REVIEW: Treatment of Hypothyroidism with Combinations of Levothyroxine plus Liothyronine

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Context: Combined infusion of levothyroxine plus liothyronine, as opposed to levothyroxine alone, is the only way of restoring the concentrations of circulating TSH, T4, and T3 as well as those of both T4 and T3 in all tissues of thyroidectomized rats. Considering the substantial differences in thyroid hormone secretion, transport, and metabolism between rats and humans, whether or not combined levothyroxine plus liothyronine replacement therapy has advantages over treatment with levothyroxine alone in hypothyroid patients is still questioned.

Evidence Acquisition: We conducted a systematic review of all the published controlled studies comparing treatment with levothyroxine alone with combinations of levothyroxine plus liothyronine in hypothyroid patients, identified through the Entrez-PubMed search engine.

Evidence Synthesis: Nine controlled clinical trials were identified that compared treatment with levothyroxine alone and treatment with combinations of levothyroxine plus liothyronine and included a sufficient number of adult hypothyroid patients to yield meaningful results. In only one study did the combined therapy appear to have beneficial effects on the mood, quality of life, and psychometric performance of the patients over levothyroxine alone. These results have not been confirmed by later studies using either T3 substitution protocols or approaches with fixed combinations of levothyroxine plus liothyronine, including those based on the physiological proportion in which T3 and T4 are secreted by the human thyroid. However, in some of these studies the patients preferred levothyroxine plus liothyronine combinations, for reasons not explained by changes in the psychological and psychometric tests employed. Yet patients’ preference should be balanced against the possibility of adverse events resulting from the addition of liothyronine to levothyroxine, even in the small doses used in these studies.

Conclusions: Until clear advantages of levothyroxine plus liothyronine are demonstrated, the administration of levothyroxine alone should remain the treatment of choice for replacement therapy of hypothyroidism. (J Clin Endocrinol Metab 90: 4946–4954, 2005)
Combined Levotyroxine plus Liothyronine Treatment for Hypothyroidism in Animal Models

We have conducted a series of animal studies to evaluate whether replacement therapy with levotyroxine alone actually resulted in euthyroidism (10–13). Thyroidectomized rats received continuous sc infusions of levotyroxine, synthetic T₃ (liothyronine), or combinations of levotyroxine plus liothyronine. Samples of plasma and most tissues were assayed for thyroid hormone measurements, and types 1, 2, and 3 deiodinase activities were measured in several tissues (Fig. 1). Tissue euthyroidism was declared when the concentrations of both T₄ and T₃ were within the normal range found in intact euthyroid animals infused with placebo.

We found in Refs. 10–13 that: 1) despite a wide range of doses infused (from 0.2–8.0 µg levotyroxine/100 g body weight per day and from 0.25–2.0 µg liothyronine/100 g body weight per day), neither levotyroxine nor liothyronine alone restored euthyroidism (Tables 1 and 2); 2) combinations of levotyroxine plus liothyronine, however, based on the amounts and proportions of T₄ and T₃ present in the rat thyroidal secretion, did ensure euthyroidism (Table 3); 3) with the levotyroxine dose that normalized plasma TSH, most tissues still had T₃ concentrations below the normal range (Table 1); 4) when levotyroxine plus liothyronine combinations were infused, the levotyroxine needed to normalize serum TSH was almost half the dose required with levotyroxine alone (Tables 1 and 3); 5) the mechanisms involved in the regulation of thyroid hormone concentrations were tissue specific, and so was the efficiency of the homeostasis of tissue T₃ concentrations (Tables 1–3); 6) when levotyroxine alone was used for replacement therapy, the cerebral cortex was extremely efficient in maintaining normal T₃ concentrations and was virtually independent from changes in serum concentrations of T₄ and T₃ (Table 1); and 7) this excellent homeostasis of brain T₃ levels was lost when liothyronine alone was infused (Table 2).

These conclusions cast doubts upon replacement therapy in humans with levotyroxine alone (11), because it might not be able to restore euthyroidism in all tissues of hypothyroid patients. Normalization of serum TSH, the usual marker of euthyroidism during treatment, might not ensure normal T₃ concentrations in some tissues.

**Infusion of T₄, T₃, T₄ + T₃, or placebo, using osmotic minipumps (5-6 rats/group)**

![Experimental design of our studies in thyroidectomized rats infused with levotyroxine alone, liothyronine, or levotyroxine plus liothyronine.](image)

**Fig. 1.** Experimental design of our studies in thyroidectomized rats infused with levotyroxine alone, liothyronine, or levotyroxine plus liothyronine.

We therefore hypothesized that a combined treatment of levotyroxine plus liothyronine might be advantageous for hypothyroid patients, compared with levotyroxine alone (11). Based on our results in the rat, we made several recommendations regarding the ideal thyroid hormone preparation (11): 1) it should contain levotyroxine and liothyronine in a molar proportion of 14:1 and deliver into the circulation approximately 100 µg T₄ and 6 µg T₃ per day, thus mimicking human thyroid secretion (4), and 2) the route of administration should warrant a constant steady supply of levotyroxine and liothyronine, by means of enteric, im, or transdermal sustained-release preparations, at least for the T₃ component. However, most of the studies conducted in hypothyroid patients after the publication of our data have ignored these recommendations, despite being rapidly adopted by other experts in the field (14).

There are substantial differences between rats and humans in thyroid hormone secretion, transport, and metabolism. The molar T₄:T₃ ratio in thyroid secretion has been calculated as 14:1 in adult man (4), whereas the corresponding mean value obtained for the adult male rat is approximately 6:1 (15–18). In humans, thyroid-binding globulin (TBG) is the principal serum transport protein for thyroid hormones, whereas only a small proportion circulates bound to transthyretin and albumin. Binding to TBG may serve as a circulating buffer that might partially alleviate the thyroid when exposed to sudden increases in the requirements of these hormones. In rat serum, transthyretin is the dominant thyroid hormone-binding protein, the concentration of TBG being extremely low in adults, approximately 2% of that circulating in humans (19, 20). Thyroid hormones' metabolism is less buffered by plasma proteins than it is in man, with a greater proportion circulating as free T₄ and free T₃ (21, 22). This may contribute to explain the need of a higher proportion of T₃ with respect to T₄ secreted by the rat thyroid.

Moreover, the regulation of tissue thyroid hormone concentrations involve deiodinative and nondeiodinative pathways of T₄ and T₃ metabolism and factors regulating the uptake and exit of iodothyronines into organs and tissues (23–27), and these mechanisms may be both tissue and species specific.

These differences between animals and humans ought to be considered before extending the rat findings to human physiology and, especially, to the issue of treatment with thyroid hormone preparations in hypothyroid patients.

**Combining Levotyroxine plus Liothyronine Treatment for Hypothyroidism in Humans**

There are few studies comparing levotyroxine replacement therapy with treatments using combinations of levotyroxine plus liothyronine (Table 4). Taylor and his coworkers observed that patients treated with levotyroxine alone had increased plasma protein-bound iodine (PBI) values compared with healthy euthyroid controls. They reported in 1970 (28) that patients’ PBIs were comparable to those of euthyroid subjects when given tablets containing 50 µg levotyroxine plus 15 µg liothyronine (Fig. 2), with maintenance of clinical euthyroidism.

Some months later, Smith et al. (29) published the first
study comparing levothyroxine therapy with combined
levothyroxine plus liothyronine treatment. Using a double-
blinded, crossover design, they assigned 87 patients to re-
ceive their usual number of tablets (two or three), containing
either 100 μg levothyroxine or 80 μg levothyroxine plus 20
μg liothyronine, with treatments rotated after 2 months.

Adverse effects (palpitations, irritability, nervousness,
dizziness, and tremor) were more frequent during combined
levothyroxine plus liothyronine treatment. Thirty-three per-
cent preferred levothyroxine tablets, 18.4% preferred levo-
thyroxine plus liothyronine treatment. Using a double-
based approach (31), substitution of a fixed amount of liothyronine for
replacement therapy” (29). We know now-
adays that all their patients were over-treated, with the ad-
verse effects using the combinations being easily explained
by the addition of 40–60 μg liothyronine to an already ex-
cessive levothyroxine dose.

The interest for a combined levothyroxine plus liothyro-
nine therapy declined until the late 1990s, when our animal
studies were published (10–13). Although actually ignoring
our recommendations for man (11), Bunevicius et al. (30)
published in 1999 their favorable experience with combined
levothyroxine plus liothyronine replacement therapy in 33
hypothyroid patients, 31 women and two men, of whom 17
were thyroidectomized thyroid cancer patients and 16 had
chronic autoimmune thyroiditis.

The study was a randomized, double-blinded crossover
trial (30), using what has been named a T3 substitution
approach (31), substitution of a fixed amount of liothyronine for

| TABLE 2. Schematic representation of plasma concentrations of T4, T3, and TSH and tissue levels of T4 and T3 in thyroidectomized rats infused with different doses of liothyronine with respect to age- and sex-matched controls |

<table>
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<th>Dose of T4 (μg/100 g)</th>
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<th>0.75</th>
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<tr>
<td>T4 T3 TSH</td>
<td>T4 T3 TSH</td>
<td>T4 T3 TSH</td>
<td>T4 T3 TSH</td>
<td>T4 T3 TSH</td>
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<tr>
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<td>↓ = ↑</td>
<td>↓ = ↑</td>
<td>↓ = ↑</td>
<td>↓ = ↑</td>
</tr>
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<td>Cerebral cortex</td>
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<td>↓ = ↑</td>
<td>↓ = ↑</td>
<td>↓ = ↑</td>
<td>↓ = ↑</td>
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<tr>
<td>Cerebellum</td>
<td>↓ = ↑</td>
<td>↓ = ↑</td>
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<tr>
<td>Pituitary</td>
<td>↓ = ↑</td>
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<td>↓ = ↑</td>
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<td>↓ = ↑</td>
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<td>↓ = ↑</td>
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<tr>
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<tr>
<td>Lung</td>
<td>↓ = ↑</td>
<td>↓ = ↑</td>
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<tr>
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<td>↓ = ↑</td>
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<td>↓ = ↑</td>
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<tr>
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<tr>
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<td>↓ = ↑</td>
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<tr>
<td>Adrenal</td>
<td>↓ = ↑</td>
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<tr>
<td>Ovary</td>
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<td>↓ = ↑</td>
<td>↓ = ↑</td>
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</table>

The symbols represent the comparison of the mean values of the liothyronine-infused rats with control rats infused with placebo. =, No statistically significant differences; ↓, low levels as compared with controls, with at least P < 0.05; ↑, elevated levels as compared with controls, with at least P < 0.05. BAT, Brown adipose tissue. [Represented with permission from data published in H. F. Escobar-Morreale et al.: Biochimie (Paris) 81:453, 1999 (13).© Elsevier.]
and tissue levels of T4 and T3 of thyroidectomized rats infused with different doses of levothyroxine, alone or in combination with different doses of liothyronine.

The benefits of T3 substitution were restricted to athyreotic thyroidectomized rats infused with different doses of levothyroxine, alone or in combination with different doses of liothyronine. A subsequent reanalysis of the data, removing from the subset of thyroid cancer patients, however, T3 substitution was not different from that in the control group.

The symbols represent the comparison of the mean values of the thyroid hormone doses, with control values as compared with T3 substitution, with at least $P < 0.05$. BAT, Brown adipose tissue. [Represented with permission from data published in H. F. Escobar-Morreale et al.: Endocrinology 137:2490, 1996 (11).] In addition to normal T4 and T3 concentrations, the molar T4:T3 ratio was not different from that in the control group.

The publication of the first study of Bunevicius et al. (30, 32) was greeted with considerable interest not only for scientific reasons but also for hypothyroid patients; combined levothyroxine plus liothyronine replacement was considered the answer to the relatively frequent complaint (35) of the persistence, with levothyroxine alone, of hypothyroid symptoms despite normalization of serum TSH.

To date, four published studies (36–39) have tried to reproduce the beneficial effects of T3 substitution described above, without success (Table 4). Walsh et al. (36) conducted a randomized, double-blinded, crossover trial in which patients were treated with their usual levothyroxine dose or a combination that contained 50 μg less of levothyroxine plus 10 μg liothyronine for 10 wk, separated by a 4-wk washout period on levothyroxine alone. Evaluation of the 101 patients completing the study revealed no substantial improvement in indexes of QoL, cognitive function, mood, or hypothyroid symptoms, and patients’ preference was equal for both treatments (36). However, it should be noted that serum TSH levels were higher during T3 substitution, and any possible improvement might have been obscured by a relative undertreatment of the patients (40).

Sawka et al. (37) evaluated the possible beneficial effects of T3 substitution in hypothyroid patients presenting with persistent depressive symptoms despite adequate replacement with levothyroxine alone. Using a randomized parallel design, 20 patients were assigned to continue with their usual

### TABLE 3. Schematic representation of the changes with respect to intact control rats in the plasma concentrations of T4, T3, and TSH and tissue levels of T4 and T3 of thyroidectomized rats infused with different doses of levothyroxine, alone or in combination with different doses of liothyronine

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<th>TSH</th>
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<tr>
<td>0.80 μg</td>
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<td>0.10 μg</td>
<td>0.15 μg</td>
<td>0.20 μg</td>
<td>No T3</td>
</tr>
<tr>
<td>Plasma</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>Cerebral cortex</td>
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<td>Pituitary</td>
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<tr>
<td>Cerebellum</td>
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<td>BAT</td>
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<td>Liver</td>
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<td>Kidney</td>
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TABLE 4. Summary of studies evaluating levothyroxine plus liothyronine combinations for the treatment of hypothyroidism

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<thead>
<tr>
<th></th>
<th>Smith et al. (29)</th>
<th>Bunevicius et al. (30, 32)</th>
<th>Walsh et al. (36)</th>
<th>Sawka et al. (37)</th>
<th>Clyde et al. (38)</th>
<th>Siegmund et al. (43)</th>
<th>Saravanan et al. (39)</th>
<th>Escobar-Morreale et al. (44)</th>
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<tr>
<td>T&lt;sub&gt;4&lt;/sub&gt;/T&lt;sub&gt;3&lt;/sub&gt; dose</td>
<td>T&lt;sub&gt;3&lt;/sub&gt; substitution</td>
<td>T&lt;sub&gt;3&lt;/sub&gt; substitution</td>
<td>T&lt;sub&gt;3&lt;/sub&gt; substitution</td>
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<td>101</td>
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<td>23</td>
<td>573</td>
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<td>T&lt;sub&gt;4&lt;/sub&gt; + T&lt;sub&gt;3&lt;/sub&gt;</td>
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* A later study by Bunevicius et al. (34) has not been included in this table because the small sample size of 10 patients precluded reaching a definite conclusion. Also, this table does not contain information of a study by Cassio et al. (42) because it included infants with congenital hypothyroidism and the outcomes are not comparable with studies conducted in adults.

* Patients received the prestudy number of tablets (two or three) throughout the study.

* *A priori* sample size calculation gave a minimum of 24 patients for an 80% power at the *P* < 0.05 significance level, but only 23 patients completed the study.

* Thyroid function tests: serum thyroid hormone levels, except in Ref. 29 in which serum PBI and T<sub>3</sub>-resin uptake were measured.
levothyroxine dose, and another 20 patients received half their usual levothyroxine dose plus 12.5 μg liothyronine twice daily (37). The liothyronine dose was titrated thereafter to maintain serum TSH concentrations within the normal range. Both treatments were maintained for 15 wk. Patients’ preference was not assessed. No improvement of mood or hypothyroid symptoms was found with T₃ substitution. A significant proportion of dropouts had occurred in both arms of treatment and a significant placebo effect detected (symptoms were ameliorated with both treatments). More importantly, power analysis was not provided despite the small sample size.

Clyde et al. (38) used a randomized parallel design to evaluate T₃ substitution that did not use a crossover design eliminating the possibility of a practice effect on the tests used for psychometric performance. In this study, 7.5 μg liothyronine was given twice daily, and 50 μg of their levothyroxine dose withdrawn for 16 wk in the patients assigned to this arm of treatment. Although supported by adequate statistical power, results from the 44 patients completing the follow-up did not show any beneficial effect of T₃ substitution on psychometric performance, QoL, mood, and a few biological end-points of thyroid hormone action. Patients’ preference was not evaluated.

Saravanan et al. (39) used 10 μg liothyronine to substitute 50 μg of the usual levothyroxine dose of the patients in a parallel randomized design including 697 patients. The main outcome was psychiatric caseness, defined by the General Health Questionnaire 12 score. They found a large and persistent placebo effect in the control group but only a minor improvement after 3 months of combined treatment, not sustained thereafter.

Considering the four negative studies published after the initial report by Bunevicius et al. (30, 32), it would appear that T₃ substitution has a minor role, if any, in thyroid replacement therapy (14, 31, 41). But this did not necessarily exclude a role of combinations of levothyroxine plus liothyronine in thyroid replacement therapy, because of important limitations of the T₃ substitution approach: 1) considering that the pre-study levothyroxine requirements were quite variable in the patients recruited for these studies, this design resulted in a large variation in the T₄:T₃ ratios and in the absolute amounts of both iodothyronines, making it impossible to mimic normal thyroid physiology (14, 31, 41, 2) these studies included both men and women, and gender might influence the response to treatment, especially in terms of mood and QoL; and 3) the previous duration and severity of hypothyroidism were quite variable, including patients presenting at diagnosis with subclinical hypothyroidism, who might retain some residual secretion of both T₄ and T₃. Therefore, the lack of beneficial effects of T₃ substitution over levothyroxine alone might depend on these confounding factors and not on the lack of an overall beneficial effect of combined levothyroxine plus liothyronine replacement therapy.

Four very recent studies (Table 4), including one from our group, have further contributed to this issue (42–45). Cassio et al. (42) compared seven infants with congenital hypothyroidism treated with levothyroxine alone with seven infants treated with a levothyroxine plus liothyronine combination in a molar T₄:T₃ ratio of 17:1. The levothyroxine dose was reduced by 20% in the following combination: every 25 g of the levothyroxine dose calculated for body weight was substituted by 20 μg levothyroxine plus 1 μg liothyronine. Psychomotor development at 6 and 12 months was similarly impaired with both treatments when compared with euthyroid controls. Treatment adjustments based on serum TSH were more difficult with the combination and more frequently needed.

Siegmund et al. (43) conducted a crossover trial in which 26 hypothyroid patients were treated for 12-wk periods either with their usual levothyroxine doses or with a combination of levothyroxine plus liothyronine. The latter had a 16:1 molar ratio, and under the assumption that bioavailability of oral liothyronine is 100%, and that of levothyroxine is 90%, the authors hypothesize a 14:1 bioavailable molar ratio. No improvement of well-being and cognitive performance was found with the combination, but the number of patients completing the study was insufficient to achieve statistical power (43). No changes were observed in serum free T₄ and free T₃, whereas TSH levels were more suppressed with the levothyroxine plus liothyronine combination, and in eight of the 23 patients analyzed, TSH was undetectable and associated with an impairment in mood indexes. Of note, one of the three patients not completing the study was removed during levothyroxine plus liothyronine combination treatment because of atrial fibrillation associated with suppression of TSH. The occurrence of this severe adverse event raises a cautionary note regarding the addition to levothyroxine of even very small quantities of liothyronine.

We have published recently a randomized, double-blinded, crossover clinical trial comparing treatment with 100 μg levothyroxine with a combination containing 75 μg levothyroxine plus 5 μg liothyronine per day (13:1 molar T₄:T₃ ratio, 15:1 by wt). However, fearing possible undertreatment, all the patients were given, for a final 8-wk add-on...
period, a combination containing 87.5 μg levothyroxine plus 7.5 μg liothyronine per day (10:1 molar T4:T3 ratio, 12:1 by wt).

We also tried to overcome most of the limitations of previous studies (Table 4) by using two fixed combinations of levothyroxine plus liothyronine, in proportions based on those secreted by the normal thyroid, thus avoiding the variable and excessive amounts of liothyronine compared with that of levothyroxine used before.

To avoid heterogeneity, we included only female patients who had long-term overt primary hypothyroidism, making any interference from residual thyroid function unlikely, and who had been treated with a 100 μg/d dose of levothyroxine for at least 1 yr before recruitment. Outcomes were not restricted to QoL and psychometric functionality but consisted in a broad evaluation of thyroid hormone biological endpoints covering most organs and systems. And finally, only our study included an external control group of healthy euthyroid women, allowing us to evaluate whether the measured outcomes were affected in the hypothyroid patients irrespective of treatment protocol, thus eliminating a potential confounding factor in previous studies.

Given these strict inclusion criteria, we were able to recruit only 28 women, of whom 26 completed the study. Yet power analysis indicated that this sample size was enough to detect the differences in the QoL, mood, and psychometric indexes previously reported by Bunevicius et al. (30, 32). Twenty healthy women served as euthyroid controls.

After treatment with the combination of 75 μg levothyroxine plus 5 μg liothyronine, serum free T4 levels decreased as compared with levothyroxine alone, whereas TSH increased slightly and free T3 remained unchanged (Fig. 3). On the contrary, the 87.5 μg levothyroxine plus 7.5 μg liothyronine combination resulted in over-replacement, given that TSH levels decreased and free T3 increased compared with levothyroxine alone (Fig. 3), and in 10 of the patients TSH levels were below the lower limit of the normal range (but not suppressed).

We were not able to demonstrate any significant improvement in QoL, mood, or psychometric indexes (44). Patients scored better in only a few indexes of psychometric performance after receiving the combination containing 87.5 μg levothyroxine plus 7.5 μg liothyronine, although this slight improvement might have resulted from overtreatment rather than from the combined therapy. Of note, our statistical analysis ruled out any significant period or sequence effect on the psychometric tests, making significant practice effects unlikely.

In fact, some items were worse in patients than in euthyroid controls, independently of the treatment they received. As previous studies have shown for hypothyroid patients on levothyroxine alone (35), it is possible that being aware of having a disease accounts for this difference (46).

We did not find any improvement in biological end-points pertaining to multiple organs and systems, including anthropometrical, biochemical, hormonal, neurological, and echocardiographic outcomes. Yet it is important to highlight that both combinations of levothyroxine plus liothyronine undesirably increased the urinary concentrations of bone remodeling markers.

Patients, however, actually preferred the combinations. Of the 26 patients, 12 preferred the combination of 75 μg levothyroxine plus 5 μg liothyronine, six preferred 87.5 μg levothyroxine plus 7.5 μg liothyronine, two preferred levothyroxine alone, and six showed no preference. Although it might be argued that patients preferred the 87.5 μg levothyroxine plus 7.5 μg liothyronine combination because of over-replacement, it should be highlighted that most patients preferred the 75 μg levothyroxine plus 5 μg liothyronine combination, which resulted in the mild under-replacement suggested by slightly increased TSH and cholesterol values.

This preference for the combined therapy might have resulted from chance. But patients in the Bunevicius et al. (30) study also preferred levothyroxine plus liothyronine combinations, and a similar result has been recently confirmed in a large study conducted in The Netherlands by Appelhut et al. (45). One hundred forty-one hypothyroid patients were randomized to continue on levothyroxine alone, on a combination of levothyroxine plus liothyronine in a molar T4:T3 ratio of 4.2:1 (5:1 by wt), or on combination in a molar T4:T3 ratio of 8.4:1 (10:1 by wt), for 15 wk. The primary outcome of this trial was patients’ preference, and indexes pertaining to mood, well-being, and fatigue were considered secondary outcomes. Study medication was preferred to usual treatment by 29.2% in the levothyroxine group, 41.3% in the 10:1 ratio group, and 52.2% in the 5:1 ratio group. Serum TSH and body weight decreased with the combinations, especially with that containing a T4:T3 ratio of 5:1 with which TSH was actually suppressed in many subjects, as indicated by median values of 0.07 μU/ml. As occurred in our study (44), the psychological tests used in the Dutch study (45) did not show any improvement with the levothyroxine plus liothyronine combinations, and only a minimal reduction in body weight.
was found (mean loss of 0.5 and 1.7 kg in 15 wk with the 10:1 and 5:1 combinations, respectively).

Although most of the limitations of the studies by Smith et al. (29) and Bunevicius et al. (30) have later been addressed, the T₃ preparation used in all of them was liothyronine, because at present no sustained-release preparations are commercially available. For this reason, we were ourselves (44) unable to follow one of the recommendations emanating from our animal work (11).

Recently, Hennemann et al. (47) have reported a preliminary description of three 6-wk treatment periods of hypothyroid patients with their usual levothyroxine dose (150 μg/d for most of them), followed by 6 wk on a combination of 125 μg levothyroxine plus 6 μg liothyronine (in a molar T₄/T₃ ratio of 17:1) containing an in-house slow-release T₃ preparation and 6 wk on the same combination but using the Cytomel liothyronine commercial preparation. Lack of information on the actual chemical nature of the slow-release preparation precludes confirmation of their findings by others.

Compared with a similar combination in which T₃ was standard liothyronine, the combination with the slow-release preparation decreased slightly the maximal serum T₃ concentration attained and increased slightly the timing of maximal concentrations of serum T₃ after ingestion, whereas the area under the curve of serum T₃ remained unchanged (47). Whether these small changes in the pharmacokinetics of this compound actually represent a major improvement is a matter of discussion (48), especially when considering that the mean serum T₄, T₃, and TSH concentrations of the patients attained after the standard and after the slow-release T₃ preparations were unchanged and that with the actual doses of levothyroxine plus liothyronine that were used, serum T₄ concentration remained increased and the serum T₃ levels remained low when compared with euthyroid controls, despite the decrease in TSH levels (47).

### Summary and Conclusions

In humans, combined levothyroxine plus liothyronine treatment does not appear to have clear advantages over the standard treatment with levothyroxine alone. The initial report of beneficial effects of T₃ substitution on mood, QoL, and psychometric functionality has not been confirmed by later studies, using both T₃ substitution and physiological approaches to combined levothyroxine plus liothyronine replacement therapy.

However, in some of these studies, the patients preferred levothyroxine plus liothyronine combinations over levothyroxine alone, for reasons not explained by changes in the psychological and psychometric tests employed or the biological end-points that were also measured. Yet patients’ preference should be balanced against the possibility of adverse events resulting from the addition of liothyronine to levothyroxine, even in the small doses used in these studies.

Therefore, until clear advantages of levothyroxine plus liothyronine are demonstrated, levothyroxine alone should remain the drug of choice for the replacement therapy of hypothyroidism.

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