0021-972X/99/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 84, No. 2
Printed in U.S.A.

Is Routine Thyroxine Treatment to Hinder Postoperative Recurrence of Nontoxic Goiter Justified?*

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ABSTRACT

Previous reports regarding the efficacy of levo-T_4 (L-T_4) in preventing postoperative recurrence of nontoxic goiter have been controversial. This study was designed to evaluate the influence of long-term L-T_4 treatment on thyroid volume after thyroidectomy for nontoxic goiter. We studied 202 consecutive patients operated on for benign nontoxic goiter and followed them for a minimum of 12 months (median, 10 yr; range, 1–14 yr). Three months after thyroidectomy, patients were randomized to L-T_4 treatment (group A, n = 100) with an initial dose of 150 μg daily and to no treatment (group B, n = 102). All were clinically and biochemically euthyroid, and preoperatively none were taking any thyroid and/or antithyroid medication. Standard thyroid function variables and ultrasonically determined thyroid volume (normal range, 9–28 mL) were determined before and 3 and 12 months after randomization and yearly thereafter. Recurrence was defined as an ultrasonically enlarged thyroid gland. Clinical data were similar between the two groups. Incidence of recurrence in group A was 19/100 (21%; 95% CL 0–42%; life-table analysis) and in group B 27/102 (35%; CL 7–64%) ($P = 0.16$) and was related to removed amount, remnant size, and pathoanatomical diagnosis but not type of operation or postoperative level of serum TSH and T_4. L-T_4 dose had to be reduced in 36 of 100 patients because of side effects of the treatment. In conclusion, the possible benefits of L-T_4 treatment should be weighed against the possible side effects. Our study does not support the routine postoperative use of L-T_4. (*J Clin Endocrinol Metab* **84:** 756–760, 1999)

IN ADDITION to indications for its use, the safety and possible side effects of long-term levo-T_4 (L-T_4) therapy has recently received increased attention (1–5). Available data, as reviewed in a recent metaanalysis, suggest that patients receiving suppressive therapy may have an increased likelihood of developing accelerated bone loss (6). However, the long-term effects on well being and the possible premature development of significant clinical syndromes have not yet been studied prospectively in a way allowing any consensus to be reached. Therefore, a critical reappraisal of the indications for L-T_4 therapy seems pertinent.

T_4 as well as T_3, if given to patients with diffuse nontoxic goiter, can suppress thyroid volume by up to 20–30% (7), an effect closely related to the suppression of serum TSH concentration. Such data are, however, controversial regarding the effect on other types of goiter or after thyroidectomy (4). Although the theoretic basis for L-T_4 administration to patients operated on for nontoxic goiter is evident, and this treatment is often recommended to prevent regenerative hyperplasia, relevant studies justifying such recommendations are lacking. In fact, most studies, mainly retrospective, have not been able to demonstrate an effect of L-T_4 treatment on goiter recurrence (8–14).

The present study aimed to investigate thyroid function and ultrasonically determined thyroid size (15) in a large consecutive group of patients operated on for nontoxic goiter and randomized postoperatively to L-T_4 treatment or no treatment, with a median follow-up period of 10 yr.

Received July 1, 1998. Revision received September 16, 1998. Rerevised received November 4, 1998. Accepted November 4, 1998.

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* This study was supported by grants from the Agnes and Knut Mørk Foundation.

Patients and Methods

Three months after operation for nontoxic goiter, 202 consecutive patients followed by one physician (J.M.H.) in an out-patient clinic were allocated by random numbers (16) to receive 150 μg T_4 daily or no treatment. Patients were included from February 1980 through July 1988 from the Copenhagen region where the average daily urinary iodine excretion is 80 μg (17). Six and 12 months after operation and yearly thereafter thyroid function and thyroid volume were reevaluated. The investigators performing the ultrasound scans were unaware of the study group to which patients had been allocated and of previous ultrasound results, other than that the study was not blinded. The study is in accordance with the Helsinki Declaration. The study was initiated before ethical committees were established in Denmark. All patients gave informed consent to the study. Table 1 summarizes the clinical details of patients in the two groups.

In a large nongoitrous group of healthy subjects, we found that thyroid volume ranged from approximately 9–28 mL (mean, 18.6; SD 4.5 mL) (15). We therefore defined recurrence of goiter as two consecutive measured volumes greater than 28 mL or, because 22 patients (11 randomized to receive T_4) had a thyroid volume of 28 mL or greater after thyroidectomy, as two consecutive volumes of more than 5 mL greater than the initial volume.

Serum concentrations of T_4 (normal range, 59–129 nmol/L) and T_3 (normal range, 1.0–2.5 nmol/L) and a T_3 uptake test (normal range, 0.80–1.25 arbitrary units) were determined by in-house methods (assay variation was 6%, 10%, and 5%, respectively). Serum concentration of TSH was determined, up to 1986, by a previously described RIA (15). From 1986 to 1989 we used an immunoradiometric assay (Boots-Celltech, England) with an intraassay coefficient of variation of 2.3–4.7% and a detection limit of 0.03 mU/L. Functional sensitivity of the TSH assays used from 1986 was 0.05 mU/L. From 1989 onward, we used the Delfia human TSH assay (Wallac, Turku, Finland), which has an intraassay coefficient of variation of 3.7–5.4% and a detection limit of 0.03 mU/L. Ultrasonic scanning and calculation of total thyroid volume (normal range, 9.6–27.6 mL) were performed as previously described (15) with compound scanners (types 3401 and 1846; Brüel and Kjær, Nærum,

TABLE 1. Postoperative data in 202 patients with nontoxic goiter subsequently randomized to T_3 or no treatment

Variable	Thyroxine treatment	No treatment
No. of patients	100	102
Unilateral resection	64	66
Bilateral resection	36	36
Male/female patients	15/85	14/88
Age (yr)	41 (15–71)	40 (19–68)
Weight of removed tissue (g)	38 (5–190)	37 (5–380)
Thyroid volume (mL)	18.0 (8–70)	18.8 (8–52)
TSH (mU/L)	2.0 (0.2–22.0)	2.0 (0.2–22.0)
T_4 (nmol/L)	94 (60–129)	92 (48–160)
T_3 (nmol/L)	2.0 (1.4–3.5)	2.0 (1.3–3.8)
Preoperative diagnosis		
Multinodular goiter	38	37
Solitary cold nodule	49	53
Diffuse goiter	3	3
Cyst	8	7
Autonomous nodule	2	2

Median values expressed with ranges in *parentheses.*

TABLE 2. Postoperative data in 202 consecutive patients with nontoxic goiter in relation to type of operation

Variable	Unilateral resection	Bilateral resection	*P* value
No. of patients	130	72	
Age (yr)	41 (19–71)	40 (15–68)	NS
Weight of removed tissue (g)	30 (5–166)	64 (8–380)	$P < 0.001$
Thyroid volume (mL)	19 (9–70)	18 (8–59)	NS
TSH (mU/L)	1.9 (0.2–22.0)	2.7 (0.2–13.0)	$P < 0.001$
T_4 (nmol/L)	96 (69–160)	89 (48–136)	$P < 0.01$
T_3 (nmol/L)	2.1 (1.5–3.8)	2.0 (1.3–2.7)	NS

Median values expressed with ranges in *parentheses.*

Denmark). The average inaccuracy of this method is 7%. The mean inter- and intraobserver variation is 5% (15, 18).

Statistical analyses

All data were analyzed according to the intention-to-treat principle. Results are expressed as medians and ranges. Unpaired data were compared by the Mann-Whitney *U* test and paired data by the Wilcoxon test (19). When calculating the incidence of recurrence, we used life-table analysis. Significance level was chosen at $P < 0.05$.

Results

Within the observation period, 17 patients randomized to L-T_4 treatment were lost to follow-up after a median of 36 months (range, 12–84 months). Twelve patients from the no-treatment group were lost to follow-up after a median of 36 months (range, 12–72 months). At the time of leaving the study, 5 patients (3 randomized to T_4) had recurrence of goiter.

Postoperative pretreatment data in the two groups were similar (Table 1). Patients with bilateral resections had significantly more thyroid tissue removed and at 3 months postoperatively had significantly higher serum TSH concentrations and lower serum T_4 concentrations (Table 2).

A significant decrease in serum TSH and increase in serum T_4 concentrations were found in the L-T_4-treated patients, whereas these values were unchanged in the no-treatment group (Figs. 1 and 2). Serum T_3 concentrations were unaltered in both groups (data not given).

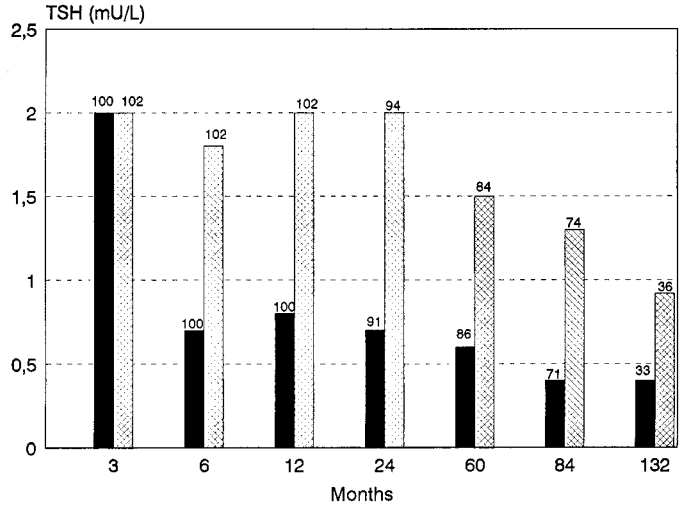

FIG. 1. Serum TSH concentration at selected time points before (3 months postoperatively) and following randomization to L-T_4 or no therapy in 202 subjects operated for benign nontoxic goiter. *Numbers at top of columns* indicate number of observations. Difference between two groups was at all time points highly significant ($P < 0.0001$). Patients randomized to L-T_4 (*solid columns*) or no therapy (*hatched columns*).

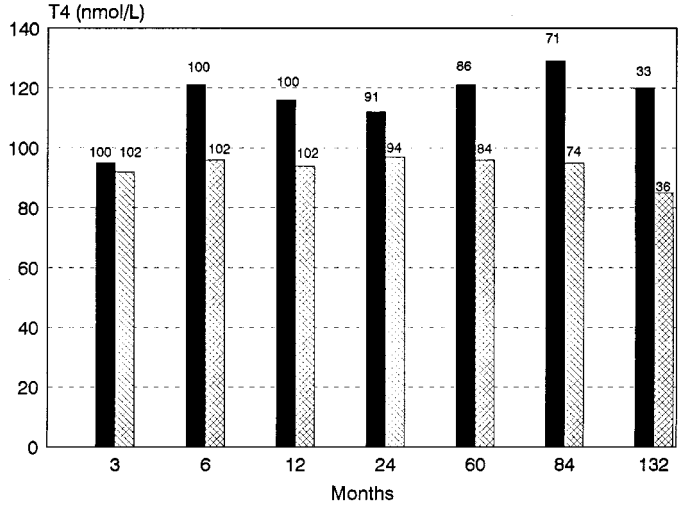

FIG. 2. Serum T_4 concentration at selected time points before (3 months postoperatively) and following randomization to L-T_4 or no therapy in 202 subjects operated for benign nontoxic goiter. *Numbers at top of columns* indicate number of observations. Difference between two groups was at all time points highly significant ($P < 0.0001$). Patients randomized to L-T_4 (*solid columns*) or no therapy (*hatched columns*).

Within the observation period, 46 patients had recurrence of goiter [28%; 95% confidence limits (CL) 9–47%; life-table analysis]. No differences in postoperative prerandomization data could be demonstrated between the two groups (Table 3). However, patients with recurrence of goiter were characterized by more thyroid tissue removed, a larger thyroid remnant, and lower serum TSH values than patients not developing recurrence (Table 4). Thus, 25 of 52 patients with a volume of ≥23 mL (upper 25%) had recurrence, compared with only 21 of the remaining 150 patients ($P < 0.001$), without relation to treatment or no treatment. Twenty of 40 pa-

TABLE 3. Postoperative data in 46 patients with recurrence of nontoxic goiter and relation to treatment group

Variable	T_4 treatment	No treatment
No. of patients	19	27
Unilateral resection	11	16
Bilateral resection	8	11
Male/female patients	6 /13	5 /22
Age (yr)	42 (15–63)	40 (25–62)
Weight of removed tissue (g)	55 (5–190)	60 (22–226)
Initial thyroid volume (mL)	24 (14–70)	23 (10–54)
Recurrence thyroid volume (mL)	33 (21–67)	35 (21–62)
TSH (mU/L)	1.7 (0.3–5.0)	1.7 (0.2–6.4)
T_4 (nmol/L)	100 (62–129)	94 (75–114)
T_3 (nmol/L)	2.2 (1.7–3.0)	2.0 (1.7–3.8)
Preoperative diagnosis		
Multinodular goiter	9	14
Solitary cold nodule	8	10
Diffuse goiter	0	0
Cyst	2	3
Autonomous nodule	0	0

Median values expressed with ranges in *parentheses.*

TABLE 4. Postoperative data in 46 patients with recurrence of nontoxic goiter and 156 patients without goiter recurrence

Variable	Recurrence	No recurrence	*P* value
No. of patients	46	156	
Male/female patients	11/35	18/138	
Age (yr)	41 (15–63)	41 (18–71)	NS
Unilateral resection	27	103	NS
Bilateral resection	19	53	NS
Weight of removed tissue (g)	60 (5–226)	34 (5–380)	$P < 0.001$
Thyroid volume (mL)	24 (10–70)	18 (8–50)	$P < 0.001$
TSH (mU/L)	1.6 (0.2–6.4)	2.2 (0.2–22.0)	$P < 0.005$
T_4 (nmol/L)	97 (62–141)	93 (48–160)	NS
T_3 (nmol/L)	2.0 (1.7–3.8)	2.0 (1.3–3.5)	NS
Preoperative diagnosis			
Multinodular goiter	23	52	
Solitary cold nodule	18	84	
Diffuse goiter	0	6	
Cyst	5	10	
Autonomous nodule	0	4	

Median values expressed with ranges in *parentheses.*

tients with removal of ≥72 g of thyroid tissue (upper 25%) had recurrence, compared with 25 of the remaining 120 ($P < 0.001$) without relation to treatment or no treatment. Twenty three of 75 patients with multinodular goiter had recurrence, compared with 18 of 102 with solitary nontoxic nodules ($P < 0.05$). No significant difference in risk of recurrence could be demonstrated between patients receiving L-T_4: 21% (95% CL 0–42%) or no treatment: 35% (95% CL 7–64%) ($P = 0.16$) (Fig. 3). The risk of overlooking a 20% difference in recurrence rate is 10%. At time of recurrence, median thyroid volume had increased from 23 mL (range, 10–54 mL) to 35 mL (range, 21–62 mL) in the no-treatment group and from a median of 24 mL (range, 14–70 mL) to 33 mL (range, 21–67 mL) in the L-T_4- treated group [not significant (NS)]. Three months after operation, 19 patients subsequently randomized to no treatment had a raised serum TSH concentration (>4.0 mU/L). The median concentration in these patients was 6.3 mU/L (range, 4.1–22.0), and their median thyroid volume was 16 mL (range, 8–33 mL). Three of these patients developed recurrence within the observation period.

Of the patients on L-T_4 treatment, 50 had suppressed serum TSH values throughout the study, whereas the remaining 50 patients did not. Eight patients with goiter recurrence receiving L-T_4 treatment had suppressed serum TSH values (<0.40 mU/L) throughout follow-up, whereas 9 patients did not (NS). Serum TSH concentration was at no time significantly higher in L-T_4-treated patients with recurrence than in those without recurrence.

Because of symptoms of hyperthyroidism, 36 of the 100 patients randomized to and receiving T_4 had their dose reduced to 100 μg daily (n = 23) or 50 μg daily (n = 9), while 4 patients stopped treatment. Six of these 36 patients had recurrence of goiter, whereas this was seen in 13 of the 64 patients receiving 150 μg T_4 daily (NS).

Discussion

The prevalence of goiter recurrence in our consecutive group of patients operated on for nontoxic goiter and followed for a median of 10 yr is 23%. Others have found similar (8, 9, 11–13, 20) or higher figures (21, 22) with a similar follow-up. Therefore, it is clearly justified to seek measures to decrease this figure. Although many have advocated routine postoperative L-T_4 treatment to hinder recurrence of nontoxic goiter, the present study does not support this recommendation.

Our study extends our previous observations (14, 23) and does not demonstrate any benefit of L-T_4 treatment. In this respect our findings are supported by that of others (8, 9, 11–14), whereas some authors have demonstrated a beneficial effect of such treatment (20, 21, 22, 24). A closer analysis of all these studies reveals that direct comparisons are impossible. In addition to varying lengths of follow-up and the inclusion of very heterogeneous groups of patients, the following circumstances have to be taken into consideration. 1) A number of studies were retrospective (8, 9, 11, 12, 20, 24). 2) Most studies were not randomized (8, 9, 11, 12, 20, 21, 24). 3) No studies included a placebo group. 4) The majority of studies did not use an objective measure of recurrence (8, 9, 12, 13, 20–22, 24). 5) The number of patients studied, especially in the T_4-treated group, was too few (11–13, 20, 22). 6) The median follow-up period was very variable. 7) The studies were not all uniform with respect to achievement of suppressed serum TSH values. 8) The studies were carried out in areas with large variations in urinary iodine excretion, although none of the studies provided adequate data regarding this.

Four studies have demonstrated an effect of L-T_4 on postoperative recurrence of nontoxic goiter (20–22, 24); they can, however, be criticized on a number of points. The study by Bergfelt and Risholm (24) was retrospective, nonrandomized, noncontrolled, and without an objective measure of recurrence of goiter. Ibis *et al.* (21) performed a nonrandomized, noncontrolled study without an objective measure of recurrence in all patients. Furthermore, it is unclear why some patients were treated with L-T_4, in varying doses, and others not. The study by Anderson *et al.* (20) had the same disadvantages, furthermore, only 14 of 185 patients received L-T_4. Finally, Miccoli *et al.* (22), although performing a prospective randomized study, had no adequate control group,

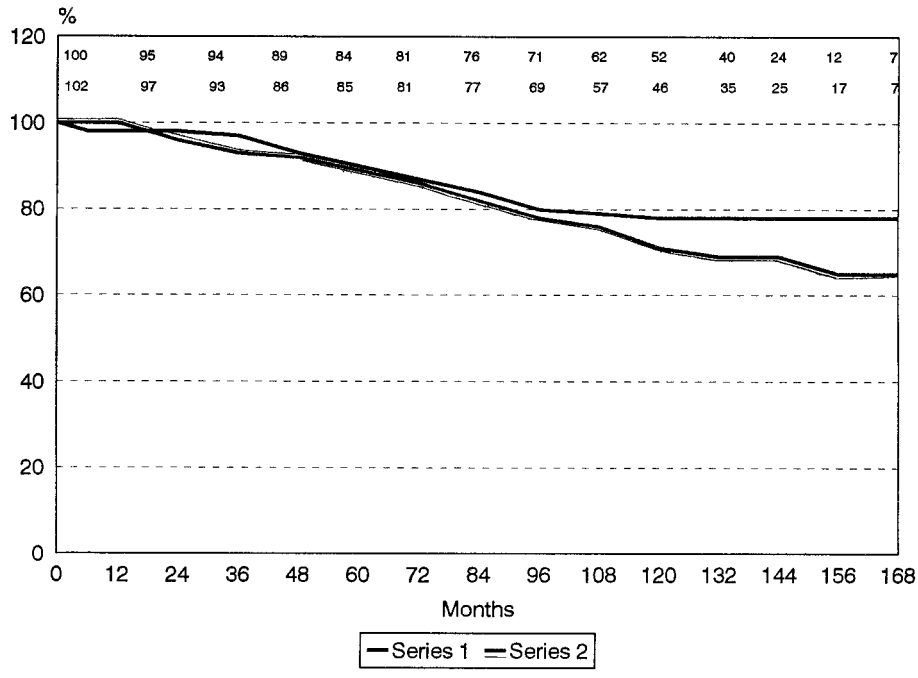

FIG. 3. Life-table analysis (Kaplan-Meier curves) of recurrence of goiter in 202 patients with benign nontoxic goiter randomized 3 months postoperatively to L-T_4 (series 1) or no therapy (series 2).

because most patients were, in fact, given L-T_4. Miccoli *et al.* (22) only studied 60 patients with a follow-up of 3 yr, and recurrence was defined as reappearance of ultrasonically detected nodular lesions. In our view, this is not an adequate definition of recurrence, because all of these patients were operated for nodular thyroid disease. Clearly, as also observed by others (11), the majority, if not all, of the patients must have had nodular lesions postoperatively, and recurrence should be defined as an objectively determined increased thyroid volume. Taking into consideration our studies demonstrating a considerable observer variation in size and type of thyroid gland, whether determined by palpation, scintiscan, or by ultrasound, this seems mandatory (25). With this point made, the fact that the studies from iodine-deficient areas (21, 22) showed an effect of L-T_4 treatment as opposed to the studies from iodine-sufficient areas (8, 11, 12) or borderline iodine-deficient areas (9, 13, and the present study), leaves open the possibility of an effect of T_4 in iodine-deficient regions. Recent studies do suggest that L-T_4, although having little effect on existing nodules, may hinder the occurrence of new nodules (22, 26, 27). The fact that this effect seems related to suppressive doses of L-T_4 (22), significant side effects (6), and probably life-long treatment, does not make this an attractive choice. In cases of recurrence, we demonstrated excellent results with radioiodine (28). This has become our primary treatment of this condition because of a clinically significant relatively rapid reduction in thyroid volume and few side effects.

Our study can be criticized. First, the maximum degree of blindedness was not achieved. Second, the study is not placebo controlled. Third, serum TSH level was not suppressed in all patients randomized to L-T_4 therapy. We chose to blind the ultrasonographer as to the group to which the patient belonged. Had the study been double blind and placebo controlled it is possible that L-T_4 dose would not have had to be reduced in 36% of the patients. The lack of suppression of serum TSH levels in a number of patients was because of 1) reduction of L-T_4 dose in patients with side effects, 2) the use of insensitive TSH assays in the first several years of the study, and 3) the fact that patients with nonsuppressed serum TSH level did not have their L-T_4 dose increased in view of a number of reports of side effects of subclinical hyperthyroidism (6, 29). The fact that only 8 of 50 patients with a suppressed serum TSH had recurrence of goiter (16%), as opposed to 27 of 102 patients receiving no treatment (26%), suggests that a larger study group or a longer follow-up could have revealed a significant difference. However, the fact that the average serum TSH level in patients on L-T_4 was not significantly different between patients with or without recurrence suggests that TSH, although a well-accepted thyroid growth factor, is not solely responsible for goiter recurrence in these patients.

Our data suggest that it will be difficult to find markers suggestive of postoperative recurrence of nontoxic goiter. The fact that patients with a larger postoperative thyroid remnant run a higher risk of recurrence suggests that thyroidectomy should be more extensive. The risk of adverse effects to reoperation is probably higher than the possible side effects of L-T_4 substitution treatment because of hypothyroidism following primary surgery leaving a small thyroid remnant. Morbidity in patients on L-T_4 treatment does not seem increased (30). Again, in our view, radioiodine treatment in case of recurrence is a more attractive choice than either reoperation or L-T_4 treatment.

Although TSH is a major and undisputed stimulator of thyroid growth, thyroid size is determined by a complex interaction between a variety of factors influencing blood flow, growth of connective tissue, and hypertrophy and hyperplasia of thyrocytes. Iodine (31), cytokines (32), and thyroid-stimulating immunoglobulins (33) all play a role. Also thyroid-growth promoting immunoglobulins seem important as evidenced by the higher prevalence of thyroid-growth

promoting immunoglobulins in patients with recurrence of goiter (11).

In conclusion, there is no evidence of a beneficial effect of routine L-T_4 treatment on recurrence rates after operation for nontoxic goiter in areas without manifest iodine deficiency. In areas where iodine deficiency prevails, the rational approach to hinder goiter recurrence is iodine supplementation and not L-T_4 treatment. In case of recurrence of goiter, we recommend radioiodine as the treatment of choice instead of L-T_4 treatment or reoperation.

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