# Hipotiroidismo en casos especiales

Caso clínico 1: Diagnóstico de hipotiroidismo en el adulto mayor

- Paciente masculino de 75 años de edad.
- Antecedente de diabetes tipo 2 de 20 años de evolución en tratamiento con insulina glargina 20 UI cada 24 horas.
- Enfermedad renal crónica grado 5 sin sustitución renal por el momento.
- HAS en tratamiento con losartán y nifedipino.
- Actualmente en protocolo de estudio por probable neoplasia de colon.
- Cuidado por sus familiares, quienes refieren pasa la mayor parte del tiempo en cama.
- Peso 45 kg, talla 1.70 m.
- Signos vitales: TA: 150/90, FC: 80, FR: 16, temperatura: 36°C.
- Al realizar laboratorios de rutina, incluyeron perfil tiroideo, donde se encontró: TSH: 11.2 mU/L (0.4-4.5) y T4L: 0.93 ng/dL (0.62-1.36).
- Acude a consulta para valorar resultados e iniciar tratamiento.

## Discusión

Es importante tener en consideración que en el adulto mayor existen algunos cambios fisiológicos con respecto a la producción de hormonas tiroideas.

Dentro de estos cambios se ha documentado disminución en la conversión periférica de T4 a T3, además de que a nivel hipotalámico disminuye la sensibilidad a la TSH.

Por tanto, podemos considerar que la elevación de TSH en el adulto mayor puede catalogarse como estado fisiológico.

Considerando esta premisa es necesario tener precaución con el sobrediagnóstico de hipotiroidismo subclínico, ya que éste nos llevaría a incorrecto tratamiento del paciente.

Actualmente no hay acuerdo sobre los niveles de TSH fisiológicos para establecer el diagnóstico de hipotiroidismo en el paciente adulto mayor. Sin embargo, algunos estudios mencionan que niveles de 7 a 8 mU/L pueden considerarse normales.

Según el estudio NHANES III, el cual fue llevado a cabo en Estados Unidos, trataba de buscarse un rango de referencia para los niveles de TSH en los diferentes grupos de edad; se observó que en el adulto mayor a 80 años los niveles de TSH eran más elevados que en el resto de los individuos que participaron en el estudio; sin embargo, concluyeron que estos niveles se encontraban en parámetros fisiológicos, considerando que el valor normal puede ser hasta 7.9 mU/L.

Con respecto al cuadro clínico en el adulto mayor, es necesario considerar que estos pacientes son menos sintomáticos que el resto. Además, hay que tener en cuenta que muchos de los síntomas que presentan son atribuibles a otras comorbilidades adicionales al hipotiroidismo, como anemia y depresión, o pueden considerarse parte normal del envejecimiento. Por ello, debemos estar atentos y considerar todas las posibilidades para hacer un diagnóstico oportuno y ofrecer tratamiento adecuado.

En el 2016, Carlé y colaboradores realizaron un estudio en busca del poder predictivo de la presencia de síntomas para realizar el diagnóstico clínico de hipotiroidismo. En el estudio se evaluaron 140 pacientes con diagnóstico reciente de hipotiroidismo, quienes fueron comparados contra 560 pacientes que representaron el grupo control. Se evaluaron 13 síntomas de hipotiroidismo, encontrando que todos ellos tuvieron mayor prevalencia en el grupo de estudio comparado con el grupo control. Sin embargo, al separar el grupo problema en pacientes jóvenes y pacientes adultos mayores, mostraron que los síntomas son excelente predictor clínico para el diagnóstico de hipotiroidismo en pacientes jóvenes. En los adultos mayores se encontró que la relación de estos síntomas presentaban poco valor predictivo para realizar el diagnóstico, con excepción de tres síntomas: cansancio, disnea y sibilancias.

Por tanto, en adultos mayores es necesario considerar que la sintomatología no es suficiente para descartar o confirmar la presencia de la patología, ya que hay disminución de los signos y síntomas del cuadro clínico.

Sin embargo, podemos hablar de un grupo de síntomas y consecuencias del hipotiroidismo en el adulto mayor. El hipotiroidismo genera aumento en el riesgo de presentar enfermedad cardiovascular debido a la aparición de falla cardíaca. Es necesario recordar que debido a menor cantidad de hormonas tiroideas, hay disminución de la actividad cardiaca por falta de acción de las catecolaminas sobre los receptores Beta-adrenérgicos, lo cual conlleva a disminución del gasto cardíaco, favoreciendo el deterioro de la actividad cardiovascular.

Dentro del apartado neurocognitivo encontramos disminución del proceso de aprendizaje, así como depresión. Actualmente existe controversia acerca de la administración de levotiroxina sobre la mejoría del aspecto neurocognitivo en este grupo de pacientes.

En el metabolismo óseo, el hipotiroidismo afecta importantemente la estructura ósea y, por tanto, hay mayor riesgo de fracturas.

## ¿Quiénes deben recibir tratamiento?

Todos aquellos pacientes que tengan hipotiroidismo manifiesto deben recibir tratamiento suplementario de hormonas tiroideas. Esto con la finalidad de prevenir las complicaciones descritas y, por tanto, mejorar su sintomatología.

Es importante confirmar si el paciente recibe medicación para otra comorbilidad, ya que muchos fármacos pueden modificar la efectividad del tratamiento con hormonas tiroideas.

Una vez que hayamos encontrado valores elevados de TSH en el adulto mayor, es necesario reconfirmar estos niveles entre 3 y 6 meses después de la primera prueba, esto con la finalidad de validar el diagnóstico antes de considerar el inicio del tratamiento.

Por otro lado, en pacientes con hipotiroidismo subclínico debemos iniciar el tratamiento para disminuir los síntomas o evitar que la enfermedad progrese a un cuadro clínico manifiesto. Además, el tratamiento en este grupo de pacientes disminuye el riesgo de muerte por factores cardiovasculares.

Recordemos que existe mayor riesgo de progresión de un cuadro subclínico a manifiesto en aquellos pacientes con valores de TSH mayores a 10 mU/L, con anticuerpos antiTPO positivos y, por tanto, hay que vigilarlos cada 6 a 12 meses por riesgo de progresión.

## ¿En quién es necesario iniciar el tratamiento y a quién debemos mantener en observación?

Aunque existe controversia acerca de cuándo debemos o no iniciar el tratamiento, hay que considerar que existen dos grupos de pacientes, que a pesar de ser adultos mayores, presentan condiciones muy diferenentes. Estamos hablando de los pacientes que se encuentran entre los 65 y 75 años, y el grupo de mayores de 75.

Para comenzar, debemos recordar que en estos dos grupos de pacientes los valores de TSH no aplican de la misma manera que en el resto de la población.

En el grupo de pacientes con más de 10 mU/L de TSH y que no presentan datos de síndrome de fragilidad, debemos considerar iniciar el tratamiento.

Mientras que en aquellos pacientes con las mismas unidades de TSH, pero que presenten síndrome de fragilidad, es recomendable mantenerlos en observación.

Como recordatorio, el síndrome de fragilidad se presenta en aquellos pacientes adultos mayores susceptibles a dependencia de algún familiar, hospitalización y disminución de la esperanza de vida. Además, hay debilidad, pérdida de peso, baja actividad, así como menor capacidad de responder al estrés.

Hay controversia en los pacientes que presentan entre 4 y 6 mU/L, porque recordemos que en el adulto mayor en algún momento de la vida, los niveles de TSH están elevados, aunque no sean indicativos de hipotiroidismo.

## Objetivo del tratamiento

Si tomamos en cuenta la premisa de que el adulto mayor presenta elevación de los niveles de TSH comparado con el paciente joven, nuestra meta será mantener los niveles de TSH entre 6 y 7 mU/L, particularmente en aquellos pacientes mayores de 70 años que presenten riesgo de arritmias cardiacas o fracturas por osteoporosis.

## Inicio del tratamiento

Se recomienda iniciar con 1.6 mcg/kg/día de levotiroxina, como en los pacientes jóvenes, aunque se exhorta a iniciar con dosis más bajas e irlas subiendo paulatinamente dependiendo de los valores del perfil tiroideo, por lo que debemos monitorizarlo cada 4 a 6 semanas.

Asimismo, debemos recordar que, para el control de la patología, este grupo de pacientes puede requerir menor dosis que un paciente joven.

## ¿Por qué es importante vigilar al paciente adulto mayor hipotiroideo en tratamiento?

Existe evidencia que al disminuir la concentración de TSH a niveles considerados normales para el paciente joven, aumenta la discapacidad y el riesgo de enfermedades no tiroideas, así como mayor probabilidad de presentar arritmias cardiacas y osteoporosis. Por ello, debemos mantener constante vigilancia para evitar la sobresustitución.

## Conclusión

Por tanto, en este paciente adulto mayor de 75 años, considerando todas sus comorbilidades, que depende de sus familiares y pasa mucho tiempo en casa (síndrome de fragilidad) y con niveles de T4 libres dentro de un rango normal, a pesar de que presenta valores de TSH mayores a 10 mU/L, se recomienda mantenerlo únicamente en observación.

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Review Article

# An Overview of Frailty in Elderly

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**Abstract**

Frailty is an ageing phenomenon and it becomes essential to understand frailty, its causes and consequences as well as the risk factors that will enable us to plan appropriate interventions to target elderly who are at risk and thus preventing them from developing frailty. Frailty is linked with multiple morbidities and it adds on to the burden of the disease on the elderly making them dependent for their basic activities of daily living further deteriorating their overall quality of life. Limited studies have been done to determine association of frailty with nutritional status in the western countries, but in developing countries like India, where the elderly population is increasing at a faster pace; there is a dearth of information regarding the prevalence rates and the associated risk factors. This article attempts to provide an overview of frailty in elderly which may help create awareness among the older age groups and in focusing the attention of the healthcare providers in preventing this phenomenon to reduce the health care costs in our country.

**Keywords:** Frailty, elderly, ageing, dependency, disability, sarcopenia, malnutrition

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## INTRODUCTION

With ageing, many body functions decline, there is accompanying change in structure and there is a loss of lean mass and relative increase in fat mass. Earlier these were considered to be essentially due to ageing; however, research over the past several decades have attributed them to be due to disuse related to age, inactivity and degenerative diseases that influence the food and nutrient intakes, food preferences and the diet patterns of older persons. The nutritional requirements also undergo considerable change with advancing age. Changes in body composition includes the changes in lean body mass, fat mass, bone health, immune function, neuro and cognitive functions, taste sensitivity, gastro-intestinal changes and difficulty in feeding.

In addition to the age-related physiological decline, there is the burden of chronic degenerative diseases in old age, e.g., hypertension, cardiovascular disorders, diabetes and cancers. In fact, multiple morbidities are very commonly found in this age group. Furthermore, there is "clustering" of multiple diseases towards the end part of life.

### Definition of Frailty

Frailty is commonly used to address older persons who are at increased risk for morbidity and mortality[1]. There is a growing consensus among experts accepting frailty as a diverse syndrome that occurs in elderly individuals who are highly susceptible and at increased risk of dependency and hospitalization and decreased life expectancy.[2,3,4] There is a agreement on the fact that frailty should be defined as a composite of multiple factors that are linked to a state of reduced physiological

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reserve resulting in decreased capacity to withstand environmental stress[5].

Frailty is a geriatric syndrome characterized by weakness, weight loss, and low activity that is associated with adverse health outcomes. Frailty is usually seen as age-related, biologically vulnerable to stressors and decreased physiological reserves resulting in a limited capacity to maintain homeostasis.[3] The Fried's Phenotype criteria that are validated and widely used five-item frailty criteria for screening: exhaustion, slowed walking speed, weakness, unintentional weight loss (10 lbs/ ~4.5 Kgs in past year), and low physical activity are composite outcomes of multiple organ systems.[4]

**Causes of frailty**

Frailty is predisposed by ageing in combination with a number of physiological changes. Frailty is associated with age, however, not all old people turn out to be frail.[4,6,7] It is generally considered that unlike the ageing process, frailty is in some parts reversible and responsive to interventions.[7] Although ageing is mainly an internal process, a person's lifestyle contributes to the ageing process in a positive or negative way. Two physical changes that are associated with ageing may be the main cause of frailty, namely, loss of muscle mass and bone density.[4,8]

Frailty has multiple etiology and genes along with environment and lifestyle all play a pivotal role in the pathway leading to frailty. As a person ages, conditions like anorexia, inactivity/lack of exercise and depression, all can lead to frailty. Anorexia or loss of appetite results in a low body weight or weight loss whereas inactivity and the development of fear of falling lead to sarcopenia (which is interrelated with weight loss) and both of which cause frailty. Chronic morbidities like diabetes, atherosclerosis and heart disease further accelerate the development of frailty in elderly. Depression in elderly along with delirium may lead to cognitive impairment which reduces the processing speed of the brain and leads to the development of frailty. Other social factors like low education, low income (lack of purchasing power), and lack of family also play role in the development of frailty.[9]

**Consequences of frailty**

There is a deterioration of activities of daily living (ADL) in frail elderly leading to increased dependency causing a higher risk for admission to a nursing home or other residential healthcare facility.[10] Frailty is the precursor of functional deterioration, which leads to recurrent hospitalization, institutionalization, and death.[8,11] Frail persons have a decreased social activity[4,12] which may be due to the fact that frailty is often associated with incontinence which is a major determinant in decreasing social activity and leading to institutionalization.[12,13]

**Nutrition, Sarcopenia and Frailty: A Complex Relationship**

Sarcopenia is defined as the loss of skeletal muscle mass and function which is associated with age. Sarcopenia strongly influences the muscle strength, gait and balance, while it contributesto the risk of falls and frailty in older persons. The causes of sarcopenia are multifactorial and include disuse (due to physical inactivity), changes in the endocrine function, and presence of chronic diseases, inflammation, insulin resistance, and nutritional deficiencies.

Sarcopenia is also defined as a condition of lowered muscle mass and decreased muscle strength that is often age-associated, but can also be caused by clinical conditions that may be independent of the process of ageing, including chronic disease and under-nutrition.[14] To qualify for the structural definition of sarcopenia, the muscle mass needs to be at least 2SD below mean for young adults. The prevalence of sarcopenia ranges from 13-24 percent in persons aged 65 to 70 years and over 50 percent for those older than 80 years.[15]

An altered endocrine function (decrease of testosterone, estrogens and growth hormones), reduced physical activity, increase in the number of chronic illness (increase of cytokines) and inadequate nutrition play an important role in the reduction of muscle mass with aging. Sarcopenia may be prevented or treated, essentially with lifestyle interventions like exercise and nutritional supplementation or pharmacological treatment like testosterone or growth hormone replacement.[16]

With ageing, there is a decline in energy requirements; this decline results mostly from physical inactivity. In many people over 65 years of age, caloric intake may be reduced beyond the point of lowered needs, thus creating a macronutrient deficit. And in addition, the vitamin and mineral requirements do not decline with aging, so older people are at risk for deficient intake of micronutrients. Studies have shown links between frailty and low protein intake[17] as well as with deficits in vitamins D, E, and other vitamins.[18,19,20] Deficient intake of energy and protein, reduced intake of vitamin D, acute and chronic co-

morbidities and reduced physical activity are some of the extrinsic conditions leading to sarcopenia.[21,22]

**Incidence of Frailty**

It is mostly seen that prevalence of frailty is higher with age, in women, and in the presence of chronic disease.[4,23,24] There are limited studies that have studied the prevalence in the west and there is a dearth of information in the Indian setting. A multi-country study by WHO Study on global health and AGEing (SAGE) in samples of adults aged 50 years and older collected health and disability data in China, Ghana, India, Mexico, Russian federation and South Africa between 2007 and 2010. A deficit accumulation criterion was used to define frailty in community-dwelling older persons and in India, it was found to be 55.5%.[25] Khandelwal et al (2012) have shown frailty to be 33.2% in a sample of 250 older hospitalized patients.[26] Further studies are needed to define the prevalence of physical frailty in India and its risk factors. A systematic review recently done, investigated the prevalence of frailty in Western countries.[27] The definitions and the criteria that were used for frailty varied between the studies, which explain the considerable variation in the reported frailty prevalence rates among these countries.

**Frailty and Nutrition**

Malnourished older persons have vitamin deficiencies leading to impairment in cognition.[8] Morley described malnutrition as a strong determinant of frailty.[29] Cognitive dysfunction may also lead to frailty due to decreased food intake [30]. A study by Smit et al showed that serum albumin, carotenoids and Se levels are lower in frail adults as compared to their non-frail counterparts. They also found frailty to be most prevalent in obese people and lowest in underweight people. Interestingly, the energy intake (independent of the Body Mass Index) was lowest in people who were frail while it was found to be the highest in people who were not frail.[31]

Low intake of protein may be a risk factor for frailty.[17,32] A study found that the intakes of protein (both animal and plant) were found to be inversely associated with frailty.[33] Not only the amount of protein intake but its distribution over the day is thought to affect the protein anabolism, though not significant. It was also seen that the participants who were frail consumed significantly less protein in the morning but more at noon than their pre-frail and non-frail counterparts.[34]

The energy intake of ≤ 21 kcal/kg/day was found to be significantly associated with frailty and a low intake of protein; vitamins D, E, C, and folate; and having a low intake of more than three nutrients were seen to be significantly and even independently related to frailty (after adjusting for energy intake)[17], although carbohydrate, fat, protein, and dietary fibre showed no consistent associations with frailty status in another study.[35]

Mortality showed a positive association with frailty in a study, the risk being significantly higher among participants who were frail and had low serum 25(OH) D [36] while lower levels of 25(OH)D were associated with being pre-frail.[37] Wilhelm-Leen et al (2010) reported that vitamin D deficiency can cause a 3.7 time increase in the risk of frailty amongst whites and a fourfold increase in the odds of developing frailty amongst non-whites.[38] Chang et al (2010) showed similar significant results.[39]

Another study by Ensrud et al (2010) reported association between 25(OH) D level and odds of frailty at baseline (though U-shaped) and also found that the lowest risk was in women with levels 20.0-29.9 ng/ml (referent group).[40] Tajar et al (2013) also showed that among the five phenotypic criteria by Fried, only sarcopenia was not associated with the serum 25(OH) D levels against the other four.[37] A number of rural elderly experience physical disabilities and exhibit an increased risk for major health problems. The sedentariness criterion of frailty was found to be the most predominant in a sample of 572 elderly.[41]

Several large epidemiological trials have elucidated potential nutritional risk factors. The Women's Health and Aging Studies I and II (WHAS) used the definition by Fried et al (2001) for identifying frailty in a cohort of 1,002 women in 1992.[17,42] Women with lower serum carotenoids were at a slightly greater risk for frailty than those in the higher quartiles. Frail women also showed lower serum levels of alpha-tocopherol, 25-hydroxyvitamin D, selenium, and zinc. No significant differences were seen in folate or vitamins A, $B_6$ or $B_{12}$ between frail and non-frail women.[42]

In an analysis of a subset of women from these studies, the strongest association demonstrated between nutrient deficiencies and frailty was for total carotenoids, betacarotene and lutein/zeaxanthin.[17]

**Frailty, Muscle Atrophy and Sarcopenia**

Functional muscle loss is manifested in frail elderly. This is termed as 'sarcopenia'. It may be

defined by the loss of muscle mass that is age-related and responsible for the decline in muscle strength. It plays a major role in the pathogenesis of frailty.[43] Ageing is often accompanied by anuncoupling phenomenon of the muscle cross-sectional area and the fibre strength of the muscle. With ageing, there is a build-up of fat in the muscle (termed as 'myosteatosis') which leads to a decline in muscle strength causing functional impairment and physical disability that bringschanges in gait and balance.[44] However, a subset of obese personsmay be sarcopenic (termed as 'sarcopenia obese' or "fat frail"). Inadequate physical activity and/or exercise may lead to frailty in this group of sarcopenic obese individuals.[45]

Loss of muscle with ageing is viewed as largely inevitable. After reaching a peak in adult life, skeletal muscle mass begins to decline by ≈0.5–1.0%$y^{-1}$at about 40 years of age. In the early stages, the loss of lean muscle mass may be gradual and gets masked by a concurrent increase in fat mass along with subtle lifestyle modifications. However, there may be a breakpoint that can occur when an individual previously asymptomatic experiences an injurious event and may get acutely/temporarily disabled.[46] In such cases, there may be accelerated loss of skeletal muscle which may facilitate a greater loss of functional capacity. Sarcopenia is associated with a high risk of disability up to 3- to 4-folds, which in turn is associated with greater socio- economic and health care spending.

A fall is seen in the level of testosterone in advancing age which is associated with a decrease in muscle strength and function. The rate of fall of testosterone with aging is nearly 1% annually.[47] Muscle mass has shown atrophy with androgen deprivation.[48] Testosterone has shown to stimulate protein synthesis and satellite cell production.[49]

The consequences of sarcopenia are continuous sense of fatigue, weakness of muscle, increased susceptibility to metabolic disorders and an increased risk of falls and fractures especially in older adults.[50] Studies suggest that loss of muscle mass can predict functional decline in older adults who are independent and those with disability.[51,52] Interestingly, Reid et al (2008) showed that the lower extremity muscle mass independently predicts functional impairment.[53] Loss of strength with aging follows a similar trajectory with loss of muscle mass in many of the physiological studies although the decline in muscle strength is sharper than the decline in muscle mass.[54]

**Frailty and Cardiovascular Health**

Studies have shown that frailty and chronic disease frequently co-exist[55] especially cardiovascular disease (CVD).[56,57] A systematic review of studies found that the odds ratios for prevalent frailty associated with CVD.[58] In individuals with no history of CVD, the extent of underlying cardiovascular disease may be related to frailty. A study by Newman et al showed that infarct-like lesions in the brain are also related to frailty.[11] A significant association exists between frailty and risk of incident heart failure in older individuals.[59]

Frailty also predicts mortality in patients with CVD independent of their age, the underlying disease severity, comorbidities and disability. The Cardiovascular Health Study (CHS) found a threefold increase in the presence of frailty in patients with CVD.[11] In another study of 2515 individuals, a 1 point increase (out of 5) in the frailty score was linked with a 35% increase in the risk of having a CVD. CVD and frailty, like any other chronic conditions, develop progressively over a course of time and exhibit a long subclinical phase.[60] Thus prevention and control of risk factors may play a significant role in evading adverse health outcomes. The chief modifiable risk factors include unsuitable eating habits, diabetes, hypertension, sedentary life style, and smoking.[61] Individuals between 45 and 69 years of age and with more of the CVD risk factors were found to have higher odds of developing frailty.[62] Factors that have been found to play a pivotal role in this relationship include inflammation, chronic kidney disease and low alanine transaminase.[63-65] Amore detailed and better insight on the cardiovascular risk profile of frail elderly is needed to permit better clinical management of such patients.

**Frailty and Exercise**

With age, there is a decline in the muscle mass and strength and it is even more distinct in frailty.[67] Studies show that exercise is favourable in older adults, even in the frailest subset benefit from it. The benefits of exercise in the elderly are numerous and include increased mobility, improved performance of activities of daily living (ADL), better gait, less incidence of falls, increased bone mineral density, and improvements in overall well-being.[68-70]

In a group of nursing home patients, Fiatarone et al (1994) found that an exercise regime comprising of resistance training significantly improved muscle strength, muscle size in the lower

extremities and gait velocity compared to a control group which showed either marginal increases or declines in these areas.[71] There is no ideal recommendation for exercise in frail elderly; however, studies have shown benefit from resistance training on as few as 2 days per week.[72] Miller et al (2000) found that walking about 1 mile per week was linked to gradual development of functional limitations over a follow-up of 6 months.[73]

## Health Care of Frail elderly

Khandelwal et al (2012) reported that almost a third of hospitalized older patients are frail, anemic, with higher frequency of CHF, have cognitive impairment, stay longer in the hospital and have higher mortality.[26] Frailty is generally found in community patients with heart failure. Frailty is also a robust and autonomous predictor of emergency department visits and hospitalizations. Since frailty is potentially modifiable, it should be integrated in the clinical assessment of patients with heart failure.[74] Older persons, especially when frail, account for the highest costs in health care in developed countries.[75] This makes it absolutely obligatory that policy-makers clearly state their target population (age group, sex) when applying these rates of frailty especially in a developing country like India.

## Conclusion

Frailty is an ageing phenomenon and it becomes critical in understanding the risk factors that lead to frailty in elderly. It is multifactorial and linked to various morbidities. It deteriorates the quality of life of the elderly by making them dependent in their basic activities of daily living. It is a commonly used term among the geriatricians and many studies have been conducted to understand the concept of frailty in terms of deficits as well as its physical manifestations. Recognizing frailty in elderly at an early stage will enable us to plan suitable interventions to prevent at-risk elderly from developing the syndrome. Limited studies have been done in India to comment on the risk factors to which our elderly are exposed to or to identify those risk factors that may be specific to a developing country like ours. Further studies are needed to establish relationships between frailty and nutrition, lifestyle, psychological factors, socio-economic factors etc. in India.

## List of Abbreviations

SAGE: Study on global AGEing and adult health

WHO: World Health Organization

25(OH)D: 25 Hydroxy Vitamin D

WHAS: Women's Health and Ageing Studies

CVD: Cardiovascular Disease

ECG: Electrocardiography

CHS: Cardiovascular Health Study

LV: Left Ventricular

DM: Diabetes Mellitus

ALT: Alanine Transaminase

CHF: Congestive Heart Failure

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CLINICAL RESEARCH STUDY

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# Hypothyroid Symptoms Fail to Predict Thyroid Insufficiency in Old People: A Population-Based Case-Control Study

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## ABSTRACT

**BACKGROUND:** Clinic-based studies have indicated that older hypothyroid patients may present only few symptoms.

**METHODS:** In this population-based study of hypothyroidism, we investigated how the power of symptom presence predicts overt hypothyroidism in both young and older subjects. We identified patients newly diagnosed with overt autoimmune hypothyroidism in a population (n = 140, median thyroid-stimulating hormone, 54.5; 95% confidence interval [CI], 28.3-94.8; median total T4, 37; 95% CI, 18-52) and individually matched each patient with 4 controls free of thyroid disease (n = 560). Participants filled out questionnaires concerning the presence and duration of symptoms. We compared the usefulness of hypothyroidism-associated symptoms in predicting overt hypothyroidism in different age groups (young: <50 years, middle age: 50-59 years, old: ≥60 years) also taking various confounders into account.

**RESULTS:** In young hypothyroid patients, all 13 hypothyroidism-associated symptoms studied were more prevalent than in their matched controls, whereas only 3 of those (tiredness, shortness of breath, and wheezing) were more prevalent in old patients. The mean numbers of symptoms presented at disease onset were 6.2, 5.0, and 3.6 at the ages of 0 to 49 years, 50 to 59 years, and 60+ years, respectively. In young versus old people with 0 to 1 symptoms, the odds ratio for being hypothyroid was 0.04 (95% CI, 0.007-0.18) versus 0.34 (95% CI, 0.15-0.78) (reference all other groups). In young versus old subjects reporting ≥4 symptoms, the odds ratio for being hypothyroid was 16.4 (95% CI, 6.96-40.0) versus 2.22 (95% CI, 1.001-4.90). Receiver operating characteristic analyses revealed that the symptom score was an excellent tool for predicting hypothyroidism in young men (area under the receiver operating characteristic curve, 0.91; 95% CI, 0.82-0.998), whereas it was poor in evaluating older women (area under the receiver operating characteristic curve, 0.64; 95% CI, 0.54-0.75).

**CONCLUSION:** Hypothyroid symptom score is a good discriminating tool to identify hypothyroidism in young patients but fails to identify hypothyroidism in the elderly. Thus, thyroid function should be tested on wide indications in old age.

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**KEYWORDS:** Age; Case-control study; Hypothyroidism; Population-based study; Symptoms; Thyroid disease

The immune system is altered in the aging process. It becomes less responsive to antigenic challenges with an increase in incidence and morbidity of infections probably due to signaling defects in the aging adaptive immune system. On the other hand, the innate immune system is activated in old age,[1] and the occurrence of autoimmune disorders increases.[2]

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Moreover, increased concentration of inflammatory cytokines causing a proinflammatory environment may accelerate and complicate degenerative diseases.

Organ-specific autoantibodies are rather common among old people.[2,3] Thus, old age is complicated by an increase in autoimmune disease frequency. Hypothyroidism is no exemption,[4] and in a previous population-based study, we have calculated the median age at disease onset to be 67.6 years.[5] Compared with people aged 0 to 30 years, hypothyroidism was diagnosed 14 times more often in those aged 50 to 60 years, and 33 times more frequently in those aged more than 70 years.[5] This overrules by far the risk associated with female gender,[5] the somewhat higher risk associated with genetic predisposition,[6] and a number of environmental factors, such as iodine intake,[5] smoking habits,[7] alcohol abstinence,[8] and previous live births.[9]

**CLINICAL SIGNIFICANCE**

- Clinical presentation in patients who are newly diagnosed with overt autoimmune hypothyroidism depends on the subject's age.
- The use of symptom presence for predicting overt autoimmune hypothyroidism is excellent in young men, good in young women, and fair in older men, whereas it poorly predicts thyroid failure in older women.
- Thyroid function should be tested on wide indications, especially when elderly people seek a doctor's help.

Hypothyroidism may present with a variety of symptoms reflecting the hormonal insufficiency in different organs.[10-16] However, none of these symptoms have high sensitivity or specificity when compared with euthyroid control persons, and previous studies have suggested scarceness of symptoms specific for hypothyroidism in the older population.[17-20] Furthermore, old people also may have a variety of other diseases, and the coexistence of thyroid disease and other comorbidities challenges which symptoms may represent which disease.

We performed a study of patients newly diagnosed with overt autoimmune hypothyroidism and aimed to investigate in detail the relative frequency and importance of various symptoms at different ages of disease onset. In particular, we evaluated the usefulness of symptoms when deciding who should have their thyroid function biochemically tested, focusing on the importance of patients' age. We previously found that symptom presence was more predictive for hypothyroidism in women than in men[21] and now studied if such sex difference was age-dependent. Four of 5 patients (79.5%) newly diagnosed with hypothyroidism are women, and approximately more than half (56.5%) are aged more than 60 years.[5] Thus, the usefulness of symptom screening before biochemical thyroid testing is pivotal in the geriatric patient.

## SUBJECTS AND METHODS

The Danish Investigation of Iodine Intake and Thyroid Diseases was established to monitor the occurrence of thyroid disease in Denmark before the introduction of iodine fortification in 2000. A cohort of 538,734 citizens were under surveillance during the study period March 1997 to December 2000. Patients newly diagnosed with overt autoimmune hypothyroidism were registered. For comparisons, we simultaneously recruited randomly selected civilians from the same population.

### Patients

Two geographic areas were chosen to be representative for the Danish population: an area in and around the city of Aalborg with moderate iodine deficiency; and in Copenhagen with only mild iodine deficiency. A register was linked to the 4 diagnostic laboratories responsible for all thyroid function testing performed in these 2 areas. Subjects with a first-time thyroid function test suggesting overt hypothyroidism, that is, elevated serum thyroid-stimulating hormone and a low T4 estimate, were identified by the register as possible new cases. They were individually canvassed to verify or disprove incident overt autoimmune hypothyroidism.[5] The use of a register linked to laboratory databases[22] and the complex and well-defined algorithm for verification of incident hypothyroidism and for classification into primary overt autoimmune hypothyroidism have been described extensively.[5,23]

In the 4-year study period, we identified 578 new cases with primary autoimmune hypothyroidism. In selected periods with staff available, we invited 247 patients, of whom 147 (59.5%) gave full participation.

### Controls

For each patient, we included from 2 simultaneously ongoing population surveys 4 randomly selected biochemically euthyroid control subjects matched on age and region. The precise matching algorithm has been described.[21,23] We were able to match 140 patients diagnosed with autoimmune hypothyroidism with 560 control subjects.

### Questionnaires

Participants filled out a questionnaire covering a variety of symptoms experienced in the last 12-month period before hypothyroidism was diagnosed. The questionnaire was based on 2 formerly used questionnaires (the first comprised symptoms selected from literature, the second questionnaire included questions on mental vulnerability, and we added symptoms comprising psychiatric symptoms and a number of symptoms associated with thyroid enlargement as previously stated[23]). Among the various symptoms, we identified 13 symptoms, which all met the criterion ($P < .0015$) of a Bonferroni statistically significant higher symptom prevalence among cases compared with controls.[23] The

group of hypothyroidism-associated symptoms were as follows: neck symptoms (globulus, difficulty swallowing, and anterior neck pain), respiratory symptoms (wheezing and shortness of breath), cardiac symptom (palpitations), gastrointestinal discomfort (constipation), dermatologic changes (hair loss and dry/sensitive skin), psychic symptoms (restlessness and mood lability), and tiredness, all experienced within 12 months preceding the hypothyroidism diagnosis. In addition, recent vertigo (or dizziness) was also expressed more often in hypothyroid patients. The presence of symptoms was combined into a hypothyroidism component score defined as the number of hypothyroidism-associated symptom (range, 0-13). Finally, patients also clarified how long they had experienced symptoms before hypothyroidism was diagnosed.

As previously outlined,[21,23] participants had their height and weight measured and filled out questions on educational level (basic school and up to 2 years vocational training vs more), smoking habits (current, previous, or never smoking), alcohol consumption (units per week), and comorbidity (cardiovascular comorbidity, defined as ever having had acute myocardial infarction, angina pectoris, cardiac arrhythmia, hypertension, or cerebral stroke, or noncardiovascular comorbidity in case of epilepsy, diabetes mellitus, asthma, chronic obstructive pulmonary disease, or gastrointestinal ulcer).

## Blood Specimen Analyses

Blood was drawn at investigation and kept frozen at −20° C. Thyroid peroxidase antibodies and thyroglobulin antibodies (both antibody measurements by DYNOtest and KRYPTORtest, Thermo Fisher Scientific Clinical Diagnostics B·R·A·H·M·S GmbH, Hennigsdorf, Germany) from participant blood specimens were measured at random order.[2,24] Subjects with serum autoantibody concentration above the functional sensitivity given by the manufacturer were regarded as antibody-positive (thyroid peroxidase antibodies+: >30 kU/L, thyroglobulin antibodies+: >20 kU/L). Thyroid-stimulating hormone was measured in serum drawn from controls. For all patients diagnosed with overt autoimmune hypothyroidism, we registered the specific serum thyroid-stimulating hormone and T4 concentrations leading to the diagnosis of overt hypothyroidism. Details on thyroid-stimulating hormone and T4 analyses have been reported.[5,22]

## Ultrasound Investigation

Participants underwent ultrasound investigation using a Sonoline Versa Pro 7.5-MHz, 70-mm linear transducer with an effective length of 62 mm (Siemens, Munich, Germany). Thyroid volume was the sum of the 2 lobes each calculated according to the ellipsoidal formula: $\pi/6 \times$ maximal length $\times$ width $\times$ depth.[25]

## Statistical Analysis

We used the IBM Statistical Package for Social Sciences version 15.0 (SPSS, Inc, Chicago, Ill) for calculations and statistical analyses. Means and 95% confidence intervals (CIs) or, when appropriate, medians and the interquartile range (25%-75%) were calculated. The percentage of subjects with hypothyroidism-associated symptoms was calculated for different age groups and compared using Pearson's chi-square test. Associations between participant state (case vs controls) and symptom presence (yes vs no) were explored by means of the diagnostic odds ratio (DOR).[21,23] The DOR, which is identical to the simple odds ratio (OR), explains the odds for being a case given the presence of a specific number of symptoms. We explored the presence of each of the 13 hypothyroidism-associated symptoms and calculated an unweighted hypothyroidism component score by adding up the total number of symptoms reported (range, 0-13). We have previously validated our hypothyroidism component score in the untruncated cohort.[23] We tested the power of discrimination by means of the area under the receiver operating characteristic curve (AUROC) (values of <0.6, >0.6, >0.7, >0.8, and >0.9 indicate that the model is useless, poor, fair, good, and excellent, respectively) and calculated the AUROC to be 0.76 (95% CI, 0.72-0.80), indicating that symptoms were fairly discriminative.[23] The calibration was tested by the cohort-size sensitive Hosmer-Lemeshow chi-square goodness-of-fit test (the higher the $P$ value, the better the test), and we found a fair $P$ value of .70. In addition, the Nagelkerke $r^2$ was calculated to be 0.25, meaning that 25% of the disease state variation (hypothyroid or not) could be explained by the variation in the symptom score. In the present study, we evaluated whether those test characteristics were influenced by age and gender. In univariate and multivariate models, we tested whether the hypothyroidism component score was correlated to a number of patient characteristics, among those serum thyroid-stimulating hormone and T4 at time of diagnosis.

The prevalences of each of the 13 hypothyroidism-associated symptoms expressed by patients newly diagnosed with overt autoimmune hypothyroidism are illustrated in a newly developed Nautilus diagram. This diagram is capable of showing the sensitivity of various symptoms, which are ordered according to their relative DORs in the combined groups of 140 cases and 560 euthyroid controls.[23] As more curves representing various age groups may be included, the size of the area between the curves is proportionate to the DOR. Thus, the spatial difference between the curves illustratively expresses the different usability of various symptoms used to suspect undiagnosed hypothyroidism. The diagram has the same shape as the outer shell of the marine cephalopod Nautilus, thereby its name.

## Ethical Approval

This study was approved by Regional Ethics Committees in North Jutland and Copenhagen. Registry permission was obtained from the Danish Data Protection Agency. All participants gave their written informed consent. No conflicts of interest have occurred during implementation or completion of the study.

## RESULTS

### Hypothyroidism Component Score

On average, each of 140 patients newly diagnosed with overt autoimmune hypothyroidism experienced 5 (of a maximum of 13) hypothyroidism-associated symptoms, but this was highly age dependent as illustrated in Figure 1. In patients aged <50 years, 50 to 59 years, and ≥60 years the mean numbers of symptoms were 6.1, 5.0, and 3.6, respectively. Euthyroid controls had on average 2.4 of those symptoms (Figure 1) with no age dependency. We confined subsequent comparisons to the young subjects (age <50 years of age, cases/controls, n = 56/224) and older subjects (age ≥60 years, n = 40/160). As described in detail in Table 1, some statistically significant differences between those groups of patients were recorded with regard to education, cardiovascular comorbidity, and body mass index. Among the euthyroid controls, younger subjects were taller, had lower body mass index, and had lower thyroid gland volume, and were better educated and had less comorbidity (Table 1).

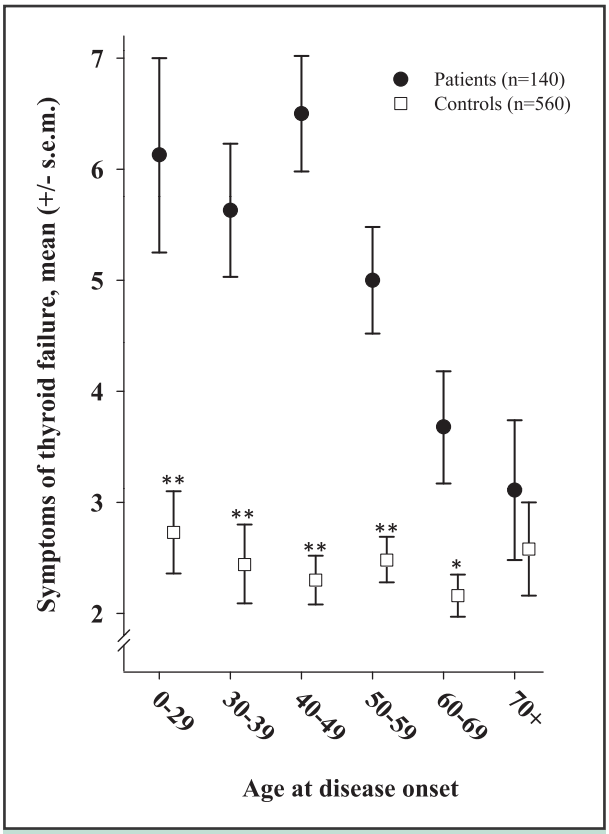


**Figure 1** Mean number of symptoms present at disease onset in autoimmune overt hypothyroidism and in age, gender-, and region-matched euthyroid controls by different age groups. Number of cases in the age groups 0 to 29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years, 60 to 69 years, and 70+ years were n = 8, 16, 32, 44, 31, and 9, respectively (corresponding numbers in controls were 4 times higher because of the individual matching). Mean numbers of symptoms presented at disease onset were 6.1, 5.6, 6.5, 5.0, 3.8, and 3.1. Mean (± standard error of the mean) duration of symptoms before hypothyroidism was diagnosed within the same age strata were 14.0 ± 3.3, 14.5 ± 4.2, 13.2 ± 3.4, 9.7 ± 1.2, 10.2 ± 2.0, and 10.4 ± 3.2. Asterisks depict statistically different number of symptoms between patients and healthy subjects (*$P < .01$, **$P < .001$). s.e.m. = standard error of the mean.

The usefulness of the symptoms studied in predicting hypothyroidism in the 2 age groups was explored by calculating the DORs (Figure 2). The presence of 0 to 1 symptoms was associated with a 25 times lower probability of being hypothyroid at a young age as DOR was 0.04 (95% CI, 0.007-0.18). On the other hand, if 4 to 8 symptoms were present, a young subject was 4.12 times (95% CI, 2.14-7.97) more likely to be a hypothyroid patient than a control person, and 8 or more symptoms were associated with a 9.17 (95% CI, 3.75-22.8) higher likelihood of having thyroid insufficiency. Even more striking, the presence of ≥4 symptoms in young subjects was more predictive for thyroid failure than if present in older subjects (OR, 16.4; 95% CI, 6.69-40.0 vs OR, 2.22; 95% CI, 1.001-4.90).

The receiver operating characteristic curve (Figure 3) demonstrated that asking for symptoms was an excellent preliminary test for overt autoimmune hypothyroidism in young men (AUROC, 0.91; 95% CI, 0.82-0.998) and was good in young women (AUROC; 0.84; 95% CI, 0.77-0.89). In contrast, it was only a fair test in older men (AUROC; 0.76; 95% CI, 0.57-0.94), whereas it was a rather poor test among older women (AUROC; 0.64; 95% CI, 0.54-0.75). Correspondingly, Nagelkerke $r^2$ values differed among those 4 groups (0.51 vs 0.33 vs 0.21 vs 0.05), meaning that 51% of the disease state variation in younger men could be explained by their symptom score variation. This was more than 10 times better than in the group of older women.

### Individual Symptoms

The prevalences of each of the 13 symptoms in patients newly diagnosed with overt autoimmune hypothyroidism are shown in Figure 4. Except for respiratory symptoms (shortness of breath and wheezing), the prevalences of symptoms were higher in young versus older hypothyroid patients, and this was statistically significant in 6 of 11 symptoms ($P < .05$). Tiredness was reported as the most prevalent symptom in both age groups with a sensitivity of 96.4% in hypothyroid patients aged less than 50 years.

When comparing the symptomatic burden between young hypothyroid and euthyroid subjects, pronounced differences were observed (Figure 5A, the hatched area between the 2 curves is proportionate to the DOR). As illustrated in Figure 5B, the usefulness of asking for symptoms in the diagnostic process was smaller among subjects aged 60 years and more.

### Determinants of Symptom Severity

The more profound symptom presentation among younger subjects may be caused not only by age but also by a number

**Table 1** Baseline Characteristics of Hypothyroid Patients and Age-, Gender-, and Sex-Matched Control Subjects

| | Overt Autoimmune Hypothyroidism† | | Euthyroid Control Subjects† | |
|---|---|---|---|---|
| | Young, <50 y n = 56 | Elderly ≥60 y n = 40 | Young <50 y n = 224 | Elderly ≥60 y n = 160 |
| Age, y | 42.6 (33.3-46.8)*** | 64.9 (62.1-69.5) | 42.6 (33.7-46.3)*** | 64.9 (62.4-68.2) |
| Female sex | 48 (85.7) | 30 (75.0) | 192 (85.7)** | 120 (75.0) |
| Inhabitancy | | | | |
| Aalborg (moderate ID) | 30 (53.6) | 27 (67.5) | 120 (53.6)* | 108 (67.5) |
| Copenhagen (mild ID) | 26 (46.4) | 13 (32.5) | 104 (46.4) | 52 (32.5) |
| Weight, kg | 72.0 (62.1-80.0) | 77.9 (68.7-87.6) | 67.4 (60.4-75.7) | 70.8 (62.2-78.1) |
| Height, m | 1.68 (1.63-1.73) | 1.64 (1.60-1.69) | 1.68 (1.63-1.72)*** | 1.65 (1.58-1.72) |
| BMI, kg/m$^2$ | 25.7 (22.9-27.8)* | 29.1 (25.5-31.9) | 24.1 (21.8-26.5)*** | 26.4 (23.3-27.9) |
| Serum TSH, mU/L | 65.3 (34.1-120) | 39.4 (22.3-79.5) | 1.34 (.92-1.85) | 1.18 (.74-1.74) |
| Full range | *5.3-288* | *5.2-241* | *0.38-4.68* | *0.22-4.86* |
| Serum total T4, nmol/L‡ | 35.0 (16.0-52.0) | 44.5 (14.3-55.0) | Not measured | Not measured |
| Full range | *0.5-59.0* | *0.5-59.0* | | |
| TPOAb, kU/L | 4381 (1535-14,199) | 3894 (787-5956) | <30 | <30 |
| TPOAb+, >30 kU/L | 52 (92.9) | 39 (97.5) | 37 (16.5) | 31 (19.5) |
| TgAb, kU/L | 157 (34-2123) | 143 (40-858) | <20 | <20 |
| TgAb+, >20 kU/L | 46 (82.1) | 34 (85.0) | 30 (13.4) | 26 (16.4) |
| Thyroid volume by ultrasonography, mL | 13.1 (7.36-17.9) | 9.0 (5.56-18.4) | 12.2 (9.85-16.0)** | 14.6 (10.4-21.1) |
| Education | | | | |
| Basic school and up to 2 y vocational training | 27 (48.2)*** | 35 (87.5) | 113 (50.4)*** | 126 (78.8) |
| More | 29 (51.8) | 5 (12.5) | 111 (49.6) | 34 (21.3) |
| Smoking history | | | | |
| Never smoker | 19 (33.9) | 9 (22.5) | 95 (42.4) | 62 (38.8) |
| Previous smoker | 18 (32.1) | 18 (45.0) | 51 (22.8) | 49 (30.6) |
| Current smoker | 19 (33.9) | 13 (32.5) | 78 (34.8) | 49 (30.6) |
| Alcohol intake | | | | |
| 0 = abstainer | 14 (25.0) | 7 (17.5) | 21 (9.4) | 27 (16.9) |
| ≥1 units per wk | 42 (75.0) | 33 (82.5) | 203 (90.6) | 133 (83.1) |
| Comorbidity | | | | |
| All-causes | 28 (50.0) | 29 (72.5) | 73 (32.6)*** | 97 (60.6) |
| Cardiovascular§ | 17 (30.4)** | 24 (60.0) | 36 (16.1)*** | 71 (44.4) |
| Noncardiovascular‖ | 11 (19.6) | 5 (12.5) | 37 (16.5) | 26 (16.3) |

*$P < .01$ (with no multicomparison correction). **$P < .05$ (Bonferroni corrected) corresponding to crude $P < .0037$ (uncorrected). ***$P < .01$ (Bonferroni-corrected) corresponding to crude $P < .00072$. Asterisks are depicted in young column if statistically different from elderly).

BMI = body mass index; ID = iodine deficiency; TgAb = thyroglobulin antibodies; TPOAb = thyroid peroxidase antibodies; TSH = thyroid-stimulating hormone.

†Depicted are number of participants (percentage) or medians (interquartile range, 25%-75% range); full range (0%-100%) in *italic*. Some data were missing for total T4 (n = 1, diagnosis based on free T4), TPOAb (n = 1), TgAb (n = 1), thyroid volume (n = 1), and time since smoking cessation (n = 3).

‡Serum total T4 in μg/dL = 0.078 × total T4 in nmol/L.

§Questionnaire obtained information on myocardial infarction, angina pectoris, cardiac arrhythmia, hypertension, or cerebral stroke.

‖Questionnaire obtained information on epilepsy, diabetes mellitus, asthma, chronic obstructive pulmonary disease, or gastrointestinal ulcers.

of other factors not evenly distributed between younger and older patients (Table 1). We performed univariate and multivariate linear regression analyses, in which the number of symptoms present (the hypothyroidism component score) was the dependent variable, and certain patient characteristics outlined in Table 1 were possible explanatory factors. In the univariate model (Table 2), significant predictors were low age (<50 years vs ≥60 years), region of inhabitancy, and education, but in the multivariate model only age was statistically associated with the symptom score ($P < .001$); for the region of inhabitancy and education, those were not significantly associated with symptom score in the multivariate model ($P = .077$ and $P = .76$, respectively). However, participants from Copenhagen tended to express more symptoms despite similar T4 and thyroid-stimulating hormone levels. High education was more common among young people, explaining the significance in the univariate model (Table 2) but not in the multivariate model. No significant association was found between the biochemical degree of hypothyroidism and the symptom score in the univariate model (Table 2). To explore such association in more detail, we performed multivariate analyses of symptom score dependence on thyroid-stimulating hormone and T4 (separate models) in both young patients (<50 years) and old patients (≥60 years). In young patients, no

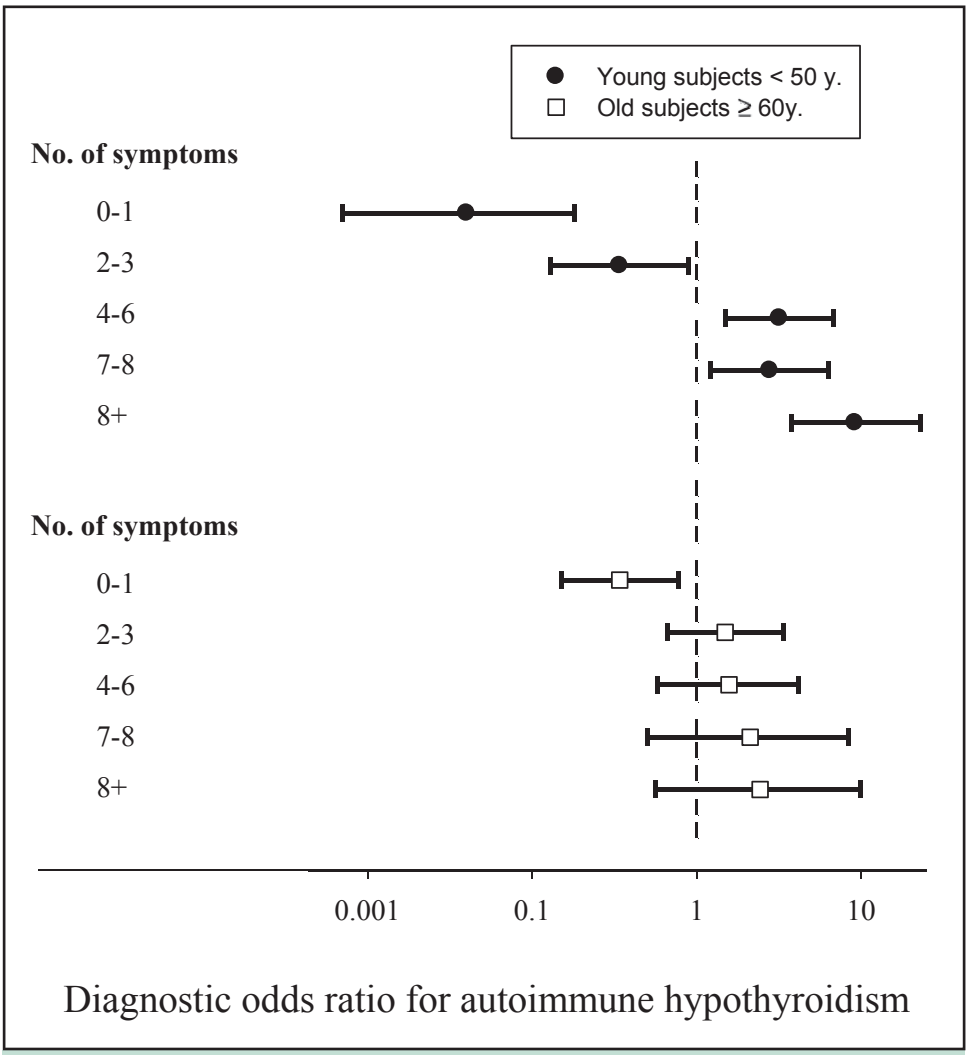


**Figure 2** ORs for autoimmune overt hypothyroidism in the presence of different number of symptoms. Calculations were performed in 2 groups (younger subjects aged <50 years [cases/controls], n = 56/224; older subjects aged ≥60 years, n = 40/160). ORs with 95% CIs for being hypothyroid in the presence of 0 to 1, 2 to 3, 4 to 6, 7 to 8, and 8+ symptoms were 0.04 (0.007-0.18), 0.34 (0.13-0.89), 3.18 (1.50-6.75), 2.78 (1.21-6.32), and 9.17 (3.75-22.8), respectively, at ages of 50 years or less. The corresponding figures were 0.34 (0.15-0.78), 1.49 (0.66-3.37), 1.57 (0.58-4.14), 2.11 (0.50-8.34), and 2.43 (0.56-9.94), respectively, among the older subjects aged 60 years or more. OR for ≥4 symptoms (16.4 [6.96-40.0] vs 2.22 [1.001-4.90]) also indicated a higher usefulness of symptoms in suspecting undiagnosed hypothyroidism in the young group. The intermediate group of patients aged 50 to 59 years was omitted from this analysis.

association was observed (*P* values for thyroid-stimulating hormone and T4 were .12 and .16, respectively). In older patients, *P* values were .75 and .03 (more symptoms with low T4), respectively.

## DISCUSSION

### Hypothyroidism Component Score

Some studies have reported the total number of signs or symptoms of hypothyroidism.[10,17,26-31] Of those, some reported weighted scores[10,26,27,30] and some reported simple scores.[17,28,29,31] Few studies have validated the discriminative ability for correct classification of a hypothyroidism-component score by measuring AUROC.[26,28] Canaris et al[26] reported an AUROC value of 0.64 using a weighted symptom score on subjects identified in a cross-sectional study and AUROC values between 0.66 and 0.72 using different unweighted symptom scores applied on 76 patients with new hypothyroidism.[28] Those figures were somewhat smaller than we previously reported in the untruncated cohort (AUROC, 0.76),[23] but are at the same levels as the AUROC value obtained in our study material on older women (AUROC, 0.64). However, we obtained higher values in younger men (AUROC,

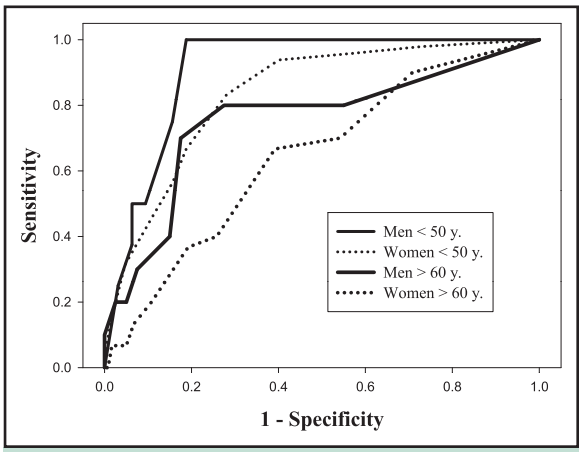


**Figure 3** Receiver operating characteristic curves for the hypothyroidism component score as a tool for suspecting overt autoimmune hypothyroidism. Four groups are depicted (men aged <50 years, women aged <50 years, men aged ≥60 years, and women aged ≥60 years). Hosmer-Lemeshow calibration chi-square goodness-of-fit test revealed statistically significant values in the 4 groups of 0.31 versus 0.28 versus 0.10 versus 0.16. ROC = receiver operating characteristic.

0.91) and younger women (AUROC, 0.84). Thus, our hypothyroidism symptom score more precisely may predict the risk of having hypothyroidism in our patient setting. Whether this is due to a better screening tool, different referral pattern, higher symptom thresholds among the older patients, or better patient recall remains an open question.

To our knowledge, only 1 study compared symptom presentation between young and old patients newly diagnosed with hypothyroidism. Doucet et al[17] studied 18 symptoms and 6 signs, and reported higher point estimates on 15 symptoms and 5 signs. Because of the low number of patients, only 4 of these met statistical significance. They also reported a higher score of symptoms/signs in younger patients (mean, 9.3 vs 6.6). Unfortunately, no discriminative power calculations were provided.

## Individual Symptoms

Many studies have described individual symptoms in hypothyroid patients, but only a few have examined the age-dependent presentation of signs and symptoms.[17,18] Doucet et al[17] studied 18 symptoms and 6 clinical signs in 121 hypothyroid patients who were referred to the hospital. Point estimates in 15 of 18 symptoms and 5 of 6 signs were higher in the younger group of patients (≤55 vs ≥70 years), but because of the relatively low number of patients, most findings were statistically insignificant.

Tiredness or fatigue was also the main symptom to be reported in many other studies but with different prevalences ranging from 29% in a Swedish study of 79-year-old subjects[32] to 98% in Wayne's classic Scottish study from 1960.[33] Parle et al[18] studied 7 symptoms and 2 signs in hypothyroid patients aged 60 years or more and found an overall presence of symptoms/signs to be as low as 31%, and thus concluded that thyroid function tests rather than symptom presence could differentiate hypothyroid patients from subjects with no thyroid failure. This is further supported by Lloyd and Goldberg,[19] who screened 3417 patients on admission to a geriatric unit and reported that only

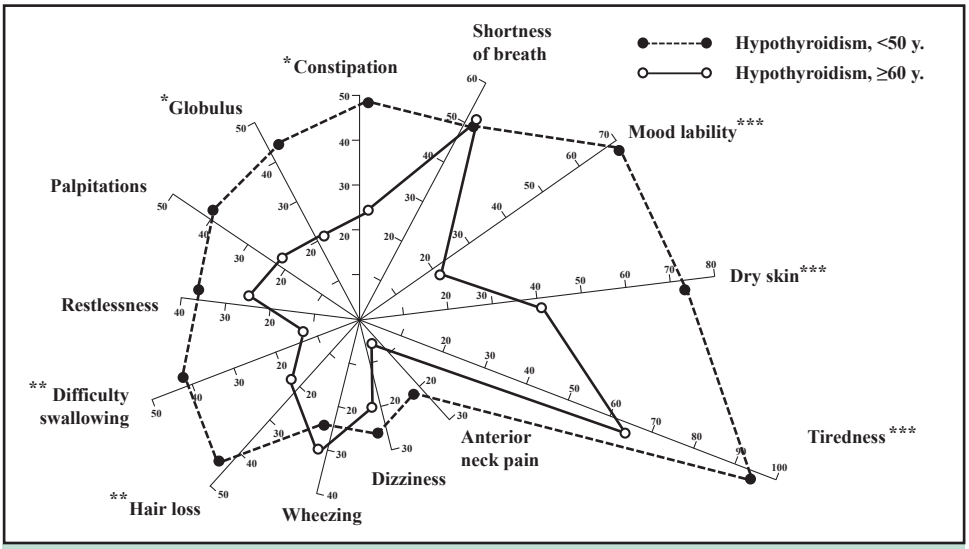


**Figure 4** Nautilus diagram depicting the prevalence of 13 hypothyroidism-associated symptoms in young patients (aged <50 years) and older patients (aged ≥60 years). Symptoms are ordered counterclockwise according to their DOR (see "Subjects and Methods"). Asterisks depict statistically different number of symptoms between patients and healthy subjects (*$P < .05$, **$P < .01$, ***$P < .001$).

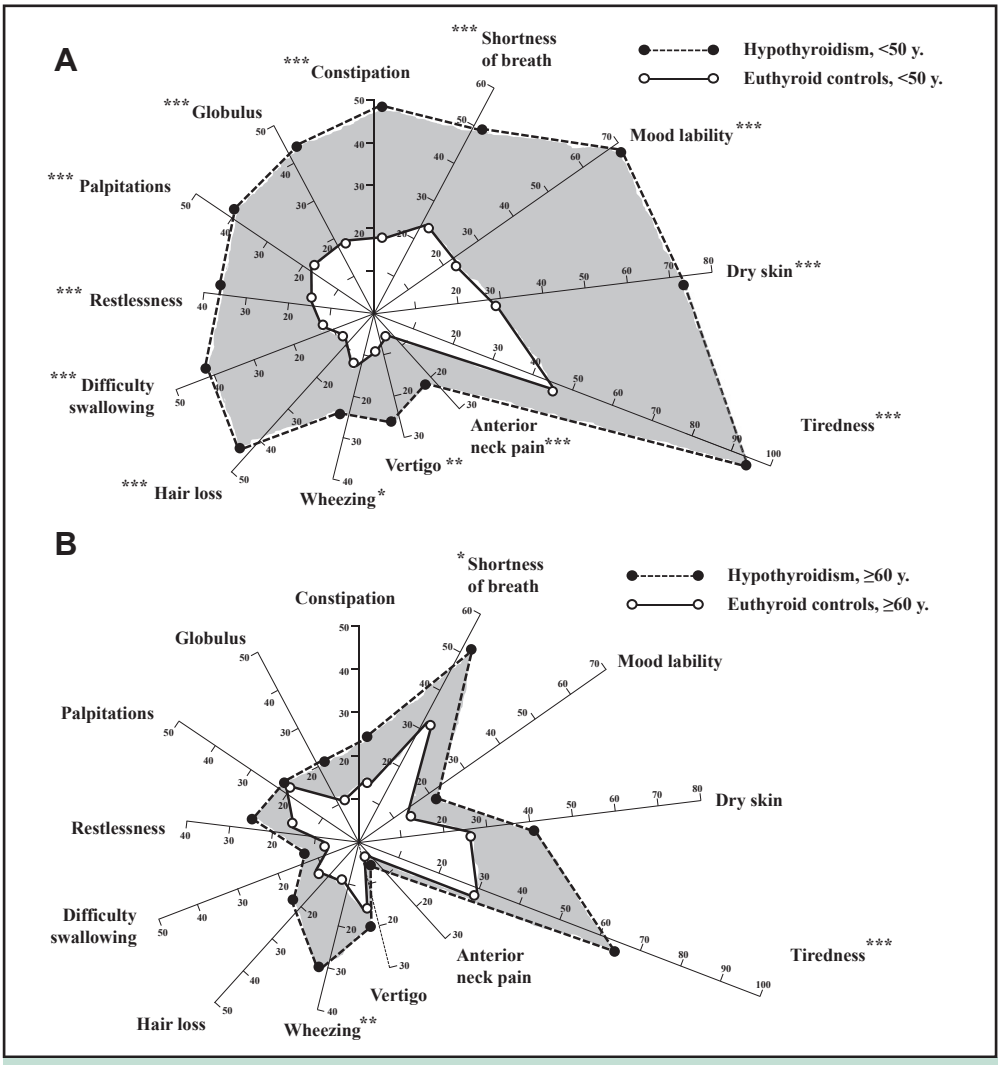


**Figure 5** Nautilus diagram depicting the prevalence of 13 hypothyroidism-associated symptoms in young patients and euthyroid controls (**A**) among young subjects (aged <50 years) and (**B**) older subjects (age ≥60 years). Symptoms are ordered counterclockwise according to the their DOR (see "Subjects and Methods"). The size of the shaded areas between the 2 lines is proportionate to DOR and reflects the usefulness of asking for symptoms when evaluating whether the subjects may be hypothyroid or not. Asterisks depict statistically different number of symptoms between patients and healthy subjects (*$P < .05$, **$P < .01$, ***$P < .001$).

4 of 42 unequivocally hypothyroid patients had typical signs or symptoms. Bahemuka and Hodkinson[20] biochemically screened 2000 geriatric patients and reported that only 13 of 46 with undiagnosed hypothyroidism had symptoms suggestive of the disease.

## Determinants of Symptom Severity

We found no association between the total number of symptoms and the biochemical degree of hypothyroidism (serum thyroid-stimulating hormone, serum T4) in any of the groups. In terms of serum T4 estimates, most[29,34,35] but not all studies[17] found an association with symptom presentation. On the other hand, most[17,29,32,34-37] but not all[28] studies reported no association between symptoms and serum thyroid-stimulating hormone. We previously found identical low serum T4 concentrations at all ages in newly diagnosed hypothyroidism.[38] However, younger patients had higher serum thyroid-stimulating hormone when stratified into the same low T4 levels and compared with older patients. Thus, the higher serum thyroid-stimulating hormone level represents a different adaptive response in young patients, but it is unlikely that higher thyroid-stimulating hormone is the cause for more symptoms in young patients.

In our analyses, we studied 4 groups of patients stratified on age and sex, and demonstrated that the hypothyroidism component score was an excellent tool for screening young men. However, only 3.5% of all autoimmune hypothyroid patients are young men aged <50 years.[5] The fact that

**Table 2** Univariate Regression Analysis to Detect Possible Predictors for Hypothyroidism Component Score (Total Number of Hypothyroid Symptoms) in Patients Newly Diagnosed with Overt Autoimmune Hypothyroidism*

| Predictors for Symptom Score | Beta-Values (95% CI) | *P* Value |
|---|---|---|
| Age at disease onset (≥60 vs <50 y) | −2.65 (−3.74 to −1.55) | <.001 |
| Region of inhabitancy (CPH vs AAL) | 1.40 (0.20-2.59) | .023 |
| Education (high vs low)† | 1.45 (0.22-0.082) | .021 |
| Sex (men vs women) | −2.52 (−1.80 to 1.29) | .75 |
| BMI, kg/m$^2$ | −0.047 (−0.16 to 0.066) | .41 |
| Serum TSH, mU/L | −0.003 (−0.013 to 0.007) | .56 |
| Serum T4, nmol/L | −0.013 (−0.044 to 0.018) | .39 |
| TPOAb, kU/L | $9 \times 10^{-6}$ ($-2 \times 10^{-6}$ to $2 \times 10^{5}$) | .12 |
| TgAb, kU/L | $4 \times 10^{-7}$ ($-7 \times 10^{-6}$ to $8 \times 10^{-6}$) | .10 |
| Thyroid volume, mL | 0.013 (−0.057 to 0.082) | .72 |
| Smoking (no vs yes) | −0.85 (−2.21 to 0.52) | .22 |
| Alcohol consumption, weekly units | 0.021 (−0.075 to 0.12) | .67 |
| Comorbidity, all-cause (yes vs no) | 0.37 (−0.85 to 1.60) | .55 |
| Comorbidity, cardiovascular (yes vs no) | −0.12 (−1.34 to 1.10) | .84 |
| Comorbidity, noncardiovascular (yes vs no) | 0.86 (−0.75 to 2.47) | .29 |

AAL = Aalborg; BMI = body mass index; CI = confidence interval; CPH = Copenhagen; TgAb = thyroglobulin antibodies; TPOAb = thyroid peroxidase antibodies; TSH = thyroid-stimulating hormone.

*Patients aged 50 to 59 years are not included.

†Patients with basic school plus at maximum 2 extra years of vocational training are compared with those with even higher education.

47.4% of all new autoimmune hypothyroid patients are women aged 60 years or more implies that the use of any symptom score is not advisable in selecting those older women who should have their thyroid function tested. Therefore, any symptoms should promptly lead to thyroid function testing in such patients.

Of all possible determinants, Doucet et al[17] also found age to be the only predictor for the disease presentation. The exact pathologic mechanism for this in unclear. Lymphocytes from older animal mice are less effective in transferring thyroiditis than lymphocytes from younger animals.[39] However, differences in neither thyroid autoantibody levels nor thyroid volume could explain the paucity of symptoms in older patients. Another possible explanation may be different levels of recall bias between younger and older patients. Finally, older people have more comorbidities and are thus likely to experience an increasing burden of symptoms as years go by, and may thus develop a higher threshold for noticing any symptoms or to seek medical help in their presence.

Our finding of very low diagnostic power of hypothyroid symptoms in elderly women has some relation to discussion on levothyroxine therapy. In 1997, a group of UK physicians promoted that hypothyroid symptoms and not biochemical testing should guide the use of levothyroxine therapy.[40] As a consequence, a prospective, randomized, double-blinded study was performed on the effect of levothyroxine in patients with symptoms but normal biochemistry. Levothyroxine had no beneficial effect above the level of placebo.[41] Recent guidelines clearly state that biochemically euthyroid patients with nonspecific symptoms should not be treated with thyroid hormone replacement therapy.[42,43]

## Study Strengths and Limitations

The strength of the study is the prospective inclusion of overtly autoimmune hypothyroid patients as they were diagnosed in the population. Thus, the present study is free of hospital referral bias, which we have previously shown may lead to overrepresentation of younger subjects.[44] However, because not all patients invited participated in the study, some self-referral bias may still be present. We chose not to invite any patient aged 80 years or more. Thus, we cannot extrapolate our results to the group of very old patients.

We deliberately chose to investigate only symptoms and not signs such as weight gain, blood pressure, and heart rate. Therefore, the present study gives no insight into the usefulness of signs in the diagnosis of hypothyroidism. Unfortunately, we had no information on cold intolerance or decreased sweating,[27-29,33,45,46] muscle weakness,[28,29] hoarseness,[26,28,29,33,45] and paraesthesiae.[29,33,45]

## CONCLUSIONS

Hypothyroidism may present with a broad spectrum of symptoms, especially in patients diagnosed at up to 60 years of age. In the older patients, only tiredness and respiratory symptoms were experienced more often than reported in age-matched control subjects. This verifies that even a minor suspicion from the clinician should lead to thyroid function tests in older subjects, because many undiagnosed patients present no or only very few symptoms. Several, but surely not all, organizations argue for screening certain age or sex groups in the population.[47] It is beyond the scope of the present article to discuss whether this should be performed or not, but a focus on testing for thyroid dysfunction in old age is important.

The mode of diagnosing hypothyroidism in our study falls within the category of case finding. Our study gives no answer whether therapy may improve morbidity, mortality, or even general health in patients with few or no symptoms. This has been discussed by LeFevre[48] and Rugge et al,[49] who stated that no study has evaluated treatment versus no treatment of screening-detected, undiagnosed thyroid dysfunction.

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**Conflict of Interest:** None.

**Authorship:** All authors had access to the data and played a role in writing this manuscript.

Clinical Interventions in Aging

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REVIEW

# Hypothyroidism in the elderly: diagnosis and management

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**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

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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-point[9] 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 μIU/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 thyroxin.[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 Whickham 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/m$^2$) 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:** [a]Measurements (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[2,b] cohort study | United Kingdom | 1877, population based | ≥38 years | TSH (not informed), FT4 (not informed) | Overt<br>Men: 0.6/1000 survivors/year<br>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<br>Men: 1.4%/5 year<br>Women: 3.5%/5 year<br>Subclinical<br>Men: 0.7%/5 year<br>Women: 2.5%/5 year |

**Notes:** [a]Measurements (cut-off for diagnosis of overt hypothyroidism); [b]as 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 Physicians[37] 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<br>Range: 60–97 years | TSH, FT4 | Men: 1.3%<br>Women: 1.0% |
| Bensenor et al[24] cross-sectional | Brazil | 1373, population based | ≥65 years | TSH, FT4 | Men: 4.8%<br>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<br>Range: 27–98 years | TSH, FT4 | Overt: 0.1% (men 0.06%, women: 0.04%)<br>Myxedema: 0.01%<br>Only 21% of patients were admitted from the emergency room with an initial impression of primary overt hypothyroidism |

**Note:** [a]As 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, puffier 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 TSH[53] 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 TSH[21] 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)<br>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%<br>Control: 16.5%; $P < 0.0001$<br>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<br>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 | 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 | 40–89 years | 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 ± 11.5 years; mean age placebo group 63 ± 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 |




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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 | 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 |

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| 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 | 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 |
| 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 | Performance in cognitive tests did not improve in subjects treated for subclinical hypothyroidism compared to placebo | 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 |

**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/m$^2$) 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<br>No information | TSH between 5–10 mIU/L/no antibodies: 2/28: 7.1%<br>TSH between 5–10 mIU/L/positive antibodies: 5/27: 18.5%<br>TSH > 10 mIU/L/no antibodies: 1/4: 25%<br>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 |
| Vanderpump et al[2] | United Kingdom | 86.2% of sample with >45 years | Incidence<br>Women<br>45–54, 15.6%<br>55–64, 20.8%<br>65–74, 15.8%<br>75–84, 18.8%<br>≥85, 10.0%<br>Total, 17.3<br>Men<br>45–54, 3.7%<br>55–64, 9.5%<br>65–74, 5.8%<br>75–84, 11.5%<br>≥85, 11.1%<br>Total, 6.6 | Women<br>with only TSH > 6 mIU/L at baseline: OR, 8 (95% CI, 3–20)<br>with only positive antithyroid antibodies at baseline:<br>OR, 8 (95% CI, 5–15)<br>with TSH > 6 mIU/L and positive antithyroid antibodies at baseline:<br>38 (95% CI, 22–65)<br>with only TSH > 6 mIU/L at baseline:<br>OR, 44 (95% CI, 19–104)<br>with only positive antithyroid antibodies at baseline:<br>OR, 25 (95% CI, 10–63)<br>with TSH > 6 mIU/L and positive antithyroid antibodies at baseline:<br>173 (95% CI, 81–370) | Evaluated progression of subclinical hypothyroidism to overt disease |
| Gopinath et al[25] | Australia | ≥55 years<br>5 years follow-up | No information | Subclinical hypothyroidism<br>in women (using men as a reference):<br>OR, 3.71 (95% CI, 1.05–13.11)<br>TSH mIU/L (as a continuous variable):<br>OR, 3.94 (95% CI, 2.21–7.04)<br>Overt hypothyroidism in women<br>(using men as a reference):<br>2.57 (95% CI, 1.01–6.54)<br>TSH mIU/L (as a continuous variable):<br>4.13 (95% CI, 2.55–6.71)<br>Fasting blood glucose (mmoL/L):<br>1.19 (95% CI, 1.00–1.42)<br>BMI ≥ 30 kg/m$^2$ (using BMI < 30 kg/m$^2$ as a reference):<br>4.05 (1.74–9.41)<br>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 ≥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 ≥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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# Hypothyroidism in the Elderly: Who Should Be Treated and How?

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Hypothyroidism is among the most frequent chronic diseases in the elderly, and levothyroxine (L-T4) is worldwide within the 10 drugs more prescribed in the general population. Hypothyroidism is defined by increased serum thyroid-stimulating hormone (TSH) values and reduced circulating free thyroid hormones, whereas subclinical hypothyroidism (sHT) is characterized by free hormone fractions within the normal ranges and has been divided into two classes, depending on circulating TSH levels (above or below 10 mIU/L). Given that during aging, a natural trend toward higher values of circulating TSH has been reported, it is necessary to verify carefully the diagnosis of sHT to tailor an appropriate follow-up and *ad hoc* therapy, avoiding unnecessary or excessive treatment. In the current review, we evaluate the state of the art on hypothyroidism in the elderly with special focus on the effect of sHT on cognition and the cardiovascular system function. We also summarize the recommendations for a correct diagnostic workup and therapeutic approach to older people with an elevated TSH value, with special attention to the presence of frailty, comorbidities, and poly therapy. In conclusion, personalized therapy is crucial in good clinical practice, and in the management of older patients with sHT, multiple factors must be considered, including age-dependent TSH cutoffs, thyroid autoimmunity, the burden of comorbidities, and the possible presence of frailty. L-T4 is the drug of choice for the treatment of hypothyroid older people, but the risk of overtreatment, potential adverse drug reactions, and patient compliance should always be considered and thyroid status periodically reassessed.



**Freeform/Key Words:** hypothyroidism, subclinical hypothyroidism, elderly, therapy, frailty, L-T4

The demographic growth in Western countries in the last decades has led to more people >65 years of age. It is estimated that in Italy (the second-oldest world population after Japan), subjects aged >65 years represent 22%, and >80 years are 6.7% of the overall population, with numbers expected to double in 25 years [1]. Thyroid diseases are frequent among the several chronic illnesses observed in the elderly, and in this review, we analyze the impact of hypothyroidism and its management in older people, especially the oldest old (>80 years).

Hypothyroidism is defined by the increase in thyroid-stimulating hormone (TSH) values, accompanied by reduced circulating free triiodothyronine ($FT_3$) and free thyroxine ($FT_4$).

Abbreviations: AD, Alzheimer's disease; $FT_3$, free triiodothyronine; $FT_4$, free thyroxine; HF, heart failure; L-T4, levothyroxine; NHANES III, National Health and Nutrition Examination Survey; QoL, quality of life; sHT, subclinical hypothyroidism; $T_3$, triiodothyronine; $T_4$, thyroxine; TgAb, antithyroglobulin; TPOAb, antithyroid peroxidase; TSH, thyroid-stimulating hormone.

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Such a condition is associated with a global mortality increase and an increased incidence of cardiovascular events; therefore, replacement therapy with levothyroxine (L-T4) is advisable and necessary [2]. However, sometimes, thyroid failure is of a mild degree, and caution needs to be taken in planning the diagnostic and therapeutic approach, particularly in the oldest old patient [3]. Subclinical hypothyroidism (sHT) is characterized by increased TSH values in the face of circulating $FT_3$ and $FT_4$ values within the normal range [3]. According to the results of large trials and meta-analyses available in scientific literature [4–8], the 2013 European Thyroid Association guideline split sHT into two distinct categories, based on cutoffs of circulating TSH values, respectively, between 4 and 10 mIU/L or >10 mIU/L [9].

The prevalence of overt hypothyroidism in the general population varies between 0.2% and 5.3% in Europe and between 0.3% and 3.7% in the United States, possibly in relation to different iodine intake [10]. According to the data from the National Health and Nutrition Examination Survey (NHANES III), the overall prevalence of hypothyroidism is 4.6%, with 0.3% for the overt and 4.3% for the subclinical type. The NHANES III study confirms hypothyroidism as the most frequent thyroid disease among the older population, with a greater prevalence in women [11]. Longitudinal studies conducted in the United Kingdom show an incidence of hypothyroidism ~3.5% to 5% [12]. sHT has a variable incidence, depending on different cohorts [13]: 7.5% in the Wickham study [12]; ~21% in women; and 16% in men in the Colorado study [14]. The NHANES III data demonstrate that circulating TSH levels increase with aging, as well as antithyroid autoantibodies; the percentage of subjects with TSH levels >4.5 mIU/L rises to 14% in the population aged 85 and above, confirming the higher prevalence in white women [11]. It is worth noting that in a British cohort of 6000 subjects aged >65 years, the prevalence of overt hypothyroidism was ~2%, but the prevalence of sHT was lower than that generally reported in literature, at ~2.9% [15]. Data from the same group have previously shown a prevalence of sHT of 11.6% in women and 2.9% in men >60 years in the same geographic area [16]. The authors explain the gap in the data, only 10 years apart, with a possible better screening campaign and wider information, as well as with an earlier treatment of sHT [17]. Indeed, the large prescription of L-T4 therapy in Western countries may reduce the crude prevalence of sHT in epidemiological surveys, evaluating only serum TSH levels of the examined population. In this setting, data from the Medicines Utilization Monitoring Centre have demonstrated that L-T4 is within the 10 drugs more prescribed among the general population in Italy, in line with worldwide projections [18].

To differentiate sHT from the age-related physiological modifications of the hypothalamus-pituitary-thyroid axis, it is crucial to consider the most frequent pathogenetic mechanisms of thyroid failure in older people. Although hypothyroidism, secondary to surgical and medical procedures (thyroidectomy or radioiodine treatment) with suboptimal L-T4 replacement therapy, should be not overlooked, chronic autoimmune thyroiditis (Hashimoto thyroiditis) is the most frequent cause of (subclinical) hypothyroidism in the elderly [19, 20]. Hashimoto thyroiditis is characterized in almost 90% of the cases by the presence of antithyroglobulin (TgAb) and antithyroid peroxidase (TPOAb) autoantibodies. These antibodies are not cytotoxic themselves; therefore, the thyroid cellular damage is supposed to be driven by T-lymphocytes ($CD8^+$) [21]. The dosage of TPOAb is the most sensitive test to determine the presence of antithyroid autoimmunity and gives information about the progression toward overt hypothyroidism, which shows a higher incidence in patients who are TPOAb positive (4.3% per year) compared with the negative ones (2.6% per year) [21, 22]. However, when the presence of serum-positive TPOAb titers has been demonstrated, repeated measurements do not add much useful information in the monitoring of individual patients, as levels of TPOAb vary in parallel with TSH [23]. In the NHANES III study, 13,000 healthy subjects have been followed up and monitored by consecutive dosage of circulating $FT_3$, $FT_4$, TSH, TgAb, and TPOAb; among them, 10% resulted in TgAb and 11% in TPOAb positive [11]. However, in almost 20% of sHT subjects, the dosage of both TPOAb and TgAb may be negative; in these cases, thyroid ultrasound examination, showing the typical tissue inhomogeneity and hypoechogenicity, is supportive for the diagnosis [24]. Another important cause of hypothyroidism

in the elderly is iatrogenic. Indeed, several classes of drugs contribute to reduce thyroid function, such as the following: thyrostatic medications (methimazole, perchlorate, and propylthiouracil), tyrosin-kinase inhibitors, $\beta$-blockers, interferon-$\alpha$, IL-2, lithium, and ethionamide. Usually, iatrogenic damage is transient and reversible when the drug is withdrawn. In these cases, periodic monitoring of thyroid function is recommended, at least twice per year. Drugs interfering with L-T4 absorption are also a frequent cause of hypothyroidism, despite proper replacement therapy, especially in the elderly [19].

## 1. The Hypothalamus/Pituitary/Thyroid Axis in the Elderly

Circulating TSH levels in healthy subjects vary according to the circadian rhythm and respond with logarithmically amplified variation to minor changes in serum $FT_4$ and $FT_3$ values. Thus, abnormal serum TSH may indicate that serum $FT_4$ and $FT_3$ are not normal for an individual [25]. In light of that, serum TSH is a sensitive marker of thyroid function, with increased values indicating a reduced function and *vice versa* for lower TSH levels [20]. However, complex modifications of the hypothalamus/pituitary/thyroid axis and of the peripheral thyroid hormone metabolism have been described in euthyroid older people [26–28]. With the exclusion of pathologic conditions, the aging process is characterized by a reduced iodine absorption and organification and a lower response to TSH, leading to reduced thyroid hormone production [29–31]. Moreover, in the oldest olds, the nocturnal surge of TSH is partially or completely lost, and the inhibitory effect of corticosteroids is attenuated [25, 28, 32]. However, there are conflicting results regarding the age-dependent TSH variation: few previous studies (generally case control) have shown a tendency toward lower TSH circulating levels in individuals >75 to 80 years of age and in centenarians [26, 33]. On the other hand, further population studies have demonstrated an opposite tendency, with circulating TSH levels rising with the aging process: in the population >80 years of age, the upper limit at the 95% interval of confidence was >6.0 mIU/L, reaching 8.0 mIU/L in over-90s [34–36] (Fig. 1). Initially, the reduced TSH levels in centenarians were interpreted as a centrally mediated way to avoid excessive catabolism and promote "physiological aging." However, it is important to distinguish this condition from the "low triiodothyronine ($T_3$) syndrome" or "euthyroid sick syndrome" (not rare in the elderly as a result of the high prevalence of comorbidities), where circulating levels of TSH and $T_3$ are reduced, whereas reverse $T_3$ is increased as a response to acute and systemic diseases. Indeed, the low $T_3$ syndrome is associated with reduced physical function and worse prognosis, both *quoad vitam* and *quoad valetudinem* [28, 37]. It is widely accepted that some of the aging effects are similar to those

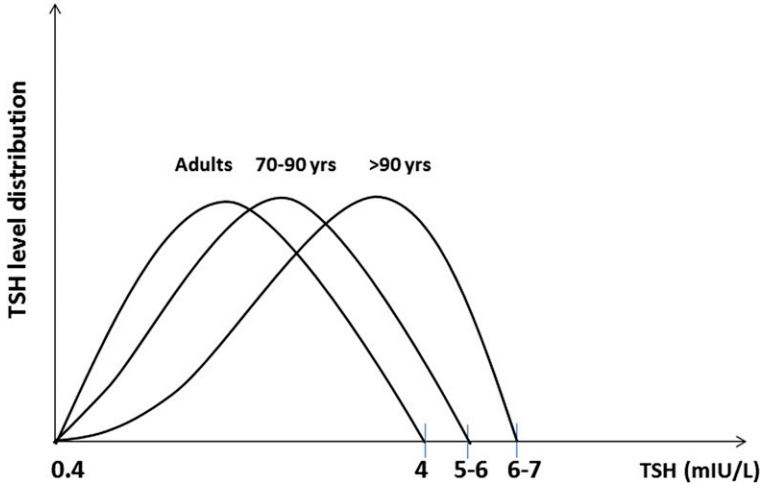


**Figure 1.** Approximate changes of serum TSH values with aging.

seen in the case of mild thyroid failure and are associated with reduction of the basal metabolism [38]. However, it is still a matter of debate whether the reduced thyroid function in the elderly (as a result of either reduced pituitary gland secretion or reduced hormone production) is just a consequence of a reduced metabolic request or instead represents a real protective condition against the increased catabolism seen in the aging process [38]. On that matter, a study conducted in North Europe has documented the potential role of genetics in longevity, which correlated with thyroid function. In particular, the offspring of 90-year-old subjects showed reduced $FT_3$ circulating values and a better metabolic profile compared with their partners with less long-lived parents [31]. Likewise, a cohort study, carried out in a population of Southern Italy, has documented reduced levels of TSH and $FT_3$ in centenarians' grandchildren compared with an age-matched control group [39]. Moreover, several huge cohort studies have demonstrated that the distribution of serum TSH levels shows a tendency to increase in relation to the age and that the extreme longevity is associated with a further increase of TSH levels, at least in the Ashkenazy population [40, 41]. Nonetheless, a recent report from the Rotterdam study, carried out on >9000 healthy home-dwelling subjects, does not confirm this trend, showing instead a progressive reduction of mean serum TSH and a concomitant rising of TPOAb values with increasing age [42]. To understand better those apparent contradictions, it is worth noticing that with the aging process, some complex changes in the thyroid functional status may occur, which cannot always be spotted just from a TSH dosage, *i.e.*, changing in the TSH bioactivity, in the thyrocyte sensitivity to TSH, in thyroid hormone metabolism, as well as in the receptors and cofactors modulating the response to $T_3$ input. Moreover, compared with young adults, the elderly presents a reduced response to TRH, as well as a reduced TSH circadian variation and an attenuated steroidal-mediated inhibitory effect [27, 43]. Finally, with the aging process, a reduced cellular ability to capture iodine and secrete thyroxine ($T_4$) and a reduced hormonal clearance rate have been described [26]. Overall, these data show how the aging process is characterized by a downregulation of the hypothalamus-pituitary-thyroid-peripheral-tissues axis, although it is yet to be established whether these changes reflect an adaptive mechanism to reduced metabolic functions or instead, represent a protective mechanism to preserve the body from excessive catabolism. Finally, the circulating TSH variability, besides being a consequence of the aging process, could be the expression of actual thyroid pathology, especially in the case of positive TPOAb and TgAb titers. With the knowledge of the extreme variability of thyroid hormone physiopathology in the elderly, it is crucial to avoid a superficial diagnosis and therefore, inappropriate treatment [44]. In light of that, the clinical relevance of sHT is still under debate, especially in the case of a slight serum TSH increase (<10 mIU/L) that is particularly relevant in the therapeutic management of the older population [44].

## 2. sHT and the Cardiovascular System

Thyroid hormones exert an important metabolic function across adulthood and in the aging phases [45]. Thyroid hormones are involved in the regulation of the oxygen consumption and heat production; moreover, they facilitate cellular glucose uptake, enhancing glycogenolysis and glycogenosis with a specific contrainsular activity [45]. The cardiovascular system is partly influenced by thyroid function: thyroid hormones are necessary for a correct protein synthesis, modulate the adrenergic system activity, and regulate the vascular peripheral resistance [20]. However, the effects and the clinical significance of sHT on the cardiovascular system are still under debate; they are usually recognized in young adults, whereas more conflicting results have been obtained in the elderly [4, 13, 46, 47]. Unfortunately, no randomized clinical trials evaluating the effect of L-T4 therapy on cardiovascular outcome in old and very old patients with sHT are available yet, leaving the decision about such a treatment without a clear and widely approved consensus [4, 48]. Overt hypothyroidism determines changes in myocardial contractility, vascular resistance, and endothelial function, which are usually reversible with adequate treatment [4]. sHT exerts similar but milder effects; thus, a potential role of such a condition in the trajectory of cardiovascular diseases could be not

excluded *a priori* [4]. In a recent large study, the possible relationship between sHT in the elderly and the metabolic syndrome, either in prevalence or incidence, has been evaluated longitudinally [5]. Over 2100 patients have been included in the study; among them, 687 had metabolic syndrome at baseline. For over 6 years of follow-up, 239 further subjects developed metabolic syndrome; the presence of serum TSH levels >10 mIU/L was associated with higher odds of prevalent metabolic syndrome [5]. The relationship between mild thyroid disorder and heart failure (HF) has been evaluated too, and an increased risk, particularly for TSH levels >10 mIU/L, has been shown in several studies [4]. The Prospective Study of Pravastatin in the Elderly at Risk study evaluated a cohort of subjects aged 70 to 82 years with known cardiovascular risk factors; an association between sHT and HF was detected over 3.2 years of follow-up (only at TSH threshold >10 mIU/L), whereas no association was found with cardiovascular events or mortality except in those with TSH higher than 10 mIU/L and not taking pravastatin [6]. Likewise, a meta-analysis of six prospective cohort studies, with individual data on >25,000 patients with 216,248 person-years of follow-up, showed an increased risk of HF events for patients with both higher and lower TSH levels, particularly for TSH ≥10 and <0.10 mIU/L [7].

sHT and coronary heart disease are also linked, although with conflicting results, and a positive association is generally observed in the youngest population only [4]. Indeed, a large, prospective cohort study on 3233 subjects older than 65 years did not show any relationship between cardiovascular disorders and sHT, apart from an association with the development of atrial fibrillation [43]. Accordingly, a large meta-analysis showed increased mortality and risk of ischemic cardiac disease in patients with sHT younger than 65 years only [49]. However, another large meta-analysis of 11 prospective studies, with collected data from 55,287 subjects over 35 years of follow-up, after adjusting for sex and age, still demonstrated a higher risk of coronary heart disease events and mortality in sHT subjects, particularly in those with serum TSH >10 mIU/L [5].

## 3. sHT and Cognition

The involvement of thyroid hormones in the correct brain development and cognitive performance is well known. The role of hypothyroidism on cognition in the elderly has been widely questioned, and few studies have been conducted to evaluate the effect of overt and sHT on cognitive function with inconsistent results [50]. Data from the Framingham study, aiming to relate serum TSH levels to the risk of developing Alzheimer's disease (AD) over an average of 12.7 years of follow-up, showed that women in the lowest (<1.0 mIU/L) and highest (>2.1 mIU/L) tertiles of serum TSH concentration were at increased risk for AD [multivariate-adjusted hazard ratio, 2.39 (95% confidence interval, 1.47 to 3.87)], whereas no increased risk was found in men [51]. In analyses limited to participants with serum TSH levels of 0.1 to 10.0 mIU/L, the U-shaped relationship between thyrotropin level and AD risk was maintained in women but not when analyses were limited to those with TSH levels of 0.5 to 5.0 mIU/L.

Other studies have reported rather negative results, instead. In a longitudinal study conducted on a population of 1077 elderly subjects (aged 60 to 90 years), cognitively normal, no association was identified between TSH or thyroid hormones and hippocampal atrophy or risk of developing AD [52]. In the Health, Aging and Body Composition Study, an elderly population (70 to 79 years of age) was assessed to evaluate the incident-adjudicated dementia and change in the cognitive performance; among the whole population, over 9 years of follow-up, the risk to develop dementia was found increased in sHT but not in sHT [53]. Accordingly, a recent meta-analysis aiming to evaluate the risk of cognitive impairment and dementia in mild thyroid dysfunction showed an association between sHT and risk of developing dementia, whereas such risk was not found in sHT [54]. Interestingly, another recent meta-analysis from 13 studies demonstrates a substantial relationship between sHT and cognitive impairment only in individuals younger than 75 years of age and those with higher TSH concentrations, whereas no correlation was found while considering all of the studies as a whole [55]. The authors conclude that the lack of use of age-related serum TSH

reference ranges and consequent potential misdiagnosis of sHT in older people may account for this. Thus, with the consideration of the important role of thyroid function in the central nervous system and the lack of homogenous results, it would be interesting and crucial to widen the age range of the studies or set up long-term longitudinal studies to evaluate better if, when, and how mild thyroid failure could increase the risk of cognitive impairment, allowing clinicians to evaluate the therapeutic approach better.

## 4. Treatment of Hypothyroidism and sHT

The fundamental clinical principle in the case of glandular deficiency is replacement therapy, while available; in the case of overt hypothyroidism, the treatment of choice is L-T4 replacement therapy, also in the elderly [56]. It has been widely demonstrated that the resolution of hypothyroidism leads to release of related symptoms (*i.e.*, fatigue, increased sensitivity to cold, constipation, dry skin, weight gain, puffy face, hoarseness, muscle weakness, *etc.*), as well as the improvement of cardiovascular, executive, and cognitive functions [44]. More caution should be considered while discussing the clinical management of sHT, especially in patients older than 75 to 80 years. The results of many studies have shown that L-T4 replacement therapy could be indicated in patients with TSH values >10 mIU/L, as they are at an increased risk of developing health disorders [4–8]. Beside the serum TSH cutoff value, clinicians should be advised to decide on a case-by-case basis, particularly if patients have other risk factors for cardiovascular disease and encompass signs and symptoms possibly associated with sHT. In this setting, it should be considered that sHT is seldom symptomatic in the elderly, and symptoms are generally nonspecific and poor predictors of actual thyroid status. Moreover, with prescriptions of new drugs, older people should be evaluated also in terms of the presence of frail syndrome and comorbidity [44]. In fact, the goal of treatment and the balance between benefits and risks may change depending on the specific needs of the patients, and also, the prescription of L-T4 replacement therapy should be tailored on the patient's clinical characteristics.

Overall, in managing older patients with sHT, we should consider the values of TSH and their trend over time, and international guidelines suggest a cutoff of 10 mIU/L and a double check of TSH level (within 3 and 6 months) before treatment is recommended [9, 19]. Beside serum TSH cutoff levels, the presence of symptoms and signs of hypothyroidism should be checked before starting any treatment [9]. Unfortunately, the identification of the clinical pattern of hypothyroidism in the elderly is quite challenging for the presence of unspecific symptoms (*i.e.*, fatigue, cognitive alterations, sleep disturbances, constipations, *etc.*), especially in frail older patients with comorbidity [57]. According to these considerations, a comprehensive, multidimensional geriatric assessment [58] may be helpful in the clinical approach to older patients with increased serum TSH values [44]. Moreover, it is conceivable to perform a complete thyroid function assessment, including either laboratory tests ($FT_3$, $FT_4$, TgAb, TPOAb) or ultrasound examination, to recognize an actual thyroid disease (*e.g.*, autoimmune thyroiditis, gland atrophy, *etc.*), which may imply permanent TSH elevation or an increasing trend. Moreover, it is crucial to collect an accurate pharmacological history and evaluate whether the patient is receiving treatments affecting thyroid function (*e.g.*, amiodarone, *etc.*), especially in the elderly with several comorbidities. However, it is worth noting that the "physiological" age-related increase of serum TSH values usually does not reach levels >7 to 8 mIU/L [59].

In this setting, a double-blind, randomized, placebo-controlled, parallel-group trial, involving 737 older patients with persistent sHT (mean age 74.4 years, 53.7% women), was recently performed to verify the efficacy and safety of L-T4 therapy [47]. The two primary outcomes were the change in the Hypothyroid Symptoms score and Tiredness score on a thyroid-related, quality-of-life questionnaire at 1 year. The mean entry TSH level was 6.40 ± 2.01 mIU/L. At 12 months, the mean TSH level was 5.48 ± 2.48 in the placebo group compared with 3.63 ± 2.11 mIU/L in the treatment group. No differences in terms of symptoms of hypothyroidism and quality of life (QoL) were observed between the treatment

and placebo group. On the other hand, no substantial excess of serious adverse events prespecified as being of special interest was reported. The authors conclude that treatment with L-T4 in older persons with sHT provided no symptomatic benefits. However, few participants had a baseline TSH level >10 mIU/L, the symptom levels at trial entry were low, and the trial was underpowered to detect any effect of L-T4 on the incidence of cardiovascular events or mortality. Finally, the circulating antithyroid autoantibody titer was not assessed, and antibody-positive patients are more likely to have progressive hypothyroidism; therefore, they may be more likely to have a benefit from long-term L-T4 therapy [47, 60]. However, data on large, randomized trials on L-T4 treatment in antibody-positive older patients are not available yet, and the presence of autoimmunity may lose its clinical impact in frail older patients in whom L-T4 therapy is not recommended at all (Table 1). Nonetheless, in our opinion, in the clinical management of older people with sHT, physicians should take into account not only the TSH cutoff value but also the presence of positive antithyroid autoantibody titers, as well as chronic comorbidities, especially if potentially impaired by hypothyroidism, such as HF [48]. Moreover, particular attention should be given to the presence of frailty, a well-described clinical entity affecting the prognosis of older patients and their QoL [57, 61]. Indeed, frail patients are more vulnerable to drug side effects for several reasons, and the prescription of L-T4 should be carefully balanced with the risk of overtreatment (*e.g.*, excessive intake of L-T4 as a result of insufficient compliance, no proper titration of dosage at the start of treatment, *etc.*).

In conclusion, we could generalize that L-T4 replacement therapy is recommended for older patients (aged 65 to 75 years) in good health status with serum TSH values >10 mIU/L [9, 19]. L-T4 therapy should also be considered in clinically "fit" patients older than 75 years with actual thyroid disease and clear signs and symptoms of hypothyroidism, considering the presence of specific comorbidities (such as HF or cognitive impairment); otherwise, a proper strategy could simply be TSH value monitoring to check a possible increasing trend during time [9]. Conversely, in frail patients with serum TSH levels >10 mIU/L, more caution is recommended regardless of the age, and a wait-and-see strategy is recommended. In case of fit patients with circulating TSH value >6 and <10 mIU/L and actual risk factors for disease progression (women and positive antithyroid autoantibody titers), the possibility of a low-dose L-T4 replacement trial could be considered; otherwise, close monitoring of thyroid function every 3 to 6 months is recommended, and L-T4 therapy could be considered in the case of a progressive increase of a serum TSH value up to 10 mIU/L and above. In frail patients younger than 75 years, with serum TSH levels between 6 and 10 mIU/L, L-T4 replacement should be generally avoided; it could be hypothesized, with extreme caution, only in the case of a progressive TSH increase up to 10 mIU/L, in the presence of positive antithyroid autoantibody titers, signs and symptoms of hypothyroidism, and concomitant diseases potentially impaired by sHT (*i.e.*, HF). In patients with serum TSH values between 4 and 6 mIU/L, a wait-and-see strategy is generally recommended. However, in fit patients

**Table 1. Suggested Strategy of Care According to Either TSH Value or the Patient Clinical Features**

| | Fit Patient | | Frail Patient | |
|---|---|---|---|---|
| **Serum TSH Value[a]** | **65–75 Y** | **>75 Y** | **65–75 Y** | **>75 Y** |
| >10 mIU/L | Treat[b] | Treat[c]/observe | Observe/treat[c] | Observe |
| 6–10 mIU/L | Observe/treat[c,d] | Observe/treat[c,d] | Observe | Observe |
| 4–6 mIU/L | Observe/treat[c,d] | Observe | Observe | Observe |

[a]Elevation of serum TSH value should be confirmed by at least a second measurement at 3- to 6-mo follow-up.
[b]L-T4 dosage starting from 0.3 to 0.4 μg/kg/d; increments by 10% to 15% after 6 to 8 wk, if necessary. Optimal TSH target value for patients >75 y receiving L-T4 therapy: 2.5 to 3.5 mIU/L.
[c]In the presence of positive antithyroid autoantibody titres, symptoms of hypothyroidism, concomitant diseases potentially impaired by mild thyroid failure (*i.e.*, HF), also according to patients' willing.
[d]In the case of progressive increase of serum TSH value up to ≥10 mIU/L.

younger than 75 years, with positive antithyroid autoantibody titres, signs and symptoms of hypothyroidism, and concomitant diseases potentially impaired by mild thyroid failure (*i.e.*, HF), a low-dose L-T4 replacement trial could be considered (Table 1).

In any case, L-T4 dosage should be titrated starting from ~0.4 to 0.5 μg/kg/d with increments by 10% to 15% after 6 to 8 weeks, if necessary, and an optimal TSH target value should be ~2.5 to 3.5 mIU/L, according to international guidelines [9, 19]. It is highly recommended, especially in the oldest olds, to monitor thyroid function over time (*e.g.*, every 6 months) to avoid over treatment and the consequent negative impact on cardiovascular and osteomuscular systems [9, 19].

## 5. L-T4 Administration

When orally administrated, L-T4 gets absorbed in the jejunum and ileus, 2 to 3 hours after ingestion. It is important to take into account that the administration of food and other drugs (*i.e.*, proton pump inhibitor), together with L-T4, impairs its absorption; therefore, it is recommended to administer L-T4 either 1 hour before breakfast or 3 or more hours after dinner [9, 19].

There are different ways of administration, depending on the pharmaceutical formulation, such as tablet, liquid, or soft gel. The formulations differ for the excipient, and the liquid or soft gel formulation could be preferred when the traditional tablets fail to normalize the TSH values. The gastrointestinal absorption is the critical event to be considered in the therapy, and it can be influenced by multiple factors of a different nature, from the patient's compliance to the therapy, to the presence of gastrointestinal diseases (*i.e.*, gastric atrophy, *Helicobacter pylori* infection, lactose intolerance, or celiac disease), and/or the concomitant intake of drugs or food [62]. The most used pharmaceutical formulation for the therapy is the L-T4 tablet, and it is the first choice in the elderly patient without a swallowing problem; it is indeed possible to swap to a different pharmaceutical formulation if the normalization of the TSH values is not met, even after a careful evaluation of the current therapy. Liquid and soft gel formulations have been developed over the last years to overcome the issue as a result of the gastric absorption, even when administered together with the food. The liquid formulation seems to have a better bioavailability compared with the L-T4 tablets, whereas the soft gel is equivalent. In a recent review by Virili *et al.* [62], several studies evaluating the use of liquid and soft gel formulation in different populations were considered. Few studies and case reports demonstrated the higher efficacy of the soft gel formulation compared with the tablets in patients with gastric disorders, impaired absorption, even iatrogenic, or during pregnancy [62]. These data, although interesting and promising, are not confirmed by long-term, controlled studies; therefore, some caution is necessary to tailor properly the therapy according to a patient's needs.

Whereas some studies suggest that the liquid formulation gives less variability in the TSH level under treatment, both in adults and elderly, it is important to consider that the timing of ingestion of the liquid formulation is different from the tablet; therefore, the results need to be interpreted carefully [55]. Indeed, there are patients who certainly would benefit from the use of a liquid formulation, such as those who underwent bariatric surgery, have enteric-tube nutrition, have drug-drug interference (in particular, proton pump inhibitors), or are less keen to comply with the timings of administration of the tablets in relation to breakfast or coffee [55]. In this respect, it has been demonstrated that circulating $FT_4$ levels, 3 and 4 hours after administration of liquid L-T4, are comparable with the levels obtained with fasting administration of L-T4 tablets [63].

The use of combined therapy with $T_4 + T_3$ is still a matter of debate. A recent review of the literature examined several studies comparing different outcomes from the combined therapy compared with the classic approach [64]. When evaluating QoL, mood, and cognitive performance, few studies reported an improvement in those outcomes, but in the majority of them, no advantages were seen, and a possible placebo effect was considered worth noticing [64]. A meta-analysis conducted on 1216 subjects and evaluating several outcomes (pain,

depression, fatigue, anxiety, cognitive performance, and QoL) did not find any difference between $T_4$ + $T_3$ and $T_4$ in monotherapy [65]. Another meta-analysis evaluating 10 randomized double-blinded studies confirmed the same outcome of no advantage with the combined therapy [66]. A limitation of the available studies is that they are all short term, not exceeding 1-year duration [64]. However, a 17-year follow-up study analyzed multiple outcomes in a population receiving $T_3$, in most cases, associated with $T_4$, compared with patients receiving only $T_4$. The outcomes in terms of cardiovascular events, diabetes, fractures, atrial fibrillation, or death were comparable; the only difference was an increased use of antipsychotic drugs in the combined therapy population, presumably as a result of the use of $T_3$ [67]. Accordingly, the 2012 European Thyroid Association guidelines suggest that the combined therapy $T_4$/$T_3$ should be used only in patients with normal TSH values reached with L-T4 alone, but with persistent complaints, and only after having educated patients about the chronic nature of their disease [68]. Moreover, the combination therapy should be avoided in pregnant women, as well as in subjects with cardiac arrhythmias, and extreme caution is required in the elderly. In the treated population, it should be stopped if there is no clinical improvement achieved after 3 months [68].

## 6. Conclusions

Hypothyroidism is frequently observed in the elderly with an increasing trend with age. A "natural" trend in a slight TSH increase has been documented in the older population, even in subjects without documentable thyroid diseases, but an age-related TSH reference range is not available yet. Thus, it is worth the performance of an extensive thyroid evaluation in older subjects with a circulating TSH rise, especially in the oldest olds, including either laboratory tests (free thyroid hormone levels and antithyroid autoantibody titers) or thyroid ultrasound examination. This diagnostic process is aimed to assess the presence of an actual thyroid disease (Hashimoto thyroiditis, gland atrophy, *etc.*), which may lead to the diagnosis of sHT rather than a physiological age-related TSH elevation, although circulating TSH values >10 mIU/L should be considered clinically relevant. The choice of treatment should also depend on the presence of clinical signs and symptoms consistent with hypothyroidism, as well as concomitant comorbidities and patient compliance. Nonetheless, several data from literature warn the clinician to be extremely cautious in treating older patients, especially the oldest olds (>80 years).

In conclusion, in the clinical management of older people with sHT, not only TSH value cutoffs need to be considered, but also, the presence of an actual thyroid disease, as well as chronic comorbidities and frailty, should be taken into account. Good clinical practice implies the prescription of L-T4 on a case-by-case manner, carefully balanced by the risk of overtreatment (*e.g.*, excessive intake of the drug as a result of mistakes in administration, no proper titration of dosage at the start of treatment, *etc.*). In any case, L-T4 dosage should be titrated starting from ~0.3 to 0.4 μg/kg/d, with increments by 10% to 15% after 6 to 8 weeks, if necessary, and optimal TSH target value should be ~2.5 to 3.5 mIU/L.

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Thyroid Research

REVIEW Open Access

# Hypothyroidism in the older population

Owain Leng[1] and Salman Razvi[2,3*]

## Abstract

**Background:** Both overt hypothyroidism as well as minor elevations of serum thyrotropin (TSH) levels associated with thyroid hormones within their respective reference ranges (termed subclinical hypothyroidism) are relatively common in older individuals. There is growing evidence that treatment of subclinical hypothyroidism may not be beneficial, particularly in an older person. These findings are relevant at a time when treatment with thyroid hormones is increasing and more than 10–15% of people aged over 80 years are prescribed levothyroxine replacement therapy.

**Main body:** The prevalence of hypothyroidism increases with age. However, the reference range for TSH also rises with age, as the population distribution of TSH concentration progressively rises with age. Furthermore, there is evidence to suggest that minor TSH elevations are not associated with important outcomes such as impaired quality of life, symptoms, cognition, cardiovascular events and mortality in older individuals. There is also evidence that treatment of mild subclinical hypothyroidism may not benefit quality of life and/or symptoms in older people. It is unknown whether treatment targets should be reset depending on the age of the patient. It is likely that some older patients with non-specific symptoms and incidental mild subclinical hypothyroidism may be treated with thyroid hormones and could potentially be harmed as a result. This article reviews the current literature pertaining to hypothyroidism with a special emphasis on the older individual and assesses the risk/benefit impact of contemporary management on outcomes in this age group.

**Conclusions:** Current evidence suggests that threshold for treating mild subclinical hypothyroidism in older people should be high. It is reasonable to aim for a higher TSH target in treated older hypothyroid patients as their thyroid hormone requirements may be lower. In addition, age-appropriate TSH reference ranges should be considered in the diagnostic pathway of identifying individuals at risk of developing hypothyroidism. Appropriately designed and powered randomised controlled trials are required to confirm risk/benefit of treatment of subclinical hypothyroidism in older people. Until the results of such RCTs are available to guide clinical management international guidelines should be followed that advocate a conservative policy in the management of mild subclinical hypothyroidism in older individuals.

**Keywords:** Hypothyroidism, Elderly, Ageing, TSH

## Background

The population of the world is ageing. In the United Kingdom, nearly one in seven people is projected to be aged over 75 years by the year 2040. [1] However, increases in health life expectancy measured at 65 and 85 are not keeping pace with improvements in numerical life expectancy. This suggests that real health improvements are being experienced by younger people, and that people over 65 years of age are spending more time in ill-health. Therefore, unless this trend can be reversed, a major challenge for an ageing population is likely to be an increasing prevalence of the health conditions associated with old age such as dementia, type 2 diabetes mellitus and cardiac diseases. Apart from the effects on individuals and their families, this demographic change will have major socio-economic and political implications.

Thyroid hormones have a major influence on all major organs/systems and adequate levels are important for optimal function. Thyroid dysfunction is a common condition that affects between 3 and 21% of the population with prevalence being more common in women and in older individuals. [2] In the UK, it is estimated that hypothyroidism treated with levothyroxine may affect nearly 800,000 older individuals aged more than 70 years. [3] The clinical

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presentation of thyroid dysfunction is non-specific and often variable; therefore, the diagnosis of thyroid dysfunction is based primarily on biochemical abnormalities. The pituitary hormone thyrotropin (TSH) has a complex inverse relationship with the thyroid hormones thyroxine (T4) and tri-iodothyronine (T3). A negative feedback mechanism exists between TSH and thyroid hormones, which means that TSH levels are the most sensitive marker of thyroid status in an individual. [4] Accordingly, overt hypothyroidism is defined as serum TSH concentrations above the reference range with low free T4 levels, while subclinical hypoth yroidism is diagnosed when TSH levels are high and circulating free T4 is normal. The relationship between TSH and thyroid hormones is influenced by a number of factors including age, smoking and thyroid peroxidase antibody status. [5] Recent data from observational studies suggest that serum TSH levels increase in older people. [6] Thus, very mild TSH elevations in older individuals may not reflect subclinical thyroid dysfunction but rather be a normal consequence of ageing. Besides, serum TSH levels are also influenced by genetic, environmental, clinical and therapeutic factors and agents, as well as trends in clinical practice [7]. Despite this, adult patients are often managed similarly utilising a uniform serum TSH reference range (usually 0.4–4.5 mU/L) and age-specific ranges are not in routine clinical use. In addition, thyroid hormone requirements change with age and older patients on replacement therapy are more susceptible to the effects of thyroid hormone excess such as osteoporosis and atrial fibrillation. Therefore, careful consideration is required in the interpretation of thyroid function test results as well as in managing thyroid disease in the older population. The interest in thyroid function in the elderly has been increasing with the recognition that thyroid status is may be linked to disability, cognitive function, cardiovascular disease risk and longevity.

This review describes the prevalence of hypothyroidism in the older population and outlines the effects of treatment in this age group.

## Main text

### Prevalence of hypothyroidism in the elderly

Hypothyroidism is more prevalent in older individuals. The Whickham survey was the first population-based study to evaluate the presence of thyroid dysfunction in community-dwelling individuals. This seminal study observed that TSH levels increased with age in women after the age of 45 years but the same phenomenon was not seen in men. [8] The main limitation of the Whickham study, however, was that it utilised the first-generation TSH assay available at that time and was therefore unable to reliably detect TSH levels lower than 1.0 mU/L. Subsequently, a number of cross-sectional studies have been performed across various geographical locations and studying various age groups. In the studies restricted to older persons, the reported prevalence of overt hypothyroidism has ranged between 0.2–5.7% and subclinical hypothyroidism between 1.5–12.5%. [9–20] Some of the main prevalence studies are outlined in Table 1. The wide variation between the various studies probably reflects the disparate nature of the populations being assessed with regards to their gender, iodine intake, age-groups, racial groups and treated thyroid disease prevalence. For example, the Zoetermeer study from the Netherlands reported the lowest prevalence of subclinical hypothyroidism of just 1.5%, most likely due to the inclusion of only men in this analysis. [19]

As the TSH distribution and the reference limits shift to higher concentrations with age, the prevalence of subclinical hypothyroidism may be overestimated. Employing a uniform TSH reference range across all age groups in the NHANES study led to approximately 70% of older individuals with a slightly high serum TSH being incorrectly classed as having subclinical hypothyroidism. [21] An analysis of TSH results from one pathology centre in Western Australia however concluded that the use of age-specific TSH reference ranges has minimal impact on reclassifying thyroid status except in the very old (85 years), in whom 2–4.7% were reclassified as being euthyroid. [22] The reference ranges for TSH are discussed in the next section in more detail.

### TSH reference range in the elderly

Biochemical testing of thyroid function is fundamental to establish a diagnosis of thyroid dysfunction including hypothyroidism. The tests include measurement of circulating TSH and thyroid hormones in the serum. Assays for estimating serum TSH have improved vastly over the last few decades and the current immunoassays have the ability to detect very low levels (less than 0.1 mU/L). On the other hand, the reference range for thyroid hormones is wide for a given population, therefore, in principle, TSH will be the first detected circulating abnormality as the pituitary registers that T4 has changed from its genetically determined setpoint for that particular individual. [24] Thus, TSH measurement has now been firmly established as the first-line thyroid function test to assess thyroid status in the vast majority of patients with suspected thyroid disease. [25, 26] However, it is important to remember that measurement of serum TSH is only reliable for diagnosing thyroid function abnormalities provided that patients are not receiving drug therapies that alter TSH secretion or have pituitary disease. Measurement of serum TSH is also considered to be the key thyroid function test for diagnosing early (also called mild or subclinical) hypo- or hyperthyroidism because of the log-linear relationship between TSH and T4: a twofold change in serum FT4 level leads to a 100-fold alteration in circulating TSH. [27]

**Table 1** Prevalence of hypothyroidism (both overt and subclinical) in older population-based cross-sectional studies

| Study [reference] | Place | Sample size | Population studied | Age range (years) | Measurement of thyroid function | Prevalence (%) Overt Subclinical Hypothyroidism |
|---|---|---|---|---|---|---|
| Framingham [9] | USA | 2139 | Both sexes | > 60 | TSH & T4 | 2.5 7.9 |
| Rotterdam [10] | Netherlands | 10,318 | Both sexes | ≥ 45 | TSH & FT4 | 0.8 9.1 |
| Nagasaki [13] | Japan | 2550 | Atomic bomb survivors of both sexes | 58.5* | TSH & FT4 | NR 10.1 |
| Cardiovascular Health S tudy [14] | USA | 3233 | Both sexes | > 65 | TSH & FT4 | 1.6 15.0 |
| Health ABC [15] | USA | 2730 | Both sexes | 70–79 | TSH & FT4 | 0.8 12.4 |
| Zoetermeer [19] | Netherlands | 403 | Men only | 73–94 | TSH, FT4, FT3, rT3 | 0.2 1.5 |
| Leiden 85+ [16] | Netherlands | 558 | Both sexes | 85 | TSH & FT4 | 7 5.0 |
| Birmingham [17] | England | 5960 | Both sexes | ≥ 65 | TSH & FT4 | 0.4 2.9 |
| Sau Paulo Ageing and Health Study [11] | Brazil | 1373 | Both sexes | ≥ 65 | TSH, FT4 | 5.7 6.5 |
| Newcastle 85+ [18] | England | 643 | Both sexes | 85 | TSH, FT4, FT3, rT3 | 0.9 12.5 |
| Longitudinal Aging Study [20] | Netherlands | 1219 | Both sexes | ≥ 65 | TSH | NR 5.3 |
| InChianti study [23] | Italy | 951 | Both sexes | ≥ 65 | TSH, FT4, FT3 | 0.5 3.0 |

*Mean age provided as minimum age not available

The American National Academy of Clinical Biochemistry formulated guidelines in 2003 which state that "TSH reference intervals should be established from the 95% confidence limits of the log-transformed values of at least 120 rigorously screened normal euthyroid volunteers who have: (a) No detectable thyroid autoantibodies, TPOAb or TgAb (measured by sensitive immunoassay); (b) No personal or family history of thyroid dysfunction; (c) No visible or palpable goitre and, (c) Who are taking no medications except oestrogen". [28] In addition, TSH secretion has a diurnal variation with a peak late at night/early hours of morning, and, therefore, sample timing and shift work should also be considered when defining the TSH reference range. [29] In the last few decades, the ability of the TSH assays to detect lower levels has improved with each generation and therefore the present lower euthyroid reference limit is set at 0.3–0.5 mU/L. This has resulted in subclinical hyperthyroidism being diagnosed with much greater precision, irrespective of the population being studied or the method used. In contrast, the upper (97.5 percentile) reference limit for nonpregnant adults is still not universally agreed. [30, 31] As a consequence, the diagnosis of subclinical hypothyroidism is still very much dependent on the value at which the upper limit of TSH is set.

The TSH reference range should also consider the intra-individual variability of the TSH measurement. Several studies provide data showing significant variation in repeated TSH measurements over time in the same individuals. [27] Each person has a specific and unique set-point for thyroid hormone concentrations, which is partly genetically determined, as shown by twin studies. [24] TSH measurements in an individual vary within 50% of the entire group's TSH distribution, with a large and clinically significant variation. [32] TSH levels are also known to increase with age when checked over many years. In both the Cardiovascular Health Study as well as the Busselton Health study, there was a significant rise in TSH levels with little or no change in FT4 levels over a 13-year period. [33, 34] This finding, however, was not confirmed in the Rotterdam study in which TSH levels remained stable over a 6.5-year interval whereas FT4 levels increased. [10] An analysis from the Baltimore Longitudinal Study of Aging has revealed that changes in thyroid function tests are common, especially in older age groups, and regression to the mean is partly responsible for this finding. Importantly, changes in both TSH and FT4 over a 7-year period were associated with increased mortality. [35]

The most robust data determining the TSH reference range was obtained from the US National Health and Nutritional Examination Survey (NHANES) III study. [36] This large study ($n$ = 16,088), designed to be representative of the US general population, analysed the median and lower and upper reference limits of serum TSH in carefully selected euthyroid individuals using current immunoassays. This study concluded that establishing an accurate TSH upper limit at an individual level from population data is not possible, as TSH has a low individuality index (the ratio between the within- and between-person variability). The overall reference range was deemed to be 0.4–4.1 U/L but there were significant differences between age groups and races. For example, the upper limit of TSH was 3.5 mU/L in the 20–29-year

olds but increased to 7.9 mU/L in the 80+ year group. Similarly, the upper TSH level was 4.2 mU/L in White people whereas it was 3.4 mU/L in Black people. Similar data obtained from a Scottish laboratory database confirms an age-related increase in the upper reference limit for serum TSH). [37] An illustration of age-specific TSH reference ranges are described in the Fig. 1.

Serum TSH is not normally distributed and has a skew to the right. However, more than 95% of healthy euthyroid individuals have serum TSH values between 0.4 and 2.5 mU/L. It is therefore argued that TSH values > 2.5 mU/L reflect underlying autoimmune thyroid disease and contribute to the skewed TSH distribution curve, [38] a view further supported by the fact that such individuals have a higher risk of progression to subsequent hypothyroidism. [39, 40] The opposing argument to retain the upper limit of the TSH reference range around the 4.0–5.0 mU/L mark is that reducing the upper TSH reference limit would lead to a vast increase in the number of people diagnosed with subclinical hypothyroidism without any evidence-based justification or proof of benefits of treatment. [31] This issue is complicated by the concern that current TSH immunoassays differ in specificity for recognizing circulating TSH isoforms and that this can give rise to a full 1.0 mU/L difference in TSH values reported by different assays.

In summary, the current upper limit of the serum TSH reference range in older people does not reflect age-related changes and leads to the over-diagnosis of hypothyroidism and, consequentially, the probable unnecessary treatment of an unknown number of people with thyroid hormones. The adoption of a universal TSH range across all adult age groups on an individual's health have not been tested in prospective trials, and unnecessary treatment will lead to a higher health and economic burden. In addition, a slightly higher serum TSH level may be normal in older individuals and not associated with worse outcomes. [18, 33] This has implications for diagnosing subclinical hypothyroidism in the elderly and also the level of serum TSH to aim for in treated hypothyroid patients in this age group. [41] Therefore, it has been suggested that age-specific reference limits should be utilised instead. [42] However, further research is required before age-specific TSH reference ranges become part of routine clinical practice.

## Consequences of overt and subclinical hypothyroidism in the elderly

### *Symptoms*

The presentation of overt hypothyroidism in the older person is varied, non-specific, and often insidious. The classic symptoms of hypothyroidism are less likely to be

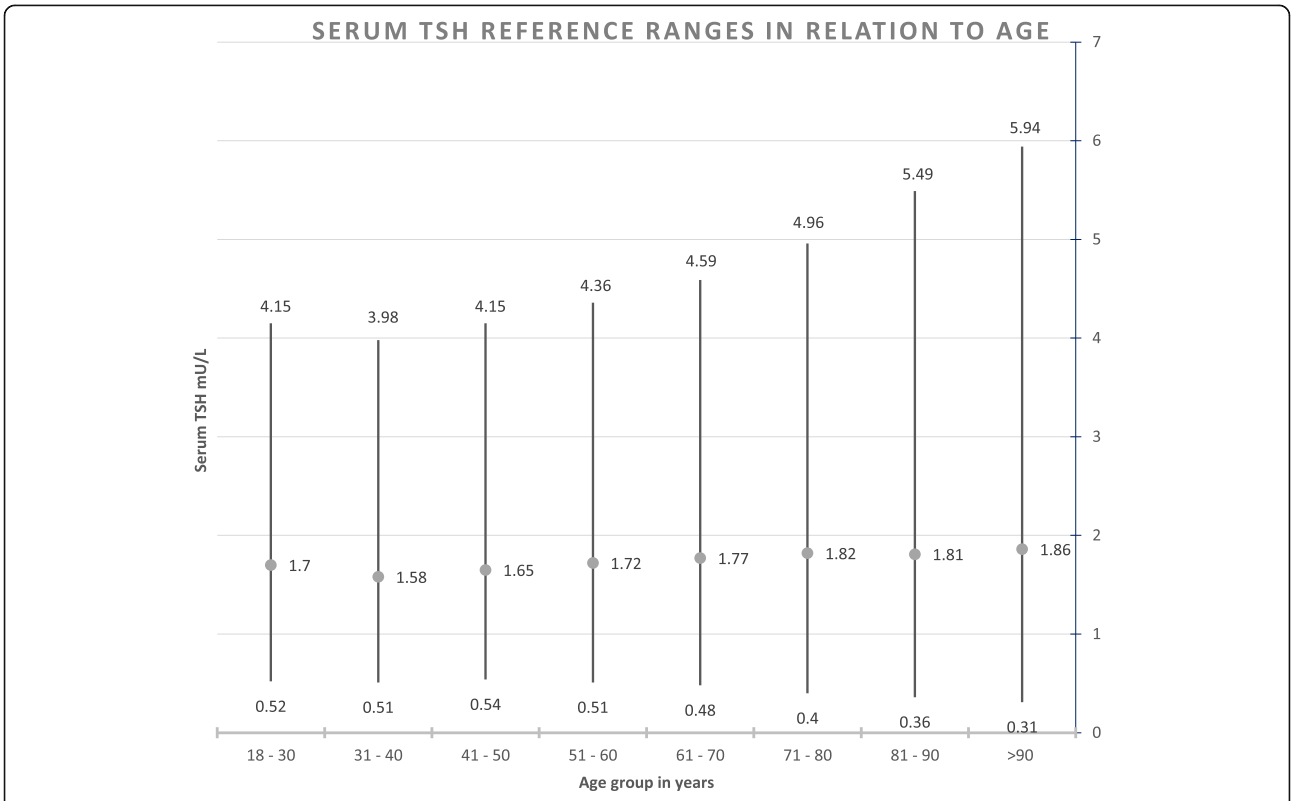


**Fig. 1** Distribution of serum Thyrotropin (TSH) in relation to age. The lower and upper limits of the TSH reference range are calculated from the 2.5th and 97.5th percentile, respectively, and the circle signifies the median value. (adapted from reference [37])

evident in the elderly population, and if present, these symptoms are more likely to be misattributed to either co-morbid conditions or a manifestation of the ageing process. [43] Older people with hypothyroidism report fewer symptoms compared to younger counterparts. [44, 45] A prospective study comparing the frequency of reported symptoms has indicated that hypothyroid patients ≥70 years are significantly less likely to report weight gain, muscle cramps or cold intolerance than hypothyroid patients < 50 years of age. [45] A study comparing patients with overt autoimmune hypothyroidism against matched euthyroid controls found that whilst younger patients were more likely to report all 13 of the surveyed symptoms of hypothyroidism than their euthyroid controls, for older patients only three of the thirteen symptoms (tiredness, shortness of breath, wheezing) were more prevalent in the hypothyroid group than in the control group. The study used receiver operating characteristic (ROC) analyses to assess the discriminatory ability of a symptom score in the prediction of hypothyroidism, and whilst they identified that this was an excellent tool for predicting hypothyroidism in young men (with an area under the ROC curve of 91%; 95% CI 82–99.8%), it was poor in evaluating older women (area under the ROC curve of 64%; 95% CI 54–75%). [44] The non-specific and subtle presentation of hypothyroidism in older people is further evidenced by the studies into the screening for hypothyroidism in the older population, which have shown only a minority of patients with confirmed biochemical overt hypothyroidism have symptoms suggestive of the disease. [46, 47]

Whilst it is apparent that for most older patients the presentation of hypothyroidism is both more subtle and less discriminatory than in younger populations, there is however also an increased risk of the most severe presentation of hypothyroidism in the population: myxoedema coma. [48] Manifesting with multisystem failure with clinical features including reduced consciousness, hypothermia, hypotension, bradycardia, hyponatremia, hypoglycaemia, and hypoventilation, this is a condition with very high morbidity and mortality. However, myxoedema coma is a rare manifestation of hypothyroidism: an analysis of a Japanese national inpatient database estimated an annual incidence of 1.08 per million population. [48] Symptoms are largely absent or very subtle in older patients with subclinical hypothyroidism. In the subclinical hypothyroid group as a whole, most patients are asymptomatic or report only non-specific symptoms. [49, 50]

Thus, symptoms of hypothyroidism are sparse and non-specific in older people. This leads to thyroid function tests being frequently requested. However, due to the uniform TSH reference range being applied across all age groups, a substantial number of individuals are being detected with mild subclinical hypothyroidism. The median level of TSH at which treatment with thyroid hormones is being commenced has been falling recently although the evidence of benefit is sparse. [51]

### *Cardiovascular manifestations*

The cardiovascular system is a major target of thyroid hormone action and sensitive to small changes in thyroid hormone concentrations. [52] A number of observational studies have suggested that even slight reductions in thyroid hormones are associated with higher risk of cardiovascular disease. [53]

Meta-analyses of observational studies have shown that subclinical hypothyroidism is related to an increased risk of ischaemic heart disease only in younger individuals and not in older populations. [54, 55] However, an individual patient meta-analysis of more than 55,000 participants contributing more than 500,000 person-years of follow-up concluded that age does not influence the relationship between subclinical hypothyroidism and coronary heart disease events nor mortality. [15]

Thyroid hormones have an inotropic effect on cardiac muscle. [56] Accordingly, some studies have shown a positive association between hypothyroidism and heart failure. [15] An individual participant data meta-analysis of 25,390 participants revealed that both low as well as high serum TSH levels. [57] In stratified analysis, there was a trend towards lower risk of heart failure in older individuals with subclinical hypothyroidism although this did not reach statistical significance.

The relationship between hypothyroidism and stroke has not been completely elucidated. A meta-analysis of individual participant data obtained from nearly half a million person-years of follow up demonstrated no overall effect of subclinical hypothyroidism on stroke although a significantly higher risk was observed in participants younger than 65 years and those with higher serum TSH levels. [58]

In a longitudinal analysis of participants from the Rotterdam study, the risk of sudden cardiac death was found to be higher with higher FT4 levels, even within the reference range. [10] In age-stratified analysis, the risk of sudden cardiac death appeared to be particularly higher in older individuals (> 65 years) with higher FT4 levels or lower TSH concentrations.

Older individuals (> 65 years) with subclinical or overt hypothyroidism were not observed to have adverse cardiovascular risk factors such as higher body mass index, increased LDL cholesterol, and prevalence of hypertension or diabetes mellitus in the Cardiovascular Health Study. [14]

### *Cognition*

The relationship between overt hypothyroidism and cognitive impairment, depression and other psychiatric manifestations has been long-considered. The term ‘myxoedema madness’ was coined to describe the constellation of confusion, disorientation and psychosis that was observed to

occasionally accompany profound hypothyroidism. [59] These early observations were later supplemented by physiological studies which showed alterations in electroencephalograms, cerebral blood flow, and visual evoked potentials in hypothyroid patients. [60, 61] Hypothyroidism has been shown to be associated in non-demented older adults with impairments in a variety of neuropsychological tests of learning, word fluency, visual-spatial abilities, and mental status. [62, 63]

Whilst hypothyroidism has classically been described as a cause of 'reversible dementia', there is a lack of evidence to show that there is complete resolution of neurocognitive deficits following treatment of hypothyroidism. [64] Further research is required to elucidate the potential role of perturbations of thyroid function as a contributor to a dementing process, as many of the studies to date have not been able to adequately address that hypothyroidism, co-morbidity, polypharmacy and alternative causes of dementia are all common in the elderly, and that interpreting the potential interplay between these factors is complex. [65]

In subclinical hypothyroidism, a number of studies have shown association with adverse cognitive function in younger individuals, [66–68] but results in older people have been conflicting. One study in individuals with a mean age of 74 years showed that people with subclinical hypothyroidism had worse performance on verbal recall and cognitive scores but working memory and processing speed were unaffected. [69] The PAQUID survey of individuals aged 65 years or more showed that increased TSH levels were significantly linked with the presence of symptoms of depression but not with impairment of cognitive function. [70] There have been other studies which do not support any association between subclinical hypothyroidism and cognitive impairment. [20, 62, 71, 72] The InCH IANTI study found a significant association between subclinical hyperthyroidism and cognitive impairment as assessed by the mini-mental state examination, but no such association with subclinical hypothyroidism. [12] A prospective observational study within the Leiden 85+ cohort, which followed up a total of 599 patients from the age of 85 to 89 years for a mean period of 3.7 years, found no significant association between thyroid dysfunction and either depression or cognitive impairment. This was a large and appropriately powered study, and the authors argue that in this very elderly cohort, whilst depression, dementia and thyroid dysfunction are all relatively common, the relationship appears coincidental rather than causal. [16] In contrast, in a notably younger cohort of predominantly euthyroid patients aged 49–71 years, a higher TSH level was associated with poorer performance in tests of memory. [19] Amongst the many as-yet unanswered questions about the relationship between thyroid status and cognitive ability, includes the possibility that the nature of this relationship changes with the aging process.

Studies which have addressed whether cognitive functioning improves with levothyroxine therapy in the context of subclinical hypothyroidism have returned conflicting results. Two small randomised controlled trials, recruiting between 19 and 37 patients respectively, have reported improvements in cognitive function with thyroid replacement therapy in subclinical hypothyroidism. [73, 74] However, two larger randomised controlled trials, including the Birmingham elderly thyroid study which enrolled 94 patients over the age of 65 years, showed no improvement with therapy. [49, 75]

### *Mobility and frailty*

Higher TSH levels and subclinical hypothyroidism have been associated with a variety of improved health outcomes in the elderly population, including in domains pertinent to the considerations of mobility and frailty. Amongst the very elderly, there is evidence from the Newcastle 85+ study that lower TSH levels correlate with an increasing burden of nonthyroidal disease and disability. [18] Indeed, there is evidence from the Health ABC study suggestive of health benefits for older patients whose TSH levels lie within the subclinical hypothyroid range, as in this elderly cohort (mean age 75 years), those with a TSH (4.5–6.99 mU/L) had faster gait speed and superior cardiorespiratory fitness than those with lower TSH levels. [76] The Leiden 85+ study found no relationship between the serum TSH or fT4 and limitations to activities of daily living in people over the age of 85 years. [16] In the Zoetermeer study, a longitudinal population study of independent ambulatory predominantly euthyroid men, lower T4 and T3 levels were associated with improved physical functional status. [19] Quality of life assessment scores have been shown not to differ between the euthyroid and subclinical hypothyroid groups in an elderly population. [49]

There is relatively scant evidence on the effects of subclinical hypothyroidism on bone health. A Japanese study which employed quantitative heel ultrasound reported that although subclinical hypothyroidism does not appear to affect bone turnover there was an observed impact on bone structure. [77] The MrOS study found no association between TSH and bone loss as measured by sequential hip dual-energy X-ray absorptiometry, nor an increased fracture risk in the subclinical hypothyroid or hypothyroid categories. [78] An American prospective observational study which followed up a cohort of 3567 people over the age of 65 years for a median duration of 13 years found that subclinical hypothyroidism was significantly associated with increased risk of hip fracture in men with a hazard ratio of 2.31 (95% CI, 1.25–4.27) but not women. [79]

In summary, there is little evidence in the literature to clearly link overt hypothyroidism with reduced mobility or increased frailty, and in subclinical hypothyroidism there is some published data suggestive of improvements

in these domains compared to euthyroid individuals, although the data is conflicting here.

### *Longevity*

As the proportion of older people worldwide is increasing rapidly, the factors associated with healthy ageing have become the focus of intense research. Several theories have connected ageing with energy metabolism. One such proposed mechanism relates the lifespan of an organism with its size due to variation in resting metabolic rate. Another theory proposes that increases in free radicals that are generated due to oxidative metabolism are associated with the negative effects of ageing. [80] Thyroid hormones, via its effects on metabolism and the oxidative stress pathways, play a crucial role in the process of ageing and longevity. Experimental data effectively demonstrate the correlation between thyroid hormones and lifespan. Animal models of longevity, either naturally long-living or genetically modified, demonstrate low thyroid hormone. [81, 82] Age-related mild hypofunction of the thyroid gland seems to confer a longevity benefit. Numerous population-based studies have shown either a survival benefit, [16, 19, 83–85] or no adverse impact of lower thyroid function. [18]

As thyroid hormones have a direct impact on the metabolic rate of an individual and can thus play a key role in modulating longevity it is possible that thyroid hormone replacement in older hypothyroid individuals needs to be tailored differently to that of younger patients. However, the target TSH and thyroid hormone levels are uniform across the age groups and age-specific ranges are not utilised. This is despite the fact that the oldest age groups comprise the largest proportion of all hypothyroid. [3] Furthermore, over-treatment with thyroid hormones is common in older women, which is a risk factor for atrial fibrillation and osteoporosis. [86] In the United Kingdom, areas with higher levothyroxine prescribing are independently associated with atrial fibrillation. [87] No definitive trial of levothyroxine treatment in elderly hypothyroid patients comparing different TSH target values is currently available. A feasibility trial of manipulating thyroid hormone doses in older hypothyroid patients aiming for a higher serum TSH level concluded that a definitive trial is viable. [41]

### Treatment of hypothyroidism in the elderly

Despite the high prevalence of hypothyroidism, there have only been a few RCTs that have investigated outcomes with levothyroxine replacement. Three small RCTs in middle aged individuals with subclinical hypothyroidism showed improvement in cognitive function with levothyroxine replacement therapy. [73, 74, 88] Two larger RCTs with longer follow up have not shown any benefit in cognition with levothyroxine replacement, with the latter study specifically being in the elderly population aged 65 years or over. [49, 75]

The dose of levothyroxine that normalises serum TSH level is lower in older patients due to changes in thyroxine turnover with age related reduction in lean body mass. [89] Other factors such as decreased absorption, concomitant medication use, and other comorbidities could also affect thyroid hormone metabolism. The elderly are more susceptible to the ill-effects of thyroid hormone excess such as AF, [90] and osteoporotic fractures. [91, 92] Therefore, careful adjustments of levothyroxine dose at regular intervals are required in this population to avoid iatrogenic hyperthyroidism. The largest study to date of 12 months of levothyroxine treatment in subclinical hypothyroidism in older persons concluded that there was no benefit of treatment on quality of life or symptoms. [93] This double-blind, randomised, placebo-controlled trial of 737 patients older than 65 years with subclinical hypothyroidism demonstrated no significant improvement in the 100-point ThyPRO score (Thyroid-Related Quality of Life Patient-Reported Outcome) with low-dose levothyroxine treatment. [93] Therefore, in addition to the lower dose requirements related to thyroxine metabolism, based on the current evidence, it is reasonable to raise the target serum TSH up to 6 or 7 mU/L in persons greater than age 70–80 years particularly if they are at risk of cardiac arrhythmias or osteoporotic fractures.

## Conclusions

Thyroid hormones have an essential role in the functioning of nearly all tissues in the body at all stages. Thyroid function changes with age and these alterations are more pronounced at both ends of the life span. Current evidence suggests that a slight lowering of thyroid function in older individuals, as evidenced by a marginally raised serum TSH and low normal FT4, may not be associated with an adverse outcome and may, in fact, be beneficial. On the other hand, high thyroid function, as evidenced by a low TSH level needs careful monitoring and treatment considered if there is evidence of end-organ damage (such as osteoporosis or AF), or if serum TSH is suppressed. Despite major advances in our understanding of thyroid function and ecology, mainly due to improvements in assay techniques and high-quality epidemiological studies, several unresolved issues remain. It is currently unclear what the precise underlying mechanisms are behind the changes in thyroid function that are observed in older individuals. Moreover, it is uncertain whether these changes are part of healthy aging or are a bio-marker of underlying disease.

More research is required to fully understand why thyroid function changes in older individuals and whether modulation of thyroid hormones is advantageous for healthy aging and longevity. Mild thyroid hormone deficiency (or subclinical hypothyroidism) is more common

in the elderly. But, if it is 'normal' and indeed desirable to have a slightly low thyroid function in older people then the current use of uniform reference ranges across all adult ages may need to be revised. Age-specific reference ranges may be required to diagnose thyroid disease with special reference to subclinical thyroid disease as well as to target serum TSH in patients on thyroid hormone replacement. And, in the future, it is possible that manipulation of thyroid function for health and longevity may be routinely practiced.

### Abbreviations

FT3: free thyroxine; FT3: free tri-iodothyronine; ROC: receiver operating characteristic; rT3: reverse tri-iodothyronine; T3: tri-iodothyronine (T3); T4: thyroxine; TgAb: Thyroglobulin auto-antibody; TPOAb: thyroid peroxidase autoantibody; TSH: thyrotropin

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### Consent to publication

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None.

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