Clinical aspects of endogenous hypothyroidism and subclinical hyperthyroidism in patients with differentiated thyroid carcinoma

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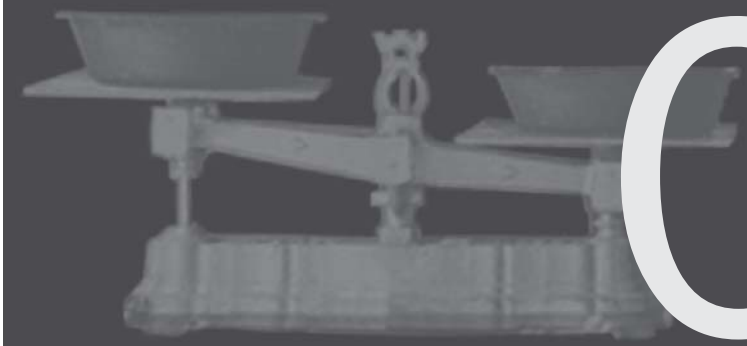

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The Effects of Thyrotropin Suppressive Therapy on Bone Metabolism in Patients with Well-Differentiated Thyroid Carcinoma

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Abstract

Patients with differentiated thyroid carcinoma (DTC) are commonly treated long-term with thyrotropin (TSH)-suppressive thyroxin replacement therapy resolving in a state of subclinical hyperthyroidism. The relationship between subclinical hyperthyroidism and osteoporosis is not clear. In this review, we systematically selected and analyzed 21 studies addressing this issue. Although multiple methodological differences between studies prevented a structured meta- analysis, our data suggest that postmenopausal women with subclinical hyperthyroidism are most at risk, whereas no increased risk was observed in men and premenopausal women. Based on these findings we believe that measurement of bone mineral density is recommended in postmenopausal women with DTC starting TSH suppressive therapy. This should be subsequently regularly measured to enable timely intervention with bone protective agents.

Background

Differentiated thyroid carcinoma (DTC) is associated with an excellent prognosis, with reported 10-year survival rates reaching 90% (1). This is because of a combination of the favorable biological behaviour of the tumor as well as the availability of effective therapy in the form of total thyroidectomy followed by radioiodine ablation. After initial therapy, all patients with DTC are treated with high doses of thyroxin aiming at significantly suppressing thyrotropin (TSH) levels, the rationale of this approach is based on the potential harmful effects of TSH on tumor recurrence (2;3). One study demonstrated a preventive effect of TSH suppression on tumor recurrence or progression only in high risk DTC patients (4). However long-term TSH suppression may be associated with potential harmful effects, so a recent European Consensus Meeting on thyroid cancer (5), recommended that not all patients with DTC should be indiscriminately treated with TSH suppressive therapy because this represents in effect a state of subclinical hyperthyroidism, as defined by suppressed serum TSH levels in the presence of normal serum levels of (free) thyroxin. The question which clearly is to be answered is whether long-term TSH suppressive therapy is beneficial and safe in patients with DTC.

Subclinical hyperthyroidism has effects on carbohydrate metabolism (6), the cardiovascular system (7-11) and psychological well being (7;12). Whether subclinical hyperthyroidism also deleteriously affects the skeleton remains the subject of discussion (13;14).

Overt hyperthyroidism is associated with an increased risk for osteoporosis (15), the pathophysiology of which is multifactoral (16), including shortening of the bone remodelling cycle (17) and acceleration of bone turnover (18). Thyroid hormone indirectly promotes osteoclast formation and activation by inducing the expression of cytokines, prostaglandins and the receptor activator of nuclear factor NF-κB ligand (RANKL) (16;19;20). RANKL is the key molecule in osteoclast differentiation. It binds to its receptor, RANK, which is expressed on dendritic cells, T cells, osteoclast precursors and mature osteoclasts (21;22). RANKL increases the survival of RANK positive T cells (21), promotes osteoclast differentiation (23-27), stimulates the activity of mature osteoclasts (24;28;29) and promotes survival of osteoclasts by preventing apoptosis (29). Osteoclast differentiation is also stimulated by contact with stromal cells and M-CSF (30;31). Thyroid hormone also inhibits chondrocyte proliferation and promotes hypertrophic differentiation, mineralization, matrix synthesis but also apoptosis of chondrocytes in the growth plate. An exciting new development has been the discovery of functional TSH receptors in bone (32;33) because of the implication that effects that traditionally have been attributed to high thyroid hormone levels may be in effect related to low TSH levels.

The relationship between subclinical hyperthyroidism and osteoporosis is not clear. Several studies have addressed this issue, but there is no consensus largely because of differences in study design, included patient groups, methodology used, follow-up time and choice of outcome parameters. It is of note that although the role of subclinical hyperthyroidism in the pathogenesis of osteoporosis has been the topic of several reviews, no attempt has been made to categorize the original studies so far published according to the various parameters above mentioned. In this review, all clinical studies on TSH suppressive thyroxin therapy in thyroid cancer patients have been systematically selected for analysis.

Methods

Searches of Medline, Cochrane and EMBASE were conducted using the keywords: “thyroid cancer AND bone mineral density”, “thyroid cancer AND osteoporosis” and “thyroid cancer AND bone metabolism”. Our aim was to include all studies in which patients with DTC were treated with TSH suppressive thyroxin therapy. We restricted our search to publications in “English language”, on “Human subjects” and “articles containing Abstracts”. The last search was conducted on January 17, 2006. Of the initial 230 publications found, 32 publications fulfilled these criteria and were selected for detailed analysis.

Each study included was scored semi-quantitatively by assessing the following: whether hormonal state of female patients was mentioned; whether they were estrogen-replete or -deplete; whether additional risk factors for osteoporosis were reported; whether a control group was included; whether duration of follow-up was shorter or longer than 5 years; and whether TSH concentrations were adequately suppressed. Eleven studies were excluded on the basis of insufficient data: Mikosch *et al.* (34) and Rosen *et al.* (35) did not report the duration of thyroxin therapy. Rosen and coworkers included patients who were taking thyroid hormone for at least 6 months. In one study patients did not have sufficiently suppressed serum TSH concentrations (36). Guo *et al.* (37) and Gonzalez *et al.* (38) did not report serum TSH levels. Mikosch *et al.* (34;39) and Taimelia *et al.* (40) did not measure bone mineral density. Subanalysis according to gender and menopausal state were not performed in two studies (35;41). In an additional 4 studies (40-43), it was not indicated if other risk factors for osteoporosis were investigated. The last 4 studies (38;40;42;44) lacked control groups.
Twenty-one studies fulfilling all criteria were finally included in the analysis, the following parameters were documented: study design, number of patients included, age, gender, hormonal status of female patients, additional risk factors for osteoporosis, dose of thyroxin prescribed, serum level of TSH, duration of TSH-suppressive therapy, the presence of a control group and the final outcome based on differences in bone mineral density (BMD). The studies were categorized according to gender and menopausal state and subgroup analyses undertaken accordingly.
Although we set out to conduct a structural meta-analysis, the heterogeneity of the available data did not allow us to do so.

Results

The results of the analyses are shown in Tables 1-5. Almost all studies excluded patients with diseases and those using glucocorticoids or other drugs potentially affecting bone metabolism. Of the 21 studies included, 4 of 6 prospective studies reported a significant decrease in BMD with time on treatment, as in 4 of 17 cross-sectional studies there was a significant difference in BMD between DTC patients and controls. The results of the subgroup analyses according to gender and menopausal state were as follows:

Premenopausal women
The effect of TSH suppressive therapy in premenopausal women is described in 15 studies, of which 12 had a cross-sectional design and 4 were prospective studies (Table 1 and 2). Two cross-sectional studies found a significant decrease in BMD in DTC patients receiving TSH suppressive therapy compared to controls: Jodar *et al*. (45) evaluated 37 DTC patients, significantly lower BMD of the distal radius was found in DTC patients compared to controls; although, this was still within the normal range for age and gender. There was a significantly positive relationship between thyroxin dose and lumbar spine and distal radius BMD. Diamond *et al*. (46) evaluated 14 DTC patients. BMD of the femoral neck in DTC patients was significantly lower (-10.6%) than in age-, gender- and menopausal state-matched controls. There were no significant differences between patients and controls in the other cross-sectional studies analyzed.
Two of the prospective studies found a significant effect of TSH suppressive therapy on BMD. Jodar *et al*. (45) studied 14 DTC patients for 18 months. He reported that BMD of the femoral neck was significantly lower in DTC patients than in age-, gender-, body- weight- and menopausal state-matched controls. There were no differences observed between premenopausal and postmenopausal women. Sijanovic *et al.* (47) studied 19 premenopausal women. There was a significant reduction in BMD of the distal radius after 4 years of follow-up.

Table 1. Premenopausal women Cross-sectional studies

Author	Patients (N)	Duration (Years)	L-thyroxin Dose (µg/day)	TSH (mU/L)	Controls	Outcome (BMD (z-scores), unless otherwise indicated)
Franklyn (13)	18	7.7 (1-19)	217 (100-300)	0.67 ± 2.20	Yes	NS
Jodar (45)	37	5.4 ± 2.8	177 ± 43	0.61 ± 1.18	Yes	BMD (z-score): DTR : -0.84 ± 1.00 (significant below 0)
Toivonen (64)	15	9-11	215 ± 53	<0.05	Yes	NS
Marcocci (65)	47 (38 DTC)	10.1 Median: 9.2 (5-28)	154.3 ± 5	No quantitative data	Yes	NS
Stepan (50)	20	6.0 ± 5.2	151.1 ± 47.1	0.10 (0.01-3.80)	Yes	NS
Goerres (66)	7	5.7 ± 6.8	Cumulative dose: 7124.5 ± 9448.6 µg/kg	0.019 ± 0.056	Yes	NS
Gianinni (67)	12	9.25 ± 0.9	152.1 ± 3.72	<0.1	Yes	NS
Diamond (46)	14	10.7 ± 1.7	Cumulative dose: 816 ± 159 mg	No quantitative data	Yes	FN 0.98 ± 0.03 vs. 1.03 ± 0.01 (p=0.01)
Florkowski (68)	20	Median: 9.6 (3-42)	167 (125-300)	< 0.2 mU/l	No	NS
Chen (69)	44	7.2 ± 2.8	No quantitative data	1.98 ± 0.44 n=22 partly suppressive n=22 suppressive	Yes	NS
Heijckmann (70)	26	Median: 4 (1-14)	2.2 ± 0.5 µg/kg/day	0.06 (< 0.05-0.35)	No	NS
Reverter (71)	44	12 ± 5	195 ± 43	0.03 ± 0.03	Yes	NS

All values expressed as mean±SD unless indicated otherwise, DTR: Distal Third of the Radius; FN: Femoral Neck, NS=Not significant

Table 2. Premenopausal women Longitudinal studies

Author	Patients (N)	Duration (Years)	L-thyroxin Dose (µg/day)	TSH (mU/L)	Controls	Outcome (BMD (z-scores) unless otherwise indicated)
Jodar (45)	14	5.4 ± 2.8	177 ± 43	0.61 ± 1.18	Yes	BMD (z-score): DTR: -0.84 ± 1.00 (significant below 0) FN: (% year): -1.50 ± 3.18 (patients) vs. -0.24 ± 1.32 (controls) (p<0.05)
Muller (48)	15	11.2 ± 0.9	200 ± 7	0.09 ± 0.01	Yes	NS
Sijanovic (47)	19 (p<0.05)	9.4 ± 6.4	171 ± 30	0.07 ± 0.062	Yes	DR baseline: 0.670 ± 0.037 4 y: 0.657 ± 0.039
Karner (54)	19	9.4 ± 6.4	171 ± 30	0.07 ± 0.62	No	NS

All values expressed as mean±SD unless indicated otherwise, DTR: Distal Third of the Radius; FN: Femoral Neck, DR= Distal Radius, NS=Not significant

A significant negative correlation was found between thyroxin dose and BMD of the distal radius. Muller *et al.* (48) studied 23 patients: 8 with a non-toxic goitre and 15 DTC, who were followed up for an average of 1.5 years. There were no significant differences in BMD of the lumbar spine, femoral neck, trunk and extremities between patients and age-, gender-, body mass index (BMI)- and years of menopause-matched controls.

Postmenopausal women

The effect of TSH suppressive therapy in post-menopausal women was investigated in 16 studies (Table 3 and 4). Fourteen studies were cross-sectional. Four found a significant difference in BMD between patients and controls. Kung *et al*. (49) studied 34 postmenopausal women. The patients had a significant lower BMD than age-, gender- and menopausal state-matched controls. Jodar *et al.* (45) studied 39 patients. Average TSH levels were 0.50 ± 1.28 mU/l. BMD of the distal radius was significantly lower than the average of controls, although is was still within the normal range. Stepan *et al.* (50) studied 15 patients using both thyroxin and liothyronine. BMD of the lumbar spine was significantly decreased compared to matched controls. Diamond *et al*. (46) studied 10 postmenopausal women. BMD measurements at the lumbar spine, femoral neck and forearm were significantly lower than those of matched controls. There were no differences in BMD observed between patients and controls in the remaining cross-sectional studies analyzed.

There was a significant difference in 2 of the 4 prospective studies analysed. Jodar *et al*. (45) studied 13 postmenopausal women for a period of 2.25 ± 0.6 years. BMD of the femoral neck was significantly lower in DTC patients than in matched controls. Kung *et al*. (51)studied 46 patients who were randomly assigned to treatment with calcitonin and calcium (n=16), calcium (n=15) or placebo (n=15) and followed for 2 years. At the end of the two years, the BMD of patients treated with calcitonin or calcium remained unchanged, whereas BMD was significantly lower in the placebo-group. In the other 2 analyzed studies (48;52) there were no differences in BMD.

Table 3. Postmenopausal women Cross-sectional studies

Author	Patients (N)	Duration (Years)	L-thyroxin Dose (µg/day)	TSH (mU/L)	Controls	Outcome (BMD (z-scores) unless otherwise indicated)
Hawkins (72)	21	6.2 ± 2.5	158.3 ± 43.7	0.03 ± 0.4 80% < 0.3	Yes	NS
Kung (49)	34	12.2 ± 6.6	179 ± 60	< 0.05	Yes	Values versus controls: BMC 1 total body 1652 ± 356 vs. 1994 ± 270 p<0.005) LS 2 0.749 ± 0.147 vs. 0.917 ± 0.161 (P<0.005) FN 3 0.622 ± 0.123vs 0.708 ± 0.127 (p<0.01) T 4 0.552 ± 0.115 vs. 0.635 ± 0.119 (p<0.001) WT 5 0.554 ± 0.139 vs. 0.630 ± 0.144 (p<0.005)
Franklyn (13)	26	8.1 (1-19)	175 (100-200)	0.26 ± 0.54	Yes	NS
Jodar (45)	39	5.8 ± 2.9	160 ± 38	0.50 ± 1.28	Yes	DTR 6 -0.77 ± 0.98 (significant below 0)
Toivonen (64)	10	9-11	215 ± 53	< 0.05	Yes	NS
Stepan (50)	25	7.4 ± 4.5	148.7 ± 49.4	0.05 (0.01-2.26)	Yes	LS -1.08 ± 1.40 vs. -0.05 ± 0.98 (controls, p<0.01)
Goerres (66)	23	10.3 ± 4.4	Cumulative dose: 9195.8 ± 5193 µg/kg	0.019 ± 0.056	Yes	NS
Diamond (46)	10	5.9 ± 1.0	Cumulative dose: 337 ± 72 mg	No quantitative data	Yes	LS 0.876 ± 0.04 vs. 1.069 ± 0.04 (-16% vs. controls, p<0.01) FN 0.702 ± 0.03 vs. 0.916 ± 0.02 (-15%), p<0.001) Forearm 33.5 ± 1.3 vs. 38.8 ± 1.5 (-11%, p<0.05)
Fujiyama (52)	24	11.6 ± 7.36 14.8 ± 9.43	152.1 ± 22.51 95.83 ± 50.94	n=12: < 0.1 n=12: > 0.1	No	NS
Gianinni (67)	13	6.0 ± 1.5	144.2 ± 4.15	< 0.1	Yes	NS
Florkowski (68)	18	9.6 (3-42)	167 (125-300)	< 0.2	No	NS
Chen (69)	25	7.8 ± 3.1	No quantitative data	1.76 ± 0.41 n=8 partly suppressive n=17 suppressive	Yes	NS
Heijckmann (70)	14	median: 5.5 (1-52)	2.2 ± 0.5 µg/kg/day	0.06 (< 0.05-0.35)	No	NS
Reverter (71)	44	12 ± 5	195 ± 43	0.03 ± 0.03	Yes	NS

All values expressed as mean±SD unless indicated otherwise. 1 BMC=Bone Mineral Content, 2 LS=Lumbar Spine, 3 FN=Femoral Neck, 4 T=Trochanter, 5 WT=Ward's triangle, 6 DTR= Distal Third of the Radius, NS=not significant

Table 4. Postmenopausal women Longitudinal studies

Author	Patients (N)	Duration (Years)	L-thyroxin Dose (µg/day)	TSH (mU/L)	Controls	Outcome (BMD (z-scores) unless otherwise indicated)
Jodar (45)	39 13	5.8 ± 2.9	160 ± 38	0.50 ± 1.28	Yes	FN change (%/year): -1.50 ± 3.18 vs. -0.24 ± 1.32 (p<0.05)
Muller (48)	10	11.2 ± 0.9	200 ± 7	0.09 ± 0.01	Yes	NS
Kung (51)	46	2	2	< 0.03	No	LS1 -5% vs. baseline FN2 -6.7% T3 -4.7% WT4 -8.8%
Fujiyama (52)	24	11.6 ± 7.36 14.8 ± 9.43	152.1 ± 22.51 95.83 ± 50.94	n=12: < 0.1 n=12: > 0.1	No	NS

All values expressed as mean±SD unless indicated otherwise. 1 LS=Lumbar Spine, 2 FN=Femoral Neck, 3 T=Trochanter, 4 WT=Ward's triangle

Men

Eight studies selected for analysis addressed the effects of TSH suppressive therapy on bone metabolism in men in a cross-sectional study design (table 5). One study was longitudinal (table 6). Only one cross-sectional study found a significant difference between patients and controls. Jodar *et al*. (53) studied 49 men, of whom 17 were treated for DTC and 32 were treated for Graves' disease. DTC patients had a mean TSH concentration of 0.20 ± 0.27 mU/mL. Graves' disease patients had a mean TSH concentration of 1.07 ± 1.85 mU/mL. BMD of patients with Graves' disease and DTC were significantly lower than that of controls. In the longitudinal study (54), 9 men were studied for one year. A significant bone loss at the distal radius, but not the lumbar spine and femoral neck was found.

Discussion

The clinical implications of long-term suppressive thyroxin therapy on bone are critical, largely because of the favourable prognosis of DTC. However, the potential deleterious effects of TSH suppressive therapy on the skeleton remain controversial. Our aim was to review the literature on the effects of TSH-suppressive therapy on bone metabolism focussing on reported changes in BMD measurements. There are many differences in the outcome of studies addressing this issue so that we have systematically categorized studies according to predefined criteria in an attempt to reach a more uniform conclusion.

The majority of studies do not report an effect of TSH suppressive therapy on BMD in men and premenopausal women. A significant effect of TSH-suppressive thyroxin replacement on BMD is reported in a substantial number of studies conducted in postmenopausal women. This suggests that there may indeed be a relevant effect of TSH-suppressive therapy on bone mass in postmenopausal women, whereas these effects are not clear in men and in premenopausal women. This conclusion is in agreement with that of other reviews and meta-analyses addressing this issue (14;15;55-57). Another important aspect of TSH suppressive therapy in young patients is that it may affect bone development and the peak bone mass as investigated together with the contribution of hypoparathyroidism by Schneider *et al*. (58).

Table 5. Men Cross-sectional studies

Author	Patients (N)	Duration (Years)	L-thyroxin Dose (µg/day)	TSH (mU/L)	Controls	Outcome (BMD (z-scores) unless otherwise indicated)
Franklyn (13)	5	7.9 (2-15)	180 (100-200	0.36 ± 0.57 n=2 <0.05 mU/l n=3 normal/smaller than normal	Yes	NS
Jodar (53)	49 (17 DTC)	9.1 ± 4.9	193 ± 50	0.20 ± 0.27	No	LS 1 -0.64 ± 1.22(p=0.046) FN 2 -0.49 ± 0.62 (p=0.007) WT 3 -0.50 ± 0.62 (p=0.004)
Toivonen (64)	4	9-11	215 ± 53	< 0.05	Yes	NS
Marcocci (73)	34 (26 DTC)	10.2 ± 0.8	172 ± 5.9	n=26 undetectable n=6: 0.1 n=2: 0.2	Yes	NS
Stepan (50)	13	4.6 ± 3.0	148.6 ± 55.8	0.06 (0.01-2.49)	Yes	NS
Goerres (66)	17	8.1 ± 5.2	Cumulative dose: 8200.4 ± 5907.0 µg/kg	0.019 ± 0.056	Yes	NS
Florkowski (68)	6	9.6 (3-42)	167 (125-300)	< 0.2	No	NS
Heijckmann (70)	19	median: 6 (1-22)	2.2 ± 0.5 µg/kg/day	0.06 (<0.05-0.35)	No	NS

All values expressed as mean±SD unless indicated otherwise, 1 LS=Lumbar Spine, 2 FN=Femoral Neck, 3 WT=Ward's triangle, NS=not significant

Table 6. Men Longitudinal studies

Author	Patients (N)	Duration (Years)	L-thyroxin Dose (µg/day)	TSH (mU/L)	Controls	Outcome (BMD (z-scores) unless otherwise indicated)
Karner (54)	9	8.1 ± 6.0	200 ± 50	0.06 ± 0.09	No	S BMD DR 0.748 ± 0.086 vs. 0.732 ± 0.083, p<0.05

All values expressed as mean±SD unless indicated otherwise. TSH, thyrotropin; DR, Distal Radius

Estrogen deprivation is the most common cause of osteoporosis. The removal of the physiological block by gonodal steroid hormones allows the release of inflammatory cytokines which in turn enhance the production of M-CSF and RANKL. RANKL is identified as an essential cytokine for the formation and activation of osteoclasts (23;24;59). This effect could be enhanced by the subclinical hyperthyroid state resulting from TSH suppressive therapy. Hofbauer *et al* (59) found that TSH inhibits RANKL mRNA levels by 60 % and upregulates OPG mRNA levels threefold. OPG inhibits osteoclastogenesis by binding to RANKL (27;59-61), thus preventing RANK-RANKL interactions. In the subclinical hyperthyroid state, TSH levels are suppressed resulting in an absence of this block.

The discrepancy in outcome between studies in postmenopausal women might be explained by a difference in duration of thyroxin therapy or additional risk factors. However, no differences in duration of thyroxin therapy or additional risk factors such as smoking, calcium intake, alcohol abuse, and physical activity were observed. A third explanation could be a difference in methodological approaches. However, all authors used BMD measurements to examine the effect of TSH-suppressive therapy on bone mass. Another explanation could be the instability of the TSH concentration in the years of TSH-suppressive therapy as suggested in the study of Pujol *et al*. (62). Other possible factors could be differences in study population with regard to additional determinants of BMD such as dietary factors, physical exercise, endogenous factors and genetic susceptibility, which become relevant only once the powerful contribution of estrogens has disappeared in postmenopausal women (63). For instance, Kung *et al* mentioned that the patients taking part in the study had a low dietary calcium (51)

Regardless of these considerations it is clear that postmenopausal women with DTC treated with TSH-suppressive therapy are most at risk for bone loss. It has also been shown that bone protecting agents such as bisphosphonates are effective in preventing bone loss in patients with DTC on TSH-suppressive therapy (35) The availability of therapeutic interventions that beneficially influence skeletal morbidity in patients with a low bone mass and consequently risk of fractures dictates that patients at high risk should be screened using BMD measurements. We have identified postmenopausal women with DTC receiving TSH suppressive therapy as a high risk group for bone loss. Based on our analysis of available data we strongly advise screening this group of patients at start of TSH suppressive therapy and at regular intervals to allow timely intervention with bone protective agents.

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