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ORIGINAL ARTICLE

Bone mineral density and bone fracture in male patients receiving long-term suppressive levothyroxine treatment for differentiated thyroid carcinoma

Jordi L. Reverter · Eulàlia Colomé · Susana Holgado · Eva Aguilera · Berta Soldevila · Lourdes Mateo · Anna Sanmartí

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Abstract Studies on the effect of exogenous subclinical thyrotoxicosis on bone mineral density (BMD) in male patients treated with suppressive doses of levothyroxine for differentiated thyroid carcinoma (DTC) are not conclusive. In order to evaluate BMD (in femoral neck, lumbar spine, and distal radius) and bone fractures in men under long-term suppressive treatment with levothyroxine for DTC, we conducted a cross-sectional, retrospective study in 33 Caucasian men (mean ± SD age: 56 ± 14 years) under treatment for DTC. The control group comprised 33 healthy age- and body mass index-matched male volunteers. BMD was assessed by dual-energy X-ray absorptiometry (DXA). Bone turnover biomarkers (calcium, phosphate, alkaline phosphatase, PTH, vitamin D, urinary calcium, and N-Telopeptide/creatinine index) and testosterone were determined. Previous bone fractures were evaluated with a questionnaire and X-ray images of thoracic and lumbar vertebrae. Patients were treated for a mean duration of 15 ± 5 years. No differences were found between patients and controls in bone turnover biomarkers or areal BMD, T-scores or Z-scores in all sites evaluated. No earlier fractures or pain episodes were registered in either group and the incidence of asymptomatic vertebral fractures did not differ significantly between patient (18.8%) and control groups (16.7%), ($P = 0.9$). In conclusion, long-term suppressive treatment with levothyroxine in men with DTC does not appear to exert deleterious effects on bone mineral density or increase the prevalence of fracture.

Keywords Bone mineral density · Bone turnover biomarkers · Bone fracture · Thyroid cancer · Levothyroxine

J. L. Reverter (✉) · E. Colomé · E. Aguilera · B. Soldevila · A. Sanmartí
Department of Endocrinology and Nutrition, Germans Trias i Pujol University Hospital, Via Canyet s/n, 08916 Badalona, Barcelona, Spain
e-mail: reverter.germanstrias@gencat.cat

J. L. Reverter · E. Colomé · E. Aguilera · B. Soldevila · A. Sanmartí
Departament de Medicina, Universitat Autònoma de Barcelona, Badalona, Barcelona, Spain

S. Holgado · L. Mateo
Department of Rheumatology, Germans Trias i Pujol University Hospital, Via Canyet s/n, 08916 Badalona, Barcelona, Spain

Introduction

Differentiated thyroid carcinoma (DTC) (follicular and papillary) is an increasingly prevalent malignancy that affects mainly women [1]. Patients with DTC are treated with thyroidectomy, postoperative administration of radioiodine (I-131) whose aim is to destroy any thyroid residue in the thyroid bed, and long-term treatment with thyrotropin (TSH) suppressive therapy with levothyroxine (LT_4) to reduce the stimulatory effect of TSH on cancer cells. The favorable prognosis of DTC allows patients to live a long life with the condition of exogenous subclinical hyperthyroidism [2].

Overt hyperthyroidism is associated with accelerated bone remodeling, reduced bone density, osteoporosis, and an increased rate of fractures predominantly affecting cortical bone in the hip and forearm more than the trabecular bone in the spine [3]. However, the effect of subclinical hyperthyroidism (defined as a serum TSH concentration below the statistically defined lower limit of the reference range when serum FT_4 and T_3 concentrations are within their reference ranges [4]) on bone mineral

density (BMD) has been a matter of debate [5]. Previous studies in premenopausal women revealed that subclinical thyrotoxicosis due to suppressive TSH treatment for DTC had no effect on bone mineral density [6–15]. Similarly, most studies in postmenopausal women found no differences in BMD among patients with thyroid cancer treated with suppressive doses of levothyroxine and controls [7, 8, 10, 11, 13–17], while other authors reported that they may constitute at least a risk group for decreased BMD, and that other factors for osteoporosis should be considered [6, 18, 19]. Despite several studies [7, 11–15, 20–23] and meta-analyses [24] on this topic, the evidence that subclinical hyperthyroidism affects skeletal integrity and is, therefore, a risk factor for osteoporosis in men is inconclusive. Since androgens influence bone integrity and knowledge on osteoporosis in men is limited, study of the influence of suppressive therapy on the male skeleton is of interest.

Previous studies evaluating BMD in men with subclinical hyperthyroidism were characterized by small sample size and heterogeneity of the population studied, different levels of TSH suppression and time of effective TSH suppression, lack of an adequate control group, and the inclusion of different thyroid disorders [25]. Remarkably, there is little information on the potentially deleterious effect of levothyroxine treatment on distal radius integrity and the risk of fracture in the male population.

The aim of our study was to evaluate the potentially deleterious effect on BMD, including the distal radius, and on the low-impact fracture rate of subclinical thyrotoxicosis due to long-term treatment with LT_4 at suppressive doses of TSH in male patients after near-total thyroidectomy for DTC.

Materials and methods

Study subjects

A cross-sectional, retrospective study was conducted in a group of Caucasian men with DTC recruited from the outpatient clinic of the Endocrinology Department of our university hospital. In order to maximize the homogeneity of the sample, strict selection criteria were followed: (1) age over 18 years; (2) near-total thyroidectomy and ablative radioiodine treatment for DTC at least 5 years before inclusion in the study; (3) hypothyroidism treated with suppressive doses of LT_4; (4) full TSH suppression at entry into the study, defined by levels under 0.1 μIU/ml in all of the determinations after thyroidectomy during the suppressive period of treatment with a visit frequency of 2 to 3/year; and (5) normal T_3 levels in all determinations performed during the previous follow-up. In our practice, prior to the publication of the European consensus for the management of patients with differentiated thyroid carcinoma [2], patients received suppressive levothyroxine treatment during follow-up. After this year, in those considered to be in complete remission, therapy was changed from suppressive to replacement.

Patients with previous or current treatment with drugs which could interfere with bone metabolism (i.e., corticosteroids, tiazides, biphosphonates, statins, and glitazones), prolonged immobilization, recent high-impact traumatic bone fractures, inflammatory osteoarticular disease, malignancy, or antiandrogen therapy for prostatic carcinoma and increased serum creatinine were excluded.

All patients had persistently undetectable thyroglobulin in the absence of thyroglobulin autoantibodies, and negative radioisotope scans indicating absence of cancer recurrence or metastasis.

The control group included otherwise healthy male volunteers, of similar age and body mass index (BMI) (weight in kg/height in m^2). These controls received no remuneration and had no thyroid illness or LT_4 treatment. The local ethics committee, in accordance with the Declaration of Helsinki, approved the study and all participants gave their written informed consent prior to inclusion.

Patients and controls completed a questionnaire on daily calcium intake (according to dairy product intake, the mean amount of calcium was estimated and then graded as deficient or sufficient if under or over 1,000 mg/day, respectively), physical activity (defined as mild if the patients were sedentary, moderate if they performed habitual exercise at work or during their normal life, or vigorous if they undertook intense activity more than three times per week), smoking (non-smokers, smokers, and ex-smokers), coffee and alcohol consumption and pain symptoms or medical reports of previous non-traumatic fractures.

Analytical and hormone determinations

Blood samples were obtained by venopuncture in an antecubital vein without occlusion after an overnight fast, including determinations of hematological and biochemical parameters. Calcium, inorganic phosphate, and alkaline phosphatase were determined with a multichannel standard autoanalyzer, and intact PTH, testosterone, free T_4, T_3, and TSH with an electrochemiluminiscent immunoassay (Modular Analytics E170, Roche Diagnostics GMBH, Mannheim. Germany; reference range: PTH 15–65 pg/ml, testosterone: 280–800 ng/dl, free T_4 0.87–1.77 ng/dl, T_3 0.8–2 ng/ml, and TSH 0.27–4.2 μIU/ml. Sensitivity of the TSH assay: 0.005 μIU/ml), 1–25 hydroxyvitamin D (1-25−$(OH)_2$ vitD) and 25 hydroxyvitamin D (25-(OH) vitD) were determined by radioimmunoassay (DiaSorin,

Stillwater, MN, USA; reference range: 1-25 hydroxyvitamin D 18–78 pg/ml, 25 hydroxyvitamin D 18–80 ng/ml). Urinary calcium excretion levels were determined in a 24-h urine sample, and cross-linked N-telopeptide of type I collagen (NTX) levels in a second micturition urine sample (Enzyme-linked Immunoassay; Osteomark NTx urine; Wample Laboratories, Inc, Princeton, NJ, USA; reference range: 5–65 nm BCE/mM creatinine).

Bone mineral density measurements

In patients and controls, BMD was measured in the lumbar spine (L2–L4), proximal femur and distal radius of the non-dominant arm by dual-energy X-ray absorptiometry (DXA) (Lunar Prodigy, Lunar Corp, Madison, WI, USA). All measurements were performed and analyzed using the manufacturer's reference data. The equipment was automatically calibrated daily using phantoms following the manufacturer's recommendations. In all cases, BMD values were expressed as g/cm^2, T-score (the difference in number of standard deviation (SD) between the value for an individual and the mean value of a group of young, usually 25 to 45-year-old adults of the same sex) and Z-score (the difference in number of SD between the mean BMD value of the individual and a group of people of the same sex and age). According to the WHO criteria [25], a T-score ≤ -2.5 SD was defined as osteoporosis, between -2.5 and -1.0 SD as osteopenia and ≥ -1.0 as normal.

Evaluation of bone fractures

Previous bone fractures were evaluated using the above-mentioned questionnaire and with conventional X-ray images of thoracic and lumbar vertebrae evaluated by two separate trained observers using Genant's method [26].

Statistical analysis

Continuous variables were expressed as means with 95% confidence intervals. Departure from normality was assessed by the Kolmogorov–Smirnov distribution test. Comparisons between subgroups of patients and controls was made by Student's *t*-test, proportions by chi-square test and correlations between BMD and other variables by Pearson's correlation analysis using the SPSS package (SPSS Inc., Chicago, Illinois, USA). In all cases, $P < 0.05$ was considered significant. Sample size was estimated in 33 patients in each group for a two-sized type 1 error set at 5%, a statistical power (1-type 2 error) set at 90% and a standardized difference of the means set at 0.80.

Results

Of the 213 eligible patients with DTC followed in our department, 170 were women and were excluded. Of the remaining 43 men, two died from causes not related to bone fracture and according to the selection criteria, 33 patients were recruited and completed the study. Thirty-three otherwise healthy men were selected as the control group. Mean duration of LT_4 treatment was 15.0 ± 5.7 years, and mean LT_4 dose was 198 ± 55 mcg/24 h (2.6 ± 0.7 μg/kg/24 h). No differences were found between patients and controls regarding anthropometric data, physical activity, unhealthy habits, or calcium intake (Table 1).

Laboratory data

Biochemical and hormonal data are shown in Table 2. As expected, TSH levels were significantly lower in the patient group compared with controls and free T_4 was higher. According to selection criteria, T_3 levels were within normal range and similar in both groups. No differences were observed between patients and controls in serum alkaline phosphatase, NTX/creatinine index, 1,25−$(OH)_2$

Table 1 Characteristics of patients treated with levothyroxine for differentiated thyroid carcinoma compared with healthy controls

	Patients ($n = 33$)	Controls ($n = 33$)	*P*
Age (years)	56 ± 14	56 ± 17	0.9
Body mass index (kg/m^2)	26.6 ± 2.7	27.9 ± 3.7	0.6
Coffee intake (%)			
0–2 units/24 h	80.8	81.5	0.8
3–4 units/24 h	19.2	18.5	0.8
Smokers (%)			
Current	19.2	18.5	0.8
Ex-smoker	46.8	40.7	0.8
Non-smoker	34.0	40.7	0.8
Alcohol intake (%)			
0–1 units/24 h	73.1	74.0	0.8
>1 units/24 h	26.9	26.0	0.7
Exercise (%)			
Mild	19.2	16.3	0.9
Moderate	57.7	56.4	0.8
Vigorous	23.1	27.3	0.9
Calcium intake			
% Deficient	53.8	59.3	0.8
Deficient mean intake (mg/day)	632 ± 54	643 ± 65	0.5
% Sufficient	46.2	40.7	0.8
Sufficient mean intake (mg/day)	1210 ± 91	1198 ± 101	0.6

Data are means ± SD

Table 2 Hormonal, calcium metabolism and bone turnover parameters of patients treated with levothyroxine for differentiated thyroid carcinoma and healthy controls

	Patients ($n = 33$)	Controls ($n = 33$)	P
TSH (μIU/ml)	0.08 ± 0.01	2.14 ± 1.10	<0.01
Free T_4 (ng/dl)	1.87 ± 0.39	1.18 ± 0.16	<0.01
T_3 (ng/ml)	1.26 ± 0.38	1.15 ± 0.21	0.2
Calcium (mg/dl)	9.3 ± 0.3	9.4 ± 0.3	0.1
Creatinine (mg/dl)	0.6 ± 0.1	0.7 ± 0.1	0.2
Phosphate (mg/dl)	3.5 ± 0.6	3.5 ± 0.5	0.9
Alkaline phosphatase (U/l)	67.2 ± 25	69.4 ± 22	0.8
PTH (pg/ml)	39.7 ± 12.7	46.2 ± 18.9	0.1
1–25−$(OH)_2$ vitD (pg/ml)	42.6 ± 21.2	51.4 ± 20.9	0.1
25-(OH) vitD (ng/ml)	42.6 ± 19.1	39.2 ± 17.9	0.2
Testosterone (ng/dl)	450.2 ± 238.9	435.3 ± 194.3	0.5
Urinary calcium (mg/24 h)	166.8 ± 92.2	217.2 ± 78.4	0.3
N-Telopeptide (nMBCE/mMcr)	38.8 ± 15.8	44.8 ± 16.4	0.2

Data are expressed as mean ± SD

vitD, 25-(OH) vitD, serum calcium levels, serum phosphate levels, serum PTH levels and urinary calcium excretion. Serum testosterone was similar among patients treated with LT_4 compared to controls, and was within normal range.

DXA evaluation

No differences were observed in BMD evaluated by DXA between patients and controls either in cortical (femoral neck 0.948 ± 0.128 vs. 0.997 ± 0.151 g/cm^2, $P = 0.18$; distal radius 0.628 ± 0.137 vs. 0.694 ± 0.069 g/cm^2, $P = 0.066$) or trabecular bone (lumbar spine 1.253 ± 0.156 vs. 1.238 ± 0.171 g/cm^2, $P = 0.72$).

No differences were observed in T-score and Z-score measurements considered as a continuous variable in femoral neck, lumbar spine, and distal radius between patients and controls (Table 3).

Low-impact fractures

No previous fractures or pain episodes were registered by the retrospective questionnaire in either patients or controls.

Table 3 T-scores and Z-scores in lumbar spine, femoral neck, and distal radius of patients and control group

	Patients ($n = 33$)	Controls ($n = 33$)	P
Lumbar spine T-score	0.18 ± 1.20	0.01 ± 1.38	0.6
Lumbar spine Z-score	0.34 ± 1.26	0.08 ± 1.56	0.5
Femoral neck T-score	−1.00 ± 0.98	−0.56 ± 1.16	0.1
Femoral neck Z-score	−0.25 ± 1.03	−0.01 ± 1.21	0.4
Distal radius T-score	−1.16 ± 1.28	−1.28 ± 0.98	0.7
Distal radius Z-score	−0.80 ± 1.15	−0.76 ± 1.44	0.9

The incidence of asymptomatic vertebral fractures evaluated by X-ray examination did not differ significantly between patients (18.8%) and controls (16.7%), ($P = 0.9$). None presented a T-score, evaluated in any site, within an osteoporotic range according to the WHO criteria, and no significant differences were detected between patients with or without a previous fracture in areal bone density in the lumbar spine (1.280 ± 0.132 g/cm^2 vs. 1.1230 ± 0.110, respectively), femoral neck (1.019 ± 0.132 g/cm^2 vs. 0.965 ± 0.092, respectively) or distal radius (0.684 ± 0.070 g/cm^2 vs. 0.698 ± 0.057, respectively) ($P > 0.05$ in all cases). All fractures were detected outside the L2–L4 vertebrae, and, therefore, did not affect the DXA evaluation.

Correlation analysis

In bivariate correlation analysis in the overall group of patients and controls, testosterone levels correlated negatively with age ($r = -0.3$, $P < 0.05$) and BMI ($r = -0.4$, $P < 0.01$). Areal BMD in the distal radius correlated with areal BMD in the femoral neck ($r = 0.6$, $P < 0.0001$) but not in the lumbar spine ($P = 0.05$). In patients, LT_4 dose, duration of treatment, free T_4 levels, and T_3 levels did not correlate with areal BMD in any of the sites evaluated. In this respect, no differences were found in BMD between patients treated more or less than 5, 10, or 15 years (data not shown).

Discussion

The results reported do not demonstrate a deleterious effect of long-term suppressive LT_4 treatment on bone integrity and fracture risk in men with DTC. In our opinion, this is a

clinically important topic because, although the current guidelines do not recommend prolonged TSH suppression in patients in complete remission [2], those with active disease and those diagnosed for many years have been treated long term with suppressive doses of levothyroxine. The relationship between exogenous subclinical thyrotoxicosis and bone integrity is a matter of debate. Data obtained from cross-sectional, prospective studies [24] demonstrate that pre-menopausal women do not seem to be affected by this treatment [6–15] and that post-menopausal status may be at least a risk situation for osteoporosis, and BMD should be evaluated before initiating levothyroxine treatment and, if needed, antiresorptive and calcium treatment instituted [6–8, 11, 13–19].

Data are scarce in men, probably owing to the lower incidence of DTC in these patients and the fact that osteoporosis in men has not generally been considered an important clinical issue [27]. However, men are also at risk for decreased BMD and vertebral fractures [28]. In this respect, the age-adjusted prevalences for osteoporosis and osteopenia in men are 6 and 7%, respectively [29]. Furthermore, the risk of vertebral fractures in men is as high as half the rate seen in women [28].

Few cross-sectional studies including age, additional risk factors for osteoporosis, dose of levothyroxine prescribed, serum TSH levels, duration of treatment, and quantification of BMD have been conducted on the effect of subclinical thyrotoxicosis secondary to suppressive TSH treatment for DTC in BMD in men [24]. Three studies evaluating a small number of patients ($n \leq 6$) showed no differences in BMD [7, 22, 23]. Of five other studies [11–13, 20, 21], only one [12] detected a significant reduction in BMD in lumbar spine, femoral neck, and Ward's triangle compared to the expected value. However, in this latter study no control group was provided and 32 of 49 patients had recent-onset Graves' disease with an unknown previous thyroid status or overt hyperthyroidism at inclusion, leading to marked heterogeneity of the sample. Three of the remaining four studies detected no differences between treated patients and controls [11, 20, 21] and the fourth found no difference compared to Z-score [13]. The only longitudinal study performed in men with suppressive LT_4 treatment for DTC showed significant bone loss at the distal radius, without changes in BMD in the spine and femoral neck [30]. Nevertheless, the small number of patients ($n = 4$), together with the lack of a control group and the reduced period after thyroidectomy in some of the cases, limits the strength of these results.

In order to avoid the criticisms mentioned, we designed a protocol with a strict definition of both case and control populations. The main strengths of our study are: (1) the number of subjects included, to our knowledge the largest series reported in the literature including only DTC; (2) the homogeneity of the sample including only patients with near-total thyroidectomy for DTC; (3) the long-term treatment in our series, lasting more than 30 years in some cases; (4) the confirmed effective suppression of TSH and normality of T_3 levels in all determinations from the onset of treatment, thus ruling out possible overt hyperthyroidism with a known effect on bone turnover; (5) the inclusion of an appropriate BMI- and age-matched control group; (6) the evaluation of BMD in the distal radius, a site of cortical bone potentially affected by hormone excess; (7) the inclusion of testosterone levels as a cause of osteoporosis; and (8) the evaluation of asymptomatic fractures.

In agreement with recent meta-analyses on this topic [24], our results do not demonstrate impairment of BMD or in bone turnover biomarkers in men with levothyroxine-induced subclinical thyrotoxicosis compared with controls with similar anthropometric data, physical activity, unhealthy habits, calcium intake, and androgen status. The normality of T_3 levels in all the subjects studied could be the basis of this lack of deleterious effect. Recently published data showed a relationship between TSH levels and fractures [31] and forearm BMD [32] in male and female patients on levothyroxine replacement therapy. However, in those studies, the observed alterations appeared only in the group of subjects with undetectable TSH and no data on T_4 and T_3 were provided; thus, a previous or current state of hyperthyroidism cannot be ruled out. In our study, TSH levels were not correlated with BMD.

As fractures are the latest and most potentially severe manifestation of the decrease in BMD, we also evaluated the incidence of asymptomatic low-impact fractures. Decreased BMD in men is associated with increased fracture risk. However, most fractures occur in men whose BMD measurements are not within osteoporotic range [27]. In this respect, only one study [13] evaluated vertebral fractures using lateral DXA and concluded that patients did not have a higher prevalence of vertebral fracture. Remarkably, in our series, although no patient or control reported back pain or previous fractures, 16.7% of patients and 18.8% of controls presented radiological manifestations of fracture without osteoporosis in any case. This incidence of asymptomatic fractures concurs with that reported in the literature [33] and although it did not differ between groups, the data highlight the underdiagnosis, underreporting, and undertreatment of bone fragility in men. Obviously, since the frequencies of fractures are low, from an epidemiological point of view large sample sizes are required to further examine the effect of suppressive therapy in the male population. However, the number of men included in our study represents a population of males with CDT under suppressive levothyroxine therapy that fulfilled the inclusion criteria, and the close follow-up after diagnosis allowed to us to control a wide range of variables.

Similar to what we reported in a previous study conducted in women [14], more than half of the men in our series had an inadequate calcium intake. Men are often unaware of the preventive measures they can take to protect themselves against osteoporosis. Thus, recommendations to increase calcium intake could reduce the incidence of vertebral fractures.

Regarding the correlation analysis made, we observed that in patients, the LT_4 dose administered, duration of treatment, concentration of free T_4, and serum T_3 were not correlated with BMD values at any of the sites evaluated, implying that these parameters do not influence bone integrity as suggested in some studies [34].

In conclusion, long-term suppressive treatment with LT_4 in men with DTC does not appear to have deleterious effects on BMD and does not increase the risk of fracture in comparison with the general population. However, loss of bone calcium is a natural part of ageing, rendering the skeleton more fragile and liable to breakage. Preventive measures should be introduced in a clinical setting and osteoporosis should be detected early in populations at risk.

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Conflict of interest or disclosures None

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