NOTE

Suppressive Therapy with Levothyroxine for Euthyroid Diffuse and Nodular Goiter

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Abstract. In this study, 35 patients with euthyroid diffuse goiter and 35 patients with euthyroid nodular goiter were treated with Levothyroxine (L-T4) for six months. The aim was to evaluate the efficacy of treatment on thyroid and nodule volumes and to evaluate the correlation between volume changes and thyroglobulin levels. Serum thyroid hormones, TSH, thyroglobulin, thyroid and nodule volumes were measured at the initial visit and after 6 months. Radioactive iodine uptakes of the thyroid gland were evaluated before treatment. The mean decrease of thyroid volume at six months was about 20% (20.4 ± 8.8 ml vs. 16 ± 7.9 ml, P<0.001) in patients with diffuse goiter. All patients with diffuse goiter showed some decrement in their goiter sizes. Thyroid nodules, in response to thyroid hormone treatment, showed a variable behavior. A reduction of 50% or more in volume was detected in 31% (11/35) of the patients. 54% of the patients (19/35) showed a 10-49% decrease in nodule volume. Five of the patients were found to be insensitive to the therapy. Their nodule volumes either increased or did not change during therapy. Free T4 and free T3 levels increased and TSH levels decreased with L-T4 treatment in all patient groups. Patients with higher TSH levels (within normal limits) showed more volume reduction in the diffuse goiter group. No uniform correlation was found between volume changes and thyroglobulin levels in either of the patient groups. In conclusion, suppressive thyroxine treatment is effective in reducing the size of the goiter, and nodules and thyroglobulin levels cannot be taken as an indicator of the efficacy of L-T4 therapy.

Key words: Goiter, Euthyroid goiter, Nodular goiter, Levothyroxine, Treatment

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LEVOTHYROXINE (LT4) suppressive therapy has been used for the treatment of diffuse and nodular goiters [1-5]. As thyrotropin (TSH) has a regulatory role on the follicular cell function and proliferation and as has a significant pathogenic role in the development of many goiters [6, 7], suppressing pituitary TSH secretion by thyroid hormone treatment (usually LT4) may eliminate the TSH mediated stimulation of goiter growth but the effectiveness of this treatment remains controversial especially in nodular goiters. Although most prospective studies have shown that such treatment leads to a reduction in thyroid nodules, some studies done by using ultrasonographic techniques and ultrasensitive immunoradiometric assay to determine TSH levels failed to show any effect of the treatment on either nodule diameters or volumes [8-10].

It has been hypothesized that a serum thyroglobulin (Tg) concentration that is persistently high during thyroid hormone treatment characterizes patients in whom thyroid hormone therapy fails, but definite proof of the validity of this hypothesis and therefore of the value of serum
Tg measurements during thyroid hormone treatment has not been provided [11, 12].

We here describe a prospective study to evaluate the efficacy of suppressive LT4 treatment, in patients with euthyroid diffuse and nodular goiters, on the size of the goiter and nodules. The serum thyroglobulin levels as an indicator of volume reduction were also evaluated.

Patients and Methods

Study design

This study was a clinical trial designed to test whether the administration of LT4 for six months would reduce the size of thyroid and nodule volumes. Serum thyroglobulin levels were also evaluated in the patients as a marker for the efficacy of treatment.

Clinical evaluations were done by the same author and ultrasound measurements were done by another author who was blinded to the first data of the patients.

Thirty-five patients with diffuse goiter and 35 patients with nodular goiters were admitted to the study. Patients who had only one or a dominant cold nodule determined by ultrasonography and pertechnetate 99m thyroid scanning and proved to be benign by fine needle aspiration biopsy were included in the nodular goiter group. Patients with cytological findings suggestive of a neoplastic process, positive for thyroid autoantibodies, pregnancy and/or any contraindication for LT4 treatment and with cystic nodules were excluded.

Thyroid function was evaluated by measurements of serum free thyroxine (FT4), free triiodothyronine (FT3), thyrotropin levels, pertechnetate 99m thyroid scanning and thyroid radioiodine uptake tests. Serum Tg levels were also determined. Patients were received LT4 treatment for six months. The drug dose was modified to decrease the serum TSH to the lowest normal or slightly below normal value (TSH< 0.4 mIU/ml). The daily suppressive dose of LT4 ranged from 0.1 to 0.2 mg. The duration of LT4 therapy was calculated from the beginning of the treatment with a suppressive dose. Six months later thyroid function tests, serum thyroglobulin level measurements and ultrasound examinations were repeated.

Serum studies

Serum FT3 (Amerlex- MAB, UK), ST4 (Incastor Corpor., USA) and thyroglobulin (DPC,USA) were measured by radioimmunometric assay, TSH (DPC, USA) was measured by ultrasensitive immunometric assay.

Ultrasonography

Ultrasonography was performed with a commercially available real time instrument which has a frequency of 7.5 MHz. Thyroid and nodule volume was calculated according to the spherical ellipsoid formula (Volume (ml) = (π/6 x AP(cm) x width (cm) x length (cm) where AP is the anteroposterior diameter) and volume was expressed in milliliters. The sonographic characteristics of the nodule were also noted (such as solid or mixed).

Statistical analysis

Results of continuous measurements are reported as the mean ± SD. The two tailed, two sample t-test for differences in the proportions and Wilcoxon rank-sum test, Mann-Whitney U test and Duncan tests for analysis of variance were used when appropriate for statistical analysis. P values less than 0.05 were considered to be significant.

Results

All patients were clinically euthyroid during the follow-up period.

Diffuse goiters

The mean age of the patients was 27.5 ± 6.4 and the male to female ratio was 4/31.

The laboratory data of the patients with diffuse goiters are given in Table 1.

Serum FT4 and FT3 increased significantly with LT4 treatment, within the normal limits (P<0.01 for FT3 and P<0.001 for FT4). Serum TSH levels decreased from 1.63 to 0.41 mIU/ml (P<0.001). Mean serum thyroglobulin levels also decreased
LEVOTHYROXINE FOR EUTHYROID GOITERS

Table 1. Laboratory data of 35 patients with euthyroid diffuse goiter before and after LT4 treatment

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>6th month</th>
<th>P</th>
<th>normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT3 (pmol/L)</td>
<td>5.22 ± 1.04</td>
<td>5.98 ± 1.06</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FT4 (pmol/L)</td>
<td>16.57 ± 2.68</td>
<td>22.35 ± 3.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TSH (mIU/L)</td>
<td>1.63 ± 1.32</td>
<td>0.41 ± 0.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tg (ng/ml)</td>
<td>43 ± 34</td>
<td>15 ± 12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Volume (ml)</td>
<td>20.37 ± 8.84</td>
<td>16 ± 7.89</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

FT3, free triiodothyronine; FT4, free thyroxine; Tg, Thyroglobulin.

Table 2. Laboratory data of 35 patients with euthyroid nodular goiter before and after LT4 treatment

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>6th month</th>
<th>P</th>
<th>normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT3 (pmol/L)</td>
<td>4.56 ± 1.09</td>
<td>5.75 ± 0.98</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FT4 (pmol/L)</td>
<td>16.42 ± 2.37</td>
<td>20.97 ± 3.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TSH (mIU/L)</td>
<td>1.38 ± 0.86</td>
<td>0.35 ± 0.33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tg (ng/ml)</td>
<td>115 ± 164</td>
<td>28 ± 29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Volume (ml)</td>
<td>2.98 ± 3.17</td>
<td>2.36 ± 2.24</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

FT3, free triiodothyronine; FT4, free thyroxine; Tg, Thyroglobulin.

with the therapy (15 ± 12 ng/ml vs. 43 ± 34 ng/ml; P<0.001).

Thyroid volumes were compared in the patients before and after treatment. The thyroid volume showed some decrease in all patients (2-53%). The mean change in the thyroid volume over a six-month treatment period was also found to be statistically significant (16 ± 7.89 ml vs. 20.37 ± 8.84 ml; 20%; P<0.001).

A correlation between pretreatment TSH levels and volume reduction rates was found. The patients who showed volume reductions more than 20% with the therapy were found to have an initial TSH level of 2.3 ± 1.6 mIU/ml (20 patients), on the other hand, the patients who showed volume reductions less than 20% were found to have an initial TSH level of 1.0 ± 0.5 mIU/ml (P<0.001). No other pretreatment parameters were found to be predictive of the degree of response to the treatment.

Initial Tg levels did not show correlation with the thyroid volumes. Response was not correlated to baseline Tg concentrations or Tg reduction during therapy.

Nodular goiters

Thirty of the patients were females and five of them males. The mean age was 30 ± 9 years.

Laboratory characteristics of the patients are given in Table 2.

Serum TSH concentrations showed a decrease in follow-ups (0.35 ± 0.33 mIU/L vs. 1.38 ± 0.86 mIU/L; P<0.001). Average serum FT4 and FT3 remained within normal limits but an increase which reached statistical significance (P<0.05 for FT3 and P<0.001 for FT4) was observed. Initial Tg levels and initial nodule volume showed no correlation. Mean thyroglobulin levels showed a decrease with the treatment but response was not correlated either with baseline Tg concentrations or with Tg change during therapy since some patients whose nodule volumes decreased by 50% or more showed an increase in Tg at the end of treatment, and a significant reduction was observed in Tg levels in patients who were unresponsive to therapy.

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Although mean nodule volume decreased from 2.98 ml to 2.36 ml (P<0.01) when examined
individually, 5 of the patients were found to be insensitive to the therapy. A reduction of 50% or more in nodule volume was detected in 31% (11/35) of the patients. 54% (19/35) of the patients showed a 10–49% decrease in nodule volume. Response to the LT4 treatment was also not correlated with the initial nodule volume, radioiodine uptakes, TSH, FT3 or FT4 levels.

Discussion

Although TSH suppression with thyroid hormones is the most accepted method in the treatment of euthyroid diffuse and nodular goiter, conflicting results, especially for the nodular goiters, have been reported in some previous series [9, 10, 13–20]. The success rate of suppressive therapy ranged from 0 to 68% in studies. Although many authors report an overall success rate from 39 to 68%, others do not find such good responses.

Gharib et al. [9] found no difference between a placebo and LT4 in reducing nodule volume. Galli [8] and Reverter [10] also reported that LT4 therapy was ineffective in the treatment of nodular goiter. In the present study, which was performed in an iodine deficient area, 31% of the patients with nodular goiter showed a 50% or more reduction in nodule volume and a 10% or more reduction was detected in 85% of nodular goiter patients. Our results are in agreement with those reported by Celani et al. [1] and Morita et al. [5] in which 76% and 36% of the patients responded to LT4 respectively. Berghout [21], Clark [16], Diacinti [3], Shimaoko [19] and Koloğlu [4] also reported significant nodule reductions with thyroid hormone treatment in their series.

Recently Papini et al. [22] found an increase in the thyroid volume, nodule volume and new nodule formation in patients who were followed up without LT4 for 5 years. They concluded that long term TSH suppression effectively prevented the appearance of new lesions and increases in nodule and thyroid volumes. Lima et al. [23] also found a 57.4% complete or partial response to LT4 treatment in their patients with solitary nodules. Another finding in this latter study was that the nodules that were less than 3 ml in volume showed the best response to the treatment. This observation can explain the rather good response in our patients since the mean nodule volume was also less than 3 ml in our study.

Nodule characteristics are also important for the efficacy of LT4 suppressive treatment. A study from Japan [5] revealed that 37% of 49 patients had more than 50% reduction in thyroid nodule size with LT4. This study included solid and cold benign nodules. In contrast, in a study from Mayo clinic, in which functional or cystic nodules were also included, LT4 treatment was not found to be significantly superior to a placebo in reducing the size [9]. We selected the patients who had either solid or mixed nodules with predominant solid areas those were cold at scan. This might play a role in our success in reducing nodule volume with LT4 suppression.

We observed a 2–53% reduction in thyroid volumes, with LT4, in patients with diffuse goiters. Our results are consistent with the data of the most studies reported previously [11, 13–15, 24, 25].

In our study, baseline TSH levels were found to predict the response to the treatment in the diffuse goiter group. Initial TSH levels were detected to be higher in patients who showed more volume reductions with the treatment. None of the pretreatment laboratory variables, including TSH, predicted the response in the nodular goiter group.

A positive correlation between the initial thyroid/nodule volume and initial Tg levels was reported by some authors [11] but we could not find any correlation between these parameters. Pezzino et al. [12] also could not detect a correlation in their study.

Morita [5] and Biersack [26] reported a positive correlation between volume reduction and Tg suppression in their patients. No uniform correlation was found between volume changes and thyroglobulin levels in the present study as with Feldt-Rasmussen [11] and Papini [18] who also failed to observe such a correlation. In our study, Tg levels increased in some patients who showed a thyroid volume reduction of more than 50% and decreased in some patients who were unresponsive to the therapy. These results of ours support the view that Tg is not an indicator of the response to the LT4 therapy.

TSH is the major growth factor in the pathogenesis of goiter development [6, 7]. Suppressing TSH with LT4 can reduce both diffuse and nodular goiter sizes. However, growth factors
other than TSH might play a role in goiter occurrence in patients who are unresponsive to LT4 suppressive treatment [7].

In conclusion results of the present uncontrolled study indicate that the suppressive LT4 treatment is effective in reducing the size of goiters and nodules at least in endemic goiter areas. Since thyroid nodules and diffuse thyroid enlargement are relatively high in iodine deficient areas and thyroid cancer is an uncommon disease, suppression therapy with LT4 after fine-needle aspiration biopsy may be useful in either volume reduction or preventing the occurrence of new lesions. Thyroglobulin levels cannot be taken as an indicator of the efficacy of LT4 therapy since no uniform correlation could be shown between nodule reduction and Tg levels.

References


