

Thyroxine Monotherapy After Thyroidectomy Coming Full Circle

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It may be the experience of many clinicians, as it has been ours, that a very small group of patients with hypothyroidism are not entirely well on thyroxine replacement alone.¹

THE CONCEPT OF HORMONE REPLACEMENT THERAPY is commonly credited to Brown-Sequard, who in 1889 at age 72 years injected himself with an extract of dog testicles and noted enhanced vitality and mental acuity.² The concept of “internal secretion” arose from these experiments, and soon thereafter Murray successfully treated myxedema with “juice” extracted from sheep thyroid glands.³ Replacement therapy with virtually all clinically relevant hormones has been possible since the middle of the 20th century. The challenge, however, is to administer these hormones in deficiency states in a way that precisely replicates the complex manner in which they are endogenously secreted. Insulin replacement in patients with type 1 diabetes is an obvious example of this difficulty. Even the most sophisticated patient using an external insulin pump and continuous glucose monitoring has difficulty mimicking normal insulin secretion without being subjected to potentially dangerous hypoglycemia.

In contrast with the difficulties in replacing protein hormones like insulin that have complex secretory patterns, substitution therapy with small molecules like steroid hormones and thyroxine (T_4) is thought to be relatively simple. However, this is clearly not the case, given the commonly observed adverse effects of hormone excess or insufficiency when clinicians attempt to treat hypogonadism with sex steroids, adrenal insufficiency with glucocorticoids, and hypothyroidism with T_4 . One might think reduplicating normal thyroid physiology with T_4 therapy would be simple, because T_4 and triiodothyronine (T_3) serum levels do not display pulsatility or have a circadian rhythm.⁴ Why then does the treatment of hypothyroidism continue to be the subject of so much clinical investigation and continue to engender so much contention?

The controversy surrounding thyroid hormone therapy stems, in part, from important aspects of normal thyroid physiology. It is T_3 rather than T_4 that mediates thyroid hormone action by binding to nuclear thyroid hormone receptors present in virtually all tissues. Serum T_3 has 2 sources: approximately 20% of daily T_3 secretion comes directly from the thyroid and the other 80% is derived from the mono-deiodination of T_4 to activate T_3 in peripheral tissues.⁵ Thus,

T_4 serves as a prohormone for T_3 , having essentially no intrinsic biological activity of its own. Specific selenoprotein deiodinases catalyze the deiodination process; variations in their activity may determine in part the serum levels of T_4 , T_3 , and thyroid-stimulating hormone (TSH) in each individual.^{6,7} The major source of T_3 within peripheral tissues is from the circulating T_3 pool, although a variable portion arises from locally deiodinated T_4 within each tissue.⁸ In adults, serum T_3 levels are also regulated by changes in deiodinase activity brought about by starvation, overfeeding, acute and chronic illness, and certain drugs.⁵

Given the complex regulation of T_4 conversion to T_3 , it is theoretically possible that replacement therapy with pure T_4 may not precisely reduplicate a thyroid hormonal milieu that involves 2 hormones, not 1. Although studies performed several decades ago showed clearly that normal serum T_3 levels can be achieved with pure T_4 ,⁹ there has been lingering doubt about whether the serum T_3 levels that are attained with T_4 therapy are truly normal for the individual patient. This uncertainty led to studies exploring combination T_4 plus T_3 therapy.^{1,10,11} Experiments in thyroidectomized rats showing that T_4 therapy alone could not completely restore tissue T_3 levels to normal further fueled misgivings about T_4 therapy's ability to match normal physiology.¹² However, except for 2 studies conducted by the same group of investigators,^{10,11} none of the numerous other randomized controlled studies comparing T_4 vs T_4/T_3 combinations has shown any benefit of combined treatment to improve hypothyroid symptoms or sense of well-being (summarized in a meta-analysis¹³). Some patients, especially those made mildly hyperthyroid by T_3 therapy,¹⁴ preferred combined T_4/T_3 therapy over pure T_4 , but patients in general had no preference for one treatment over another.^{13,15} It has also been suggested that patients with thyroidectomy might benefit more from combined T_4/T_3 treatment than patients with spontaneous hypothyroidism who usually have some remaining endogenous thyroid function,¹⁶ but this also could not be confirmed.¹³

The reasons for the failure of virtually all studies to show the benefit of T_4/T_3 therapy have been variously ascribed to the insensitivity of the instruments used to assess well-being, incorrect T_3 dosing, or the relatively short half-life of T_3 leading to fluctuating unphysiological serum T_3 levels. To ad-

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dress the latter objection, a slow-release T₃ preparation has been developed¹⁷ but is not available commercially. This notion has also led to the availability of “long-acting” T₃ preparations from compounding pharmacies; these preparations do not have US Food and Drug Administration approval and have been associated with severe iatrogenic thyrotoxicosis due to errors in the compounding process.¹⁸

It is against this backdrop that Jonklaas and colleagues¹⁹ performed a rather simple but important proof-of-principle study, published in this issue of *JAMA*. These investigators asked whether T₄ therapy alone could restore serum T₃ values to normal. However, in contrast with older studies that have shown that pure T₄ therapy returned serum T₃ levels to within the broad reference range of normal,⁹ Jonklaas et al¹⁹ investigated whether serum T₃ levels could be returned to the same level in an individual person that it had been before the development of hypothyroidism. In this study, patients about to undergo total thyroidectomy for goiter or a suspicious or malignant thyroid nodule had thyroid function testing performed on 2 occasions 1 week apart before surgery. Thyroid hormone levels were then remeasured 16 weeks after surgery while patients were receiving T₄ therapy. Participants received a dose that either normalized the serum TSH if they proved to have benign disease, or one that suppressed the serum TSH if they had thyroid cancer.²⁰

The authors found that the postoperative serum T₃ levels, with a few notable exceptions, were similar to the mean of the 2 preoperative values, as long as the serum TSH was within or below the normal range. As shown by another study,⁹ serum free T₄ levels were significantly higher postoperatively than they had been preoperatively, likely a necessary requirement in thyroidectomized individuals to generate sufficient T₃ to replace the 20% of normal daily T₃ production that arises from the thyroid gland itself. However, Jonklaas et al¹⁹ did not assess preoperative and postoperative mood, cognitive function, well-being, or hypothyroid symptoms in the participants in their study. This might have been possible using control groups who had undergone similar nonthyroidal surgery (eg, parathyroidectomy), as well as other controls with a new diagnosis of a non-life-threatening form of cancer.

Despite the demonstration that normal serum T₃ levels can be achieved with pure T₄ therapy,¹⁹ and a small cohort study showing normal quality of life in patients treated with T₄,²¹ a number of recent articles show that some patients with hypothyroidism who were treated with T₄ have worse physical and psychological well-being,²²⁻²⁴ cognitive function,^{23,24} and lower mood²⁴ compared with a control population. How is it possible to account for the fact that participants in these studies, who were biochemically euthyroid as judged by normal serum TSH, free T₄, and T₃ levels, continued to have significant morbidity from their disease? There are 2 leading possibilities: replacement therapy with T₄ imperfectly replaces the normal thyroid hormonal milieu or patients with hypothyroidism score lower on quality of life scales because they per-

ceive themselves to have a chronic illness. A third less likely hypothesis is that patients with Hashimoto thyroiditis, the leading cause of hypothyroidism, have low mood and other somatic complaints because of an underlying autoimmune diathesis unrelated to their thyroid function.²⁵

It is unknown why some patients do not feel well even when their thyroid function is normal. Among the 50 patients studied by Jonklaas et al,¹⁹ there were 6 patients whose serum T₃ levels, for whatever reason, appeared to be much lower postoperatively than their T₃ levels had been preoperatively. One might speculate that some patients, perhaps approximately 10%, might potentially benefit from T₃ supplementation after thyroidectomy. It would, therefore, be of interest to repeat the study performed by Jonklaas et al¹⁹ to identify those few patients whose postoperative T₃ is much lower than it had been before surgery. These patients would then be randomized to receive combined T₄/T₃ therapy, a higher dose of T₄ monotherapy, or no change in their current T₄ dose. They would then be tested to see whether any change in their regimen resulted in improvements in mood, symptoms, cognitive function, or quality of life. Approximately 75 000 patients undergo thyroidectomy annually in the United States,²⁶ so the study could be performed quite easily. However, the data of Jonklaas et al¹⁹ seem to lay to rest, once and for all, the notion that T₄ therapy alone is inadequate to replace serum T₃ levels back to normal in the overwhelming majority of patients.

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Mass Antibiotic Administration for Eradication of Ocular *Chlamydia trachomatis*

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TRACHOMA, A CHRONIC KERATOCONJUNCTIVITIS CAUSED by the bacterium *Chlamydia trachomatis*, is the leading infectious cause of blindness in the world. Until the 20th century it was endemic in Europe and North America, and eye hospitals established in the 19th century were founded to treat trachoma. As living standards improved, trachoma disappeared from the developed world, but it remains endemic in poor rural communities in some 55 countries, most of them in Africa and Asia. The World Health Organization (WHO) estimates suggest that more than 100 million individuals have the disease, of whom 7.6 million have potentially blinding sequelae, and 1.3 million are blind.^{1,2}

In its early stages, mainly seen in children, trachoma causes few symptoms, but clinical signs may be observed in the conjunctiva of the everted upper eyelid, which takes on a roughened appearance due to the presence of subconjunctival lymphoid follicles. In older children and adults, repeated episodes of infection eventually lead to conjunctival fibrosis, which may distort the lid margin and cause the lashes to rub against the cornea (trichiasis). This ultimately causes blindness due to corneal opacity.³

In trachoma-endemic communities, *C trachomatis* infection is spread from eye to eye and from person to person by fingers, flies, and shared cloths or towels. Trachoma can be controlled by improvements in living standards and per-

sonal hygiene that reduce transmission or by mass treatment with antibiotics to eliminate the reservoir of infection. Until the 1990s, tetracycline ointment applied to the conjunctiva twice daily for 6 weeks was the recommended treatment, but it was difficult to persuade entire communities to adhere to this regimen.

A 1993 study in the Republic of The Gambia showed single-dose oral azithromycin was sufficient to cure ocular *C trachomatis* infection,⁴ an advance that enabled WHO to establish a global alliance in 1997 for the elimination of blinding trachoma by the year 2020.⁵ ("Elimination" in this context implies reduction in the prevalence of disease to the point at which it ceases to be a public health problem, not reduction in the prevalence of disease or infection to zero.) The manufacturer of azithromycin agreed to donate the drug for trachoma control in selected countries, following the example of another manufacturer that donated ivermectin for the control of river blindness due to the parasite *Onchocerca volvulus*. To date, 135 million doses of azithromycin have been given or pledged.⁶

The strategy for trachoma elimination is based on an approach reflected in the acronym SAFE: Surgery for the correction of trichiasis, Antibiotics for the elimination of *C trachomatis* infection, Facial cleanliness, and Environmental improvement to reduce transmission. Health education programs to encourage face washing and efforts to control fly populations through the provision of latrines or by insect-

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