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MINI REVIEW

Hypothyroidism Revisited: Defining the Subgroups on Optimal Thyroxine Replacement Who Have Persistent Symptoms

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Abstract

Hypothyroid patients on optimal replacement but with persisting symptoms continue to be a challenge for their treating physicians. This commentary is based on a substantial clinical experience with this subpopulation.

With the focus on laboratory tests to achieve a diagnosis, aspects of the traditional clinical examination have been overlooked. In particular the routine testing of tendon reflexes has lapsed. A delay in the relaxation phase of tendon reflexes (hypothyroid hyporeflexia), once known as a positive Woltman's sign, has long been the hallmark sign of overt hypothyroidism. The majority will do well when treated with appropriate thyroxine replacement.

This sign is also positive in those patients on thyroxine (T4) with normal T4 and Thyrotropin (TSH) levels if they have symptomatic intracellular Triiodothyronine (T3) deficiency. These patients will respond promptly to combination therapy (T4+T3). This subgroup accounts for more than half of the thyroxine-dissatisfied population. They should be described as having **T3-hypothyroidism**.

The remaining symptomatic patients with normal reflexes have unrelated conditions. A small clearly defined subgroup with autoimmune symptoms and very high anti-Thyroperoxidase (anti-TPO) antibodies (>10 times the upper limit of normal) will respond to total thyroidectomy with a marked improvement that is maintained for 3-5 years. They can be categorised as having **TPO-toxic hypothyroidism**.

Many patients can have persistent symptoms because of psycho-social issues and the burden of having a chronic disease. They have **In-denial-hypothyroidism**. There are very rare cases of **Thyroxine allergy**.

This nomenclature should assist physicians in their diagnosis and management of the several subgroups of patients on thyroxine with persistent symptoms.

Introduction

There is a crisis in the management of hypothyroid patients who remain symptomatic after appropriate thyroxine replacement therapy. They have normal levels of plasma Thyroxine (T4) and Thyrotropin (TSH). There are no clear guidelines describing this population, nor is there as yet any useful descriptive terminology to categorise the subgroups. Initial

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estimates that 5 to 10% of hypothyroid patients had persisting symptoms [1] increased to 15% [2], and most recently to 15-20% [3]. There are no reliable epidemiological data to confirm these estimates.

The subject has occasioned much cross-talk without resolution. The focus has been on combination therapy, that is, the addition of Triiodothyronine (T3) to Thyroxine (T4). In 2012 the European Thyroid Association suggested that combined therapy could be used as an experimental approach for accredited internists or endocrinologists [1]. A more recent email survey of American Thyroid Association members who routinely prescribed therapy for hypothyroidism in 2017 [4] indicated that approximately one third of these physicians were willing to prescribe treatment additional to T4 by adding triiodothyronine or by switching to Desiccated Thyroid Extract (DTE). Clearly there is a need for guidelines that will inform all doctors who treat hypothyroidism.

In 1970 the earliest report of a positive response to T4+T3 therapy described a small number of hypothyroid patients who were unwell on T4 alone and had a rapid subjective improvement to the addition of T3 [5]. In 1999 the seminal trial of Bunevicius and colleagues reignited considerable interest in combination therapy [6]. Their randomised crossover study of T4-plus-placebo versus T4+T3 showed improved mood and neuropsychological function in hypothyroid patients when taking combination therapy. The report has been criticised because of its borderline significance and concern about the single daily dosage of T3 (12.5 mcg) which was considered non-physiological. But the main flaw of this clinical trial was that the selection of hypothyroid patients was indiscriminate. Selection should have been confined to those patients with persistent symptoms. An abundance of similar clinical trials followed this report. All of the trials selected hypothyroid patients without reference to the presence or absence of symptoms. It is not surprising that the results were almost entirely negative. By 2021, 18 trials that involved 1563 participants provided data for meta-analysis [7]. The conclusion was that there was no difference in clinical outcomes for combination therapy in the general population of hypothyroid patients. .

By 2021 the American, British, and European Thyroid Associations had recognised the flawed selection process and in a consensus document unanimously recommended that future trials must include only patients dissatisfied with T4 therapy [8].

There are four case reports available in the literature outlining a positive response to combination therapy:

1). **2011:** A nuclear medicine physician who was hypothyroid after radio-iodine therapy for Graves' disease reported a dramatic response when triiodothyronine was added to her thyroxine regimen. She stated that there is no question that a subgroup of patients perceive an improved in quality of life with combination therapy [9].

2). **2020:** A female with long-standing hypothyroidism with persistent symptoms on T4 sought alternative treatment. The fifth doctor that she attended recommended adding T3. Within two weeks her 10-year clinical depression disappeared, she "felt great", and she lost a considerable amount of weight [10].

3). **2020:** A female with post-thyroidectomy hypothyroidism on thyroxine complained of severe mental clouding, weight gain, and fatigue. She had delayed relaxation of her tendon reflexes. With the addition of Triiodothyronine (T3) 10 mcg twice daily to her thyroxine 100 mcg daily, her symptoms vanished and her reflexes became normal [11].

4). **2023:** A 40-year-old female with post-surgical hypothyroidism on 125 mcg T4 daily had persisting fatigue, brain fog and weight gain. Her compliance with medications was checked. Autoimmune diseases were excluded. Her thyroxine dosage was increased so as to achieve low normal TSH levels. This caused palpitations, insomnia, and nervousness and a suppressed TSH. A trial of 5 mcg T3 twice daily was commenced with the reduction of her T4 dosage from 125 mcg to 100 mcg daily. Her symptoms resolved apart from persistent weight gain [3].

Collectively these cases reflect the extent of distress experienced by some patients, and their unequivocal response to low doses of T3 administered twice daily. Case 3 is unique in describing the positive clinical sign of delayed tendon reflexes. Case 4 gives a good account of the stepwise clinical approach that is appropriate for these patients.

A considerable clinical experience indicates that those dissatisfied patients on thyroxine who

respond to the introduction of T3 can be identified by the presence of delayed relaxation of tendon reflexes [11]. Hypothyroid-induced hyporeflexia [12] - a positive Woltman's sign [13,14] - is typical of overt hypothyroidism, but it is also seen in intra-cellular T3 deficiency. I believe that this condition is present in more than half of the total population of T4-dissatisfied hypothyroid patients. A convenient designation for this subgroup is that they have **T3-hypothyroidism**, an eponym which describes both the condition and its treatment.

Thyroxine (T4) is the major thyroid hormone in the blood and thyroid gland, but it circulates as an inert pro-hormone with no intrinsic peripheral activity until converted to intra-cellular Triiodothyronine (T3). T3 is responsible for most, if not all, of the physiological effects of thyroid hormone in peripheral tissues [15,16]. Knowing this we should *expect* to see end-organ evidence of intracellular T3 deficiency, that is, abnormal tendon reflexes, in those patients who respond to combination therapy. A commonly inherited variation in the DIO2 deiodinase gene is associated with an enhanced response to combination therapy in one study, and this requires replication [17].

In the 2012 ATA/AACE guidelines [18] the authors comment that early as well as more recent studies strongly correlate the degree of hypothyroidism with ankle reflex relaxation time, 'a measure rarely used in current clinical practice today'. Why should this be? A generation of Endocrinologists has overlooked the importance of a simple clinical sign in relation to identifying T3-hypothyroidism. Formal testing of reflexes may be a thing of the past, now that physicians are empowered with accurate blood tests to confirm diagnosis of hypothyroidism. Possibly the procedure of examining ankle jerks is a disincentive to physicians. But this neglected clinical sign is the key to combination therapy. A small clinical trial will quickly resolve the combination therapy controversy. Within the group of thyroxine-dissatisfied patients, selecting those with the typical abnormal reflexes should require only 12 to 16 patients for a trial that should yield a positive result within three to six months [19].

There are patients on thyroxine with persisting symptoms but with normal reflexes who have impaired health due to extra-thyroidal causes unrelated to the hypothyroidism per se. Hashimoto's disease patients can have prominent autoimmune disease symptoms including chronic fatigue, irritability, joint and muscle tenderness, dry mouth and eyes, and poor sleep quality [20,21]. A carefully conducted surgical study of 150 such patients with extremely high anti-Thyroperoxidase (anti-TPO) antibody titres > 1000 IU/ml (normal < 100 IU/ml) showed that total thyroidectomy achieved a remarkable resolution of symptoms compared to the control group on standard medical treatment [22]. Sham surgery for the controls was not conducted for ethical reasons. In any case, sham surgery would not have masked the persistence of goitre in these patients. Five year follow-up of the surgical group [23] indicates that the marked improvement is maintained, making placebo responses unlikely. Ten patients (7%) in the surgical group had permanent complications including recurrent laryngeal nerve paralysis and/or hypoparathyroidism. This important, well-defined category of dissatisfied patients has not been sufficiently acknowledged in position statements or guidelines. These patients could be designated as having TPO-toxic hypothyroidism.

The THESIS Collaboration ('Treatment of Hypothyroidism in Europe by Specialists') reports the opinions of thyroid specialists explaining why patients on T4 with normal TSH have persisting symptoms [24]. These are listed here in descending order of frequency: Psychosocial factors, comorbidities, patients' unrealistic expectations, chronic fatigue syndrome, the burden of chronic disease, and the burden of having to take medication, presence of underlying inflammation due to autoimmunity, and inability of T4 to restore normal physiology. If one excludes the latter two categories (that must include TPO-toxic hypothyroidism and T3-hypothyroidism), the remaining patients will require understanding supportive care. They could be labelled as having **In-denial-hypothyroidism**.

Finally thyroxine hypersensivity: Most often these are adverse drug reactions due to excessive dosage. True hypersensitivity is extremely rare [25,26] and is associated with skin rash, urticaria, pruritis, and angioedema. These patients have **Thyroxine-allergy**.

The approach to diagnosing and treating hypothyroidism has improved immensely over a lifetime. Most patients do extremely well on thyroxine monotherapy. It is time to focus on the subpopulation of patients with persistent symptoms and enable their appropriate evaluation and treatment. A delayed relaxation phase of the tendon reflexes indicates

florid hypothyroidism, but it can also indicate an intracellular T3 deficiency which will respond to combination therapy. The plantar tap or alternative methods to elicit Woltman's sign should be re-introduced as an essential clinical skill to identify these patients.

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Conflict of Interest

There is no conflict of interest to declare.

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