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New insights into the variable effectiveness of levothyroxine monotherapy for hypothyroidism

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Thyroid hormone replacement has been the mainstay of treatments for hypothyroidism since the 19th century. Animal thyroid preparations, which contain thyroxine (T_4) and tri-iodothyronine (T_3), were the first pharmacotherapies, and synthetic agents—eg, levothyroxine (also known as LT_4)—are the current standard of care.[1] Chemical composition of hormone replacement therapy is important in view of the clinical data suggesting that levothyroxine monotherapy does not consistently normalise serum T_3 concentrations[1] or universally restore clinical euthyroidism. Although the clinical significance is not clear, increasing serum T_3 with a combination of levothyroxine plus liothyronine (also known as LT_3) results in weight loss and improves psychological function in some patients.[1]

Before 1970, the predominant treatment for hypothyroidism was desiccated thyroid, typically porcine, given at doses to resolve symptoms and normalise the basal metabolic rate and serum protein-bound iodine concentration.[2] Thyrotoxic side-effects were not uncommon, but were remediable by dose reduction; patients with residual hypothyroid symptoms were not routinely reported. Although the efficacy of desiccated thyroid was inconsistent and the costs of levothyroxine had fallen, desiccated thyroid remained the preferred agent because concerns had arisen that levothyroxine monotherapy resulted in a relative T_3 deficiency.[2]

In the 1970s, the therapeutic approach changed after the development of the serum thyroid-stimulating hormone (TSH) radioimmunoassay,[3] which showed that typical doses (200–400 μg per day of levothyroxine)[2] were supratherapeutic, and the discovery that most circulating T_3 is derived via extrathyroidal conversion of T_4.[4] From that point on, normalisation of serum TSH has become the treatment target to avoid the deleterious effects of iatrogenic thyrotoxicosis on the skeleton and heart, doses of levothyroxine have been substantially decreased, and levothyroxine monotherapy has become the preferred treatment in view of its excellent safety profile.[1] Today, most patients do well with levothyroxine monotherapy, establishing normalisation of serum TSH concentrations and symptomatic remission. It is widely accepted that levothyroxine restores the T_4 pool and deiodinases regulate peripheral T_3 production.[1]

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However, after this transition, some patients given levothyroxine (about 12%) were reported to have residual symptoms of hypothyroidism.[1] Although psychological issues could have been coexisting in these patients, this finding suggests that adoption of this supposedly physiologically sensible regimen has set the scene for a new category of so-called euthyroid patients—ie, those given levothyroxine who have normal serum TSH but residual symptoms of hypothyroidism. In fact, other markers of thyroid hormone economy might not be fully normalised in patients given levothyroxine; the basal metabolic rate can remain subnormal,[5] lipid abnormalities can persist,[6] and the serum T_4:T_3 ratio is raised, with relatively lower serum T_3 concentrations.[1] Notably, less attention has been given to the raised T_4:T_3 ratio because serum TSH dominates as the therapeutic target and the medical community has dogmatic confidence in the deiodinases to appropriately regulate tissue T_3 generation.

To challenge this dogma, investigators studied thyroidectomised rats and discovered that serum T_3 is hardly normalised with levothyroxine monotherapy if serum TSH remains within the normal range. In fact, this finding results from T_4-mediated down-regulation of the type 2 deiodinase (D2).[7] Notably, hypothalamic D2 that mediates the thyrotropin-releasing hormone–TSH feedback mechanism is relatively more stable in the presence of T_4, such that the dose of levothyroxine that normalises serum TSH is insufficient to normalise serum T_3. Additionally, serum lipid concentrations, tissue T_3 concentrations,[8] T_3-dependent metabolic markers, and gene expression profiles are not corrected in levothyroxine-treated thyroidectomised rats with normal serum TSH;[7] these variables were corrected with continuous administration of liothyronine plus levothyroxine. For these studies, an animal model was justified because analysis of hypothalamic tissue was required. These findings would seem to explain the mechanism underlying the increase in serum T_4:T_3 ratio in the setting of normal serum TSH in patients given levothyroxine.

A genetic factor, the Thr92Ala D2 polymorphism, was associated with response to thyroid hormone replacement in a large clinical trial in which patients had improved wellbeing with combination therapy compared with those receiving levothyroxine alone.[9] This finding was heralded as a possible explanation for the inability of levothyroxine monotherapy to universally restore euthyroidism. Initial hypotheses had focused on a defect in the Thr92Ala D2 pathway; however, investigators have shown that the enzyme kinetics associated with the Thr92Ala D2 polymorphism are normal.[10,11] Only recently have the cellular abnormalities associated with expression of the Thr92Ala D2 protein been elucidated; this version of the protein has a longer half-life than the wild type, is ectopically localised in the Golgi apparatus, and alters the genetic profile of one area of the human brain in a pattern reminiscent of neurodegenerative disease, without evidence of reduced thyroid hormone signalling.[12] This finding suggests that the Thr92Ala D2 polymorphism might be a potential risk factor for impaired cognition. As the molecular basis for these clinical observations is better characterised, it remains to be confirmed whether carriers of Thr92Ala D2 might benefit from combination therapy. Such data could represent a personalised medicine approach in the treatment of hypothyroidism.

Available clinical evidence suggests that levothyroxine monotherapy does not represent a universally adequate replacement for thyroid function.[1] The rationale underlying the transition to this strategy in the 1970s was not necessarily flawed—levothyroxine provided a

safe, consistent dose and the clinical sequelae of the rise in T_4:T_3 ratio were not understood. Now that the mechanism underlying the inability of levothyroxine monotherapy to universally normalise serum T_3 in patients with normal serum TSH concentrations is understood, it is important that future investigations into the clinical significance of a low serum T_3 concentration or high T_4:T_3 ratio are done. High-quality randomised controlled clinical trials are also justified to assess whether patients with the Thr92Ala D2 polymorphism have a unique response to combination therapy. With continued investigations and evolving clinical insight, we hope that treatment strategies will be devised to help all patients achieve clinical and biochemical euthyroidism.

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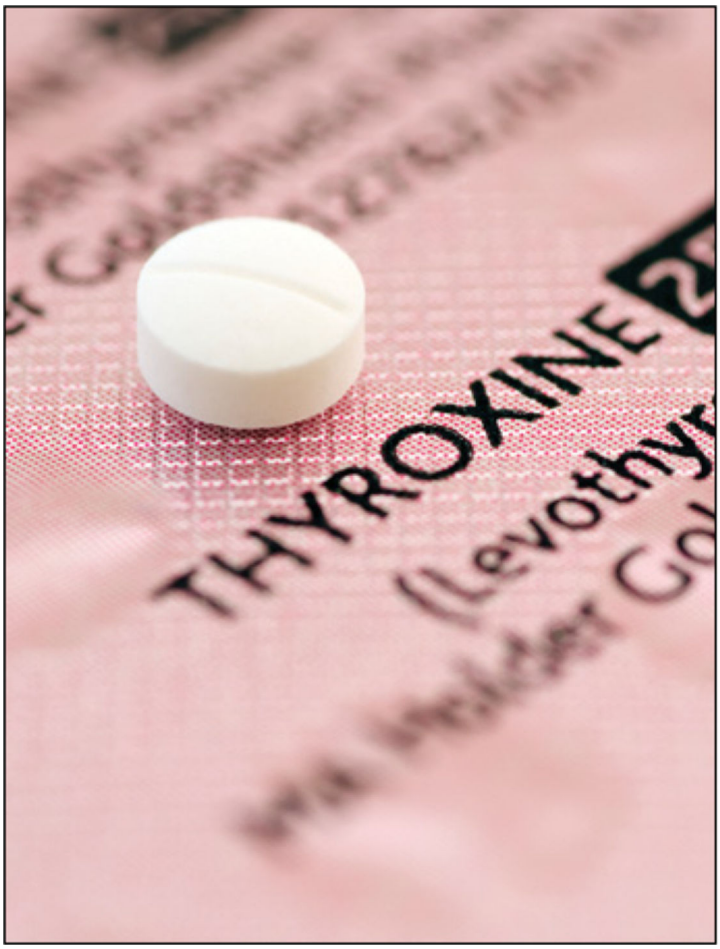

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