Hormone Replacement Therapy in the Geriatric Patient: Current State of the Evidence and Questions for the Future—Estrogen, Progesterone, Testosterone, and Thyroid Hormone Augmentation in Geriatric Clinical Practice: Part 2*

* Thyroid section

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KEYWORDS
• Thyroid hormone • T_3 • T_4 • TSH • Hypothyroidism
• Reverse T3 • Pituitary dysfunction

THYROID

Hypothyroidism is a common disorder characterized by inadequate amounts of thyroid hormones available to meet the need for thyroid at the cellular level. Typical symptoms of hypothyroidism include fatigue, weight gain/obesity, depression, cold extremities, thin/friable nails, muscle aches, headaches, decreased libido, low basal body temperature (consistently below 98.6°F), weakness, cold intolerance, loss of temporal eyebrow hair, water retention, and dry skin.

The incidence of thyroid dysfunction with its attendant cellular thyroid deficiency increases significantly with age.[63–66] Because many of the symptoms attributable to subclinical hypothyroidism are often seen with normal aging, significant cellular hypothyroidism often goes undetected and subsequently untreated.

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Historically, elevated thyroid-stimulating hormone (TSH) with normal T4 and T3 levels was considered compensated hypothyroidism and thus euthyroid in need of no treatment. Studies have demonstrated that, despite the normal T3 and T4 levels, subclinical hypothyroidism is often associated with significant symptoms and an increased risk of morbidity and mortality. Compensated hypothyroidism and subclinical hypothyroidism are becoming misnomers, because they present clinically significant signs and symptoms of hypothyroidism that do benefit from correct treatment.[67] The symptoms studied and directly connected to hypothyroidism include neuromuscular dysfunction,[68] depression,[69,70] memory loss and cognitive impairment,[66,71] high cholesterol levels,[72] deteriorating general function,[65] skeletal muscle abnormalities,[73] decreased exercise tolerance and myocardial dysfunction.[74–77] Significant improvement in symptoms occurs when thyroid hormone supplementation is instituted (note increased use of T3 in addition to T4).[78–80] In aging patients, low thyroid mimics normal aging and other conditions as noted.[81–93]

Diagnosis

TSH, a pituitary hormone whose function is to stimulate thyroid hormone production by the thyroid gland, is considered the only diagnostic test for hypothyroidism and the most sensitive marker of peripheral tissue availability of thyroid hormones. We have been trained to implicitly assume that TSH levels within the normal range indicate a euthyroid condition necessitating no further testing or clinical substantiation for the condition. To date, in most clinical practices in the United States, hypothyroidism is diagnosed solely when the TSH level is consistently above the upper limit of normal of 4.0 to 5.0 ng/dL. Unfortunately, this assumption no longer holds true when we delve into the domain of thyroid function in the aging population. With significant physiologic stress, illness, or inflammation there is demonstrable suppression of TSH, making the TSH test unreliable because it stays within normal range failing to reflect true thyroid status.[82,94] Under these conditions, tissue T3 levels are diminished owing to a reduction in uptake of T4, leading to decreasing T4 to T3 conversion.[82,83,95] Consequently, serum measurements reflect increased serum T4 levels and reduced TSH levels despite the absence of sufficient thyroid hormone in the peripheral tissues.

As a result, when relying on serum tests only, clinicians do not treat patients presenting with this thyroid picture assuming they are euthyroid (normal T3, low T4, and normal TSH). Unfortunately, this situation limits our understanding of the physiologic changes occurring at the cellular level leaving a gaping hole and missing the opportunity to help the patients' condition.[83,84]

Aging and chronic illness also affect the hypothalamic–pituitary–thyroid– cellular axis. Both states tend to present with decreased TSH, decreased conversion of T4 to T3 in the cell, and increased reverse *T3* levels.[84,85] In these cases, serum reverse T3 levels may be a useful indicator of low tissue T3 levels because diminished cellular uptake of T4, diminished T4 to T3 conversion and diminished cellular T3 levels correlate inversely with serum reverse T3 levels.[85]

Another finding in the aging patient is a reduction in TSH response to thyrotropin-releasing hormone from the pituitary, resulting in depressed levels of TSH. This suppression is similar to the TSH suppression found in severely ill patients with documented nonthyroidal illness (**Fig. 1**).[94,96]

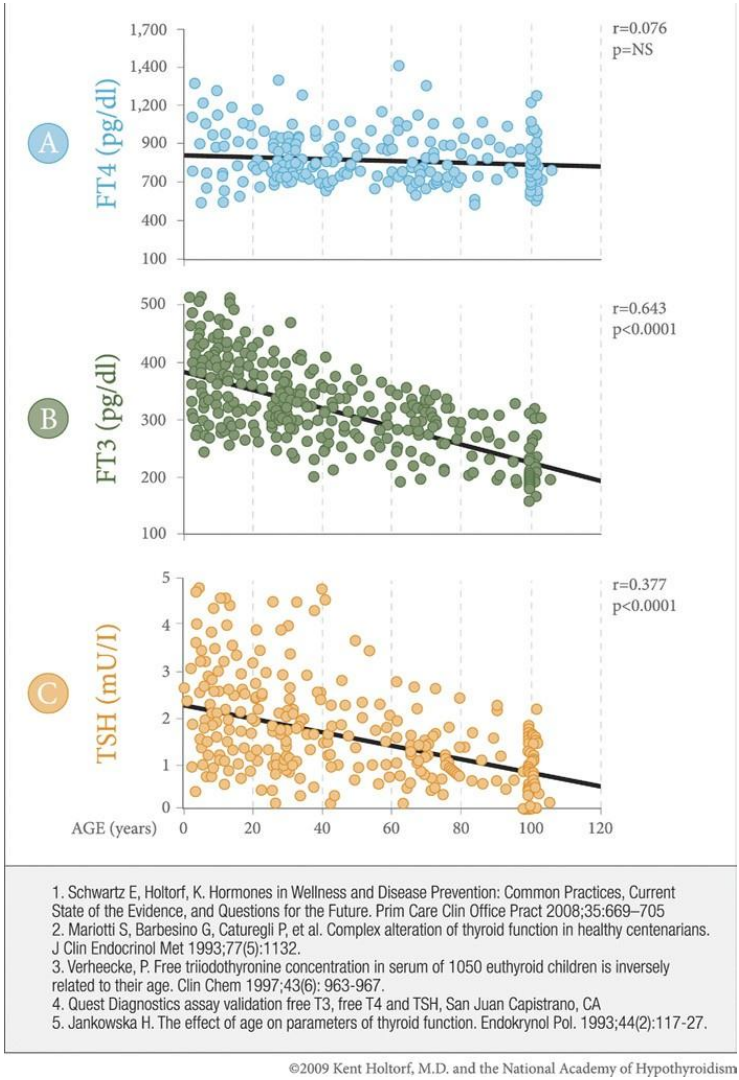

Fig. 1. Age dependent variations in mean serum levels of Free T4 (A), Free T3 (B) and TSH (C) in healthy individuals-a combined analysis of the literature. Demonstrates that TSH is not a reliable marker of active thyroid (T3) levels (low T3 levels are associated with decreased, not increased, TSH levels). (*Courtesy of* Kent Holtorf, MD and the National Academy of Hypothyroidism.)

TSH failure to respond to thyrotropin- releasing hormone stimulation in the elderly further contributes to confusing information gained from standard thyroid testing in this population. Increased incidence of systemic illness and multiple medications in the elderly also directly affect thyroid function, further reducing the accuracy of the standard thyroid tests (T4 and TSH) as markers of true thyroid status.

In aging patients who present with symptoms consistent with hypothyroidism but have a normal TSH and T4 level, a T3/rT3 ratio may help gain more insight of tissue thyroid status. Optimal tissue levels are associated with a free T3/rT3 ratio greater than 1.8. (free T3 is reported in picograms per deciliter and reverse T3 in picograms per deciliter).[81–93]

Although there are limitations in all type of testing for this age group, obtaining free triiodothyronine, reverse triiodothyronine, and triiodothyronine/reverse triiodothyronine ratios may be helpful to provide a somewhat accurate evaluation of tissue thyroid status and may predict favorable responders to thyroid supplementation.

Treatment

Thyroid replacement is not reported as beneficial during acute stress. When the stress is chronic or age-related treatment with T3 (liothyronine [Cytomel; Jones Pharma,

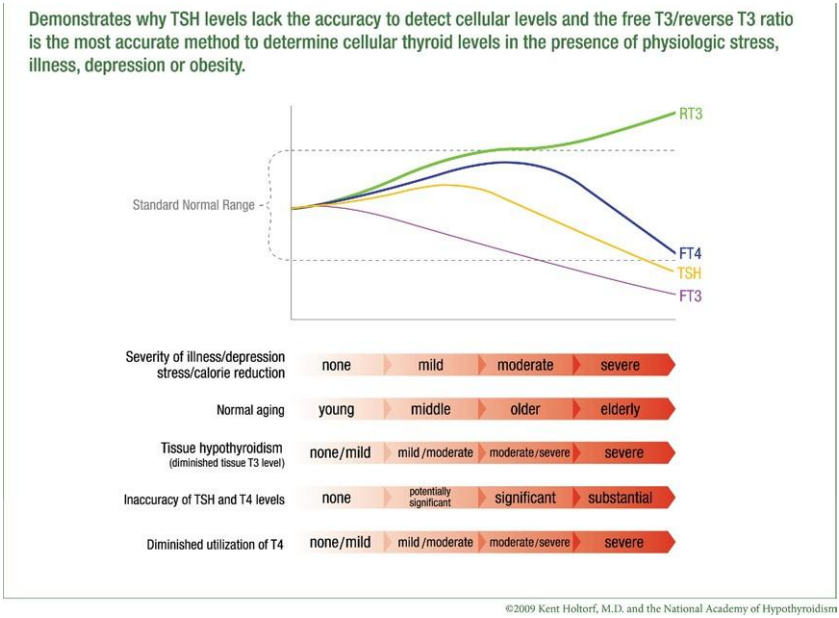

Fig. 2. Associated serum thyroid levels with progressively decreasing tissue thyroid levels due to stress, illness, depression, calorie reduction or aging (Why standard blood tests lack sensitivity to detect low thyroid in the presence of such conditions). (*Courtesy of Kent* Holtorf, MD and the National Academy of Hypothyroidism.)

Bristol, TN, USA]) containing preparations as opposed to T4 only preparations (levothyroxine [Synthroid, Abbott, Abbott Park, IL, USA]) has been proven to be of significant benefit. Serum testing demonstrating improvement demonstrate reduced fee T3/reverse T3 ratio, but clinical improvement is striking (**Fig. 2**).[81–93,97–99]

Many symptomatic patients with low tissue thyroid levels (as defined by a free T3/reverse T3 ratio of 1.8 and symptoms of hypothyroidism) with normal TSH and T4 levels may benefit from T3 thyroid replacement, often with significant improvement in fatigue, depression,[100,101] weight gain and obesity,[102] heart failure,[90] fibromyalgia,[103,104] cholesterol levels,[72,105] and numerous other chronic conditions.

In conclusion, the data reviewed herein have shown hormone therapies to improve some conditions associated with aging. Additionally, some of the long-held fears of significant side effects associated with hormone supplementation may be overstated, especially when providing patients with individualized care and optimal monitoring. We encourage clinicians to consider such interventions based on the evidence presented. More long-term studies are needed to further quantify and substantiate the risks and benefits associated with the use of such therapies.

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