0021-972X/05/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 90(8):4946–4954

doi: 10.1210/jc.2005-0184

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, T_4, and T_3 as well as those of both T_4 and T_3 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 T_3 substitution protocols or approaches with fixed combinations of levothyroxine plus liothyronine, including those based on the physiological proportion in which T_3 and T_4 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)**

AT PRESENT, SODIUM levothyroxine is the preparation of choice to restore well-being and euthyroidism in hypothyroid patients (1–3). The latter is believed to occur when serum TSH returns to the reference range (2), with serum TSH concentrations usually used to monitor levothyroxine therapy. Reliance on circulating TSH is supported by many years of experience, and most patients are satisfied with the results, but it implies assumptions that are not supported by direct evidence.

First, although approximately 80% of the T_3 circulating in blood is originated by peripheral 5′-deiodination of the T_4 secreted by the thyroid gland, as much as 20% is secreted directly by the gland (4), suggesting a physiological role for the latter fraction. When patients are given levothyroxine alone, it is assumed that peripheral conversion of T_4 to T_3 provides the exact amount of T_3 needed by each particular tissue or organ that is usually provided by the missing thyroid secretion.

But the scarce evidence available for man does not support this. Hypothyroid patients on levothyroxine replacement therapy have higher serum T_4 levels when serum TSH and T_3 concentrations are similar to those of euthyroid controls (5). In as many as 25–32% of hypothyroid patients on levothyroxine therapy, serum T_4 has to reach the upper limit of the normal range, or even exceed it, to normalize serum TSH and its normal response to TSH-releasing hormone (6, 7). These findings suggest that the levothyroxine doses needed to normalize serum TSH in hypothyroid patients are relatively supraphysiological, possibly to compensate for the absence of the fraction of circulating T_3 secreted directly by the thyroid.

Second, TSH is widely used to monitor levothyroxine replacement therapy (1–3, 6), assuming implicitly that its level within the normal range indicates euthyroidism in all tissues of hypothyroid patients. Serum TSH levels, however, only reflect the feedback effect of thyroid hormones at the hypothalamic-pituitary level. In patients on long-term replacement with levothyroxine presenting with biochemical abnormalities suggestive of hyperthyroidism, free T_4 was raised in 85% of them, whereas an undetectable serum TSH was present in only 67% (8). Moreover, athyreotic patients present a differential end-organ responsiveness to suboptimal thyroid hormone concentrations (9). It is thus unlikely that a single end-point of thyroid hormone action, such as serum TSH, accurately reflects the thyroid hormone concentrations in all tissues and organs.

First Published Online May 31, 2005

Abbreviations: PBI, Protein-bound iodine; QoL, quality of life; TBG, thyroid-binding globulin.

Combined Levothyroxine plus Liothyronine Treatment for Hypothyroidism in Animal Models

We have conducted a series of animal studies to evaluate whether replacement therapy with levothyroxine alone actually resulted in euthyroidism (10–13). Thyroidectomized rats received continuous sc infusions of levothyroxine, synthetic T_3 (liothyronine), or combinations of levothyroxine 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 T_4 and T_3 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 levothyroxine/100 g body weight per day and from 0.25–2.0 μg liothyronine/100 g body weight per day), neither levothyroxine nor liothyronine alone restored euthyroidism (Tables 1 and 2); 2) combinations of levothyroxine plus liothyronine, however, based on the amounts and proportions of T_4 and T_3 present in the rat thyroidal secretion, did ensure euthyroidism (Table 3); 3) with the levothyroxine dose that normalized plasma TSH, most tissues still had T_3 concentrations below the normal range (Table 1); 4) when levothyroxine plus liothyronine combinations were infused, the levothyroxine needed to normalize serum TSH was almost half the dose required with levothyroxine 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 T_3 concentrations (Tables 1–3); 6) when levothyroxine alone was used for replacement therapy, the cerebral cortex was extremely efficient in maintaining normal T_3 concentrations and was virtually independent from changes in serum concentrations of T_4 and T_3 (Table 1); and 7) this excellent homeostasis of brain T_3 levels was lost when liothyronine alone was infused (Table 2).

These conclusions cast doubts upon replacement therapy in humans with levothyroxine 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 T_3 concentrations in some tissues.

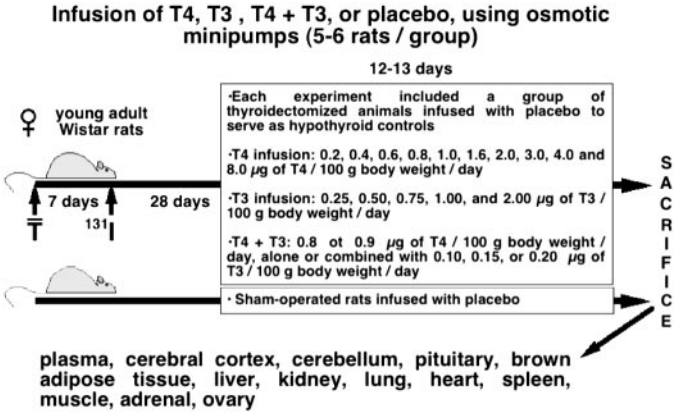

FIG. 1. Experimental design of our studies in thyroidectomized rats infused with levothyroxine alone, liothyronine, or levothyroxine plus liothyronine.

We therefore hypothesized that a combined treatment of levothyroxine plus liothyronine might be advantageous for hypothyroid patients, compared with levothyroxine alone (11). Based on our results in the rat, we made several recommendations regarding the ideal thyroid hormone preparation (11): 1) it should contain levothyroxine and liothyronine in a molar proportion of 14:1 and deliver into the circulation approximately 100 μg T_4 and 6 μg T_3 per day, thus mimicking human thyroid secretion (4), and 2) the route of administration should warrant a constant steady supply of levothyroxine and liothyronine, by means of enteric, im, or transdermal sustained-release preparations, at least for the T_3 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 T_4:T_3 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 T_4 and free T_3 (21, 22). This may contribute to explain the need of a higher proportion of T_3 with respect to T_4 secreted by the rat thyroid.

Moreover, the regulation of tissue thyroid hormone concentrations involve deiodinative and nondeiodinative pathways of T_4 and T_3 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.

Combined Levothyroxine plus Liothyronine Treatment for Hypothyroidism in Humans

There are few studies comparing levothyroxine replacement therapy with treatments using combinations of levothyroxine plus liothyronine (Table 4). Taylor and his coworkers observed that patients treated with levothyroxine 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 levothyroxine plus 15 μg liothyronine (Fig. 2), with maintenance of clinical euthyroidism.

Some months later, Smith *et al.* (29) published the first

TABLE 1. Schematic representation of plasma concentrations of T_4, T_3, and TSH and tissue levels of T_4 and T_3 in thyroidectomized rats infused with different doses of levothyroxine with respect to age- and sex-matched controls

	Dose of T_4 (μg/100 g·d)																														
	0.2			0.4			0.6			0.8			1.0			1.6			2.0			3.0			4.0			8.0		
	T_4	T_3	TSH	T_4	T_3	TSH	T_4	T_3	TSH	T_4	T_3	TSH	T_4	T_3	TSH	T_4	T_3	TSH	T_4	T_3	TSH	T_4	T_3	TSH	T_4	T_3	TSH	T_4	T_3	TSH
Plasma	↓	↓	↑	↓	↓	↑	=	↓	↑	=	↓	↑	=	=	↑	↑	=	=	↑	↑	↓	↑	↑	↓	↑	↑	↓	↑	↑	↓
Cerebral cortex	↓	↓		↓	=		↓	=		↓	=		↑	=		↑	↑		↑	=		↑	=		↑	=		↑	=	
Cerebellum	↓	↓		↓	↓		=	↓		↑	=		=	=		↑	=		=	=		↑	=		↑	↑		↑	↑	
Pituitary	↓	↓		↓	↓		=	↓		↑	↓		=	=		↑	=		=	=		=	=		↑	↑		↑	↑	
BAT		↓			=			=			=			=			↓			=			=			=			=	
Liver	↓	↓		↓	↓		↓	↓		↓	↓		=	↓		↑	=		↑	=		↑	=		↑	↑		↑	↑	
Kidney	↓	↓		↓	↓		↓	↓		↓	↓		=	↓		↑	=		↑	↑		↑	↑		↑	↑		↑	↑	
Lung	↓	↓		↓	↓		=	↓		=	↓		=	↓		↑	↓		↑	=		↑	↑		↑	↑		↑	↑	
Heart	↓	↓		↓	↓		=	↓		=	↓		=	↓		=	↓		↑	=		↑	↑		↑	↑		↑	↑	
Muscle	↓	↓		=	↓		=	↓		↑	=		↑	=		↑	↑		↑	↑		↑	=		↑	↑		↑	↑	
Spleen	↓	↓		↓	↓		=	↓		=	=		=	↓		↑	↑		↑	=		↑	↑		↑	↑		↑	↑	
Adrenal	↓	↓		↓	↓		=	↓		=	↓		=	↓		↑	↓		↑	=		=	↓		↑	=		↑	=	
Ovary	↓	↓		↓	↓		↓	↓		=	↓		=	↓		=	↓		=	=		=	=		=	=		=	=	

The symbols represent the comparison of the mean values of the levothyroxine-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. [Redrawn with permission from data published in H. F. Escobar-Morreale *et al.*: *J Clin Invest* 96:2828, 1995 (10).]

study comparing levothyroxine therapy with combined levothyroxine plus liothyronine treatment. Using a double-blinded, crossover design, they assigned 87 patients to receive 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 percent preferred levothyroxine tablets, 18.4% preferred levothyroxine plus liothyronine tablets, whereas 48.3% showed no preference. Adverse effects influenced patients' preference (29).

With levothyroxine plus liothyronine, the plasma PBI and the free T_4 index decreased, whereas the T_3-resin uptake values were not altered (29). They concluded that "the shortcomings of combined therapy suggested overall advantages of thyroxine for replacement therapy" (29). We know nowadays that all their patients were overtreated, with the adverse effects using the combinations being easily explained by the addition of 40–60 μg liothyronine to an already excessive levothyroxine dose.

The interest for a combined levothyroxine plus liothyronine 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 T_3 substitution approach (31), substitution of a fixed amount of liothyronine for

TABLE 2. Schematic representation of plasma concentrations of T_4, T_3, and TSH and tissue levels of T_4 and T_3 in thyroidectomized rats infused with different doses of liothyronine with respect to age- and sex-matched controls

	Dose of T_3 (μg/100 g·d)														
	0.25			0.50			0.75			1.0			2.0		
	T_4	T_3	TSH	T_4	T_3	TSH	T_4	T_3	TSH	T_4	T_3	TSH	T_4	T_3	TSH
Plasma	↓	=	↑	↓	↑	↓	↓	↑	↓	↓	↑	↓	↓	↑	↓
Cerebral cortex	↓	↓		↓	=		↓	=		↓	=		↓	↑	
Cerebellum	↓	=		↓	=		↓	↑		↓	↑		↓	↑	
Pituitary	↓	↓		↓	=		↓	=		↓	↑		↓	↑	
BAT	↓	↓		↓	↓		↓	=		↓	=		↓	=	
Liver	↓	↓		↓	↑		↓	↑		↓	↑		↓	↑	
Kidney	↓	↓		↓	=		↓	↑		↓	↑		↓	↑	
Lung	↓	=		↓	↑		↓	↑		↓	↑		↓	↑	
Heart	↓	↓		↓	↑		↓	↑		↓	↑		↓	↑	
Muscle	↓	=		↓	↑		↓	↑		↓	↑		↓	↑	
Spleen	↓	=		↓	↑		↓	↑		↓	↑		↓	↑	
Adrenal	↓	=		↓	↑		↓	↑		↓	↑		↓	↑	
Ovary	↓	=		↓	=		↓	↑		↓	↑		↓	↑	

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.]

TABLE 3. Schematic representation of the changes with respect to intact control rats in the plasma concentrations of T_4, T_3, and TSH and tissue levels of T_4 and T_3 of thyroidectomized rats infused with different doses of levothyroxine, alone or in combination with different doses of liothyronine

	0.80 μg T_4												0.90 μg T_4											
	No T_3			0.10 μg T_3			0.15 μg T_3			0.20 μg T_3			No T_3			0.10 μg T_3			0.15 μg T_3			0.20 μg T_3		
	T_4	T_3	TSH	T_4	T_3	TSH	T_4	T_3	TSH	T_4	T_3	TSH	T_4	T_3	TSH	T_4	T_3	TSH	T_4	T_3	TSH	T_4	T_3	TSH
Plasma	=	↓	↑	=	=	↑	=	=	↑	=	=	=	=	↓	↑	=	=	↑	=	=	=[a]	=	=	=
Cerebral cortex	=	=	[a]	=	=		=	=		=	↑		=	=	[a]	=	↑		=	=	[a]	=	=	
Pituitary	=	↓		=	↓		=	=	[a]	=	=	[a]	=	↓		=	=	[a]	=	=		=	=	
Cerebellum	=	=	[a]	=	=	[a]	=	=	[a]	=	=	[a]	=	↓		=	=	[a]	=	=	[a]	=	=	[a]
BAT	=	=	[a]	↑	=		=	=	[a]	=	=	[a]	=	↓		=	↑		=	=		=	=	
Liver	=	↓		=	=	[a]	↓	=		=	=	[a]	=	↓		=	↓		=	=	[a]	=	=	[a]
Kidney	=	↓		=	=	[a]	=	=	[a]	=	=	[a]	=	↓		=	↓		=	=	[a]	=	=	[a]
Lung	=	↓		=	↓		=	=	[a]	↓	=		=	↓		=	↓		=	=	[a]	=	=	[a]
Heart	=	↓		=	↓		=	=	[a]	↓	=		=	↓		=	↓		=	=	[a]	=	=	[a]
Spleen	=	↓		=	=	[a]	=	↓		=	=	[a]	=	↓		=	=	[a]	=	=		=	=	[a]
Muscle	=	↓		=	=	[a]	=	=	[a]	=	↑		=	↓		=	=	[a]	=	=	[a]	=	=	[a]
Adrenal	↑	↓		↓	=		↓	=		↓	=		=	=	[a]	↑	=		=	=	[a]	=	↑	
Ovary	=	↓		=	=	[a]	=	=	[a]	=	=	[a]	=	↓		=	=	[a]	=	=		↓	=	

T_4 and T_3 doses were administered as micrograms per 100 g per day. The symbols represent the comparison of the mean values of the thyroidectomized rats infused with different doses of levothyroxine, alone or in combination with different doses of liothyronine, 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.*: *Endocrinology* 137:2490, 1996 (11).© The Endocrine Society.]

[a] In addition to normal T_4 and T_3 concentrations, the molar T_3:T_4 ratio was not different from that in the control group.

a fixed amount of the daily levothyroxine dose, irrespective of total levothyroxine dose received by the patient. For 5-wk periods, patients received their usual levothyroxine dose, or a combination in which 50 μg levothyroxine was withdrawn and 12.5 μg liothyronine added. Although the order of treatments was randomized, the groups starting on the combination had normal mean TSH values, whereas those starting on levothyroxine alone had mean TSH values below the normal range. The levothyroxine doses ranged from 100–300 μg/d, with a mean ± SD of 175 ± 53 μg/d. Therefore, T_3 was not in an enteric sustained-release form, and the molar T_4:T_3 ratios of the combinations received by the patients were quite variable, ranging from 3.4:1 (4:1 by wt) to 17:1 (20:1 by wt).

Despite the marked variability in prestudy levothyroxine doses and serum TSH levels and in the T_4:T_3 ratios of the combinations actually administered, Bunevicius *et al.* (30) found that the combinations of levothyroxine plus liothyronine improved several indexes of quality of life (QoL), mood, and psychometric performance (30). Patients preferred levothyroxine plus liothyronine combinations compared with replacement with levothyroxine alone (30). However, it should be noted that the statistical analysis applied in this study did not facilitate any information about possible period and sequence effects.

A subsequent reanalysis of the data, removing from the initial study the data from the two men, from four depressed women, and from a woman who presented with increased serum TSH levels at baseline, revealed that the findings originally reported were maintained only in the subset of athyreotic patients and not in women with autoimmune thyroiditis (32). This was unexpected, because the presumed benefits of T_3 substitution were restricted to athyreotic thyroid cancer patients, who had received proportionally less liothyronine than patients with autoimmune thyroiditis. In the subset of thyroid cancer patients, however, T_3 substitution actually decreased the overall thyroid hormone dose, and the recovery from an iatrogenic thyrotoxic state might account for the improvement in QoL, similar to that occurring soon after levothyroxine withdrawal in thyroid cancer patients (33).

In a later study, Bunevicius *et al.* (34) tried to reproduce their initial results in a sample of 10 patients thyroidectomized for Graves' disease, but no improvements were found with T_3 substitution. However, the very small sample size in this study precludes a definite conclusion.

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 T_3 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 T_3 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 T_3 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 4. Summary of studies evaluating levothyroxine plus liothyronine combinations for the treatment of hypothyroidism

	Smith *et al.* (29)	Bunevicius *et al.* (30, 32)[a]	Walsh *et al.* (36)	Sawka *et al.* (37)	Clyde *et al.* (38)	Siegmund *et al.* (43)	Saravanan *et al.* (39)	Escobar-Morreale *et al.* (44)	Appelhof *et al.* (45)
Treatment approach	$T_{4\ 80\ \mu g}+T_{3\ 20\ \mu g}$ *vs.* $T_{4\ 100\ \mu g}$ tablets[b]	T_3 substitution	T_3 substitution	T_3 substitution	T_3 substitution	Physiological T_4/T_3 proportion	T_3 substitution	Physiological T_4/T_3 proportion	Supraphysiological T_4/T_3 proportions
T_4/T_3 doses	Variable	Variable	Variable	Variable	Variable	Variable	Variable	Fixed	Variable
Design	Crossover	Crossover	Crossover	Parallel	Parallel	Crossover	Parallel	Crossover	Parallel
Degree of hypothyroidism	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Overt hypothyroidism	Not specified
Prestudy period with stable T_4 dose	>6 months	>3 months	>2 months	>6 months	>3 months	Not specified	>3 months	>12 months	>6 months
Treatment periods	8 wk	5 wk	10 wk	12–15 wk	16 wk	12 wk	12 months	8 wk	15 wk
Patients analyzed	87	33/26	101	39	44	23	573	26	130
Sample size analysis	No	No	Yes	No	Yes	Yes[c]	Yes	Yes	No
Outcomes[d]	Thyroid function Preference	Thyroid function QoL Mood Psycho Preference Few biological end-points	Thyroid function QoL Mood Psycho Preference Few biological end-points	Thyroid function QoL Mood Psycho	Thyroid function QoL Mood Psycho Few biological end-points	Thyroid function QoL Mood Psycho Pharmacokinetics	Thyroid function QoL Mood Psycho Several biological end-points	Thyroid function QoL Mood Psycho Preference Multiple biological end-points	Thyroid function QoL Mood Psycho Few biological end-points
External euthyroid control group	No	No	No	No	No	No	No	Yes	No
Benefits of T_4 + T_3	No	Yes	No	No	No	No	No	No	No
Undesirable effects of T_4 + T_3	Yes (Hyperthyroid symptoms)	No	Not reported	Not reported	Not reported	Yes (serum TSH suppression and atrial arrythmia)	No	Yes (serum TSH suppression and increased urinary bone remodeling markers)	Yes (serum TSH suppression and increased serum bone remodeling markers)
Patients' preference	T_4	T_4 + T_3	T_4 = T_4 + T_3	Not assessed	Not assessed	Not assessed	Not assessed	T_4 + T_3	T_4 + T_3

Psycho, Test of psychometric performance. [Modified with permission from H. F. Escobar-Morreale *et al.*: *Ann Intern Med* 142:412, 2005 (44).© American College of Physicians.]

[a] 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.

[b] Patients received the prestudy number of tablets (two or three) throughout the study.

[c] *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.

[d] Thyroid function tests: serum thyroid hormone levels, except in Ref. 29 in which serum PBI and T_3-resin uptake were measured.

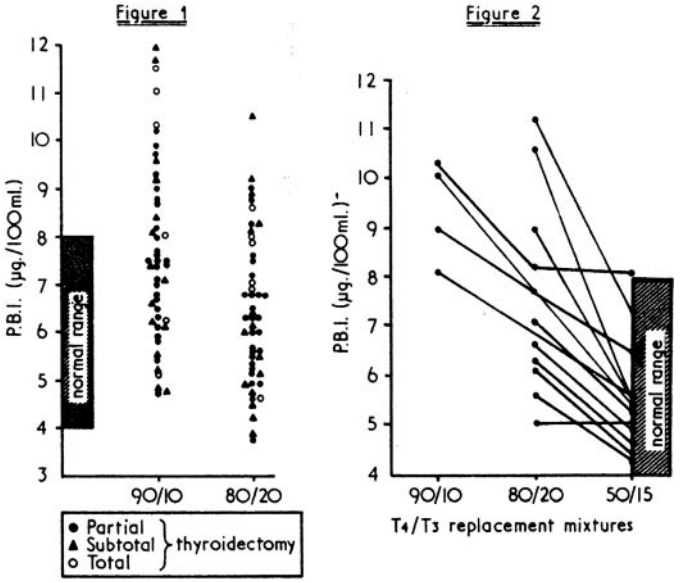

FIG. 2. Plasma PBI values in hypothyroid patients on different combinations of levothyroxine plus liothyronine. [Reproduced with permission from S. Taylor *et al.*: *Br Med J* 1:270, 1970 (28). © BMJ Publishing Group.]

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 T_3 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 T_3 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 T_3 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 persisting 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 T_3 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 T_3 substitution approach: 1) considering that the prestudy levothyroxine requirements were quite variable in the patients recruited for these studies, this design resulted in a large variation in the T_4:T_3 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 T_4 and T_3. Therefore, the lack of beneficial effects of T_3 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 T_4:T_3 ratio of 17:1. The levothyroxine dose was reduced by 20% in the following combination: every 25 μg 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 T_4 and free T_3, 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 T_4:T_3 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 T_4:T_3 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 end-points 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 T_4 levels decreased as compared with levothyroxine alone, whereas TSH increased slightly and free T_3 remained unchanged (Fig. 3). On the contrary, the 87.5 μg levothyroxine plus 7.5 μg liothyronine combination resulted in over-replacement, given that

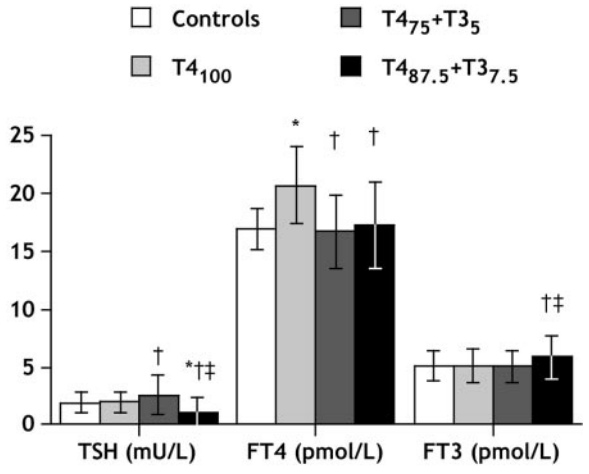

FIG. 3. Serum TSH, free T_4 (FT4), and free T_3 (FT3) concentrations in patients treated with 100 μg/d levothyroxine alone ($T4_{100}$), 75 μg of levothyroxine plus 5 μg of liothyronine per day ($T4_{75}$+$T3_5$), or 87.5 μg levothyroxine plus 7.5 μg liothyronine per day ($T4_{87.5}$+$T3_{7.5}$), compared with euthyroid controls. Data are means ± SD. *, $P < 0.05$ compared with euthyroid controls; †, $P < 0.05$ compared with $T4_{100}$; ‡, $P < 0.05$ compared with $T4_{75}$+$T3_5$. [Redrawn with permission from H. F. Escobar-Morreale *et al.*: *Ann Intern Med* 142:412, 2005 (44). © American College of Physicians.]

TSH levels decreased and free T_3 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 Appelhof *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 T_4:T_3 ratio of 4.2:1 (5:1 by wt), or on combination in a molar T_4:T_3 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 T_4:T_3 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 T_3 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 T_4:T_3 ratio of 17:1) containing an in-house slow-release T_3 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 T_3 was standard liothyronine, the combination with the slow-release preparation decreased slightly the maximal serum T_3 concentration attained and increased slightly the timing of maximal concentrations of serum T_3 after ingestion, whereas the area under the curve of serum T_3 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 T_4, T_3, and TSH concentrations of the patients attained after the standard and after the slow-release T_3 preparations were unchanged and that with the actual doses of levothyroxine plus liothyronine that were used, serum T_4 concentration remained increased and the serum T_3 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 T_3 substitution on mood, QoL, and psychometric functionality has not been confirmed by later studies, using both T_3 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.

Acknowledgments

Received January 27, 2005. Accepted May 20, 2005.

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This work was supported by Grant 01/0430/01 from the Consejería de Educación, Comunidad de Madrid (to J.I.B.-C.) and by grants from the Fondo de Investigación Sanitaria, Instituto de Salud Carlos III (01/F072 to J.I.B.-C.; and RCMN 03/08 and PI 03/1417 to G.M.d.E.).

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