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Treatment of hypothyroidism with levothyroxine or a combination of levothyroxine plus L-triiodothyronine

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At present, the drug of choice for the treatment of hypothyroidism is levothyroxine sodium, even though the thyroid gland secretes both thyroxine and 3′,3,5-triiodothyronine; the latter is the more active of the two at the cellular level because of its higher affinity for the nuclear thyroid hormone receptors. To date, combined levothyroxine plus liothyronine treatment for hypothyroidism has been evaluated in 15 clinical trials in humans. In two studies, combined therapy seemed to have beneficial effects on mood, quality of life, and psychometric performance of patients, compared with levothyroxine alone; in some of these studies, the patients preferred levothyroxine plus liothyronine combinations. This preference should be balanced against the possibility of adverse events resulting from the addition of liothyronine to levothyroxine. Until clear advantages of levothyroxine plus liothyronine are

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demonstrated, the administration of levothyroxine alone should remain the treatment of choice for replacement therapy of hypothyroidism.

Practice points

- Oral administration of synthetic levothyroxine sodium is considered to be the treatment of choice for patients with hypothyroidism.
- Because the thyroid gland secretes both thyroxine and triiodothyronine, combined levothyroxine plus liothyronine replacement therapy might be needed to completely restore euthyroidism in people with hypothyroidism.
- Even though animal studies support combined levothyroxine plus liothyronine replacement therapy, clinical trials in humans have not shown clear advantages of such an approach over administration of levothyroxine alone.
- The preference of some patients for combined therapy found in some trials, which may have a genetic background, should be balanced against the possibility of adverse events resulting from the addition of liothyronine to levothyroxine.

Research agenda

- Currently available oral liothyronine preparations have an inadequate pharmacokinetic profile.
- Similarly, commercial preparations that contain levothyroxine and liothyronine contain an excess of the latter and do not mimic the proportion of levothyroxine to triiodothyronine present in the normal human thyroidal secretion.
- These considerations may have influenced negatively the outcome of the clinical trials conducted to date in humans.
- Thyroid hormone preparations that warrant a constant steady supply of levothyroxine and liothyrodine are needed.
- Such preparations may require enteric, intramuscular or transdermal sustained-release preparations, al least for the liothyronine component.

Current recommendations for the management of hypothyroidism in humans and the assumptions underlying them

Levothyroxine sodium is the drug of choice for the treatment of hypothyroidism at present in almost all clinical situations [1–7]. The aim of levothyroxine is to restore well-being and euthyroidism [8], which is believed to occur when serum thyroid-stimulating hormone (TSH) returns to the reference range [9]. Accordingly, serum TSH concentrations are usually used to monitor levothyroxine therapy, a practice that is based on several implicit assumptions that are far from being supported by direct evidence.

First, the healthy adult thyroid gland secretes both T4 and T3. Although approximately 80% of the T3 that circulates in blood is originated by peripheral 5'-deiodination of the T4 secreted by the thyroid gland, as much as 20% comes from direct thyroidal secretion [10], suggesting a physiological role for this fraction of circulating T3. When patients with hypothyroidism are given levothyroxine alone, the