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Review Article

Thyroid-stimulating Hormone Suppressive Therapy and Osteoporosis: A Review and Meta-analysis

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Abstract

Background: Osteoporosis is a common morbid and mortal disease; thyroid-stimulating hormone (TSH) suppression is the state-of-the-art for postoperative differentiated thyroid carcinoma (DTC). However, its association with osteoporosis remains controversial. The current meta-analysis assessed the relationship between TSH suppressive therapy and osteoporosis among patients with DTC.

Methods: We systematically searched PubMed, Cochrane Library, EBSCO, and the first 100 articles in Google Scholar for relevant articles published in English during the period from 2008 to November 2020. The keywords differentiated thyroid cancer, TSH suppression, osteoporosis, low bone mineral density, osteopenia; fracture risk, disturbed bone micro-architecture, bone loss, and trabecular bone were used. One hundred and eighty-four articles were retrieved; of them, fourteen were eligible and met the inclusion and exclusion criteria. The RevMan system was used for data analysis.

Results: We included 36 cohorts from 15 studies, the studies showed higher osteoporosis and osteopenia among TSH-suppressed women, odd ratio, 2.64, 1.48–4.68 and 2.23, 0.33–14.96, respectively. High heterogeneity was observed, I^2 = 68% and 96%, respectively). The sub-analysis showed a lower bone mineral density among postmenopausal women at both femoral neck and lumbar spines, odds ratio, –0.02, –0.07 to 0.04, and –0.03, –0.06 to 0.01, I^2 for heterogeneity, 69%, and 51% in contrast to men and premenopausal women who showed normal or higher bone density.

Conclusion: TSH suppression for DTC was associated with osteoporosis and osteopenia among postmenopausal women but not premenopausal women or men. Studies focusing on trabecular bone scores are needed.

Keywords: TSH suppression, differentiated thyroid carcinoma, osteoporosis

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1. Introduction

Thyroid carcinoma is among the most common malignancies with an incidence of 1.7 to 4.1/100.000/yr in men and 4.5 to 8.7/100.000/yr in women [1]. DTC is on the rise worldwide due to the increasing age. Patients diagnosed with thyroid carcinoma are

usually hypothyroid or euthyroid. However, thyrotoxicosis may be observed in 3.38% of metastatic thyroid diseases [2, 3]. Endogenous hyperthyroidism shortens the bone turnover cycle, accelerates bone turnover, and leads to low bone mineral density (BMD) [4]. Supra-physiological doses of thyroxine are the mainstay of therapy to suppress the TSH among postoperative patients with DTC for >60 years [5]. Whether TSH suppression can lead to osteoporosis is a matter of controversy. On the other hand, hypoparathyroidism observed among patients with DTC was shown to increase BMD [6]. The relationship between osteoporosis and DTC is complex and when coexist may lead to deleterious consequences. Although thyrotoxicosis is well-known for its effects on BMD, the supraphysiological doses of thyroid hormone and their exact contribution to bone turnover are not well-established [7, 8]. The literature on this important health problem is scarce. Given the above, we conducted this meta-analysis to assess TSH suppression effects on BMD among patients with DTC.

2. Materials and Methods

2.1. The selection criteria according to PICOS

2.1.1. *The included studies*

We included cross-sectional, prospective and retrospective cohorts, and controlled trials. Studies must assess thyroid-stimulating hormone (TSH) suppression on BMD among patients with differentiated thyroid carcinoma (DTC).

2.1.2. *Outcome measures*

To be included, the studies must investigate osteoporosis, osteopenia, BMD, or bone loss as primary or secondary outcomes. No specifications were applied for subgroups (pooled females, premenopausal, men, and postmenopausal were included). DTC is affecting all age groups, males and females. Besides, osteoporosis risks are not limited to postmenopausal status. Thus, including all the patients and controlling for possible risk factors might be appropriate. Case reports, animal studies, and experimental studies were not included.

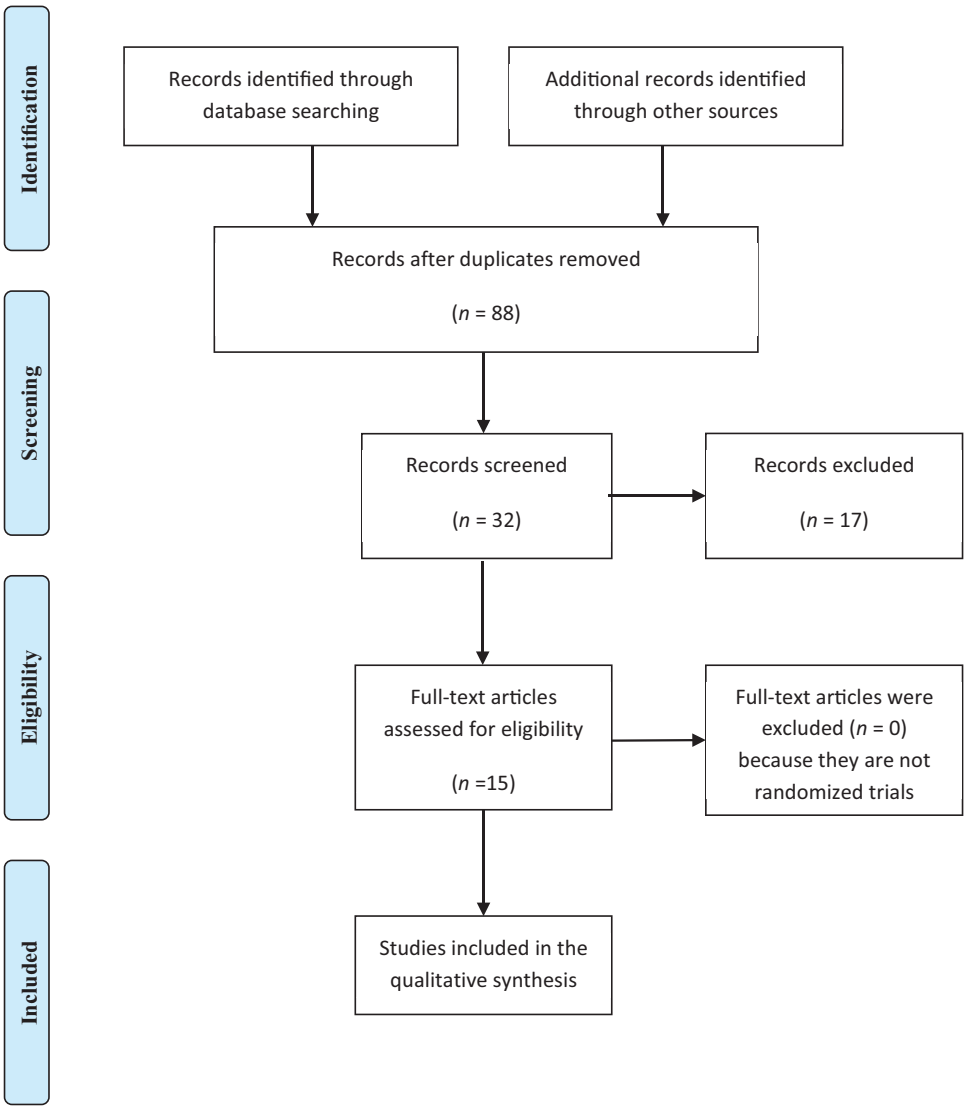

Figure 1: The effect of long thyroid-stimulating hormone (TSH)-suppressive therapy (following surgery for differentiated thyroid carcinoma) on bone mineral density (osteoporosis).

2.1.3. *Patients*

The patients who underwent TSH suppression following thyroidectomy for DTC (males, and females, premenopausal or postmenopausal) were included. Patients with other thyroid disorders that need TSH suppression including toxic goiter and thyroid cancer other than DTC were excluded.

2.2. Literature search and articles selection

A systematic electronic search was conducted in Pub Med, Cochrane library, EBSCO, and the first 100 articles in Google Scholar for relevant articles published in the English

language. The search engine was set to include studies from the first published article up to November 2020. The terms "differentiated thyroid cancer," "TSH suppression," "osteoporosis," "low BMD," "osteopenia," "fracture risk," "disturbed bone microarchitecture," "bone loss," and "trabecular bone" were used. The protean "AND" and "OR" were applied. The two authors independently screened the titles and abstracts. One hundred and eighty-four articles were retrieved, the number stood at 88 after duplication removal. Of them, 32 full-texts were screened, and only 15 were eligible after applying the inclusion and exclusion criteria (nine texts were excluded due to missing information, and another eight needed subscription). The authors resolved any discrepancy among the articles by consensus. The data were exported into an extraction sheet detailing the author's name, year, country of publication, the study type and period, the T and Z-scores of bone densitometry (DEXA scan), and the number of both the interventional and control groups. The study's risk of bias and quality was assessed using the Ottawa Newcastle scale (Table 1). The different phases of the literature search are shown in Figure 1.

2.3. Statistical analysis

The authors used the RevMan version 5.4 for data analysis, data were entered manually, the fixed effect was used unless a significant heterogeneity was observed (>50%). The funnel plot was used to test for sensitivity (lateralization). *P*-value < 0.05 was considered significant.

3. Results

Out of the 184 studies included, 15 articles were included in the meta-analysis, 6 were cross-sectional, 5 were prospective cohorts, and 4 were case–control studies. Most of the included studies also have a retrospective arm. Seven studies were published in Europe, five in Asia, one in South America, one was from the USA, and one from Canada. The study periods ranged from14.93 ± 2.17 months to 12.2 ± 6.6 years, and the total number of patients was 2180 versus 2707 controls.

In the current meta-analysis, six studies assessed osteoporosis among women (menopausal status not uniform); of them, five studies showed a higher rate of osteoporosis in the interventional group [9–13], while one showed lower osteoporosis [14]. However, due to the significant heterogeneity observed (I^2 = 68%), the random effect

Table 1: Ottawa Newcastle assessment for the included studies.

Author	Selection	Compatibility	Outcome	Score
Franklyn *et al.* (1992) [16]	3	2	4	9
Kung *et al.* (1993) [18]	3	2	4	9
Muller *et al.* (1995) [9]	3	2	4	9
Fujiyama *et al.* (1995) [17]	3	2	4	9
Goerres *et al.* (1998) [22]	3	2	4	9
Eftekhari *et al.* (1998) [23]	3	2	4	9
Reverter *et al.* (2005) [20]	3	2	4	9
De Melo *et al.* (2015) [11]	3	2	4	9
Wang *et al.* (2015) [10]	3	2	3	8
Tournis *et al.* (2015) [21]	3	2	4	9
Moon *et al.* (2016) [19]	3	2	3	8
De Mingo Dominguez *et al.* (2018) [15]	4	1	2	7
Vera *et al.* (2016) [14]	3	2	3	8
Mazziotti *et al.* (2018) [12]	4	1	3	8
Zhang *et al.* (2018) [13]	4	2	3	9

showed a net effect favoring high osteoporosis among the TSH suppression group, odd ratio, 2.64, 1.48–4.68. The funnel plot showed significant lateralization (Figure 2).

Regarding osteopenia, among the three studies included, two [11, 12] showed more osteopenia in the control group, and one reported a marked rate of osteopenia in the interventional group [13], the overall effect is more osteopenia among the TSH suppression, odd ratio, 2.23, 0.33–14.96 (Figure 3).

Regarding the effects of TSH suppression among postmenopausal women, no differences in BMD was observed in lumbar spines [11, 15–21], and femoral neck [11, 16, 18–21], odd ratio, –0.02, –0.07 to 0.04, and –0.03, –0.06 to 0.01, respectively, I^2 for heterogeneity, 69% and 51%, respectively, *P*-values, 0.52 and 0.1, respectively (Figures 4 & 5). A higher value of BMD was observed among premenopausal women compared to controls in both the lumber spines [11, 16, 19, 21, and 22] and femoral neck [16, 19, 21, and 22], odd ratios, 0.05, 0.0–0.09, and 0.03, 0.0–0.06, *P*-values, 0.04 and 0.03, respectively (Figures 6 & 7).

No difference in BMD was evident between males with suppressed TSH and their counterparts, no heterogeneity was observed, odd ratio, 0.0, –0.7 to 0.06, *P*-value, 0.87 (Figure 8).

Table 2: The effect of long thyroid-stimulating hormone (TSH) suppressive therapy (following surgery for differentiated thyroid carcinoma) on bone mineral density.

Author	Year	Country	Type	Patients (interventional vs controls)	Study period	Results
Muller *et al.* [9]	1995	Canada	Prospective	25 DTC (matched for menopausal status, BMI, and age), 0/25 vs 13/25 for EXT, 0/25 vs 1/25 for other sites	11 years	Cancer patients showed insignificant reductions of 2–5% in BMD of LS, FN, and TK and a significant 5% reduction in BMD of EXT (DTC, higher T4, same TSH suppression)
Wang *et al.* [10]	2015	USA	Prospective comparing TSH < 0.4 mU/l and 0.4	125/537 vs 29/537 for premenopausal and postmenopausal	66 months	Osteoporosis increased, with no change in the recurrence rate. No increased risk of TSH level around 1 mU/l
de Melo *et al.* [11]	2015	Brazil	Cross-sectional,	21/109 for osteoporosis and 44/109 for osteopenia vs 17/109 and 49/109, postmenopausal	88 ± 70.6 months	Not significant
Vera *et al.* [14]	2016	Italy	Case–control	62/74 hip, 49/74 lumbar vs 92/120, 75/120, women	36 months	No relation of T4 dose, level, or duration of therapy to osteoporosis Mean ± SD available
Mazziotti *et al.* [12]	2018	Italy	Cross-sectional, TSH < 0.05 and >1	35/83 vs 9/46 for osteoporosis and 35/83 vs 21/46 for osteopenia, women	5.5 years	Vertebral fractures were common among patients on long-term T4 and TSH levels <1 mU/l
Zhang *et al.* [13]	2018	China	Prospective cohort	90/152, 13/152 vs 23/68, 9/68 for osteopenia and osteoporosis, respectively, post-menopausal women	2 years	Osteopenia was observed, no osteoporosis. (TSH > 0.3 & TSH < 0.3 μIU/mL)

4. Discussion

Osteoporosis is common among men and postmenopausal women in contrast to pre-menopausal women; therefore, much less interest is observed regarding this morbid and mortal disease in this age group [23]. TSH-suppressive therapy is on the rise due to the increasing diagnosis of DTC mirrored by improving diagnostic and screening tools [24]. We found a higher rate of osteoporosis among women (pooled and postmenopausal).

Table 3: TSH suppression for differentiated thyroid carcinoma and bone mineral density among women.

Author	Year	Country	Type	Premenopausal	Postmenopausal	Study period
Franklyn *et al.* [16]	1992	UK	Prospective	18 vs 18 controls 0.760 ± 0.140 vs 0.780 ± 0.150 Lumbar spines and 1.000 ± ± 0.110 vs 0.970 ± 0.130 femoral neck	26 vs 26 controls 0.540 ± 0.170 vs 0.540 ± 0.220 lumbar spines and 0.810 ± 0.080 vs 0.830 ± 0.130 femoral neck	7.9 years
Kung *et al.* [18]	1993	Hong Kong	Cross-sectional		34 vs 34 controls 0.749 ± 0.147 vs 0.917 ± 0.161 lumbar spines and 0.622 ± 0.123 vs 0.708 ± 0.127 femoral neck	12.2 ± 6.6 years
Fujiyama *et al.* [17]	1995	Japan	Prospective		12 vs 12 0.849 ± 0.605 vs 0.849 ± 0.605 lumbar	
Goerres *et al.* [22]	1998	Switzerlan	Cross-sectional	7 vs 7 controls 1.006 ± 0.143 vs 0.903 ± 0.128 lumbar spines and 0.892 ± 0.141 vs 0.861 ± 0.094 femoral neck		
Reverter *et al.* [20]	2005	Spain	Cross-sectional		44 vs 44 controls 1.094 ± 0.248 vs 0.978 ± 0.355 lumbar spines and 0.927 ± 0.124 vs 0.921 ± 0.148 femoral neck	
de Melo *et al.* [11]	2015	Brazil	Cross-sectional		109 vs 109 1.09 ± 1.43 vs 1.11 ± 1.3, lumbar, 0.12 ± 1.1 vs 0.37 ± 1.06 femur	88 ± 70.6 months
Tournis *et al.* [21]	2015	Greece	Case-control	40 vs 29 1.200 ± 0.100 1.100 ± 0.100 lumbar 0.940 ± 0.100 vs 0.900 ± 0.100 femoral	40 vs 60 1.100 ± 0.100 vs 1.100 ± 0.100 lumbar and 0.840 ± 0.100 vs 0.870 ± 0.100 femoral	
Moon *et al.* [19]	2016	South Korea	Case–control	25 vs 75 1.210 ± 0.110 vs 1.180 ± 0.120 Lumbar, and 0.930 ± 0.100 vs 0.900 ± 0.090, femoral	74 vs 222 1.050 ± 0.150 vs 1.070 ± 0.140 lumbar, and 0.830 ± 0.110 vs 0.830 ± 0.100 femoral	36 months
De Mingo Dominguez *et al.* [15]	2018	Spain	Case–control	14 vs 84 1.00 ± 0.12 vs 0.98 ± 0.11, lumbar	14 vs 84 0.86 ± 0.12 vs 0.84 ± 0.15, lumbar	10 years

BMD was higher among women with DTC who received thyroxine for TSH suppression, no difference in BMD was observed among males compared to their counterparts without TSH suppression. The current findings were similar to Ku and colleagues who conducted a meta-analysis and found similar results [25]. The current findings supported the conclusion of a recent meta-analysis that included only 11 studies and focused on

Table 4: TSH suppression for differentiated thyroid carcinoma and bone mineral density among men.

Author	Year	Country	Type	BMD	Study period
Franklyn *et al.* [16]	1992	UK	Prospective	5 vs 5 controls 0.710 ± 0.270 vs 0.750 ± 0.280 Lumbar spines and 0.890 ± 0.110 vs 1.000 ± 0.210 femoral neck	7.9 years
Goerres *et al.* [22]	1998	Switzerlan	Cross-sectional	17 vs 18 controls 0.965 ± 0.173 vs 1.003 ± 0.132 lumbar spines	
Reverter *et al.* [20]	2005	Spain	Cross-sectional	33 vs 33 controls 1.253 ± 0.156 vs 1.238 ± 0.171 lumbar spines and 0.948 ± 0.128 vs 0.997 ± 0.151 femoral neck	
Eftekhari *et al.* [23]	2008	Iran	Cross-sectional	11 vs 11 controls 1.110 ± 0.210 vs 1.040 ± 0.090 lumbar spines	14.93 ± 2.17 months

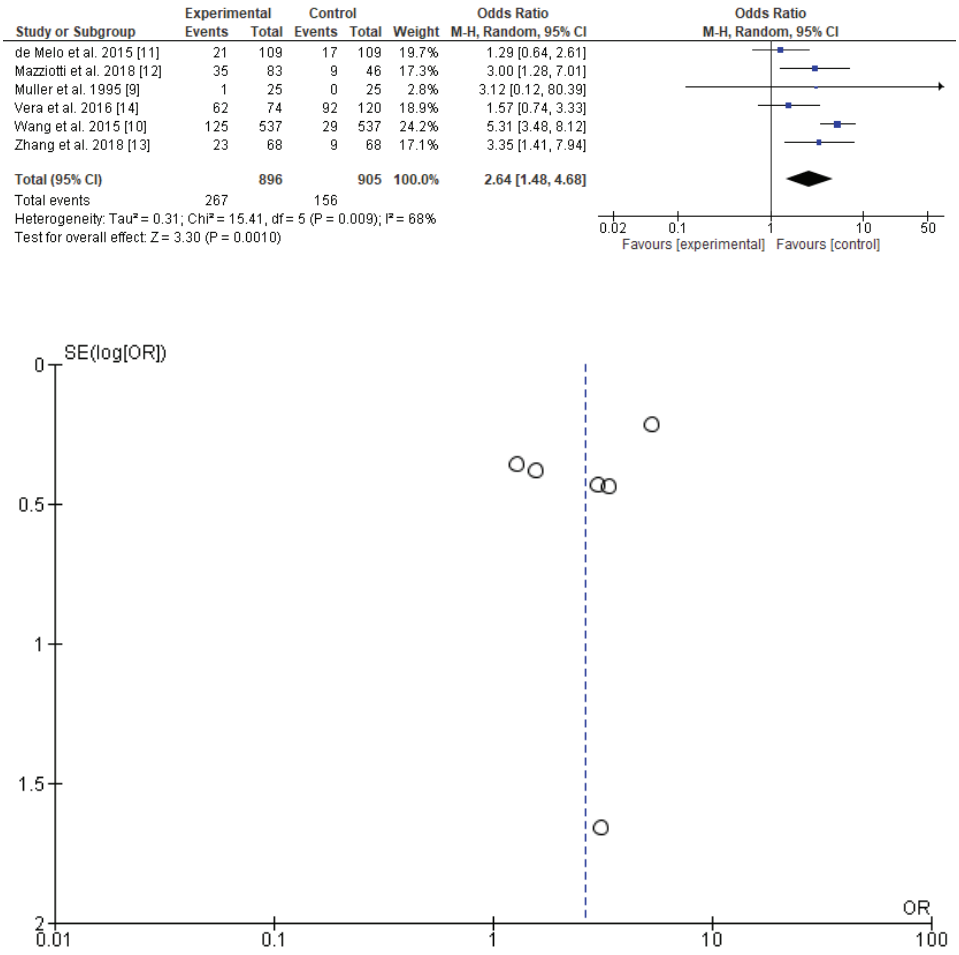

Figure 2: The effect of long thyroid-stimulating hormone (TSH)-suppressive therapy (following surgery for differentiated thyroid carcinoma) on bone mineral density (osteoporosis).

the site of BMD, our study assessed additional women with osteopenia and a broad category of women without specification of menopausal status. A recent meta-analysis

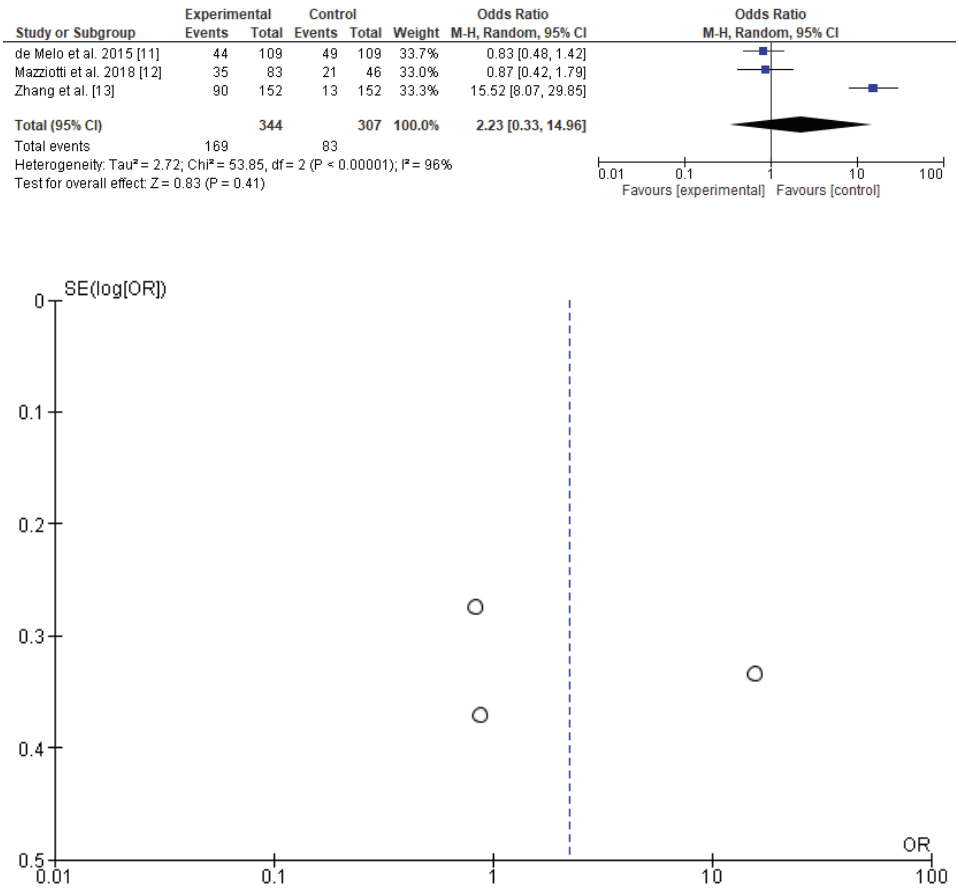

Figure 3: The effect of long thyroid-stimulating hormone (TSH)-suppressive therapy (following surgery for differentiated thyroid carcinoma) on bone mineral density (osteopenia).

[26] concluded the negative effects of TSH suppression on BMD (the study assessed postmenopausal women only). A broader insight for TSH suppression, which might be of minimal contribution to mortality and morbidity was suggested [27, 28]. A previous study based on American Thyroid Association has categorized patients into nine categories including the patient's character, the aggressiveness of the tumor, the duration and levels of TSH suppression, and cardiovascular adverse effects [29]. Besides, the time to develop osteoporosis was found to be shorter in postmenopausal women and those with a family history of the disease [30]. Recent studies have suggested that trabecular bone score combined with BMD measurement might be more useful than the current practice of depending on BMD alone [31]. The contradicting findings of a higher BMD in premenopausal women might be explained by estrogen effects or lifestyles. The strength of this analysis is that we investigated both osteoporosis and osteopenia. The study limitations were: including studies with different methods of

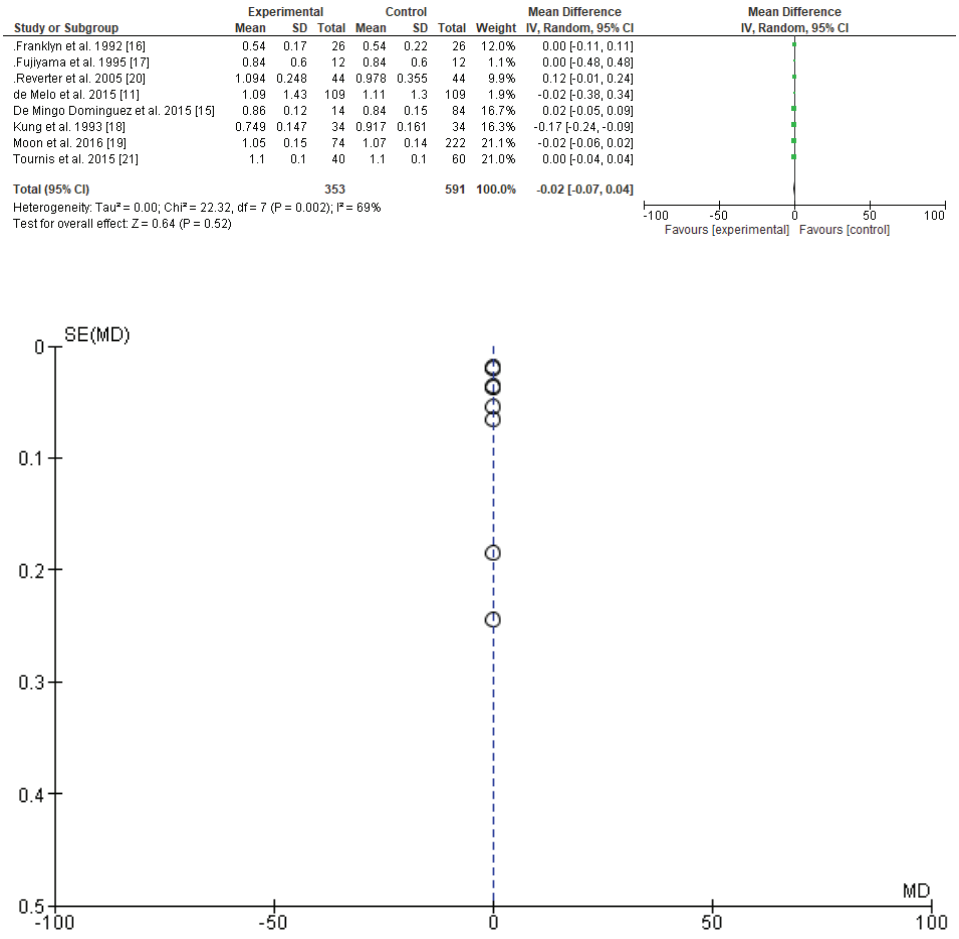

Figure 4: TSH suppression and bone mineral density among postmenopausal women lumbar spines.

outcomes assessments, the unlimited period of database search, and the heterogeneity observed in the meta-analysis.

5. Conclusion

TSH-suppressive therapy was associated with increased osteopenia and osteoporosis risk in postmenopausal women, no association was found between TSH suppression and osteoporosis in premenopausal women and men. Further studies investigating the combined use of trabecular bone score for bone quality in addition to BMD are recommended.

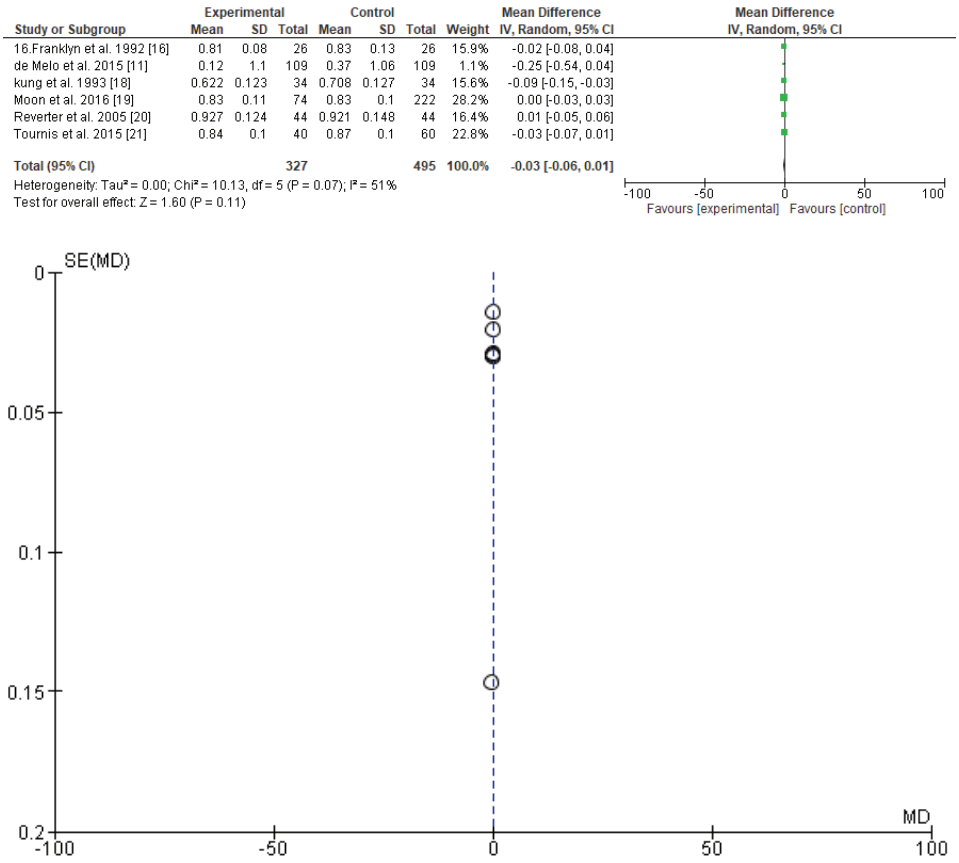

Figure 5: TSH suppression and bone mineral density among postmenopausal women femoral neck.

6. The implications for research, policy, or practice:

Extreme caution is needed regarding the use of TSH suppression in low-risk DTC in patients at risk of/with osteoporosis. If needed, TSH suppression may need careful follow-up to keep the TSH levels at the recommended levels (<0.1 mU/l for aggressive malignancies and [<21 mU/l for low-intermediate grades) follow-up by the indicated techniques DEXA-Scans or qualitative computed tomography) at shorter periods may be needed.

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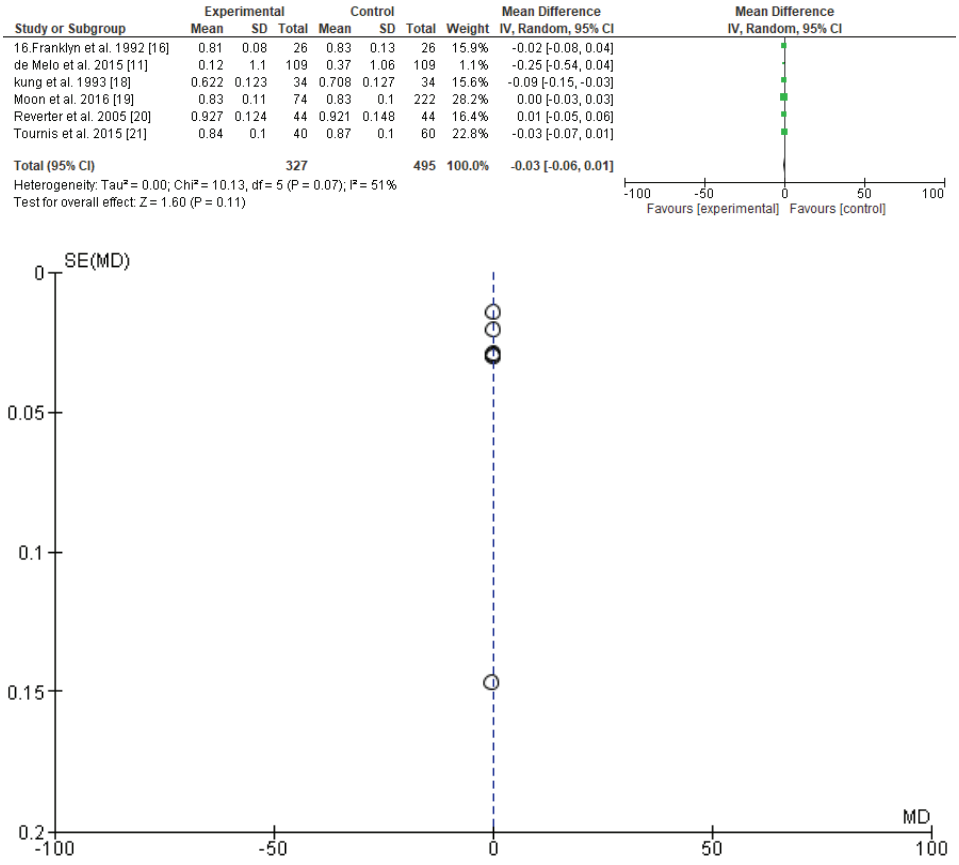

Figure 6: TSH suppression and bone mineral density among premenopausal women lumbar spines.

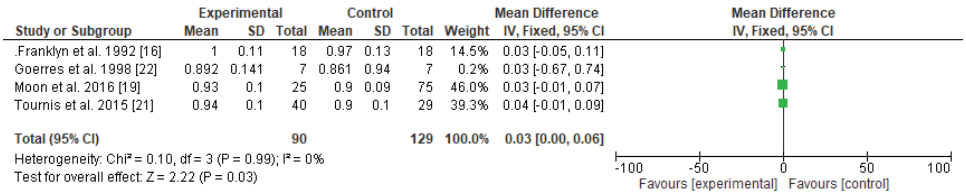

Figure 7: TSH suppression and bone mineral density among premenopausal women lumbar spines.

Ethical Considerations

The current meta-analysis did not include any research on humans or animals published by the authors.

Competing Interests

The authors declare that they have no competing interests.

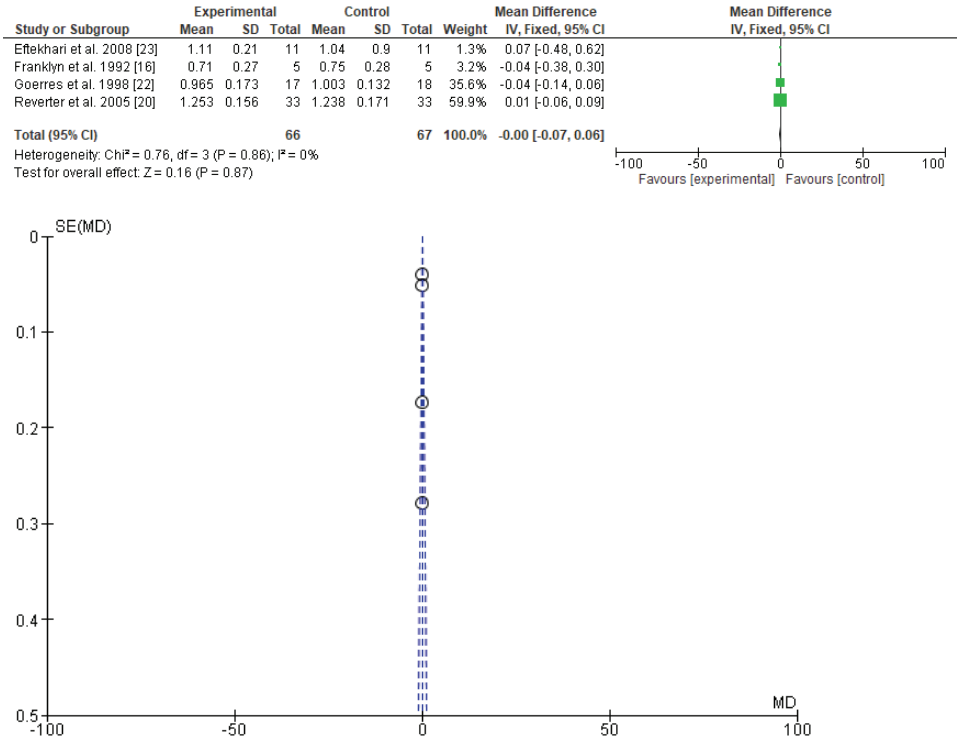

Figure 8: TSH suppression and bone mineral density among men lumbar spines.

Availability of Data and Materials

The dataset used in this meta-analysis are available upon request.

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