Opinion

Is thyroxine plus triiodothyronine combined therapy an option to treat some hypothyroid patients?

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Since the beginning of the 20s of the last century, the combined treatment T4+T3 in the form of desiccate animal thyroid, thyroid extract or thyroglobulin was the usual treatment of patients with hypothyroidism for many decades, and it stayed that way even though there were already synthetic formulations of T4 and T3. In the 70s, concerns arose regarding the potency and consistency of the desiccated thyroid hormone due to the publication of cases that failed to compensate for hypothyroidism and in others that presented iatrogenic thyrotoxicosis. This together with the fact that at that time immunoassays for measured serum TSH was available, the existence of easily accessible levothyroxine formulations and the discovery that most of the circulating T3 derives from T4 by deiodination; they resulted in levothyroxine (LT4) monotherapy being the standard care for patients with hypothyroidism and serum TSH levels within the reference range the goal of the treatment.

However, in the last 2 decades, some publications, report that not all hypothyroid patients treated with LT4 monotherapy with TSH in the normal range achieve symptom relief.[1] Residual symptoms associated with LT4 monotherapy include cognitive impairment, depression and decreased psychomotor performance.[2–4] Studies in thyroidectomized patients shown that when LT4 doses are adjusted to maintain TSH values within normality, in around 15 % of the hypothyroid patients the ability of deionidases to appropriately regulate T3 availability fails. It has been suggested that this putative T3 deficiency may be associated with failure to fully reverse the symptoms of hypothyroidism in those patients,[5,6] but the true clinical relevance of the relatively low levels of serum T3 is pending to be determined. A systematic review and meta-analysis showed that T3-dependent metabolic markers, such as total and LDL cholesterol, remain significantly higher in LT4 monotherapy treated patients with normal serum TSH values compared to healthy controls.[7] Thr92Ala polymorphism in the type 2 deiodinase (Thr92AlaD2) is a prevalent genetic polymorphism that disrupts cellular morphology, has a prolonged half-life and exhibit decreased catalytic activity,[8] this factor has been associated with response to thryroxine plus triidothyronine combination therapy in some clinical trials, patients carriers the Thr92AlaD2 polymorphism exhibit improved quality of life measures and preferred combination therapy.[9] Furthermore, there are some evidence that raising serum T3 levels using T4 plus T3 therapy improves the symptoms of some of the patients.[10, 11]

On the contrary, many clinical trials and meta-analysis have found no advantages in the use of combined treatment even in total thyroidectomized patients.[12,13] Moreover, a recent study by Ito et al,[14] concluded that in total thyroidectomised patients treated with levothyroxine, those with mildly suppressed serum TSH values were close to euthyroidism, while those with normal or strongly suppressed TSH were mildly hypothyroid or thyrotoxic respectively.

Finally, the main guidelines from professional societies do not recommend combining treatment with T4+T3 for regular treatment in clinical practice.[15–17] Only ETA guidelines,[18] recommend that combination therapy might be considered as an experimental approach in hypothyroid patients who have persistent complaints despite serum TSH values within reference range.

In conclusion, taking into account that currently most of the patients with hypothyroidism that we attend have subclinical hypothyroidism and those with athyreotic hypothyroidism, euthyroidism can be achieved by keeping TSH levels close to the lower limit of the reference range, need to use a combined treatment would be exceptional.

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Conflicts of interest

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