

COMMENTARY

Do we need still more trials on T₄ and T₃ combination therapy in hypothyroidism?

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Abstract

Approximately 10% of hypothyroid patients are dissatisfied with the outcome of levothyroxine replacement. It is unlikely that slight over- or under-treatment with thyroxine (T₄) explains remaining complaints. Meta-analysis of randomized clinical trials shows no advantage of T₄/tri-iodothyronine (T₃) combination therapy over T₄ monotherapy. However, each of these trials can be criticized, and none is perfect: most of them failed to mimic the physiological ratio of serum free T₄ (FT₄) to free T₃ (FT₃) concentrations. Development of a sustained-release T₃ preparation given as a single nighttime dose (together with levothyroxine once daily) might maintain physiological serum FT₄–FT₃ ratio's throughout 24 h. Genetic polymorphisms in deiodinase 2 and thyroid hormone transporters have been associated with well-being, fatigue, depression, and greater improvement on combination therapy. Future trials should target carriers of these polymorphisms to see whether they do better on T₄/T₃ combination therapy than on T₄ monotherapy.

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Introduction

In 2006, a meta-analysis of 11 randomized controlled trials (RCT) with in total 1216 patients concluded that thyroxine (T₄)–tri-iodothyronine (T₃) combination therapy used as replacement therapy for patients treated for hypothyroidism provided no advantage when compared with standard T₄ monotherapy (1). The authors of the meta-analysis stated 'It is doubtful whether further trials evaluating combination therapy are needed because the chances that the accumulated evidence will change are low'. So why did the editors of the journal decide to publish another RCT on the same topic (2)? Probably not because the outcome of the meta-analysis would change significantly when the results of the present paper (which are in favor of combination therapy) are also taken into account. Reasons for publication might have been avoidance of publication bias (the present RCT was started before the meta-analysis was done) and paying attention to the unresolved issue of persisting complaints in a subset of hypothyroid patients despite what we call adequate doses of T₄ replacement.

Dissatisfaction in hypothyroid patients on T₄ replacement

Whereas the vast majority of hypothyroid patients are satisfied with T₄ replacement therapy, some are not.

A Dutch study reports impaired cognitive functioning in T₄-replaced hypothyroid patients relative to a reference population, as evident from worse scores on tests of cognitive motor speed, attention span, and learning and memory tasks (3). An English study reports a higher proportion of distressed subjects in T₄-replaced hypothyroid patients than in controls, as evident from general health questionnaires (32.3 vs 25.6%) and thyroid symptom questionnaires (46.8 vs 35.0%; $P < 0.01$ after correction for age, sex, chronic diseases and chronic medication) (4). The significant difference with controls remained when only hypothyroid patients with TSH values between 0.4 and 4.0 mU/l were analyzed. Subtracting the proportion of distressed subjects in controls from that in the T₄-replaced hypothyroid patients leaves us with an excess of about 10% of distressed subjects among T₄-replaced patients.

How can we explain the dissatisfaction, assuming that associated autoimmune diseases have been ruled out? The first explanation is nonspecific in nature. It could be that simply being aware of having a chronic disease requiring lifelong treatment and regular control visits makes the patients feel unhappy and less healthy. The second explanation is specifically related to the way in which we replace the deficit in thyroid hormone with T₄, failing to mimic precisely the thyroidal secretion rates of T₄ and T₃, and the serum concentrations of free T₄ (FT₄) and free T₃ (FT₃) of healthy subjects. I will focus exclusively on putative mechanisms involved in the second explanation. To this end, I will first

critically assess the present RCT as well as those included in the meta-analysis. Secondly, I will try to delineate avenues along which further trials might be helpful in finding a solution for patients with persisting complaints.

Randomized controlled trials: a reappraisal

The RCTs in the meta-analysis (5–15) are heterogeneous with respect to the cause of hypothyroidism, which could be thyroidectomy and/or ^{131}I therapy for Graves' disease or thyroid cancer, besides Hashimoto's disease (1). Although no relation was observed in the meta-analysis between the percentages of included athyreotic patients and the effect of combination therapy on symptoms, it is preferable to restrict inclusion to spontaneous autoimmune hypothyroidism as was done in the present RCT (2). Six studies in the meta-analysis had a crossover study design (5, 6, 7, 10, 12, 13), and five studies had a parallel study design (8, 9, 11, 14, 15). Observations in crossover studies are not independent because the same patients receive both combination and monotherapy (1). There may be a significant carry-over effect, especially because the biological effects of thyroid hormones in tissues like brain may last for a long time. Nevertheless, the meta-analysis observed similar effects on outcome parameters when comparing noncrossover and crossover designs. The present RCT has a crossover design, but the statistical analysis done by the authors did not reveal a significant carry-over effect.

Of prime importance is the administered T_3 dose and its relation to the T_4 dose during combination therapy. In 7 of the 11 RCTs in the meta-analysis (5–9, 11, 12) and, in the present RCT, 50 μg of the daily T_4 dose was replaced by a fixed T_3 dose (ranging from 10 to 25 μg T_3), giving rise to a wide variation between patients within each RCT in the ratio of the administered T_4 – T_3 dose (ranging from 20:1 to 1:1 by weight in the RCT of the meta-analysis, and from 2.5 to 8.1 in the present study). This is a far cry from mimicking the ratio of T_4 to T_3 secretion by the human thyroid gland under physiological conditions, which is close to 13:1 by weight (16). Only four of the trials in the meta-analysis (10, 13–15) used a variable T_3 dose in order to reach the same ratio of administered T_4 – T_3 dose in all study subjects; the fixed T_4 – T_3 ratios by weight in these studies were 5:1, 10:1, 15:1, and 19:1. Nevertheless, in these four trials, combination therapy was also judged not to be better than monotherapy. To obtain TSH values similar to controls during T_4 monotherapy, serum FT_4 concentrations higher than controls are required, whereas serum FT_3 values are similar to those in controls (17). It follows that the serum FT_4 – FT_3 ratio is higher in T_4 -replaced hypothyroid patients than in controls. Indeed, the serum FT_4 – FT_3 ratio in

patients randomized to receive T_4 monotherapy in the meta-analysis ranges from 4.0 to 6.7 (7, 8, 10, 11, 13), higher than the value of 3.3 observed in controls (18). The serum FT_4 – FT_3 ratio during combination therapy ranged from 2.2 to 4.8; in only two of the RCTs, the ratios (3.3 and 3.4 respectively) were close to control values, but both studies still failed to demonstrate superiority of combination therapy over monotherapy (7, 13).

Applied outcome measurements in the various trials are a number of questionnaires on health-related quality-of-life, cognition, mood, and thyroid symptoms. The used questionnaires are the same in most but not all studies. Remarkably, the present study reports significantly better outcome of combination therapy in quality-of-life and depression scales (2), in contrast to all previous RCTs, except two early biased ones (5, 6) and one (11) in which the benefit at 3 months was lost at 12 months. When asking the patients themselves, 49% preferred combination therapy and 15% monotherapy in the present study; 36% had no preference. That 15% felt better in the period in which the same T_4 dose was used as before entering the study, indicates a strong Hawthorne effect also observed in a previous study (14): patients feel better just by participating in a trial. It underlines once again the need for RCT.

But can we trust the results of the present RCT? One may argue that the study was not adequately blinded (T_3 and T_4 tablets could be distinguished by patients, and dose adjustments were done by the investigators themselves), there was no intention to treat analysis (outcomes of 13% of included patients were not available), and there might have been overreplacement during combination therapy (although the authors should be applauded for their efforts to keep serum TSH similar during treatment periods, the TSH during combination therapy was lower – albeit just missing statistical significance – supporting slight overtreatment). However, in defense of the authors, I would say that many of the critical comments apply also to the other RCTs. Obviously, none of the RCTs are perfect, and these trials are indeed very demanding to perform.

If we accept the outcome of the present study, how do we explain the success of the combination therapy? Could it be the loss of body weight caused by slight overtreatment because most patients love to lose weight? At the end of the combination therapy, patients were on average 1.7 kg lighter than after monotherapy, and a similar loss of 1.7 kg during combination therapy was observed in another trial (14) in which patients also preferred the combination. Could it be selection of patients at study entrance? Most patients included in the present study had a high baseline psychological morbidity. But subset analyses of previous trials do not support this explanation (6, 7, 12, 14), although there may be a sample size problem. Could it be something else?

Slight over- or under-treatment in T₄ monotherapy: unlikely to be involved

Could it be that the T₃ level of a patient on T₄ treatment is in the normal range but differs from the T₃ level the patient had prior to the illness? This issue has been clarified in a recent study by Jonklaas *et al.* (19). She measured thyroid function in euthyroid patients before total thyroidectomy and after surgery when the patients were fully replaced with T₄. Values before and after surgery were not different for TSH (1.18 ± 0.58 vs 1.30 ± 1.89 mU/l, NS), were as expected higher after surgery for FT₄ (13.5 ± 2.4 vs 18.1 ± 3.7 pmol/l $P < 0.001$), but not different for T₃ (1.99 ± 0.41 vs 1.96 ± 0.43 nmol/l, not significant, NS).

Could it be that we are slightly over- or under-treating patients with T₄ in view of the marked inter-individual variation in the set point of the hypothalamus–pituitary–thyroid axis (20)? This has been investigated in a double-blind randomized study with a crossover design, in which T₄-replaced patients were asked to continue with their usual T₄ dose, or take 25 µg less or more T₄ (21). So the mean T₄ doses in each of the 6-week study periods were 100, 125, and 150 µg daily. TSH values at the low, middle, and high T₄ dose were 2.8 ± 0.4 , 1.1 ± 0.2 , and 0.3 ± 0.1 mU/l respectively ($P < 0.001$), and FT₄ values were 14.1 ± 0.3 , 16.1 ± 0.3 and 18.3 ± 0.4 pmol/l respectively ($P < 0.001$). The body responded to these changes with alterations in cholesterol levels (5.7 ± 0.1 , 5.6 ± 0.2 and 5.3 ± 0.1 nmol/l respectively, $P < 0.001$). Nevertheless, the three different T₄ doses did not affect scores of well-being, cognitive function, and quality of life and thyroid symptoms questionnaires. Consequently, it is unlikely that slight over- or under-treatment provides a reasonable explanation for remaining complaints.

Mode of T₃ administration: possibly involved

During combination therapy, the T₃ dose is given once or twice daily. It results in wide peak-to-trough variation in serum FT₃, e.g. FT₃ increased by 42% in the first 4 h after T₃ but did not change after T₄ (22). A slow-release formula of T₃ might circumvent the marked changes in FT₃ levels, and proof of principle of such a preparation has been obtained in a recent study (in which the serum T₄–T₃ ratio was lower during T₄ + slow release T₃ than during T₄ monotherapy, but still higher than in controls) (23). Serum FT₃ has – in contrast to FT₄ – a circadian rhythm; the FT₃ acrophase occurs in early morning hours around 0300 h, ~90 min after the TSH acrophase (24). If one's goal is to replicate the circadian T₃ rhythm and maintain a physiological ratio of serum FT₄–FT₃ throughout 24 h in hypothyroid patients, replacement should provide constant FT₄ levels and an early morning rise in serum FT₃. This goal possibly

can be reached by the administration of levothyroxine once-daily in combination with a single nighttime dosing of a sustained-release T₃ preparation.

Genetic polymorphisms: likely to be involved

Genetic polymorphisms in deiodinases and thyroid hormone transporters may not only affect serum thyroid hormone concentrations but also the biological availability of thyroid hormone in particular tissues (25). Deiodinase type 1 (D1) catalyzes the conversion of T₄ into T₃ and is highly expressed in liver. Two single-nucleotide polymorphisms (SNPs) in the *DIO1* gene are associated with the serum FT₄–FT₃ ratio. The SNP C785T is dose-dependently associated with a higher ratio caused by higher serum FT₄. The opposite was found for SNP A1814G (26), but haplotype analysis showed C785T is driving the associations as determined in different populations (27) and may account for 1.24% of variation in T₄–T₃ ratio (26). Neither SNP affects serum TSH. The effect on FT₄–FT₃ ratio is also observed in hypothyroid patients on T₄ replacement (27). Psychological well-being is negatively correlated with serum FT₄ (not with FT₃) and FT₄–FT₃ ratio in T₄-treated patients, but none of the SNPs in *DIO1* showed any association with psychological well-being (28, 29).

D2 converts T₄ in T₃ (especially in the central nervous system, CNS and pituitary), whereas D3 inactivates T₄ by conversion into rT₃. Studies on polymorphisms in *DIO2* and *DIO3* genes have not revealed associations with circulating thyroid hormones (25, 30, 31). The D2 polymorphism Thr92Ala is also not associated with the need for higher T₄ doses to achieve normal TSH values in Hashimoto's hypothyroidism (31). However, thyroid hormone action in tissues like brain is regulated to a large extent by local thyroid hormone transporters and deiodinases. T₄ is transported across the blood–brain barrier by OATP1C1 (and likely by other transporters as well) and then converted into T₃ within glial cells by D2; T₃ is transported into neurons by MCT8. Higher T₄ levels decrease D2 activity and vice versa, serving to maintain thyroid hormone homeostasis in the brain. One may hypothesize that particular *DIO2* polymorphisms may result in suboptimal T₃ concentrations in brain, explaining persistent complaints. An early report did not find an association between D2 Thr92Ala polymorphism and well-being, neurocognition or preference for combination therapy, but the sample size of 141 was limited (32). A much larger study ($n = 552$) observed associations of the rarer CC genotype of the D2 Thr92Ala polymorphism (present in 16% of the study population) with worse baseline scores for general health and greater improvement on combination therapy (29). Lastly, several polymorphisms in the brain-specific thyroid hormone transporter OATP1C1 are associated with fatigue and depression in hypothyroid patients on levothyroxine, but not with neurocognitive functioning or preference for combination therapy (33).

Future directions

In my opinion, there is a strong case for further RCTs comparing T₄ monotherapy and T₄/T₃ combination therapy for two reasons. First, trials so far have been largely unsuccessful in mimicking physiological serum FT₄-FT₃ ratios throughout 24 h. The development of sustained-release T₃ preparations might be essential for reaching the goal of 'physiological' thyroid hormone replacement. Secondly, an increasing number of polymorphisms in deiodinases and thyroid hormone transporters are associated with psychological well-being, depression, fatigue, and preference for combination therapy. Could it be that subjects not satisfied with monotherapy are frequent carriers of these polymorphisms, and will have a better response to combination therapy? In this respect, one could envisage RCTs restricted to patients who are carriers of one or more of these polymorphisms (34). Studies should be carefully designed, with special attention to sample size calculation, T₄/T₃ ratio's in combination therapy, and dynamic monitoring of TSH in order to maintain a normal level by adjusting study medications if needed (35). Six years ago, three editorialists had an impossible dream: thyroid hormone replacement therapy that treats all symptoms in all hypothyroid patients (35). Hopefully, their dream will come true in the next 6 years.

Declaration of interest

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