

A grayscale image of a human spine, viewed from the side. Two vertebrae are highlighted with black outlines, one in the upper thoracic region and one in the lower thoracic region. The rest of the spine is in a lighter, semi-transparent gray.

Chapter 3

Hip bone mineral density, bone turnover
and risk of fracture in patients on long-term
suppressive L-thyroxine therapy for
differentiated thyroid carcinoma

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Abstract

Background

Untreated hyperthyroidism and treatment with high doses of thyroid hormone are associated with osteoporosis. However, their effect on bone turnover, their contribution to bone mineral density (BMD) in the context of other clinical risk factors for osteoporosis and the prevalence of vertebral fractures is not well documented.

Methods

We studied 59 patients receiving L-thyroxine suppressive therapy for differentiated thyroid carcinoma (DTC). BMD of the hip was measured by dual X-ray absorptiometry (DXA) and lateral DXA pictures of the lumbar and thoracic vertebrae were performed. Bone resorption was measured by carboxy-terminal cross-linked telopeptide or type 1 collagen (ICTP) and bone formation by procollagen type I amino-terminal propeptide (PINP). Clinical risk factors for osteoporosis were evaluated using a questionnaire.

Results

Z-scores of BMD were similar as the NHANES (National Health and Nutrition Examination Survey) III reference group in women and men, also after long-term (≥ 10 years) suppression therapy. Patients in the lowest and highest quartile of BMD showed significant differences in the presence of clinical risk factors. ICTP levels were significantly higher than in age-matched controls, PINP levels were not different. We found four patients with a prevalent vertebral deformity.

Conclusions

We conclude that patients with well-differentiated thyroid carcinoma are not at increased risk of developing low bone mass nor have a higher prevalence of vertebral deformities at least when treated with relatively low doses of L-thyroxine.

Introduction

Patients with differentiated thyroid carcinoma (DTC) usually have a good prognosis and a near normal life expectancy. After initial ablative treatment with radioactive iodine these patients are treated with L-thyroxine (L-T4) in relatively high doses in order to suppress endogenous thyrotropin (TSH) levels and to minimize potential TSH-mediated stimulation of tumor growth.^{1,2} Adequate monitoring of TSH suppression has become possible since the development of second and third generation TSH assays.^{3,4} The degree of TSH lowering required to obtain maximal suppression of tumor growth has been subject of discussion.⁵⁻⁸ Most recommendations suggest maintaining TSH levels lower than 0.1 mU/l¹, although in recent guidelines TSH levels between 0.1 and 0.5 mU/l are recommended in case there is no residual disease after one year in low risk DTC patients.⁹ Long-term administration of supraphysiological doses of L-T4 may have adverse side-effects. In addition to physical discomfort, loss of weight, atrial fibrillation and cardiac dysfunction,^{10,11} the possible negative effects on bone mineral density (BMD) and bone remodelling resulting in osteopenia and loss of bone strength are an important issue.¹² Several mechanisms may be involved in the development of osteopenia secondary to suppressive therapy with L-T4 such as direct or indirect stimulation of osteoclast activity by this hormone. Recently also direct effects of TSH on bone remodelling have been described.¹³ TSH inhibits osteoclast formation and survival and also inhibits osteoblast differentiation, and is therefore a negative regulator of skeletal remodelling.

Loss of bone mass is a uniform feature of overt hyperthyroidism; in several studies a bone loss of 10-20% has been reported.¹⁴⁻¹⁶ A history of overt hyperthyroidism is a risk factor for hip fracture later in life,^{17,18} and is one of the causes of excess late mortality in previously hyperthyroid patients.¹⁹ Symptomatic bone disease is not a prominent feature of subclinical hyperthyroidism. However, mild (subclinical) hyperthyroidism in subjects with multinodular goiter was associated with decreased forearm bone density, while in postmenopausal women with hyperthyroidism who were treated with methimazole a higher bone density of the distal forearm was found compared to untreated women.^{20,21} In addition the risk of osteoporotic fractures may be increased.²²

Studies in patients with suppressive L-T4 therapy for DTC have generated conflicting results. Some authors²³⁻²⁶ found no evidence of lower bone mass in this patient group, while others reported more or less deleterious effects on bone mass.²⁷⁻²⁹ In most of these studies numbers were however small, patient selection was not well defined and characterization of patients was limited.

The aim of our study was to evaluate the impact of long-term suppressive therapy with L-T4 on BMD in a large cohort of well-characterized patients with

DTC, and in the subgroup of patients with suppressive therapy for more than 10 years. In addition, the prevalence of vertebral deformities was assessed and markers of bone formation and resorption were measured in serum.

Subjects and methods

Patients

Between January 2002 and July 2003 all 85 patients with differentiated thyroid carcinoma from the outpatient clinic of the University Hospital Maastricht were asked to take part in this cross-sectional study. Sixty patients agreed to participate. They all had undergone total thyroidectomy and radioactive iodine ablation and were taking a suppressive dose of L-T4 (goal of therapy: TSH <0.05 mU/l) for a median period of five years (range 1-52 years). In the last six months prior to entering this study, TSH-levels were below 0.05 mU/l in 32 patients and below 0.6 mU/l in the remaining subjects (mean TSH in the total group 0.06 mU/l, range <0.05-0.6 mU/l). One patient who had a TSH-level of 6.1 mU/l was excluded from the study. Therefore complete data are available from 59 patients; written informed consent was obtained in all. To affirm that this patient group was under continuous suppressive therapy with L-T4 we checked serial serum TSH levels in a group of 32 patients with suppressive dose of L-T4 for more than five years resulting in a mean TSH of 0.06 mU/l (range <0.05-0.35 mU/l).

The general characteristics of the patients studied are summarized in Table 3.1. Of the 40 women, 26 were premenopausal and 14 postmenopausal. All patients had histologically proven differentiated papillary or follicular thyroid cancer. FT4 levels were 21.9 ± 3.3 pmol/l (reference parameter: 8-18 pmol/l) and the mean dose of L-T4 therapy was 2.2 ± 0.5 mcg/kg/day. Ten patients used a vitamin D analogue and calcium supplementation because of postoperative hypoparathyroidism. None of the patients had taken estrogen replacement therapy or bisphosphonates.

Calcium intake of all patients was assessed on the basis of a detailed dietary list. Risk factors for osteoporosis as well as daily activities and exercise were assessed by a validated questionnaire,³⁰ in which sports, daily and work activities are scored with a minimum of zero and a maximum of eighteen. None of the 25 patients who declined to participate had impaired mobility or symptoms related to vertebral fractures. Mean age of this group was 49 years and there were seven postmenopausal women in this group.

Table 3.1 Patient characteristics.

Variable	Female		Male n=19
	premenopausal n=26	postmenopausal n=14	
Age (years)	40 ± 7	63 ± 9	52 ± 12
Body mass index (kg/m ²)	24.4 ± 3.2	25.5 ± 3.5	28.8 ± 3.2
Years of suppressive therapy	4 (1-14)	5.5 (1-52)	6 (1-22)
Postop. hypoparathyroidism	6	1	3
Dose L-T ₄ (µ/kg per day)	2.3 ± 0.5	1.9 ± 0.4	2.2 ± 0.5
Papillary carcinoma	13	8	12
Follicular carcinoma	10	4	6
Mixed carcinoma	3	2	1
Serum FT ₄ (pmol/l)	22.0 ± 3.2	22.7 ± 3.8	21.1 ± 3.2

Data are given as mean ± SD, median (range) or numbers if appropriate; Reference parameters: serum FT₄ 8-18 pmol/l; Abbreviations: L-T₄, L-thyroxine; FT₄, free thyroxine.

BMD and morphometric measurements

BMD of the hip was measured by dual energy X-ray absorption (DXA, Hologic QDR 4500, NHANES-III reference group). The hip was measured in the standard projection, and results were reported for femoral neck, trochanter and total hip. No data on bone mineral density of the lumbar spine were obtained. Standard procedures supplied by the manufacturer for scanning and analysis were performed. Calibration with the manufacturer's spine phantom and quality control analysis were performed daily. The coefficient of variation for BMD measurements was 1.0%.

Furthermore after bone density measurements, a lateral single energy densitometry of the spine for vertebral fracture assessment was performed. This was done by one classified and experienced person with morphometry. Anterior, middle and posterior heights were recorded in all vertebrae from T4 to L4 (if possible). On the basis of these morphometric measurements prevalent vertebral deformity was defined as a reduction of height of 20% or more (Genant method³¹).

Laboratory assays

All serum samples were frozen at -20°C immediately after collection. All analyses were measured within one badge at the same time to reduce variability. Serum TSH was measured using the commercially available delayed enhanced Lanthanide fluorescence immunometric assay (DELFLIA-method, Perkin Elmer, Wallac, Turku, Finland), measured on an automatic immunoanalyser of the same manufacturer. Serum FT₄ was measured using a commercially available solid phase fluoroimmunoassay (DELFLIA-method,

Perkin Elmer, Wallac, Turku, Finland); the normal reference range in our laboratory is 8-18 pmol/l. As marker for bone formation serum procollagen type I amino-terminal propeptide (PINP) was measured and as marker for bone resorption serum level of carboxy-terminal cross-linked telopeptide of type I collagen (ICTP). PINP and ICTP were determined using commercial RIA kits (Orion Diagnostica Oy, Espoo, Finland). For PINP the interassay coefficient of variation was 3.2%, the intraassay CV 2.5% and the lowest detectable concentration was found to be 0.4 µg/l. For ICTP the interassay CV was 3.5%, the intraassay CV 2.3% and the lowest detectable concentration was found to be lower than 0.1 µg/l.

Study samples were compared to serum samples from age and sex-matched controls.

All gave informed consent. None of them were known to have thyroid diseases, and all had normal physical examination and normal results of routine lab measurements.

Statistical analysis

Results are reported as mean \pm SD or median and (range) where appropriate. T- and Z-scores of the femoral neck, trochanter and total hip (using NHANES-III) were calculated for the total group, for men, for pre- and postmenopausal women, and for a group of patients who received suppressive L-T4 therapy for ten years or more. Comparison between groups was done using Student t-test with correction for multiple comparisons among groups if the data were normally distributed and by Kruskal-Wallis test if the data were not normally distributed. Pearson's correlations were used to calculate the relationship between BMD and duration of suppressive therapy. To assess the influence of confounding factors on the bone mineral density measurements, a multiple regression analysis (stepwise method) was performed with BMD of the total hip (Z-score) as a dependent variable and known risk factors for osteoporosis (weight below 60 kg, hip fracture mother, fractures in previous medical history, postmenopausal state and corticosteroid use), duration of suppressive therapy, BMI, calcium intake, physical activity, L-T4 /kg per day, serum FT4, and postoperative hypoparathyroidism as independent variables. Another multiple regression analysis (stepwise method) was done with BMD Z-scores as dependent variable and age, weight, L-T4 /kg per day, serum FT4, number of risk factors and physical activity index as independent variables. Patients in the highest and lowest quartile of BMD T-scores were compared on presence of risk factors with a chi-square test. All analyses were done using SPSS (version 11.5). A p-value below 0.05 was considered statistically significant.

Results

BMD and general characteristics

Relative to the background population (NHANES reference group) bone mineral density was not decreased in the three study groups (Table 3.2). Five patients (two men, three postmenopausal women) had a T-score ≤ -2.5 in the femoral neck or trochanter and thus met the WHO-criteria for osteoporosis. Fifteen patients had suppressive L-T4 therapy for ≥ 10 years (median 14 yrs, range 10-52 yrs). Also in these patients no difference in BMD relative to age-matched controls (Z-score total hip: median 0.40 (range -1.3–1.4) was observed, and no correlation was found between the duration of suppressive therapy and BMD of the hip ($r=0.01$, $p=0.91$). Moreover we compared the group of subjects with TSH levels below 0.05 with the patients who had a slightly higher TSH and these groups were similar with regards to T-score and Z-score of total hip. BMD of the hip was also not different in patients with or without postoperative hypoparathyroidism (Z-score 0.49 versus 0.34), although the Z-score of the femoral neck was slightly higher in patients with postoperative hypoparathyroidism (0.70 versus 0.05, $p=0.029$).

Table 3.2 BMD variables.

	Female		Male
	premenopausal n=26	postmenopausal n=14	n=19
Z-score			
total hip	0.44 \pm 0.87	0.23 \pm 1.07	0.37 \pm 0.84
femoral neck	0.22 \pm 0.81	0.12 \pm 0.95	0.09 \pm 0.93
trochanter	0.61 \pm 1.10	0.29 \pm 1.03	0.49 \pm 0.91

Data are expressed as mean \pm SD

Data regarding the presence of risk factors for osteoporosis and the daily calcium intake and physical activities have been summarized in Table 3.3. The activity index had a mean of nearly ten reflecting an average in showing activities in this patient group. The calcium intake is with a mean of 807 mg/day moderate and insufficient for the postmenopausal group.

Table 3.3 Risk factors and questionnaires.

	Female		Male
	premenopausal	postmenopausal	
Number	26	14	19
Years since menopause		12 ± 10	
Fracture >50 years	0	1	1
Vertebral fracture	1	1	2
Hip fracture mother	0	4	1
Low body weight (<60 kg)	3	5	0
Immobilisation	0	0	0
Corticosteroids in last 10 years	0	0	0
Calcium intake (mg/day)	810 ± 357	782 ± 290	822 ± 326
Physical activity (Elders)	10.6 ± 4.0	8.6 ± 4.1	9.9 ± 3.6

Data are given as mean ± SD or number.

Multiple regression analysis, including age, weight, L-T4 /kg per day, serum FT4, number of risk factors and physical activity, revealed that higher body weight was a significant contributor to BMD of the total hip as expressed as Z-score. There were 22 patients with in total 33 known clinical risk factors (postmenopausal state, hip fracture mother, vertebral deformity, fracture >50 year, body weight <60 kg, immobilization and corticosteroid use). Patients in the lowest and highest quartile of BMD (T-score of the total hip below -0.70, mean -1.4, and above 0.6, mean 1.03) showed differences in the presence of clinical risk factors as earlier defined: in the lowest quartile, eleven of fifteen patients had one or more risk factors, in the highest quartile, two of the fifteen patients had any risk factor ($p=0.001$) (Table 3.4).

Table 3.4 Number of patients with clinical risk factors in all 4 quartiles of BMD (T-score of total hip).

	Number of patients in quartile	Number of patients with one or more clinical risk factor
T-score ≤ -0.7	15	11
-0.7 < T-score ≤ 0	15	7
0 < T-score ≤ 0.5	14	2
T-score > 0.5	15	2

Markers of bone formation and resorption

Results of the measurement of markers of bone turnover are summarized in Table 3.5. Relative to an age matched control group, ICTP was increased by about 25% in all patient groups. PINP levels however, as marker of bone formation, did not significantly differ from the control group. Comparing patients with and without postoperative hypoparathyroidism, markers of bone formation (-44%, $p<0.05$) and resorption (-7%) were decreased in the

hypoparathyroidism group and this resulted in a slightly higher BMD mainly in the femoral neck.

Table 3.5 Bone markers total group (in serum in µg/l).

	Female				Male	
	premenopausal	controls	postmenopausal	controls	patients	controls
Number	24	24	10	10	19	19
ICTP (mg/l)	3.8 ± 1.3 ^a	3.0 ± .7	4.4 ± 1.0 ^a	3.3 ± 1.1	4.1 ± .9 ^a	3.5 ± 7
PINP (mg/l)	31.0 ± 17.3	28.4 ± 10.1	39.7 ± 21.1	42.8 ± 20.9	36.8 ± 15.5	37.2 ± 11.3

^a p<0.05 vs age matched controls; Abbreviations: ICTP, serum carboxy-terminal cross-linked telopeptide of type I collagen; PINP, serum procollagen type I amino-terminal propeptide.

Vertebral deformities

Fifty-four lateral DXA pictures of the lumbar and thoracic vertebrae were of adequate quality for the identification of vertebral deformities, suggestive of fracture. Four patients were found to have pre-existing vertebral deformity, i.e. 7% of patients; two men, one pre- and one postmenopausal woman. These patients did not report earlier fractures or pain episodes. All these patients had a BMD of the hip within the age-matched reference range (Z-score 0.53±0.91).

Discussion

This study demonstrates that long-term suppressive L-T4 therapy in patients with DTC does not result in reduced bone mineral density of the hip, neither in pre- and postmenopausal women nor in men. BMD, expressed as Z-score, was not correlated with duration of L-T4 therapy and even in patients with suppressive therapy for more than ten years no significant decrease in BMD was found.

The goal of suppressive L-T4 therapy is to maintain TSH levels <0.05 mU/l with a high normal FT4. In our study the dose needed to achieve this level of suppression was 2.2 µg/kg of body weight per day, which resulted in FT4 levels of 20% above the upper limit of normal. In all studies on this subject in which a significant bone loss was observed patients used a 30-50% higher dose of L-T4 compared to our patients.^(27-29, 32, 33) In a cross-sectional study Kung et al. found significantly lower BMD in the lumbar spine, femoral neck and trochanter (-18%, -12% and -13%) in a group of 34 postmenopausal women, and their L-T4 dose was 3.3 µg/kg of body weight per day.²⁸ The same group followed a small group of 15 postmenopausal women (3.0 µg L-T4 /kg of body weight per day) and found a bone loss of 6.7% in the total hip after two years,³² which could be prevented by calcium supplementation (1000 mg/day). Diamond et al

demonstrated a negative effect on BMD in both pre- and postmenopausal women ($n=24$)²⁷ with a mean L-T4 dose of 2.8 $\mu\text{g}/\text{kg}/\text{day}$ and found a significant correlation between the total cumulative dose of L-T4 and BMD, suggesting that overzealous L-T4 therapy may lead to bone loss. Studies in which doses lower than 2.5 $\mu\text{g}/\text{kg}$ body weight per day were used, such as the more recent study of Rosen et al.^{24,26,34} did not observe any negative effect on BMD. Before the introduction of second and third generation TSH assays in the late eighties, it was more difficult to monitor suppressive L-T4 therapy, because the detection limit was within the normal range. Therefore dosing of L-T4 could not be titrated optimally and was probably unnecessary high. These high L-T4 doses could affect BMD as was shown in the studies mentioned before. The presently available TSH assays are more sensitive and thereby allow better dose titration, thereby preventing unwanted loss of BMD.

The presence of postoperative parathyroid dysfunction could also contribute to the low incidence of osteoporosis in our population. PTH is generally thought to have a net catabolic effect on bone, including a more pronounced stimulatory effect on osteoclast than on osteoblast activity.³⁵ Abugassa et al. found a higher bone mass in the proximal femur, lumbar spine and distal radius in a group of thirteen patients treated with calcium and/or dihydroxyvitamin D₃ because of postoperative hypoparathyroidism after thyroidectomy for DTC, compared to patients with normal parathyroid function after the same surgical procedure.³⁶ We also found in the ten subjects with postsurgical hypoparathyroidism a significantly higher BMD of the femoral neck. However the total hip measurements showed no difference between these two groups, and mean Z-scores in the group without hypoparathyroidism were not lower than the reference population.

A total of five patients met the WHO criteria for osteoporosis in the measurements of total hip, trochanter or femoral neck BMD. Our risk factor analysis indicated that this group could be identified with the known clinical risk factors such as postmenopausal state, mother with hip fracture, fracture above 50 years, immobilization, corticosteroid use and low body weight.

Although no long-term effect on BMD was found, a significant increase of bone resorption as measured by serum levels of carboxy-terminal cross-linked telopeptide of type I collagen (ICTP) was observed. The marker of bone formation PINP was not altered. Other studies in DTC patients with suppressive L-T4 therapy reported an increase in markers of both bone formation and resorption. Kung reported increases in hydroxyproline in the urine of 130% and osteocalcin levels of 150%²⁸ suggesting increased bone turnover. It is not clear why this change in balance between bone formation and bone resorption in our patients did not lead to bone loss in the long-term. Perhaps the increase in bone resorption is not substantial enough to affect BMD. One might also speculate that the compliance with L-T4 therapy might be

lower in between hospital visits.^{37,38} Also a catch-up effect might have occurred in the periods of thyroid hormone withdrawal and subsequent hypothyroidism for diagnosis or treatment of recurrent or metastatic disease.

Vertebral fracture is a hallmark of osteoporosis. Only one of the previous studies in patients with DTC has evaluated prevalent vertebral fractures in a very small group (n=12) and reported no significant difference in the incidence of spinal deformities between TSH-suppressed patients and nonsuppressed patients.³⁹ We found four patients in this group (7%) with one or more vertebral deformities defined as a reduction of 20% or more of the anterior, middle or posterior height. In a very large cross-sectional population based study on the prevalence of vertebral deformity in European men and women (EVOS) in a group of 15570 males and females aged 50-79 years, a prevalent vertebral deformity was observed in 12% (range 6-21%).⁴⁰ We report 7% in a group with lower mean age; these patients did not have any clinical sign of vertebral fracture nor did they have a lower BMD of the hip. Although the group is small we have no indication that the prevalence of vertebral deformity is higher than in a European reference population.

We conclude that L-T4 therapy in doses which suppress TSH just below the detection limit of a second generation TSH assay, did not result in significant bone loss in our studied population and probably also not in increased fracture risk. We suggest that specific screening for osteoporosis in this patient group is therefore not recommended, other than on the basis of the known clinical risk factors.

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