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Combined T_4 and T_3 Therapy—Back to the Drawing Board

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"Hormone replacement therapy" was originally reported by Murray, who in 1891 described the successful treatment of myxedema with injections of sheep thyroid extract.[1] By 1898, therapy for this chronic, severely debilitating condition was hailed as "unparalleled by anything in the whole range of curative measures" by Osler.[2] Seven decades later, desiccated thyroid was characterized by the standard thyroid textbook of the day as ". . . as perfect a form of therapy as any known to medicine. . . ."[3] With the subsequent identification of thyroxine (T_4) and triiodothyronine (T_3) as the 2 major thyroid hormones, it was assumed that replacement therapies containing both compounds were more physiological than treatment with either alone. Thus, despite the availability of synthetic T_4 in the early 1960s, the prescription of desiccated animal thyroid or synthetic combinations of T_4 and T_3 continued well into the 1970s.

However, following the report in 1970 that T_4 was deiodinated in peripheral tissues to form the more biologically active T_3,[4] it was realized that T_4 monotherapy would yield normal circulating levels of both T_4 *and* T_3.[5] This fact, coupled with concerns about iatrogenic hyperthyroidism from a surge in serum T_3 levels following the ingestion of T_3-containing preparations, as well as variability in the hormonal content of desiccated thyroid, led to a progressive decrease in their use throughout the 1970s and 1980s.[6] Review articles and guidelines on thyroid hormone therapy written in the 1990s all recommend synthetic T_4 alone as the treatment of choice for patients with hypothyroidism.[7-10] This advice was supported by a small study showing that patients treated with synthetic T_4 alone have a quality of life that is similar to that of individuals without a history of thyroid disease.[11]

Nevertheless, virtually all primary care physicians have in their practices hypothyroid patients with persistent symptoms, despite adequate doses of T_4 that are "proven" to be sufficient by normal serum thyroid hormone and thyroid-stimulating hormone (TSH [thyrotropin]) concentrations. This all too frequent scenario was quantified in a recent study showing that hypothyroid patients treated with T_4 alone do not score as well on validated scales of psychological well-being and have more hypothyroid symptoms compared with euthyroid controls, despite having normal thyroid function results.[12] Whether this finding represents the inability of T_4 monotherapy to reproduce the exact hormonal milieu of a euthyroid individual or whether it is the result of having been "labeled" as having an illness (ie, hypothyroidism) remains uncertain.[13,14]

See also p 2952.

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The use of T_4 monotherapy as the treatment of choice for hypothyroidism was challenged in 1999 by a study comparing T_4 alone with a combination of T_4 and T_3.[15] In a randomized, blinded crossover design, hypothyroid patients taking the combination of T_4 and T_3 for 5 weeks had improved cognitive performance, mood, and physical well-being compared with a similar period when they received T_4 alone. A post hoc analysis of these data suggested that most of the improvement occurred in athyreotic thyroid cancer patients rather than in patients with autoimmune thyroid disease, who presumably had some residual thyroid function.[16] The authors proposed that a combination of T_4 and T_3 might be a more physiological form of therapy than T_4 alone, particularly in individuals without a source of endogenous thyroid hormone. This conclusion has some experimental support; in thyroidectomized rats, T_4 and T_3 concentrations in a variety of tissues cannot be normalized by any dose of T_4, but they can be restored to normal with a combination of both hormones.[17] The only exception is the brain, where, because of a very active central nervous system deiodinase, T_4 treatment alone yields normal brain levels of T_3 over a wide range of administered T_4 doses.[18]

The idea that T_4 monotherapy might be a less effective treatment than a combination of T_4 and T_3 was greeted with skepticism by some.[19] On the other hand, symptomatic patients felt a sense of vindication, particularly those who hoped that their persistent hypothyroid symptoms might finally be alleviated with T_4 and T_3 combination treatments considered by many physicians to be obsolete, ie, "natural" desiccated thyroid or combinations of synthetic T_4 plus T_3.[20]

In this issue of THE JOURNAL, Clyde and colleagues[21] have attempted to reproduce the results that were reported in 1999, using a randomized parallel-group study design. These investigators intentionally avoided the crossover design used in the original study to eliminate the possibility that performance on psychometric testing could be influenced by a "practice effect." Forty-six hypothyroid patients were enrolled, most of whom had thyroid failure from autoimmune (Hashimoto) thyroiditis. They were randomized to continue to receive either their current dose of T_4 or to receive 50 µg less than their current T_4 dose, the deficit replaced by T_3 at a dose of 7.5 µg twice daily (equivalent metabolically to 50 µg of T_4). The authors were careful to adjust the T_4 doses in each group to maintain normal TSH levels as best they could throughout the 4-month observation period. At the end of the study, there were no differences between the 2 groups in body weight, blood pressure, or lipid levels. There were also no significant differences in any of the standardized tests that were administered, including a validated hypothyroid symptom scale and a battery of neurocognitive tests.

Interpretation of these negative results is made difficult by the significant improvement in the hypothyroid symptom score in the "control" group, who simply continued to take their usual dose of T_4. Why this would be so is uncertain, but it emphasizes the power of the placebo effect. Another problem with the current study, as well as with the 1999 study, is that the doses of T_4 and T_3 used do not replicate the ratio of T_4 to T_3 secreted by the normal thyroid gland (14:1 molar ratio).[22] Nevertheless, free T_4, T_3, and TSH levels were normal throughout the study in the majority of patients. This is important, since serum TSH levels were subnormal in some patients in the original study, suggesting that they were made iatrogenically hyperthyroid on the T_4 plus T_3 combination, a circumstance that has been associated experimentally with an improved sense of well-being.[23]

Within the last 2 months, 2 additional studies have been published that also failed to confirm the benefits of combined T_4 and T_3 therapy.[24,25] In one report, 110 hypothyroid patients were randomized in a crossover design to receive their usual T_4 dosage or 50 µg less than their usual dosage of T_4 plus 10 µg of T_3.[24] Each treatment period lasted for 10 weeks, with a 4-week washout between treatment periods. No changes in cognitive function, quality of life, or hypothyroid symptoms were observed. In the other report, 40 hypothyroid individuals with depressive symptoms who were receiving stable doses of T_4 were randomized to continue to receive their chronic dose of T_4 or one half of their T_4 dose plus 12.5 µg of T_3 twice a day.[25] No improvements in hypothyroid symptoms or mood were noted after 15 weeks of observation.

Given these 3 negative studies, it would appear, at least superficially, that the putative beneficial role of combined T_4 plus T_3 therapy cannot be substantiated. However, none of these studies enrolled a large number of patients with surgical or postablative hypothyroidism. Therefore, it remains a possibility that patients with no endogenous thyroid function may benefit from combined therapy, even if patients with residual thyroid secretory capacity do not, as suggested by Bunevicius and Prange.[16] Also, none of the 4 published studies used a T_4 plus T_3 combination that precisely matched the normal hormonal secretion of the thyroid gland. Finally, a long-acting or "slow-release" form of T_3, which does not currently exist commercially, would be required to mimic normal physiological endogenous T_3 production. Therefore, until studies are performed in thyroidectomized individuals using a combination of drugs formulated at the correct ratio containing a slow-release form of T_3, the hypothesis that combination therapy might be superior to T_4 monotherapy cannot be completely rejected.

From a practical point of view, autoimmune thyroiditis is the cause of hypothyroidism in the majority of patients living in iodine-sufficient areas of the world.[26] Given the negative results from the study by Clyde et al[21] and the other 2 recently published controlled trials,[24,25] combination treatment cannot be recommended. Treatment of patients with thyroid failure who have persistent hypothyroid or depressive symptoms while taking an adequate dose of T_4 (defined by serum TSH levels between 0.5 and 2.5 mIU/L[27]) re-

mains a major challenge. However, combined T_4 plus T_3 is not the answer.

After more than a century of successful treatment of hypothyroidism, it is fascinating that such seemingly simple hormonal replacement therapy would be the subject of so much continuing controversy. Before another century elapses, let us hope that the optimum treatment for all hypothyroid patients will be revealed by additional well-designed clinical trials using novel thyroid hormone preparations that precisely mirror normal thyroid physiology. Then, and only then, will thyroid replacement be ". . . as perfect a form of therapy as any known to medicine."[3]

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