Effect of Thyrotropin Suppression Therapy on Bone in Thyroid Cancer Patients

MARIA PAPALEONTIOU, a,c SARAH T. HAWLEY, c MEGAN R. HAYMART a,b,c
aDivision of Metabolism, Endocrinology and Diabetes and bDivision of Hematology/Oncology, cDepartment of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Thyroid neoplasms • Thyrotropin • Risk • Bone density

ABSTRACT

Background. The thyroid cancer incidence is rising. Despite current guidelines, controversy exists regarding the degree and duration of thyrotropin suppression therapy. Also, its potential skeletal effects remain a concern to physicians caring for thyroid cancer patients. We conducted a review of published data to evaluate existing studies focusing on the skeletal effects of thyrotropin suppression therapy in thyroid cancer patients.

Materials and Methods. A systematic search of the PubMed, Ovid/Medline, and Cochrane Central Register of Controlled Trials databases was conducted. The retained studies were evaluated for methodological quality, and the study populations were categorized into premenopausal women, postmenopausal women, and men.

Results. Twenty-five pertinent studies were included. Seven studies were longitudinal and 18 were cross-sectional. Of the 25 included studies, 13 were assigned an excellent methodological quality score. Three of 5 longitudinal studies and 3 of 13 cross-sectional studies reported decreased bone mineral density (BMD) in premenopausal women; 2 of 4 longitudinal studies and 5 of 13 cross-sectional studies reported decreased BMD in postmenopausal women. The remaining studies showed no effect on BMD. The only longitudinal study of men showed bone mass loss; however, cross-sectional studies of men did not demonstrate a similar effect.

Conclusion. Studies to date have yielded conflicting results on the skeletal effects of thyrotropin suppression therapy and a knowledge gap remains, especially for older adults and men. Existing data should be cautiously interpreted because of the variable quality and heterogeneity. Identifying groups at risk of adverse effects from thyrotropin suppression therapy will be instrumental to providing focused and tailored thyroid cancer treatment.

Implications for Practice: The standard treatment for thyroid cancer includes total thyroidectomy with or without radioactive iodine ablation, often followed by thyrotropin suppression therapy. Despite current guidelines, controversy exists regarding the degree and duration of thyrotropin suppression therapy, and discordant results have been reported on its adverse effects on bone. The present review provides physicians with existing data on the skeletal effects of thyrotropin suppression therapy, highlighting the need for further research to identify the groups at risk of adverse skeletal effects. This knowledge will aid in developing tailored thyroid cancer treatment.

INTRODUCTION

The incidence of thyroid cancer is rising in the United States, with an estimated 62,450 new cases in 2015 [1]. The incidence is highest in older adults [1], the same cohort at greatest risk of adverse events from thyroid hormone suppression therapy. The standard treatment for differentiated thyroid cancer includes total thyroidectomy with or without radioactive iodine ablation, followed by thyrotropin (TSH) suppression therapy in most cases [2]. Experimental studies and clinical data have demonstrated that thyroid cell proliferation is TSH-dependent [3, 4]. This provides a rationale for TSH suppression as a treatment modality for differentiated thyroid cancer to inhibit growth of residual neoplastic thyroid tissue. Current American Thyroid Association guidelines recommend initial TSH suppression to less than 0.1 mIU/L for patients with high-risk well-differentiated thyroid cancer. Also, maintenance of the TSH at or slightly less than the lower limit of normal (0.1–0.5 mIU/L) is considered appropriate for low-risk and intermediate-risk patients [2]. Despite the current guidelines, controversy remains regarding the appropriate use of thyrotropin suppression therapy,
including the degree of TSH suppression and duration of therapy.

Thyrotropin suppression therapy induces a state of subclinical hyperthyroidism. It has been recognized that excess thyroid hormone and the absence of TSH-mediated osteoclast suppression stimulate bone resorption [5, 6]. This leads to increased bone turnover and decreased bone mineral density (BMD), thus increasing the risk of fractures [6]. This is important, because most patients with differentiated thyroid cancer have a favorable prognosis, with patients living long enough to develop bone loss later in life.

We conducted a comprehensive literature review to identify those studies that examined the skeletal effects of thyrotropin suppression therapy in the treatment of differentiated thyroid cancer. We systematically reviewed these studies to determine the gaps in knowledge for population subgroups.

**Materials and Methods**

**Data Sources and Searches**
The PubMed, Ovid/Medline, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to identify pertinent studies for review. The medical subheading terms used included thyrotropin, thyroid neoplasms, risk, bone and bones, bone density, and adverse effects. Other keywords included fracture(s), skeletal, TSH suppression, and levothyroxine treatment. The citation abstracts identified in the searches were reviewed in detail to determine their relevance for inclusion in the review. A careful review of the reference lists of the retained studies was also performed to identify other salient studies.

**Study Selection**
Studies were included in the review if they fulfilled the following eligibility criteria: published in English, evaluated thyrotropin suppression therapy in patients with thyroid cancer, and reported skeletal outcome measures (including bone mineral density, bone mass, bone turnover markers, and fractures). Studies that evaluated the effects of thyrotropin suppression therapy in patients with benign thyroid disease or the effects of endogenous subclinical or overt hyperthyroidism were excluded. Studies conducted in the pediatric population were also excluded.

**Data Abstraction**
The abstracted information from each retained report included (a) study design and sample size, (b) characteristics of the study sample (e.g., mean age, sex), (c) menopausal status if the sample included female patients, (d) outcome measure variables on skeletal risk (e.g., bone mineral density at various sites, bone turnover markers), and (e) secondary outcomes, if present (e.g., duration of thyroid hormone suppression treatment). For the purposes of the present review, the study populations were categorized into premenopausal women, postmenopausal women, and men.

**Quality Assessment**
The retained studies were evaluated for methodological quality using a standardized validated instrument, addressing reporting quality, external validity, bias, confounding factors, and the power of the randomized and nonrandomized studies [7]. Threshold scores were used to assign a quality score of “excellent.” A score of ≥12 (score range, 0–32) was considered excellent [7].

**Results**

**Study Characteristics and Quality**
Of the initial 384 studies identified, 25 addressed the effect of thyrotropin suppression therapy on bone quality in thyroid cancer patients and were included in the present review. Of the 25 studies, 7 were longitudinal and 18 were cross-sectional in design. The patients for all the studies had been recruited from outpatient clinics. Only 6 of the retained articles included all 3 population groups (premenopausal women, postmenopausal women, and men) [8–13]. Although several of the reviewed studies included patients >65 years old, none of them had specifically focused on older adults, and only one study’s participants had a mean age >65 years, which was in the group of postmenopausal women [8].

Of the 25 included studies [8–32], 13 were assigned an excellent methodological quality score, with a median quality score of 13 (score range, 6–20) [8, 10, 15–17, 19, 22, 24–26, 29–31] (Tables 1–3).

**Studies of Premenopausal Women**
A total of 18 studies included premenopausal women receiving thyrotropin suppression therapy for differentiated thyroid cancer, and these studies are summarized in Table 1 [8–25]. Of these 18 studies, 5 were longitudinal and 13 were cross-sectional in design. Their findings showed conflicting results, with 12 studies showing no significant change and 6 showing a decrease in bone mineral density.

A recent longitudinal study with a mean follow-up of 6.5 years showed that the risk of postoperative osteoporosis in women with low- or intermediate-risk thyroid cancer, adjusted for age, increased fourfold when their TSH was suppressed long-term, without decreasing cancer recurrence [25]. Jódar et al. [17] conducted a longitudinal study of 37 premenopausal women, who had been receiving thyrotropin suppression therapy for a mean of 5.6 years. They found no difference in the bone mineral density at the lumbar spine, femoral neck, or Ward’s triangle. They did, however, find a small, but statistically significant, reduction at the distal ulna, but this was considered minimal when compared with the controls [17]. Two other longitudinal studies showed similar findings (i.e., no difference was found in bone mineral density when compared with the controls) [18, 20]. Neither study showed a change in bone mineral density between the initial and follow-up bone mineral density scans. In contrast, a smaller longitudinal study [22] (n = 8) found a significant reduction in bone mineral density in the lumbar spine 1–3 years after the initiation of thyrotropin suppression therapy.

Most cross-sectional studies did not find a significant change in bone mineral density in premenopausal women [8–14, 16, 19, 24] (Table 1). The largest of these [14] was a Taiwanese retrospective study (n = 44) in which the bone density was measured at the lumbar spine, femoral neck, Ward’s triangle, and total hip, following an average of 7.3 years of thyrotropin suppression therapy. No significant change was seen in bone density at all sites between patients and the age- and body mass index-matched controls. No correlation was found between the bone mineral density and the degree of thyrotropin suppression or duration of levothyroxine therapy.
Table 1. Summary of studies investigating effect of thyrotropin suppression therapy in premenopausal female thyroid cancer patients on bone

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size (n)</th>
<th>Age (yr)</th>
<th>Control group</th>
<th>Effect/outcome</th>
<th>Length of thyroid hormone treatment (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Longitudinal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang et al. [25]b,c</td>
<td>569</td>
<td>48 ± 14</td>
<td>62 Thyroid cancer, female patients with TSH &gt;0.4 postoperatively</td>
<td>Osteoporosis (T score 2.5)</td>
<td>6.5 (median)</td>
</tr>
<tr>
<td>Jódar et al. [17]</td>
<td>37</td>
<td>47 ± 13</td>
<td>50 Healthy, matched for age, sex, weight, menopausal status</td>
<td>Decrease in distal radius BMD</td>
<td>5.6 ± 3.2</td>
</tr>
<tr>
<td>Karner et al. [18]</td>
<td>19</td>
<td>39 ± 8.0</td>
<td>100 None</td>
<td>No change in BMD</td>
<td>9.4 ± 6.4</td>
</tr>
<tr>
<td>Muller et al. [20]</td>
<td>15</td>
<td>47 ± 3.0</td>
<td>40 Healthy, matched for age, sex, BMI, menopausal status</td>
<td>No change in BMD</td>
<td>11</td>
</tr>
<tr>
<td>Pioli et al. [22]b</td>
<td>8</td>
<td>43 ± 6.8</td>
<td>100 Healthy, matched for age, sex, menopausal status</td>
<td>Decrease in spine BMD</td>
<td>1–3 (range)</td>
</tr>
<tr>
<td><strong>Cross-sectional</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen et al. [14]</td>
<td>44</td>
<td>38.6 ± 6.7</td>
<td>100 Healthy, matched for age, sex, BMI, menopausal status</td>
<td>No change in BMD</td>
<td>7.3 ± 3.0</td>
</tr>
<tr>
<td>Tournis et al. [24]b</td>
<td>40</td>
<td>40.2 ± 6.4</td>
<td>100 Healthy, matched for age, sex, BMI, menopausal status, calcium intake</td>
<td>No change in markers of bone resorption or bone formation, no change in BMD</td>
<td>4.4</td>
</tr>
<tr>
<td>Marcocci et al. [19]b</td>
<td>38</td>
<td>39</td>
<td>95 Healthy, matched for age, sex, weight</td>
<td>No change in BMD</td>
<td>10.1</td>
</tr>
<tr>
<td>Heijckmann et al. [10]b</td>
<td>26</td>
<td>40 ± 7.0</td>
<td>100 None</td>
<td>No change in BMD</td>
<td>4</td>
</tr>
<tr>
<td>Lehmke et al. [11]</td>
<td>25</td>
<td>49 ± 16.0</td>
<td>100 None</td>
<td>No change in BMD</td>
<td>5 ± 4.3</td>
</tr>
<tr>
<td>Stepan et al. [12]</td>
<td>20</td>
<td>40.4 ± 5.9</td>
<td>100 None</td>
<td>No change in vertebral BMD or biochemical indexes of bone resorption and osteoblastic activity</td>
<td>6.0 ± 5.1</td>
</tr>
<tr>
<td>Franklyn et al. [8]b</td>
<td>18</td>
<td>41.1 ± 4.9</td>
<td>72 Healthy, matched for age, sex, BMI, menopausal status, smoking, calcium intake</td>
<td>No change in BMD</td>
<td>7.7</td>
</tr>
<tr>
<td>Toivonen et al. [13]</td>
<td>15</td>
<td>45 (median)</td>
<td>100 Healthy, matched for age, sex</td>
<td>Increased markers of bone formation and bone resorption, no change in BMD</td>
<td>9–11 (range)</td>
</tr>
<tr>
<td>Görres et al. [9]</td>
<td>15</td>
<td>35.5 ± 6.0</td>
<td>93 Healthy, matched for age, sex</td>
<td>No change in BMD</td>
<td>5</td>
</tr>
<tr>
<td>Diamond et al. [15]b</td>
<td>14</td>
<td>41.6 ± 1.9</td>
<td>100 Healthy, matched for age, sex, BMI, menopausal status</td>
<td>Decrease in femoral neck BMD</td>
<td>10.7 ± 1.7</td>
</tr>
<tr>
<td>Giannini et al. [16]j</td>
<td>12</td>
<td>41/1 ± 2.0</td>
<td>100 Healthy, matched for age, sex, menopausal status</td>
<td>No change in BMD</td>
<td>9.25</td>
</tr>
<tr>
<td>Paul et al. [21]</td>
<td>5</td>
<td>36.5 ± 1.2</td>
<td>100 Healthy, matched for age, sex, weight</td>
<td>Decrease in femoral neck and femoral trochanter BMD</td>
<td>9.2 ± 1.0</td>
</tr>
<tr>
<td>Ross et al. [23]</td>
<td>4</td>
<td>37 ± 4.0</td>
<td>NA Healthy, matched for age, sex, menopausal status</td>
<td>Decrease in BMD</td>
<td>≥5</td>
</tr>
</tbody>
</table>

Abbreviations: BMD, bone mineral density; BMI, body mass index; NA, not applicable (the investigators had documented that, overall, 82% of patients had suppressed TSH; however, they did not specify whether this included the patients with thyroid cancer); TSH, thyrotropin.

aData presented as mean ± SD, unless otherwise noted.

bExcellent methodological quality per Downs and Black [7].

cMenopausal status not reported; because of the mean age, most patients included were assumed to be premenopausal.
Three small cross-sectional studies demonstrated a decrease in bone mineral density with thyrotropin suppression therapy of varying duration [15, 21, 23]. The largest of these studied 14 premenopausal women with differentiated thyroid cancer in Australia who had been receiving thyrotropin suppression therapy for at least 5 years [15]. None of the patients had been taking estrogen, calcium, or vitamin D supplementation. Compared with the controls matched for age and menopausal status, the patients were found to have decreased bone mineral density in the femoral neck but not in the lumbar spine or forearm.

A few studies also examined the effect of thyrotropin suppression therapy on markers of bone turnover in premenopausal women [12, 13, 24]. Only one study found a significant increase in both markers of bone formation and resorption; however, no change in bone mineral density was seen [13].

Studies of Postmenopausal Women
A total of 17 studies included postmenopausal women [8–17, 20, 24, 26–30] (Table 2). Of these, 4 were longitudinal and 13 cross-sectional in design.

The largest longitudinal study (n = 120) showed decreased bone mineral density only in women aged ≥50 years receiving thyrotropin suppression therapy compared with women with thyroid cancer who had normal TSH levels postoperatively at 1 and 5 years of follow-up [29]. A longitudinal study by Jódar et al. found a decrease in bone mineral density at the distal radius but not at any other site in 39 postmenopausal women [17]. This finding was similar to their finding in the cohort of premenopausal women [17]. However, only 50% of the cohort had a level of TSH suppression of <0.1 mIU/L. Also, the absolute numbers compared with those in the controls were not reported. Another longitudinal trial [26] reported no change in bone mineral density over 2 years in postmenopausal women receiving thyrotropin suppression therapy for an average of 7 years. A smaller longitudinal study also did not report a change in bone mineral density [20].

Cross-sectional studies have yielded inconsistent results. The largest of these studies [30] included 109 postmenopausal women and found no significant differences between the lumbar or femoral T-score for patients and age-matched controls after an average of 7.3 years of thyrotropin suppression therapy. Several other cross-sectional studies did not demonstrate a change in bone mineral density in postmenopausal women receiving thyrotropin suppression therapy [8–10, 13, 16, 24, 27]. However, two of these demonstrated an increase in markers of bone resorption [13, 24] (Table 2). Kung et al. [28] found a significant reduction in bone mineral density at all measured sites (femoral neck, femoral trochanter, Ward’s triangle, lumbar spine) in southern Chinese postmenopausal women (n = 34) after an average of 12.2 years of thyrotropin suppression therapy. The patients were matched for age and menopausal status. The investigators noted two fractures in the treatment group compared with none in the control group, as well as increased osteocalcin levels. Four smaller cross-sectional studies also reported decreased bone mineral density at different measured sites in patients [11, 12, 14, 15]; however, two of these lacked control groups [11, 12] (Table 2). Several other cross-sectional studies did not demonstrate a change in bone mineral density in postmenopausal women receiving thyrotropin suppression therapy (Table 2).

Studies of Men
Nine of the reviewed studies included men [8–13, 18, 31, 32] (Table 3). All except one study [18] were cross-sectional studies, and all had a small sample size (n = 4–33). The only longitudinal study was conducted by Karner et al. [18]. Their study included 9 men with thyroid cancer. They performed an initial bone mineral density measurement after an average of 8.1 years of thyrotropin suppression therapy, with a follow-up bone mineral density measurement taken 1 year later [18]. No significant difference was found in bone mineral density values from the first and second measurements for the lumbar spine and femoral neck, although a statistically significant difference was demonstrated at the distal radius. However, no control groups were included in their study [18].

None of the cross-sectional studies that included men found a change in bone mineral density in male patients with thyroid cancer receiving thyrotropin suppression therapy of variable duration [8–13, 31, 32]. Two of these studies lacked a control group [11, 12] (Table 3). One small cross-sectional study (n = 4), in which men underwent thyrotropin suppression therapy for a range of 9–11 years, found an increase in both bone formation and bone resorption markers but no change in bone mineral density [13].

Discussion
To prevent thyroid cancer recurrence, thyrotropin suppression therapy has been recommended for patients with intermediate- and high-risk well-differentiated thyroid cancer after surgical resection and radioactive iodine ablation [2]. Despite this clinical practice, consensus is lacking regarding the optimal TSH concentration to reduce cancer recurrence and minimize the toxicity from exogenous subclinical hyperthyroidism. In addition, the optimal duration of thyrotropin suppression therapy remains unknown. Biondi and Cooper suggested a risk-adapted approach, in which the potential benefits of thyrotropin suppression therapy were weighed against its potential adverse effects, taking into account age and comorbidities [33]. However, to date, no age-specific guidelines exist.

The present review has shown that existing studies on the effect of thyrotropin suppression therapy on bone in thyroid cancer patients have yielded conflicting results. This is largely because of differences in study design, study population, methodology, degree of TSH suppression, follow-up duration, and measured outcomes. In addition, most of the studies reviewed were limited by a small sample size, insufficient power, and varying degrees of control for confounding variables.

The relationship between exogenous subclinical hyperthyroidism and skeletal integrity remains controversial. The data obtained from previous studies on the effect of thyrotropin suppression therapy in thyroid cancer patients demonstrated no deleterious consequences in premenopausal women. However, these data suggest that postmenopausal women might constitute a risk group for decreased bone mineral density.

Data from men are scarce, as evidenced by the small sample sizes of the studies that included men. This was most likely because of the lower incidence of differentiated thyroid cancer in this population. However, despite the notion that
Osteoporosis is thought to affect predominantly women, it has recently been shown that it is underdiagnosed and undertreated in older men, leaving them vulnerable to early death and disability [34]. A need exists to address the gap in knowledge regarding the influence of thyrotropin suppression therapy on bone quality in the male population. Only a few studies have

Table 2. Summary of studies investigating effect of thyrotropin suppression therapy in postmenopausal female thyroid cancer patients on bone

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size (n)</th>
<th>Mean agea (yr)</th>
<th>Patients with TSH suppression (%)</th>
<th>Control group</th>
<th>Effect/outcome</th>
<th>Length of thyroid hormone treatmentb (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Longitudinal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sugitani et al. [29](^c)</td>
<td>120</td>
<td>50.2 ± 13.3</td>
<td>100</td>
<td>Thyroid cancer, female patients with normal TSH postoperatively</td>
<td>Decrease in BMD in women aged ≥ 50 y</td>
<td>5</td>
</tr>
<tr>
<td>Jódar et al. [17](^a)</td>
<td>39</td>
<td>47 ± 13</td>
<td>50</td>
<td>Healthy, matched for age, sex, weight, menopausal status</td>
<td>Decrease in distal radius BMD</td>
<td>5.6 ± 3.2</td>
</tr>
<tr>
<td>Guo et al. [26](^b)</td>
<td>23</td>
<td>61 ± 9.0</td>
<td>100</td>
<td>Healthy, matched for age, sex, menopausal status</td>
<td>No change in BMD</td>
<td></td>
</tr>
<tr>
<td>Muller et al. [20]</td>
<td>10</td>
<td>47 ± 3.0</td>
<td>40</td>
<td>Healthy, matched for age, sex, BMI, menopausal status</td>
<td>No change in BMD</td>
<td>11</td>
</tr>
<tr>
<td><strong>Cross-sectional</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Melo et al. [30](^b)</td>
<td>109</td>
<td>58.4 ± 8.3</td>
<td>100</td>
<td>Healthy, matched for age, sex, BMI, menopausal status, calcium intake</td>
<td>No change in BMD</td>
<td>7.3 ± 5.9</td>
</tr>
<tr>
<td>Tournis et al. [24](^b)</td>
<td>40</td>
<td>56.7 ± 3.9</td>
<td>100</td>
<td>Healthy, matched for age, sex, BMI, menopausal status, calcium intake</td>
<td>Increase in bone resorption markers, no change in bone formation markers, no change in BMD</td>
<td>5</td>
</tr>
<tr>
<td>Kung et al. [28]</td>
<td>34</td>
<td>62 ± 8.0</td>
<td>100</td>
<td>Healthy, matched for age, sex</td>
<td>Decrease in spine, femoral neck, and hip BMD</td>
<td>12.2 ± 6.6</td>
</tr>
<tr>
<td>Görres et al. [9]</td>
<td>32</td>
<td>60.8 ± 11.4</td>
<td>96</td>
<td>Healthy, matched for age, sex</td>
<td>No change in BMD</td>
<td>11.1 ± 6.1</td>
</tr>
<tr>
<td>Chen et al. [14]</td>
<td>25</td>
<td>57.7 ± 6.9</td>
<td>100</td>
<td>Healthy, matched for age, sex, BMI, menopausal status</td>
<td>Decrease in lumbar spine, femoral neck, total hip BMD</td>
<td>7.3 ± 3.0</td>
</tr>
<tr>
<td>Stepan et al. [12]</td>
<td>25</td>
<td>60.4 ± 9.6</td>
<td>100</td>
<td>None</td>
<td>Decrease in vertebral BMD, increase in biochemical indexes of bone resorption and osteoblastic activity</td>
<td>6.0 ± 5.1</td>
</tr>
<tr>
<td>Hawkins et al. [27]</td>
<td>21</td>
<td>59.6 ± 7.5</td>
<td>80</td>
<td>Healthy, matched for sex, menopausal status</td>
<td>No change in BMD</td>
<td>6.2 ± 2.2</td>
</tr>
<tr>
<td>Lehmke et al. [11]</td>
<td>16</td>
<td>49 ± 16.0</td>
<td>100</td>
<td>None</td>
<td>Decrease in calcaneus and midshaft radius BMD</td>
<td>5 ± 4.3</td>
</tr>
<tr>
<td>Heijckmann et al. [10](^b)</td>
<td>14</td>
<td>63 ± 9.0</td>
<td>100</td>
<td>None</td>
<td>No change in BMD</td>
<td>5.5</td>
</tr>
<tr>
<td>Giannini et al. [16](^b)</td>
<td>13</td>
<td>57.6 ± 1.7</td>
<td>100</td>
<td>Healthy, matched for age, sex</td>
<td>No change in BMD</td>
<td>7.6</td>
</tr>
<tr>
<td>Toivonen et al. [13]</td>
<td>10</td>
<td>45 (median)</td>
<td>100</td>
<td>Healthy, matched for age, sex</td>
<td>No change in BMD</td>
<td>9-11 (range)</td>
</tr>
<tr>
<td>Diamond et al. [15](^b)</td>
<td>10</td>
<td>59 ± 2.8</td>
<td>100</td>
<td>Healthy, matched for age, sex, BMI, menopausal status</td>
<td>Decrease in spine, femoral neck, and radius BMD</td>
<td>5.9 ± 1.0</td>
</tr>
<tr>
<td>Franklyn et al. [8]</td>
<td>2</td>
<td>65.4 ± 8.1</td>
<td>76</td>
<td>Healthy, matched for age, sex, BMI, menopausal status</td>
<td>No change in BMD</td>
<td>8.1</td>
</tr>
</tbody>
</table>

Abbreviations: BMD, bone mineral density; BMI, body mass index; TSH, thyrotropin.

\(^a^Data presented as mean ± SD, unless otherwise noted.

\(^b^Excellent methodological quality per Downs and Black [7].

\(^c^Randomized controlled trial; menopausal status not reported; mean age 50.2 ± 13.3 years; patients aged ≥ 80 years and those with severe osteoporosis were excluded.
been conducted to date on the effect of subclinical hyperthyroidism secondary to thyrotropin suppression therapy for differentiated thyroid cancer on bone in men, and all of them have been of poor quality and underpowered. Only one longitudinal study has been conducted to date in men; however, it had a small sample size ($n = 9$) and lacked a control group [18].

Existing cross-sectional studies of men have also been limited by inadequate power and some lacked control groups. The risk of vertebral fractures in men has been shown to be as high as one half the rate seen in women; however, men and women experience equal morbidity from them [35]. In addition, men have been shown to sustain fractures at a higher bone mineral density than women, and the mortality in the year after a hip fracture has been twice as high as that in women [36–39].

Also, a need exists to delineate the implications of long-term thyrotropin suppression therapy on bone health in older adults (age $\geq 65$ years) with thyroid cancer. Although several studies have included patients aged $\geq 65$ years, none of the studies to date have focused exclusively on older adults (age $\geq 65$ years) or the oldest adults (age $\geq 80$ years). Because this older cohort is the most vulnerable to bone loss and fracture risk, treatment targets with thyroid hormone replacement therapy might need to be modified in these patients to minimize adverse skeletal effects.

Exogenous subclinical hyperthyroidism in thyroid cancer patients and its potential effects on bone health remain a concern to physicians involved in the long-term care of these patients. Identifying the groups at risk of adverse effects from treatment is key to tailoring therapy and guiding clinical practice in a more focused pattern, rather than a “one size fits all” approach. Future research, including longitudinal studies and randomized controlled trials, is needed to provide further insight into the skeletal effect of thyrotropin suppression therapy in different subgroups of thyroid cancer patients. Further studies are also needed to evaluate the potential effect of exogenous subclinical hyperthyroidism in female and male thyroid cancer patients aged $\geq 65$ years.

### CONCLUSION

The standard treatment for differentiated thyroid cancer includes total thyroidectomy with or without radioactive iodine ablation, often followed by TSH suppression therapy. Studies to date have yielded conflicting results on the effects of thyrotropin suppression therapy for the treatment of thyroid cancer on bone density. A large gap exists in knowledge, especially for older adults and men with thyroid cancer. Identifying the groups at risk of adverse effects of thyrotropin suppression therapy is instrumental to providing focused and tailored therapy.

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**AUTHOR CONTRIBUTIONS**

Conception/Design: Maria Papaleontiou, Megan R. Haymart

Provision of study material or patients: Maria Papaleontiou

Collection and/or assembly of data: Maria Papaleontiou

**REFERENCES**


2. Haugen BR, Alexander EK, Bible KC et al. American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2015 [Epub ahead of print].


20. Müller CG, BayleY TA, Harrison JE et al. Possible limited bone loss with suppressive thyroxine therapy is unlikely to have clinical relevance. Thyroid 1995;5:81–87.


24. Tournis S, Antoniou JD, Liakou CG et al. Volumetric bone mineral density and bone geometry assessed by peripheral quantitative computed tomography in women with differentiated thyroid cancer under TSH suppression. Clin Endocrinol (Oxf) 2015;82:197–204.


