

# Combination Levothyroxine and Levotriiodothyronine Therapy for Hypothyroidism Treatment-Is it Worth the Risks?

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## Editorial

About 4.6% of the U.S. population ages 12 and older and 3.05% of European population has hypothyroidism [1,2]. Thyroid produces thyroxine (T4) and triiodothyronine (T3) but T3 is more active at the cellular level because of its higher affinity for the nuclear thyroid hormone receptors. In humans, approximately 80% of the T3 produced daily derives from monodeiodination of T4 in extrathyroidal tissues [3]. Current guidelines consistently recommend Levothyroxine (LT4) monotherapy as treatment of choice for hypothyroidism management [4,5]. The goal of therapy is to restore physical and psychological wellbeing and normalize serum TSH. Although LT4 monotherapy is effective, up to 5-10% of hypothyroid patients with normal TSH on LT4 does not feel entirely well and reports persistent symptoms [5]. Given the high prevalence of patients who are not satisfied with LT4 monotherapy, a review of the literature evaluating efficacy and safety of combination levothyroxine and levotriiodothyronine therapy (LT4/LT3) is worthwhile.

Several studies have compared combination LT4/LT3 therapy and LT4 monotherapy prospectively in patients with primary hypothyroidism but results have been inconsistent. Bunevicius et al. [6] studied 33 patients with primary hypothyroidism for two 5-wk periods in a randomized and blinded crossover study. During one period, the patient received LT4 at usual dose and during the other, 12.5 µg of LT3 was added and LT4 dose was reduced by 50 µg. Patients performed significantly better on tests for cognitive performance and assessment of mood and physical status after treatment with combination LT4/LT3. At the end of study 20 patients preferred combination LT4/LT3, 11 had no preference, and 2 preferred LT4 alone (P=0.001).

Finding of this study was not consistently replicated in future studies. Many studies compared combination LT4/T3 therapy to LT4 monotherapy; however, only a few studies showed beneficial effects of combination LT4/LT3 therapy and rest were neutral, finding no consistent advantage for monotherapy or combination treatment. In some of these studies patients preferred combination LT4/LT3 even though no or minimal statistically significant differences were observed in primary outcomes [6-19].

Although, there is insufficient evidence that combination LT4/LT3 therapy is superior to LT4 monotherapy, it's important to note that none of the study found that LT4 monotherapy compared to combination LT4/LT3 therapy produced significant improvements in quality of life, mood and/or cognition. Current guidelines recommend against the routine use of LT4/LT3 combination treatment, and the use of desiccated thyroid extract mainly due to concerns regarding long term safety of LT3 therapy, and unavailability of LT3 formulations that

mimic natural physiology. American Association of Clinical Endocrinologists/American Thyroid Association clinical practice guidelines, 2012 (AACE/ATA) does not support using LT4/LT3 combination therapy and based on unanimous expert opinion, recommends against use of desiccated thyroid hormone for the treatment of hypothyroidism. European Thyroid Association guidelines, 2012 (ETA) on the other hand recommends that LT4/LT3 combination therapy may be considered as an experimental approach in compliant LT4-treated hypothyroid patients who have persistent complaints despite normal serum TSH values, provided they have received adequate chronic disease support and associated autoimmune diseases have been ruled out [4,5]. Both guidelines strongly recommend that LT4 remains the therapy of choice in hypothyroidism.

There have been concerns regarding safety of long term LT3 use mainly due to lack of data. Leese et al. [20] reported a 17yrs large observation population based study of all patients prescribed thyroid hormone replacement in Tayside Scotland from 1997 to 2014. LT3 was prescribed to 400 patient compared to 33,955 patients who were treated with LT4 monotherapy. Patient using long term LT3 did not show any additional risk of atrial fibrillation, cardiovascular disease or fractures or receive increased prescriptions for bisphosphonates or statins. There was an increased incident use of antipsychotic medication during follow-up. Even though more studies are needed to validate these findings, this study provides much needed data and suggests that long-term LT3 treatment in patients with hypothyroidism may be safe.

Taken together, it's important to acknowledge that a significant proportion of hypothyroid patients on LT4 monotherapy have persistent symptoms, even when TSH is within normal reference range, that they attribute to hypothyroidism. These patients should be thoroughly evaluated for other etiologies; such as endocrine and autoimmune disorders and nutritional deficiencies. In our view, if detailed evaluation for alternate causes is unremarkable, a trial of combination LT4/LT3 may be considered given recent data suggesting that long term LT3 therapy may be safe but these trials should be limited to endocrinologist. Treating endocrinologist should have a detailed discussion with patient regarding limited data on long term safety of LT3 therapy and insufficient evidence of superiority of combination LT4/LT3. Further studies are needed to evaluate safety and efficacy of long term LT3 therapy and identify individual characteristics of patients, such as deiodinase type 2 gene expressions, which may help delivering personalized medical care to hypothyroid patients.

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