INTRODUCTION

The intricate relationship between aging and endocrine systems has been well recognized for decades. Important changes in endocrine signaling occur during aging and vice versa; modification of endocrine signaling may largely affect longevity. The latter is exemplified in many species in which mutations of the growth hormone/insulinlike growth factor 1 pathway prolong life span.¹

Serum thyroid parameters are well known to change with aging.² It is important to recognize nonpathologic changes in thyroid function tests (TFTs) and possible confounders, in particular because features of thyroid disease in elderly patients are often less prominent. In the first part of this article, the authors focus on changes in TFTs during aging and possible confounders, with an emphasis on the serum thyroid stimulating hormone (TSH) reference range. The second part describes the features of thyroid disease in the elderly as well as the challenges and debates on diagnosis and treatment, in particular on subclinical hypothyroidism and hyperthyroidism.

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CHANGES IN TFTS

Many studies have reported changes in serum thyroid parameters with advancing age. Conflicting data may arise from differences in baseline characteristics of the populations studied such as ethnicity and genetic background, nature and prevalence of thyroid diseases, iodine status, and coexisting disease. In this section the authors discuss the changes in TSH and the iodothyronines T4, T3, and rT3 in serum as well as the prevalence and implications of thyroid autoantibodies.

Tsh

Some earlier studies indicated that serum TSH levels do not change during life and remain within the standard reference range or reported even decreased TSH levels in the elderly. However, these studies were relatively small and mainly conducted in iodine-deficient areas. Later (cross-sectional) studies in the United States analyzed serum thyroid parameters sampled from more than 15,000 people (the National Health and Nutrition Examination Survey [NHANES] and Montefiore studies) and showed increased TSH levels with advancing age in iodine-sufficient areas but not in a population with borderline sufficient iodine intake (see also “reference range”). The increase in TSH with age was confirmed in other large longitudinal population studies.

Several mechanisms have been proposed to explain the changes in serum TSH levels with advancing age. Some studies have suggested that the pituitary sensitivity is changed in the elderly. However, discordant results have been found in the response of the pituitary to thyrotropin-releasing hormone or thyroid hormone (TH). Therefore, it remains to be clarified if pituitary gland function changes upon aging and if the negative feedback loop between free T4 (FT4) and TSH is altered in the elderly. Also, the observations that (F)T4 levels are mostly unchanged (see later discussion) may suggest that TSH glycosylation and thus TSH bioactivity is affected.

Although the mechanism is unclear, there is increasing evidence indicating that serum TSH levels change in the elderly, up to values above the upper limit of the traditional reference range. Because TSH is regarded as the most sensitive test to detect primary thyroid disorders, it is of utmost importance to realize that changes in serum TSH levels do not necessarily reflect thyroid disease but rather may be physiologic in the elderly. The relevance for clinical practice is discussed later in this article (see section “TSH reference range”).

The Iodothyronines T4, T3, and rT3

Several studies have shown that serum T4 concentrations remain unaffected during aging, although most of the studies included a limited number of participants. However, the large NHANES study reported an age-dependent decrease in serum T4 concentration. Cross-sectional studies mainly reported normal or slightly decreased serum FT4 levels in the elderly. Two recent longitudinal studies noted unchanged and slightly increased serum FT4 levels.

In strong contrast with conflicting data regarding serum TSH and (F)T4 levels, all studies consistently show a decline in serum T3 and FT3 levels with advancing age. The consistency of this finding is striking and it is tempting to speculate about its biologic meaning. It has been postulated that decreasing T3 will lower basal metabolic rate and, consequently, lower the production of reactive oxygen species and may also reduce damage to biomolecules (eg, DNA) and slow down the aging process. Obviously, such hypotheses need to be confirmed by future (animal) studies.
Serum levels of rT3 are either normal or increased in elderly subjects. In particular, serum rT3 levels may be affected by confounding factors such as illness (see later discussion).

Changes in T4, T3, and rT3 serum levels may result from changes in thyroid gland function and/or peripheral TH metabolism. An early study demonstrated that both TH synthesis and secretion decline with age, in particular in subjects older than 60 years of age. This observation is underscored by the lower levothyroxine (LT4) substitution dose required in hypothyroid elderly patients compared with younger patients.

This study also demonstrated that peripheral degradation of T4 was diminished. These results suggest that T4 concentrations in the elderly are seemingly unaffected because the decrease in T4 degradation equals the decrease in thyroidal T4 secretion. The age-dependent decline in serum T3 levels is likely explained by a decrease in peripheral T4 to T3 conversion, which may contribute to the decreased T4 degradation. However, an increased T3 clearance may also contribute to the declining T3 levels.

The major route of TH metabolism is its stepwise deiodination. The type 1 deiodinase (D1) catalyzes the conversion of T4 to T3 and the degradation of rT3 to T2. The type 2 deiodinase (D2) “activates” TH by catalyzing the conversion of T4 to T3, whereas the type 3 deiodinase (D3) “inactivates” TH by terminating the action of its preferential substrate T3 and preventing the activation of T4. The relative contribution of the deiodinases to the changes in TH levels in aging humans has been inferred from the changes in concentrations of iodothyronines. Furthermore, genetic variation in D1 was associated with lower serum T3 levels in aging men. However, direct assessment of the deiodinase activities in aging humans has not been performed. Theoretically, an increased D3 activity may also explain the decrease in serum T3 levels. Animal studies to investigate age-dependent changes in deiodinase activities are limited.

The increased serum rT3 levels reported in some studies likely reflect changes in deiodinase activities. Diminished activity of D1, whose preferred substrate is rT3, may largely contribute to this observation. D1 is not only known to decrease during illness and caloric restriction, but also reported to diminish in normal aging. To which extent aging per se or confounders contribute is still elusive.

In recent years, the paradigm has evolved that local TH signaling can be modified independent of serum TH levels. Because deiodinases and TH transporters govern cellular thyroid state, changes in these key players of TH regulation may affect thyroid state in a tissue-specific manner. Indeed, it has been shown that T3 uptake into the liver is reduced in aged rats, which agrees with a reduced hepatic expression of the TH transporter MCT8 as well as reduced T3-dependent D1 expression during aging. Future studies are needed to clarify which mechanisms contribute to age-dependent changes in serum and tissue TH levels.

Thus, from the above mentioned observations the picture emerges that during aging serum T3 levels decrease, whereas TSH levels increase (at least in iodine-sufficient areas). Serum T4 levels largely remain unaffected, whereas rT3 levels tend to increase.

Thyroid Autoantibodies

It is well recognized that the prevalence of thyroid antibodies (anti-Tg, anti-TPO) increases during life, particularly in women. This increase in prevalence reaches a plateau between the sixth and eighth decade. Interestingly, in centenarians the prevalence of thyroid antibodies is much lower. Also in subjects of 65 to 85 years of age, the prevalence of thyroid antibodies did not change. Furthermore, thyroid antibodies
were not associated with mortality or TFTs in this age range. From these observations, the clinical relevance of thyroid antibodies in the elderly is not clear. Although thyroid antibodies usually indicate an increased risk for thyroid disease, this does not appear to be true in the elderly. In the NHANES study, exclusion of patients with thyroid antibodies did not alter the median TSH or its age-specific reference range.

A vast amount of evidence suggest that the presence of thyroid antibodies in the elderly neither has harmful effects on morbidity and mortality nor does it predict development of thyroid disease. Therefore, the additional value of measuring thyroid antibodies in the elderly is limited.

THE OLDEST OLD

Several studies have reported on changes in TFTs in the oldest old. Mariotti and colleagues reported that healthy centenarians had lower serum TSH and FT3 levels and higher serum rT3 levels, whereas FT4 levels remained normal as compared with other age groups. In a population of healthy centenarians of Ashkenazi Jewish origin, serum FT4 levels were also similar to younger controls, but serum TSH levels were increased. Offspring of these centenarians also had slightly higher serum TSH levels than controls, suggesting that longevity and higher TSH levels are genetically interrelated. Offspring from subjects with reported familial longevity also had lower serum FT4 and T3 and a trend for higher TSH levels, supporting the hypothesis that TH and longevity are genetically related.

Two studies investigated longitudinal changes in TFTs and survival in subjects older than 80 years of age. The Leiden 85+ Study followed subjects from age 85 years through 89 years and showed that elevated serum TSH level, whether or not accompanied by low serum FT4 concentrations, was associated with decreased all-cause mortality. Also within the normal range, the hazard ratios (HRs) for risk of mortality were decreased at increasing TSH and increased at increasing FT4 levels. Of interest, these HRs remained after adjustment for potential confounders such as sex, C-reactive protein levels, and number of chronic diseases. The Cardiovascular Health Study All Stars cohort noted an increase in serum TSH and FT4 and a decrease in T3 levels in individuals older than 65 years who were observed for 13 years. However, in this study changes in TFTs were not associated with effects on mortality. In a large meta-analysis of more than 50,000 subjects, no effects (positive or negative) of subclinical hypothyroidism on all-cause mortality could be demonstrated. However, it should be noted that all subjects in the Leiden-85+ Study were older than 85 years of age at baseline, whereas in all other cohorts the mean age was lower.

FACTORS INFLUENCING TFTS

The measurement of TFTs is influenced by many factors that are not necessarily age-related but more common in the elderly. Of particular relevance in the elderly are the changes in TFTs due to illness, in which diminished T3 and elevated rT3 levels occur in the absence of thyroid disease. These alterations in TFTs are therefore called nonthyroidal illness (NTI). Acute and chronic diseases may produce NTI. In addition, caloric deprivation gives rise to similar TFT changes. Alterations in deiodinase activities (decreased D1 and increased D3 activity) may underlie the TFT changes observed in NTI and caloric restriction. Possibly, the changes observed in NTI and malnutrition may be part of a beneficial adaptation response, aiming to minimize further damage. Similarly, a decrease in T3 in aging may also be beneficial by reducing DNA damage and thereby slowing down the aging process (see earlier discussion).
However, this remains purely speculative and needs to be determined in future studies analyzing the role of TH in the aging process.

Because aging subjects are particularly prone to malnutrition and (as-yet-unrecognized) disease, it is of utmost importance to take the patient-specific situation into account when interpreting the obtained TFTs. This point is well illustrated in a study of elderly man in which TFTs were correlated to disease and physical function and mortality. Isolated lower T3 levels were associated with better physical performance, whereas subjects with the combination of lower T3 and higher rT3 serum levels had the worst physical performance. Such interpretations explain findings in which higher serum rT3 levels are associated with shorter survival.

Since drugs are more commonly prescribed in older patients, it is important to realize that some drugs may interfere with TFTs. Drugs may directly interfere with thyroid function (eg, lithium, amiodarone, glucocorticoids) or peripheral TH metabolism (eg, amiodarone, propranolol), whereas others mainly interfere with the assay (eg, furosemide, antiepileptic drugs, heparin).

Thus, especially in the elderly patient, medical history, condition, and prescribed drugs should be considered when interpreting abnormal TFTs.

**TSH REFERENCE RANGE**

The publication of different large-population studies during the last decade has resulted in a large debate whether the standard reference range for serum TSH levels (0.4–4.5 mU/L) should be applied to the elderly. Using an upper limit of 4.5 mU/L, up to 15% of subjects older than 70 years are classified having an increased TSH. Because most of these individuals have normal serum FT4 values, they would be diagnosed with subclinical hypothyroidism. This assumption has been fueled by the observation that TSH does not fit a Gaussian curve, but displays a right-skewed distribution. It has been proposed that subjects with serum TSH levels within this right-skewed part of the distribution (2.5–4.5 mU/L) reflect patients with thyroid disease or at an early stage of thyroid failure. Indeed, it was shown that individuals with positive thyroid antibodies and TSH levels between 2.5 and 4.5 mU/L are more prone to develop thyroid disease. However, only a minority of subjects with TSH levels in this range will develop thyroid disease. In addition, median and TSH reference ranges were similar between subjects with and without thyroid antibodies.

Alternatively, the possibility that the right-skewed TSH curve is a composite of several unique curves for subpopulations is an attractive explanation. Indeed, the right-skew in TSH curves disappears if a race-specific data analysis is applied. Similar right-shifted curves are produced from age-specific analysis (Fig. 1). These analyses suggest that the reference ranges for older people shift to the right. The 97.5 percentiles derived from these studies indicate an upper normal limit of around 7 mU/L. Thus, the application of an age-specific TSH reference range would largely prevent the misclassification of many elderly people having (subclinical) thyroid disease. Older subjects are likely to benefit more from adjustment of the reference range, although absolute percentages of misclassification differ amongst several studies. If age-specific TSH distribution curves are applied, they should be representative for particular regions and countries, because serum TSH levels are importantly influenced by iodide state.

Thus, multiple studies have shown that subclinical hypothyroidism in the elderly is not associated with adverse outcomes. Only randomized controlled intervention trials will provide a definitive answer whether subclinical hypothyroidism in the elderly should be treated with levothyroxine substitution therapy or not.
DIAGNOSIS AND TREATMENT OF (SUBCLINICAL) THYROID DISEASE

Thyroid function testing is advised for the work-up of several conditions, such as heart failure and cognitive decline, which are prevalent in older age. When thyroid function is tested, it is important to realize that TFTs in the elderly can be confounded by factors such as the increased prevalence of chronic (nonthyroidal) illness and/or drug-induced changes (see earlier discussion). Furthermore, clinical signs and symptoms of thyroid disease are different in older versus younger populations.

Hypothyroidism

The frequency of overt hypothyroidism varies from 0.1% to 2%, but the prevalence may increase up to 5% in subjects older than 60 years of age. Hypothyroidism is 5 to 8 times more common in women than men. Prevalence may be dependent on dietary and other environmental factors, especially iodine intake. Hypothyroidism has a higher prevalence in iodine-sufficient regions than in areas of mild iodine deficiency. Autoimmune thyroiditis is the most frequent cause of hypothyroidism, including in the elderly, followed by iatrogenic hypothyroidism induced by treatment of thyrotoxicosis. Iodine-induced hypothyroidism is more frequently seen in older patients than in younger patients, because of exposure to iodine overload with certain drugs (particularly amiodarone and iodinated radiographic contrast agents) and coexistent organification defects such as Hashimoto thyroiditis or Graves disease. Interestingly, amiodarone-induced hypothyroidism is more common in iodine-sufficient areas.

It is important to realize that elderly patients with hypothyroidism may lack the classical symptoms of hypothyroidism (Table 1). Because of the coexistence of age-related diseases and overlap between signs and symptoms of hypothyroidism (fatigue, cold intolerance, constipation, congestive heart failure, depression, etc) and the aging process, hypothyroidism in the elderly can easily be missed. For this reason, the diagnosis of hypothyroidism in the elderly can be a difficult task. As an illustration, thyroid function was determined in a population of more than 2000 elderly subjects. None of the 95 subjects with increased serum TSH concentrations were suspected to be hypothyroid on the basis of a routine clinical examination.
TH replacement therapy should be initiated in all patients with overt hypothyroidism, independent of age. It is generally advised that elderly hypothyroid patients are given a lower starting dose than younger adults. TH increases myocardial oxygen demand, and may thereby induce angina pectoris, myocardial infarction, or cardiac arrhythmias in older patients. For this reason, initiation of LT4 treatment in elderly hypothyroid patients should be started at a low dose, especially in patients with (an increased risk of) coronary heart disease. In a prospective study, in which hypothyroid patients were randomly assigned to a full starting dose or to 25 μg LT4 per day with dose adjustments every 4 weeks, symptoms of hypothyroidism improved at a similar rate in both groups, although serum TSH and FT4 normalized more rapidly in the full-dose group. These data suggest no clinical benefit of a higher starting dose of LT4. An additional argument for starting with a low LT4 dose in elderly patients is the observation that elderly patients need lower doses of LT4 to suppress serum TSH levels. Close monitoring is necessary to avoid overtreatment, because unintended TSH

<table>
<thead>
<tr>
<th>Symptoms and Clinical Signs (Percentages)</th>
<th>Old Patients ≥70 Y (n = 67)</th>
<th>Young Patients ≤55 Y (n = 54)</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>67.7</td>
<td>83.4</td>
<td>NS&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Weakness</td>
<td>52.5</td>
<td>66.8</td>
<td>NS</td>
</tr>
<tr>
<td>Mental slowness</td>
<td>45.3</td>
<td>48.1</td>
<td>NS</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>39.7</td>
<td>42.6</td>
<td>NS</td>
</tr>
<tr>
<td>Chilliness</td>
<td>34.9</td>
<td>64.8</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Dry skin</td>
<td>34.5</td>
<td>45.3</td>
<td>NS</td>
</tr>
<tr>
<td>Constipation</td>
<td>32.8</td>
<td>41.2</td>
<td>NS</td>
</tr>
<tr>
<td>Deafness</td>
<td>32.1</td>
<td>24.5</td>
<td>NS</td>
</tr>
<tr>
<td>Depression</td>
<td>28.4</td>
<td>51.9</td>
<td>NS</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>28.1</td>
<td>29.4</td>
<td>NS</td>
</tr>
<tr>
<td>Skin infiltration</td>
<td>26.9</td>
<td>42.6</td>
<td>NS</td>
</tr>
<tr>
<td>Anorexia</td>
<td>26.6</td>
<td>13.2</td>
<td>NS</td>
</tr>
<tr>
<td>Paleness</td>
<td>26.6</td>
<td>17.8</td>
<td>NS</td>
</tr>
<tr>
<td>Slowed reflexes</td>
<td>23.8</td>
<td>30.8</td>
<td>NS</td>
</tr>
<tr>
<td>Weight gain</td>
<td>23.7</td>
<td>58.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cramps</td>
<td>20.3</td>
<td>54.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Snoring</td>
<td>18.4</td>
<td>21.6</td>
<td>NS</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>17.9</td>
<td>61.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14.3</td>
<td>33.3</td>
<td>NS</td>
</tr>
<tr>
<td>Weight loss</td>
<td>13.8</td>
<td>3.8</td>
<td>NS</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>12.1</td>
<td>18.5</td>
<td>NS</td>
</tr>
<tr>
<td>Hair loss</td>
<td>11.9</td>
<td>27.8</td>
<td>NS</td>
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<td>Buzzing</td>
<td>11.3</td>
<td>26.4</td>
<td>NS</td>
</tr>
<tr>
<td>Disorientation</td>
<td>9.0</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>

<sup>a</sup> After Bonferroni correction for multiple comparisons, a P<.002 was considered statistically significant.

<sup>b</sup> NS: not significant.

Suppression therapy is a very frequent cause of subclinical hyperthyroidism (see also the section on subclinical hyperthyroidism).\textsuperscript{10,45–47}

**Subclinical Hypothyroidism**

Subclinical hypothyroidism is defined as an elevated TSH in combination with an FT4 within the reference range, and it is generally considered to represent early, mild thyroid failure.\textsuperscript{48,49} Most patients with subclinical hypothyroidism have thyroid autoantibodies, suggestive of Hashimoto thyroiditis.\textsuperscript{4,48} Patients treated for overt hypothyroidism may have subclinical hypothyroidism due to inadequate substitution therapy.\textsuperscript{4,45,47}

Most patients with subclinical hypothyroidism have a mildly elevated TSH level (above the reference range, but below 10 mU/L).\textsuperscript{45} The frequency of subclinical hypothyroidism varies from 4\% to 10\% in different populations.\textsuperscript{4,38,45,50} This percentage is more prevalent in iodine-sufficient countries,\textsuperscript{51} and the incidence increases with age when nonage adjusted TSH reference ranges are used (see earlier discussion). Subclinical hypothyroidism may be present in up to 20\% of elderly women and in 8\% of elderly men. Of subjects with subclinical hypothyroidism older than 55 years, approximately a few percent per year progress to overt hypothyroidism.\textsuperscript{28,52} However, it should be noticed that TSH levels may also normalize in almost 50\% of patients.\textsuperscript{53} For this reason, serum TSH measurements should always be redetermined after 3 to 6 months, to rule out a temporary increase in TSH.\textsuperscript{48,54} The most powerful predictor for progression to overt hypothyroidism is magnitude of TSH elevation, but the presence of thyroid antibodies, clinical symptoms of hypothyroidism, goiter, and/or a low normal FT4 are also related to an increased risk of progression.\textsuperscript{38,55–57} These predictors might be different in elderly subjects, because thyroid antibodies seem to have less effect in this age group.\textsuperscript{2}

Subclinical hypothyroidism may be associated with similar symptoms as overt hypothyroidism, but in the elderly it may very well be asymptomatic. In subjects older than 65 years, subclinical hypothyroidism was not associated with cognitive function or depression in 2 large studies,\textsuperscript{58,59} and in subjects older than 70 years it was even associated with a better preservation of physical function compared with euthyroid controls.\textsuperscript{60}

In addition to symptoms, subclinical hypothyroidism has also been associated with a wide variety of cardiovascular risk factors and cardiovascular mortality (see Biondi & Cooper\textsuperscript{54} for a detailed overview of the literature), as well as an increased risk of hip fractures.\textsuperscript{61} A recent participant-based meta-analysis demonstrated an increased risk of cardiovascular events and cardiovascular mortality, but not all-cause mortality, in subjects with an elevated TSH, especially in those with a TSH level greater than 10 mU/L (Fig. 2).\textsuperscript{22} Various studies have assessed the effects of treatment on signs and symptoms. Although it has been shown that LT4 treatment improves systolic and diastolic function, lipid profile, endothelial function, and carotid intima-media thickness (see Refs.\textsuperscript{48,54,62} for reviews), no randomized studies on the effect of treatment of subclinical hypothyroidism on cardiovascular events or mortality are yet available. However, this topic has been addressed indirectly by 2 cohort studies, in which patients with subclinical hypothyroidism who received LT4 treatment were compared with patients who were not treated. Patients who received LT4 therapy had a significantly lower risk of heart failure\textsuperscript{63} and lower all-cause mortality.\textsuperscript{64} The issue of treatment in relation to age was not addressed specifically in these studies, but it was in a study of data from general practitioners in the United Kingdom in which lower rates of ischemic heart disease were found in LT4-treated younger patients, but not in LT4-treated older patients.\textsuperscript{65} In very old subjects (ie, aged 80 years), the
Fig. 2. HRs for coronary heart disease (CHD) events, CHD mortality, and total mortality according to elevated TSH categories. (Data from Rodondi N, den Elzen WP, Bauer DC, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA 2010;304:1365–74.)
consequences of LT4 therapy may be different than in younger subjects, because observational studies in older subjects (older than 73 and 85 years, respectively) have shown that high TSH and/or low FT4 levels are associated with a lower mortality rate\cite{8,21,26} (see earlier discussion). However, results from studies in these selected populations may also be because of selection bias and randomized clinical trials are urgently needed.\cite{66–68}

In general, treatment is recommended for patients who have a TSH level greater than 10 mU/L. For patients with a mildly elevated TSH, the decision to treat or not to treat is based on clinical judgment and expert opinion, until the results of large scale randomized clinical trials are available.

**Hyperthyroidism**

The prevalence of hyperthyroidism is increased in the elderly, with frequencies varying from 0.5% to 3% in populations older than 60 years of age.\cite{2,4,39,69} Whereas toxic (multinodular) goiter is the most frequent cause of hyperthyroidism in areas with a low iodine intake, Graves disease is a more common cause of hyperthyroidism in elderly living in areas with a relatively high iodine intake such as the United States and Northern Europe.\cite{2,70,71} In aged patients, hyperthyroidism may also be precipitated by excess iodine intake from drugs or radiographic contrast agents,\cite{28,41} especially in patients with underlying thyroid disease and functional autonomy.

Similar to hypothyroidism, elderly patients with hyperthyroidism usually display fewer signs and symptoms of hyperthyroidism than younger patients (Table 2).\cite{2,36} They often lack a tremor, nervousness, increased appetite, heat intolerance, ocular signs, and nervousness. However, the frequency of atrial fibrillation and unexplained weight loss is higher in the elderly.\cite{72,73} About 15\% of elderly individuals with atrial fibrillation have elevated T4 levels or a history of thyrotoxicosis.\cite{36,74,75} Hyperthyroidism in the elderly may even present as depression or mania.\cite{76}

Administration of radioactive iodine is a good choice in most cases of hyperthyroidism in the elderly, resulting in a definitive cure and avoidance of the risks of surgery.\cite{28} Alternatively, long-term thionamide treatment may be considered in the elderly with Graves disease,\cite{34} but this may not be practical because of difficulties in patients' compliance and side effects.\cite{2} Beta-blockers should be administered to elderly patients with hyperthyroidism, also in the initial phase after radioiodine administration, to reduce the heart rate and the risk of tachyarrhythmias. A potential concern is post-radioiodine exacerbation of hyperthyroidism due to radiation-related thyroiditis. The precise frequency of this complication in the elderly is unknown, but may be roughly around 10\%.\cite{2} Thus, hyperthyroidism in the elderly warrants treatment, preferably with 131-I.

**Subclinical Hyperthyroidism**

Subclinical hyperthyroidism is defined as a low serum TSH, combined with an FT4 and FT3 in the reference range.\cite{49} The prevalence of subclinical hyperthyroidism is relatively low compared with subclinical hypothyroidism and varies from 1\% to 2.5\% in iodine-sufficient populations\cite{4,77,78} and up to 9\% in iodine-deficient populations.\cite{79} Its prevalence increases in older populations, especially in women.\cite{28} Before making the diagnosis of subclinical hyperthyroidism, other causes of a low TSH such as non-thyroidal illness, fasting, and the administration of drugs (eg, glucocorticoids) should be excluded (see earlier discussion). Furthermore, a second measurement is necessary because low serum TSH levels are often transitory.\cite{80,81}

Subclinical hyperthyroidism may be caused by similar mechanisms as overt hyperthyroidism but it may also result from excessive LT4 substitution therapy.\cite{48,75}
Whereas Graves disease is the most common cause of endogenous subclinical hyperthyroidism in young patients, toxic multinodular goiter and toxic adenomas may be more common causes in elderly patients. In the elderly, exogenous subclinical hyperthyroidism is more common than endogenous subclinical hyperthyroidism and can be intentional (ie, TSH suppressive therapy in patients with thyroid cancer) as well as unintentional in case of overtreatment of hypothyroid patients. It should be realized that 20% to 40% of patients older than 65 years of age who are on LT4 treatment have a low serum TSH.45–47 Older patients are especially prone to exogenous subclinical hyperthyroidism, because LT4 requirements decrease with age.10 Whether or not an altered sensitivity of the pituitary to the negative feedback of T4 plays a role as well remains to be determined.2

Approximately 1% to 5% of patients older than 60 years of age with subclinical hyperthyroidism progress to overt hyperthyroidism.81–84 Progression to overt hyperthyroidism occurs more often in patients with a TSH less than 0.1 mU/L than in patients with a TSH between 0.1 and 0.4 mU/L and in patients with Graves disease than in patients with toxic multinodular goiter.54 In addition to progression to overt hyperthyroidism, subclinical hyperthyroidism is also related to an increased risk of atrial fibrillation, cardiac dysfunction, cardiovascular and overall mortality, decreased bone mineral density, and decreased quality of life and cognition61,72,73,85,86 (see48,54 for 2 excellent reviews).

Table 2
Comparison between young and old patients with symptoms and clinical signs of hyperthyroidism

<table>
<thead>
<tr>
<th>Symptoms and Clinical Signs</th>
<th>Percentage of Old Patients ≥70 Y (n = 34)</th>
<th>Percentage of Young Patients ≤50 Y (n = 50)</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia</td>
<td>71</td>
<td>96</td>
<td>.01</td>
</tr>
<tr>
<td>Fatigue</td>
<td>56</td>
<td>84</td>
<td>.01</td>
</tr>
<tr>
<td>Weight loss</td>
<td>50</td>
<td>51</td>
<td>.87</td>
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<tr>
<td>Tremor</td>
<td>44</td>
<td>84</td>
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</tr>
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<td>Dyspnea</td>
<td>41</td>
<td>56</td>
<td>.20</td>
</tr>
<tr>
<td>Apathy</td>
<td>41</td>
<td>25</td>
<td>.20</td>
</tr>
<tr>
<td>Anorexia</td>
<td>32</td>
<td>4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nervousness</td>
<td>31</td>
<td>84</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hyperactive reflexes</td>
<td>28</td>
<td>96</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Weakness</td>
<td>27</td>
<td>61</td>
<td>.01</td>
</tr>
<tr>
<td>Depression</td>
<td>24</td>
<td>22</td>
<td>.87</td>
</tr>
<tr>
<td>Increased sweating</td>
<td>24</td>
<td>95</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Polydipsia</td>
<td>21</td>
<td>67</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>43</td>
<td>.02</td>
</tr>
<tr>
<td>Confusion</td>
<td>16</td>
<td>0</td>
<td>.01</td>
</tr>
<tr>
<td>Muscular atrophy</td>
<td>16</td>
<td>10</td>
<td>.52</td>
</tr>
<tr>
<td>Heat intolerance</td>
<td>15</td>
<td>92</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Constipation</td>
<td>15</td>
<td>0</td>
<td>.01</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>0</td>
<td>57</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

a After Bonferroni correction for multiple comparisons, a P<.002 was considered statistically significant.

There is a lack of prospective, randomized controlled trials investigating the benefits of treatment of subclinical hyperthyroidism. The choice between treatment and a wait-and-see policy depends on the level of TSH (<0.1 mU/L vs 0.1–0.4 mU/L), clinical risk factors (atrial fibrillation, osteoporosis, etc), and the cause of subclinical hyperthyroidism. However, it is generally accepted that treatment of subclinical hyperthyroidism should be initiated more readily in older subjects than in younger subjects. In patients with toxic multinodular goiter or toxic adenoma, radioactive iodine is the preferred treatment of choice because it is definitive and remission is very unlikely to occur. In patients with subclinical hyperthyroidism due to Graves disease, medical therapy can be considered as well. If it is decided not to treat the subclinical hyperthyroidism in elderly patients, provision of a beta-blocker should be considered, as well as calcium supplementation and treatment with a bisphosphonate in patients with a low bone mineral density or at risk for osteoporosis.

**SUMMARY**

Significant changes in thyroid parameters are observed during aging. Most of these changes naturally occur during the aging process and may be regarded as physiologic. The most important consequence is that the traditional TSH reference range may not be applicable for elderly patients and this implies that an age-specific TSH reference range is desired to avoid misclassification of patients. The value of additive testing for thyroid antibodies is much less in the elderly. Furthermore, confounders such as illness and malnutrition, which are more common in the elderly, may disturb the interpretation of TFTs.

Diagnosing thyroid disease in elderly patients may be challenging, because clinical features of abnormal thyroid function are less pronounced. Whereas overt hypothyroidism requires prompt treatment, this is less clear for subclinical hypothyroidism. In subclinical hypothyroidism with TSH levels up to 10 mU/L, watchful waiting can be an appropriate strategy. Also overt hyperthyroidism needs immediate treatment in which I-131 therapy appears a logical choice. Depending on TSH levels and clinical symptoms, subclinical hyperthyroidism does not necessarily warrant immediate treatment. However, treatment is more strongly indicated in older patients than in younger patients. Randomized controlled trials should provide the definitive answer whether or not to treat elderly patients with subclinical thyroid disease.

Because life expectancy in western populations is still increasing, the topics discussed in this article will remain of great importance. Therefore, future studies should be dedicated to investigating the mechanisms underlying physiologic changes in thyroid function and metabolism as well as optimal treatment strategies for thyroid diseases in the elderly.

**REFERENCES**


49. Surks MI, Ortiz E, Daniels GH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 2004;291:228–38.


