L-T4 and L-T3 combined treatment vs L-T4 alone

W.M. Wiersinga

Department of Endocrinology and Metabolism, Academic Medical Center, University of Amsterdam, The Netherlands

Available online 08 August 2007

1. Introduction

It is not unusual that hypothyroid patients have persistent symptoms despite apparently adequate thyroxine replacement. In other words, they still feel “hypo but not happy”. Two community-based studies indeed confirm that patients on L-T4 replacement therapy, even with a normal TSH, display impairment in psychological well-being and neurocognitive functioning compared to controls. Distress was observed more often in hypothyroid patients with TSH values between 0.4 and 4.0 mU/l while on L-T4 treatment than in controls, both on a general health questionnaire (35.1% vs 25.6% respectively, p < 0.01) and on a thyroid symptoms questionnaire (48.5% vs 35.0%, p < 0.01) [14]. Similarly, L-T4 treated hypothyroid patients with TSH values of 0.11 - 4.0 mU/l did worse than a reference group on scales for mental health and vitality, with no difference between patients having TSH<2 and > 2 mU/l; patients also performed poorly relative to controls in tests of cognitive motor speed, attention, learning and memory [19].

The question is whether the remaining symptoms in hypothyroid patients despite normal TSH values during thyroxine treatment, are specifically related to suboptimal thyroid hormone replacement, or that they are non-specifically associated with chronic diseases requiring lifelong treatment.

2. Biologic rationale of combined T4 and T3 treatment

Under physiologic conditions thyroidal secretion of T3 is responsible for about 20% of the daily production rate of T3; 80% of daily T3 production is derived from extrathyroidal deiodination of T4 into T3 catalysed by deiodinases type 1 and type 2. The molar ratio of T4 to T3 secretion by the thyroid gland is in the range of 14:1 to 11:1 in humans (but 6:1 in rats). T3 secretion by the thyroid gland is about 6 μg per day. The thyroidal contribution to the daily T3 production is largely lacking in hypothyroid patients on L-T4 replacement.

When patients with primary hypothyroidism start L-T4 treatment, the elevated serum TSH values gradually return into the normal reference range, under simultaneous increase of the initially decreased serum FT4 values. Normalisation of serum TSH, however, requires serum FT4 concentrations which are slightly but significantly higher than observed in healthy subjects, whereas serum T3 concentrations do not differ between both groups [9]. It follows that the ratio of serum FT4 to FT3 concentrations in T4-treated hypothyroid patients is higher than under physiological circumstances. The biologic availability of the active thyroid hormone T3 in tissues depends on local uptake of T4 and T3 and local deiodination of T4. As these mechanisms vary from tissue to tissue, one can argue that the altered FT4 to FT3 ratio in serum of T4-treated hypothyroid patients may interfere with the biologic availability of thyroid hormone in some organs.

Support for this line of reasoning is provided by a series of elegant experiments in rats by the group of Morreale de Escobar. They infused thyroidectomized rats with placebo or T4 in doses ranging from 0.2 to 8.0 μg/100 g body weight/day. Plasma and tissue T4 and T3 were measured after 12 days when equilibrium had been reached. They observed that treatment with thyroxine could not ensure euthyroidism (defined as normal tissue contents of T4 and T3) simultaneously in all investigated tissues (cerebral cortex, cerebellum, brown adipose tissue, heart, lung, kidney, liver, spleen and muscle) [6]. E.g. a particular dose of T4 could result in normal T4 and T3 contents of some tissues, but would give rise to too low or too high T4 and T3 contents in other tissues. In a follow-up experiment they demonstrated that only the combined treatment with T4 and T3 ensured euthyroidism simultaneously in all tissues of thyroidectomized rats [7]. This was the case when rats were infused with 0.9 μg T4 and 0.15 μg T3/100 g body weight/day, that is in a T4 to T3 ratio of 6:1. In these rats, plasma TSH and deiodinase activities in cerebral cortex, pituitary and liver were not different from those in intact rats. The outcome of the rat studies provided a clear biologic rationale for human studies.
evaluating the usefulness of the combined T4 and T3 treatment of hypothyroid patients.

3. Outcome of randomized controlled trials

Eleven randomized controlled trials have been published so far, comparing T4/T3 combination therapy with T4 monotherapy [1,3–5,8,12,13,15–18]. These studies differ in many aspects: in recruitment of patients, in sample size, in study design, in dosing schedule, and in outcome measurements. The studies were conducted in Australia, Canada, USA and various European countries.

3.1. Recruitment of study participants

Recruitment was done through outpatients clinics, advertisement, or family practices. The way in which patients are recruited, is relevant in order to minimise the risk that only dissatisfied patients will participate. In this respect it is noteworthy to mention that in the two studies with recruitment by advertisement, 55% of participants in the one study were dissatisfied and 100% of participants in the other study had depressive symptoms. Recruitment by inviting all eligible patients in family practices is apparently preferable in obtaining a study population more representative for all hypothyroid patients on L-T4 replacement; this was done in only two studies.

3.2. Cause of primary hypothyroidism

Included were patients with primary autoimmune hypothyroidism or hypothyroidism after 131I therapy and/or thyroidectomy for Graves’ hyperthyroidism or thyroid carcinoma. It is conceivable that outcome measurements like cognition and mood state are influenced by the underlying disease. A homogeneous study population might be preferable, but in only three studies participation was restricted to Hashimoto’s hypothyroidism.

3.3. Thyroxine medication prior to randomization

Most studies required a stable dose of L-T4 replacement prior to randomization over a period of 2 up to ≥12 months, but this was not specified in two studies.

3.4. Sample size

Sample size varied from 13 to 50 subjects in eight studies, it was 110, 141 and 697 respectively in three studies.

3.5. Study design

Six trials had a crossover design without wash-out between the two treatment periods which ranged from 5 to 16 weeks. In the five non-crossover studies the assigned treatment period lasted for 15-16 weeks in three, and 9-12 months in two trials. All studies were double-blind in nature.

3.6. Dosing schedule

When assignment was to treatment with L-T4 alone, patients continued their usual pre-randomization L-T4 dose. When assigned to combined treatment, eight studies decreased the usual daily L-T4 dose by 50 μg, and L-T3 was added in doses ranging from 10-25 μg per day giving rise to a ratio of T4 to T3 replacement dose of 2:5:1 to 20:1 by weight; only in one of these studies the L-T3 dose was adjusted to result in a fixed 15:1 ratio, whereas the ratio’s differed widely between patients within each of the other seven studies. Fixed ratio’s were also obtained in the three remaining studies: T4:T3 ratio’s were 19:1 in one study (usual T4 dose minus 5%, variable T3 dose), 15:1 in another study (fixed doses of 75 μg T4 and 5 μg T3), and 10:1 or 5:1 in the last study (usual T4 dose minus 25 μg, and variable T3 doses in two daily gifts). It is interesting to note that a serum FT4 to FT3 ratio closely resembling that in healthy subjects was obtained only in the trials that accomplished a fixed T4 to T3 replacement dose ratio of 15:1 and 19:1. One may criticize the absence of a fixed ratio in the majority of the trials.

3.7. Outcome measurements

Main outcome measurements were general health-related quality-of-life questionnaires (like HRQL, MOS, SCL-90, SF36), visual analogs scales, thyroid symptoms questionnaires, mood state (POMS, BDI, STAI) and cognitive tests like digit symbol test, digit spar test forward and backward). All studies used several tests as primary outcome measurements except one in which patient preference was taken as the primary outcome.

Seven of the 11 trials observed no difference in outcome measurements between the combined T4 and T3 treatment and monotherapy with L-T4. The four trials observing better outcome in patients assigned to the combination treatment deserve close attention. The first study has been heavily criticized because of a small sample size (n=33), and later analysis showed the beneficial effect of T4 & T3 treatment was restricted to the patients with thyroid cancer and not evident in the patients with Hashimoto’s disease who comprised 48% of the study population [3]. Likewise, the second study favouring combination treatment is subject to criticism in view of the very limited sample size (n=13) and involving exclusively hypothyroid patients after thyroidectomy for Graves’ hyperthyroidism [4]. The third study had the largest sample size (n=697); after three months of treatment patients on combination therapy did better than after T4 monotherapy as evident from a lower Likert score on HRQL questionnaires and a lower percentage of ‘caseness’, but after twelve months of treatment no differences between both groups were found any longer (not in well-being, nor in thyroid symptoms, anxiety or depression) [15]. The fourth study (sample size N=141)
demonstrated preference of patients for the combined treatment [1]: preference for their usual treatment with L-T4 monotherapy after 15 weeks was 29% (indicative a marked Hawthorne effect), for T4 + T3 therapy in a dose ratio of 10:1 it was 41%, and for T4 + T3 therapy in a dose ratio of 5:1 it was 52% (p=0.024 for trend). The patient preference was not evident in any of the secondary outcome measurements (SCL-90, POMS, digit symbol and digit span tests). In an attempt to explain the discrepancy between primary and secondary outcome measurements, the authors looked at changes in body weight. Patients on L-T4 monotherapy had put on weight by 0.1 kg, but those on combination treatment had lost 0.5 kg (T4:T3 dose = 10:1) and 1.7 kg (T4:T3 dose = 5:1)(p=0.01 for trend). Patients on combination therapy had clearly been overtreated as evident from TSH values (median with 25 and 75 percentiles in brackets), which were 0.64 mU/l (0.18-1.9) in the T4 alone group, 0.35 mU/l (0.09-1.3) in the T4:T3 = 10:1 group and 0.07 mU/l (0.02-1.05) in the T4:T3=5:1 group (p<0.01 for trend). Loss of body weight might be an important outcome for the patient, but if accomplished by a too high dose of thyroid hormone replacement resulting in suppressed TSH values might put the patient at risk for developing atrial fibrillation.

Taken together, the outcome of the randomized controlled trials do not justify to recommend combined treatment with T4 and T3 for treatment of hypothyroidism.

4. Meta-analysis of randomized controlled trials

The eleven randomized controlled trials differ greatly in many aspects, and each of them can be criticised. An important limitation of most trials is that a fixed amount of T4 was substituted with a fixed amount of T3, leading to very variable ratio’s of T4 and T3 that are unlikely to have comparable effects. Although none of the trials seems to be perfect, a total of 1216 patients had been randomized in these studies, allowing to perform a meta-analysis. This was done by Grozinsky-Glasberg and colleagues [10]. Outcome was the same for studies with or without a crossover design. No difference was found in the effectiveness of combination vs monotherapy in any of the following symptoms: bodily pain (standardized mean difference SMD 0.00, 95% confidence interval CI - 0.34, 0.35), depression (SMD 0.07, CI - 0.20, 0.34) anxiety (SMD 0.00, CI - 0.12, 0.11), fatigue (SMD - 0.12, CI - 0.33, 0.09) quality of life (SMD, CI - 0.09, 0.15), body weight, and serum lipids. Adverse effects were similar between study groups (relative risk 1.19, 95% CI 0.63 – 2.24).

It must be concluded that there is no evidence base to support T4 + T3 combination therapy as a better alternative to standard T4 monotherapy. The implication is that T4 monotherapy should remain the treatment of choice for patients with hypothyroidism.

5. Further developments

The outcome of the meta-analysis does not preclude the possibility that a certain subgroup of patients may still benefit from combined T4 and T3 therapy. Recently identified polymorphisms (i.e. in type 2 deiodinase), important in the regulation of T3 availability, may help to identify such subgroups. However, a recent study looking into two particular polymorphisms of type 2 deiodinase, demonstrated an equal proportion of patients preferring combination therapy over T4 monotherapy in homozygotes, heterozygotes and wild type [2]. Another interesting line of research is the development of slow-release T3 preparations, allowing to obtain a more physiological ratio of serum T4 to T3 concentrations [11]. It remains doubtful if such formula will solve the problem of persistent symptoms in some hypothyroid patients, because no benefit of combination treatment was found in the trials which came closest to the physiological ratio of serum T4 to T3.

References


