

Subclinical Hyperthyroidism: Considerations in Defining the Lower Limit of the Thyrotropin Reference Interval

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BACKGROUND: Although numerous reports have discussed the upper limit of the thyrotropin (TSH) reference interval, none have dealt with the lower limit. Recent recommendations regarding subclinical thyroid dysfunction give different advice about its management, depending on whether the TSH concentration is <0.1 mIU/L or 0.1–0.4 mIU/L.

CONTENT: We review key studies that have investigated the links between low TSH concentrations, cardiovascular morbidity, and mortality, with a focus on the TSH measurement threshold and assay type.

SUMMARY: Despite numerous consensus guidelines and publications of expert opinion, the management of subclinical hyperthyroidism remains largely intuitive and “nonevidence-based.” The primary reason for this unsatisfactory situation is the absence of clinical-intervention trials. Important aspects that remain to be addressed are the influence of the method used to measure TSH, the definition of “normality,” and the lack of evidence to base the grading of cardiovascular risk on the degree of TSH suppression. A risk-based approach should be adopted to determine the thresholds that would justify interventions. Such considerations assume, of course, that proof will emerge from ongoing clinical trials to support the medical utility of treating subclinical hyperthyroidism.

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Subclinical thyroid diseases are defined by an isolated thyrotropin (TSH)³ abnormality accompanied by thy-

roid hormone concentrations within the laboratory reference interval in patients who usually are asymptomatic or have nonspecific clinical complaints. The serum TSH concentration is considered the most sensitive marker of thyroid dysfunction because of the logarithmic inverse relationship between TSH and the serum concentrations of thyroid hormones: slight variation in free thyroxine or free triiodothyronine leads to large variation in TSH (1). The reference interval for TSH in the population, however, presents an important question, because each individual is considered to have a unique “set point” for the relationship between thyroid hormone concentrations and TSH (2). Thus, the TSH reference interval is currently a subject of intense interest among clinicians who care for patients with subclinical thyroid diseases.

Over the past 5 years, numerous reports have discussed the upper reference limit for TSH, e.g., (3–7), and several arguments in support of changing the reference interval, such as the necessity to take into account patient age (8), have been published. No study, however, has addressed the question of the lower limit of the TSH reference interval. Moreover, several recent recommendations regarding subclinical thyroid dysfunction have imparted different advice on clinical management, depending on whether the TSH concentration is <0.1 mIU/L or between 0.1 and 0.4 mIU/L, while not mentioning anything about the lower reference limit. Such recommendations imply a gradation in the risk associated with subclinical hyperthyroidism, but the evidence for such a gradation is weak, partly because the studies that have demonstrated cardiovascular complications or considered the mortality associated with low TSH concentrations have used varying thresholds and different assays. The aim of this mini-review is to reassess the evidence in key studies that have investigated the links between low TSH concentrations, cardiovascular morbidity, and mortality, with a focus on the TSH threshold and type of assay. Other clinical consequences of subclinical hyperthyroidism have recently been reviewed (7); however, the relationships between this thyroid abnormality and other characteristics, such as cognitive function, quality of life, and bone metabolism, remain controversial and cur-

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³ Nonstandard abbreviations: TSH, thyrotropin (thyroid-stimulating hormone); AF, atrial fibrillation; NHANES III, Third National Health and Nutrition Examination Survey; NACB, National Academy of Clinical Biochemistry.

Table 1. Epidemiologic studies on AF and/or mortality in subclinical hyperthyroidism.

Reference	TSH assay	Manufacturer	TSH threshold, mIU/L	Subclinical/total patients, n	Age, years	Increased risk of AF?	Increased risk of mortality?
Sawin et al. (9)	ICMA ^a	Nichols Institute	0.1–0.4	61 + 187/2007	≥60	Yes	NA
Auer et al. (10)	IRMA	Henning/Behring	0.4	613/22 300	67.9 (9.2) ^b	Yes	NA
Cappola et al. (11)	LumaTag ICMA	Nichols Institute	0.44	47/3233	≥65	Yes	No (see text)
Parle et al. (13)	MAIA Clone ICMA	Serono Diagnostics	0.5	70/1191	≥60	NA	Yes
Gusseklou et al. (14)	Elecsys 2010 EICMA	Roche Diagnostics	0.3	17/530	≥85	NA	No
Van den Beld et al. (15)	Amerlite TSH-30 ICMA	Ortho Clinical Diagnostics	0.4	44/403	73–94	NA	No
Walsh et al. (16)	Immulite 2000 ICMA	Diagostic Products Corporation	0.4	37/2108	≥50	NA	No

^a ICMA, immunochemiluminescence assay; NA, data not available; IRMA, immunoradiometric assay; EICMA, electroimmunochemiluminescence assay.
^b Data are presented as the mean (SD).

rently appear less clinically relevant than cardiovascular endpoints.

Atrial Fibrillation

In 1994, Sawin et al. (9) first reported an association between an increased risk of atrial fibrillation (AF) and low TSH concentrations for individuals in the Framingham cohort. The risk of developing AF was 3 times greater in individuals with TSH concentrations below 0.1 mIU/L ($n = 61$) than in individuals with so-called normal TSH concentrations (0.4–5 mIU/L, $n = 1576$). The assay used in this study (from Nichols Institute Diagnostics) was one of the first third-generation assays available, with a limit of detection of 0.005 mIU/L. Of note is that individuals with “slightly low” TSH concentrations (i.e., 0.1 mIU/L < TSH < 0.4 mIU/L; $n = 187$) had a lower but still significantly increased risk of AF (relative risk, 1.6; $P = 0.05$). In 2001, Auer et al. (10) confirmed the association of subclinical hyperthyroidism with AF in a transversal study of 23 638 patients from Austria. AF was present in 78 patients (12.7%) with TSH concentrations ≤0.4 mIU/L and typical thyroid hormone concentrations, in 100 patients (13.8%) with overt hyperthyroidism, and in only 2.3% of patients with euthyroidism. The assay used in this study (initially commercialized by Henning and then by Behring) was a second-generation assay with an analytical limit of detection of 0.01 mIU/L. The functional sensitivity was not defined, but the CV at 0.04 mIU/L was only 11%, which suggests that the assay was sufficiently sensitive. More recently, Cappola et al. (11) found the same association with AF [adjusted hazard ratio, 1.98 (95% CI,

1.29–3.03)] in a cohort of 3233 American patients ≥65 years of age. Forty of these patients had TSH concentrations between 0.10 and 0.44 mIU/L, and 7 patients had a TSH concentration <0.10 mIU/L and a typical free thyroxine concentration. The investigators pooled these 47 patients for the analysis and measured TSH with a third-generation immunochemiluminescence assay (LumaTag hTSH; Nichols Institute) with a functional sensitivity of 0.008 mIU/L.

These 3 studies thus have independently demonstrated with a modern second- or third-generation assay that TSH concentrations <0.4 mIU/L are associated with a 2- to 3-fold increase in risk for developing AF (Table 1). The justification for distinguishing 2 thresholds for TSH relies only on the study of Sawin et al., who found the increased risk of AF appeared to be less marked in individuals with TSH concentrations between 0.1 and 0.4 mIU/L. Nonetheless, the increased risk of developing AF was statistically significant in this study, and this result was confirmed in the other 2 studies. All 3 studies used sensitive TSH assays that allowed a distinction between markedly reduced TSH concentrations and moderately reduced TSH concentrations. Consequently, there is little evidence to justify the recommendation of different approaches to the management of patients with subclinical hyperthyroidism that depend on the degree of TSH suppression.

Cardiovascular and Global Mortality

Völzke et al. (12) recently reviewed the association between thyroid dysfunction and mortality and con-

cluded that no strong evidence currently existed for such a causal relation. Of the 8 studies on hyperthyroidism cited in their review, 5 focused solely or partially on patients with subclinical hyperthyroidism (see Table 1). Parle et al. (13) reported an increase in global and cardiovascular mortality in an English cohort of patients ≥ 60 years of age who had a TSH concentration below 0.5 mIU/L. The risk was particularly significant in the first 5 years of follow-up, with a hazard ratio of 1.8 (95% CI, 1.2–2.7) for all-cause mortality and 2.2 (95% CI, 1.1–4.4) for cardiovascular mortality. Twenty of the study participants had TSH values below 0.1 mIU/L (only one had overt hyperthyroidism), and 51 had TSH concentrations between 0.1 and 0.5 mIU/L. The second-generation assay used to measure TSH concentration (Serono Diagnostics) had an unsatisfactory functional sensitivity of 0.1 mIU/L. There were no separate analyses for the 2 different TSH thresholds.

Gusseklou et al. (14) investigated a cohort of 530 Dutch patients ≥ 85 years of age, 17 of whom had a TSH concentration < 0.3 mIU/L, and found no relationship between low TSH concentration and mortality over a 4-year follow-up period. The TSH assay used in this study was a third-generation electroimmunochemiluminescence technique (Roche Diagnostics), with a functional sensitivity that was not mentioned in the report but was 0.014 mIU/L according to the manufacturer. Surprisingly, the investigators found a link between high TSH concentrations and a lower risk of mortality, but others have yet to confirm this result.

Van den Beld et al. (15) used an immunometric technique (Amerlite TSH-30; Ortho Clinical Diagnostics) to study the mortality rate of a Dutch cohort of 403 elderly men 73–94 years of age. The TSH concentration was < 0.4 mIU/L in 44 of the men, 6 of whom had TSH concentrations < 0.1 mIU/L. Although the authors found no association between a low TSH concentration and mortality, they suggested that the low TSH concentrations in some of the men could have been due to other causes, such as aging or nonthyroidal illnesses, and not necessarily to subclinical hyperthyroidism.

Thirty-seven individuals (1.8%) of an Australian cohort of > 2000 individuals ≥ 50 years of age had TSH concentrations < 0.4 mIU/L, but the number of individuals with TSH concentrations below 0.1 mIU/L was not given (16). TSH was measured in this study by an assay with the Immulite 2000 chemiluminescence analyzer (Diagnostic Products Corporation/Siemens Healthcare Diagnostics), which had a functional sensitivity of 0.02 mIU/L. The adjusted hazard ratios for cardiovascular death and cardiovascular events were not statistically significant [1.0 (95% CI, 0.2–4.3) and 1.3 (95% CI, 0.6–3.3), respectively]. Again, the sample

size was small, and the patients with coronary heart disease at baseline had been excluded from participating in the study.

Cappola et al. (11) found an increased mortality risk in individuals with subclinical hyperthyroidism (58.1 vs 34.2 deaths per 1000 person-years, $P = 0.02$), although the statistical significance of the difference disappeared after adjusting for age and sex.

In conclusion, there is no convincing evidence to support a link between low TSH concentration and mortality. The reviewed studies were not designed for that purpose, however; most had insufficient statistical power and included specific patient populations. Although there were no convincing data to support a relationship between low TSH concentration and mortality, neither were there any data to suggest the absence of a clinically significant link.

Guidelines for the management of subclinical hyperthyroidism are based not only on the studies reviewed in this mini-review but also on numerous other studies relating to cardiac and hemodynamic modifications revealed by echocardiographic, electrocardiographic, or other sophisticated approaches (7, 17). The latter studies rely on surrogate markers, however. The clinical pertinence of these studies has not been established, and no clinical trial has shown any benefit of treating subclinical hyperthyroidism for the prevention of cardiovascular morbidity and mortality. Experts in the field (7, 18, 19) recommend performing prospective clinical trials. According to available databases (such as at <http://clinicaltrials.gov> or <http://www.controlled-trials.com>), only 2 such trials are currently being conducted: one in France and the other in the UK. The 2 trials have chosen different TSH thresholds, 0.1 mIU/L for the UK trial and 0.4 mIU/L for the French trial. The initial threshold of 0.1 mIU/L in the French trial was amended following the publication of the study of Cappola et al. (11). There appears to be no ongoing trial in the US.

In the American Thyroid Association consensus statement, the cases of patients with TSH concentrations < 0.1 mIU/L and those with TSH concentrations between 0.1 and 0.45 mIU/L are discussed separately. No justification was given for the choice of 0.45 mIU/L instead of 0.4 mIU/L. The decision was probably based on the data of the Third National Health and Nutrition Examination Survey (NHANES III) study, which proposed a TSH reference interval (2.5th–97.5th percentile) of 0.45–4.12 mIU/L for a “selected” typical population (20). This population excluded, in particular, patients with a known thyroid disorder, such as nodular goiter, and individuals positive for antithyroperoxidase antibodies. The consensus statement did not mention or give any recommendations regarding potential differences that depended on the type of TSH assay.

Of note is that no data have demonstrated subclinical hyperthyroidism to have deleterious consequences in patients <50 years of age. Aging is the main risk factor for AF, and the evidence for the cardiac effects of subclinical hyperthyroidism that has been demonstrated in young patients [particularly in patients with exogenous subclinical hyperthyroidism; see (7) for a review] again relies on surrogate markers, the clinical significance of which remains unknown. Finally, we note that a physiological decrease in TSH occurs during the first trimester of pregnancy due to human chorionic gonadotropin-mediated thyroidal stimulation. Thus, the TSH reference interval for the first trimester is lower, but the general question of the implications of this reference interval during pregnancy for the mother and the child is beyond the scope of this review (21).

Does the Choice of TSH Assay Matter?

Since the mid 1980s, the development of methods for measuring TSH in plasma has shown considerable progress—from the initial first-generation assays with functional sensitivities of 1 mIU/L to the current third-generation assays that have functional sensitivities of 0.01 mIU/L. Functional sensitivity, defined as the lowest concentration with an interassay imprecision of $\leq 20\%$, must be established over a clinically relevant interval (at least 6–8 weeks for TSH) with human serum pools and at least 2 different reagent lots and instrument calibrations. The National Academy of Clinical Biochemistry (NACB) has defined third-generation assays as having a functional sensitivity of 0.01–0.02 mIU/L (22). This improved sensitivity has permitted the distinction between completely suppressed TSH concentrations (<0.01 mIU/L with a third-generation assay) and moderately suppressed TSH concentrations. Thus, the lower reference limit for TSH should be reconsidered in view of the performance of modern assays. Very few studies, however, have compared the performance characteristics of modern assays, which are mostly based on nonisotopic immunometric principles. In a recent study comparing 6 third-generation TSH assays, Rawlins and Roberts (23) demonstrated significant differences between the methods, particularly at TSH concentrations <0.2 mIU/L, and concluded that “additional harmonization efforts” were needed. For example, the TSH concentration of one of the controls in this study ranged from 0.362 to 0.530 mIU/L, depending on the assay. Beckett and MacKenzie (24) reported the same discrepancies in a UK National External Quality Assessment Service survey, in which a pooled sample with a mean endogenous TSH concentration

of 0.13 mIU/L exhibited concentrations that varied from 0.04–0.15 mIU/L with the 8 different methods. These differences may be due in particular to differences in the specificities of the assays’ various anti-TSH monoclonal antibodies with respect to TSH isoforms (25).

Defining Normal Thyroid Function

Numerous controversies exist regarding the appropriate method for determining the TSH reference interval. As for every biological variable, the classic population-based method consists of studying the distribution of TSH values in a large sample of a typical population. In the case of TSH, the prevalence of thyroid diseases or thyroid “abnormalities” such as euthyroid goiter, isolated positivity for antithyroid antibodies, and a family history of thyroid abnormalities often has led to the selection of “supernormal” individuals. The aim of this review has not been to discuss the pertinence of these choices but rather to discuss their consequences. Kratzch et al. (25) established a TSH reference interval for the 2.5th and 97.5th percentiles with a German sample of 870 individuals: 0.30–3.63 mIU/L for the entire group and 0.40–3.77 mIU/L for the “constraint group.” Thus, the lower limit of the TSH reference interval in this study could be 0.3 or 0.4 mIU/L, depending on the definition of a “normal” population. Finally, iodine status has an impact on the risk and type of thyroid dysfunction. Hyperthyroidism due to thyroid autonomy is more frequent in iodine-deficient areas, whereas hypothyroidism is more frequent in iodine-replete areas. Thus, iodine intake may also influence the lower limit of the TSH reference interval in a given area (26).

Conclusion

Despite numerous consensus guidelines and expert opinions, the management of subclinical hyperthyroidism remains largely intuitive and not based on evidence. The main reason for this unsatisfactory situation is the absence of clinical-intervention trials, although other causes should also be discussed. Some issues that need to be addressed in recommendation reports are the importance of the method used to measure TSH, the definition of “normality,” and the lack of evidence to grade cardiovascular risk according to the degree of TSH suppression. In our opinion, it is time for the medical community to adopt a risk-based approach, not for determining reference intervals but for establishing thresholds that could justify interventions. This conclusion assumes, of course, that proof will emerge that supports the medical utility of treating sub-

clinical hyperthyroidism. We hope that the 2 ongoing European trials will produce this evidence.

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acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

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