Role of levothyroxine suppressive therapy for benign cold nodules of thyroid: a randomized, double-blind, placebo-controlled clinical trial

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Introduction: There is no consensus on the appropriate management of benign cold nodules of the thyroid gland. This study addresses the problem in an iodine-deficient area, evaluating the efficacy of levothyroxine suppression therapy on a 2-year course.

Methods: A total of 58 patients affected with benign cold nodules of the thyroid were enrolled. With a double-blind placebo-controlled design, levothyroxine (1.5–2 µg/kg/day) was delivered to the 31 cases over 2 years. The consequences of this treatment were compared with 27 controls. Nodule size was measured with high-resolution ultrasonography.

Results: In the treatment group, the mean volume on baseline was 12.8 ± 11.9 ml and changed to 9.4 ± 9.8, 12.4 ± 16.7 and 10.8 ± 9.7 ml in months 6, 12 and 24, respectively. In the placebo group, these figures were 13.0 ± 10.2, 11.5 ± 8.0, 11.7 ± 13.6 and 11.6 ± 8.5 ml, respectively. No significant difference between the two groups was observed.

Conclusion: Thyroid-stimulating hormone suppression with levothyroxine for 2 years was not effective in reducing the size of benign cold nodules of the thyroid gland.

Materials & methods
The randomized clinical trial was conducted over a 2-year period. A total of 62 patients were enrolled. All had a single palpable thyroid nodule on physical examination and cytology consistent with benign nature of the nodule on fine needle aspiration biopsy (FNAB). Fine-needle biopsy was taken using a 25-gauge needle without local anesthesia. All cytologic studies were performed by a single cytopathologist at the department of pathology in Shariati Hospital. Patients with suspicious or malignant FNAB results were not considered eligible. Also disqualified from the study were patients:
- With a history of levothyroxine consumption, at least in the preceding year
- With abnormal levels of thyroxine (T4), triiodothyronine (T3) and TSH
- With more than one palpable nodule on physical examination
- Who are pregnant
- With a history of cardiovascular disease
- Who were aged 15 years or younger
- Who were aged 60 years or older

Patients were randomly assigned to either the levothyroxine group or the placebo group, with the use of a random number table. A total of 58 patients of the primary enrolled patients completed the second year of study (31 cases and 27 controls). One of the four dropouts was a middle-aged woman who underwent surgery by choice.

Thyroid hormone profiles were determined at the beginning of the study, 6 weeks later and then on a 3-monthly basis. TSH level was measured by a sensitive immunoradiometric (IRMA) method (Kavoshyar, Tehran, Iran;
Reference intervals: 0.3–5 mIU/ml). Complete TSH suppression was the goal (<0.1 mIU/ml). Given the sensitivity of the assay used at the time, the thyroid-releasing hormone (TRH) suppression test was applied to ten randomly selected patients in each group so as to ensure adequate suppression of TSH (synthetic TRH, 400 µg after week 6).

Both clinical and ultrasonographic studies were applied blindly. The patients were visited on a monthly basis at the endocrinology clinic. The size of nodules was measured by ultrasonography at the beginning and at 6, 12 and 24 months during the study period. A single sonologist performed all ultrasonographic studies with a real-time instrument (Kretz) and a medium-resolution 7.5-megahertz linear probe with the patients lying supine. The three diameters of each nodule (longitudinal [L], transverse [T] and anteroposterior [AP]) were measured. The volume of the nodules was then calculated using the spherical ellipsoid formula:

\[
\text{Volume} = \frac{4}{3}\pi \times \frac{1}{6} 	imes L \times T \times AP
\]

In each session, measurements were performed twice, and the mean measurement was reported to decrease intraobserver variation. In patients, who had more than one nodule, the largest one was selected and further measurements were performed on that nodule.

To compare the quantitative variables, we used Student's t-test. Each group was evaluated separately by the paired t-test to compare each measurement with the basal size. To analyze changes in nodule size over time, a repeated measures ANalysis Of VAriance (ANOVA) was used. Differences at p < 0.05 were considered significant. The two possible treatments (surgical and medical) and their advantages and disadvantages were described to each patient. The attending physician and sonographer were blind to the treatment protocol. Informed consent was obtained from all patients and the study was sanctioned by the responsible ethics committee. At the end of the study, all patients who had detectable nodules were referred to an endocrinologist for appropriate treatment measures.

Results

Table 1 summarizes the clinical and laboratory findings of the 58 subjects of our study (31 cases and 27 controls). In the treatment group, mean TSH was 1.7 ± 0.09 mIU/ml at baseline and 0.18 ± 0.3 mIU/ml after 6 weeks (p < 0.001). The figures in the control group were 0.92 ± 0.8 at baseline and 0.78 ± 0.7 mIU/ml 6 weeks later.

Hormonal alterations in both groups are shown in Table 2. Evidence of suppression was present in all subjects who remained in the study by the end of the second year. In the treatment group, the mean nodule volume was 12.8 ± 11.9 ml at baseline, which decreased to 9.4 ± 9.8 ml after 6 months (p < 0.003). However, at month 12 this increased again to 12.4 ± 16.7 ml, where no significant difference existed with the baseline size (p > 0.05). At month 24, mean nodule size was 10.8 ± 9.7 ml, again not significantly different from the baseline value (p > 0.05).

In the placebo group the mean nodule volume was 13.02 ± 10.2 ml at baseline, which was equivalent to the mean nodule size of the treatment group at baseline (12.8 ± 11.9 ml; p > 0.05). At month 6 the size decreased to 11.55 ± 8.0 ml (p < 0.003). In addition to the treatment group showing an increase in nodule size, an increase of 11.7 ± 13.6 ml was observed in the placebo group at month 12 – although this was not significantly different from baseline

| Table 1. Clinical and laboratory characteristics of cases and controls at the beginning of the trial. |
|------------------------------------------|------------------------------------------|------------------|------------------|
| **Cases (n)** | Levothyroxine group | Control group | p-value | Normal values |
| Cases (n) | 31 | 27 | | |
| Sex (F/M) | 25/6 | 20/7 | | |
| Age (years) | 34.4 ± 9.4 | 37.1 ± 11.8 | >0.05 | |
| TSH (mIU/ml) | 1.7 ± 1.0 | 0.9 ± 0.8 | >0.05 | 0.2–5.0 |
| T3 (ng/dl) | 129.4 ± 46.0 | 132.6 ± 41.0 | >0.05 | 80–230 |
| T4 (µg/dl) | 8.7 ± 2.0 | 8.5 ± 2.8 | >0.05 | 4.5–12.8 |
| Nodule volume (ml) | 12.8 ± 11.9 | 13.2 ± 10.0 | >0.05 | |

F/M: Female/male; T3: Triiodothyronine; T4: Thyroxine; TSH: Thyroid stimulating hormone.
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At month 24, mean nodule size was 11.6 ± 8.5 ml, and was neither significantly different from the baseline value (p > 0.05), nor the treatment group at the same time. These observations are summarized in Table 3. A total of 15 patients had more than one nodule, with the largest nodule in these patients being followed. All smaller nodules were less than 1 cm.

As shown in Table 4, the participants were divided into three categories based on the nodules' decrease in size:

- Complete responders: 50% or higher decrease in nodule volume
- Partial responders: less than 50% decrease in nodule volume
- Nonresponders: constant or increase in nodule volume

Repetitive FNAB in the nonresponder group did not show any abnormal cytologic finding.

Discussion

Diagnosis and treatment of cold thyroid nodules has remained a challenging issue in the field of internal medicine – the possibility of malignant transformation of these nodules over years has made the issue even more critical. While sample follow up of patients is suggested by some internists, suppressive therapy with levothyroxine is recommended by others. Medical management is suggested in more than 50% of the patients with single nodules who have benign FNAB findings and do not need surgery [3,13].

As thyrotropin can stimulate growth events in the thyroid gland, it is logical to assume that its suppression may arrest nodular tissue growth [22]. There are reports indicating significant decrease in the nodule size [22,23] or higher frequency of regression after a year of TSH suppression [24]. In contrast, several studies have failed to show a significant reduction after the introduction of levothyroxine suppressive therapy to these patients [13–15]. In a controlled trial, with follow-up after 5 years, Papini and colleagues came to the conclusion that long-term TSH suppression was ineffective to induce significant nodule volume reduction, but levothyroxine treatment had prevented any further increase in nodule volume or emergence of new nodules [9]. The success rate of levothyroxine suppressive therapy of thyroid nodules has ranged between 0 and 68% in previous studies [2]. This can be attributed to imprecise definition of the nodules being treated, failure to document suppression of thyrotropin [11], imprecise estimation of nodules size or lack of a placebo-control group [13].

The current study has used meticulous means to compare the placebo and levothyroxine groups. All measurements were done by high resolution ultrasonography, and suppression of TSH was confirmed by the TRH stimulation test. The observed initial decrease in the nodule size in the current study, which might have occurred secondary to the resorption of fluid in cystic nodules, was significant in both cases and controls, although somewhat more marked in

### Table 2. Hormonal changes of levothyroxine and control groups.

<table>
<thead>
<tr>
<th></th>
<th>Levothyroxine group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (mean ± SD)</td>
<td>6 weeks (mean ± SD)</td>
</tr>
<tr>
<td>TSH (mIU/ml)</td>
<td>1.7 ± 1.09</td>
<td>0.18 ± 0.3</td>
</tr>
<tr>
<td>T4 (µg/dl)</td>
<td>8.7 ± 2.00</td>
<td>10.5 ± 1.5</td>
</tr>
<tr>
<td>TSH after TRH test</td>
<td>0.8 ± 0.2</td>
<td>8.2 ± 3.8</td>
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</tbody>
</table>

*TRH test was given to only ten participants in each group.

SD: Standard deviation; T4: Thyroxine; TRH: Thyroid releasing hormone; TSH: Thyroid stimulating hormone.

### Table 3. Nodule volumes at baseline, 6, 12 and 24 months in levothyroxine and control groups.

<table>
<thead>
<tr>
<th></th>
<th>Baseline (mean ± SD)</th>
<th>6 months (mean ± SD)</th>
<th>p-value</th>
<th>12 months (mean ± SD)</th>
<th>p-value</th>
<th>24 months (mean ± SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levothyroxine group</td>
<td>12.8 ± 11.9</td>
<td>9.4 ± 9.8</td>
<td>0.003</td>
<td>12.4 ± 16.7</td>
<td>&gt;0.05</td>
<td>10.8 ± 9.7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Control group</td>
<td>13.0 ± 10.2</td>
<td>11.5 ± 8.0</td>
<td>0.003</td>
<td>11.7 ± 13.6</td>
<td>&gt;0.05</td>
<td>11.6 ± 8.5</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

SD: Standard deviation.
the placebo group. Nevertheless, measurements on months 12 and 24 indicated that the volume of the nodules had returned to baseline. No significant difference with regards to the nodule size was observable on months 12 and 24.

Ramelli and colleagues have proposed two possible mechanisms for the development of thyroid nodules – excessive accumulation of colloid and proliferation of thyroid follicles in the nondistensible connective tissue [25]. Resorption of colloid or follicular necrosis causes a reduction in the blood supply, eventually resulting in fibrosis and degeneration of the nodule. In this setting, levothyroxine suppressive therapy will not influence the pathologic processes within the nodule [26,27]. A number of other factors, including epidermal growth factor [28], insulin-like growth factor [29] and thyroid stimulating immunoglobulins [29], have been suggested to induce the growth of thyroid nodules. However it remains to future studies to verify whether such mechanisms really exist.

Vermiglio and colleagues compared the effects of 12 months of thyrotropin suppressive levothyroxine therapy in terms of initial cytological features. They observed decrease in size of nodules in a third of patients, irrespective of their cytologic features. They also reported a trend towards an augmentation of hypercellular, adenomatous and suspicious characteristics in increasing nodules. Hence they advised repeat FNAB should be used for thyroid nodules which increase in volume despite levothyroxine therapy [30].

In our study, cytological re-evaluation of months 12 and 24 did not show any change. On the whole it seems that, in the absence of an implicating change, repeated FNAB in the follow-up of benign thyroid nodules would be of limited value. Many previous reports were neither conducted in a randomized nor double-blind fashion. The two exceptions were conducted by Gharib and colleagues and Shimaoka and colleagues; however, TSH suppression was only conducted by Gharib and colleagues [13,31].

More recently, Papini and colleagues conducted a 5-year clinical trial to study long-term changes in thyroid cold nodules after suppressive therapy. They reported less frequent new nodules and more frequent nodule shrinkage in patients with complete TSH suppression than in the controls. They concluded that long-term TSH suppression could induce volume reduction in only a subgroup of thyroid nodules, but effectively prevent the appearance of new lesions and increases in nodule and thyroid volume [9]. Zelmanovitz and colleagues also observed that suppressive T4 treatment led to a reduction in volume and prevented the growth of nodules in a higher proportion of patients than the placebo group, although this difference did not reach statistical significance. They then analyzed their data together with the results of six other similar trials in a meta-analysis, and showed that suppressive T4 treatment was effective in decreasing the volume and impeding the growth of solitary thyroid nodules [32].

It is clear that more evidence from other studies will be necessary to further clarify the subject. Nevertheless, possible changes in the natural history of nodular goiter related to prolonged TSH suppression can be accompanied by unfavorable side effects of levothyroxine suppressive therapy [33–35]. In this line, some studies which have compared low- or high-level TSH suppression, have advised low-level TSH suppression if one considers levothyroxine suppressive therapy to reduce thyroid nodule size given the equal effectiveness of the two methods [36].

In conclusion, suppressive therapy with levothyroxine for 2 years failed to reduce the size of benign cold thyroid nodules. Moreover, sufficient suppression of TSH, as an effective factor in the growth of thyroid, produced no significant change in the natural course of the benign cold thyroid nodules.

Acknowledgment
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