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A Randomized Trial Comparing Levothyroxine with Radioactive Iodine in the Treatment of Sporadic Nontoxic Goiter

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ABSTRACT

A randomized clinical trial was performed in consecutive patients with sporadic nontoxic nodular goiter to compare efficacy and side effects of iodine-131 (^{131}I) therapy with suppressive levothyroxine (L-thyroxine) treatment. Sixty-four patients were randomized after stratification for sex and menopausal age to receive ^{131}I (4.44 MBq/g thyroid; group A) or suppressive L-thyroxine treatment aiming at TSH values between 0.01 and 0.1 mU/L (group B). The main outcome measurements after 2 yr were goiter size by ultrasound, serum thyroid function tests, markers of bone turnover, and bone mineral density (BMD). Fifty-seven patients completed the trial. Goiter size was reduced after 2 yr by 44% in group A and by 1% in group B ($P < 0.001$). Nonresponders (goiter reduction <13%) were 1 of 29 patients in group A and 16 of 28 patients in group B ($P = 0.00001$). In responders, goiter reduction in group A (46%) was greater than in group B (22%; $P < 0.005$). In group A, 45% of patients developed hypothyroidism. In group B, 10 patients experienced thyrotoxic symptoms, requiring discontinuation of treatment in 2 (in 1 because of atrial fibrillation). Markers of bone formation and bone resorption increased significantly in group B, related to a mean decrease of 3.6% of BMD at the lumbar spine after 2 yr (from 1.09 ± 0.22 to 1.05 ± 0.23 g/cm^2; $P < 0.001$), both in pre- and postmenopausal women. No changes in BMD were observed in group A. In conclusion, ^{131}I therapy is more effective and better tolerated than L-thyroxine treatment in patients with sporadic nontoxic goiter. Suppressive L-thyroxine treatment results in significant bone loss. (*J Clin Endocrinol Metab* **86:** 998–1005, 2001)

SPORADIC NONTOXIC GOITER (SNG) is defined as a benign enlargement of the thyroid gland of unknown cause, in euthyroid subjects living in an area without endemic goiter (1). The natural history of the disease is characterized by a gradual increase of goiter size, under simultaneous development of increasing thyroid nodularity and thyroid autonomy (2). Thus, large multinodular goiters may arise, often with obstructive signs and symptoms. Hyperthyroidism is observed in 9–10% of the patients after a follow-up of 12 yr (3, 4). Treatment options are surgery, levothyroxine (L-thyroxine), and radioactive iodine. Thyroidectomy is very effective, at the expense of a low but unavoidable morbidity. Postoperative recurrence of the goiter occurs in 5–19% (5–8) and apparently cannot be prevented by the administration of T_4 (5, 9–11). L-thyroxine treatment in TSH-suppressive doses is not well studied in iodine-sufficient areas: in the placebo-controlled randomized clinical trial of Berghout *et al.* (12), a goiter reduction of only 25% was demonstrated in 59% of patients with SNG, irrespective of baseline TSH value. Moreover, a suppressed TSH constitutes a risk for developing atrial fibrillation in patients 60 yr of age and older (13) and for bone loss, especially in postmenopausal women (14, 15). Thus, it is understandable that the good results of iodine-131 (^{131}I) therapy of SNG, as reported in several open studies in older patients with contraindications for surgery in the last few years, have attracted much attention (16–23).

Because ^{131}I treatment has never been compared directly with L-thyroxine treatment, we performed a randomized clinical trial comparing the efficacy, tolerability, and safety of L-thyroxine with ^{131}I therapy in the treatment of sporadic nontoxic nodular goiter. The very study design—via the instantaneous induction of a suppressed TSH in the patients randomized to receive L-thyroxine—allowed us to evaluate prospectively the effect of thyroid hormone-suppressive therapy on bone density in a controlled manner. The main outcome measurements, as assessed after 2 yr, were goiter size, bone mineral density (BMD), and thyroid function.

Patients and Methods

Patients

One hundred consecutive patients with SNG, referred because of goiter, were included. The diagnosis of SNG was ascertained by ultrasound (nodular goiter), ^{99m}Tc-pertechnetate thyroid scintigraphy (inhomogenous uptake), and by fine-needle aspiration cytology indicating the benign (dysplastic) nature of the goiter. None had been treated for goiter in the preceding 2 yr, and all patients lived in an iodine-sufficient region (the mean 24-h urinary iodine excretion of healthy Dutch adults is 147 μg; Refs. 12 and 24). Exclusion criteria were severe obstructive symptoms and signs (n = 2), cardiac disorders precluding L-thyroxine treatment (n = 3), pregnancy (-wish) or breastfeeding precluding radioiodine treatment (n = 3), and inability to complete follow-up (n = 2). Of the 90 eligible patients, 64 gave informed consent to enter the trial (Fig. 1), which was approved by the local medical ethics committee. None of them used medication affecting bone metabolism, except four premenopausal women who continued to use oral contraceptives during the

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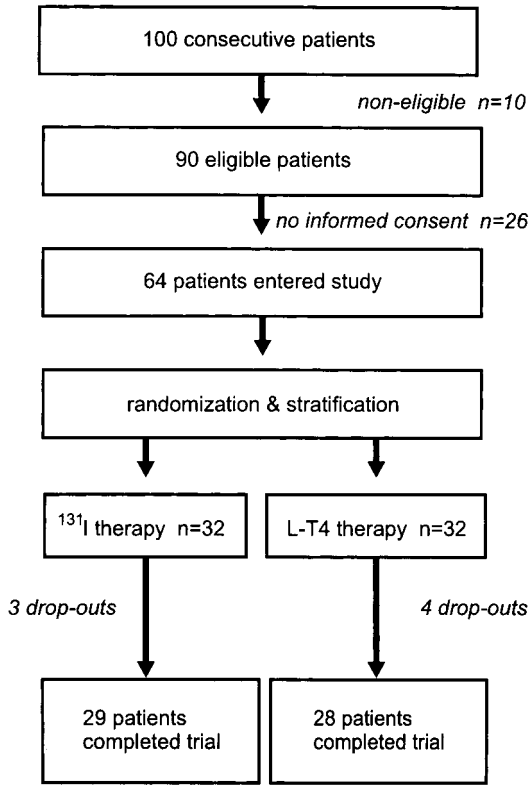

FIG. 1. Flow diagram of patients with SNG selected for the trial.

whole duration of the study. According to a sample size calculation, at least 44 patients were required to have an 80% chance of detecting a difference of 50% ($P < 0.05$) in reduction of goiter size between both groups.

Patients were randomized to ^{131}I treatment (group A) or L-thyroxine treatment (group B), after stratification for sex and menopausal status. Premenopause was defined as having regular periods, perimenopause as having irregular periods with at least one period in the last year, and postmenopause as no periods for at least 1 yr. Stratified randomization was done independently of treating physicians, by preparing envelopes for each stratum with a block size of four.

In patients randomized to ^{131}I, pretreatment thyroidal radioiodine uptake was measured with a tracer activity of 3.7 MBq Na ^{131}I. The therapeutic ^{131}I dose (aiming at 4.44 MBq/mL thyroid tissue) was calculated by the following formula: ^{131}I dose (MBq) = [4.44 (MBq) × 100/24 h uptake (%)] × TV (thyroid volume; mL, measured by ultrasonography). Patients were hospitalized for ^{131}I treatment for 2–6 days. After ^{131}I therapy, L-thyroxine was given if TSH increased above 4.0 mU/L, aiming at TSH values in the normal range.

In patients randomized to L-thyroxine, the initial dose of L-thyroxine was 2.5 μg/kg body weight, aiming at TSH values between 0.01 and 0.1 mU/L. If pretreatment TSH was already suppressed, free T_4 (FT_4) values were aimed at 20–22 pmol/L. Dose adjustments of L-thyroxine (25 μg at a time) were performed on the basis of TSH values, or of clinical signs and symptoms of thyrotoxicosis. L-thyroxine tablets were taken late in the evening.

Patients were evaluated at 0, 1.5, 3, 6, 9, 12, 18, and 24 months; the main outcome measurements were obtained before treatment and after 1 and 2 yr.

Methods

At each visit at the outpatient clinic, complaints related to the goiter were noted, together with signs and symptoms of thyrotoxicosis or hypothyroidism. The daily calcium intake was determined by a dietician. Serum thyroid function tests were obtained at every visit. At baseline and at 1 and 2 yr of follow-up, markers of tissue thyrotoxicosis and bone turnover were determined in fasting blood samples and 2-h fasting urine samples, collected between 0800 and 1000 h.

Thyroid volume was measured by ultrasonography using a contact B-scanner (Searle Pho/Sonic-SM, Siemens AG, Munich, Germany) with a 5.0-MHz, 14-mm transducer (focal length, 4.5 cm). Transverse scans of the thyroid were obtained in supine position at 5-mm intervals from caudal to cranial with hyperextension of the neck. The sum of all partial volumes equals the total thyroid volume. All determinations were performed by one radiologist (N.J.S.), who was blinded to the given treatment. The accuracy and precision of the method has been reported earlier (24). A significant decrease in thyroid volume was defined as a decrease greater than 13% (*i.e.* the mean + 2 SD of the coefficient of variation).

BMD of the lumbar spine, femoral neck, and trochanter was measured by dual-energy x-ray absorptiometry, using a Norland XR26 (Norland Corp., Fort Atkinson, WI; coefficients of variation: 2.4% for the lumbar spine, 2.3% for the femoral neck, and 2.4% in the trochanteric region, as measured in 51 volunteers). Z-scores were calculated for comparison with a reference population. During the study, the Norland densitometer was replaced by a Hologic 2000 (Hologic, Inc., Waltham, MA); BMD was, thus, measured on two different densitometers in 20 patients. In 14 of them we measured BMD on both densitometers on the same day at 1-yr follow-up and found a correlation coefficient of 0.99 at the lumbar spine. We calculated Norland values from Hologic values with the formula y (Norland value) = −0.04 + 1.06x (Hologic value), obtained by regression analysis. The same procedure was applied to the femoral neck (r = 0.90, y = 0.07 + 0.99x) and trochanter (r = 0.85, y = 0.10 + 0.88x).

Plasma T_4 and T_3 were measured by in-house RIAs, FT_4 by fluoroimmunoassay using the Delfia technique (Ultra; Wallac Oy, Turku, Finland), and TSH by an immunochemiluminometric assay (Behring, Amsterdam, The Netherlands; functional sensitivity, 0.01 mU/L). The reference values were: T_4, 60–160 nmol/L; T_3, 1.3–2.7 nmol/L; FT_4, 10–22 pmol/L; and TSH, 0.4–4.0 mU/L. Autoantibodies against thyroid peroxidase (TPO) and thyroglobulin were measured by chemiluminescence immunoassays (LUMI-test; Brahms, Berlin, Germany). Serum TSH-binding inhibiting immunoglobulins were measured by TRAK assay (Brahms) in patients who developed a suppressed TSH after ^{131}I treatment. Serum osteocalcin was measured by RIA (INCSTAR Corp., Stillwater, MN), bone alkaline phosphatase (BAP) by Alkphase-B (Metra Biosystems, Mountain View, CA), insulin-like growth factor I (IGF-I) by immunoradiometric assay (Diagnostic Systems Laboratories, Webster, TX), sex hormone-binding globulin (SHBG) also by immunoradiometric assay (Farmos Diagnostica, Turku, Finland), and 25-hydroxyvitamin D by competitive protein binding assay (TNO, Zeist, The Netherlands).

Statistical analysis

Differences in (baseline) values between groups were analyzed by Student's *t* test, Mann-Whitney *U* test, or χ^2 test (to compare percentages between groups), where appropriate. Changes in (outcome-) variables were analyzed by ANOVA using repeated measurements (and applying log transformation, where appropriate). To compare the series of changes between the two treatment groups, multivariate ANOVA was performed. Correlation tests were performed by single linear regression analysis, using a PC software program (SPSS, Inc., Chicago, IL). For calculations, undetectable serum concentrations were considered as corresponding to one half the functional sensitivity (*i.e.* 0.005 mU/L for TSH). The level of significance was taken as $\alpha = 0.05$.

Results

Randomization and treatment

Initial clinical and laboratory data of the eligible but not randomized patients and the two randomization groups are given in Table 1. No differences were found between the three groups. Patients were accrued in the period 1993–1996. We included one patient below the age of 30 yr, a woman of 29 yr old, who was operated on before (subtotal thyroidectomy) and had complaints of a goiter of 139 mL at study entry. Fourteen patients older than 60 yr were included, of

TABLE 1. Initial clinical characteristics and laboratory data of 90 patients with SNG

	Eligible, not randomized	Randomization groups	
		^{131}I therapy	L-thyroxine therapy
Number	26	32	32
Sex (M/F)	1/25	1/31	1/31
Pre/peri/postmenopausal	12/2/11	16/2/13	18/2/11
Age (yr)	51 (15)	49 (14)	50 (12)
Body weight (kg)	72 (11)	75 (13)	78 (13)
Complaints of goiter	20	27	25
Recent goiter growth	6	8	6
Duration of goiter (yr)	6 (1–64)	8 (1–28)	5 (1–20)
Family history	12	16	15
Thyroid grade I/II/III	4/17/5	0/24/8	0/22/10
Thyroid volume (mL)	50 (17–225)	60 (17–198)	57 (18–260)
Uni/multinodular goiter	3/23	2/30	3/29
T_4 (nmol/L)	102 (20)	104 (20)	103 (23)
T_3 (nmol/L)	2.01 (0.41)	1.87 (0.29)	2.00 (0.48)
TSH (mU/L)	0.8 (<0.01–2.2)	0.6 (<0.01–2.2)	0.7 (0.02–3.7)
TgAb/TPOAb +ve	4/4	3/9	5/5

Values as mean (SD) or as median (range).

whom six were randomized to receive L-thyroxine and eight to receive ^{131}I; slightly low baseline TSH values (>0.1–0.39 mU/L) were observed in three and two of these subjects, respectively; none had a TSH value of 0.1 mU/L or less.

The goiter caused complaints in 81% of the 64 randomized patients: discomfort in the neck in 69%, cosmetic complaints in 31%, fear of malignancy in 27%, and dyspnea in 13%. In five patients the goiter extended to the retrosternal compartment, which part could not be measured by ultrasonography. During follow-up, three patients of group A were excluded: two because, by mistake, the ^{131}I dose was calculated on the scintigraphic instead of the ultrasonographic thyroid volume, resulting in a much lower dose of ^{131}I; and one because hospital admission could not be realized due to severe illness of the patient's partner. In group B, four patients discontinued L-thyroxine treatment prematurely: one patient because of thyrotoxic symptoms not responding to a dose reduction, one because of pregnancy, one patient (55 yr old) because of atrial fibrillation (who already had a suppressed baseline TSH), and one because of noncompliance. Thus, data of 29 patients in group A and 28 patients in group B were available for evaluation of treatment efficacy. In group A, the median pretreatment ^{131}I uptake was 26% (range, 15–58) and a median ^{131}I dose of 888 MBq (range, 444–3330) was administered. In group B, the mean starting dose of L-thyroxine was 192 ± 34 μg/day, which at 1 yr had been reduced to 146 ± 44 μg/day ($P < 0.001$), corresponding to 1.89 ± 0.47 μg/kg·day.

Efficacy

In group A, a median decrease in goiter size of 38% at 1 yr and of 44% at 2 yr was found (Table 2). Twenty-eight patients (97%) were responders to treatment (defined as a decrease in thyroid volume >13%) with a median decrease in thyroid volume of 39% after 1 yr and 46% after 2 yr (Fig. 2). In group B, goiter size decreased with 7% at 1 yr and 1% at 2 yr. Twelve patients (43%) were responders to treatment with a median decrease in thyroid volume of 23% after 1 yr and 22% after 2 yr. There were 16 nonresponders with a median decrease in thyroid volume of 1% after 1 yr and a median increase in thyroid volume of 16% after 2 yr (Fig. 2). Intention-to-treat analysis resulted in comparable results: in group A, a median decrease in goiter size of 41% at 2 yr was found, whereas in group B goiter size decreased with 5% at 2 yr of treatment ($P < 0.0001$). Compliance with L-thyroxine treatment was good as judged by laboratory evaluation (Fig. 3). Taking together all time points, TSH values were below 0.01 mU/L in 38%, between 0.01 and 0.1 mU/L in 46%, and between 0.1 and 1.0 mU/L in 16%. No significant differences in TSH values were observed between responders and nonresponders to L-thyroxine treatment.

The decrease in goiter size in responders of group B was smaller than the median decrease in thyroid volume of responders in group A ($P < 0.005$). Pretreatment goiter size was inversely related to goiter reduction in group A ($r = -0.44$, $P < 0.05$) but not in group B ($r = 0.01$, not significant). No correlation was found between age or duration of goiter and the response to treatment in the two groups. Goiter reduction was directly related to baseline TSH in group B ($r = 0.40$, $P < 0.05$) but not in group A. Before treatment, 17 patients had subclinical hyperthyroidism. Ten were treated with ^{131}I (nine responders and one nonresponder), and TSH normalized in all; none became hypothyroid. Seven patients were treated with L-thyroxine, without developing symptoms of thyrotoxicosis, of whom only one responded. Goiter reduction after 2 yr of treatment with L-thyroxine was greater in patients with baseline TSH 0.4 mU/L or greater (median change, −12%) than in patients with baseline TSH less than 0.4 mU/L (median change, +28%; $P < 0.05$).

In both treatment groups at 2 yr of follow-up, fewer patients had complaints of their goiter than at baseline; after 2 yr of treatment only 2 of 20 patients in group A and 9 of 19 patients in group B still had complaints of discomfort in the neck, 1 of 8 patients in group A and 5 of 10 patients in group B still had cosmetic complaints, whereas dyspnea disappeared in 4 of 4 patients of group A but persisted in 2 of 3 patients of group B. The remaining complaints after 2 yr of treatment were significantly less frequent in group A than in group B (3 of 32 *vs.* 16 of 32, respectively; $P < 0.05$).

TABLE 2. Thyroid volume (TV) and thyroid function tests of patients with SNG, randomized to receive ^{131}I therapy (group A) or TSH-suppressive doses of L-thyroxine (group B)

	Group A (n = 29)				Group B (n = 28)			
	Baseline	At 1 yr	At 2 yr	ANOVA	Baseline	At 1 yr	At 2 yr	ANOVA
TV (mL)	56 (17–198)	36 (4–130)	30 (6–165)	$P < 0.001$	57 (18–260)	54 (18–243)	60 (20–287)	$P = 0.12$
TV (%)	100	62 (14–94)	56 (16–94)	$P < 0.001$	100	93 (59–164)	99 (49–206)	$P = 0.17$
TSH (mU/L)	0.64 (<0.01–2.20)	1.70 (0.04–5.70)	1.50 (0.05–4.50)	$P < 0.001$	0.77 (0.03–3.70)	0.02 (<0.01–0.74)	0.02 (<0.01–0.41)	$P < 0.001$
L-thyroxine dose (μg/day)		115 (32) (n = 13)	126 (30) (n = 13)			146 (44)	147 (50)	
FT_4 (pmol/L)	15.3 (3.1)	13.3 (3.1)	13.8 (3.4)	$P < 0.05$	14.0 (2.1)	22.4 (6.7)	22.5 (6.0)	$P < 0.001$
T_3 (nmol/L)	1.85 (0.28)	1.96 (0.37)	1.97 (0.34)	$P = 0.24$	1.95 (0.46)	2.15 (0.54)	2.18 (0.53)	$P < 0.05$

Values as mean (SD) or median (range).

FIG. 2. Relative changes in thyroid volume after ^{131}I treatment (group A) or during L-thyroxine treatment (group B).

FIG. 3. TSH values at baseline and during 24 months follow-up after treatment with ^{131}I or during L-thyroxine treatment.

Side effects

Clinical and biochemical data. One week after ^{131}I treatment, four patients noted anterior neck tenderness and slight symptoms of thyrotoxicosis lasting 1–3 weeks, compatible with mild radiation thyroiditis. No obstructive symptoms were noted. No patient developed Graves'-like hyperthyroidism. Of the eight patients who developed TSH values below 0.4 mU/L 6 weeks to 9 months after ^{131}I treatment, *de*

novo serum TSH-binding inhibiting immunoglobulins appeared in one without symptoms (TRAK before treatment, <5 U/L; after 9 months, 29 U/L; after 12 months, 20 U/L). After 2 yr, 16 patients were euthyroid (55%), 10 patients had developed hypothyroidism (35%), and 3 patients developed subclinical hypothyroidism (10%) in the first year after ^{131}I treatment. Patients with a normal pretreatment TSH had a significantly higher risk of developing hypothyroidism after ^{131}I treatment than patients with a suppressed baseline TSH (χ^2, $P < 0.005$). The presence of TPO antibodies at baseline also carried a higher risk of developing hypothyroidism after ^{131}I (χ^2, $P < 0.05$).

In group B, 10 patients experienced symptoms of mild thyrotoxicosis, disappearing after dose adjustment in all but 1 patient. A small but significant increase in pulse rate of 9% was observed during treatment, without changes in body weight. Serum SHBG and IGF-I concentrations did not indicate tissue thyrotoxicosis in either group because no significant changes were found during follow-up [group A, SHBG as mean (SD): at baseline, 58 (24) nmol/L; at 2 yr, 67 (29) nmol/L; group A, IGF-I: at baseline, 28 (12) nmol/L; at 2 yr, 27 (11) nmol/L; group B, SHBG: at baseline, 64 (45); at 2 yr, 78 (69) nmol/L; group B, IGF-I: at baseline, 22 (8) nmol/L; at 2 yr, 23 (9) nmol/L]. Serum lipids (total cholesterol, low-density lipoprotein cholesterol, and triglycerides) did not change either in both treatment groups.

Markers of bone turnover

Markers of bone formation and resorption are listed in Table 3. Males (n = 2) and perimenopausal women (n = 4) were excluded from evaluation as well as two other patients, one because of hypoparathyroidism due to previous thyroidectomy and one because of the appearance of bone metastases of breast cancer. Baseline values in group A (n = 24; 13 pre- and 11 postmenopausal women) and group B (n = 25; 15 pre- and 10 postmenopausal women) did not differ. Daily calcium intake (group A, 1110 mg; range, 418–2440 *vs.* group B, 886 mg; range, 480–1905) and serum 25-hydroxyvitamin D concentrations [group A, 55 (22) nmol/L, mean (SD), *vs.* group B, 53 (30) nmol/L] were similar in both groups. Markers of bone turnover did not change in group A, except an increase in total and BAP, although less marked than in group B ($P < 0.0005$). Serum osteocalcin, total and BAP, and urinary hydroxyproline increased in group B. After 2 yr of treatment with L-thyroxine, TSH values were inversely correlated with alkaline phosphatase ($r = -0.70$, $P < 0.001$), BAP ($r = -0.72$, $P < 0.001$), osteocalcin ($r = -0.36$, $P = 0.08$), and the hydroxyproline to creatinine (Hp/Cr) ratio ($r = -0.62$, $P < 0.001$). At 2 yr, a positive correlation was noted between osteocalcin and the Hp/Cr ratio ($r = 0.70$, $P < 0.001$) in group B, but not in group A.

BMD changes

Measurements of BMD are given in Table 3. No differences between groups A and B were noted in smoking history, alcohol and coffee intake, physical activity, body weight, menarche, time and duration of menopause, and use of oral contraceptives. Pretreatment values of patients of groups A and B were not different. Z-scores in groups A and B were

TABLE 3. Bone parameters before and after 1 yr and 2 yr of treatment with ^{131}I (group A) or L-thyroxine (group B)

	Group A (n = 24)				Group B (n = 25)				
	Baseline	At 1 yr	At 2 yr	P^a	Baseline	At 1 yr	At 2 yr	P^a	P^b
Ca corrected (mmol/L)	2.15 (0.09)	2.12 (0.07)	2.15 (0.08)	0.22	2.17 (0.08)	2.18 (0.09)	2.19 (0.09)	0.43	0.77
AP, total (U/L)	59 (19)	64 (15)	68 (21)	<0.001	55 (11)	74 (24)	73 (22)	<0.001	<0.005
AP, bone fraction (U/L)	10 (6–25)	12 (5–29)	14 (5–36)	<0.001	11 (5–22)	16 (6–43)	15 (5–39)	<0.001	<0.005
Osteocalcin (μg/L)	1.74 (0.99)	2.25 (1.18)	2.12 (1.08)	0.39	1.72 (1.03)	2.99 (1.75)	2.63 (1.51)	<0.001	0.05
Ca/Cr (mmol/mmol)	0.18 (0.07–0.60)	0.20 (0.11–1.86)	0.25 (0.04–1.11)	0.61	0.21 (0.05–0.64)	0.25 (0.08–1.14)	0.25 (0.07–1.08)	0.13	0.89
Hp/Cr (umol/mmol)	15 (5)	15 (8)	13 (6)	0.25	14 (5)	22 (8)	18 (10)	<0.001	<0.005
Lumbar spine (g/cm^2)	1.09 (0.19)	1.09 (0.19)	1.09 (0.18)	0.75	1.09 (0.22)	1.06 (0.22)	1.05 (0.23)	<0.001	0.001
Femoral neck (g/cm^2)	0.88 (0.16)	0.88 (0.16)	0.87 (0.15)	0.88	0.88 (0.13)	0.86 (0.12)	0.86 (0.12)	0.19	0.46
Trochanter (g/cm^2)	0.73 (0.11)	0.73 (0.11)	0.72 (0.10)	0.62	0.74 (0.11)	0.73 (0.11)	0.73 (0.10)	0.46	0.81

Values as mean (SD) or median (range). Ca, Calcium; AP, alkaline phosphatase.

[a] P value for the comparison in changes within groups; analysis by ANOVA, repeated measurements.

[b] P value for the comparison in changes between groups; analysis by ANOVA, repeated measurements (time × group).

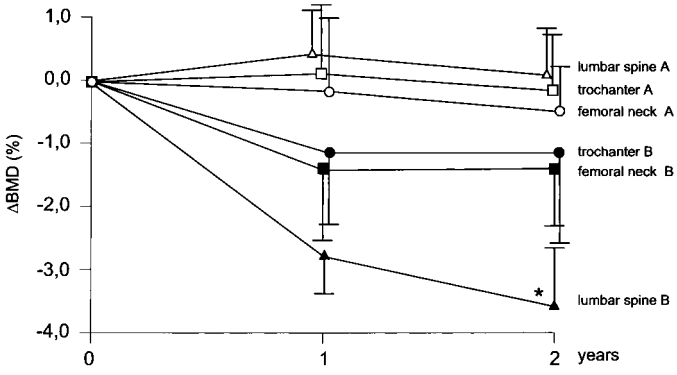

FIG. 4. Relative changes of BMD (given as mean and SEM) at the lumbar spine, femoral neck, and trochanter 1 and 2 yr after treatment with ^{131}I (group A) or L-thyroxine (group B).

not different either: lumbar spine as mean (SD), 0.22 (1.02) *vs.* 0.19 (1.18); femoral neck, 0.34 (1.10) *vs.* 0.32 (0.94); and trochanter, 0.23 (0.90) *vs.* 0.26 (0.94). Postmenopausal women had significantly lower BMD values than premenopausal women. In group A, BMD did not change during treatment. In group B, BMD at the lumbar spine was reduced by 3.6% after 2 yr ($P < 0.001$; Fig. 4); the decrease was similar in pre- and postmenopausal women [from 1.19 (0.19) to 1.16 (0.19) g/cm^2 ($P = 0.002$; mean decrease, 2.6%) and from 0.93 (0.17) to 0.89 (0.18) g/cm^2 ($P = 0.003$; mean decrease, 5.0%), respectively]. BMD of femoral neck and trochanter also decreased in group B, although not significantly (Fig. 4). Patients in group B with a baseline TSH below 0.4 mU/L had a lower baseline BMD at the lumbar spine ($P < 0.05$) and a larger decrease in BMD at the lumbar spine after 2 yr of treatment [from 0.94 (0.19) to 0.88 (0.21) g/cm^2, $P = 0.002$] than patients with a normal baseline TSH value [from 1.15 (0.21) to 1.12 (0.20) g/cm^2, $P = 0.001$; mean change, -7.2% *vs.* -2.2%, $P < 0.05$]. An inverse relationship was found between the changes in BMD at the lumbar spine and the changes in BAP ($r = -0.42$, $P < 0.05$) or the Hp/Cr ratio ($r = -0.48$, $P < 0.05$) in group B, but not in group A.

Discussion

Efficacy

The present study demonstrates that radioiodine treatment is far more effective in reducing the size of SNGs than suppressive doses of L-thyroxine: in the ^{131}I-treated patients, there were 97% responders with a decrease in goiter size of 46% compared with 43% responders in the L-thyroxine-treated patients in whom goiter size decreased by 22%. The observed effect size of both treatment modalities is in good agreement with earlier studies: a reduction in goiter size of 40–60% has been reported in 80–100% of the patients treated with ^{131}I in open studies (19–23) and of 25% in 59% of the patients treated with L-thyroxine in a placebo-controlled trial (12).

Chances for goiter reduction on T_4 treatment were less if pretreatment TSH was already suppressed. Moreover, patients with a suppressed baseline TSH value had a larger decrease in BMD at the lumbar spine after 2 yr of treatment, and one patient of 55 yr developed atrial fibrillation after 15 months of L-thyroxine treatment. Our observations extend on an earlier finding that among people 60 yr of age and older, a serum TSH of less than 0.1 mU/L is associated with a 3-fold higher risk for developing atrial fibrillation in the next decade (13). We conclude that T_4 treatment is apparently contraindicated if TSH is below 0.1 mU/L, irrespective of age.

The administered dose of ^{131}I is obviously a determinant of goiter reduction by radioiodine treatment (23). This could not be evaluated in the present study because all patients received the same dose of 4.44 MBq/g thyroid. We calculated the ^{131}I dose on goiter size measured by ultrasonography. Scintigraphic measurement of the size of nodular goiters may differ considerably from ultrasonographic measurements (25–27). The precise method of assessing nodular goiter size should, thus, be taken into account when comparing literature data on the outcome of ^{131}I therapy. In our series, the outcome of radioiodine treatment was inversely related to goiter size: the larger the goiter, the smaller the relative decrease in size. To enhance the efficacy of ^{131}I therapy and to limit the theoretical risk of cancer induction through the radiation burden of large doses of ^{131}I, one could argue to administer radioiodine at an earlier stage when the goiter is still smaller, allowing a lower ^{131}I dose. The gain, however, must be weighted against an increased risk on postradioiodine hypothyroidism, because patients with smaller goiters are less likely to have suppressed TSH values, which in the present study protected against the development of hypothyroidism.

Side effects

The price to be paid for the good efficacy of ^{131}I therapy is the rather high incidence of hypothyroidism. Our figure of 45% is relatively high compared with some, but not all, previous studies (17, 19, 20, 23); the differences may be explained by the fact that in our study ^{131}I-treated patients were given L-thyroxine as soon as TSH rose above 4.0 mU/L, aiming at TSH levels in the normal range to prevent regrowth of the goiter. Knowing that hypothyroidism may be transient after ^{131}I treatment for hyperthyroidism (28), we, thus, could have overestimated the percentage of patients with permanent hypothyroidism in our study. Determinants of postradioiodine hypothyroidism in our series were baseline TSH and the presence of TPO antibodies, as reported before (29). Other side effects of ^{131}I therapy were transient in nature and limited in number.

Among the patients of group B receiving T_4, 10 developed thyrotoxic symptoms, necessitating premature discontinuation of T_4 in 2 (in 1 because of atrial fibrillation). The administration of TSH-suppressive doses of T_4 did not change serum concentrations of SHBG, lipids, and IGF-I. These markers for the effect of thyroid hormones on peripheral tissues, thus, did not indicate tissue thyrotoxicosis in the liver. Our findings are in disagreement with two previous cross-sectional studies reporting lower total and (low-density lipoprotein) cholesterol values in spontaneous subclinical hyperthyroidism (30) and in L-thyroxine-treated patients with suppressed TSH compared with controls (31). A longer exposure time in these studies than the 2 yr in the present study might explain the discrepancy.

In bones, however, the consequences of induced subclinical hyperthyroidism maintained for 2 yr were striking. Stratification for sex and menopausal age at randomization allowed us to compare BMD and bone turnover in two homogeneous

groups composed of pre- and postmenopausal women, who had received radioiodine or T_4 treatment. BMD and markers of bone turnover did not change in the ^{131}I-treated group, except for an increase of total and BAP, which remains unexplained. In the T_4-treated group, the increase of BAP was larger than after ^{131}I ($P < 0.005$) and was accompanied by an increase in serum osteocalcin and urinary hydroxyproline, indicating a rise of both bone formation and bone resorption, which were related to the fall of TSH. The inverse relationship between serum TSH and bone turnover has been noted before (32). The increased bone turnover was associated with a decrease of BMD at the lumbar spine, which was present both in pre- and postmenopausal women (2.6% and 5.0%, respectively); a decrease of BMD at the femoral neck and trochanter was also observed but failed to reach significance, probably due to a small sample size. Two meta-analyses of published studies (all cross-sectional) on suppressive thyroid hormone therapy showed significant bone loss in postmenopausal, but not in premenopausal, women (14, 15). The authors recommended a large, double-blind, placebo-controlled trial (in patients with benign nodules, receiving suppressive T_4 treatment for at least 2 yr), to get definitive answers. Our trial seems to meet this ideal study design to a large extent and demonstrates that prolonged subclinical hyperthyroidism has an adverse effect on bone mass not only in post- but also in premenopausal women. Two other recent prospective, although nonrandomized, trials are in agreement with our findings. A longitudinal study in premenopausal women indicated spinal bone loss of $0.2 \pm 1.2\%$ per year in controls, significantly less than $2.6 \pm 1.9\%$ in patients on suppressive T_4 therapy after (sub)total thyroidectomy for goiter or cancer (33). Another study in nontoxic goiter patients on suppressive therapy with T_4 also suggests reduction of BMD relative to age-matched controls, in both pre- and postmenopausal women (34). One may question the appropriateness of the radioiodine-treated patients as a control group in our study. One could argue that the preserved BMD in the radioiodine group is explained by correction of slight thyroid hormone excess (35) and that the observed bone loss in the T_4-treated patients is due to natural history. However, a decrease in BMD at the lumbar spine of 2.6% in premenopausal women treated with L-thyroxine is far more than expected by aging with 2 yr, and the absence of any change in BMD in our radioiodine-treated patients was found irrespective of baseline TSH levels, both in pre- and postmenopausal women.

Treatment perspectives

The side effects of suppressive T_4 therapy are not negligible, because suppressed TSH levels (defined as <0.1 mU/L) increase the risk for atrial fibrillation and the observed bone loss constitutes a risk factor for fractures. Because reduction of goiter size during T_4 treatment is lost on discontinuation of the drug (12), continuous treatment is necessary; long-term exposure to suppressed TSH values raises concern as to the safety of this treatment modality for nontoxic goiter. Taken together with the modest efficacy of T_4, we do not recommend it any longer for the treatment of nontoxic nodular goiter, also because an attractive nonsurgical alternative is available: radioactive iodine. ^{131}I therapy is simple, devoid of major side effects, and effective. Although hypothyroidism develops in approximately half of the patients, it is easily treated with T_4, not requiring TSH-suppressive doses. The efficacy of ^{131}I can be enhanced by treatment at an earlier stage when the goiter is still smaller; this will also add to the long-term safety of radioactive iodine, by allowing the application of a lower dose of ^{131}I.

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