Editorial

The Normal TSH Reference Range: What Has Changed in the Last Decade?

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Serum TSH assessment is the most sensitive screening test for the diagnosis of thyroid dysfunction in the absence of pituitary or hypothalamic disease. This test has been used increasingly in the last decade to detect subclinical thyroid dysfunction (STD). Recent data suggest that STD is a common disorder that may be associated with important adverse events (1–5). The American Association of Clinical Endocrinologists (AACE) and American Thyroid Association (ATA) 2012 guidelines recommend treatment of subjects with persistent increased serum TSH levels $\geq$ 10 mIU/L and undetectable serum TSH ($<$0.1 mIU/L) (6, 7). The treatment of mild thyroid hormone excess (TSH 0.1–0.4 mIU/L) or deficiency (serum TSH $<$ 10 mIU/L) is controversial (1, 2). However, what is the normal TSH reference range? Obviously, this issue is critical in deciding whether or not to treat patients with mild STD and in identifying individuals with high-normal or low-normal serum TSH. It is also important in defining the TSH target level in patients receiving thyroid hormone replacement therapy.

In 2002, the National Health and Nutrition Examination Survey (NHANES) III, a US population-based study, evaluated the normal TSH range in the "thyroid disease-free adult population" (8). The authors excluded subjects with risk factors and a family history of thyroid dysfunction, self-reported thyroid disease or goiter, and thyroid autoimmunity. The study suggested that 95% of the US disease-free population had a serum TSH concentration between 0.45 and 4.12 mIU/L (8). However, TSH values did not have a Gaussian distribution because the curve was skewed by individuals with occult autoimmune thyroid dysfunction despite negative thyroid peroxidase antibodies (9). In 2005, the National Academy of Clinical Biochemistry (NACB) recommended that thyroid ultrasonography be performed in euthyroid subjects to exclude the presence of occult thyroid autoimmunity in order to define the serum TSH reference interval more accurately (10). They suggested that the upper limit of the TSH reference range be lowered to 2.5 mIU/L (10).

The upper and lower limits of the normal serum TSH concentration continue to be debated by expert clinical thyroidologists. In 2005, two back-to-back articles appeared in the *JCEM*: one article, by Wartofsky and Dickey (11), favored a narrower TSH reference range, but according to the other, by Surks et al (12), the TSH range should remain unchanged.

It should be mentioned that the sensitivity and specificity of TSH assays can affect the evaluation of serum TSH because some assays may detect biologically inactive circulating TSH isoforms (1). The upper TSH reference limit has progressively declined over the last decade thanks to more sensitive TSH assays, more accurate thyroid antibody tests, and a more accurate selection of the reference population.

Different TSH cut-off limits have been reported in population-based studies conducted in various countries (1). Subsequent findings confirmed that ethnicity, iodine intake, gender, age, and body mass index can influence the reference range of serum TSH. In fact, the normal TSH upper limit was lower in African Americans (3.6 mIU/L) than in Mexican Americans or Caucasians (4.2 mIU/L) (8). Reanalysis of these data 5 years later showed that the upper limit of normal serum TSH at the 97.5th percentile was 3.5 mIU/L in individuals 20–29 years old, 4.5 mIU/L in those 50–59 years old, and 7.5 mIU/L in those older than 80 years (13). Variations in thyroid function within the reference range have been associated with body weight in several cross-sectional and longitudinal studies (14). Moreover, serum TSH levels at the upper limit of the normal range have been found in obese adults and have been positively correlated with body mass index (14).

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Abbreviations: BMD, bone mineral density; CI, confidence interval; FT4, free T_4; OR, odds ratio; STD, subclinical thyroid dysfunction.

It is noteworthy that some particular physiological and pathological conditions may confound the interpretation of the normal TSH range. A case in point is pregnancy. In fact, in 2007, The Endocrine Society and the ATA recommended that the upper limit of the TSH reference range be lowered to less than 2.5 mIU/L in the first trimester and less than 3 mIU/L in the second and third trimesters of pregnancy (15, 16). In accordance with these findings, in 2012 The Endocrine Society guidelines recommended treating pregnant women or women planning a pregnancy when serum TSH exceeds 2.5 mIU/L in the first trimester and 3 mIU/L in the second and third trimesters (17). To complicate the issue further, Andersen et al. (18) showed that the interindividual variability in serum TSH is greater than the intraindividual variability. In fact, there is an individual set-point of the hypothalamic-pituitary-thyroid axis that is determined by genetic and environmental factors (18).

Interestingly, two longitudinal studies showed that serum TSH concentrations across the reference range may be strongly associated with the risk of developing hypothyroidism and hyperthyroidism. An upper limit of the normal TSH range of 2 mIU/L and a lower limit of 0.4 mIU/L have been associated with a lower incidence of a progressively more deranged TSH value than other TSH values within the reference range (19, 20). In a large meta-analysis of thyroid-related traits carried out in 2013, the authors examined serum levels of TSH and free T_4 (FT4) in euthyroid subjects and identified 26 independent associations, including novel genetic loci for TSH and FT4 levels (21). Importantly, the TSH-associated genetic loci contributed not only to the variation within the TSH normal range but also to the values outside the reference range, which suggests that they could be involved in thyroid dysfunction (21). These findings may explain the consequences of genetic regulation of the hypothalamic-pituitary-thyroid axis function and the genetic variation for hypo- or hyperthyroidism.

A large body of evidence, which began to emerge in 2005, indicates that differences in thyroid function within the euthyroid TSH reference range are associated with negative health outcomes (22). Thyroid hormone plays an essential role in energy expenditure, lipid and glucose metabolism, and vascular integrity (1, 2). Overt and subclinical hypothyroidism (TSH $\geq$ 10 mIU/L) are linked to an increased risk of coronary heart disease and heart failure (3, 4). Moreover, thyroid dysfunction may worsen the prognosis of such associated comorbidities as diabetes, kidney dysfunction, metabolic syndrome, and heart failure (22–24). Therefore, screening of serum TSH levels is recommended for newly diagnosed patients with heart failure and diabetes type 1 (25, 26). Mildly increased serum TSH (4.5–9.9 mIU/L) is associated with diastolic dysfunction, dyslipidemia, and vascular alterations in young and middle-aged patients (1, 2). These adverse effects improved after replacement therapy with L-thyroxine in randomized controlled studies (1, 2). The most recent AACE and ATA guidelines support treatment of mild subclinical hypothyroidism in patients with evidence of atherosclerotic cardiovascular disease and heart failure or in the presence of risk factors associated with these disorders (6). This issue of the *JCEM* contains an important meta-analysis, carried out by Dr Peter Taylor and colleagues (22), of the effects of the variation of thyroid function across the reference range on cardiovascular, bone, and metabolic outcomes. They assessed studies in which high-normal serum TSH levels were associated with an adverse serum lipid profile, high blood pressure, high body mass, and metabolic syndrome and fatal coronary heart disease. Their meta-analysis indicated that there was an increased risk of adverse cardiovascular outcomes (odds ratio [OR] = 1.21; 95% confidence interval [CI], 1.15–1.27) and of adverse metabolic outcomes (OR = 1.37; 95% CI, 1.27–1.48) in individuals with TSH levels in the upper part of the reference range than in subjects with TSH levels in the lower part of the reference range. Accordingly, the authors conclude that their meta-analysis provides the evidence base for the association of high-normal serum TSH with negative cardiovascular and metabolic effects. These results suggest that the entire spectrum of hypothyroidism, from high-normal serum TSH to mild and frankly elevated serum TSH, is associated with relevant metabolic risk factors, coronary heart disease events and mortality. Moreover, L-thyroxine has been found to exert a beneficial effect on atherogenic lipid profile and impaired vascular function in patients with TSH levels between 2.5 and 4.5 mIU/L (1).

On the other hand, overt and subclinical hyperthyroidism are associated with an increased risk of atrial fibrillation, heart failure, stroke, coronary heart disease, and bone fractures, especially in patients with undetectable serum TSH levels (<0.1 mIU/L) (1, 2, 4, 5). In line with these findings, the combination of TSH at the lower limits of the normal range and high-normal FT4 levels has been associated with the risk of atrial fibrillation in elderly subjects (27–29). Moreover, hypothyroid patients were found to have a low risk of atrial fibrillation (29). Regarding the skeletal system, physiological variations in thyroid function within the upper normal range have been associated with lower bone mineral density (BMD) and an increased risk of fracture in healthy euthyroid women (22, 30). Moreover, it is feasible that TSH exerts a protective role by inhibiting bone turnover. In fact, low-normal TSH levels have been associated with significantly reduced BMD and an increased risk of osteoporosis and fractures in euthyroid postmenopausal women, irrespective of thyroid hormone

(22). In the meta-analysis by Taylor et al (22), there were lower odds of adverse bone outcomes (OR = 0.55; 95% CI, 0.41–0.72) in individuals with high-normal serum TSH levels. Taken together, these findings suggest that there is a continuum in the risks of atrial fibrillation and bone fractures across the spectrum of the TSH reference range. These risks progressively increase as TSH values go from low-normal to undetectable and as FT4 levels go from high-normal to high levels, especially in the elderly. On the contrary, high-normal to high TSH values exert a protective effect against the risk of atrial fibrillation and bone fractures.

Whether to treat persistent mild thyroid hormone excess, characterized by low but detectable serum TSH (0.1–0.4 mIU/L), is much debated (1, 2). The AACE and ATA guidelines recommend treating this condition in elderly patients (age, ≥65 y) and in patients with cardiac disease, osteoporosis, or symptoms of hyperthyroidism (7). Low serum TSH levels may unintentionally occur during replacement therapy with thyroid hormone, thereby increasing the cardiovascular risk and the risk of fractures in elderly patients (2). In fact, minimally suppressed serum TSH (0.1–0.4 mIU/L) was associated with an increased risk of atrial fibrillation in elderly patients in the Cardiovascular Health Study (31).

It is important to state that replacement therapy with thyroid hormone is not advised in elderly patients with a mild TSH increase (TSH < 7 mIU/L) (2). Increased serum TSH in subjects 85 years or older was not associated with decreased cognitive or functional impairment and predicted lower mortality in the Leiden study (32). Cardiovascular and total mortality did not increase in elderly patients with raised serum TSH levels in the Cardiovascular Health Study (33). Moreover, replacement therapy with L-thyroxine in elderly patients with a mild TSH increase was not associated with any beneficial or protective effects (34).

These findings suggest that mildly raised serum TSH in the elderly indicates a physiological change in TSH with aging. It simply reflects the decreased TSH biological activity or its abnormal glycosylation, the change in the set-point of the hypothalamic pituitary thyroid axis, and the decreased deiodinase type 2 activity that occurs in the elderly (2).

According to the 2012 AACE and ATA cosponsored guidelines, if the upper and lower limits of normal for a third-generation TSH assay are not available, an upper limit of 4.12 mIU/L and a lower limit of 0.45 mIU/L should be considered in iodine-sufficient areas (6). The NACB recommendation to lower the upper limit of the TSH normal range to 2.5 mIU/L (10) should be balanced with the health and economic impact of a reduced serum TSH range (35). In fact, about 20–26% of the population would be hypothyroid if the upper limit of the normal range is lowered to 2.5–3.0 mIU/L. Moreover, no large prospective studies have yet demonstrated the beneficial effects of treating patients with TSH values at the lower and upper limit of the normal range when associated with adverse cardiovascular, metabolic, or bone risk factors. In the meantime, what should clinicians do when they encounter patients with high-normal or low-normal serum TSH? First, it is essential to accurately analyze the results of the TSH and free thyroid hormone assays before deciding whether a specific TSH level is abnormal or not. Clinicians should also consider gender, age, physiological and pathological conditions, drugs, symptoms, and quality of life. Importantly, they should request serial TSH evaluations to assess the progressive increase or decrease in serum TSH levels. Peripheral parameters of thyroid hormone action (such as cholesterol and lipid levels, blood pressure, bone markers, and cardiovascular parameters) might be useful in symptomatic patients to establish whether a TSH value is pathological for a specific individual. An accurate medical history and clinical assessment will show whether L-thyroxine replacement therapy is necessary in symptomatic young patients with serum TSH at the upper limit of the normal range, especially if associated with adverse cardiovascular risk factors. Careful monitoring should be considered for asymptomatic subjects with high-normal or low-normal serum TSH levels to assess the risk of progression to overt disease and the potential development of adverse health outcomes. Thyroid function should be normalized in elderly patients with low-normal serum TSH to improve cardiovascular parameters in cases of atrial fibrillation or heart failure (36) and to improve the recovery of BMD during treatment with antiresorptive drugs in patients with osteoporosis (37). Treatment with antithyroid drugs could be considered in elderly patients in the presence of atrial fibrillation and osteoporosis in order to normalize TSH levels to their physiological values. Large randomized controlled studies are needed to evaluate the benefits of treating high-normal serum TSH with L-thyroxine and of normalizing low-normal and undetectable serum TSH with antithyroid drugs. Lastly, studies are required to assess whether the genes that establish the hypothalamic-pituitary-thyroid axis set-point influence the genetic predisposition to dyslipidemia, obesity, coronary heart disease, atrial fibrillation, and bone fracture.

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