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TSH - Clinical Aspects of its Use in Determining Thyroid Disease in the Elderly How does it Impact the Practice of Medicine in Aging?

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Abstract

The last four decades have seen enormous growth in the efficacy of serum thyroid stimulating hormone (thyrotropin, TSH) assay methodology, establishing TSH as the hallmark of thyroid testing. At the center of the considerations is the strong positive correlation between serum thyrotropin and free thyroxine concentrations. While it is widely accepted that elevated serum TSH concentrations are consistent with thyroid dysfunction, a vast multitude of additional factors must be considered before an accurate clinical diagnosis can be made followed by an appropriate treatment. Epidemiological studies have demonstrated slightly elevated serum TSH concentrations among the elderly population. There is, however, a debate whether these elevated TSH levels reflect an increased prevalence of hypothyroidism among the elderly or a normal aspect of healthy aging. A comprehensive analysis of the many variables associated with this debate and TSH measurement as a diagnostic tool in aging, should provide insight into the clinical efforts to diagnose and treat thyroid disease, particularly in the elderly population.

Keywords: Hypothyroid; Hyperthyroid; Thyrotropin; Aging; Thyroxine

Introduction

Hypothyroidism has multiple etiologies and manifestations. Consequently, appropriate treatment requires accurate laboratory analysis and clinical diagnosis. The 2012 clinical practice guidelines for the management of hypothyroidism in adults, co-sponsored by the American Association of Clinical Endocrinologists (AACE) and the American Thyroid Association (ATA), maintain that serum TSH is the single best screening test for primary thyroid dysfunction for the vast majority of outpatient clinical situations. Similar recommendations were made by the clinical guidelines of the ATA for the diagnosis and management of thyroid disease during pregnancy and postpartum for more extreme situations of thyroidal stress, such as pregnancy [1,2].

Thyroid-Stimulating Hormone (TSH) is a 28 kDa glycoprotein released from thyrotrophs in the anteromedial region of the pituitary which, in turn, stimulates thyroidal thyroxine (T4) and triiodothyronine (T3) synthesis [3]. Serum TSH concentrations can provide the most sensitive index to reliably detect thyroid function abnormalities and is the primary means of studying thyroid function [4-6]. The diagnostic superiority of TSH measurement arises principally from the inverse log/linear relationship between circulating TSH and free thyroxine (FT4) concentrations [4,7,8]. This inverse log-linear relationship between FT4 and serum TSH concentrations is based on the negative hypothalamic-pituitary-thyroid feedback mechanism in which minor reductions in FT4 concentrations correlate with a logarithmic increase in serum TSH. Although TSH has been considered the most reliable indicator of thyroid function abnormalities, there are several issues that challenge current knowledge.

This review will examine potential confounding factors in the measurement of TSH, the recent controversy surrounding TSH reference intervals, genetic predisposition to particular TSH concentrations, the observed correlation between thyroid function and longevity, and the peer-reviewed literature on age-related changes in TSH in differing populations and subject sets.

When TSH Elevations may not Reflect True Hypothyroidism

Not all individuals with TSH elevations are hypothyroid, and therefore they would not require thyroid hormone therapy. It has been demonstrated that in individuals who are anti-TPOAb or TgAb negative, serum TSH concentration greater than 3.0 mIU/L occur with increasing frequency with aging. In the elderly over 80 yrs of age, 23.9% had serum TSH concentrations between 2.5 and 4.5 mIU/L, and 12 % had serum TSH concentrations above 4.5 mIU/L [9]. Thus, very mild TSH elevations in older individuals may not reflect subclinical thyroid dysfunction, but rather be a normal manifestation of aging. This presents a dilemma: while normal TSH reference intervals, particularly for some sub-populations, may need to be narrowed [10,11]. The normal reference interval of TSH may need to be widened with increasing age, with the upper reference limit higher than the upper limit for younger adults. By adjusting the normal reference interval of serum TSH concentrations based on aging, unnecessary thyroid hormone therapies may be avoided [1].

In addition to the elderly, young adults with Down's syndrome have a higher prevalence of thyroid autoimmune disorders than the general population. In fact, 3% of children with Down's syndrome have overt thyroid diseases. Yet, in the same population the frequency varies from 13 to 50% of children with TSH>10 mIU/L. In general, for young adults with Down's syndrome anti-thyroid antibodies from an autoimmune disorder produce the elevated levels of TSH [12].

TSH Assay Interferences

The current standard of care calls for the use of third generation

TSH assays with functional sensitivity of <0.02 mIU/L [4,13-15], a level of sensitivity necessary for detecting degrees of TSH suppression. For example, TSH concentrations ranging between 0.01-0.1 mIU/L represent a significant risk for atrial fibrillation in older patients and are often an iatrogenic consequence of levothyroxine (LT4) suppression or an unintended result of replacement therapy [16,17]. Targeting the degree of TSH suppression plays a critical role in the management of thyroid cancer, and in ambulatory hypothyroid patients serum TSH concentrations are used as the target for adjusting LT4 replacement [18-21]. Since thyroxine (and LT4) have a very narrow therapeutic index, TSH sensitivity can be critical, and serum TSH monitoring provides better sensitivity than does FT4 testing.

TSH assay methods vary in their susceptibility to interfering substances [22]. A physician may suspect assay interference when a reported value is inconsistent with the clinical status of a patient. Clearly, without such a request it is difficult for a laboratory to proactively detect assay interference from a single measurement, such as an isolated TSH test. The most practical way to investigate a suspected interference is to test the specimen by a different manufacturer's method and check for discordance between the test results. Occasionally, a biological check can be made using TRH-stimulation or thyroid hormone suppression to validate a suspected inappropriate serum TSH level. Interferences producing a falsely elevated TSH value will usually be associated with a blunted (<2-fold increase) response to stimulation.

Some examples of potential TSH assay interference include: (1) issues with cross reactivity, (2) endogenous antibodies to TSH, (3) heterophile (animal) antibody interference with assay reagents and (4) in vivo or in vitro drug interactions. It should be noted that there are clinical situations in which the measurements of serum TSH alone may yield misleading results (Table 1).

(1) Cross-reactivity. The specificity of an immunoassay depends on the ability of the antibody reagent to discriminate flawlessly between the analyte and structurally related ligands. The use of monoclonal antibodies for developing TSH immunoassay methods has virtually eliminated the cross-reactivity problems with other glycoprotein hormones, such as LH or hCG, that had plagued early TSH radioimmunoassay methods. However, because each monoclonal

antibody differs in its specificity for recognizing various circulating TSH isoforms, these antibody differences can result in the reporting of TSH values that may differ by as much as 1.0 mIU/L for a given serum sample [23].

(2) Endogenous Antibodies. Endogenous antibody interferences are characterized by either falsely low or falsely high values, depending on the type and composition of the antibody assay employed.

(3) Heterophile Antibodies (HAb)/Human Anti-Mouse Antibodies (HAMA). Heterophile antibodies represent a group of relatively weak multispecific, polyreactive antibodies with specificity for poorly defined antigens that react with immunoassays derived from two or more species [24,25]. Most frequently, such HAb interferences result from IgM Rheumatoid Factor or HAMA. Immunometric assay methods that use monoclonal antibodies of murine origin are more prone to HAMA interference than competitive immunoassays and create a signal that is reported as a falsely high value [26]. Such HAMA interference can produce inappropriately normal values in patients that eventually prove to have clinical disease [27]. Despite the measures used by manufacturers to neutralize interferences, both the clinician and the laboratory must be aware of this possibility when an apparently inappropriate test result is encountered.

(4) Drug Interferences. Certain drugs may interfere with TSH levels in-vitro or in-vivo [28,29]. Drugs can have in-vitro or in vivo effects if serum samples contain sufficient concentrations of certain therapeutic and diagnostic agents to produce methodological interference. For example, glucocorticoids can have in-vivo effects on thyroid function by altering TSH, thyroid hormone secretion, and/or thyroid hormone metabolism [28,29].

A number of drugs cause hypothyroxinemia in euthyroid patients by decreasing TBG concentrations (androgens, niacin), decreasing T4 binding to TBG (high dose salicylates, phenytoin, carbamazepine), and/or increasing T_4 metabolism (carbamazepine, phenobarbital and phenytoin). Some drugs cause hyperthyroxinemia in euthyroid patients by increasing TBG concentrations (clofibrate, estrogen, 5FU, heroin/methadone) [28-30], while other drugs may raise circulating T_4 levels by inhibiting the conversion of T_4 to T_3 (amiodarone, iopanoic acid and high-dose propranolol and nadolol).

TSH with Impaired Biological Activity

A high level of serum TSH may be the result of a laboratory issue, although rare, namely the presence of biologically inactive isoforms of TSH. This would result from pituitary-hypothalamic disease in an individual whose basal TSH levels measured by immunoassay were elevated, yet when measured by a cytochemical bioassay were found to be normal [31]. This finding, coupled with the absence of the normal rise of thyroid hormones in response to thyrotrophin-releasing hormone (TRH)-mediated release of TSH, confirm the secretion of bio-inactive TSH. Primary thyroid disease as a cause for the elevated immunoreactive TSH can be excluded by the absence of circulating thyroid antibodies and by a normal thyroidal radioiodine uptake response to exogenous TSH. In patients with idiopathic central hypothyroidism due to biologically inactive TSH, there is an excess of circulating TSH-beta and TRH is implicated in the secretion of TSH of full biological potency [32]. Such sera will indicate elevated TSH concentrations (immunoacivity) although the bioactivity may be normal.

High TSH levels are often observed in long-lasting and severe hypothyroidism. Yet, a case report of a 25 year old man with Down's

Condition	Serum TSH	Consequences of Clinical Action based on Serum TSH value Alone	Serum FT4
Heterophile antibodies	Normal	Failure to diagnose thyrotoxicosis	High
Central hypothyroidism	Normal*	Failure to diagnose hypothyroidism and investigate hypothalamic-pituitary structure function	Low
TSH-secreting pituitary adenoma	Normal*	Failure to diagnose thyrotoxicosis and investigate pituitary structure and function	High
Thyroid hormone resistance	Normal*	Failure to recognize the condition	High
Poor compliance with T4 therapy	High	Inappropriate increase in dose of T4	High
Delayed recovery of TSH secretion after treatment of hyperthyroidism	Normal or low	Failure to diagnose impending hypothyroidism	Low

*Serum TSH concentrations may also be high in these conditions, which should prompt measurements of serum FT_4 and further investigation

Table 1: Clinical situations in which measurements of serum TSH alone may yield misleading results.

Syndrome showed that having high TSH levels does not necessarily result in the clinical manifestation of hypothyroidism. In this study, the patient had TSH levels of 1392 mIU/L (normal reference interval 0.25-4.0 mIU/L) and FT4 of 0.66 pmol/L (8.2-18 pmol/L). This discrepancy between the clinical symptoms and immunoassay results is not uncommon, and may be explained by impaired biological activity of specific TSH isoforms [12].

Defining TSH Reference Intervals

Setting reference intervals for TSH is critical for diagnosing mild (subclinical) hypo- or hyperthyroidism. The current clinical guidelines recommend that TSH reference intervals should be established from the 95% confidence limits of the log-transformed TSH concentrations of at least 120 rigorously screened normal euthyroid volunteers who have: (a) no detectable anti-thyroid peroxidase autoantibodies (TPOAb) or anti-thyroglobulin autoantibodies (TgAb) measured by sensitive immunoassay; (b) no personal or family history of thyroid dysfunction; (c) no visible or palpable goiter; and (d) who are taking no medications except estrogen [4].

TSH upper reference limits (97.5th percentile)

Multiple factors influence the calculation of the TSH upper reference limit for a population. These include factors such as sex, age, ethnicity, iodine intake, body mass index (BMI), smoking, subclinical autoimmune thyroid disease, education level, medications, socioeconomic status [33] and may affect thyroid function resulting in elevated TSH listed in table 2. Over the last two decades, the upper reference limit for TSH has steadily declined from approximately 10 mIU/L to 2.5-3.5 mIU/L. This decrease reflects a number of factors including the improved sensitivity and specificity of current monoclonal antibody-based immunometric TSH assays, the elimination of high values resulting from gonadotropin cross-reactivity, and the exclusion of individuals with subclinical autoimmune thyroid disease who have higher TSH values [4,34].

Some guidelines propose the adoption of an empirical upper limit of 2.5-3.0 mIU/L, which is in accordance with the TSH interval associated with the lowest prevalence of anti-thyroid antibodies [4,35]. However, this remains controversial, since the majority of persons with serum TSH levels between 2.5 and 4.0 mIU/L have no evidence of thyroid disease serologically or on ultrasonography [9,36,37]. In 2002, the American Association of Clinical Endocrinologists suggested that the serum TSH reference range upper limit be lowered to 3.0 mIU/L [5], while others support an additional decrease to 2.5 mIU/L [38], based

Assay-related	Bioactive TSH secretion Heterophile antibodies
Dysfunctions of the thyroid gland	Family history of thyroid disease (latent thyroid disorder) TSH resistance syndromes Thyroid hormone resistance Germline mutations of TSH receptor Hashimoto thyroiditis Other autoimmune conditions Recovery phase of subacute thyroiditis
Dysfunctions of the pituitary gland	Pituitary tumors (TSH-producing)
Environmental	Pregnancy Iodine deficiency Radioactive iodine treatment Medications (steroids, dopamine, iodine, amiodarone) Nonthyroidal illness Insufficient medication in individuals with a thyroid disorder

Table 2: Causes of Elevated Serum TSH Concentrations.

on a recent report by the National Academy of Clinical Biochemistry that over 95% of normal, healthy individuals have serum TSH between 0.4 and 2.5 mIU/liter, and that those with TSH >2.5 mIU/liter may be in the early stages of thyroid failure, particularly when TPOAb are present [39]. Similar findings suggest the use of TSH cutoff values of 2.5 and 4.0 mIU/L in addition to thyroid antibodies as clinically useful estimates of long-term risk of hypothyroidism [40].

Although Surks acknowledges equivalently that serum TSH levels between 3.0 and 4.5 may indicate the earliest signs of subclinical hypothyroidism, the concern is that an upper limit of 2.5-3.0 mIU/liter would create a 300-400% increase in individuals diagnosed as hypothyroid (22-28 million additional individuals) when in reality they are not clinically in need of any treatment [41]. Fatourechi [42] comments on this phenomenon, noting that, as TSH distribution and peak frequency (most commonly occurring serum TSH level) shift toward higher levels with increased age in both a disease-free population and thyroid antibody-negative reference population for subjects who are without any evidence of thyroid disease, the lowering of the upper limit of the TSH reference range could result in a tripling of abnormal results in individuals over 50 years of age, again, causing unrealistic concern for clinical intervention.

TSH lower reference limits

Using current third generation IMA methodology, the lower TSH reference limit (2.5th percentile) is approximately 0.3 to 0.4 mIU/L, irrespective of the population studied or the method used [43]. TSH in the 0.1 to 0.4 mIU/L range may represent mild thyroid hormone excess, and in elderly patients might be associated with an increased risk of atrial fibrillation and cardiovascular mortality [44]. It is also important to note a shift in TSH distribution in blacks [36], leading to possible over-diagnosis of subclinical hyperthyroidism. It is therefore important to carefully evaluate patients with TSH levels in this low range for underlying thyroid disease.

Hospitalized patients

Non-thyroidal illnesses (NTI) can frequently alter thyroid hormone peripheral metabolism and Hypothalamic-Pituitary-Thyroidal (HPT) function resulting in thyroid test abnormalities, including both decreased and increased serum TSH levels [45]. It is important to distinguish the generally mild, transient TSH alterations typical of NTI from the more profound and persistent TSH changes associated with hyper- or hypothyroidism [46].

One would be remiss to exclude mention of the fact that population-based reference intervals include not only between-individual variation, but within-individual as well. Research studies report that *within-person* (*intra-individual*) TSH variability is relatively narrow, and varies by only 0.5 mIU/L when tested every month over a span of one year. In comparison, *between-person variability* is more variable [47-49]. Consequently, it is highly possible that abnormal test results for a single individual may go largely undetected if still within the normal range for the wider population-in fact, when the index of individuality for a thyroid test is below 0.6 mIU/L, population-based reference intervals are fairly unreliable at gauging individual change [50]. This somewhat limits the usefulness of population-based reference intervals to detect thyroid dysfunction in individuals [7,51]. Theoretically, it may be important to evaluate individuals with marginally (yet confirmed) low (e.g, 0.3-0.4 mIU/L) or high (3.0-4.5 mIU/L) TSH levels relative to patient-specific risk factors for cardiovascular disease, rather than relative to the normal TSH reference interval [52]. However, there are

no data to show increased morbidity and mortality if an individual's TSH levels are not within their own normal range, as long as they are within the population reference interval.

Diurnal variation

Serum TSH normally exhibits a *diurnal variation* with a peak between midnight and 04:00 and the lowest values between 10:00 and 16:00 hours [20]. This variation should not influence the diagnostic interpretation of test results since most clinical TSH measurements are performed on ambulatory patients between 08:00 and 18:00 hours, and the reference intervals for TSH are typically established using specimens collected at a similar time. Further, because serum T4 with a half-life of approximately 7 days does not change sufficiently in one day to raise TSH secretion, there is no need to withhold LT4 therapy on the day of blood testing for TSH [4].

Population-Based Reference Intervals

Population-based studies rely on non-homogenous populations with varying genetic, dietary intake, environmental exposures and behaviors. As noted, a positive relationship is detected between elevated serum TSH levels and the presence of TPOAb antibodies [53,54] and is directly related to the diagnosis of subclinical (mild) hypothyroidism when serum T4 levels are within normal. The third National Health and Nutrition Examination Survey (NHANES III) (1988-1994), is a cross-sectional study representative of the US population and includes 17,353 individuals aged ≥ 12 yr [55]. Analysis of NHANES III concluded that the geometric mean serum TSH concentration for the US population was 1.47 (95% confidence interval 1.44-1.51) mIU/liter, and a median TSH concentration of 1.39 (1.35-1.47) mIU/liter. The 2.5% TSH lower reference limit was 0.45 (0.42-0.47) mIU/liter and the 97.5% 4.12 (3.94-4.45) mIU/liter [55].

Serum TSH Levels In The Elderly And In Centenarians

Several epidemiological studies indicate that the population's mean TSH levels increase with age [55,56]. In the NHANES III survey of the U.S. population, the 97.5[th] percentile for serum TSH has been shown to be higher in groups of elderly, or white individuals, women, and those with higher iodine intake than in other population subgroups, suggesting specific TSH reference limits, which are not currently available, should be considered for specific populations [10,36,57,58].

Epidemiological studies illustrate that TSH distribution and reference limits shift to higher concentrations with age, even up to centenarians, and are unique for different racial/ethnic groups, being at higher concentrations in Caucasians than either Blacks or Hispanics. The distribution curve for TSH derived by the traditional approach represents a composite of curves from specific subpopulations that do not provide appropriate reference limits for those unique groups [36]. However, other more controlled studies claim that serum TSH concentrations *decrease* in healthy elderly subjects due to an age-related decrease in TSH secretion by the pituitary [59]. Several studies have reported an association between low serum TSH and cognitive impairment in the elderly, predicting the risk of mild cognitive disease. However, despite new data and meta-analysis the association between serum TSH concentrations and cognition in the elderly remains a controversial issue [60-64].

In the elderly, the nocturnal TSH peak is blunted and there is a 1-1.5 hour shift in the circadian rhythm of TSH secretion, resulting in an earlier TSH peak [65,66]. The mechanism of this reduction in TSH secretion is currently unknown. It may very well be an increased

sensitivity of the thyrotrophs to the negative feedback by T4, but other mechanisms such as a reduced hypothalamic thyrotropin releasing hormone (TRH) secretion cannot be excluded [4]. Although reduced TSH levels result in a reduced thyroidal T4 secretion in the elderly [67,68], serum TT4 and FT4 concentrations remain unchanged [4,69]. This is because T4 degradation by outer ring deiodination decreases with age resulting in age-dependent decline in TT3 and FT3 levels and an increase in the biologically inactive serum reverse T3 (rT3) levels. It is currently unknown whether an increased inner ring deiodination by deiodinase 3, which would result in an increased clearance of T4 and T3 and an increased production of rT3, also contributes to these changes. This has recently been shown to be a major factor in non-thyroidal illness [70,71]. A multitude of other studies negates that elevated TSH is indicative of increased prevalence of hypothyroidism, proposing that there is simply an age-related increase in serum TSH concentrations based on an alteration in TSH set point rather than thyroid disease [7]. Additionally, the definition of what should, in fact, be considered a "normal" reference interval for TSH concentration is still under debate.

The reliability of TSH reference intervals based on population data that includes individuals who are positive for anti-thyroid antibodies has been questioned due to the association between elevated TSH concentrations and the presence of anti-thyroid antibodies, which could be associated with occult thyroid disease. Such population-based studies reported that the likelihood of having TPOAb increased with a TSH level greater than 2 mIU/L, approaching 80% prevalence when TSH concentrations were greater than 20 mIU/L and both TPOAb and TgAb were present. However, no thyroid antibodies were detected in 31% of males and 11% of females with TSH >10 mIU/L. Namely, even when there are no thyroid antibodies detected, the upper reference range limit is still skewed [35].

Surks et al. [9] argues that the TSH distribution curve is in fact a composite of separate curves for unique subpopulations (i.e. ages, ethnicities, genders) that contributes to an apparent skew toward higher TSH values [9,36]. The authors propose that increasing mean TSH levels above 4.5 mIU/L with advanced age are not associated with thyroid disease, but rather due to distinct TSH reference ranges for separate age groups that shift toward higher values with increasing age. It is suggested that age-specific reference intervals should be used to avoid misclassification of patients with abnormal TSH as hypothyroid [9].

These findings are consistent with those of a study that analyzed NHANES III data to recommend a more practical approach for establishing age-specific TSH reference ranges that do not include individuals who are positive for circulating anti-thyroid antibodies, whose presence is associated with thyroid dysfunction [10]. This study found that the 2.5[th], 50th, and 97.5[th] percentiles of TSH increase with age, with the most significant effects seen at the 97.5[th] percentile, which increases by 0.3 mIU/L with each 10 year increase in a subject's age [10].

The second, and more controversial, debate over TSH reference ranges is in defining their limits. There is limited information on the lower limit apart from an association between risk of atrial fibrillation and low TSH concentrations (three times greater risk in TSH <0.1 mIU/L, 1.6 times the risk in 0.1 mIU/L<TSH<0.4 mIU/L) [5,72,73]. Others maintain that in the absence of clinical-intervention trials on hyperthyroidism, the medical community should adopt a risk-based approach for establishing thresholds to justify interventions rather than determining reference intervals [73].

The debate over TSH reference ranges is complex and ongoing,

and relies heavily on interpretations of data that report elevated TSH concentrations in relation to either thyroid dysfunction or merely as another aspect of healthy aging. Several studies, in fact, draw correlations between elevated serum TSH (and thus decreased thyroid function) and increased longevity in the elderly [74-76], an association to be discussed later in this article. Nevertheless, it is essential that a certain consensus is reached regarding the most appropriate TSH reference range, for misclassification of healthy patients as hypothyroid could result in unnecessary levothyroxine treatment and its related consequences, while incorrectly characterizing a thyroid disorder as normal may enhance the risk of progression from mild to overt hypothyroidism [52].

Isolated abnormalities of serum TSH levels do not necessarily connote sustained thyroid dysfunction. Some causes of isolated TSH elevation may include: (1) mild (subclinical) hypothyroidism, (2) recovery from hypothyroxinemia of nonthyroid illnesses, and (3) medications such as amiodarone, which can inhibit thyroid hormone synthesis and metabolism and may cause transient reversible elevation of serum TSH [77]. Hyperthyroid patients are expected to have serum TSH concentrations of less than 0.01 mIU/L except in TSH-induced thyrotoxicosis and T4/T3 resistance. Patients with resistance to thyroid hormones may have mixed thyroid status, with hypothyroidism in some tissues and thyrotoxicosis in others, resulting in normal or mildly elevated TSH levels. Isolated TSH suppression can be observed in cases of mild (subclinical) hyperthyroidism, recovery from overt hyperthyroidism, nonthyroidal illnesses, or in patients using medications such as dopamine and high-dose glucocorticoids.

Is Higher TSH Related to Genetic Predisposition to Longevity?

A comparison study based on 1981 and 1994 cross-sectional Busselton Health Surveys concluded that there is a significant positive correlation between age and serum TSH concentrations ($r=0.092$, $p<0.001$) [78]. Based on reference populations free of thyroid disease, the study demonstrated that there was an increase of 0.08 mIU/L serum TSH per decade of age at baseline, with the largest increases occurring in the oldest participants and those with the lowest TSH at baseline [78]. A different study of a thyroid disease-free Ashkenazi Jewish population determined that mean serum TSH was significantly higher in centenarians with median age 98 yr [1.97 (0.42-7.15) mIU/L] than in Ashkenazi controls of a younger age [1.55 (0.46-4.55) mIU/L], and NHANES III controls median age 68 yr [1.61 (0.39-6.29) mIU/L] [76]. Based on the inverse relationship between TSH and FT4, the age-related changes in the negative feedback mechanism, namely the slowing down in reactive response between TSH and thyroid hormones may be a factor contributing to longevity. The age-related increase in TSH concentrations for subjects older than 90 years of age were only slightly more elevated than those of younger adults [79].

Despite major studies and surveys such as NHANES III, several publications challenge the notion of elevated TSH in centenarians. In a small cross-sectional study conducted in Italy serum TSH concentrations were *lower* in centenarians (mean age 101.96 ± 0.38 SEM) than in healthy older subjects (mean age 84.75 ± 1.25 SEM), while reverse-T3 concentrations were higher, suggesting an age-dependent reduction of the 5'-deiodinase activity rather than to important changes of nutritional markers [80]. The study, however, was based on a small sample size and Italy is known to be mildly iodine deficient and thus results must be interpreted cautiously.

A genetic association between longevity and higher TSH is another

possibility. It has been observed, among those centenarians with elevated TSH, their offspring have raised serum TSH concentrations in comparison with age-matched controls, suggesting an effect on TSHR gene expression inherited from centenarians and contributing to increased TSH [81]. The 2010 Leiden Longevity Study similarly finds an association between lower family mortality history scores among parents of nonagenarian siblings and higher serum TSH levels, suggesting that decreased thyroid function (represented by the elevated serum TSH) is a heritable phenotype contributing to exceptional longevity [82].

Further research would suggest that extreme longevity correlates not only with TSH values, but also with thyroid function itself. Based on the possible relationship between elevated TSH and decreased thyroid function, Atzmon et al. hypothesize that there is an inverse correlation between thyroid function and life span [81], while animal studies suggest that the relationship may be causal [83,84]. An analysis of the subjective well-being of hypothyroid patients seems to corroborate these findings, concluding that elevated serum TSH concentrations in the elderly subjects are significantly less indicative of hypothyroid disease and its repercussions than in younger subjects [85,86]. Thyroidal production of thyroid hormones may decrease in advanced age, perhaps reflecting centenarians' adaptations to new physical requirements rather than true deficits in thyroid system functioning [87-89].

Conclusion

Changes in serum TSH concentrations are often described in elderly subjects; however, their pathophysiologic significance and the possible contributory role of both malnutrition and nonthyroidal illness are still debated. Despite the occasional challenge of any relation between TSH level and age, the general assumption is that either hypothyroidism is increasingly prevalent among older members of the population, or there is merely an age-related rise in TSH set point beyond any evidence of thyroid disease. And yet, age is only one of many variables with a moderately strong influence on TSH level. Factors such as laboratory assessment, sex, ethnicity, diet, education level, medications, socioeconomic status, body mass index and smoking [33] may play affect in thyroid function resulting in elevated TSH. It is, therefore, essential to be mindful of the interplay of variables on thyroid function, and proceed accordingly in terms of treatment and diagnosis.

The controversy arising from the distinction of elevated TSH levels in the elderly as a normal consequence of aging or potentially as a sign of increased prevalence of hypothyroidism in the elderly is vast. It includes efforts to define more adequate serum TSH reference intervals for older adults, research into the potential contribution of decreased thyroid function to increased longevity, and the ever-present question of whether or not to treat for a dysfunction that may or may not be present.

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