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The Love-Hate Relationship With Levothyroxine

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Up to 7% of the general population has hypothyroidism,[1] which is corrected with thyroid hormone treatment. The general goals of thyroid hormone replacement are to (1) provide resolution of patient symptoms and hypothyroid signs, including biological and physiologic markers of hypothyroidism; (2) achieve normalization of serum thyroid-stimulating hormone (TSH) concentrations with improvement in circulating thyroid hormone concentrations; and (3) avoid overtreatment (eg, iatrogenic thyrotoxicosis), especially in elderly persons.[2]

Levothyroxine, a synthetically made thyroxine (T4), is the predominant form of thyroid hormone replacement used for patients with hypothyroidism. Let's discuss the important issues surrounding the use of levothyroxine—what are the expected benefits, and why do some people supplement with therapies containing T3 (triiodothyronine)?

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Understanding T4 and T3

In healthy and iodine-sufficient individuals, the majority of thyroid hormone produced is T4, synthesized exclusively by the thyroid gland, with a smaller amount (~20%) of T3, which is produced by the thyroid and in peripheral tissues via deiodination of circulating T4.[3]

In the setting of fluctuating T4 levels, deiodinase activity is tightly regulated to maintain normal T3 levels at the various target tissues.[4] In hypothyroidism, the 5′ deiodinase (type II deiodinase) is activated to allow greater conversion of T4 to the bioactive form of thyroid hormone, T3.

> A genetic variant of the type II deiodinase may result in impaired conversion of T4 to T3.

At target tissues, the small quantity of available circulating free T3 (as the active thyroid hormone) binds to intranuclear thyroid hormone receptors, alters gene expression, and regulates cellular function to determine the tissue's thyroid status.

A genetic variant of the type II deiodinase has been identified in both hypothyroid and euthyroid individuals, the clinical significance of which is unclear but may result in impaired conversion of T4 to T3.[3] This polymorphism is currently not widely available for individual commercial testing, and its significance may not be fully understood even if one were to obtain the test in the clinical setting.

Available research data[5,6] suggest that persons with the polymorphism have very small changes in serum T3 and T4 levels that may not be perceptible through serologic testing, because serum thyroid function tests may remain within the normal range.

Furthermore, levels of T3 in target tissues differ from serum T3 concentrations, and much more research is needed to determine their relative importance with regard to hypothyroid symptoms.[7]

Love for Levothyroxine

Levothyroxine is the recommended form of thyroid hormone for routine treatment of primary hypothyroidism by the American Thyroid Association[2] and the American Association of Clinical Endocrinologists,[8] in part because of its efficacy in resolving the symptoms of hypothyroidism, favorable side-effect profile, ease of administration, good intestinal absorption, long serum half-life, and low cost, as well as our long-term experience of its benefits.[4]

Given the high prevalence of hypothyroidism in the general population, levothyroxine has consistently been the most frequently prescribed medication in the United States over the past several years.[9] In 2016, approximately 123 million prescriptions for levothyroxine were dispensed.[9]

Some patients and clinicians opt for brand-name formulations of synthetic levothyroxine, usually to get a more uniform dose with each lot of the medication dispensed. However, the better consistency of hormone content with branded formulations is mostly a historical concern.

Since 2007, the US Food and Drug Administration (FDA) has required that the synthetic T4 content in pills be within 5% of the stated dose, such that brand-name prescriptions can now be therapeutically interchanged with generic levothyroxine unless explicitly stated against by the prescriber.[10]

When 'Lev' Is Not Enough

However, some patients and clinicians have an interest in replacing T3 along with T4. Reasons include the persistence of hypothyroid symptoms despite achieving biochemically normal serum TSH concentrations with levothyroxine therapy,[11,12] the desire to have more options for therapy,[13,14] or concern about possibly having the type II deiodinase polymorphism.

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Although there is some evidence that patients prefer the use of regimens containing T3,[15] outcomes evaluating quality of life or psychological endpoints have been inconsistent.[8] Some might have a preference for animal-derived, nonsynthetic, natural forms of treatment, such as desiccated thyroid extract (DTE) from bovine and porcine sources, which contain both T3 and T4 at an approximate physiologic ratio of 1:4.

DTE has been in use since at least 1891, before the FDA in 1938 was required to begin regulating the efficacy and safety of new medications in the United States.[10] Thus, DTE formulations are considered "grandfathered" drugs, which technically remain FDA-unapproved for thyroid hormone replacement to this day.[10]

Some Practical Recommendations

Weighing all the factors mentioned above, here is my approach to discussing thyroid hormone replacement.

Women of childbearing age. If the patient is biochemically hypothyroid and thinking about pregnancy, currently pregnant, or lactating, I discuss with her that there is absolutely no role for any therapy containing T3—whether it be synthetic or animal-derived—until pregnancy and lactation are complete.[16]

The reason for this is that adequate maternal thyroid hormone is crucial for normal fetal and neonatal brain development, but the developing central nervous system is relatively impermeable to T3. Thus, the fetus and early brain development depend solely on an appropriate dose of T4 given to the mother.

Other adult patients. For male or nonpregnant, nonlactating female adult patients, I recommend synthetic generic levothyroxine as my initial choice of treatment. Costs of generic formulations are the most favorable, and in most cases, the available doses (with an occasional extra or skipped half-tablet per week) are able to achieve the target serum TSH concentration (or serum free T4 in those with central hypothyroidism). Because primary hypothyroidism is the most common indication for thyroid hormone replacement, the rest of our discussion will focus on this.

To optimize intestinal thyroid hormone absorption, patients should be counseled to take their medication on an empty stomach, ideally a minimum of 30-60 minutes before eating breakfast, drinking anything other than water, or taking other medications or supplements.

People with an unstable serum TSH concentration. If a reasonable trial (ie, 3-6 months) of titrating the dose of generic levothyroxine is unable to produce a stable serum TSH concentration, or the patient has persistently large fluctuations in serum TSH despite taking a stable dose of the medication as instructed, I offer a screen for celiac disease. *Helicobacter pylori* infection and atrophic gastritis may also be considered, because these may be relatively asymptomatic in some individuals.

If the screen is negative, moving to a brand-name formulation, such as Synthroid®, may be reasonable, although both generic and brand-name synthetic formulations should in theory contain a uniform range of variation.

If a reasonable period of treatment with Synthroid fails to achieve a stable serum TSH concentration or the celiac screen is positive, I discuss the potential benefits of brand-name Tirosint®. Although more costly, Tirosint is a gel capsule of synthetic levothyroxine that contains no sugars, dyes, alcohols, gluten, lactose, or other additives.

At the time of this writing, the lowest available prices for a bulk supply of common thyroid hormone formulations are $0.20/tablet for synthetic generic levothyroxine,[17] $1.02/tablet for brand-name Synthroid,[18] and $4.76/tablet for brand-name Tirosint.[19]

Adding T3 Therapy

Desiccated thyroid extracts. Patients may have a desire to try some component of T3 in their thyroid hormone replacement regimen, particularly those who remain with hypothyroid symptoms despite achieving a normal serum TSH concentration.

I discuss with these patients that the physiologic ratio of T3:T4 secretion by the thyroid gland in humans is approximately 1:14.[4] In contrast, the makeup of DTE is approximately 1:4; thus, there is a relatively higher proportion of T3 than T4 in animal-derived sources of thyroid hormone.

I also discuss the fact that although DTE has been used for much longer than synthetic formulations, there is a lack of high-quality, controlled studies to demonstrate that DTE is superior to synthetic levothyroxine.

Synthetic T3+T4 combination therapy. Given the potential risks for cardiac arrhythmias and worsened bone health associated with perhaps any T3 therapy, I offer two separate prescriptions for synthetic T3 and T4 as the initial step to hypothyroid individuals who strongly prefer trying T3. To best replicate the physiologic ratio of T3:T4 production, the separate prescriptions should be about 1:13-1:20 that of T3 to T4.[20]

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T3 also has a much shorter half-life than T4; thus, twice-daily dosing may be best. For example, an individual who has been taking 112 µg of synthetic T4 once daily and wants to try incorporating T3 would be prescribed 5 µg of synthetic T3 twice daily combined with 100 µg of synthetic T4 to reach a total of 110 µg of thyroid hormone per day, which is as close to the previous weight-based dose as possible.

The full replacement dose of thyroid hormone is approximately 1.6 µg/kg/day, although lower doses should be initiated in elderly persons or those with cardiac disease.

For patients who decide to pursue synthetic T3+T4 combination therapy or who strongly prefer DTE, I make sure that they understand all of the points discussed above before prescribing a 3- to 6-month trial. At the conclusion of the trial, we review their symptoms and discuss whether they improved, did not change, or worsened before deciding whether to continue the therapy.

Finally, I discuss with patients that although hypothyroidism is one of the most common medical conditions, much about treatment remains incompletely understood and my recommendations are based on the scientific evidence currently available. Rigorous, long-term, well-done studies are needed to better examine such questions as why certain patients with hypothyroidism remain symptomatic despite normalization of their serum TSH concentration, the clinical significance of the deiodinase II polymorphism, and the potential risks associated with chronic T3 therapy.

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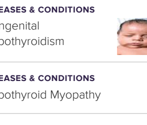

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