

LONG-TERM EFFECT OF LEVOTHYROXINE THERAPY AFTER PARTIAL THYROIDECTOMY

EFFET A LONG TERME DE LA THERAPIE A LA LEVOTHYROXINE APRES UNE THYROIDECTOMIE PARTIELLE

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Abstract

Goiters and thyroid nodules are common diseases. Their pathogenesis is not well understood despite the important role that was attributed to TSH. Thus, Levothyroxine was used to prevent recurrence of thyroid nodules. We studied 34 euthyroid women who underwent partial thyroidectomy for non-toxic multi nodular goiter or non-toxic single nodule. The sample was divided into two groups depending on whether the patient was on Levothyroxine or not. The average dose of Levothyroxine was 71.4 µg/d. After 5 years of follow-up, free T4 was normal in both groups and did not significantly increase for patients on Levothyroxine. The mean TSH level was low for treated patients compared to controls ($P = 0.005$). The recurrence rate was significantly lower for treated women (56.2% versus 21.4%) ($P = 0.002$). Similarly, the mean number of nodules was significantly smaller for treated patients. Mean goiter and nodule sizes were 6.2 mm and 23.8 mm in the L-T4 group versus 30 mm and 50 mm in the control group, $P=0.03$ and 0.002 , respectively. Partial thyroidectomy associated with treatment with Levothyroxine decreases the risk of recurrence. Indeed, the suppressive hormonal treatment of TSH reduces the size of goiter and thyroid nodules.

Key words: Partial thyroidectomy; Levothyroxine; Nodular thyroid pathology; Thyroid-stimulating hormone.

Résumé

Les goitres et les nodules thyroïdiens sont des maladies fréquentes. Leur pathogénie n'est pas bien élucidée malgré qu'un rôle important fût attribuée à la TSH. Ainsi la Levothyroxine était utilisée pour prévenir les récurrences des nodules thyroïdiens. Nous avons étudié 34 femmes en euthyroïdie ayant subi une thyroïdectomie partielle pour goitre multi nodulaire non toxique ou nodule unique non toxique. L'échantillon était divisé en deux groupes selon que le patient était mis ou non sous Levothyroxine. La dose moyenne de Levothyroxine était de 71.4 µg/j. Après 5 ans de suivie la T4 libre était normale dans les deux groupes et n'a pas significativement augmenté chez les patientes mise sous Levothyroxine. Le taux moyen de TSH était bas chez les patientes traitées par rapport aux contrôles ($P=0,005$). Le taux de récurrence était significativement bas chez les femmes traitées (56.2% versus 21.4%) ($P= 0.002$). De même, le nombre moyen de nodules était significativement plus petit chez les patientes traitées. La tailles moyennes des goitres et des nodules étaient de 6.2 mm and 23.8 mm dans le L-T4 groupe versus 30 mm and 50mm dans le groupe control, $P=0,03$ et $0,002$ respectivement. La thyroïdectomie partielle associée à un traitement par Levothyroxine diminue le risque de récurrence. En effet le traitement hormonal suppressif de la TSH réduit la taille du goitre et des nodules thyroïdiens.

Mots clés : Thyroïdectomie partielle ; Levothyroxine ; Pathologie thyroïdienne nodulaire ; Thyroid-stimulating hormone.

ملخص

تضخم الغدة الدرقية والعقيدات الدرقية هي أمراض شائعة. درسنا 34 امرأة الذين خضعوا لاستئصال الغدة الدرقية الجزئي لتضخم الغدة الدرقية أو العقيدات غير سامة. هذه الآلية المرضية ليست مفهومة جيدا على الرغم من أن تم تعيينه بدور للهرمون. واستخدمت ليفوثيروكسين لمنع تكرار ذلك العقيدات الدرقية. ودرسنا 34 من النساء الذي خضعن إلى استئصال الغدة الدرقية جزئيا لمتعددة العقيدات أو عقيدة واحدة. وقسمت العينة إلى مجموعتين تبعاً لما إذا كان المريض أو لا بموجب ليفوثيروكسين. وكان متوسط الجرعة من ليفوثيروكسين 71.4 ميكروغرام/د. بعد 5 سنوات من اتباع T4 الحرة في كلا الفريقين وكان لم يزد كثيرا في المرضى على ليفوثيروكسين. وكان متوسط معدل الهرمون منخفضة بين المرضى الذين عولجوا بالمقارنة مع عناصر التحكم. وكان معدل العود أقل بكثير في تعامل المرأة (56.2%) مقابل (21.4%). وبالمثل، كان متوسط عدد العقيدات أصغر بكثير في معالجة المرضى. كان متوسط حجم تضخم الغدة الدرقية والعقيدات 6.2 و 23.8 مم في لمجموعه T4 مقابل 30 و 50 ملم في مجموعة المراقبة. استئصال الغدة الدرقية الجزئي المرتبطة مع العلاج ليفوثيروكسين يقلل من خطر تكرار العقيدات. العلاج الهرموني يقلل من حجم العقيدات تضخم الغدة الدرقية، والغدة الدرقية.

الكلمات المفتاحية: استئصال الغدة الدرقية الجزئي ; ليفوثيروكسين ; الهرمون الغدة الدرقية ; أمراض الغدة الدرقية العقيدية.

INTRODUCTION

Nodular thyroid disease is a common entity with an estimated 5%-7% of adults having palpable thyroid nodules and 30%-50% having nodules upon ultrasound [1]. Physicians responsible for the care of patients with thyroid nodules are increasingly aware of the need for a safe, expedient and cost-effective therapy for this common disorder. The prevalence of benign nodular thyroid disease is high, and pathogenesis is not obvious although an important role has been attributed to the thyroid-stimulating hormone (TSH). Therefore the interest in Levothyroxine (L-T4) therapy revived [2-4]. This therapy has been used for many years to suppress the growth of goiter and thyroid nodules in euthyroid patients. In the operated patients L-T4 therapy was used to prevent recurrence after the partial thyroid surgery, but, there are conflicting views on the efficacy of this therapy [5]. Our aim is to study the long-term effect of L-T4 therapy on the recurrence rate of nodular disease in patients previously treated with partial thyroid surgery for unilateral benign nodules and/or goiter.

SUBJECTS AND METHODS

The study was a retrospective and comparative clinical experiment. Thirty-four consecutive female patients were admitted in our department of endocrinology in Hedi Chaker Hospital in Sfax, Tunisia between 1998 and 2007 for management of the nodular thyroid disease. Inclusion criteria were benign thyroid disease detected by palpation and/or ultrasonography and approved by histological diagnosis. Surgical treatment was indicated for patients having, nodule size > 3 cm or signs suggestive of malignancy objected by ultrasonography evaluation (hypoechoic nodules, irregular halo sign, micro calcifications....). All patients were initially in a euthyroid state and patients taking suppressive therapy for thyroid cancer were excluded. All patients had undergone thyroid lobectomy or lobo-isthmectomy at the division of ORL surgery in Habib Bourguiba Hospital. L-T4 therapy was indicated for patients having patent hypothyroidism or subclinical hypothyroidism with elevated risk to process to patent hypothyroidism (TSH>10mUI/L, positive Antithyroid antibodies, pregnancy...). They were divided into 2 groups based on whether or not they had been given L-T4 therapy after surgery.

Group 1: 25 women who receiving L-T4 therapy. The mean Levothyroxine dose was 71.4 µg/day (range 25-125 µg/day).

Group 2: 9 women without LT4 therapy (controls) Every 6 months a physical examination was performed on all women including weight, blood pressure, thyrotoxicosis features and thyroid palpation. Echographic evaluations were performed in the same center when palpable nodule was objected. The patients were also tested by measurement of the serum levels of TSH and the free thyroid hormone (FT4). Normal TSH: 0.3-5 µIU/ml and FT4: 7.5-21 µg /dl. Mean follow-up period was 8.4 years ± 1.3 year over at least 5 years.

Statistical analysis: The statistical analysis was performed with the SPSS program. The results were given in mean or frequency values. Statistical comparisons of clinical and hormonal patterns were performed using one-way ANOVA and a comparison test for paired data. A P-value of less than 0.05 was accepted as significant.

RESULTS

Patients and thyroid characteristics at baseline

Thirty four women were included in the study. Their mean age was 46.7 years (24-76 years) at the time Antithyroid antibodies of surgery. The thyroid disease was solitary non-toxic thyroid nodule in 23 patients (67.6%) and multinodular non-toxic goiter in 11 patients (32.4%). Surgical treatment was indicated for all patients due to, nodule size > 3 cm (44.1%), cold nodule on scintigraphy (20.6%) and signs suggestive of malignancy objected to by ultrasonography evaluation (hypoechoic nodules, irregular halo sign, micro calcifications....) (11.8%). Surgery consisted in loboisthmectomy for 91.2% of our patients and lobectomy for 8.8% of them. Histological evaluation confirmed the benign nature of the lesion in all included patients. At baseline, the two groups were matched for age (45.3± 14.06 vs 50.6± 13.9 years), weight (69.6±15.6 Kg VS 64±20.2 Kg), heart rate (75.4±10 vs 77.2±16.2 beats), blood pressure, and lipid parameters. Clinical and laboratory characteristics at baseline for the 2 groups are listed in table I. indicated for all patients due to, nodule size > 3 cm (44.1%), cold nodule on scintigraphy (20.6%) and signs suggestive of malignancy objected to by ultrasonography evaluation (hypoechoic nodules, irregular halo sign, micro calcifications....) (11.8%).

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No differences were observed in baseline TSH concentrations (1.98 ± 1.24 vs 1.7 ± 0.95 μ UI/ml, $P=0.25$) and free thyroid hormone (13.9 ± 38 vs 11.7 ± 7.03 μ g/dl, $P=0.29$). Thyroid disease consisted in a solitary nodule in 18 patients (G1) and in 5 patients (G2) in multi nodular goiter in 7 patients (G1) and in 4 patients (G2). The ultrasonography evaluation of the thyroid disease showed no significant difference in nodule number (1.38 ± 0.66 vs 1.57 ± 0.78) and maximum goiter diameter (57 ± 16.9 vs 35 mm). However, the mean nodule diameter was significantly higher in the treated group (34.8 ± 13.9 vs 28.8 ± 8.8 mm $p=0.05$). The clinical and hormonal features of thyroid disease at baseline for the 2 groups are listed in table II.

After 5 years of follow up, we compared all parameters for the two groups listed in tables III and IV. The mean heart rate of the treated patients was higher than in the control subjects (77 ± 9.1 beats per minute vs 72 ± 11.4 beats per minute, $P=0.04$). There were no differences in systolic and diastolic blood pressure, but we paradoxily noted that the mean body weight was higher in the L-T4 group than in the control group. Our data showed that mean total cholesterol level was significantly

higher in the non-treated group, whereas the mean triglycerides level did not differ significantly between the two groups.

Hormonal changes: In the L-T4 treated group, the TSH mean value was maintained constant at the lower normal limit, whereas it increased in the control group reaching the upper limits of normal ($P=0.03$). The average FT4 did not change significantly, remaining within the lower normal limits in the 2 groups. The mean serum FT4 concentration did not significantly increase in group 1 (11.3 ± 2.08 vs 10.9 ± 1.6 μ g/dl, $P=0.3$). The mean TSH concentration was significantly lower in the L-T4-treated patients than in the controls (2 ± 2.7 vs 7.2 ± 11.1 ; $P=0.005$).

After a mean follow-up of 8.4 years goiter and/or nodule recurrence was observed in 21% of the L-T4 patients and in 56.2% of the controls ($P=0.002$). Echographic evaluation showed that the mean nodule number was lower in the L-T4-treated subjects, but no significant difference was noted. The mean nodule size and mean goiter size were significantly lower in the L-T4-treated patients than in the controls ($P=0.008$ and 0.03 respectively). Reoperation with total thyroidectomy was indicated for one patient in each group because of suspected malignancy.

Recurrence was noted in 10 cases (5 patients in G1 and 5 patients in G2). On multivariate analysis, only the lack of postoperative Levothyroxine therapy was predictive of recurrence after thyroid surgery (table V). In patients with recurrence, 40% of them did not receive L-T4 therapy versus 20.8% for patients without recurrence ($P=0.05$). No significant difference was observed with age, type of thyroid disease and TSH concentration after L-T4 therapy.

Table I: Clinical and laboratory characteristics at base line

	G1	G2	P value
Age (years)	45,38 \pm 14,06	50,6 \pm 13,9	0,29
Weight (Kg)	69,6 \pm 15,6	64 \pm 20,2	0,6
SBP (mmHg)	12,3 \pm 1,7	11,5 \pm 1,73	0,9
DBP (mmHg)	7 \pm 1	7 \pm 0,8	0,29
HR (beats per minute)	75 \pm 10	77 \pm 16,2	0,1
Cholesterol mmol/l)	4,8 \pm 1,27	4,7	0,7
Triglyceride (mmol/l)	1,29 \pm 0,6	1,1	0,5

HR: heart rate SBP: systolic blood pressure DBP: diastolic blood pressure

Table II: Clinical and hormonal features of thyroid disease at baseline

	G1	G2	P value
FT4 (µg/dl)	13,9±3,8	11,7±7,03	0,29
TSH (µIU/ml)	1,9±1,24	1,7±0,95	0,25
Nodule number	1,38±0,66	1,57±0,78	0,5
Nodule size (mm)	34,8±13,9	28,8±6,5	0,05
Goiter size (mm)	57±16	9 35±9,9	0,1

Table III: Clinical and biochemical findings after 5 years of follow-up

	G1	G2	P value
Weight (Kg)	76,25±16,3	66,2±15,5	0,06
SBP (mmHg)	13,2±2,08	13,6±2,1	0,4
DBP (mmHg)	7,8±1	8,2±1,16	0,17
HR (beats per minute)	77±9,1	72±11,4	0,04
Cholesterol mmol/l)	5,31±1,34	5,7±0,99	0,009
Triglyceride (mmol)	1,3±0,47	1,08±0,31	0,7

Table IV: Evaluation of thyroid disease after 5 years of follow-up

	G1	G2	P value
FT4 (µg/dl)	11,3±2,08	10,9±1,6	0,2
TSH (µIU/ml)	2±2,7	7,2±11,1	0,005
Nodule number	0,27±0,55	0,44±1	0,1
Nodule size (mm)	6,2±4,3	30	0,008
Goiter size (mm)	23,8±6,3	50±14,1	0,03
Recurrence rate	21,4%	56,2%	0,002

Table V: Analysis of predictive factors for recurrence after partial thyroidectomy

	Recurrence	No recurrence
Number	10	24
Age	45±14,9	47,3±13,7
Solitary nodule/Goiter	70%/30%	66,7%/33,3%
LT4 therapy/no LT4 therapy	60%/40%	79,2%/20,8%
TSH at 5years	4,3±3,2	3,1±2,4

DISCUSSION

The pathological process of goiter involves the whole gland, which leads us to perform total thyroidectomy to prevent the risk of recurrence. However other therapies such as LT4 suppressive therapy may help to avoid recurrence. This study examined the effect of long-term LT4 therapy after thyroid lobectomy for benign nodular disease. For these patients we chose either observation or thyroid hormone therapy which had been used widely [6]. Several controlled studies failed to demonstrate a significant reduction in goiter or thyroid nodule size after the L-T4 suppressive therapy [7–10]. In fact short trials were inadequate to evaluate the efficacy of L-T4 in decreasing spontaneous growth, usually too slow. Our data was therefore designed to evaluate the efficacy of long-term L-T4 therapy.

Despite controversies regarding this therapy and ambiguous recommendations on its use, even

in published guidelines, it is still preferred by a large number of clinicians [3,5,11–13]. In fact, post-operative LT4-treatment for euthyroid patients was recommended after surgery by approximately one third of the physicians [11,14]. The effectiveness of LT4 therapy was confirmed by Cherkasov who noted that LT4 therapy helps reduce the number of goiter recurrences from 8,2% to 2,5% [15]. Alba M et al in a recent study reported that in patients who have undergone hemithyroidectomy for benign nodular disease, the recurrence rate was significantly lower in treated patients (27.7% versus 64.4%) [16].

Our data confirmed these findings, and we noted 21.4% of recurrence in treated patients and 56.1% in controls. In this study no significant difference was observed between patients receiving an LT4 suppressive dose and patients receiving LT4 substitutive therapy.

Our treated patients were receiving L-T4 at TSH substitutive dose ($TSH \geq 0.3$ and ≤ 8.3 MUI/L), which was sufficient to prevent aggravation and recurrence of nodular thyroid disease. Three quarters of the clinicians who recommended LT4 therapy suggested that the TSH level should be between 0.1-0.3 MU/l. This target was associated with thyrotoxic symptoms and significant bone mineral loss in more than 30% [5,17,18]. In our study the mean TSH level was at 2 UI/ml, which explains the absence of such complications. We suggest that very low TSH levels may not be required for prevention of recurrence in the remnant thyroid tissue. The present study and the one realized by Bellantone [19] also demonstrated that the lack of postoperative substitutive therapy is a strong predictive factor of recurrence. Other trials that address this argument have led to contradictory results, probably because of the lack of objective methods for the diagnosis of recurrence and of the different durations of follow-up [20,21]. The results of our clinical trial reported a significant reduction of nodular size in the treated group but not in the control group. The results of the cumulative metanalysis of studies concerning the capacity of L-T4 therapy to decrease the solitary thyroid nodule volume showed that T4 treatment reduced the volume and prevented the growth of the thyroid nodule in a higher proportion of patients than observed in the placebo group [5,7,13,22-24]. Papini et al observed that LT4-treated patients did not show decrease in thyroid nodule size after 5 years of treatment, but thyroid nodule size increased significantly in the control group where there was a higher number of new nodules [7]. Our data showed a decrease in nodule number in both groups. However, the mean nodule size decreased only in treated patients and increased in controls. These observations confirm the clinical usefulness of long-term L-T4 treatment as more effective in reducing nodule size than in preventing new lesions.

Concerning pretreatment variables, Papini et al proved in their data that age, nodule size and TSH levels at baseline did not predict nodule response to L-T4 therapy [7]. The present data proved in addition that the type of preoperative thyroid disease (goiter or solitary nodule) at baseline did not predict response to Levothyroxine treatment.

CONCLUSION

The question of postoperative substitutive or suppressive therapy after thyroid lobectomy for

non-toxic nodule and goiter is still a subject of debate [4,5,13,25,26]. In fact, the present study demonstrates that, after hemithyroidectomy for benign nodular disease, LT4 therapy may prevent the recurrence of nodular disease. Long term LT4 suppressive therapy induces significant volume reduction, effectively prevents the development of new lesions and increases in nodule and goiter size. We suggest that TSH suppression may not be required for the prevention of recurrence and that treatment could be maintained at lower doses of T4, just to obtain TSH levels around the lower normal limit.

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