Review Article

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

Hyder Osman Mirghani¹ and Albaraa Altowigri²

¹Associate Professor of Internal Medicine and Endocrine, Faculty of Medicine, University of Tabuk, Saudi Arabia
²Assistant Professor of Orthopedics, Faculty of Medicine, University of Tabuk, Saudi Arabia

ORCID:
Hyder Osman Mirghani: https://orcid.org/0000-0002-5817-6194

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

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 micro-architecture,” “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 from 14.93 ± 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
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.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Type</th>
<th>Patients (interventional vs controls)</th>
<th>Study period</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muller et al. [9]</td>
<td>1995</td>
<td>Canada</td>
<td>Prospective</td>
<td>25 DTC (matched for menopausal status, BMI, and age), 0/25 vs 13/25 for EXT, 0/25 vs 1/25 for other sites</td>
<td>11 years</td>
<td>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)</td>
</tr>
<tr>
<td>Wang et al. [10]</td>
<td>2015</td>
<td>USA</td>
<td>Prospective comparing TSH &lt; 0.4 mU/l and 0.4</td>
<td>125/537 vs 29/537 for premenopausal and postmenopausal</td>
<td>66 months</td>
<td>Osteoporosis increased, with no change in the recurrence rate. No increased risk of TSH level around 1 mU/l</td>
</tr>
<tr>
<td>de Melo et al. [11]</td>
<td>2015</td>
<td>Brazil</td>
<td>Cross-sectional,</td>
<td>21/109 for osteoporosis and 44/109 for osteopenia vs 17/109 and 49/109 postmenopausal</td>
<td>88 months ± 70.6 months</td>
<td>Not significant</td>
</tr>
<tr>
<td>Vera et al. [14]</td>
<td>2016</td>
<td>Italy</td>
<td>Case–control</td>
<td>62/74 hip, 49/74 lumbar vs 92/120, 75/120, women</td>
<td>36 months</td>
<td>No relation of T4 dose, level, or duration of therapy to osteoporosis Mean ± SD available</td>
</tr>
<tr>
<td>Mazziotti et al. [12]</td>
<td>2018</td>
<td>Italy</td>
<td>Cross-sectional, TSH &lt; 0.05 and &gt;1</td>
<td>35/83 vs 946 for osteoporosis and 35/83 vs 2146 for osteopenia, women</td>
<td>5.5 years</td>
<td>Vertebral fractures were common among patients on long-term T4 and TSH levels &lt;1 mU/l</td>
</tr>
<tr>
<td>Zhang et al. [13]</td>
<td>2018</td>
<td>China</td>
<td>Prospective cohort</td>
<td>90/152, 13/152 vs 23/68, 9/68 for osteopenia and osteoporosis, respectively, postmenopausal women</td>
<td>2 years</td>
<td>Osteopenia was observed, no osteoporosis. (TSH &gt; 0.3 &amp; TSH &lt; 0.3 μIU/mL)</td>
</tr>
</tbody>
</table>

### 4. Discussion

Osteoporosis is common among men and postmenopausal women in contrast to premenopausal 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).
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>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Type</th>
<th>Premenopausal</th>
<th>Postmenopausal</th>
<th>Study period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Franklyn et al. [16]</td>
<td>1992</td>
<td>UK</td>
<td>Prospective</td>
<td>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</td>
<td>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</td>
<td>79 years</td>
</tr>
<tr>
<td>Kung et al. [18]</td>
<td>1993</td>
<td>Hong Kong</td>
<td>Cross-sectional</td>
<td>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</td>
<td>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</td>
<td>12.2 ± 6.6 years</td>
</tr>
<tr>
<td>Fujiyama et al. [17]</td>
<td>1995</td>
<td>Japan</td>
<td>Prospective</td>
<td>12 vs 12 0.849 ± 0.605 vs 0.849 ± 0.605 lumbar</td>
<td>109 vs 109 1.09 ± 1.1 vs 1.1 ± 1.3, lumbar, 0.12 ± 11 vs 0.37 ± 1.06 femur</td>
<td>88 ± 70.6 months</td>
</tr>
<tr>
<td>Goerres et al. [22]</td>
<td>1998</td>
<td>Switzerland</td>
<td>Cross-sectional</td>
<td>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</td>
<td>40 vs 29 1.200 ± 0.100 vs 1.100 ± 0.100 lumbar, 0.940 ± 0.100 vs 0.900 ± 0.100 femoral</td>
<td>10 years</td>
</tr>
<tr>
<td>Reverter et al. [20]</td>
<td>2005</td>
<td>Spain</td>
<td>Cross-sectional</td>
<td>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</td>
<td>40 vs 60 1.100 ± 0.100 vs 1.100 ± 0.100 lumbar and 0.840 ± 0.100 vs 0.870 ± 0.100 femoral</td>
<td>36 months</td>
</tr>
<tr>
<td>de Melo et al. [11]</td>
<td>2015</td>
<td>Brazil</td>
<td>Cross-sectional</td>
<td>109 vs 109 1.09 ± 1.1 vs 1.1 ± 1.3, lumbar, 0.12 ± 11 vs 0.37 ± 1.06 femur</td>
<td>14 vs 84 1.00 ± 0.12 vs 0.98 ± 0.11 lumbar</td>
<td>10 years</td>
</tr>
<tr>
<td>Tournis et al. [21]</td>
<td>2015</td>
<td>Greece</td>
<td>Case-control</td>
<td>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</td>
<td>40 vs 29 1.200 ± 0.100 vs 1.100 ± 0.100 lumbar, 0.940 ± 0.100 vs 0.900 ± 0.100 femoral</td>
<td>10 years</td>
</tr>
<tr>
<td>Moon et al. [19]</td>
<td>2016</td>
<td>South Korea</td>
<td>Case-control</td>
<td>25 vs 75 1.210 ± 0.110 vs 1.180 ± 0.120 lumbar, and 0.930 ± 0.100 vs 0.900 ± 0.090 femoral</td>
<td>74 vs 222 1.050 ± 0.150 vs 1.070 ± 0.140 lumbar, and 0.830 ± 0.110 vs 0.830 ± 0.100 femoral</td>
<td>36 months</td>
</tr>
<tr>
<td>De Mingo Dominguez et al. [15]</td>
<td>2018</td>
<td>Spain</td>
<td>Case–control</td>
<td>14 vs 84 1.00 ± 0.12 vs 0.98 ± 0.11 lumbar</td>
<td>14 vs 84 1.00 ± 0.12 vs 0.98 ± 0.11 lumbar</td>
<td>10 years</td>
</tr>
</tbody>
</table>
TABLE 4: TSH suppression for differentiated thyroid carcinoma and bone mineral density among men.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Type</th>
<th>BMD</th>
<th>Study period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Franklyn et al.</td>
<td>1992</td>
<td>UK</td>
<td>Prospective</td>
<td>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</td>
<td>79 years</td>
</tr>
<tr>
<td>Goerres et al.</td>
<td>1998</td>
<td>Switzerland</td>
<td>Cross-sectional</td>
<td>17 vs 18 controls 0.965 ± 0.173 vs 1.003 ± 0.132 lumbar spines</td>
<td></td>
</tr>
<tr>
<td>Reverter et al.</td>
<td>2005</td>
<td>Spain</td>
<td>Cross-sectional</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Eftekhari et al.</td>
<td>2008</td>
<td>Iran</td>
<td>Cross-sectional</td>
<td>11 vs 11 controls 1.110 ± 0.210 vs 1.040 ± 0.090 lumbar spines</td>
<td>14.93 ± 2.17 months</td>
</tr>
</tbody>
</table>

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

Acknowledgements

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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.

Funding

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References


