Thyroid Function Changes in the Elderly and Their Relationship to Cardiovascular Health: A Mini-Review

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Abstract
Background: Thyroid hormones have significant effects on the cardiovascular systems. In general, hyperthyroidism is associated with an increased risk of dysrhythmias, while hypothyroidism may cause atherosclerosis. Recent large studies have sought to identify aging-associated changes in thyroid function and their relevance to cardiovascular morbidity and mortality in the elderly. Conflicting results have often been published, likely due to the heterogeneity of the studied populations. Objective: This review seeks to briefly summarize the most recent large population studies analyzing thyroid changes with aging and interpreting their effects on cardiovascular health in the elderly. Methods: Selective review of recent literature. Results: The emerging pattern suggests a slight decrease in thyroid function in the elderly leading to slightly higher thyroid stimulating hormone (TSH) levels. However, the incidence of mild hyperthyroidism also increases, especially in populations with historical or current iodine deficiency. Large observational studies suggest that the potential harm from mild hypothyroidism seen in younger population tends to diminish in older subjects, while the harm from mild hyperthyroidism becomes more significant. A markedly increased risk of atrial fibrillation is a well-established consequence of subclinical hyperthyroidism in patients in the sixth decade of life and beyond. Conclusions: The absence of large prospective interventional data does not allow the formulation of strict clinical recommendations, but a higher TSH threshold for treating both subclinical hypothyroidism and subclinical hyperthyroidism in the elderly seems reasonable.

Introduction
The scientific developments of the last century have brought an unprecedented expansion of human longevity. Biomedical disciplines have faced new challenges, with the goal of understanding health and disease in the...
Thyroid Function Changes in Aging

Thyroid function is precisely assessed by measurements of serum thyroid stimulating hormone (TSH) and thyrotropin. In the absence of pituitary disease, a precise inverse relationship between free thyroxine (FT4) and the logarithm of TSH can be derived across the spectrum of primary thyroid function and dysfunction. Given the logarithmic response of TSH to changes in FT4 levels, TSH measurement allows for more precise estimation of thyroid function than the thyroid hormones themselves. In addition, compared with many other hormonal axes, thyroid secretion is fairly stable over time, so that much of the variation appears to be inter-individual rather than intra-individual [1]. Part of the inter-individual variation has indeed been linked to distinct genetic loci in several genome-wide association studies [2]. Interestingly, many of the loci seem to involve genes expressed in thyroid cells, either in the TSH receptor pathway, or transcription factors expressed in the thyroid cell, while factors related directly to TSH secretion and expressed in the thyrotrope have not been involved. This is in keeping with studies in the mouse, indicating a strain-dependent difference in thyroidal T4 production in response to TSH [3]. The genetically determined variation in thyroid function tests is contained within the normal range in most large studies; however, it may change the threshold for developing an abnormal TSH, for example, as a consequence of thyroid autoimmunity [4].

In spite of its variability, TSH remains the primary test of thyroid function [5]. Statistical methods applied to large populations, have established a fairly wide, but reproducible reference range for TSH, typically 0.5–4.5 mU/L [6]. Whether this TSH range should be applied to define normal thyroid function in all populations has been much debated over the past 15 years. In subjects classified as normal, TSH levels are not distributed normally to the high end of the normal range, suggesting the existence of one or more subgroup that may have been misclassified as “normal” and therefore skewed the high end of the normal range [7]. Among other aspects, this controversy has prompted studies on the effect of age on thyroid function. This problem is further intensified by the finding that thyroid autoimmunity is quite common in the general population and becomes more common with aging. Since thyroid autoimmunity (as manifested in Hashimoto’s thyroiditis or Graves’ disease) is the main cause of overt and subclinical thyroid dysfunction, carefully excluding patients with thyroid autoimmunity is critical in selecting a reference population expected to have a truly normal thyroid function. Indeed, thyroid peroxidase antibody can be found in up to 30% of unselected subjects aged 70 and older [8]. The NHANES survey is not the largest, but maybe the most detailed study in this field. The authors were able to measure TSH levels in 13,344 healthy subjects, excluding all those with known thyroid disease or on thyroid medications, and most importantly, all those with thyroglobulin or thyroid peroxidase antibody. While autoantibodies, such as the rheumatoid factor, are common in the elderly without clear clinical consequences, the presence of thyroid autoantibodies is associated with thyroid function changes in the elderly as well as in the young. In the NHANES reanalysis, people >70 years old with TPO antibodies had an incidence of TSH >4.5 of about 50%, compared to 10% in the “disease free” group [9], validating the removal of elderly subjects with thyroid autoantibodies from the “healthy control” groups. In the NHANES survey, the 2.5th and 97.5th percentile TSH concentration in the whole population were 0.45 and 4.12 mU/L respectively. However, in the groups aged 70–79 and older than 80 the 97.5th percentile TSH was found at 5.9 and 7.5 mU/mL respectively. In the same population, total thyroxine decreased with age. These findings were confirmed in at least 2 larger population-based studies that made an effort to exclude subjects with pre-existent thyroid disease [10, 11]. It is worth mentioning that earlier studies had shown conflicting result, suggesting no change or even a decline in TSH levels with age [12, 13]. However, those studies involved populations 2 or 3 orders of magnitude smaller than the 3 more recent studies, which included approximately 300,000 subjects altogether [6, 10, 11]. It is also possible that older case series had a higher inci-
dence of non-thyroidal illnesses in the older subgroups, while this confounder might have become less common with the overall improving health of aged people seen over the very last 2 or 3 decades in Western countries. In addition, the iodine nutritional status of the populations studied may result in different thyroid function patterns during aging. A large cross-sectional study in a population with borderline sufficient iodine intake actually showed a gradually decreasing median TSH in older age groups [14]. A recent follow-up report of the Rotterdam study also showed a progressive increase in FT4, with relatively stable TSH level [15]. These limitations notwithstanding, the most recent and larger datasets suggest a progressive mild increase in the TSH level, at least in iodine sufficient populations. As a result, when applied to the older age groups, the general population-derived reference range for TSH would result in a larger proportion of older people being classified as hypothyroid, although the forecasted impact varies depending on which study the data is derived from [16].

The pathophysiology of these thyroid function changes remains uncertain. From a population perspective, the increase in median TSH could result from the progressive age-dependent selection of subjects with a slightly elevated TSH, or, as an alternative from a mechanism through which many subjects see their TSH slightly increase over time. The first hypothesis would imply a slight elevation in TSH to be advantageous in older age. Studies have suggested a strong intra-individual stability of TSH levels over time [1]; however, the period of observation was short, a year. A study in a large group of twins showed a strong (65%) heritability of the TSH to T4 relationship [17] and genome-wide genetic analyses have indicated genomic loci or gene variations implicated in individual TSH/T4 levels [18, 19]. In yet another study, slightly elevated TSH levels observed in centenarians were found to be inheritable, as similar findings were observed in their already elderly offspring [20]. These observations being cross-sectional, however, do not rule out interactions of environmental factors with genetic determinants causing TSH changes over decades. A few prospective studies have provided useful information. Bremner et al. [21] followed a group of middle-aged subjects without thyroid disease for 13 years and confirmed a progressive increase in the TSH level during the observation period. Waring et al. [22] obtained very similar results in a similarly designed study, a prospective study over a median period of 13 years. The authors observed a slight increase in median TSH over time, a decrease in T3 levels and a mild increase in FT4 levels. Of note, as in previous studies [6], the 2.5th percentile for TSH was also lower in the oldest age group. The population studied was significantly older than in the Bremner study, which may explain some differences in the results. These findings from prospective studies suggest that the age-related right-shift observed in TSH distribution is not the result of the selection of surviving individuals with a previously higher-than-median TSH but rather an upward drift in individuals with previously normal TSH levels.

At the organism level, an increase in TSH could be seen with a decrease in sensitivity to T4 of the pituitary/hypothalamus, with the production of a less bioactive TSH, or with a lower responsiveness of the thyroid to TSH stimulation. The first hypothesis seems unlikely, as it would be associated with an increase in FT4, a finding not supported by any study. More complex models may also be hypothesized, involving changes in the peripheral metabolism and use of thyroid hormones. There are not enough in vivo human data to support either hypothesis. Either way, the current interpretation is that these changes in TSH signal lower thyroid hormone levels, at least in stably iodine-replete populations.

Interestingly, all 3 largest studies also indicated a drop of the 2.5th percentile TSH level in older groups [6, 11, 23]. Some of these findings are probably the effect of a progressively increasing prevalence of thyroid autonomy in populations with a current or remote history of iodine deficiency, as supported by a consistent increase in FT4 (discussed in further detail in another section). Indeed, while some studies used serological studies to exclude patients with thyroid autoimmunity, none of the studies employed robust criteria to exclude patients with thyroid nodules, a common cause of mild hyperthyroidism in the elderly, especially in areas of moderate to severe iodine deficiency [24]. Therefore, based on the available data, it is presently difficult to consider a low TSH “physiologic” in the elderly. This is an aspect that will require further studies, considering the accumulating evidence suggesting adverse effects of mild hyperthyroidism in the older population (see below, section on hyperthyroidism).

**Effects of Lower Thyroid Hormone Levels in the Elderly**

Hypothyroidism is characterized by reduced thyroid hormone availability both in the target tissues and the pituitary level. Hypothyroidism is best identified by an
elevation in TSH levels to all practical effects. Overt hypothyroidism is defined by an elevated TSH with concurrent abnormally low FT4. Overt hypothyroidism causes significant morbidity [25] and, probably, mortality. Even though there are no evidence-based studies, there is very little controversy on the advantages of treating overt hypothyroidism [26]. Subclinical hypothyroidism (SCHO), on the other hand, is much more common. SCHO is most commonly defined as an elevation in TSH above 4.5 mcU/mL, with normal FT4. Less commonly, SCHO is diagnosed in subjects with TSH between 4.5 and 10 mcU/mL. The NHANES survey [6] reported a prevalence of SCHO of 4.3%, compared to 0.3% for overt hypothyroidism, hence representing a much more significant public health problem. SCHO is by no means limited to elderly subjects, but given the evidence suggesting an increase in TSH with age, the question must be asked whether this phenomenon is neutral, beneficial, or detrimental in the aging person. While a higher TSH level may be “normal” in the elderly, we still need to understand the consequences of the slightly lower thyroid hormone level on the aging population. In several animal studies, a lower thyroid hormone level is associated with longevity and among animals of similar size, the species with lowest thyroid hormone levels live the longest [27]. On the other hand, SCHO in humans is variably associated with adverse changes in several surrogate markers of cardiovascular disease. For example, there is reasonable evidence from large studies that patients with SCHO may present with higher LDL and total cholesterol than euthyroid subjects [23]. Several other studies, generally in small and selected groups of patients have shown an increased prevalence of diastolic and/or systolic dysfunction, increased endothelial media thickening, and other cardiac parameters (reviewed in [28]). However, the actual clinical consequences at-large of these laboratory or instrumental abnormalities remain to be clarified, in the elderly as well as in the young. The relationship between thyroid function and morbidity and mortality in humans has been studied through 2 broad categories of studies. The first encompasses a large number of relatively small case-control studies comparing a large variety of parameters or outcomes in patients with SCHO versus euthyroid subjects. The advantage of this approach is the ability of fully control for a relative large number of well characterized pre-selected variables and also, by using firm criteria for a dichotomous variable such as “SCHO,” to provide clear guidelines to be applied in clinical practice. There are unfortunately, several drawbacks to this method, the most important being the risk of ascertain-
identified 4,735 subjects with SCHO and older than 39 from a large British primary care database. The authors showed a clear reduction in the risk of cardiovascular events only in patients treated with levothyroxine younger than 70. The effect was not detectable in subjects older than 70 [38].

In summary, the question of the effects of mild hypothyroidism in elderly subjects remains yet to be answered in full, but it appears that untoward effects of mild thyroid hypofunction become less significant or even disappear with progressing age. One possible interpretation for this finding is statistical. It is possible that the effects of thyroid dysfunction, demonstrable by current studies in the young, are overcome and masked by the concurrent effect of traditional risk factors, such as dyslipidemia in the elderly. If that is the case, then larger and therefore more powerful studies should be able to confirm an effect of mild thyroid underactivity in the elderly. It is indeed possible that in the future, when cardiovascular and other mortality causes in the elderly improve, a biological effect of SCH in this age group is detected. The other possible explanation is more fundamental and based on evidence that a lower metabolic rate may lead to longevity in several species. In this view, the untoward cardiovascular marker profile seen with hypothyroidism would be counteracted by the metabolic effects in aged subjects, leading to a neutral or even beneficial effect of mild hypothyroidism in older age. This could have led to the selection of a physiologic mechanism providing a slight decrease in thyroid function in the elderly as an evolutionary advantage. No matter what the interpretation, current studies seem to suggest that the TSH threshold for treating hypothyroidism in the elderly should be progressively higher with progressive age. However, the described limitations and contradictions in the available data have failed to allow the generation of precise guidelines to be used in clinical practice [39]. The difficulty of obtaining definitive data is illustrated by the fact that the most ambitious randomized, placebo-controlled trial of levothyroxine treatment in the hypothyroid elderly was unable to provide information on cardiovascular morbidity and mortality due to insufficient recruitment [40].

**Effects of Hyperthyroidism in the Elderly**

Mirroring hypothyroidism, hyperthyroidism can be classified as overt, with subnormal TSH and elevated thyroid hormone, or subclinical (SCHE), with subnormal TSH and normal thyroid hormone levels. Hyperthyroidism is clearly less common than hypothyroidism: the Colorado Health Fair study showed a prevalence of subnormal TSH in 2.2% of the studied population [23], while the NHANES survey indicated a slightly lower prevalence of 1.3% almost equally subdivided between SCHE, and overt hyperthyroidism cases [6]. The latter study, however, showed a clear increase in the prevalence of hyperthyroidism with age, with 4–7% subjects affected in the age groups 70 and older. Manifestations of hyperthyroidism are age-dependent, with cardiovascular symptoms more prominent in aged persons, while sympathetic symptoms prevail in the young [41]. This phenomenon may reflect a shift in the etiology of hyperthyroidism. Graves’ disease’s incidence peaks in women in the 4th and 5th decade. With aging, autonomously functioning thyroid nodules become the predominant cause of new onset hyperthyroidism, especially in iodine-deficient areas [42]. The natural history of the 2 diseases is quite different. In Graves’ disease, the sudden onset of moderate to severe hyperthyroidism is typically quite sudden, with symptoms developing rapidly over a period of weeks, or a few months at most. In autonomously functioning thyroid nodular disease, a smoldering process lasting many years is most often observed, with very slow progressive depression of TSH levels through the low end of normal, often times never exceeding SCHE in terms of severity. This difference in the tempo of onset may affect the clinical presentation and also the timeliness of the diagnosis. It is also possible, however, that the tissue sensitivity to thyroid hormone changes with age in different directions. No matter the etiology of the hyperthyroidism, atrial fibrillation (AF) is distinctly more common in older than younger patients: 35 vs. 2% in one study [41]. Since overt hyperthyroidism is associated with a multiplicity of symptoms and an increased risk of AF, heart failure and osteoporosis in all age groups studied, it is typically treated in all age groups given the overwhelming clinical evidence of benefit. The approach to SCHE is more controversial, given that most people are asymptomatic. It is important to distinguish endogenous SCHE from iatrogenic SCHE, often seen in patients treated with levothyroxine for hypothyroidism. The thyroid hormone profile in iatrogenic SCHE is different from endogenous forms in that the triiodothyronine is lower due to the partial inhibition of D2 deiodinase exerted by thyroxine excess. Therefore, results of studies done on endogenous SCHE, which are the majority, may not apply to iatrogenic cases.
SCHE and Cardiovascular Morbidity

A relatively large retrospective study including 2004 persons with endogenous SCHE compared with 10,111 subjects from the same Scottish town demonstrated increased cardiovascular morbidity in general and dysrhythmias in particular. This important study was not limited to the elderly, but the average patient age in cases was 66.5, reflecting more intensive thyroid function testing in the elderly. Importantly, the hazard ratio for cardiovascular disease was 1.67 in the whole group of patients with SCHE and slightly higher (1.75) in subject with undetectable TSH, suggesting causality [43]. In contrast, a very large, also retrospective study including greater than 17,000 patients treated with levothyroxine (average age 61), demonstrated an increased risk for non-specified cardiovascular disease and dysrhythmias in those with an undetectable TSH, but not in those with a subnormal TSH alone [44]. This finding supports the view that exogenous SCHE may have a lower impact than its endogenous counterpart.

AF and atrial arrhythmias are specific cardiac complications of overt hyperthyroidism and have been studied in greater detail. A landmark study first demonstrated a markedly increased incidence of AF in subjects older than 60, with TSH < 0.1 mU/L [45]. In this cohort, the relative risk for AF was 3 times as high as in people with normal of slightly low TSH and, remarkably, the cumulative incidence of AF in the 10 years following inclusion in the study was 28%. Cappola et al. [30] later confirmed these findings in a subsequent larger study and demonstrated an increased risk for non-specified cardiovascular disease and dysrhythmias in those with an undetectable TSH, but not in those with a subnormal TSH alone [44]. These findings suggest a higher TSH threshold for treating AF, but there might also be an increase in CHD.

The link between SCHE and coronary heart disease (CHD) has been less clear, as some large studies have offered discordant results [30, 48]. A very large and more recent participant-level meta-analysis was only able to show a 1.2, not statistically significant relative risk for CHD events in a very large cumulative cohort from multiple prospective studies [49]. In the same paper, there was a barely significantly increased mortality from CHD. These data suggest that the influence of SCHE on the risk of CHD is quite weaker than on AF.

SCHE and Cardiovascular Mortality

A number of studies have examined the relationship between SCHE and mortality in large populations. The first large study, in 2001, included 1,191 subjects aged 60 or older followed for 10 years after the initial inclusion and thyroid function testing. The authors observed excess mortality form cardiovascular causes in subject with TSH < 0.5 mU/mL. The mortality was not higher when subjects with undetectable TSH alone were included, but this possibly reflected too small a sample for further subgrouping. Further subdivision by mortality causes showed both cardiac disease proper and cerebrovascular disease among the causes [50]. Other studies, while confirming the association with AF, failed to demonstrate increased mortality in older subjects with SCHE [30]. As previously noted, a large meta-analysis showed a slight increased mortality in subjects older than 65 with SCHE [49].

Conclusive Remarks

In this mini-review, the current understanding of thyroid function changes in aging and their consequences on cardiovascular health has been summarized. In spite of a large body of population data, a unifying model has not been established yet. The incidence of both slightly elevated and slightly suppressed TSH increases with age. The emerging picture suggests a progressively less significant negative effect of mild hypothyroidism with aging. This may represent a shift in the balance from the effect of the atherogenic changes seen with mild hypothyroidism in the young toward potential protective effects caused by a lower metabolic rate in the elderly, but this interpretation remains hypothetical, if attractive. On the other hand, mild hyperthyroidism is clearly responsible for increasing cardiovascular morbidity. The predominant and well-established consequence is an increase in the risk of AF, but there might also be an increase in CHD. These findings suggest a higher TSH threshold for treatment at both ends of thyroid dysfunction, especially with regard to hyperthyroidism. In the absence of large prospective intervention studies, however, it is difficult to formulate strict clinical guidelines.
References


