The Oncologist®

Endocrinology

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]

[a]Division of Metabolism, Endocrinology and Diabetes and [b]Division of Hematology/Oncology, [c]Department 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. ***The Oncologist*** 2016;21:165–171

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,

CME

Correspondence: Maria Papaleontiou, M.D., Division of Metabolism, Endocrinology and Diabetes, Department of Internal Medicine, University of Michigan, 24 Frank Lloyd Wright Drive, Lobby G, Room 1649, Ann Arbor, Michigan 48105, USA. Telephone: 734-764-9733; E-Mail: mpapaleo@med.umich.edu Received April 30, 2015; accepted for publication September 28, 2015; published Online First on December 9, 2015. 1083-7159/2015/$20.00/0 http://dx.doi.org/10.1634/theoncologist.2015-0179

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.

CME

Table 1. Summary of studies investigating effect of thyrotropin suppression therapy in premenopausal female thyroid cancer patients on bone

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

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.
[a]Data presented as mean ± SD, unless otherwise noted.
[b]Excellent methodological quality per Downs and Black [7].
[c]Menopausal status not reported; because of the mean age, most patients included were assumed to be premenopausal.

CME

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

CME

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

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

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.

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

CME

Table 3. Summary of studies investigating effect of thyrotropin suppression therapy in male thyroid cancer patients on bone

Study	Sample size (*n*)	Age[a] (yr)	Patients with TSH suppression (%)	Control group	Effect/outcome	Length of thyroid hormone treatment[a] (yr)
Longitudinal						
Karner et al. [18]	9	41.8 ± 10.0	100	None	Loss of bone mass in distal radius	8.1 ± 6.0
Cross-sectional						
Reverter et al. [31][b]	33	56 ± 14.0	100	Healthy, matched for age and BMI	No change in BMD	15 ± 5.7
Marcocci et al. [32]	26	42.8 ± 1.6	76	Healthy, matched for age and weight	No change in BMD	10.2 ± 0.8
Heijckmann et al. [10][b]	19	52 ± 12.0	100	None	No change in BMD	6
Görres et al. [9]	18	52.1 ± 15.6	94	Healthy, matched for age and sex	No change in BMD	8.5 ± 5.3
Stepan et al. [12]	13	58.2 ± 14.0	100	None	No change in vertebral BMD, no change in biochemical indices of bone resorption and osteoblastic activity	4.6 ± 3.0
Lehmke et al. [11]	9	51 ± 13.0	100	None	No change in BMD	5 ± 4.3
Franklyn et al. [8][b]	5	56.8 ± 16.4	40	Healthy, matched for age, sex, BMI, menopausal status, smoking, calcium intake	No change in BMD	7.9
Toivonen et al. [13]	4	45 (median)	100	Healthy, matched for age, sex	Increased markers of bone formation and bone resorption, no change in BMD	9–11 (range)

Abbreviations: BMI, body mass index; BMD, bone mineral density; TSH, thyrotropin.
[a]Data presented as mean ± SD, unless otherwise noted.
[b]Excellent methodological quality per Downs and Black [7].

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 >65 years) with thyroid cancer. Although several studies have included patients aged ≥65 years, none of the studies to date have focused exclusively on older adults (age >65 years) or the oldest adults (age >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 ≥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.

Acknowledgments

We acknowledge Brittany Gay, who helped with the manuscript formatting and submission process. Maria Papaleontiou was supported by an Institutional National Research Service Award (Grant 5T32DK007245-37) from the National Institutes of

CME

Health. Megan R. Haymart is funded by Grant 1K07CA154595-01 from the National Institutes of Health.

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
Data analysis and interpretation: Maria Papaleontiou, Sarah T. Hawley, Megan R. Haymart
Manuscript writing: Maria Papaleontiou, Sarah T. Hawley, Megan R. Haymart
Final approval of manuscript: Maria Papaleontiou, Sarah T. Hawley, Megan R. Haymart

Disclosures

The authors indicated no financial relationships.

References

1. Surveillance, Epidemiology, and End Results Program. SEER Stat Fact Sheets: Thyroid Cancer. Available at http://seer.cancer.gov/statfacts/html/thyro.html. Accessed April 1, 2015.

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].

3. Biondi B, Filetti S, Schlumberger M. Thyroid-hormone therapy and thyroid cancer: A reassessment. Nat Clin Pract Endocrinol Metab 2005;1:32–40.

4. Roger P, Taton M, Van Sande J et al. Mitogenic effects of thyrotropin and adenosine 3′,5′-monophosphate in differentiated normal human thyroid cells in vitro. J Clin Endocrinol Metab 1988;66:1158–1165.

5. Baliram R, Sun L, Cao J et al. Hyperthyroid-associated osteoporosis is exacerbated by the loss of TSH signaling. J Clin Invest 2012;122:3737–3741.

6. Abe E, Marians RC, Yu W et al. TSH is a negative regulator of skeletal remodeling. Cell 2003;115:151–162.

7. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998;52:377–384.

8. Franklyn JA, Betteridge J, Daykin J et al. Long-term thyroxine treatment and bone mineral density. Lancet 1992;340:9–13.

9. Görres G, Kaim A, Otte A et al. Bone mineral density in patients receiving suppressive doses of thyroxine for differentiated thyroid carcinoma. Eur J Nucl Med 1996;23:690–692.

10. Heijckmann AC, Huijberts MSP, Geusens P et al. Hip bone mineral density, bone turnover and risk of fracture in patients on long-term suppressive L-thyroxine therapy for differentiated thyroid carcinoma. Eur J Endocrinol 2005;153:23–29.

11. Lehmke J, Bogner U, Felsenberg D et al. Determination of bone mineral density by quantitative computed tomography and single photon absorptiometry in subclinical hyperthyroidism: A risk of early osteopaenia in post-menopausal women. Clin Endocrinol (Oxf) 1992;36:511–517.

12. Stěpán JJ, Límanová Z. Biochemical assessment of bone loss in patients on long-term thyroid hormone treatment. Bone Miner 1992;17:377–388.

13. Toivonen J, Tähtelä R, Laitinen K et al. Markers of bone turnover in patients with differentiated thyroid cancer with and following withdrawal of thyroxine suppressive therapy. Eur J Endocrinol 1998;138:667–673.

14. Chen CH, Chen JF, Yang BY et al. Bone mineral density in women receiving thyroxine suppressive therapy for differentiated thyroid carcinoma. J Formos Med Assoc 2004;103:442–447.

15. Diamond T, Nery L, Hales I. A therapeutic dilemma: Suppressive doses of thyroxine significantly reduce bone mineral measurements in both premenopausal and postmenopausal women with thyroid carcinoma. J Clin Endocrinol Metab 1991;72:1184–1188.

16. Giannini S, Nobile M, Sartori L et al. Bone density and mineral metabolism in thyroidectomized patients treated with long-term L-thyroxine. Clin Sci (Lond) 1994;87:593–597.

17. Jódar E, Begoña López M, García L et al. Bone changes in pre- and postmenopausal women with thyroid cancer on levothyroxine therapy: Evolution of axial and appendicular bone mass. Osteoporos Int 1998;8:311–316.

18. Karner I, Hrgović Z, Sijanović S et al. Bone mineral density changes and bone turnover in thyroid carcinoma patients treated with supraphysiologic doses of thyroxine. Eur J Med Res 2005;10:480–488.

19. Marcocci C, Golia F, Bruno-Bossio G et al. Carefully monitored levothyroxine suppressive therapy is not associated with bone loss in premenopausal women. J Clin Endocrinol Metab 1994;78:818–823.

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.

21. Paul TL, Kerrigan J, Kelly AM et al. Long-term L-thyroxine therapy is associated with decreased hip bone density in premenopausal women. JAMA 1988;259:3137–3141.

22. Pioli G, Pedrazzoni M, Palummeri E et al. Longitudinal study of bone loss after thyroidectomy and suppressive thyroxine therapy in premenopausal women. Acta Endocrinol (Copenh) 1992;126:238–242.

23. Ross DS, Neer RM, Ridgway EC et al. Subclinical hyperthyroidism and reduced bone density as a possible result of prolonged suppression of the pituitary-thyroid axis with L-thyroxine. Am J Med 1987;82:1167–1170.

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.

25. Wang LY, Smith AW, Palmer FL et al. Thyrotropin suppression increases the risk of osteoporosis without decreasing recurrence in ATA low- and intermediate-risk patients with differentiated thyroid carcinoma. Thyroid 2015;25:300–307.

26. Guo C-Y, Weetman AP, Eastell R. Longitudinal changes of bone mineral density and bone turnover in postmenopausal women on thyroxine. Clin Endocrinol (Oxf) 1997;46:301–307.

27. Hawkins F, Rigopoulou D, Papapietro K et al. Spinal bone mass after long-term treatment with L-thyroxine in postmenopausal women with thyroid cancer and chronic lymphocytic thyroiditis. Calcif Tissue Int 1994;54:16–19.

28. Kung AWC, Lorentz T, Tam SCF. Thyroxine suppressive therapy decreases bone mineral density in post-menopausal women. Clin Endocrinol (Oxf) 1993;39:535–540.

29. Sugitani I, Fujimoto Y. Effect of postoperative thyrotropin suppressive therapy on bone mineral density in patients with papillary thyroid carcinoma: A prospective controlled study. Surgery 2011;150:1250–1257.

30. de Melo TG, da Assumpção LV, Santos AO et al. Low BMI and low TSH value as risk factors related to lower bone mineral density in postmenospausal women under levothyroxine therapy for differentiated thyroid carcinoma. Thyroid Res 2015;8:7.

31. Reverter JL, Colomé E, Holgado S et al. Bone mineral density and bone fracture in male patients receiving long-term suppressive levothyroxine treatment for differentiated thyroid carcinoma. Endocrine 2010;37:467–472.

32. Marcocci C, Golia F, Vignali E et al. Skeletal integrity in men chronically treated with suppressive doses of L-thyroxine. J Bone Miner Res 1997;12:72–77.

33. Biondi B, Cooper DS. Benefits of thyrotropin suppression versus the risks of adverse effects in differentiated thyroid cancer. Thyroid 2010;20:135–146.

34. International Osteoporosis Foundation. Osteoporosis in men: Why change needs to happen. Available at: http://share.iofbonehealth.org/WOD/2014/thematic-report/WOD14-Report.pdf. Accessed April 1, 2015.

35. Gennari L, Bilezikian JP. Osteoporosis in men. Endocrinol Metab Clin North Am 2007;36:399–419.

36. Roberts SE, Goldacre MJ. Time trends and demography of mortality after fractured neck of femur in an English population, 1968-98: Database study. BMJ 2003;327:771–775.

37. Goldacre MJ, Roberts SE, Yeates D. Mortality after admission to hospital with fractured neck of femur: Database study. BMJ 2002;325:868–869.

38. Parker MJ, Anand JK. What is the true mortality of hip fractures? Public Health 1991;105:443–446.

39. Cauley JA, Thompson DE, Ensrud KC et al. Risk of mortality following clinical fractures. Osteoporos Int 2000;11:556–561.

CME This article is available for continuing medical education credit at CME.TheOncologist.com.

CME