

Hypothyroidism in the elderly: diagnosis and management

Isabela M Bensenor^{1,2}
Rodrigo D Olmos^{1,2}
Paulo A Lotufo^{1,2}

¹Division of Internal Medicine,
Hospital Universitário, University
of São Paulo, São Paulo, Brazil;

²Department of Internal Medicine,
School of Medicine, University of São
Paulo, São Paulo, Brazil

Abstract: Thyroid disorders are highly prevalent, occurring most frequently in aging women. Thyroid-associated symptoms are very similar to symptoms of the aging process; thus, improved methods for diagnosing overt and subclinical hypothyroidism in elderly people are crucial. Thyrotropin measurement is considered to be the main test for detecting hypothyroidism. Combined evaluations of thyroid stimulating hormone (TSH) and free-thyroxine can detect overt hypothyroidism (high TSH with low free-thyroxine levels) and subclinical hypothyroidism (high TSH with normal free-thyroxine levels). It is difficult to confirm the diagnosis of thyroid diseases based only on symptoms, but presence of symptoms could be an indicator of who should be evaluated for thyroid function. The most important reasons to treat overt hypothyroidism are to relieve symptoms and avoid progression to myxedema. Overt hypothyroidism is classically treated using L-thyroxine; elderly patients require a low initial dose that is increased every 4 to 6 weeks until normalization of TSH levels. After stabilization, TSH levels are monitored yearly. There is no doubt about the indication for treatment of overt hypothyroidism, but indications for treatment of subclinical disease are controversial. Although treatment of subclinical hypothyroidism may result in lipid profile improvement, there is no evidence that this improvement is associated with decreased cardiovascular or all-cause mortality in elderly patients. In patients with a high risk of progression from subclinical to overt disease, close monitoring of thyroid function could be the best option.

Keywords: overt hypothyroidism, subclinical hypothyroidism, diagnosis, treatment, elderly

Introduction

Thyroid disorders are highly prevalent, most frequently afflicting aging women.¹ It is crucial to advance the means of diagnosing thyroid diseases, especially overt and subclinical hypothyroidism in elderly people, because thyroid-associated symptoms are very similar to symptoms of the normal aging process.^{2,3}

Up till the early 1980s, laboratory diagnosis of thyroid dysfunction was made using radioimmunoassay for thyroid stimulating hormone (TSH); however, this method did not detect decreased TSH values, and is not a good test for the diagnosis of hyperthyroidism. After the 1980s, immunometric assays for TSH emerged as the most cost-effective test for thyroid disease screening.^{4,5} The second-generation immunoassays can detect TSH values of 0.1 mIU/L and the third-generation assays are able to detect TSH values of 0.01 mIU/L.

Thyroid gland hormone production is directly stimulated by TSH, which is synthesized and secreted in the anterior pituitary under stimulation of thyrotropin-releasing hormone produced in the hypothalamus. In patients with an intact

Correspondence: Isabela M Bensenor
Hospital Universitário, Av Lineu Prestes
2565, 3º andar, Centro de Pesquisa
Clínica, CEP 05508-000, Brazil
Tel +55 11 3091 9300
Fax +55 11 3091 9241
Email isabensenor@hu.usp.br

hypothalamic-pituitary-thyroid axis, a negative feedback regulatory mechanism controls thyroid gland metabolism. The pituitary serves as a biosensor of thyroid hormone levels and regulates TSH levels according to the feedback of free-thyroxine (FT4) and free-triiodothyronine (FT3) levels. Decreases in thyroid hormone production stimulate more TSH secretion. The control system has a relatively slow response time and during periods of non-equilibrium, as occurs in the beginning of hypothyroidism, it is possible to find some discordance between the plasma thyroid hormone concentrations and the levels of TSH.

TSH measurement is considered to be the main test for detecting thyroid disease, specifically overt and subclinical hypothyroidism, for three main reasons. Firstly, there is an inverse log-linear relationship between the concentrations of TSH and FT4. Consequently, small linear reductions in FT4 concentrations are associated with an exponential increase in TSH concentrations. Secondly, most cases of hypothyroidism in clinical practice are due to primary disease of the thyroid gland. Thirdly, immunometric assays for TSH present greater than 99% sensitivity and specificity.^{4,5}

The second step in the screening of thyroid disorders is to determine the FT4 level. FT4 measurement is highly cost-effective compared to previously used measurements of total T4 or triiodothyronine. The combined measurements of TSH and FT4 can detect two types of hypothyroidism: overt and subclinical.

Overt hypothyroidism is defined as a combination of high TSH with low FT4, while subclinical hypothyroidism is defined as a combination of high TSH with normal FT4 levels. There is some controversy regarding the presentation of subclinical hypothyroidism; some guidelines define it as a situation in which the patient is asymptomatic, while others state that subclinical hypothyroidism might include a few symptoms, but without any specific information about what symptoms can be involved.^{5,6} Data from some studies have shown a positive relationship between increased TSH levels and the presence of antithyroid peroxidase antibodies.^{2,7} As subclinical hypothyroidism is defined by "high TSH with normal FT4," the exact normal range of TSH is very important. The TSH range must be assessed in people with no evidence of disease – without positive antibodies in the serum and with no alteration detected upon ultrasonographic examination.⁸ Another important point is that there is an individual hypothalamic-pituitary-thyroid axis set-point⁹ that is genetically determined;¹⁰ differences in the individual set-point could explain the spectra of different symptoms presented in subjects with similar TSH values.⁸

This is a selective review that primarily includes data about thyroid diseases in elderly men and women. However, several studies have included subjects aged 40 years or more and it is difficult to separate younger subjects from the older ones; therefore, some of the included data concern people of ≥ 40 years old or at least a sample with a mean age ≥ 40 years.

Epidemiology of thyroid diseases

Epidemiological studies have revealed that several changes in thyroid hormone concentrations occur with aging. The Whickham Survey undertaken in Britain provided data showing that TSH levels did not vary with age among males, but increased markedly among females after the age of 45 years. Furthermore, this rise in TSH with age among women was virtually abolished when persons with antithyroid antibodies were excluded from the sample.¹ Data from the National Health and Nutrition Survey (NHANES III) confirmed that both TSH levels and the presence of antithyroid antibodies are greater in women, increase with age, and are more common in whites than in blacks.¹¹

The Framingham study evaluated an unselected population of elderly subjects (>60 years) and found a 4.4% prevalence of thyroid deficiency, as evidenced by a clearly elevated serum thyrotropin level greater than 10 $\mu\text{IU/mL}$. Women exhibited thyroid deficiency (5.9%) more often than men (2.3%). The level of serum thyroxine (T4) was not a sensitive measure of thyroid deficiency. Of those with clearly elevated serum TSH levels, only 39% had low serum T4 levels; the remainder had serum T4 levels in the lower half of the normal range. An elevated serum TSH level has been noted as a sensitive marker of thyroid deficiency in the elderly, and is often the only way to detect it.¹²

More recently, data from several studies in healthy individuals without thyroid diseases have indicated that aging appears to be associated with decreased concentrations of TSH in healthy elderly humans, especially after inclusion of centenarians in the sample.¹³ This decrease could be attributed to an increased sensitivity to physiological negative feedback by thyroxine.¹⁴ The low serum concentrations of TSH result in clear, age-dependent declines in serum total and FT3 levels, whereas the reduction of both T4 secretion and peripheral T4 degradation of thyroxine results in no change in serum total and FT4 concentrations.^{14,15} In contrast, serum reverse-triiodothyronine, an inactivate metabolite of T4, seems to increase with age, especially in individuals with other chronic diseases.¹⁶

For a physician to correctly interpret a high TSH level in terms of a hypothyroidism diagnosis, the positive and negative predictive values must be known; these depend on the prevalence of the disease in the general population. As a general rule, higher hypothyroidism prevalence in a population sample indicates a higher positive predictive value of an increased TSH level for hypothyroidism diagnosis. So, in a population with a high prevalence of thyroid disease, the finding of an isolated increased TSH value should be sufficient to confirm the diagnosis.

A review published by the American College of Physicians in 1998 estimated that population studies showed a pooled prevalence of overt hypothyroidism of 2% in women ≥ 70 years, and of 0.1% for men ≥ 60 years.^{17,18} Table 1 shows the results of recent surveys for prevalence of overt and subclinical hypothyroidism in older subjects. We included only studies that used similar methodology – high sensitive TSH and FT4 – to evaluate thyroid function. Most studies showed prevalence of between 1% to 10% of overt hypothyroidism, and of 1% to 15% of subclinical hypothyroidism, considering both genders. Frequencies of overt and subclinical hypothyroidism vary among the studies. Such variations could be associated with several local factors, including differences in iodine intake

among populations, differences in cut-off values used for thyrotropin and FT4 levels and strategies of sample selection among studies.

Table 2 shows the results of two studies that evaluated the incidence of thyroid diseases in older people. Twenty years after the Wickham Survey, a follow-up of the cohort estimated the incidence and natural progression of thyroid disease. Of the 1877 surviving subjects, 91% were tested for clinical, biochemical, and immunological evidence of thyroid dysfunction.² Among people with raised TSH levels alone at baseline, the odds ratio (OR) of having developed hypothyroidism at follow-up was eight (95% Confidence Interval [CI], 3 to 20) for women and 44 (95% CI, 19 to 104) for men. Among people with positive thyroid antibodies alone, the OR of having developed hypothyroidism at follow-up was eight (95% CI, 5 to 15) for women and 25 (95% CI, 10 to 63) for men. The ORs among people with both conditions were 38 (95% CI, 22 to 65) for women and 173 (95% CI, 81 to 370) for men. In women, neither a positive family history nor parity showed an association with future development of hypothyroidism.² Gopinath et al showed that the 5-year incidence of hypothyroidism in the older population was relatively low, and was associated with obesity (body mass index ≥ 30 kg/m²) and serum TSH levels >2 mIU/L.²⁵

Table 1 Prevalence of overt and subclinical hypothyroidism in elderly people

Reference	Place	Sample	Age of participants	Measurements ^a	Prevalence (%)
Flatau et al ¹⁹ cross-sectional	Israel Kibbutz members	751 (289 men and 462 men)	≥ 65 years Range: 65–92 years	TSH (>4.5 mIU/L), FT4 (14 to 28 pmol/L)	Overt and subclinical in men: 9.7% Overt and subclinical in women: 18.2% 38% of all hypothyroid subjects presented subclinical hypothyroidism
Cappola et al ²⁰ cohort study	US, community dwelling individuals	3233 (1307 men and 1926 women)	≥ 65 years	TSH (>4.5 mIU/L), FT4 (not informed)	Overt: 1.6% Subclinical: 15.0%
Gussekloo et al ²¹ cohort study	The Netherlands, population based	558 (189 men and 369 women)	≥ 85 years	TSH (>4.8 mIU/L) FT4 (<13 pmol/L)	Overt: 7.0% Subclinical: 5.0%
Wilson et al ²² cross-sectional	United Kingdom, community sample registered with 20 family practices	5960 (2892 men and 2980 women)	≥ 65 years	TSH (>5.5 mIU/L), FT4 (<9 pmol/L), FT3 (<3.5 pmol/L)	Overt: 0.4% (men 0.4% and women 0.4%) Subclinical: 2.9% (men 2.0% and women 3.7%)
Diaz-Olmos et al ²³	Brazil, women at workplace	314	≥ 40 years Mean age: 47.6 years	TSH (>4.0 mIU/L), FT4 (<10 pmol/L)	Overt: 3.5% Subclinical: 7.3%
Bensenor et al ²⁴ cross-sectional	Brazil population-based	1373 (538 men and 835 women)	≥ 65 years-old	TSH (>5.0 mIU/L), FT4 (<10 pmol/L)	Overt Men: 5.4% Women: 5.9% Subclinical Men: 6.1% Women: 6.7%

Abbreviations: TSH, thyrotropin or thyroid stimulating hormone; FT4, free-thyroxine; FT3, free-triiodothyronine.

Note: ^aMeasurements (cut-off points for diagnosis of overt hypothyroidism).

Table 2 Incidence of overt hypothyroidism in elderly people

Reference	Place	Sample	Age of participants	Measurements ^a	Incidence (%)
Vanderpump et al ^{2b} cohort study	United Kingdom	1877, population based	≥38 years	TSH (not informed), FT4 (not informed)	Overt Men: 0.6/1000 survivors/year Women: 3.5/1000 survivors/year
Gopinath et al ²⁵ cohort study	Australia	951, population based	≥55 years	TSH (>4.0 mIU/L), FT4 (<11.5 pmol/L)	Overt Men: 1.4%/5 year Women: 3.5%/5 year Subclinical Men: 0.7%/5 year Women: 2.5%/5 year

Notes: ^aMeasurements (cut-off for diagnosis of overt hypothyroidism); ^bas there are few studies evaluating incidence of overt hypothyroidism in elderly people, this study was included; mean age was 58 years (range 38–93 years).

Abbreviations: TSH, thyrotropin or thyroid stimulating hormone; FT4, free-thyroxine.

Diagnosis of hypothyroidism in elderly people

Diagnosis of hypothyroidism is not easy because most of the symptoms, especially in mild cases, are nonspecific and are frequently attributed to other causes or to the aging process itself. This is especially a problem in older patients because symptoms such as fatigue, lack of concentration, dry skin, and many others are considered – correctly or not – to be normal parts of the aging process. Three different clinical conditions – hypothyroidism, depression, and presence of anemia – share common and nonspecific symptoms and are each common conditions in older people. The frequency of anemia, defined according to the World Health Organization, is higher than 10% in community-dwelling adults aged 65 years and older, and is frequently associated with other clinical conditions.^{26,27} Depressive symptoms, or even depression, are common in elderly people, especially associated with other physical comorbidities.^{28,29} Within this setting, the differential diagnosis of these three conditions is crucial.

It is impossible to confirm a diagnosis of hypothyroidism based on clinical symptoms alone, without TSH and FT4 determinations. Due to the increased prevalence according to age and the impossibility of ruling out the diagnosis without laboratory measurements, several guidelines recommend routinely screening for thyroid diseases after a certain age.³⁰ The American Thyroid Association recommends screening both women and men at 35 years of age, and every 5 years thereafter.³¹ Also assertively in favor of screening, The American Association of Clinical Endocrinologists recommends screening in older patients, especially for women,³² and the American College of Pathologists recommends evaluations for women aged over 50 years with one or more general symptoms that could be caused by thyroid disease.³³ The American Academy of Family Physicians recommends

screening for patients over 60 years old, independent of gender,³⁴ and the American College of Physicians recommends high-risk strategy for people aged over 50 years with nonspecific complaints.^{17,18} Among organizations that encourage screening, there is no agreement regarding the guidelines for age and sex.

In contrast, other institutions such as the US Preventive Services Task Force,³⁵ the Canadian Task Force on the Periodic Health Examination,³⁶ and the British Royal College of Physicians³⁷ do not recommend screening for adults or for the elderly. The Institute of Medicine evaluated evidence for a benefit of screening for thyroid disorders in the Medicare population, but decided against screening based on a cost-effectiveness analysis.³⁸ In 2004, an independent panel sponsored by three major professional societies – the American Thyroid Association, the American Association of Clinical Endocrinologists, and the Endocrine Society – recommended against screening;³⁹ however, the three sponsoring societies did not endorse a statement in favor of screening.

Table 3 shows the results of studies that evaluated the diagnosis of unrecognized hypothyroidism in elderly people in different scenarios. The frequency of overt thyroid diseases without previous diagnosis is low, around 1% in men and 2% in women. In many cases, symptoms of hypothyroidism are insidious and may go unnoticed for months or even years, making medical diagnosis difficult.⁴⁴ It is important to note that the diagnosis of overt thyroid disease now occurs earlier in the disease progression, so the comprehensive list of symptoms described in internal medicine books is almost never fully present. The only study that evaluated unrecognized hypothyroidism diagnosis in an emergency department found a very small number of cases.⁴³ However, it was a retrospective study using data from hospital admissions, with the typical limitations of this type of strategy.

Table 3 Unrecognized cases of overt hypothyroidism in elderly people at different scenarios

Reference	Place	Sample	Age of participants	Measurements	Frequency of unrecognized cases of overt hypothyroidism (%)
Primary care					
Petersen et al ⁴⁰ cross-sectional	Sweden	1154, population based	≥50 years	TSH, FT4	Women: 1.3%
Bemben et al (Part 1) ⁴¹ retrospective	US	283, retrospective analysis in a Department of Family Medicine	>60 years Range: 60–97 years	TSH, FT4	Men: 1.3% Women: 1.0%
Bensenor et al ²⁴ cross-sectional	Brazil	1373, population based	≥65 years	TSH, FT4	Men: 4.8% Women: 3.4%
Outpatient clinics					
Nyström et al ⁴² cross-sectional	Sweden	496, users of an outpatient clinic	≥50 years	TSH, FT4	Women: 2.2%
Ward					
Nyström et al ⁴² cross-sectional	Sweden	383, inpatients of emergency ward	≥50 years	TSH, FT4	Women: 1.3%
Emergency department					
Chen et al ^{43,a} retrospective	Taiwan	54,756, hospital admissions at emergency department	Mean age: 75.8 ± 12.8 Range: 27–98 years	TSH, FT4	Overt: 0.1% (men 0.06%, women: 0.04%) Myxedema: 0.01% Only 21% of patients were admitted from the emergency room with an initial impression of primary overt hypothyroidism

Note: ^aAs there are no studies evaluating unrecognized cases of overt hypothyroidism in emergency department only in samples of elderly people, this study (age range 27–98 years) was included; however mean age of subjects was 75.8 ± 12.8 years.

Abbreviations: TSH, thyrotropin or thyroid stimulating hormone; FT4, free-thyroxine.

Table 4 lists the most recent studies that have addressed the presence of symptoms in subjects with subclinical hypothyroidism compared to controls. Most of these studies did not show differences in the presence of clinical symptoms, anxiety and depressive symptoms, or worse cognitive performance in subjects with subclinical hypothyroidism compared to controls with normal thyroid function in different scenarios. Although it is not often possible to confirm the diagnosis of thyroid diseases based only on symptoms, the presence of symptoms could be an indicator of who should be screened for thyroid function.⁵¹

Canaris et al evaluated the use of a positive likelihood ratio (LR) associated with several symptoms to identify hypothyroidism.⁴⁴ They applied a questionnaire, asking about 14 symptoms associated with hypothyroidism, in patients with and without overt hypothyroidism who were selected from the laboratory according to their levels of TSH and FT4. They also asked the patients to report if each of the symptoms had changed in the last year. Euthyroid subjects reported a mean of 16.5% and hypothyroid subjects reported 30.2% of listed symptoms ($P < 0.0001$). Symptoms that occurred more frequently in cases than controls were hoarse voice (17% versus 4%; positive LR, 4.2; 95% CI, 1.7–10.6), dry skin (71% versus 54%; positive LR, 1.3; 95% CI, 1.1–1.6), and muscle cramps (34% versus 15%; positive LR, 2.2; 95% CI,

1.4–3.7). When asked if the symptoms had changed in the last year, increased frequency of symptoms was reported more often in hypothyroid subjects compared to controls, with 13 symptoms presenting statistically significant differences: hoarse voice, deeper voice, drier skin, colder, more tired, puffer eyes, more muscle cramps, weaker muscles, more constipated, more depressed, slower thinking, poorer memory, and more difficulty with math. For diagnosing hypothyroidism, the LR was 0.5 for no reported symptoms compared to an LR of 8.7 (95% CI, 3.8–20.2) for the presence of seven or more symptoms.⁴⁴ Using data from the literature to determine a pretest probability of hypothyroidism according to age and sex, this knowledge of the LR enables calculation of the post-test probability using the nomogram of Fagan, and to consequently “rule in” or “rule out” the diagnosis of hypothyroidism.⁵²

Treatment of overt hypothyroidism

The most important reasons to treat overt hypothyroidism are the relief of symptoms and to avoid progression of disease to myxedema. In elderly people, low levels of TSH⁵³ or high levels of FT4 that are still in the normal range are associated with higher mortality,³ but the same is not clear for high levels of TSH²¹ or low levels of FT4.³ Gussekloo et al evaluated a general population of people who were 85 years of age at

Table 4 Studies that estimated presence of symptoms in groups of subjects with overt and/or subclinical hypothyroidism compared to euthyroid subjects

Reference	Place	Sample	Age of participants	Symptoms	Frequency of symptoms
Cooper et al ⁴⁵ randomized clinical trial	US	14 receiving thyroxine and twelve receiving placebo	Mean age 55 years old	Symptoms of hypothyroidism	Symptoms improved in 57.1% in the active group and 25% in the placebo group; $P < 0.05$
Canaris et al ⁴⁴ cross-sectional	US	76 cases and 147 controls	Mean age 44.4 years (cases) and 45.8 years (controls) Range 19–86 years	Hoarse voice, deep voice, dry skin, coarse hair, cold sensitivity, tiredness, presence of puffy eyes, muscle cramps, muscle weakness, constipation, depression, slow thinking, poor memory, difficult for math, irregular menses, heavy menses	Hypothyroid: 30.2% Control: 16.5%, $P < 0.0001$ More frequent symptoms in hypothyroid patients: hoarse voice, dry skin, muscle cramps
Bemben et al (Part 2) ⁴⁶ retrospective	US	205 women and 78 men; 15.4% of men and 14.6% of women with subclinical hypothyroidism	≥ 60 years Range: 60–97 years	Clinical symptoms of hypothyroidism	No significant difference in the frequency of symptoms in subjects with subclinical hypothyroidism compared to subjects with normal thyroid function
Kong et al ⁴⁷ clinical trial	United Kingdom	Only women: 23 in the thyroxine group and 17 in placebo group	Mean age thyroxine group 53 (3) years; mean age in the placebo group 45 (4) years 40–89 years	Fatigue, weight gain, anxiety symptoms	Only a significant worsening of anxiety scores in the group receiving L-thyroxine
Engum et al ⁴⁸ cross-sectional	Norway	30,589 people; 745 men and women with subclinical hypothyroidism		Hospital Anxiety and Depression Scale	No association found between anxiety and depression symptoms and subclinical hypothyroidism
Grabe et al ⁴⁹ cross-sectional	Germany	3790, 18 cases of overt hypothyroidism, and 27 of subclinical hypothyroidism	Mean age overt hypothyroidism group 52.1 (14.2); mean age subclinical hypothyroidism group 51.9 (12.5); mean age euthyroid group 59.2 (46.9)	Zerrssen Complaint Scale	No difference in the number of symptoms and complaints in subjects with overt and subclinical hypothyroidism compared to euthyroid controls
Jorde et al ⁵⁰ clinical trial	Norway	36 subjects with subclinical hypothyroidism, and 33 controls	Mean age intervention group 61.6 \pm 11.5 years; mean age placebo group 63 \pm 12.4 years	14 tests of cognitive function, Beck Depression Inventory, General Health Questionnaire, questionnaire about symptoms of hypothyroidism	After 1 year of thyroxin there is no difference in the performance of cognitive tests, Beck Depression Inventory and in the frequency of hypothyroidism symptoms between the two groups; subjects with subclinical hypothyroidism scored significantly better than controls on the GHQ-30

the beginning of the study;²¹ after a follow-up of 4 years, they concluded that elderly individuals with high TSH levels have a prolonged life span. The hazard ratio for mortality was 0.77 (95% CI, 0.63 to 0.94) for a standard deviation increase of 2.71 mIU/L of thyrotropin. Likewise, van den Beld et al showed that low serum FT4 levels are associated with a longer 4-year survival, reflecting a possible adaptive mechanism to prevent excessive catabolism in the elderly.³

Overt hypothyroidism is classically treated by oral replacement with synthetic L-thyroxine. L-thyroxine is peripherally converted to FT3, the active form of thyroid hormone; it has a half-life of 6 days and is typically administered as a once-daily dose of 1.6 µg/kg.⁵⁴ Although, some authors recommend to use an initial dose lower than the usual dose to treat overt hypothyroidism in elderly patients,^{8,54} there is little evidence about this issue. A small study suggested that elderly patients need a lower dose of L-thyroxine compared to younger patients.⁵⁵ Contrasting, a recent clinical trial concluded that a full starting dose of levothyroxine in asymptomatic patients (mean-age of 47 years, range of 25–86 years) is safe and may be more convenient and cost-effective than a low starting dose regimen. No patients were excluded from the analysis based on the presence of side effects of L-thyroxine. However, patients with previous history of coronary heart disease were excluded from the samples and most of them were elderly.⁵⁶ A retrospective study evaluated L-thyroxine replacement doses and found no differences between younger and older patients regarding the L-thyroxine doses used.⁵⁷ After stabilization, TSH levels can be monitored yearly. The most frequent complications of treatment in older people are myocardial ischemia and arrhythmias, especially atrial fibrillation, although these still occur at a low rate.^{8,13,58}

Some researchers have evaluated whether a combination of T4 and triiodothyronine or even liothyronine could provide better treatment for patients with persistent symptoms following treatment with L-thyroxine alone. Liothyronine is another form of thyroid hormone; it reaches peak concentrations at 2–4 hours after oral administration with a half-life of 1 day, and thus cannot be used as a once-daily dose.⁵⁹ Combined treatment using L-thyroxine and triiodothyronine produced some positive results related to cognition and sensation of well-being in small trials,^{60,61} but most results showed no improvement with combined treatment.^{62–64} Clyde et al tested a combination of levothyroxine plus liothyronine in the treatment of overt hypothyroidism and showed no beneficial changes in body weight, serum lipid levels, hypothyroid symptoms, or standard measures of

cognitive performance from the combination treatment compared to L-thyroxine alone.⁵⁹ Walsh et al also evaluated a combined thyroxine/liothyronine therapy with similar results.⁶⁵

In a double-blind, placebo-controlled, crossover trial of L-thyroxine, Pollock et al evaluated the effect of treatment in people who exhibited symptoms of hypothyroidism but had thyroid function tests within the reference range. The same protocol was used for patients and controls.⁶⁶ L-thyroxine was no more effective than placebo in improving cognitive function or psychological well-being in patients or controls.⁶⁶

Treatment of subclinical hypothyroidism

The most important reasons to treat subclinical hypothyroidism are to relieve symptoms, to avoid progression to overt disease, and to possibly prevent cardiovascular and all-cause mortality that may be associated with subclinical disease. Most patients diagnosed as having subclinical hypothyroidism have a low risk of complications and it is possible that their being labeled as having a “disease” is more dangerous than the actual risk of possible problems.

Table 5 shows the results of several clinical trials that have evaluated the effects of L-thyroxine administration in elderly people with subclinical hypothyroidism. Most of these studies were performed in subjects aged ≥ 50 years, or at least with a great part of the sample being ≥ 45 years old. Several trials did not show improvement of clinical symptoms of hypothyroidism,^{45,67–69,76} while only one trial showed improvement in tiredness after treatment with L-thyroxine.⁷² However, several trials showed some kind of improvement in cardiovascular risk factors related to lipid profile.^{69,71–74} One trial that evaluated C-reactive protein did not find any improvement after treatment with L-thyroxine.⁷⁰ Another trial verified an improvement in pulse-wave velocity after treatment with L-thyroxine.⁷⁵

A second reason to treat subclinical hypothyroidism is to avoid progression to overt disease. The two most important characteristics suggesting a progression of subclinical hypothyroidism to overt disease are high TSH levels, especially when > 10 IU/L, and the presence of antithyroid peroxidase antibodies. Both measurements can be followed by periodic testing every year or every 6 months. Table 6 shows two studies that evaluated the risk of developing overt hypothyroidism in subjects who had baseline levels of high TSH, antithyroid antibodies, or both. The combination of high TSH with antithyroid peroxidase antibodies was associated with

Table 5 Results of clinical trials for treatment of subclinical hypothyroidism focusing on different outcomes

Reference	Place	Sample/follow-up	Age of participants	Results	Observations
Cooper et al ⁴⁵ randomized, placebo-controlled clinical trial	Boston, US	14 subjects in active group (4) and twelve in the placebo group (97% women); 1-year on LT4	Mean age 55 years	No difference between groups regarding symptoms of hypothyroidism	All patients included in the study presented subclinical hypothyroidism after treatment with Iodine-131 20 years earlier
Nyström et al ⁶⁷ randomized, double-blind, crossover trial	Gothenburg, Sweden	17 women; 6 months for placebo and 6 months for hormone	>50 years	No difference between groups regarding symptoms of hypothyroidism	All women diagnosed in a screening program
Jaeschke et al ⁶⁸ randomized, placebo-controlled clinical trial	Hamilton, Canada	32 subjects	>55 years	No difference between groups regarding symptoms of hypothyroidism	All subjects selected from an outpatient clinic in a community hospital
Meier et al ⁶⁹ randomized, placebo-controlled, double-blind clinical trial	Switzerland	63 women, 31 assigned to LT4 and 32 assigned to placebo; 48 weeks of follow-up	Mean age 58.6 (1.3) years	Results showed that physiological LT4 replacement in patients with subclinical hypothyroidism has a beneficial effect on low density lipoprotein cholesterol levels and clinical symptoms of hypothyroidism	Some patients included in the trial presented subclinical hypothyroidism after treatment with Iodine-131 20 years earlier. The proportion was similar in the active and the placebo group
Christ-Crain M et al ⁷⁰ randomized, double-blind, placebo-controlled trial	Basel, Switzerland	63 subjects with subclinical hypothyroidism (31 in the L-T4 group and 32 in the placebo group)	Mean age 57.5 ± 9.8 years	CRP values increases with progressive thyroid failure; supplementation of LT4 did not improve significantly CRP levels	Thyroid Research Unit of the Division of Endocrinology, Department of Medicine at the University Hospital, Basel
Iqbal et al ⁷¹ randomized, placebo-controlled clinical trial	Norway	64 subjects with subclinical hypothyroidism; 32 assigned to LT4 and 32 assigned to placebo	62.0 (11.9) years in the LT4 group and 62.7 (12.4) years in the placebo group	Reduction in the levels of serum lipids in the group treated with LT4	Subjects with subclinical hypothyroidism selected from the 5143 subjects of the 5th Tromso Study
Razvi et al ⁷² randomized placebo-controlled clinical trial	United Kingdom	150 subjects with subclinical hypothyroidism; 50 assigned to LT4 and 49 to placebo; 12 weeks of follow-up	Mean-age 53.8 (12.6) years	Subjects with subclinical hypothyroidism treated by LT4 presented a significant improvement in cardiovascular risk factors (Total cholesterol, LDL-cholesterol, waist to hip ratio, endothelial function) and symptoms of tiredness	Community-dwelling patients
Teixeira et al ⁷³ randomized double-blind, placebo-controlled clinical trial	Brazil	32 subjects: 18 in the LT4 group and 20 in the placebo group; 6 months follow-up	Mean age LT4 group 52.5 (10.1) years; mean age in the placebo group 46.6 (9.9) years	Reduction of serum lipids especially on the subgroup of subjects with antithyroid peroxidase antibodies, TSH > 8 IU/L, body mass index ≥25 kg/m ² and in menopause	Endocrinology Outpatient Clinic, University Hospital Clementino Fraga Filho, Federal University of Rio de Janeiro
Teixeira et al ⁷⁴ randomized placebo-controlled clinical trial	Brazil	26 subjects: eleven receiving LT4 and 15 receiving placebo; 1-year follow-up	Mean age LT4 group 54.4 (9.0) years; mean age in the placebo group 48.1 (10.0) years	A significant lipid profile improvement occurred 1 year after L-T4 replacement therapy in the active group compared to placebo group	Endocrinology Outpatient Clinic, University Hospital Clementino Fraga Filho, Federal University of Rio de Janeiro

Nagasaki et al ⁷⁵ randomized placebo- controlled, double-blind clinical trial	Japan	95 women: 48 assigned to LT4 and 47 assigned to placebo; 5-month follow-up	Mean age in LT4 group 64.4 (2.6) years; mean age in placebo group 66.0 (3.0) years	Sustained normalization of thyroid function during LT4 replacement therapy significantly decreases brachial-ankle pulse wave velocity in female subclinical hypothyroid patients suggesting possible prevention of cardiovascular disease Performance in cognitive tests did not improve in subjects treated for subclinical hypothyroidism compared to placebo	Ninety-five consecutive patients with newly detected subclinical hypothyroidism due to chronic thyroiditis with antithyroglobulin or antithyroid peroxidase antibodies of the Osaka City University Hospital Patients with subclinical hypothyroidism were recruited from a community-based cross-sectional study describing the prevalence of thyroid dysfunction in the elderly identified by screening of thyroid function
Parle et al ⁷⁶ randomized, placebo- controlled double-blind clinical trial	England	94 subjects: 52 assigned to LT4 and 42 assigned to placebo; 1-year follow-up	≥65 years		

Abbreviation: LT4, L-thyroxine.

a high increase in the risk of developing overt disease.^{2,76} In a prospective 5-year analysis of a cohort study, Gopinath et al evaluated the prognostic risk factors at baseline associated with forthcoming subclinical or overt hypothyroidism. Female sex and high TSH as continuous variables were associated with increased risk of subclinical hypothyroidism. Fasting blood glucose, total white cell count (as a continuous variable), and obesity (body mass index ≥ 30 kg/m²) were associated with increased risk of progression to overt disease.²⁵ Although progression to overt disease is higher in the presence of these risk factors, it is possible to closely monitor the progression of subclinical hypothyroidism to overt disease.

As subclinical hypothyroidism has been associated with a worse profile of cardiovascular risk factors such as lipid alterations, one possible complication of not treating subclinical hypothyroidism could be an increased cardiovascular risk. Another possible risk is if hypothyroidism is associated with an increased all-cause mortality mediated by some unknown factors beyond the causal pathway of dyslipidemia-heart disease.

Table 7 shows a list of cohort studies that estimated the incidences of cardiovascular disease or fractures in subjects with subclinical hypothyroidism. Only one study found an increased risk of congestive heart failure of 2.58 (95% CI, 1.19–5.60) in subjects with TSH between 7.0 mIU/L to 9.9 mIU/L, and of 3.26 (95% CI, 1.37–7.77) in subjects with TSH ≥ 10.0 mIU/L.⁷⁸ Another showed an increased risk of hip fracture, only in men, with a multivariable-adjusted hazard ratio of 2.31 (95% CI, 1.25–4.27).⁸³ Regarding mortality, only one study found an increased risk of all-cause mortality;⁸⁰ another showed a higher risk of cardiovascular mortality associated with subclinical hypothyroidism.⁸⁰ So, although subclinical hypothyroidism is associated with a higher frequency of cardiovascular risk factors, most evidence indicates that the effect is not sufficient to increase cardiovascular mortality or all-cause mortality. There is insufficient evidence that treatment of subclinical hypothyroidism could be associated with a decrease in all-cause or cardiovascular mortality in the elderly.

This was reinforced by the results of a meta-analysis that analyzed the influence of age on the relationship between subclinical hypothyroidism and ischemic heart disease. It included 15 studies with 2531 participants with subclinical hypothyroidism and 26,491 euthyroid individuals. Incidence and prevalence of ischemic heart disease were higher in subjects aged <65 years with subclinical hypothyroidism, but not in studies that included subjects aged >65 years.

Table 6 Progression of normal thyroid status to subclinical hypothyroidism and of subclinical hypothyroidism to overt hypothyroidism

Reference	Place	Age/follow-up	Antithyroid peroxidase	Evolution to overt disease	Observations
Parle et al ⁷⁷	United Kingdom	Mean age men 70.1 (6.1) years; mean age men women 70.7 (7.3) years	Incidence No information	TSH between 5–10 mIU/L/no antibodies: 2/28; 7.1% TSH between 5–10 mIU/L/positive antibodies: 5/27; 18.5% TSH > 10 mIU/L/no antibodies: 1/4; 25% TSH > 10 mIU/L/positive antibodies: 5/14; 35.7%	Evaluated progression of subclinical hypothyroidism to overt disease according to TSH and antithyroid antibodies levels Evaluated progression of subclinical hypothyroidism to overt disease
Vanderpump et al ²	United Kingdom	86.2% of sample with >45 years	Incidence Women 45–54, 15.6% 55–64, 20.8% 65–74, 15.8% 75–84, 18.8% ≥85, 10.0% Total, 17.3 Men 45–54, 3.7% 55–64, 9.5% 65–74, 5.8% 75–84, 11.5% ≥85, 11.1% Total, 6.6	with only TSH > 6 mIU/L at baseline: OR, 8 (95% CI, 3–20) with only positive antithyroid antibodies at baseline: OR, 8 (95% CI, 5–15) with TSH > 6 mIU/L and positive antithyroid antibodies at baseline: 38 (95% CI, 22–65) with only TSH > 6 mIU/L at baseline: OR, 44 (95% CI, 19–104) with only positive antithyroid antibodies at baseline: OR, 25 (95% CI, 10–63) with TSH > 6 mIU/L and positive antithyroid antibodies at baseline: 173 (95% CI, 81–370)	
Gopinath et al ²⁵	Australia	≥55 years 5 years follow-up	No information	Subclinical hypothyroidism in women (using men as a reference): OR, 3.71 (95% CI, 1.05–13.11) TSH mIU/L (as a continuous variable): OR, 3.94 (95% CI, 2.21–7.04) Overt hypothyroidism in women (using men as a reference): 2.57 (95% CI, 1.01–6.54) TSH mIU/L (as a continuous variable): 4.13 (95% CI, 2.55–6.71) Fasting blood glucose (mmol/L): 1.19 (95% CI, 1.00–1.42) BMI ≥ 30 kg/m ² (using BMI < 30 kg/m ² as a reference): 4.05 (1.74–9.41) White cell count (×10 ⁹ /l) as a continuous variable: 1.19 (1.01–1.40)	Evaluated progression of normal thyroid status to subclinical and overt hypothyroidism

Abbreviations: TSH, thyrotropin or thyroid stimulating hormone; FT4, free-thyroxine; OR, odds ratio; 95% CI, 95% confidence interval; BMI, body mass index.

Table 7 Incidence of cardiovascular events, death, and other outcomes in people with subclinical hypothyroidism in cohort studies

Reference	Place	Sample/follow-up	Age of participants	Results	Observations
van den Beld et al ³	US	403 independent and ambulatory living men; follow-up of 4 years	73–94 years	Low FT4 was associated with a better 4-year survival	These results may reflect an adaptive mechanism to prevent excessive catabolism
Rodondi et al ⁷⁸	US	2730 men and women; follow-up of 4 years	70–79 years	In multivariate analysis using euthyroid subjects as the reference category, relative risk of congestive heart failure in subjects with TSH of 7.0–9.9 mIU/L was of 2.58 (95% CI, 1.19–5.60); and TSH \geq 10.0 mIU/L, 3.26 (95% CI, 1.37–7.77)	Subclinical hypothyroidism was not associated with increased risk for coronary heart disease, stroke, peripheral artery disease, or cardiovascular or total mortality
Cappola et al ²⁰	US	3233 community-dwelling individuals; follow-up of 2 years	65 years or older	There was no difference in the cardiovascular or mortality outcomes in subjects with overt or subclinical hypothyroidism compared to euthyroid subjects	Individuals with subclinical hypothyroidism had an adjusted hazard ratio of 1.07 (95% CI, 0.90–1.28) for incident coronary heart disease
Kalra et al ⁷⁹	United Kingdom	131 elderly patients that underwent surgical treatment for hip fracture; 1-year follow-up	Mean age 82.0 (8.9) years Range 61–94 years	Presence of subclinical hypothyroidism (15%) did not affect 1-year mortality	
Sgarbi et al ⁸⁰	Brazil	1110 Japanese-Brazilians; follow-up of 7.5 years	57 years (68.8% of the sample with age \geq 50 years)	In multivariate analysis, subclinical hypothyroidism was associated to all-cause mortality (HR, 2.3; 95% CI, 1.2–4.4) but not with cardiovascular mortality, using euthyroid subjects as the reference category	
Razvi et al ⁸¹	United Kingdom	2376 community-dwelling subjects	Mean age 45.5 years	There is an association between incident ischemic coronary heart disease and ischemic heart disease mortality with subclinical hypothyroidism (HR, 1.76; 95% CI, 1.15–2.71 and HR 1.79; 95% CI, 1.02–3.56, respectively)	Subsequent treatment of subclinical hypothyroidism with L-thyroxine appears to attenuate ischemic heart disease morbidity and mortality
De Jongh et al ⁸²	The Netherlands	1219 subjects without thyroid diseases from a population-based cohort; follow-up of 10.7 years	65 years or older	Subclinical hypothyroidism was not associated with increased overall mortality risk (HR, 0.89; 95% CI, 0.59–1.35) using euthyroid subjects as the reference group	The study does not support disadvantageous effects of subclinical thyroid disorders on physical and cognitive function, depression, or mortality in an older population
Lee et al ⁸³	US	3567 US community dwelling adults; follow-up of 14 years	65 years or older	Men with subclinical hypothyroidism presented a higher risk of hip fracture compared to euthyroid men (OR, 2.45, 1.27–4.73); no relationship between subclinical hypothyroidism and hip fractures was observed in women	

Abbreviations: F4, free-thyroxine; OR, odds ratio; 95% CI, 95% confidence interval; HR, hazard ratio.

Cardiovascular and all-cause mortality were also elevated in subjects of <65 years of age, but not in subjects aged >65 years (OR, 1.37; 95% CI, 1.04–1.79 vs OR, 0.85; 95% CI, 0.56–1.29) suggesting that increased vascular risk may only be present in subjects with subclinical hypothyroidism who are less than 65 years old.⁸⁴

When subclinical hypothyroidism is treated, an initial L-thyroxine dose of 0.05 µg to 0.075 µg per day is sufficient to normalize thyroid function. Patients with cardiovascular disease should receive smaller doses of 0.0125 µg to 0.025 µg per day. Measurements of thyrotropin levels should be repeated 4 to 6 weeks after starting therapy.⁸⁵

Potential bias in the treatment of hypothyroidism regarding age and sex

Several studies have discussed possible biases in overt hypothyroidism treatment. Gussekloo et al observed 558 participants and found that 39 new cases of overt thyroid disease were not being treated 2 years after diagnosis because the primary care physicians did not start hormone reposition therapy for disorders identified by screening.²¹ These findings suggested the possibility that a diagnosis of hypothyroidism via screening could be a bias in hypothyroidism treatment; age could also be a bias in these cases if this was the real motivation behind the lack of treatment. Interestingly, nothing happened to these untreated patients, possibly suggesting a protective effect of no treatment in overt hypothyroidism since the hazard ratio for mortality for standard deviation increase of 2.71 mIU/L thyrotropin was 0.77 (95% CI, 0.63–0.94; $P = 0.09$). However, as stated by the authors, a well-designed randomized placebo-controlled clinical trial is required to answer this question.

In the two cohorts of the Cardiovascular Health Study (mean age of 73 years; range 65–100 years), Somwaru et al evaluated the use of thyroid hormones along time. Use of thyroid hormones was observed from 1989 to 2006 in the original cohort of 4737 participants, and from 1992 to 2006 in the new cohort of 643 predominantly African-American participants. At the beginning of the study, frequency of hormone use was 8.9% (95% CI, 8.1–9.7).⁸⁶ However, hormone use increased to 20% during the 16 years of follow-up, at a rate of approximately 1% per year. Predictors of the initiation of hormone use during the 16-year follow-up period included being a white woman, being over 85 years old, being more educated, having a higher body mass index, and past history of coronary heart disease. The authors concluded that the differences in thyroid hormone use by sex and race

corresponded to the reported demographic differences in TSH distributions, suggesting a minor role of biases in screening practices by sex and race.⁸⁶ These results are similar to those of two other studies.^{87,88}

In a sample of 1373 older people living in an economically deprived area, Bensenor et al found more frequent diagnosis of previous overt hypothyroidism in women compared to men ($P = 0.006$).²⁴ The authors speculate that this could be because women seek medical treatment more frequently than men. There could also be some kind of gender bias, since thyroid diseases are more frequent in women compared to men and, consequently, physicians may screen thyroid function with higher frequency in elderly women than men.

Wilson et al reported evidence of an association between socioeconomic deprivation and subclinical thyroid dysfunction.²² This association persisted after adjusting for the effects of age, gender, comorbidity, and current drug therapies, and thus could be another source of bias regarding clinical diagnosis of thyroid diseases.

Conclusion

Subclinical and overt hypothyroidism are common disorders in elderly people, especially women. There is no doubt about the indication for treatment of overt disease; however, the same is not true for subclinical disease. Some data indicates that treatment of subclinical disease results in lipid profile improvement, but there is no evidence that this improvement is associated with a decrease in cardiovascular or all-cause mortality in elderly patients. Close monitoring of thyroid function could be the best option for patients at high risk of progression from subclinical to overt disease.

Disclosure

The authors report no conflicts of interest in this work.

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