Paradigm shifts in thyroid hormone replacement therapies for hypothyroidism

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Abstract | Impaired psychological well-being, depression or anxiety are observed in 5–10% of hypothyroid patients receiving levothyroxine, despite normal TSH levels. Such complaints might hypothetically be related to increased free T_4 and decreased free T_3 serum concentrations, which result in the abnormally low free T_4:free T_3 ratios observed in 30% of patients on levothyroxine. Evidence is mounting that levothyroxine monotherapy cannot assure a euthyroid state in all tissues simultaneously, and that normal serum TSH levels in patients receiving levothyroxine reflect pituitary euthyroidism alone. Levothyroxine plus liothyronine combination therapy is gaining in popularity; although the evidence suggests it is generally not superior to levothyroxine monotherapy, in some of the 14 published trials this combination was definitely preferred by patients and associated with improved metabolic profiles. Disappointing results with combination therapy could be related to use of inappropriate levothyroxine and liothyronine doses, resulting in abnormal serum free T_4:free T_3 ratios. Alternatively, its potential benefit might be confined to patients with specific genetic polymorphisms in thyroid hormone transporters and deiodinases that affect the intracellular levels of T_3 available for binding to T_3 receptors. Levothyroxine monotherapy remains the standard treatment for hypothyroidism. However, in selected patients, new guidelines suggest that experimental combination therapy might be considered.

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Introduction

In the 1970s, synthetic levothyroxine gradually replaced desiccated thyroid derived from animal thyroid glands in the treatment of patients with hypothyroidism.[1] Guidelines serve to facilitate decision-making in daily clinical practice and reflect the state of the art in a particular field at that time. Thus, guidelines published in the 1980s and 1990s unequivocally recommend levothyroxine and hardly mention other treatment modalities for these patients.[2–4] By contrast, all guidelines published in the 2000s, although still endorsing levothyroxine as the standard treatment, contain sections describing why combination therapy consisting of levothyroxine and liothyronine should not be used.[5–7] Only the European Thyroid Association guidelines of 2012 have offered specific guidance for the use of levothyroxine and liothyronine combination therapy, but still consider it experimental.[8]

This Review discusses paradigm shifts in the treatment of hypothyroidism and how they affect clinical practice. This issue is not a trivial one, in view of the vast number of patients treated with these thyroid hormones. In England, prescriptions of thyroid hormones more than doubled between 1998 and 2007.[9] In the Netherlands, the number of people using any thyroid hormone preparation increased by 53% in 2005–2011, which is not explainable by the 2.1% increase in the Dutch population during this period. Interestingly, the proportion of patients receiving levothyroxine monotherapy gradually decreased from 99.05% in 2005 to 98.98% in 2011, whereas the opposite trend was observed in patients taking levothyroxine and liothyronine combination therapy: an increase from 0.82% ($n = 2,499$) in 2005 to 0.90% ($n = 4,179$) in 2011.[10]

Paradigm shifts

The famous 1888 report of the Clinical Society of London established unequivocally that loss of function of the thyroid gland results in what we now call hypothyroidism, but did not offer any therapeutic recommendations.[11] The situation changed when George Murray described the cure of a patient with myxoedema by subcutaneous injection of sheep thyroid extract in 1891,[12] which was soon followed by reports that ground or fried sheep thyroid or tablets of dried thyroid tissue were also effective.[13] This transition from no therapy to an available effective therapy might be viewed as the first paradigm shift in the treatment of hypothyroidism.

The active principle in thyroid extract was isolated in 1914,[14] and in 1926 Harrington elucidated the structure of this molecule, synthesized it, and called it thyroxine.[15] Thyroxine initially seemed to be less therapeutically effective than desiccated thyroid, because thyroxine given as the free acid is poorly absorbed from the gut.[16] Consequently, desiccated thyroid remained the mainstay of treatment for hypothyroidism. The synthesis of large quantities of sodium L-thyroxine (levothyroxine, which in contrast to thyroxine is well absorbed from the gut)

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Key points

- Impaired psychological well-being and depression or anxiety affect about 5–10% of hypothyroid patients on levothyroxine, despite normal TSH levels
- Persistent symptoms might be explained by factors unrelated to thyroid disease, unrecognized autoimmune disease, or inability of levothyroxine to restore T_3 levels in serum and all target tissues
- Randomized clinical trials have in general not shown superiority of levothyroxine plus liothyronine combination therapy over levothyroxine monotherapy
- Some reports suggest a preference of patients for levothyroxine plus liothyronine combination therapy over levothyroxine monotherapy, which might be associated with weight loss
- Levothyroxine remains the standard treatment modality for hypothyroidism, but levothyroxine plus liothyronine combination treatment might be offered to selected patients as an experimental modality, according to guidelines published in 2012

became possible in 1949.[16] In 1952, T_3 was identified as a second thyroid hormone.[17,18] In 1961, MacGregor argued in favour of using levothyroxine for replacement therapy, because desiccated thyroid preparations varied in therapeutic potency.[19]

The advent of radioimmunoassays for TSH, T_4 and T_3 in the late 1960s and early 1970s enabled detailed studies of the various treatment modalities to be conducted. Researchers observed that normal plasma T_3 concentrations could be reached in athyreotic patients whose only source of thyroid hormones was exogenous levothyroxine, owing to extensive extrathyroidal deiodination of T_4 into T_3.[20] By contrast, plasma T_3 levels were elevated in the majority of patients treated with desiccated thyroid, and this finding was sometimes associated with thyrotoxic symptoms; after changing to levothyroxine, plasma T_3 levels in these patients decreased to within the normal range and their thyrotoxic symptoms diminished or disappeared.[1] During 1960–1988 the use of desiccated thyroid gradually declined in the USA, alongside a simultaneous increase in the use of levothyroxine. After 1978, the number of levothyroxine prescriptions dispensed by pharmacies surpassed that of desiccated thyroid and, by 1988, 84% of patients receiving thyroid hormones were using levothyroxine.[21] The establishment of this preference for synthetic levothyroxine over desiccated thyroid, which was subsequently endorsed by all guidelines, can be called the second paradigm shift in the treatment of hypothyroidism, and occurred about 50 years after thyroxine was synthesized for the first time.

In the 1970s and thereafter, extrathyroidal thyroid hormone metabolism was further elucidated. These investigations revealed that, in healthy individuals, 20% of daily T_3 production is secreted by the thyroid gland, whereas 80% is generated extrathyroidally by iodothyronine deiodinases. Extrathyroidal tissues seemed to be capable of modulating the amount of T_3 locally available for binding to its nuclear receptors via upregulation or downregulation of the tissue iodothyronine deiodinases. Type I and type II iodothyronine deiodinase both produce T_3 from T_4, and type III iodothyronine deiodinase degrades T_3 into the inactive compounds T_2 (3,3'-diiodothyronine) and reverse T_3 (rT_3, or 3,3',5'-triiodothyronine), with wide variation in enzyme levels and activities between tissues.[22]

Physicians came to realize that plasma hormone concentrations do not always accurately reflect hormone action at the tissue level.[23]

Animal experiments in the mid-1990s demonstrated that euthyroidism (defined as normal T_4 and T_3 concentrations in target tissues) after thyroidectomy could not be reached simultaneously in all tissues by levothyroxine replacement, but required the combination of levothyroxine and liothyronine.[24,25] In the meantime, anecdotal reports continued to surface concerning patients who said that they felt better when taking desiccated thyroid than they did on levothyroxine. Associations of patients with hypothyroidism came into being, some of which demanded prescription of levothyroxine and liothyronine combination therapy.[26] However, the results of randomized clinical trials conducted in the 2000s to compare levothyroxine monotherapy with levothyroxine plus liothyronine did not, in general, find evidence of superiority for the combination therapy.[27] One possible explanation might well be that polymorphisms in the genes encoding particular deiodinases and thyroid hormone transporters could be responsible for persistent symptoms in a subset of hypothyroid patients receiving levothyroxine replacement therapy.

Moreover, *bona fide* case reports also suggest that at least some patients do better on levothyroxine and liothyronine combination therapy than they do on levothyroxine alone.[28] If further studies can identify this specific subgroup of hypothyroid patients, a third paradigm shift in the treatment of hypothyroidism might occur—perhaps heralding the use of personalized medicine in this setting.[29] Finally, a landmark paper in 2012 described for the first time the generation of functional thyroid tissue from embryonic stem cells.[30] We can speculate that this work could ultimately lead to a fourth paradigm shift, in which hypothyroid patients can be treated with thyroid-generating stem cells.

Levothyroxine monotherapy

Most experienced clinicians have encountered some patients who remain dissatisfied with the outcome of levothyroxine monotherapy;[31] however, only a few community-based, controlled studies have attempted to quantify the degree of patient-reported dissatisfaction (Table 1). The UK study results show an excess of psychological distress in patients receiving levothyroxine (OR 1.35, 95% CI 1.03–1.78).[32] The results of the Dutch study likewise recorded impaired well-being and decreased health-related quality of life in these patients; in addition, neurocognitive tests demonstrated impairments in cognitive psychomotor speed, attention, learning and memory.[33] The large Norwegian population-based study indicated an increased prevalence of anxiety (OR 1.39, 95% CI 1.22–1.59) and depression (OR 1.46, 95% CI 1.27–1.68) in patients taking levothyroxine.[34] Two case–control studies from the USA and Germany, albeit with much smaller sample sizes than the Norwegian trial, similarly report decrements in health status, psychological function, working memory and motor learning in levothyroxine-treated patients compared to controls.[35,36]

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Table 1 | Patient-reported outcomes in hypothyroid patients on levothyroxine

n (Patients/ controls)	Test	Outcome parameter	Results in patients versus controls*	*P* value
***UK*[32]**				
572/535	GHQ-12‡	Score≥3	32.3% versus 25.6%	0.012
583/534	TSQ‡	Score ≥3	46.8% versus 35.0%	<0.001
***Netherlands*[33]**				
140/1,778	MCT‡	Time to complete task	21.6 s versus 17.7 s	0.001
134/124	PASAT§	Total score	146 versus 171	0.001
141/492	CVLT§	Recall score‖	–1.1 versus 0.0	0.001
139/284	RIVER§	Recall score¶	42 versus 50	0.001
140/2,368	SCL-90‡	Total score	156 versus 118	0.001
140/1,068	SF-36§	Mental health score	65 versus 77	0.001
140/1,063	SF-36	Vitality score	43 versus 67	0.001
***Norway*[34]**				
1,546/18,137	HADS‡	Anxiety score ≥8	23.4% versus 18.3%	<0.001
1,546/18,137	HADS	Depression score ≥8	18.4% versus 12.7%	<0.001

*Absolute values, except where units are given. ‡Higher scores indicate worse outcomes. §Higher scores indicate better outcomes. ‖Standardized against a value of 0 in controls. ¶Standardized against a value of 50 in controls. Abbreviations: CVLT, California Verbal Learning Test; GHQ, General Health Questionnaire; HADS, Hamilton Anxiety and Depression Score; MCT, Memory Comparison Task (paper and pencil version); PASAT, Paced Auditory Serial Addition Task; RIVER, Rivermead Behavioural Memory Test Story Recall; SCL-90, Symptom Check List; SF-36, RAND-36 version of the Medical Outcome Study Short Form General Health Survey; TSQ, Thyroid Symptom Questionnaire.

Although more studies are required in this area, the available evidence supports the conclusion that patient-reported outcomes of levothyroxine replacement therapy are not always optimal. On the basis of differences in symptom frequencies between cases and controls, impaired psychological well-being and depression or anxiety related to thyroid disease might occur in about 5–10% of hypothyroid patients taking levothyroxine. Several explanations might account for the suboptimal outcomes in some levothyroxine-treated hypothyroid patients, addressed below.

Awareness of having a chronic disease

Hypothyroidism in the vast majority of patients is not transient but permanent in nature and requires lifelong medication. Awareness of being dependent on medicines for the remainder of one's life could induce feelings of 'unwellness', and such patients might be inclined to attribute nonspecific complaints to either the disease or its treatment,[8,31] although this possibility has not been investigated specifically in the setting of hypothyroidism.

Presence of other autoimmune diseases

Autoimmune thyroid disease is present in about 70% of hypothyroid individuals, and patients with autoimmune thyroid disease are at high risk of developing other autoimmune diseases.[37–39] The frequency of having an additional autoimmune disorder is 9.67% in patients with Graves disease and 14.3% in those with Hashimoto thyroiditis.[38] Rheumatoid arthritis is the most common coexisting autoimmune disease in patients with autoimmune thyroid disease, and occurs in 3.15% of patients with Graves disease and 4.24% of individuals with Hashimoto thyroiditis.[38] Almost all other autoimmune diseases (such as pernicious anaemia, systemic lupus erythematosus, Addison disease, coeliac disease, type 1 diabetes mellitus and vitiligo) occur in about 1%, but the relative risks of these conditions are still high (>10) in patients with autoimmune thyroid disease.[38] The development of these associated conditions might go unnoticed; consequently, screening for other autoimmune disorders is prudent in patients with autoimmune thyroid disease who have persistent nonspecific symptoms during levothyroxine therapy.[8]

Presence of thyroid autoimmunity

A few reports suggest the possibility that thyroid autoimmunity itself might give rise to nonspecific symptoms, independent of decreased thyroid function, but the data are conflicting. A large population study in Norway observed no relationship between levels of autoantibodies to thyroid peroxidase (TPO-Ab) and depression or anxiety, after adjustment for age, sex and TSH levels.[40] By contrast, a Dutch community-based study of perimenopausal women reported an association between TPO-Ab levels >100 kU/l and depression (OR 3.0, 95% CI 1.3–6.8). However, depression was not related to thyroid dysfunction (defined as abnormal free T_4 and/or TSH levels) in these women.[41] A Danish study also described statistically significant relationships between TPO-Ab levels and scores for depressivity and anxiety in patients with autoimmune hypothyroidism, independent of their thyroid function.[42] An Austrian study found increased rates of several chronic symptoms (fatigue, irritability and nervousness) and lower quality of life among women undergoing thyroidectomy for benign goitre who had TPO-Ab levels >121 kU/l, independent of their TSH levels.[43] However, scores on a general health questionnaire did not differ between TPO-Ab-positive and TPO-Ab-negative hypothyroid women on levothyroxine replacement in an English study.[44]

Inadequacy of levothyroxine dose

According to current guidelines, the levothyroxine replacement dose used should result in normal serum TSH levels.[6,7] However, a minority of patients prefer dosages of levothyroxine that result in low-normal or even below-normal TSH values.[45,46] A population-based study of all patients taking levothyroxine replacement therapy in Tayside, Scotland, reported suppressed TSH levels (≤0.03 mU/l) in 6.1%, low TSH levels (0.04–0.40 mU/l) in 21.1%, normal TSH levels (0.4–4.0 mU/l) in 61.7%, and high TSH levels (>4.0 mU/l) in 11.2%.[47] Compared with patients who had normal TSH levels, the patients with suppressed TSH had increased risks of cardiovascular disease, arrhythmias and fractures (adjusted HRs 1.37, 95% CI 1.17–1.60; 1.6, 95% CI 1.10–2.33; and 2.02, 95% CI 1.55–2.62, respectively). Increased risks of these adverse outcomes were also observed in patients with high TSH levels (adjusted HRs 1.95, 95% CI 1.73–2.21; 1.80, 95% CI 1.33–2.44; and 1.83 95% CI 1.41–2.37, respectively), but not in patients with low TSH levels.[47]

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These observations suggest that aiming to achieve normal TSH levels makes sense, but clearly normalization of TSH does not safeguard against persistent complaints in levothyroxine-treated patients with hypothyroidism. None of the three community-based studies that reported such persistent complaints found a relationship with serum TSH levels, even when the analysis was restricted to patients with TSH values within the reference range.[32–34] One study in patients on levothyroxine replacement showed that high free T_4 and low TSH levels were associated with improved well-being (that is, decreased scores on general health questionnaires), whereas no such association was observed with free T_3 levels; moreover, no correlation was seen between thyroid function test results and anxiety or depression.[48] This issue has been explored further in a double-blind, randomized clinical trial in 52 hypothyroid patients on levothyroxine replacement.[48] Each patient received three different levothyroxine doses, in a random order, for three consecutive periods of 8 weeks each: low dose, medium dose (25 μg more than low dose) and high dose (25 μg more than medium dose), to result in serum TSH values of 2.8 ± 0.4 mU/l, 1.1 ± 0.2 mU/l and 0.3 ± 0.1 mU/l, respectively. These small dose adjustments did not produce measurable changes in hypothyroid symptoms, well-being or quality of life. Taken together, these data do not support the suggestion that the target TSH range for patients receiving levothyroxine replacement should differ from the usual TSH reference range.

Lastly, some researchers have expressed concern that normalization of serum TSH levels by treatment with levothyroxine might not always result in appropriate normalization of serum T_3 levels.[49] This possibility has been evaluated in two studies that compared native thyroid function with postoperative thyroid function (under levothyroxine replacement) in the same individual, before and after undergoing total thyroidectomy. The findings of the first study revealed similar preoperative and postoperative values for both serum TSH (1.18 ± 0.58 versus 1.30 ± 1.89 mU/l) and T_3 (1.99 ± 0.41 versus 1.96 ± 0.43 nmol/l).[50] In the second study, postoperative serum free T_3 levels were increased in individuals with postoperative TSH levels <0.03 mU/l, unchanged in those with postoperative TSH 0.03–0.30 mU/l, and decreased in those with postoperative TSH 0.3–5.0 mU/l, suggesting that moderately TSH-suppressive doses of levothyroxine are required to achieve preoperative native serum T_3 levels.[51] However, taken together, these studies do not provide good evidence that inadequate levothyroxine doses explain persistent complaints in hypothyroid patients in whom serum TSH has been normalized.

Inadequacy of levothyroxine treatment modality

Normalization of TSH levels by levothyroxine replacement is obtained at the expense of high serum free T_4 concentrations, possibly as a compensation for the absence of thyroidal T_3 secretion.[52] A large study of 1,811 athyreotic patients who had normal TSH levels while receiving levothyroxine and 3,875 euthyroid controls provides quantitative data.[53] Free T_4 levels were higher

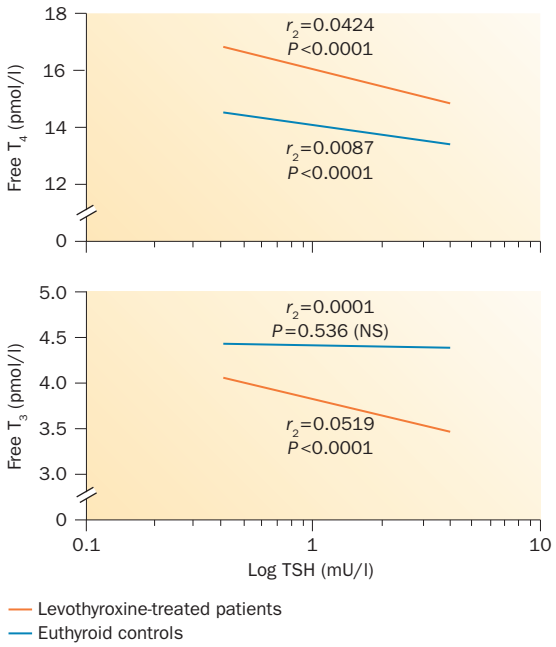

Figure 1 | Correlation between serum TSH and free thyroid hormone levels in 3,875 euthyroid controls and 1,811 athyreotic patients receiving levothyroxine monotherapy. Abbreviation: NS, not significant. © Gullo, D. *et al. PLoS ONE* **6**, e22552 (2011).[53] Published under a CC-BY licence.

and free T_3 levels were lower in athyreotic individuals than in controls, and this relationship was present for any given serum TSH level; free T_4 levels above the upper limit of normal occurred in 7.2%, free T_3 below the lower limit of normal in 15.2%, and a free T_3:free T_4 ratio below the lower limit of normal in 29.6%. The wide range of free T_3:free T_4 ratios indicates major interindividual heterogeneity in peripheral T_3 production capacity, which apparently is not always adequate to compensate for the absent thyroidal T_3 secretion.[53]

These observations raise the question of whether normal serum TSH levels are a reliable marker of euthyroidism in nonpituitary tissues during levothyroxine replacement. Low levels of serum sex-hormone-binding globulin (SHBG) in patients receiving levothyroxine who have normal TSH levels suggests the presence of tissue hypothyroidism in the liver.[54] Furthermore, regression lines for the correlation between serum TSH and free T_4 levels display a much steeper slope in levothyroxine-treated patients than in euthyroid controls, indicating that a greater change in serum free T_4 levels is required in hypothyroid patients to obtain the same effect on serum TSH as is observed in controls (Figure 1).[53] This situation might be related to differences in serum free T_3 levels: for each stratum of TSH levels, free T_3 levels are consistently lower in levothyroxine-treated patients than in euthyroid controls.[53] The regression line of the correlation between serum TSH and free T_3 levels is also steep in levothyroxine-treated patients, but is flat in euthyroid controls. The pituitary response to changes in serum free T_4 and T_3 in levothyroxine-treated patients is, therefore, different from that in euthyroid individuals

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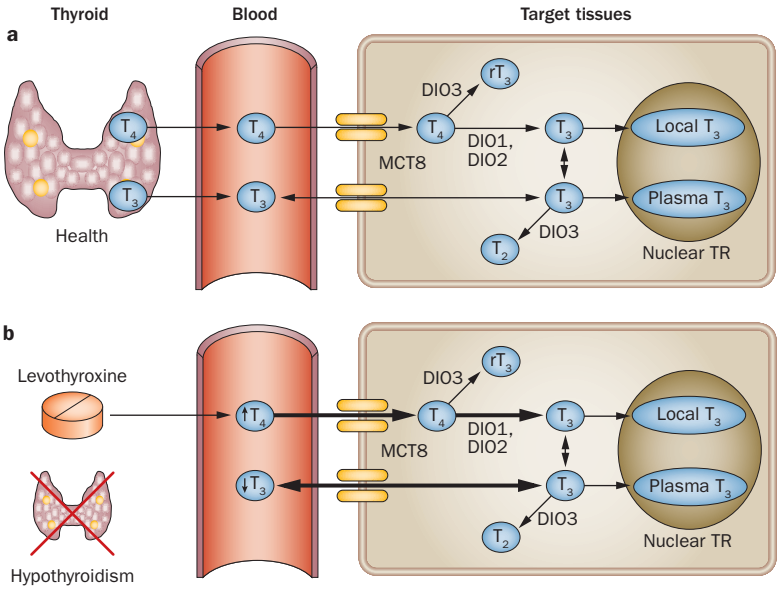

Figure 2 | Thyroid hormone production and metabolism. **a** | In healthy individuals, 100% of T_4 production is thyroidal; by contrast, only 20% of T_3 production is thyroidal, with the remaining 80% derived from extrathyroidal conversion of T_4 into T_3, mediated by DIO1 and DIO2. The amount of intracellular T_3 available for binding to nuclear TRs is further modulated by thyroid hormone transporters (such as MCT8) in the plasma membrane, and DIO3-mediated conversion of T_3 into inactive T_2. Wide variation exists between target tissues in the expression and activity of thyroid hormone transporters and deiodinases, and in the relative contributions of locally generated and plasma-derived T_3 to receptor-bound T_3. **b** | In hypothyroid patients on levothyroxine replacement therapy, increased extrathyroidal T_3 production compensates for the lack of thyroidal T_3 secretion. However, serum free T_4 levels above the upper limit of normal and serum free T_3 levels below the lower limit of normal are observed in 7% and 15% of levothyroxine-treated patients, respectively, indicating limited peripheral T_3 production capacity. Nonphysiological changes in nuclear T_3 receptor occupancy in target tissues might also be aggravated by polymorphisms in thyroid hormone transporters and deiodinases. Abbreviations: DIO, iodothyronine deiodinase; TR, thyroid hormone receptor.

(Figure 1).[53–55] In untreated patients, total deiodinase activity is positively correlated with serum TSH levels, but the correlation is lost under increasing levothyroxine doses.[55] The disjoint between free T_4–TSH feedback and T_3 production in levothyroxine-treated patients implies that although levothyroxine replacement therapy results in compensatory adaptations, it does not completely restore previous euthyroid physiology.[55] Normal TSH levels consequently do not guarantee euthyroidism in all tissues that are targets of thyroid hormone.

Extrathyroidal tissues vary in their regulation of intracellular T_3 (namely, that available for binding to nuclear T_3 receptors), which is derived from plasma T_3 and/or local production of T_3 from T_4 catalysed by type II iodothyronine deiodinase. Thyroid hormone uptake can also be modulated by thyroid hormone transporters, and intracellular T_4 and T_3 can be degraded by type III iodothyronine deiodinase into the inactive compounds rT_3 and T_2, respectively.[22,56] In the brain, for example, 80% of intracellular T_3 is locally generated from T_4 via type II iodothyronine deiodinase; this enzyme is downregulated by high T_4 levels and upregulated by low T_4 levels.[57] The results of animal experiments, in which euthyroidism could not be obtained in all tissues of thyroidectomized rats by administration of levothyroxine alone, but only by the combination of 0.90 μg levothyroxine and 0.15 μg liothyronine (that is, a molar ratio of 5:1, which is similar to the molar ratio of T_4 to T_3 secreted by the thyroid in rats), also supports this line of reasoning.[24,25] In these studies, the addition of small doses of T_3 decreased the amount of levothyroxine needed to normalize T_3 levels in most tissues by about 50% compared to levothyroxine monotherapy.[24,25] Thus, levothyroxine monotherapy might not be the optimal replacement modality for patients with hypothyroidism (Figure 2).

Levothyroxine plus liothyronine

The above studies provided a clear biological rationale for exploring the merits of levothyroxine plus liothyronine combination therapy. In 2006, a meta-analysis of 11 randomized clinical trials was published.[27] The included studies were performed between 1999 and 2005 in 1,216 hypothyroid patients on levothyroxine replacement, and compared levothyroxine monotherapy with levothyroxine plus liothyronine combination therapy.[58–68] No difference was found between the two regimens with regard to bodily pain, depression, anxiety, fatigue, quality of life, body weight, serum lipids or adverse events.[27] Another meta-analysis published in 2009 reached similar conclusions.[69] Although the rate of adverse events was no higher during combination therapy, which is reassuring, these results cannot exclude the possibility that long-term treatment with levothyroxine and liothyronine is associated with cardiac arrhythmias and bone loss. The verdict is clear: levothyroxine monotherapy should remain the treatment of choice for hypothyroid patients, as stated in all current guidelines.

A further three randomized clinical trials have since been published.[70–73] A double-blind crossover study from Denmark found that levothyroxine plus liothyronine combination therapy was superior to levothyroxine monotherapy in terms of quality-of-life and depression scores, whereas final serum TSH levels were similar in both groups (0.76 mU/l versus 0.99 mU/l).[70] In the subgroup of patients who underwent testing of peripheral tissue functions, compared to those receiving levothyroxine alone, patients in the combination therapy arm had higher serum SHBG, higher pro-collagen-1 N-terminal peptide and similar N-terminal pro-brain natriuretic peptide levels (representing hepatocyte, osteoblast and cardiomyocyte thyroid hormone activity, respectively).[71] In a Russian trial, serum cholesterol levels were lower, osteocalcin levels were higher and deoxypyridinoline:creatinine ratios were higher at the end of levothyroxine plus liothyronine combination therapy than after levothyroxine alone, although thyroid symptom scores and serum TSH levels (1.9 mU/l versus 2.4 mU/l) did not differ significantly between the two groups.[72] However, in this study, randomization was done before initiating treatment for hypothyroidism. By contrast, in all other published randomized controlled trials, randomization was done after TSH levels had been normalized with levothyroxine monotherapy. The third randomized controlled trial had a double-blind, crossover design, and was unusual

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Table 2 | Serum free T4:free T3 ratios in treated hypothyroid patients

Study	Baseline	Levothyroxine monotherapy	Levothyroxine plus liothyronine
Saravanan *et al.*[59]	5.5	5.5	3.9
Walsh *et al.*[61]	4.5	4.2	3.3
Sawka *et al.*[63]	3.9	4.0	2.2
Escobar-Morreale *et al.*[66]	4.1	4.1	3.4
Siegmund *et al.*[67]	4.3	4.6	4.0
Mean free T4:free T3 ratio	4.3	4.5	3.4

All values in pmol/l. Measurements taken at baseline and after randomization to levothyroxine monotherapy or levothyroxine plus liothyronine combination therapy. Permission obtained from Karger © Wiersinga, W. M. *et al. Eur. Thyroid J.* **1**, 55–71 (2012).[8]

because it compared desiccated thyroid extract (Armour® Thyroid, Forest Laboratories, Inc., New York, NY, USA, in which each grain of 65 mg contains 38 μg T_4 and 9 μg T_3) with levothyroxine monotherapy;[73] the source of T_3 in all other randomized controlled trials was synthetic liothyronine. No differences were found between the two regimens in patients' general health and thyroid symptom questionnaire responses, depression scores and neurocognitive functioning. TSH levels were slightly higher during desiccated thyroid therapy than during levothyroxine treatment (1.67 ± 0.77 and 1.30 ± 0.63 mU/l respectively, $P = 0.003$). However, desiccated thyroid was preferred by 48.6% of the patients (18.6% preferred levothyroxine, and the remainder did not express a preference) and was associated with modest weight loss.[73]

Incorporation of data from the 165 patients enrolled in these three randomized controlled trials is unlikely to change the outcome of the previous meta-analyses, which challenges our basic assumptions regarding the potential benefit of levothyroxine plus liothyronine combination therapy over levothyroxine alone. The strengths and weaknesses of the various randomized controlled trials have, therefore, been scrutinized in several papers,[8,29,74,75] which provide some interesting avenues to explain their mostly negative results.

Marked heterogeneity

Each of the trials can be criticized and none is perfect, but the design of studies in this field is notoriously difficult, specifically with regard to selecting doses of levothyroxine and liothyronine and the dose ratio of these agents, and whether or not dose adjustments should be made during treatment in order to maintain normal TSH levels. The 14 randomized controlled trials differ markedly in sample size (>100 in only three trials), in the method of recruiting participants (and thereby in susceptibility to selection bias), in the cause of hypothyroidism (which is relevant because outcomes might differ between patients with Hashimoto thyroiditis and thyroid cancer), and in study design (crossover in eight and parallel-group in six trials). However, subset analyses indicated that these differences between trials generally could not explain the negative results. For example, carryover effects were not observed in any of the crossover studies that specifically tested for its presence,[61,65,66,70] and similar effects on outcome parameters were reported in both parallel-group and crossover studies.[27]

Marked differences in doses and goals used

In all but one trial, which involved previously untreated individuals,[72] the patients randomly assigned to levothyroxine monotherapy continued their usual levothyroxine dose. For those assigned to combination therapy, part of the levothyroxine dose was then replaced by liothyronine. This alteration was done in nine trials by replacing a fixed amount of levothyroxine (50.0 μg) by a fixed amount of liothyronine (10.0, 12.5, 15.0 or 20.0 μg), resulting in wide variation in levothyroxine:liothyronine dose ratios both within and between these trials. In another four studies, part of the levothyroxine dose was replaced by a variable liothyronine dose, resulting in the same levothyroxine:liothyronine dose ratio being used for all participants in each trial, although there were still between-trial differences in dose ratio. The levothyroxine:liothyronine dose ratios used in these trials ranged from 20:1 to 4:1, and this wide variation also constitutes a potential bias. Most ratios used were quite different from the T_4:T_3 secretion ratio of the human thyroid gland, which is close to 16:1 by weight.[76] However, the outcome of combination therapy was not better than that of levothyroxine monotherapy in four trials that applied levothyroxine:liothyronine dose ratios of 19:1, 15:1 or 10:1.[58,60,66,67]

Serum free T_4:free T_3 concentration ratios, which are about 3.1–3.3 in healthy individuals, could also be relevant.[53,74] As expected, this ratio is increased during levothyroxine replacement, and ranged from 2.2 to 4.0 during levothyroxine plus liothyronine therapy in the five trials where this parameter was measured (Table 2). Nevertheless, even for the studies in which combination therapy resulted in serum free T_4:free T_3 ratios of 3.3 and 3.4 (close to control values), levothyroxine plus liothyronine was not superior to levothyroxine monotherapy.[61,66]

Primary outcomes linked to thyroid function

Assessments of primary outcomes related to thyroid function (such as quality of life, symptoms, mood and cognitive function) varied slightly between the 14 trials, but overall similar methods have been applied. Combination therapy resulted in better outcomes than monotherapy in four randomized controlled trials, despite the lack of differences in final TSH levels between the groups.[64,68,70] Mean TSH levels at the end of intervention were not suppressed in all but one trial, in which levothyroxine plus liothyronine treatment (with a dose ratio of 5:1) resulted in TSH levels of 0.07 mU/l.[60]

Secondary outcomes linked to thyroid function

Patients' preferences for a specific treatment (either combination therapy or monotherapy) were evaluated in seven studies (Table 3). Preference for levothyroxine monotherapy was about 25%; however, as the applied levothyroxine dose in the monotherapy arm was the same as that used before randomization, this finding indicates a substantial Hawthorne effect—namely, that

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Table 3 | Preference of hypothyroid patients for different types of therapy

Study	*n* (Patients)	Preference for levothyroxine monotherapy	No preference	Preference for levothyroxine plus liothyronine	*P* value
Crossover studies					
Walsh *et al.*[61]	100	46	18	36	0.320
Bunevicius *et al.*[64]	33	2	11	20	0.001
Escobar-Morreale *et al.*[66]	26	2	6	18*	0.015
Bunevicius *et al.*[68]	10	2	2	6	—
Nygaard *et al.*[70]	59	9	21	29	0.002
Hoang *et al.*[73]	70	13	23	34	0.002
Total (crossover studies)	298	74 (25%)	81 (27%)	143 (48%)	—
Parallel-group studies					
Appelhof *et al.*[60]	140	14/48 (29%)	NA	43/92 (47%)	0.024

All trials were double-blind randomized, controlled trials. *Including six patients who went on to receive their preferred therapy for a further 8 weeks, during a nonrandomized extension. Abbreviation: NA, not applicable. Permission obtained from Karger © Wiersinga, W. M. *et al. Eur. Thyroid J.* **1**, 55–71 (2012).[8]

patients feel better just because they are participating in a trial. A remarkably high proportion of patients (on average 48% across the six crossover trials) preferred the combination therapy, and this preference was associated with improvements in primary outcomes in three of these studies.[64,68,70] Differences in final serum TSH levels could not explain this patient preference, with one exception (the trial that applied a levothyroxine:liothyronine dose ratio of 5:1, which caused suppression of TSH).[60] In this trial, observed changes in body weight were +0.1 kg in patients receiving levothyroxine monotherapy, −0.5 kg in those receiving levothyroxine:liothyronine 10:1, and −1.7 kg in those receiving levothyroxine:liothyronine 5:1 ($P = 0.01$ for trend).

Weight loss resulting from overtreatment could potentially explain those patients' preference for combination therapy.[60] However, this explanation cannot account for the findings of two other randomized controlled trials: despite similar (nonsuppressed) TSH values in both groups, body weight changed by +0.2 kg in the levothyroxine monotherapy group and by −1.5 kg in the levothyroxine plus liothyronine combination therapy group in one study,[70] whereas in the other study the weight loss during combination therapy exceeded that during monotherapy by 1.3 kg.[73] Although the determinants of patients' preferences for thyroid hormone replacement therapy remain unknown, we can speculate that higher serum T_3 levels could be relevant. Higher serum T_3 levels might be a surrogate marker of higher brain T_3 content, associated with improvement in T_3-dependent functions of the central nervous system, including regulation of body weight.

Genetic polymorphisms

Polymorphisms that affect thyroid hormone pathways might modulate the effects of thyroid hormones in target tissues.[77] The single nucleotide polymorphism (SNP) resulting in the amino-acid change Asp727Glu in the TSH receptor (frequency 7.2%) has a modest positive effect on fatigue in some hypothyroid patients on levothyroxine.[78] Variants in the *PDE8B* gene (which encodes high-affinity cAMP-specific and IBMX-insensitive 3',5'-cyclic phosphodiesterase 8B) are associated with serum levels of TSH (+0.20 SD per allele) and free T_4 (−0.07 SD per allele), but the association is lost in patients on thyroid hormone replacement therapy.[79–82] Polymorphisms in *DIO1* (the gene encoding type I iodothyronine deiodinase) are associated with serum levels of free T_4 but not TSH levels.[81–85] The C allele of SNP rs2235544 in *DIO1* is associated with increased activity of type I iodothyronine deiodinase, and thereby with increased serum free T_3 levels, decreased levels of free T_4 and rT_3, and with decreased free T_4:free T_3 ratios. The effects of this polymorphism are also noted in hypothyroid patients taking levothyroxine (free T_4:free T_3 ratios are 5.79, 5.44 and 5.22 in patients with AA, AC and CC genotypes, respectively; $P = 0.001$ for trend).[84] However, SNPs in *DIO1* are not related to psychological well-being or response to levothyroxine plus liothyronine combination therapy.[86] Polymorphisms in *DIO2* and *DIO3* are not associated with serum levels of TSH or thyroid hormones.[81,82,84] Early reports that SNPs in *DIO2* were related to serum free T_4 and rT_3 levels, and that patients bearing such SNPs required increased levothyroxine doses to obtain normal TSH levels, could not be replicated.[87–89] However, SNPs in type II iodothyronine deiodinase might affect T_3 levels in the brain by catalysing local conversion of T_4 into T_3.[90] A common variation in *DIO2* (rs225014, which is present in 16% of individuals) is associated with decreased psychological well-being in patients receiving levothyroxine and an improved response to levothyroxine plus liothyronine combination therapy;[86] the absence of such an association in another similar study is probably due to its much smaller sample size.[91] Finally, SNPs in the brain-specific thyroid hormone transporter gene, *SLCO1C1* (also known as *OATP1C1*) in levothyroxine-treated patients are associated with fatigue and depression, but not with neurocognitive test results or a preference for combination therapy.[92]

These findings raise questions as to whether still more trials on levothyroxine plus liothyronine therapy would be useful to perform. I think they would, as do other experts, for a number of reasons.[8,29,75,90,93] First, most published randomized controlled trials failed to achieve free T_4, free T_3 and free T_4:free T_3 ratios similar to those of euthyroid controls in patients treated for hypothyroidism, owing to the use of nonphysiological levothyroxine:liothyronine dose ratios. Second, the factors that influence patients' preferences for combination therapy remain poorly understood. Third, genetic polymorphisms in thyroid hormone transporters and deiodinases might affect tissue responses to thyroid

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Box 1 | ETA recommendations for use of combination thyroid hormone therapy

Selection of patients

Indications: compliant levothyroxine-treated hypothyroid patients with persistent symptoms despite normal TSH values, provided:

- Psychological support has been offered regarding acceptance of the chronic nature of the disease
- Associated autoimmune diseases have been ruled out
- Informed consent has been obtained about the experimental nature of combination treatment

Contraindications: pregnancy, cardiac arrhythmias

Dose and administration

- The levothyroxine:liothyronine dose ratio should be between 13:1 and 20:1 by weight
- Thus, the daily levothyroxine dose that normalizes TSH levels (x) can be used to calculate the required liothyronine dose (y): $y=x/20$
- The corresponding levothyroxine dose (z) is calculated as $z=x-3y$
- Levothyroxine is administered once daily, whereas liothyronine is preferably administered twice daily, with the largest dose before sleeping
- Avoid using current commercially available combination tablets

Monitoring

- Aim at normalization of TSH, free T_4, and free T_3 levels, as well as free T_4:free T_3 ratio
- If dose adjustments are necessary, change one component at a time (preferably the liothyronine dose)
- Discontinue combination therapy if no improvement after 3 months
- Monitor cardiovascular and bone health

Abbreviation: ETA, European Thyroid Association. Information in this Box was summarized from the 2012 ETA guidelines.[8]

hormones, which could become clinically manifest when thyroidal T_3 secretion is lacking.

Liothyronine monotherapy

Long-term treatment of hypothyroid patients with liothyronine monotherapy is not practiced in view of the short half-life of T_3 (which necessitates >1 daily dose) and its rather low therapeutic index. In a double-blind, crossover trial, 14 hypothyroid patients receiving levothyroxine after thyroidectomy were randomly assigned to either levothyroxine or liothyronine monotherapy, with the aim of maintaining TSH values of 0.5–1.5 mU/l for at least 30 days.[94–96] To reach this target, the average required daily doses were 115 ± 38.5 μg for levothyroxine and 40 ± 11.3 μg for liothyronine. Pharmacodynamic equivalence of levothyroxine and liothyronine therapy is, therefore, achieved at a dose ratio of approximately 3:1, in agreement with previous estimates.[76] Morning serum T_3 levels were 1.43 nmol/l and 2.65 nmol/l in the levothyroxine and liothyronine groups, respectively. No differences were observed between the groups in cardiovascular function, insulin sensitivity, quality of life scores or adverse events, but liothyronine treatment was associated with weight loss of 1.2 kg (versus weight gain of 0.9 kg in patients receiving levothyroxine), decreased serum total and LDL cholesterol levels, and increased serum SHBG levels. Total calorie intake, macronutrient preference and degree of hunger were not different. TSH values at baseline and after stimulation by TSH-releasing hormone did not differ between the groups, indicating that the favourable metabolic changes associated with liothyronine treatment are secondary to peripheral effects, and that normal pituitary levels of TSH do not necessarily equate to euthyroidism in all target tissues.[96]

Conclusions

Advancements in basic and clinical science have already led to several paradigm shifts in the treatment of hypothyroid patients over the past 100 years. However, levothyroxine plus liothyronine combination therapy has not been proven to be superior to levothyroxine monotherapy, nor does combination therapy relieve persistent symptoms effectively. Consequently, the universal recommendation of current guidelines is justified—levothyroxine monotherapy remains the standard treatment for hypothyroidism. Nevertheless, a convincing argument can be made that combination therapy might have benefits if levothyroxine:liothyronine dose ratios are applied that result in normal serum TSH levels and free T_4:free T_3 concentration ratios, or when given to patients who harbour specific genetic polymorphisms. Trials to address these issues are forthcoming, but it will take a number of years until matters have been clarified.

In the meantime, endocrinologists must consider what can be done in daily clinical practice for the hypothyroid patient who reports persistent symptoms despite supposedly adequate levothyroxine doses. The European Thyroid Association guidelines, although still considering levothyroxine plus liothyronine combination therapy to be an experimental modality, provide several practical suggestions (Box 1), although the level of evidence for these recommendations is necessarily low given the absence of definitive studies. The formulas for calculating levothyroxine and liothyronine doses are based on the assumption that mimicking the physiological T_4:T_3 thyroidal secretion ratio of 16:1 by weight[76] will ensure euthyroidism in all target tissues. Consequently, the levothyroxine dose that results in normalized TSH should be divided by 17 (or, to simplify the calculation, by 20) to give the required liothyronine dose. The required levothyroxine dose will be the levothyroxine dose that results in normalized TSH levels, minus three times the calculated liothyronine dose (to adjust for the pharmacodynamic equivalence of 3 μg levothyroxine to 1 μg liothyronine).[94] The resulting levothyroxine:liothyronine dose ratio is about 17:1 (for example, TSH-normalizing levothyroxine doses of 100 μg, 150 μg and 200 μg during monotherapy translate into combination therapy doses of 85 μg levothyroxine plus 5 μg liothyronine, 125 μg levothyroxine plus 7.5 μg liothyronine and 175 μg levothyroxine plus 10 μg liothyronine, respectively). Commercially available levothyroxine plus liothyronine combination tablets are not recommended because their levothyroxine:liothyronine dose ratio is lower than 13:1.[73] Splitting the daily liothyronine dose into two (a smaller dose given in the morning and a larger dose given at bedtime, the exact proportions depending on which of the locally available liothyronine preparations is used) could help to mimic the circadian rhythm of free T_3 levels, which reach their acrophase around 0300 h.[97] A slow-release preparation of liothyronine would be very helpful in this respect.[98]

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These recommendations are hoped to enhance the safety of levothyroxine plus liothyronine combination treatment and discourage its indiscriminate use.[8] Are we really on the brink of another paradigm shift in the treatment of hypothyroidism? Or are we "in search of the impossible dream",[99] as an editorialist put it, of a thyroid hormone replacement therapy that treats all symptoms in all hypothyroid patients?

Review criteria

A search for original articles published between 1960 and 2013 on the treatment of hypothyroidism was performed in MEDLINE and PubMed. The search terms used were "hypothyroidism", "treatment", "levothyroxine" and "liothyronine". All articles identified were English-language, full-text papers. We also searched the reference lists of identified articles for further relevant papers.

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