Lack of deleterious effect on bone mineral density of long-term thyroxine suppressive therapy for differentiated thyroid carcinoma

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Abstract

The effect of subclinical hyperthyroidism on bone mineral density is controversial and could be significant in patients with differentiated thyroid carcinoma who receive suppressive doses of levothyroxine (LT4). To ascertain whether prolonged treatment with LT4 to suppress thyrotropin had a deleterious effect on bone mineral density and/or calcium metabolism in patients thyroidectomized for differentiated thyroid cancer we have performed a cross-sectional study in a group of 88 women (mean $\pm$ SD age: 51 ± 12 years) treated with LT4 after near-total thyroidectomy and in a control group of 88 healthy women (51 ± 11 years) matched for body mass index and menopausal status. We determined calcium metabolism parameters, bone turnover marker N-telopeptide and bone mass density by dual-energy X-ray absorptiometry. No differences were found between patients and controls in calcium metabolism parameters or N-telopeptide except for PTH, which was significantly increased in controls. No differences were found between groups in bone mineral density in femoral neck (0.971 ± 0.148 gr/cm² vs 0.956 ± 0.130 gr/cm² in patients and controls respectively, $P=0.5$). In lumbar spine, bone mineral density values were lower in controls than in patients (1.058 ± 0.329 gr/cm² vs 1.155 ± 0.224 gr/cm² respectively, $P<0.05$). When premenopausal ($n=44$) and postmenopausal ($n=44$) patients were compared with their respective controls, bone mineral density was similar both in femoral neck and lumbar spine. The proportion of women with normal bone mass density, osteopenia and osteoporosis in patient and control groups was similar in pre- and postmenopausal women. In conclusion, long-term suppressive LT4 treatment does not appear to affect skeletal integrity in women with differentiated thyroid carcinoma.

Endocrine-Related Cancer (2005) 12 973–981

Introduction

Osteoporosis is a limiting condition that affects almost 50% of US women over the age of 50 and the number is expected to rise concomitantly with life expectancy, with an increase from 32 to 69 million persons affected between 1999 and 2050 (Cooper *et al.* 1992). Furthermore, the number of femoral neck fractures could reach 8.2 million by that date (Gullberg *et al.* 1997). On the other hand, carcinoma of the thyroid, a less common site of malignancy (accounting for only 0.85% and 2.5% of new cancer cases in men and

women respectively) is the most rapidly increasing tumour in women and the second most rapidly increasing in the general US population (Jemal *et al.* 2003). After thyroidectomy and iodine 131 therapy for thyroid remnant ablation, and since most differentiated thyroid carcinomas (follicular and papillary) contain functional thyrotropin (TSH) receptors, adjunct therapy with levothyroxine (LT4) to inhibit this stimulating hormone is effective for reducing tumour recurrence rates (Thyroid Carcinoma Task Force 2001). Thus, owing to the favourable prognosis of differentiated thyroid carcinoma, patients could live

longer and receive suppressive LT4 treatment for many years (Gilliland *et al.* 1997). It is therefore important to understand the effect of supraphysiological LT4 treatment on bones (Greenspan & Greenspan 1999). The relationship between hyperthyroidism and accelerated bone turnover has been well defined since it was first described in 1891 (Von Recklinhausen 1891), and hyperthyroidism appears to affect the predominantly cortical bone in the hip and forearm more than the trabecular bone in the spine (Ross 1994). Nevertheless, the effects of subclinical hyperthyroidism (undetectable TSH levels and total triiodothyronine (TT3) and/or free thyroxine (FT4) in normal range) on bone mineral density (BMD) are less well defined (Toft 2001). Despite publication in the last decade of several studies (Franklyn *et al.* 1992, Kung *et al.* 1993, Giannini *et al.* 1994, Marcocci *et al.* 1994, McDermott *et al.* 1995, Muller *et al.* 1995, Rosen *et al.* 1998) and meta-analyses on this topic (Faber & Galloe 1994, Uzzan *et al.* 1996), evidence that subclinical hyperthyroidism affects skeletal integrity and is therefore a risk factor for osteoporosis, is inconclusive (Greenspan & Greenspan 1999, Toft 2001, Quan *et al.* 2002, Murphy & Williams 2004). The meta-analyses and systematic reviews reported either a decrease in bone mineral density during prolonged subclinical hyperthyroidism, mainly in postmenopausal women, or no changes (Faber & Galloe 1994, Uzzan *et al.* 1996, Greenspan & Greenspan 1999, Lau *et al.* 2001, Toft 2001, Quan *et al.* 2002, Murphy & Williams 2004). Among premenopausal women, the effect does not appear to be significant (Marcocci *et al.* 1994). Furthermore, individual studies reported both accelerated BMD loss (Kung *et al.* 1993, McDermott *et al.* 1995), increased risk of hip fractures (Quan *et al.* 2002) and no effect (Franklyn *et al.* 1992, Giannini *et al.* 1994, Marcocci *et al.* 1994, Muller *et al.* 1995, Rosen *et al.* 1998) in a similar number of reports. Thus, the quality of evidence on the strength of the association between serum TSH and BMD reported in the American Medical Association guidelines for diagnosis and management of subclinical thyroid disease was negative, or only fair in postmenopausal women with a history of overt hyperthyroidism (Surks *et al.* 2004). The heterogeneity of selected patients, different levels of TSH suppression and measurement techniques for BMD determination could explain this disparity in results (McDermott *et al.* 1995, Toft 2001, Murphy & Williams 2004). A study of skeletal integrity in a homogeneous cohort of women under long-term treatment with LT4 for differentiated thyroid carcinoma and sustained TSH suppression is presented.

Methods

Participants

This was a cross/sectional study of a group of Caucasian women recruited from the outpatient clinic of the Endocrinology and Nutrition Department of our hospital. Strict selection criteria were applied to minimize the heterogeneity of the sample: (1) age 18 years or older, (2) hypothyroidism due to a near-total thyroidectomy and ablative radioiodine treatment for differentiated thyroid carcinoma at least 3 years before entry to the study, (3) treatment with LT4 at suppressive doses of TSH for more than 3 years prior to entry, (4) full TSH suppression defined by levels under 0.05 $\mu\text{IU/ml}$ in all of the determinations during previous follow-up with a visit frequency of 2 to 3/year, (5) normal TT3 levels in all determinations during previous follow-up with a visit frequency of 2 to 3/year, (6) absence of recurrent or metastatic disease (all patients had persistently undetectable thyroglobulin and negative radioisotope scans). Patients with previous or current treatment with calcium, hormonal replacement therapy, thiazide diuretics, corticosteroids, bisphosphonates, raloxifene, tamoxifen, vitamin D or other drugs which could interfere with bone metabolism, prolonged immobilization, recent bone fracture, inflammatory osteoarticular disease, diabetes mellitus, serum creatinine levels $>1.3 \text{ mg/dl}$, increased alkaline phosphatase or severe analytical alterations were excluded.

A group of healthy female volunteers, members of hospital staff and first degree relatives of patients, with similar age, body mass index (BMI) (weight in $\text{kg}/\text{height m}^2$) and menstrual status served as controls. These controls received no remuneration and had never have been treated with LT4.

Patients and controls completed a questionnaire on menstrual history, previous contraceptives, calcium intake, physical activity, smoking habit, coffee and alcohol consumption. Daily calcium intake was estimated on the basis of dairy product intake and graded as deficient or sufficient if under or over 1000 $\text{mg}/24 \text{ h}$. Physical activity was defined as mild (sedentary, minimal activity at home), moderate (habitual exercise at work, walking, stairs) and vigorous (intense or sport activity more than three times per week). In our usual clinical practice we do not recommend vitamin D supplements because sunlight exposure is high in our country.

Analytical and hormone determinations

In all cases, BMI was registered and a blood sample obtained by venopuncture in an antecubital vein

without occlusion after an overnight fast. Haematological and biochemical parameters including calcium, inorganic phosphate and alkaline phosphatase were determined in patients and controls by a multichannel standard autoanalyzer. Intact parathormone (PTH) and TSH were determined by chemiluminiscent enzyme-labeled immunomeric assay (Immulate 2000 DPC, Los Angeles CA, USA. Reference range: 12–65 pg/ml and 0.3–5.5 μ IU/ml respectively. Sensitivity of TSH bioassay: 0.004 μ IU/ml), 1-25 dihydroxy-vitamin D (1-25(OH)₂ vit D) was determined by chemiluminiscence (Dia-Sorin, Stillwater, MN, USA. Reference range: 18–78 pg/ml) and 25 hydroxyvitamin D (25(OH) vit D) by radioimmunoassay (Dia-Sorin. Reference range: 18–80 ng/ml). FT4 was determined by a competitive analog chemiluminiscent ELISA (Immulate 2000 DPC. Reference range: 0.8–1.9 ng/dl) and TT3 by competitive chemiluminiscent ELISA (Immulate 2000 DPC. Reference range: 0.7–1.7 ng/ml). Levels of urinary calcium excretion were determined in a 24-h urine sample and cross-linked N-telopeptide of type I collagen (NTX) 6 levels in second micturition urine sample (uNTX Osteomarc; Ostex International, Inc., Seattle, WA, 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) and proximal femur (femoral neck, total proximal femur) by dual-energy X-ray absorptiometry (DEXA) (Lunar Prodigy, Lunar Corp, Madison, WI, USA). Precision of the system was 0.5%. The equipment was automatically calibrated daily using phantoms following the manufacturer's recommendations. In all cases, BMD values were expressed as g calcium/cm², T-score (standard deviation (SD) compared with a healthy Spanish population aged 20 and 40), and Z-score (SD compared with a population adjusted for age, weight and ethnic origin). According to the WHO criteria (Kanis *et al.* 1994), a T-score < –2.5 SD was defined as osteoporosis, between –2.5 and –1.0 SD as osteopenia and > –1.0 as normal.

Statistics

Comparison 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, significance was considered if *P* < 0.05. The study had at least 90% statistical power to detect

differences in comparisons between LT4 treated patients and no treated controls. For categorical variables the estimated sample size required to detect a difference of 20% in the percentage and with a two-sided alpha error of 0.05 and a beta error of 0.1 was 79 subjects per group. For continuous variables the estimated sample size required to detect a difference of 0.5 times the SD (standardized difference) with a two-sided alpha-error of 0.05 and a beta-error of 0.1 was 85 subjects per group.

Results

Of the 217 eligible patients with differentiated thyroid carcinoma followed in our department, 47 were men and were excluded. Of the remaining 170 women, and according to selection criteria, 91 were recruited, of whom, 88 completed the study (mean $\pm$ SD age: 51 ± 12 years, BMI 27.9 ± 4.6 kg/m²). Eighty-eight women were selected as controls (51 ± 11 years, BMI 27.0 ± 4.2 kg/m²) and all completed the study.

Overall group

In a first analysis, the 176 women included in the complete group of patients (*n* = 88) and controls (*n* = 88) were studied. Mean duration of LT4 treatment was 12 ± 5 years and mean LT4 dose to achieve effective TSH suppression was 195 ± 43 μ g/24 h (2.7 μ g/kg/24 h). No differences were found between patients and controls in anthropometric data, physical activity, unhealthy habits or contraceptive therapy. Appropriate dietary calcium intake did not differ in patients and controls (46 vs 47% respectively). Remarkably, nearly half of the women did not achieve the recommended daily intake of 1000 mg of calcium. As expected, TSH levels were significantly lower (0.03 ± 0.03 vs 1.93 ± 1.1 μ IU/ml, *P* < 0.01) and FT4 higher (1.9 ± 0.4 vs 1.3 ± 0.1 ng/dl, *P* < 0.01) in the LT4-treated group compared with controls, and TT3 levels were similar (1.2 ± 0.2 vs 1.3 ± 0.3 ng/ml, *P* = 0.2). Serum calcium (9.3 ± 0.5 vs 9.4 ± 0.4 mg/dl, *P* = 0.1), serum phosphate (3.5 ± 0.7 vs 3.4 ± 0.7 mg/dl, *P* = 0.3), 1-25(OH)₂ vitD (37.5 ± 26.6 vs 38.2 ± 19.3 pg/ml, *P* = 0.8), 25(OH) vitD (39.9 ± 19.3 vs 34.0 ± 20.8 ng/ml, *P* = 0.1) and urinary calcium excretion (171.0 ± 90.6 vs 150.6 ± 75.8 mg/24 h, *P* = 0.2) showed no differences between patients and controls. PTH levels were significantly higher in the control group vs the patient group (48.7 ± 18.0 vs 39.6 ± 17.8 pg/ml respectively, *P* < 0.01). Increased PTH levels with respect to normal range were observed in 4.8% of patients and 13.6% of controls. However in

all these cases calcium, phosphate, 1-25(OH)₂ vitamin D and 25(OH) vitamin D were within normal range and no hyperfunctioning parathyroid adenomas were detected in subsequent evaluations. The bone resorption marker NTX was similar between patients and controls (41.3 ± 22.0 vs 41.0 ± 22.6 nm BCE/mM creatinine, $P = 0.9$, respectively). With respect to bone mineral density, DEXA results were similar in patients and controls in predominantly cortical bone. Thus, BMD was 0.971 ± 0.148 g/cm² in patients vs 0.956 ± 0.130 g/cm² in controls ($P = 0.5$) in femoral neck. However, BMD values in trabecular bone (in lumbar spine) were significantly decreased in controls compared with patients (1.058 ± 0.329 g/cm² vs 1.155 ± 0.224 g/cm² respectively, $P < 0.05$). T-score and Z-score values in both groups are shown in Fig. 1. The proportion of women with normal bone density and criteria of osteopenia and osteoporosis according to T-score and WHO criteria (Kanis *et al.* 1994) did not significantly differ between patient and control groups either in femoral neck or lumbar bone. Furthermore, more normal femoral DEXA T-scores and lumbar T-scores and Z-scores were observed, though not statistically significant, in patients than in controls.

Premenopausal women

In order to assess whether oestrogen status could protect against possible bone loss, premenopausal women ($n = 44$, age 39 ± 9 years) were analyzed separately and compared with their respective controls (Table 1). Except for TSH, FT4 and PTH, neither biochemical and calcium metabolism parameters nor BMD, expressed as calcium per area unit, differed between patients and controls (Table 2). In these premenopausal women, femoral neck BMD values were 1.032 ± 0.124 vs 1.017 ± 0.125 g/cm² ($P = 0.6$) and in lumbar spine 1.229 ± 0.167 vs 1.223 ± 0.155 g/cm² ($P = 0.9$) in patients and controls respectively. The bone resorption marker, NTX, was normal in all subjects, with no significant differences between groups. Compared T-score and Z-score results in predominantly cortical and trabecular bone in premenopausal patients and controls are shown in Fig. 1. The proportion of normal and osteopenic subjects was comparable in all measured bones.

Postmenopausal women

As shown in Tables 1 and 2, in the postmenopausal subgroup of patients ($n = 44$, age 58 ± 9 years), anthropometric data, calcium, phosphate, urinary calcium excretion, 1-25 (OH)₂ vitamin D, 25(OH) vitamin D and NTX did not differ between patients and controls.

PTH levels, as observed in premenopausal women, were higher in controls, but parathyroid dysfunction was ruled out. BMD in femoral neck, was 0.921 ± 0.148 g/cm² in controls and 0.927 ± 0.124 g/cm² in patients ($P = 0.8$) and in lumbar spine 0.978 ± 0.355 g/cm² in controls and 1.094 ± 0.248 g/cm² in patients ($P = 0.09$). The values of T-score and Z-score were similar in patients and controls and the proportion of normal and osteopenic subjects based on T-scores did not significantly differ (Fig. 1) and, as in the overall group, a higher, but not significant, proportion of patients with normal skeletal integrity was detected than in controls, particularly in femoral T-score and lumbar T and Z-scores.

Correlation analysis

In correlation analysis, age showed a significant negative correlation with BMD expressed as g/cm² in femoral neck and lumbar spine both in patient and control groups (Pearson's coefficient, $r = -0.4$, $P < 0.01$ in both cases). A significant positive correlation was also found between age and BMI ($r = 0.3$, $P < 0.01$), and PTH levels correlated weakly with age ($r = 0.3$, $P < 0.05$) but not with other bone turnover markers or with 1-25(OH)₂ vit D or 25(OH) vit D. No correlation was found between menopause duration and BMD.

Discussion

The results reported in our study do not demonstrate a deleterious effect of long-term suppressive LT4 treatment on bone integrity in women with differentiated thyroid carcinoma, regardless of their estrogen status. The potential changes in BMD in endogenous or induced subclinical hyperthyroidism remains a controversial issue and previous articles have failed to demonstrate uniform results (McDermott *et al.* 1995, Toft 2001, Quan *et al.* 2002, Murphy & Williams 2004). Owing to the observed 80–90% disease-free survival in differentiated thyroid carcinoma patients at 10 years of follow-up (Gullberg *et al.* 1997) and the recommendations for full suppression of TSH to < 0.1 µIU/ml (Harris 2002), the potentially deleterious effect of LT4 treatment in BMD is a matter of concern. In fact, the Clinical Practice Recommendations for the Management of Thyroid Carcinoma suggest a risk of accelerated bone turnover but do not express definitive recommendations for its monitoring (Thyroid Carcinoma Task Force 2001). Previous studies have been focused both on endogenous and drug-induced subclinical hyperthyroidism (Franklyn *et al.* 1992, Kung *et al.* 1993, Giannini *et al.* 1994, Marcocci

Figure 1 Comparison between patients and controls of bone mineral density expressed as normal, osteopenia and osteoporosis (according to T-score) and normal Z-score ($Z > -1.0$) in femoral neck (left panels) and lumbar spine (right panels) in the overall group ($n = 88$), in premenopausal ($n = 44$) and in postmenopausal women ($n = 44$). Bars represent percentage of subjects in each group (black bars, controls; white bars, patients).

et al. 1994, McDermott *et al.* 1995, Muller *et al.* 1995, Rosen *et al.* 1998). In two studies, patients with nodular goitre and endogenous subclinical hyperthyroidism had lower BMD than comparable normal subjects (Mudde *et al.* 1992, Foldes *et al.* 1993), although in one trial significant reductions in BMD occurred only in postmenopausal and in sites rich in cortical bone (Foldes *et al.* 1993). Some authors described decreased BMD in pre- and postmenopausal women with a significant negative correlation with T3 levels (Tauchmanová *et al.* 2004). In other reports only postmenopausal women were affected (Faber & Gallo

1994) or no diminution was observed (Franklyn *et al.* 1992, Giannini *et al.* 1994, Marcocci *et al.* 1994, Muller *et al.* 1995, Rosen *et al.* 1998). With respect to hyperthyroidism due to suppressive LT4 treatment, some trials included premenopausal women with little or no change in BMD between controls and long-term treated patients (Franklyn *et al.* 1992, Giannini *et al.* 1994, Marcocci *et al.* 1994, Muller *et al.* 1995). Studies performed in postmenopausal women showed decreased BMD in all measured sites in two trials (Diamon *et al.* 1991, Kung & Yeung 1996) and no changes in another six (Franklyn *et al.* 1992, Giannini

Table 1. Characteristics of premenopausal and postmenopausal patients treated with levothyroxine for differentiated thyroid carcinoma compared with healthy controls. Data are means $\pm$ SD. No significant differences were detected between patients and controls

	Premenopausal		Menopausal	
	Patients (n = 44)	Controls (n = 44)	Patients (n = 44)	Controls (n = 44)
Age (years)	39 $\pm$ 9	41 $\pm$ 11	58 $\pm$ 9	57 $\pm$ 2
Body mass index (Kg/m ²)	26.1 $\pm$ 5	25.5 $\pm$ 4.1	28.0 $\pm$ 2.6	27.2 $\pm$ 3.6
Menarche (years)	12.1 $\pm$ 1.3	12.6 $\pm$ 1.3	12.7 $\pm$ 1.3	12.3 $\pm$ 1.4
Menopause (years)	-	-	46 $\pm$ 4	47 $\pm$ 5
Menopause duration (years)	-	-	10 $\pm$ 3	10 $\pm$ 3
Previous contraceptives				
Subjects (n)	12	12	12	11
years	3.2 $\pm$ 1.7	4.4 $\pm$ 2.6	4.0 $\pm$ 2.2	4.5 $\pm$ 1.5
Coffee intake (n)				
0-2 units/24 h	36	37	36	37
3-4 units/24 h	8	7	8	7
Smokers (n)	14	13	5	5
Alcohol intake (n)				
0 units/24 h	38	37	39	40
1-2 units/24 h	6	7	5	4
Exercise (n)				
Mild	3	4	4	3
Moderate	39	38	38	39
Vigorous	2	2	2	2

Table 2. Hormonal, calcium metabolism and bone turnover parameters of premenopausal and postmenopausal patients treated with thyroxine for differentiated thyroid carcinoma and healthy controls. Data are means $\pm$ SD

	Premenopausal		Postmenopausal	
	Patients (n = 44)	Controls (n = 44)	Patients (n = 44)	Controls (n = 44)
TSH (μ IU/mL)	0.02 $\pm$ 0.01	2.1 $\pm$ 0.9*	0.04 $\pm$ 0.03	1.8 $\pm$ 1.0*
FreeT4 (ng/dL)	2.0 $\pm$ 0.3	1.3 $\pm$ 0.2*	1.9 $\pm$ 0.4	1.2 $\pm$ 0.1*
Total T3 (ng/mL)	1.2 $\pm$ 0.3	1.3 $\pm$ 0.2	1.3 $\pm$ 0.3	1.3 $\pm$ 0.3
Calcium (mg/dL)	9.1 $\pm$ 0.4	9.3 $\pm$ 0.4	9.4 $\pm$ 0.5	9.4 $\pm$ 0.4
Phosphate (mg/dL)	3.5 $\pm$ 0.5	3.4 $\pm$ 0.7	3.5 $\pm$ 0.7	3.3 $\pm$ 0.8
PTH (pg/mL)	33.9 $\pm$ 13.9	45.1 $\pm$ 17.2*	43.6 $\pm$ 20.6	50.7 $\pm$ 17.6 [#]
1-25(OH) ₂ vitD (pg/mL)	36.0 $\pm$ 20.0	30.0 $\pm$ 10.0	34.7 $\pm$ 17.4	35.8 $\pm$ 24.3
25(OH)vitD (ng/mL)	43.0 $\pm$ 37.7	37.3 $\pm$ 17.2	33.9 $\pm$ 14.9	38.5 $\pm$ 20.4
Urinary calcium (mg/24 h)	180.6 $\pm$ 68.0	143.5 $\pm$ 55.0	165.0 $\pm$ 102.9	152.1 $\pm$ 83.4
N-Telopeptide (nMBCE/mMcr)	34.7 $\pm$ 11.1	29.6 $\pm$ 9.9	46.4 $\pm$ 26.9	44.2 $\pm$ 24.2

* $P < 0.01$ compared with controls.[#] $P < 0.05$ compared with controls.

et al. 1994, Hawkins et al. 1994, Marcocci et al. 1994, Muller et al. 1995, Görres et al. 1996, Guo et al. 1997). Factors such as case-control matching, dietary calcium intake, alcohol, smoking, exercise and bone mass measurement techniques, could explain in part this conflicting evidence (Greenspan & Greenspan 1999, Murphy & Williams 2004). In our study, subjects and methods were carefully selected in order to minimize these confounding factors. First, only women were

included, since osteoporosis is an important cause of morbidity in women and the great proportion of female patients in our series of thyroid carcinoma was high (near 85%). Second, we selected only cases with stable TSH levels, below 0.05 μ IU/ml in all the determinations performed during follow-up previous to entry in the study. Third, TT3 levels were within normal range in all patients in all the previous follow-up determinations, thus ruling out possible

overt hyperthyroidism with a known effect on bone turnover. Fourth, treatment in our series is long-term, lasting more than 30 years in some cases. Fifth, the measurement technique was a modern DEXA evaluation with higher precision and reproducibility than other older techniques (Baran *et al.* 1997), and sixth, in our series, careful matching for age, BMI, menopausal status, unhealthy habits, calcium intake and physical activity was made with a healthy control group. In agreement with a previous long-term treatment study in which all patients achieved complete TSH suppression and pre- and postmenopausal patients were evaluated with DEXA (Giannini *et al.* 1994), our results suggest that suppressive LT4 treatment does not affect bone mineralization or bone turnover parameters. It is of particular interest that in the postmenopausal group, more patients than controls had normal T-scores, i.e. our treated patients could have good bone mineralization despite receiving LT4 for many years. In successive reviews on suppressive treatment for thyroid carcinoma, the conclusions and recommendations seem unclear and have changed over time and with authors. In 1999, Greenspan & Greenspan suggested that exogenous hyperthyroidism seemed to have an adverse effect on bone, which was greater in postmenopausal women (Greenspan & Greenspan 1999). Two years later, Toft reported that the evidence of exogenous subclinical hyperthyroidism as a risk factor for osteoporosis was inconclusive (Toft 2001). Finally, the 2004 Guidelines for diagnosis and management of subclinical thyroid disease (Surks *et al.* 2004) and Murphy & Williams's review (Murphy & Williams 2004) suggested that suppressive doses of LT4 had little or no effect on the BMD of premenopausal women or men. The situation in postmenopausal women remained less clear and it is recommended that all other risk factors for osteoporosis be considered in these patients (Murphy & Williams 2004). In our series, we detected consistently elevated levels of PTH in controls compared with patients. This increase was not due to an undetected subclinical hypoparathyroidism in patients because in all cases PTH was within normal range and maintained the physiological positive correlation with age, as observed in controls. We do not have an explanation for this observation. The effect of radioiodine on parathyroid glands could produce a diminution in their secretion capacity (Cooper 2005) and hypoparathyroidism has been reported after radioiodine therapy, however this probably does not exceed the normal incidence (Pauwels *et al.* 2000). On the other hand, an effect of chance cannot be ruled out for this finding. In

differentiated thyroid carcinoma, the dose of LT4 usually required to maintain full suppression of TSH to levels less than 0.01 $\mu\text{IU}/\text{ml}$ is approximately 2.2 $\mu\text{g}/\text{kg}$ (Burmeister *et al.* 1992) and some studies suggest that higher doses are associated with greater bone loss (Mikosch *et al.* 2003). In our treated group, median LT4 dose was 2.7 $\mu\text{g}/\text{kg}$, without bone loss. The normality of TT3 levels in all cases could explain this lack of effect. According to our data, long-term treatment with supraphysiological doses of LT4 in patients with differentiated thyroid carcinoma and complete suppression of TSH, even for a period of more than 30 years, does not appear to contribute to bone demineralization. However, individual management is required in these patients and other risk factors for osteoporosis and DEXA evaluation should be considered in postmenopausal women. It is of interest that, as detected in our study population, nearly 50% of women did not achieve the recommended daily calcium intake. Thus, recommendations focused on daily physical activity, increased calcium intake and, specifically in countries with low sunlight exposure, adequate vitamin D supplementation, could be of interest to prevent the physiological loss of bone mass with age.

Acknowledgement

The authors thank Christine O'Hara for valuable help with the English version of the manuscript. Part of this work has been accepted for poster presentation at 7th European Congress of Endocrinology, Göteborg, Sweden, 3–7 September 2005.

Funding

The authors declare no conflict of interest that would prejudice the impartiality of this study and no financial disclosure.

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