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Effects of Thyroid-Stimulating Hormone Suppression with Levothyroxine in Reducing the Volume of Solitary Thyroid Nodules and Improving Extranodular Nonpalpable Changes: A Randomized, Double-Blind, Placebo-Controlled Trial by the French Thyroid Research Group

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The efficacy of suppressing TSH secretion with levothyroxine (L-T_4) in reducing solitary thyroid nodule growth is still controversial. In this prospective multicenter, randomized, double-blind, placebo-controlled trial, 123 patients with a single palpable benign nodule were included and randomly allocated to an 18-month treatment with L-T_4 or placebo. Individual dose was adjusted to allow a serum TSH level below 0.3 mIU/liter. Clinical and ultrasonographic nodule characteristics were assessed before treatment and 3, 6, 12, and 18 months thereafter.

The largest mean nodule size assessed on palpation and largest volume, assessed by ultrasonography, decreased in the L-T_4 group and increased slightly in the placebo group [size, −3.5 ± 7 mm *vs.* +0.5 ± 6 mm ($P = 0.006$); volume, −0.36 ± 1.71 ml *vs.* +0.62 ± 3.67 ml ($P = 0.01$), respectively]. The proportion of clinically relevant volume reduction (≥50%) rose significantly in the L-T_4 group [26.6% *vs.* 16.9% ($P = 0.04$)]. The proportion of patients with a reduced number of infraclinical additional nodules was significantly higher in the L-T_4 group [9.4% *vs.* 0 ($P = 0.04$)].

It is concluded from this study that suppressive L-T_4 therapy is effective in reducing solitary thyroid nodule volume and improving infraclinical extranodular changes. (*J Clin Endocrinol Metab* 87: 4928–4934, 2002)

THYROID NODULES ARE a common clinical dilemma for which physicians and surgeons are often asked to make a diagnostic or management decision (1). Clinically visible nodules are present in 4–7% of the general adult population (2–4). Autopsy (5), surgery (6), and ultrasound studies (7) have revealed discrete nodules in up to 50% of individuals. The efficacy of levothyroxine (L-T_4) in reducing thyroid nodule size remains controversial. The purpose of L-T_4 administration was originally to reduce the growth-promoting effect of TSH (8–10). However, during the last 15 yr, several authors have undermined this concept by failing to prove the efficacy of L-T_4 (11–14). Others believe that nodules should be left to regress spontaneously (15–17). Concern was also expressed about the risk-benefit ratio of L-T_4 administration (17, 18). Nevertheless, general clinical experience, controlled studies (12, 19), as well as a recent meta-analysis (20) and a study using the so-called quantitative research synthesis (21) indicate that at least some nodules shrink under L-T_4. Furthermore, negative studies may have been hampered by imprecise definition of the nodules, insufficient L-T_4 dosage or duration of treatment, or insufficiently restrictive inclusion criteria. Many previous trials were not randomized or placebo-controlled. Finally, little information is available on factors predictive of nodule shrinkage as well as on the possible beneficial effect of L-T_4 treatment on extranodular nonpalpable changes.

The French Thyroid Research Group therefore undertook a multicenter, prospective, randomized, double-blind, placebo-controlled trial to assess the efficacy of TSH-suppressing L-T_4 therapy in reducing the volume of solitary benign thyroid nodules and in modifying perinodular thyroid tissue.

Abbreviations: fT_3, Free T_3; fT_4, free T_4; L-T_4, levothyroxine.

Patients and Methods

Study design

This study was a multicenter, randomized, double-blind, placebo-controlled clinical trial designed to establish whether or not the administration of L-T_4 reduces the volume of thyroid nodules found to be solitary by clinical examination. We enrolled patients when they had a single palpable nodule proven to be benign by fine-needle aspiration biopsy and they were identified less than 1 yr before the study began. The following were excluded from the study: patients with more than one palpable nodule, and patients with a history of cardiovascular disease, osteoporosis, previous thyroid surgery, neck irradiation, and/or thyroiditis. Also excluded were patients with abnormal serum thyroid hormone or TSH levels, circulating autoantibodies, patients who

had nodules with a cystic component exceeding 20%, and patients with hot nodules and suppression of surrounding tissue at thyroid imaging. No patient included was taking any medication. Only patients aged from 18–55 yr were enrolled. All patients were from France, an area in which median urinary iodine excretion (8 μg/100 ml) suggests a quite sufficient iodine supply (22).

Nodule size, location, shape (oval or round), consistency, and boundaries were carefully recorded. Nodule size was measured by high-frequency ultrasonography. Thyroid scanning was performed. We also measured the following in all patients: serum levels of free T_3 (fT_3) and free T_4 (fT_4; radioimmunometric assays), TSH (immunochemoluminometric assays), and antithyroglobulin, antithyroperoxidase, and anti-TSH receptor antibodies (hemagglutination or solid immunoradiometric assays). Patients were then randomly allocated to the L-T_4 treatment or placebo group using a table of random numbers, without stratification according to site. Oral L-T_4 was given at an initial dose of 2.5 μg/kg body weight per day, to be taken in a single dose in the morning. The dose was individually adjusted after the first 4 wk, to maintain serum TSH levels below normal values (<0.3 mIU/liter). Both L-T_4 and placebo were administered as externally identical tablets.

Patients were seen after 3, 6, 12, and 18 months of L-T_4 treatment. At each visit, they were assessed by the same physician for weight, blood pressure, heart rate, nodule palpation, and signs and symptoms of thyrotoxicosis. β-Blocker prescription was allowed if a patient complained of tachycardia (bisoprolol, 5–10 mg/d). Compliance with therapy was individually checked by careful questioning of the patient and measurement of serum TSH levels. Serum thyroid hormones were measured at each visit and additionally when L-T_4 dose had been changed. Ultrasonography was repeated at 6, 12, and 18 months, and the ultrasonography examiner had no access to previous findings about the nodule, TSH levels during the study, or the treatment code. Fine-needle aspiration biopsy was repeated at 12 months. All patients admitted to the study had given informed consent to the protocol, which was approved by our institutional Ethics Committee.

Ultrasonography

High-resolution ultrasonography imaging was performed with a commercially available real-time instrument (10 MHz). The maximal diameter of the palpable nodule was measured in three planes. Patients with nodules larger than 3 cm in any dimension were excluded, because such nodules could not be accurately measured. The sonographic characteristics of the nodule were recorded to determine whether the internal contents were cystic, solid, or mixed, or whether peripheral halo (hypoechogenic pad surrounding the nodule) or calcifications were present. The ultrasonography examiner also mentioned the presence of other nonpalpable thyroid nodules, and extranodular nonpalpable changes were defined as the presence of at least one additional nonpalpable nodule. The volume of the palpable nodule was calculated according to the spherical ellipsoid formula: volume (ml) = $\pi/6 \times$ AP (cm) $\times$ width (cm) $\times$ length (cm), where AP is the anteroposterior diameter (23). The dimensions of the thyroid lobes homolateral and contralateral to the palpable nodule were also measured in three planes. In all patients, ultrasound examinations were carried out before fine-needle aspiration biopsies (24).

Fine-needle aspiration biopsy

Direct or ultrasonography-guided fine-needle aspiration biopsies were performed by a trained cytologist or clinician according to the recommended techniques (25). Several samples of each nodule were obtained, and smears were prepared on microscopic slides, immediately fixed in 95% ethyl alcohol while still wet, and stained by the Papanicolaou method (25).

Thyroid scanning

Thyroid scans were performed after pertechnetate-99m iv administration. Nodules were classified as follows, according to the activity recorded in the region of the nodule: nonfunctional, if only background activity was seen; hypofunctional, if isotope activity was equal to or less than that of the surrounding parenchyma; and functional, if isotope activity was increased with no suppression of the surrounding parenchyma.

Statistical analysis

According to previous reports, a reduction of 0.5 ml in nodule volume could be expected after 6 months of suppressive L-T_4 treatment. We considered therapy successful when it induced a 0.75-ml reduction in nodule volume after 18 months of suppressive L-T_4 treatment. Given a type I error of 0.05 (two-sided) and a power of 0.9, we estimated the necessary sample size to be 127 patients in each group. Considering that about 10% of patients might not complete the protocol, the total sample size necessary was estimated at 300.

Analyses were completed on an intention-to-treat basis. Results for continuous measures are expressed as means $\pm$ SD. All comparisons between the L-T_4 and placebo groups were based on two-tailed, two-sample *t* tests for quantitative variables, except for skewed variables that were analyzed using the Wilcoxon rank-sum test. The χ^2 and Fisher exact tests were used to calculate differences between proportions.

Results

Pretreatment findings

Despite an expected total sample of 300 patients, patient recruitment was difficult, and it was stopped after 135 informed patients had been enrolled at 25 study centers. In all, 123 patients (91%) were available for evaluation of the main judgment criteria, *i.e.* variations in nodule volume. Sixty-four of these 123 patients were randomly assigned to the L-T_4 group, and 59 to the placebo group. All patients were clinically and biologically euthyroid on entry into the study. At baseline, there were no apparent differences between the distribution of demographic or other characteristics between the two groups (Table 1).

Of the 123 patients included, 106 (86%) completed the 18-month protocol, and 17 did not. In the L-T_4 group, 4 patients were treated for 6 months, 2 for 12 months, and 58 for 18 months. In the placebo group, 2 patients complied with the procedure for 6 months, 9 for 12 months, and 48 for 18 months. Six of the 17 patients who did not complete the protocol spontaneously decided to withdraw from the study. Of the remaining 11, 2 patients receiving L-T_4 treatment dropped out (one developed iatrogenic thyrotoxicosis and required dose reduction, and the other requested thyroidectomy because of nodule growth). The 9 other patients, who were in the placebo group, dropped out for the following reasons: 5 underwent hemithyroidectomy because of a suspect fine-needle aspiration biopsy at 12 months (papillary carcinoma in 1 patient), 1 patient refused further treatment at 12 months because of nodule pain, 1 patient decided to have surgery at 6 months for a benign follicular adenoma, 1 patient was diagnosed as having myeloproliferative syndrome at 1 month, and 1 patient was diagnosed at 10 months as having hyperthyroidism and Graves' disease. The characteristics of the patients who dropped out and of their nodules were similar to those of the patients who completed the study (data not shown).

Treatment tolerance and patient compliance

Compliance with treatment was good in all patients studied, according to patient self-reporting, clinical examination, and laboratory. Compliance was also evaluated by systematically getting tablet packaging back. In all patients receiving L-T_4, the serum TSH level was less than 0.3 mIU/liter after 3, 6, and 12 months of treatment (Table 2). However, at 18 months, mean TSH level was 0.38 $\pm$ 0.66 mIU/liter, sug-

TABLE 1. Initial clinical, biological, and thyroid nodule characteristics in patients given L-T_4 or placebo

	L-T_4 group (n = 64)	Placebo group (n = 59)
Mean age (yr)	40.0 ± 9.03	38.2 ± 9.24
Sex (M/F, %)	9.4/90.6	10.2/89.8
Weight (kg)	63.22 ± 11.6	59.6 ± 9.77
Height (cm)	163.4 ± 6.2	162.6 ± 6.6
Systolic blood pressure (mm Hg)	122.7 ± 9.8	123.5 ± 8.92
Diastolic blood pressure (mm Hg)	73.6 ± 7.67	72.3 ± 8.48
Heart rate (beats/min)	71.5 ± 8.81	73.7 ± 8.43
Nodule characteristics on palpation		
Largest dimension (mm)	19 ± 5	20 ± 5
Consistency (hard/soft, %)	93.8/6.2	94.9/5.1
Location (right/left/isthmus, %)	67.2/25/7.8	54.2/35.6/10.2
Upper/middle/lower third of the lobe[a]	9.4/34.4/51.6	8.5/30.5/54.2
Regular nodule limits (%)	100	100
Nodule shape (round/oval, %)	45.3/54.7	45.8/54.2
Thyroid scan imaging		
Nodule function (functional/hypofunctional, %)	1.6/98.4	5.1/94.9
Surrounding parenchyma (homogeneous/heterogeneous, %)	95.3/4.7	94.9/5.1
Nodule characteristics on ultrasonography		
Nodule largest dimension (mm)	21 ± 6	22.8 ± 6.3
Nodule volume (ml)	2.76 ± 2.47	3.50 ± 2.95
Nodule cystic component (%)	4.35	8.47
Perinodular halo (%)	39.1	33.9
Nodule calcifications (%)	4.7	1.7
Thyroid parenchyma on ultrasonography		
Extranodular nonpalpable changes (%)	42.2	33.9
Homolateral lobe height (mm)	50.5 ± 9	48.1 ± 13.2
Homolateral lobe thickness (mm)	17.2 ± 5.2	18.3 ± 6.7
Homolateral lobe volume (ml)	18.3 ± 11.6	19.9 ± 13.1
Contralateral lobe height (mm)	46.5 ± 9.6	41.9 ± 11.1
Contralateral lobe thickness (mm)	13.8 ± 3.7	14.6 ± 4.7
Contralateral lobe volume (ml)	11.4 ± 6.6	10.9 ± 5
TSH (0.15–3 mIU/liter)	1.12 ± 0.59	1.07 ± 0.76
fT_3 (3.2–6 pmol/liter)	4.23 ± 0.69	4.25 ± 0.63
fT_4 (9–30 pmol/liter)	18.1 ± 4.35	17.5 ± 4.36

M, Male; F, female.
[a] Not available in 4.6% and 6.8% in L-T_4 and placebo groups, respectively.

TABLE 2. Levels of TSH in the L-T_4 group at each measurement point

	Before L-T_4	3 months	6 months	12 months	18 months
TSH < 0.01	0	4 (6.25%)	7 (10.9%)	0	2 (3.6%)
0.01 ≤ TSH < 0.05	0	20 (31.25%)	16 (25%)	10 (16.9%)	8 (14.3%)
0.05 ≤ TSH < 0.1	0	14 (21.9%)	9 (14.1%)	10 (16.9%)	6 (10.7%)
0.1 ≤ TSH	64 (100%)	26 (40.6%)	32 (50%)	39 (66.2%)	40 (71.4%)
Total	64 (100%)	64 (100%)	64 (100%)	59 (100%)	56 (100%)

TSH levels are given in milli IU per liter. In the placebo group, all patients had TSH levels higher than 0.01 mIU/liter at each measurement point except one patient at 12 months who developed hyperthyroidism (TSH < 0.01 mIU/liter) further related to Graves' disease.

gesting mild lack of compliance at the end of the study. In this group, the mean dose of L-T_4 necessary to obtain effective TSH suppression without hyperthyroidism was 2.24 ± 0.45 μg/kg·d. A significant difference was observed in TSH levels in the L-T_4 and placebo groups at the end of the study (Table 3). Although in the average, fT_3 levels were not significantly different, the difference between the average fT_4 levels also reached statistical significance (Table 3). Furthermore, at the end of the study, ultrasonography showed significant differences between the two groups as regards the mean size and volume of the thyroid lobe contralateral to the palpable nodule (Table 3). The mean size and volume of the ipsilateral lobe also decreased, although not significantly.

Variations in heart rate and blood pressure (systolic and diastolic) were not different in the two groups (Table 3). Although the proportion of patients requiring at least one dose of β-blocker during the study was larger in the L-T_4 group than the placebo group, the difference did not reach significance (Table 3). One patient in each group developed severe hyperthyroidism requiring withdrawal from the study. Subsequently, the patient in the placebo group proved to have underlying Graves' disease.

Nodule response to treatment

The maximal dimensions of the nodule, as assessed by palpation and ultrasonography, were compared in the two groups before and at the end of the study. In the L-T_4 group, the mean maximal nodule diameter measured by palpation before treatment was not different from that in the placebo

TABLE 3. Mean variations in the clinical, biological, and ultrasonographic characteristics of patients with a solitary thyroid nodule after 18 months of treatment with L-T_4 or placebo

	L-T_4 (n = 64)	Placebo (n = 59)	*P*
Weight (kg)	+0.25 ± 0.46	+0.64 ± 0.31	0.885
Heart rate (beats/min)	−1.59 ± 9.94	−1.36 ± 8.52	0.95
Systolic blood pressure (mm Hg)	−0.47 ± 11.6	+0.08 ± 12.5	0.76
Diastolic blood pressure (mm Hg)	−0.89 ± 8.97	+1.39 ± 9.37	0.15
TSH levels (mIU/liter)	−0.73 ± 0.81	+0.05 ± 0.98	0.0001
fT_3 levels (pmol/liter)	+0.25 ± 1.03	−0.02 ± 0.82	0.14
fT_4 levels (pmol/liter)	+8.41 ± 8.14	−0.49 ± 5.19	0.0001
Homolateral lobe size			
Height (mm)	−4.37 ± 10.1	+0.65 ± 13.6	0.17
Thickness (mm)	−1.16 ± 5.02	−0.71 ± 6.4	0.08
Volume (ml)	−3.32 ± 8.45	−0.88 ± 8.72	0.17
Contralateral lobe size			
Height (mm)	−4.74 ± 10.3	+3.8 ± 13.2	0.0001
Thickness (mm)	−0.77 ± 2.92	−0.05 ± 0.05	0.004
Volume (ml)	−2.21 ± 3.52	+0.72 ± 3.53	0.0001
Need for β-blockers (%)	17.4	10.6	0.33

Homolateral and contralateral lobes are defined according to the localization of palpable thyroid nodule.

group (19 ± 5 *vs.* 20 ± 5 mm). At the end of the study, a significant decrease in the size of the largest nodules, as assessed by palpation, was observed in the L-T_4 group (mean change, −3.5 ± 7 mm), whereas in the placebo group nodule size increased by a mean +0.5 ± 6 mm (Table 4). The change in the largest size of the nodule was significantly different in the two groups ($P = 0.006$). It was also different, although not significantly (−1.25 ± 5.57 mm *vs.* +0.44 ± 6.9 mm; $P = 0.07$), when nodule diameter was assessed by ultrasonography (Table 4).

Nodule volume assessed ultrasonographically was also used to compare responses to therapy (Table 4). In the L-T_4 group, compared with the initial value (2.76 ± 2.47 ml), a clear decrease was observed as soon as the sixth month (2.30 ± 2.01 ml), whereas no clear change was noted in the placebo group (3.50 ± 2.95 and 3.62 ± 3.24 ml, respectively). At the end of the study, the decrease in nodule volume was confirmed in the L-T_4 group (mean change, −0.36 ± 1.71 ml). However, in the placebo group, nodule volume increased (mean change, +0.62 ± 3.67 ml). The change in volume was significantly different in the two groups ($P = 0.01$).

On the basis of the nodule volume recorded at the end of L-T_4 therapy, the 123 patients were classified as responders (≥50% decrease), partial responders (≥20% to 50%), and nonresponders (<20%). As shown in Fig. 1, there were 17 responders among the 64 patients given L-T_4 (26.6%), and 10 responders among the 59 patients receiving placebo (16.9%). The proportions of responders, partial responders, and nonresponders were significantly different in the two groups ($P = 0.04$).

Factors predictive of nodule shrinkage

In managing patients with a solitary thyroid nodule, it would be helpful to identify the nodules likely to shrink. We therefore attempted to define clinical, biological, ultrasonographic, or scintiscan characteristics predictive of nodule shrinkage. Using regression analysis, we failed to correlate shrinkage with any of the following characteristics: age, sex, nodule shape and location on palpation, pretreatment TSH and fT_4 levels, and ultrasonographic nodule characteristics such as size, presence, or absence of perinodular halo, echotexture, and nodule function shown by thyroid scan imaging. However, we did find that nodule shrinkage was related to the initial nodule volume as assessed ultrasonographically, *i.e.* the larger the pretreatment nodule volume, the larger the reduction in that volume. We checked that when adjusted for pretreatment volume, the effect of L-T_4 on the nodule volume was still significantly different from that of placebo ($P = 0.03$).

TABLE 4. Mean changes in solitary thyroid nodule size and volume after 18 months of L-T_4 or placebo treatment

	L-T_4	Placebo	*P*
Palpation			
Largest nodule dimension (mm)	−3.5 ± 7	+0.5 ± 6	0.006
Ultrasonography			
Largest nodule dimension (mm)	−1.25 ± 5.57	+0.44 ± 6.9	0.07
Nodule volume (ml)	−0.36 ± 1.71	+0.62 ± 3.67	0.01

Response of extranodular nonpalpable changes to treatment

Although according to palpation, each patient was diagnosed as having only a single nodule, 27 patients in the L-T_4 group (42.2%) and 20 in the placebo group (33.9%) were found to have at least one additional nodule on ultrasonography. At the end of the study, these proportions were 40.6% (26 patients) and 47.5% (28 patients), respectively. Extranodular nonpalpable changes were classified as improved (disappearance of at least one of the additional infraclinical nodules), unchanged (no change in the number of these nodules), or worse (appearance of at least one other additional infraclinical nodule). Figure 2 depicts the evolution of extranodular nonpalpable changes at the end of the study. The respective distributions of improvement, lack of change, and worsening were significantly different in the L-T_4 and placebo groups ($P = 0.04$). Compared with placebo, L-T_4 therapy therefore improved or arrested the evolution of extranodular nonpalpable changes.

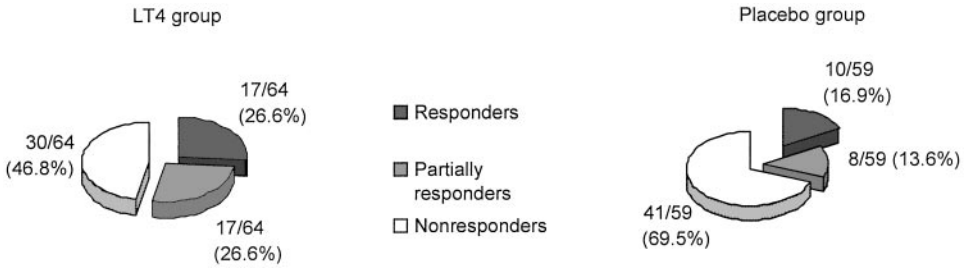

FIG. 1. Distribution of clinically relevant reductions in thyroid nodule volume in patients given L-T_4 and those given placebo. Significantly different distribution in the L-T_4 and placebo groups ($P = 0.04$, χ^2 test). Responders, volume reduction $\geq 50\%$; partial responders, $20\% \leq$ volume reduction $< 50\%$; nonresponders, volume reduction $< 20\%$.

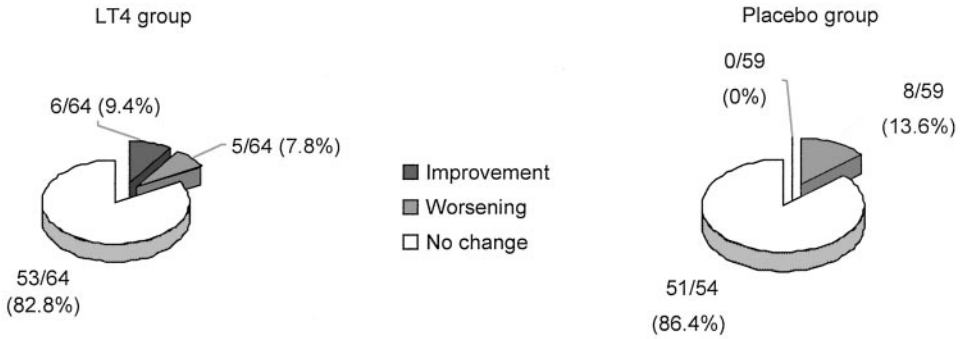

FIG. 2. Distribution of changes in extranodular nonpalpable changes in patients given L-T_4 and those given placebo. Significantly different distribution in the L-T_4 and placebo groups ($P = 0.04$, Fisher exact test). Improvement, disappearance of at least one of additional infraclinical nodule; No change, no change in the number of additional infraclinical nodules; Worsening, appearance of at least one other additional infraclinical nodule.

TABLE 5. Summary of the randomized studies addressing the efficiency of L-T_4 in reducing nodule growth

First author	Gharib	Cheung	Reverter	Papini	La Rosa	Zelmanovitz	Papini	Larijani	Present study
Reference no.	11	28	14	13	19	20	29	30	
Year	1987	1989	1992	1993	1995	1998	1998	1999	2001
No. of patients	53	74	40	101	45	45	83	62	123
Treatment duration (months)	6	18	11	12	12	12	60	12	18
Placebo-controlled	Yes	No	No	Yes	No	Yes	No	Yes	Yes
Double-blind	Yes	No	No	Yes	No	Yes	No	Yes	Yes
Ultrasound examination	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Significant change in nodule sizes	No	No	No	Yes	Yes	No	No	No	Yes
Significant differences in the proportion of responders between L-T_4 and control or no-treatment groups	No	NA	No	Yes	Yes	No	NA	NA	Yes

NA, Not available.

Discussion

This multicenter, prospective, randomized, double-blind, placebo-controlled trial, conducted in 123 patients, shows that the mean size of a palpable thyroid nodule, as well as the mean nodule volume assessed ultrasonographically, decreased in patients treated for 18 months with TSH-suppressive L-T_4 therapy, compared with the patients given placebo. We observed a clinically relevant reduction in nodule volume ($\geq$50%) in 17 of the 64 patients receiving L-T_4 and in 10 of the 59 placebo-treated patients. In addition, we showed that L-T_4 therapy has a favorable effect on the development of extranodular nonpalpable changes.

The effectiveness of L-T_4 in reducing the size of thyroid nodules remains controversial (1), although survey data suggested that many endocrinologists would recommend maintaining serum TSH concentrations below, or at least within the low normal range (21, 26). The effect of L-T_4 treatment on thyroid nodule volume has been extensively studied. However, except for one study published in 1963 (27), the results of which are questionable because of inappropriate methodology (21), only eight trials were randomized (Table 5; Refs. 11, 13, 14, 19, 20, 28–30). Six of them were negative, with no beneficial effect of L-T_4 therapy on nodule size (11, 14, 20, 28–30). Discrepancy between these six studies and the present one may be due to the absence of ultrasonography evaluation (28, 31), the lack of a placebo control group (14, 28), uncontrolled or inefficient TSH suppression (11, 32), insufficient treatment duration (11, 14, 20, 30), inclusion of hot or cystic nodules (11, 14), excessive dropout rate in the L-T_4 group (14, 33), and/or an insufficient number of patients

(20, 30). In the present study, we evaluated nodule size and volume in a double-blind manner, using high-resolution ultrasonography imaging. As many as 123 patients were given L-T_4 or placebo for 18 months, and effective TSH suppression was routinely checked at each visit. Our results are in keeping with those of a recent meta-analysis and of a quantitative research synthesis showing that suppressive L-T_4 therapy is effective in reducing nodule volume and impeding nodule growth (20, 21). They are also consistent with the last two randomized trials published (13, 19). These trials showed a significant decrease in nodule size or volume, as assessed by palpation and/or ultrasonography, in L-T_4-treated patients compared with baseline values. However, their authors did not compare the mean changes in nodule size in the L-T_4 and placebo groups, as was done in our study. This comparison enabled us to demonstrate that L-T_4 is significantly more effective than placebo in reducing thyroid volume.

In fact, the relevant issue is not the average nodule shrinkage, but rather the proportion of nodules that shrink relevantly (≥50% reduction) during L-T_4 therapy, compared with the substantial shrinkage reported for placebo-treated nodules (16, 21). Of the six previous randomized trials (Table 5), one (28) did not indicate the proportion of responders. This proportion was higher in the L-T_4 groups than in the placebo or no-treatment groups in three of the five other trials (13, 19, 20), but the difference was only significant in two (13, 19). Our results clearly confirm that the proportion of responders is significantly increased by L-T_4 treatment.

There is increasing concern (34–36) about the risk-benefit ratio of L-T_4 therapy for thyroid nodule. Some authors reported bone mineral density decreases in L-T_4-treated patients (18, 37) as well as undesirable effects on the heart (38, 39) and suggested that the potential benefits of L-T_4 might be outweighed by the long-term potential risks, especially in postmenopausal women (40). In the present study, we did not evaluate the long-term effect of L-T_4 on bone. However, the deleterious effect of L-T_4 therapy remains questionable. Thus, no increase in bone fracture rate has been reported so far in any study of women treated with L-T_4 (16, 36), and in a recent study (20) no change was found in the mean bone mineral density of women after 1 yr of L-T_4 therapy for benign solitary thyroid nodules (TSH $<$ 0.3 mIU/liter). Another study (41) showed a significantly increased risk for new hip and vertebral fractures in women older than 65 yr of age who had low TSH levels, but not in those with L-T_4 therapy. Heart rate, blood pressure, and body weight were not significantly affected by L-T_4 compared with placebo in our study, despite daily doses sufficient to suppress TSH. No other similar clinical trial has consistently demonstrated a higher risk for L-T_4 than placebo or no treatment (12, 13). An interesting way of improving the risk-benefit ratio of L-T_4 would be to identify a subgroup of patients whose nodules will presumably respond to this drug. Baseline thyroglobulin levels and their decrease during treatment have been advocated as useful predictors of the outcome of L-T_4 therapy (42, 43), but we did not study these levels. In fact, in the present study as well as in others (13, 14), neither patient nor nodule characteristic was found to be a reliable predictor of nodule shrinkage during L-T_4 treatment, except for pretreatment nodule volume (44). Taking into account these consistent observations as well as the well known natural heterogeneity of thyroid follicles (45), it is suggested that intrinsic parameters of nodule biology are in themselves likely involved in variable response to L-T_4 therapy. For instance, the dependence of nodule development on growth factors different from TSH (46) might be responsible for these findings, in addition to the possible presence of mutations in the TSH receptor.

Another point of interest is the ability of L-T_4 to reduce or even prevent the development of additional nodules. This question has been rarely addressed in the literature (16). Papini *et al.* (29) observed that L-T_4-treated patients did not exhibit decreased thyroid nodule volume after 5 yr of treatment, but the nodule volume increased in the control group, in which there was a larger number of newly formed nodules. Our results suggest that L-T_4 therapy is more efficient than placebo in preventing the development of additional nodules and could reduce the occurrence of nodule volume-related complaints and the number of subsequent surgical operations for multinodular goiters (47).

In conclusion, we demonstrated that 18 months of TSH-suppressive L-T_4 therapy are effective in reducing the growth of solitary thyroid nodules as well as in preventing the further development of additional nodules in patients originating from an area with quite sufficient iodine supply. Clinically relevant reductions in thyroid nodule size were observed after L-T_4 therapy, without significant untoward effect. Complete regression of thyroid nodules seems anecdotal, but treatment with L-T_4 is worth recommending to reduce nodule size as well as to prevent further nodule growth and multinodular goiter development. Many questions remain to be answered, such as the optimal level of thyroid suppression, or the optimal duration of treatment. Further studies are also required to distinguish patients who are likely to benefit from suppressive L-T_4 therapy from those who are not.

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