in 12 researches were systematically evaluated. Results showed that the effect of TSH-suppressive therapy on bone mineral density in different parts of DTC patients had some differences. For instance, bone mineral density of the trochanter of femur and Ward triangle area was significantly affected. The reason may be that the lumbar spine is dominated by cancellous bone, while the femur is dominated by cortical bone. The osteoclast activity of cortical bone is higher than that of cancellous bone. Besides, an excessive thyroid hormone will increase osteoclast activity. The TSH receptor is expressed on both osteoblasts and osteoclasts. Therefore, TSH has a direct impact on bone metabolism. Low TSH can reduce the inhibition of osteoclast activity, and eventually lead to bone loss and decreased bone density. Furthermore, different parts of the femur have a different sensitivity to changes in the bone mineral density. Therefore, they show different changes in different bone mineral density. Among them, the Ward triangle is the most sensitive area among several hip measurement points. Currently, it has been reported that the change of bone mineral density in the Ward triangle is prior to that in the lumbar spine and femoral neck.

Conclusions

In summary, TSH-suppressive therapy mainly reduced the proximal femur bone mineral density of DTC patients, suggesting that the patients should monitor the bone mineral density regularly during the long-term follow-up. Also, special attention was given to the trochanter and Ward triangle to early intervene and prevent the occurrence and development of osteoporosis. However, this work has also some shortcomings: (1) the results of the meta-analysis are easily affected by the inclusion of experimental methodology; (2) the literature language is limited to English; (3) there were differences in dosage, duration, and TSH-suppressive targets in human studies. All these factors may have some influence on

the results. Therefore, the results obtained in this work need to be further confirmed by high-quality studies.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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