Thyroid Function and Longevity: New Insights into an Old Dilemma

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Thyroid function changes in the elderly, and many studies in the last 30 yr have investigated the role of thyroid function in the aging process. Recent reports have convincingly shown that serum TSH levels increase with age, independent of the presence of antithyroid antibodies. This suggests that thyroid function decreases with age (1, 2). In contrast, other studies have shown low levels of serum TSH in the elderly (3). With regard to other thyroid function tests, most studies demonstrated an age-dependent decline in serum free T_3 levels, whereas free T_4 (FT_4) levels remained relatively unchanged and rT_3 levels increased with age (3).

The difficulty in interpreting these results is that the evaluation of thyroid function in the elderly is often complicated by the increased prevalence of chronic illness and the use of medication. Chronic illness is associated with low levels of T_3 and high levels of rT_3, and, depending on the duration and the severity of the illness, TSH and FT_4 levels may be low as well (4). Some of these changes are similar to the changes in thyroid hormone levels observed in the elderly. Therefore, distinguishing between changes related to "normal" aging *per se* and changes that are abnormal, *i.e.* disease-related, is a major challenge. In addition, differences in iodine intake and in the presence of autoimmune thyroid disease between these study populations may play an important role as well (5, 6).

There is evidence that a low activity of thyroid hormone might be beneficial in the elderly (1, 7, 8), whereas subclinical hyperthyroidism is a predictor of mortality (9). It has been demonstrated that subjects with exceptional longevity (centenarians; median age, 98 yr) have higher levels of TSH compared with controls (1). Furthermore, increased levels of TSH (7) and low levels of FT_4 (8) have been associated with a better survival in elderly subjects (mean age, 85 and 78 yr, respectively). Based on these studies, it has been argued that the treatment of elderly subjects with elevated TSH levels may be of very limited clinical benefit or may even be unfavorable (7).

The study by Atzmon *et al.* (10) published in this issue of the *JCEM* provides further insights into the role of thyroid hormone activity and longevity. This study demonstrates that also the offspring of people with exceptional longevity have higher serum TSH levels than age-matched controls without familial longevity (median age, 70 yr). This is an important finding because it suggests that the higher TSH levels in centenarians are at least in part due to their genetic background.

One could speculate that the higher levels of TSH in centenarians are a representation of their relative good health, creating a selection bias. However, the study by Atzmon *et al.* (10) makes this option less likely, by demonstrating that the offspring of centenarians have a higher TSH than age-matched controls as well, and by showing a significant but modest degree of heritability for TSH in Jewish centenarians and their offspring. Furthermore, no significant effect of medication on serum TSH levels was detected in their study.

In healthy subjects, serum TSH and thyroid hormone levels show substantial interindividual variability, whereas the intraindividual variability is usually within a narrow range (11). It is estimated that heritability accounts for approximately 40–65% of the overall variation in serum TSH, in addition to environmental factors such as diet, smoking, and medication (12). The causative genes are, however, not well established. In recent years, polymorphisms in different thyroid hormone pathway genes have been associated with se-

Abbreviation: FT_4, Free T_4.

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rum thyroid hormone levels, but so far their contribution to the overall variance is modest (13–16).

To further examine the role of these genetic factors, Atzmon *et al.* (10) analyzed two polymorphisms upstream of the promoter region of the TSHR gene (rs10149689 and rs12050077). There is a high degree of linkage disequilibrium between these two polymorphisms [$r^2 = 0.95$ in Jewish centenarians (Ref. 10); $r^2 = 1.0$ in Caucasians (www.hapmap.org)], implying that these two polymorphisms should not be considered as independent contributing factors. Both polymorphisms were associated with higher levels of TSH in the offspring and control groups (10). In addition, their allele frequency was significantly higher in centenarians and their offspring than in controls, supporting the concept of genetic predisposition for higher TSH levels in families with longevity. However, the allele frequency of both polymorphisms did not differ between centenarians and their offspring, whereas a direct survival benefit of these polymorphisms should have resulted in an increasing allele frequency of these polymorphisms with age.

It is important to realize that only Ashkenazi Jews were analyzed in the study by Atzmon *et al.* (10). Ashkenazi Jews are known for their genetic homogeneity due to founder effects, and this may very well have caused a selection bias. Furthermore, the data have not yet been replicated in an independent cohort. For these reasons, the results from this study cannot be extrapolated to other populations at this point, as is also underscored by the authors in their discussion (10). In addition, consistent associations with serum TSH levels in independent populations have been shown for several other thyroid hormone pathway gene polymorphisms [such as rs4704397 in PDE8B and rs1991517 in TSHR (13, 17)], and there is convincing evidence that polymorphisms in intron 1 of the TSHR gene are associated with Graves' disease (18). It is not specified why two different polymorphisms outside the TSHR promoter region were studied instead. It would be interesting to study whether the allele frequency of these and other polymorphisms, which are known to be related to serum thyroid hormone levels and thyroid disease, are altered in the centenarians and their offspring as well. Moreover, it has been shown that polymorphisms in thyroid hormone pathway genes can have different consequences in different age groups (16). Studying the difference in effect of these polymorphisms on serum thyroid hormone levels in different age groups can provide valuable new insights on the influence of age on the regulation of thyroid hormone bioactivity.

Why would higher levels of TSH be related to longevity? A possible explanation could be that the higher TSH in centenarians and their offspring represents a lower bioactivity of thyroid hormone, although the higher levels of FT_4 in female offspring compared with controls in the study by Atzmon *et al.* (10) do not support this hypothesis. In addition, TSH levels in the study by Atzmon *et al.* were within the normal range in both centenarians and their offspring. However, even thyroid hormone levels within the normal range might be associated with thyroid hormone-related endpoints. This is illustrated by the observation that even in euthyroid subjects with normal TSH, FT_4 is independently associated with atrial fibrillation, especially in the elderly (19). In addition, in ambulatory elderly men, a higher FT_4 within the reference range is associated with lower physical performance, independent of age and illness (8). So these higher levels of TSH within the normal range could still represent a slightly lower bioactivity of thyroid hormone. A lower activity of thyroid hormone, and thus a lower basal metabolic rate, could possibly serve as an adaptive mechanism to prevent catabolism in the elderly. Furthermore, lowering oxidative metabolism will reduce DNA damage reactive oxygen species (20).

Considering all of this, the question remains whether a mildly elevated TSH should be considered as protective in the elderly or whether it should be treated? First of all, it is important that studies in the elderly should not be extrapolated to young or middle-aged individuals. Subclinical hypothyroidism at a younger age has been linked to cardiovascular risk, cognitive function, and neuromuscular dysfunction in multiple studies, although data remain conflicting (21–23). In the elderly, this relationship seems different (24). Two recent meta-analyses of prospective population-based studies that assessed the relationship between subclinical hypothyroidism, ischemic heart disease, and mortality demonstrated an increased risk of ischemic heart disease and cardiovascular mortality in subjects younger than 65 yr with subclinical hypothyroidism (25, 26). In contrast, this risk was not increased in subjects with subclinical hypothyroidism older than 65 yr of age (25, 26). On the other hand, there was no significant protective effect of subclinical hypothyroidism on mortality in the elderly in these studies either.

The few available studies investigating the relationship between serum thyroid function tests and mortality in the elderly suggest that lower levels of T_4 and high levels of TSH might be protective (1, 7, 8). Furthermore, there is convincing evidence that TSH distribution shifts toward a higher level with age (2). The 97.5th percentile of the TSH distribution is 7.5 mU/liter in subjects age 80 yr and older. In other words, the prevalence of subclinical hypothyroidism is clearly overestimated in this group, unless an age-specific reference range is used. Another argument for being reluctant to initiate thyroid hormone substitution therapy in the oldest old could be that TSH suppression is a very common complication of thyroid hormone substitution therapy, especially in the elderly (3, 27).

Ultimately, the question whether or not a mildly elevated TSH should be treated in the elderly can only be

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answered by a well-designed, randomized, placebo-controlled clinical trial. However, is such a trial ethically justified considering the available evidence? The study by Atzmon *et al.* (10), which demonstrates that the higher TSH levels in centenarians are at least in part due to their genetic background, is a valuable addition to the current evidence, but it does not provide additional answers to this question. The currently available evidence suggests that the old adagium "primum non nocere" might be the best answer.

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