LONG-TERM EFFECT OF LEVOTHYROXINE THERAPY AFTER PARTIAL THYROIDECTOMY

EFFET A LONG TERME DE LA THÉRAPIE À LA LEVOTHYROXINE APRÈS 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 and0.002, 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 attribué à la TSH. Ainsi, la Levothsiroxine était utilisée pour prévenir les récidives 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 Levothsiroxine. La dose moyenne de Levothsiroxine 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 traitées. Le taux moyen de TSH était bas chez les patientes traitées. Le nombre de nodules était significativement plus petit chez les patientes traitées. La taille moyenne du goitre et des nodules était significativement plus petite chez les patientes traitées. La taille moyenne des nodules était significativement plus petite chez les patientes traitées.

Mots clés : Partial thyroidectomy; Levothyroxine; Nodular thyroid pathology; Thyroid-stimulating hormone.

ملخص

تتضمّن الغدة الدرقية والعقيدات الدرقية أمراض شائعة. درّست 34 إمرأة ذات نسيج خضعنا لأستعمل الغدة الدرقية الجذعية تم تضمّن الغدة الدرقية والعقيدات غير سامة. هذه الآلية المرضية ليست مفهومة جيداً على الرغم من أنّه تم تعيينه للهرمون. واستخدمت ليفوثيريوكسين لمنع تكاثر تلك العقيدات الدرقية. ودرسنا 34 نسبياً لمساء kötü خضعنا إلى استعمل الغدة الدرقية الجزئية متعاطى تأميم السيدان للعديد وعديد واحد. وقيمت النتائج إلى مجموعتين فيما إذا كان المرضي أو لا دمج ليفوثيريوكسين. وكان متسي تجربة من ليفوثيريوكسين 71.4 ميكروغرام/ك. بعد 5 سنوات من اتباع T4 ساءت في كل الفرعين ولكن لم يزيد كثيراً في المربي على ليفوثيريوكسين. وكان متسي معدل الهرمون مخصصة بين المرضي الذين خضعنا بالناءرة مع عناصر التحكم. وكان معدل الهرمون أقل بكثير في استعمال المرأة (56.2%) مقابل 21.4%. وسُلّم، كان متسي عدد العقيدات أكبر بكثير في عناصر المرضي. كان متسي حجم تضمّن الغدة الدرقية والعقيدات 6.2 و 23.8 ملم في مجموعة T4 مقابل 30 و 50 ملم في مجموعة الجذعية المرضية، مع العلاج ليفوثيريوكسين يقلل من خطر تكرار العقيدات. العلاج الهرموني من الهرمون يقلل من حجم العقيدات تضمّن الغدة الدرقية، والعدة الدرقية.

الجملة المفيدة: أعراض الغدة الدرقية الجزئية: ليفوثيريوكسين: الهرمون الغدة الدرقية: أمراض الغدة الدرقية العقيدات.
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 loboisthmetony 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 (41.1%), 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 µUI/ml, P=0.25) and free thyroid hormone (13.9±38 vs 11.7±7.03 µg/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 µg/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

<table>
<thead>
<tr>
<th></th>
<th>G1</th>
<th>G2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ( years)</td>
<td>45.38±14,06</td>
<td>50.6±13,9</td>
<td>0.29</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>69.6±15.6</td>
<td>64±20.2</td>
<td>0.6</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>12.3±1.7</td>
<td>11.5±1.73</td>
<td>0.9</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>7±1</td>
<td>7±0.8</td>
<td>0.29</td>
</tr>
<tr>
<td>HR (beats per minute)</td>
<td>75±10</td>
<td>77±16.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Cholesterol mmol/l</td>
<td>4.8±1.27</td>
<td>4.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Triglyceride (mmoll)</td>
<td>1.29±0.6</td>
<td>1.1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th></th>
<th>G1 (μg/dl)</th>
<th>G2 (μg/dl)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>FT4</td>
<td>13.9±3.8</td>
<td>11.7±7.03</td>
<td>0.29</td>
</tr>
<tr>
<td>TSH (μIU/ml)</td>
<td>1.9±1.24</td>
<td>1.7±0.95</td>
<td>0.25</td>
</tr>
<tr>
<td>Nodule number</td>
<td>1.38±0.66</td>
<td>1.57±0.78</td>
<td>0.5</td>
</tr>
<tr>
<td>Nodule size (mm)</td>
<td>34.8±13.9</td>
<td>28.8±6.5</td>
<td>0.05</td>
</tr>
<tr>
<td>Goiter size (mm)</td>
<td>57±16</td>
<td>935±9.9</td>
<td>0.1</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>G1 (Kg)</th>
<th>G2 (Kg)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>76.25±16.3</td>
<td>66.2±15.5</td>
<td>0.06</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>13.2±2.08</td>
<td>13.6±2.1</td>
<td>0.4</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>7.8±1</td>
<td>8.2±1.16</td>
<td>0.17</td>
</tr>
<tr>
<td>HR (beats per minute)</td>
<td>77±9.1</td>
<td>72±11.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.3±1.34</td>
<td>5.7±0.99</td>
<td>0.009</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>1.3±0.47</td>
<td>1.08±0.31</td>
<td>0.7</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>G1 (μg/dl)</th>
<th>G2 (μg/dl)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT4</td>
<td>11.3±2.08</td>
<td>10.9±1.6</td>
<td>0.2</td>
</tr>
<tr>
<td>TSH (μIU/ml)</td>
<td>2±2.7</td>
<td>7.2±11.1</td>
<td>0.005</td>
</tr>
<tr>
<td>Nodule number</td>
<td>0.27±0.55</td>
<td>0.44±1</td>
<td>0.1</td>
</tr>
<tr>
<td>Nodule size (mm)</td>
<td>6.2±4.3</td>
<td>30</td>
<td>0.008</td>
</tr>
<tr>
<td>Goiter size (mm)</td>
<td>23.8±6.3</td>
<td>50±14.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Recurrence rate</td>
<td>21.4%</td>
<td>56.2%</td>
<td>0.002</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Recurrence</th>
<th>No recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td>Age</td>
<td>45±14.9</td>
<td>47.3±13.7</td>
</tr>
<tr>
<td>Solitary nodule/Goiter</td>
<td>70%/30%</td>
<td>66.7%/33.3%</td>
</tr>
<tr>
<td>LT4 therapy/no LT4 therapy</td>
<td>60%/40%</td>
<td>79.2%/20.8%</td>
</tr>
<tr>
<td>TSH at 5 years</td>
<td>4.3±3.2</td>
<td>3.1±2.4</td>
</tr>
</tbody>
</table>
Our treated patients were receiving L-T4 at TSH
substitutive dose (TSH≥0.3 and < 8.3 MIU/L), which
was sufficient to prevent aggravation and
reoccurrence 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 MIU/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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