New insights into the variable effectiveness of levothyroxine monotherapy for hypothyroidism

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. 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 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$_4$) results in weight loss and improves psychological function in some patients.

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. 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.

In the 1970s, the therapeutic approach changed after the development of the serum thyroid-stimulating hormone (TSH) radioimmunoassay, which showed that typical doses ($200–400$ μg per day of levothyroxine) were supratherapeutic, and the discovery that most circulating $T_3$ is derived via extrathyroidal conversion of
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. 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.

However, after this transition, some patients given levothyroxine (about 12%) were reported to have residual symptoms of hypothyroidism. 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, lipid abnormalities can persist, and the serum $T_4$:$T_3$ ratio is raised, with relatively lower serum $T_3$ concentrations. 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 $T_3$-mediated down-regulation of the type 2 deiodinase (D2). 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, $T_3$-dependent metabolic markers, and gene expression profiles are not corrected in levothyroxine-treated thyroidectomised rats with normal serum TSH; 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. 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. 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. 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. 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.

*Elizabeth A McAninch, Antonio C Bianco
Division of Endocrinology and Metabolism, Rush University Medical Center, Chicago, IL 60612, USA
elizabeth_a_mcaninch@rush.edu

We declare no competing interests.


The marketing of unproven drugs for diabetes and dyslipidaemia in India

India has about one sixth of the worldwide population of patients with diabetes. In 2013, the value of the therapeutics market for type 2 diabetes in Asia-Pacific countries was estimated to be US$6·5 billion, and is expected to grow at a compound annual growth rate of 7·1% between 2013 and 2020 to $10·5 billion.1 This rapid growth is due to the anticipated approval and introduction of new products such as glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and sodium glucose transporter 2 inhibitors, and the increasing prevalence of diabetes in the Asia-Pacific region, especially in India and China.1

Manufacture and sale of oral antidiabetic drugs on the Indian subcontinent is therefore a lucrative business opportunity for the pharmaceutical industry.

The generic pharmaceutical market, a distinctive feature of the Indian drug industry, is among the largest in the world. Notably, in international guidelines for the management of diabetes (most popularly those of the American Diabetes Association and European Association for the Study of Diabetes), consensus only extends as far as lifestyle measures and metformin, leaving substantial scope for national variation. In India, where regulation and monitoring of the pharmaceutical industry is fairly weak, some drugs are being aggressively marketed and promoted, despite less than adequate evidence for their efficacy and safety. For example, promotion of drugs in the media and at medical conferences is often laudatory and based on scant scientific facts.2 In this Comment, we illustrate this issue using three case studies (appendix).

Saroglitazar (marketed as Lipaglyn; Zydus Cadila, Ahmedabad, India), launched in India in September, 2013, is a dual peroxisome proliferator-activated receptor α (PPARα) and PPARγ agonist. The premise is that it might have a favourable effect on both lipid (PPARα agonism) and glycaemic (PPARγ agonism) variables in patients with type 2 diabetes. Overall, the manufactures have not addressed safety issues adequately in human trials. Importantly, pioglitazone (a PPARγ agonist used to treat diabetes) can lead to oedema and weight gain, and fenofibrate (a PPARα agonist used to treat dyslipidaemia) might cause myositis and hepatic dysfunction. Incidentally, phase 3 trials of previous dual PPAR agonist, muraqlitazar, were completed a decade ago. However, in May, 2006, Bristol-Myers Squibb discontinued development of the drug because of an increased...