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Combined levothyroxine/liothyronine therapy – where are we now?

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Title Combined therapy with levothyroxine and liothyronine in two ratios, compared with levothyroxine monotherapy in primary hypothyroidism: a double blind, randomised controlled clinical trial

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SUMMARY

Most patients with hypothyroidism are treated with LT4, but still continue to complain of ill health despite normalisation of TSH values. The metabolic effects of T4 occur through peripheral conversion to T3, and the thyroid also secretes about 20% of the body's total T3 production. This is the latest of eight published randomised clinical trails in six years investigating the value of combined LT4 and LT3 therapy.

One hundred and forty-one patients with stable LT4 treated autoimmune hypothyroidism from general practice in the Netherlands were randomised to three groups. (1. Continuation of LT4; 2. LT4/LT3 ratio of 10:1; 3. LT4/LT3 ratio of 5:1.) Outcomes at 15 weeks included subjective preference of medication (primary outcome), questionnaires on mood, fatigue and psychological symptoms, and neurocognitive tests.

The study medication was preferred to usual treatment by 29%, 41% and 52% in the LT4, 10:1 combination and 5:1 combination ratio groups respectively. There were no differences in any other outcome measures. TSH was suppressed (subclinical hyperthyroidism) in 16% of those in the LT4 group and in 30% and 54% in the 10:1 combination and 5:1 combination groups respectively. This did not correlate with preference for any medication, but there was a correlation with weight loss in the combination therapy groups with mean decreases of 0·5kg and 1·7kg in the 10:1 and 5:1 groups respectively (the LT4 group had a slight increase in mean weight by 0·1kg). There were no changes in mood, wellbeing or neurocognitive function to explain the primary outcome in favour of LT4/LT3 combination therapy. The authors conclude that the study does not support combined LT4/LT3 therapy for hypothyroidism.

OPINION

Thyroxine replacement has been used for over 100 years but controversy continues on replacement strategies. Despite biochemically normal thyroid function on LT4 therapy, many patients remain dissatisfied. Explanations include: patients' preference for being slightly hyperthyroid; hypothyroid symptoms such as fatigue and weight gain and are common and possibly unrelated to thyroid function; and self selection of patients with these complaints for testing and treatment with thyroxine. Biological explanations include relative tissue hypothyroidism and differing peripheral conversion of T4 to T3 depending on levels and activities of deiodinases in different tissues.

Several recent trials have been conducted and have concluded overwhelmingly against combined T4/T3 replacement. The latest studies have addressed criticisms of the first small study which suggested positive benefit. All subsequent studies have found no mood, quality of life or psychological benefits. Truly physiological ratios of LT4 and LT3 are difficult to achieve in humans and this study looked at two ratios of the drugs. Two recent studies, including this study found that patients prefer combination therapy though no other quality of life or neurocognitive outcome was significantly different. Both studies concluded that there is no evidence to support T4/T3 therapy. A large placebo effect was found in some studies adding complexity to outcome assessment. The dangers of subclinical hyperthyroidism, mainly of bone and heart effects, are well recognised and physicians need to be cautious about contributing to this by thyroxine overreplacement. However, based on the existing evidence, the most appropriate therapy for primary hypothyroidism is LT4 alone.