Endocrine (2019) 66:63–69
https://doi.org/10.1007/s12020-019-02067-9

REVIEW

Check for updates

Diagnosis and treatment of hypothyroidism in the elderly

Leonidas H. Duntas[1] · Paul Michael Yen[2]

Received: 15 July 2019 / Accepted: 21 August 2019 / Published online: 3 September 2019
© Springer Science+Business Media, LLC, part of Springer Nature 2019

Abstract

The global population is aging with millions of people today living into their 90 s. Thyroid disease, particularly hypothyroidism, is widespread among all age groups, and it is expected to steadily increase as the population gets older. Clinical diagnosis of hypothyroidism is challenging, as the TSH reference range needs to be evaluated according to age, while evaluation of TSH levels must also take into account body weight and other variants such as polypharmacy, comorbidities, and general health condition. Since thyroid hormone has a potent regulatory effect on cholesterol metabolism, the possibility of thyroid dysfunction should be considered in cases of unexplained dyslipidemia. Once hypothyroidism has been confirmed, treatment requires caution, frequent cardiovascular monitoring, and individualized (precision) medicine. Treatment of subclinical hypothyroidism (SCH) in the elderly should be undertaken with care, guided by age and the degree of SCH: a TSH higher than 10 mU/l seems a reasonable threshold, though it should be regularly re-evaluated, while the LT4 dose needs to be tailored, taking into account the patient's health condition and the potential presence of dyslipidemia as well as other metabolic derangements.

Keywords Thyroxine · TSH · Elderly · Aging · Hypothyroidism · Subclinical hypothyroidism

Introduction

"The afternoon knows what the morning never suspected" Robert Lee Frost, 1874-1963. The past century has been marked by the rapid growth of the oldest age groups due to the overall increase of populations in almost all regions of the world as well as the concurrent decrease in leading causes of death [1]. It is estimated that by 2030, there will be 72.1 million people over the age of 65 years, and by 2040, the number of very old (85 and above) is expected to reach 14.1 million [2]. Clearly, this demographic transformation will severely impact health care resources. It is thus obvious that radical changes in both health care and socioeconomic systems urgently need to be implemented, for which, however, we are largely unprepared.

✉ Leonidas H. Duntas
ledunt@otenet.gr

[1] Evgenideion Hospital, Unit of Endocrinology, Diabetes and Metabolism, University of Athens, 11528 Athens, Greece

[2] Cardiovascular and Metabolic Disorders Programme, Duke-NUS Medical School, Singapore, Singapore

Hypothyroidism is a frequent disease among the elderly, affecting 5–20% of women and 3–8% of men, its severity depending on the degree of thyroid insufficiency [3]. Subclinical hypothyroidism (SCH) is defined as peripheral free thyroxine (FT4) and free triiodothyronine (FT3) levels within the normal range, while serum thyroid stimulating hormone (TSH) is increased. It represents the most common form of thyroid failure with an estimated prevalence in the general population ranging between 3 and 8% and is projected to increase as populations age [4]. Currently, normal TSH values, which are based on a general population-derived reference range, are routinely used to identify thyroid dysfunction in elderly adults. However, accepted values for the upper limit of normal of TSH may be inappropriate for diagnosing SCH in individuals aged 65 and older resulting in potential overestimation of the prevalence of SCH in this population.

The aim of this review is to summarize the current evidence on observed alterations in thyroid hormone levels in the elderly and the interactions of the various forms of thyroid failure on lipid metabolism, while attention is also given to the challenge faced in diagnosing hypothyroidism, particularly SCH, and to the prerequisites for levothyroxine (LT4) treatment in the elderly.

Diagnosis and clinical signs of hypothyroidism in the elderly

In the Whickham Study carried out in Great Britain over a 20-year period, it was found that 10% of the population above the age of 75 years had elevated serum TSH levels [5]. However, it is now well established that an age-related rise in serum TSH is common among older individuals who may have no apparent thyroid disease or else nonsignificant outcomes. In agreement with the above, the NHANES study demonstrated that the upper limit of the reference range (97.5% confidence interval) increases from 3.56 mU/L in 20–29 years old and to 7.9 mU/L in persons more than 80 years of age [6], a shift which, in the diagnosis of hypothyroidism, needs to be taken seriously into account. In the Thyroid Epidemiology, Audit, and Research Study conducted in Scotland and assessing TSH distribution among different age groups, a significant increase in median TSH and 97.5th centile TSH (1.86 and 5.94 mU/L at >90 years, respectively) was detected with increasing age [7]. The introduction of age-specific reference intervals for TSH in the elderly, as suggested by Leng and Razvi [8], and particularly for those aged over 70, is highly advisable for reclassification of TSH results in this population, thus, crucially, avoiding unnecessary treatment. In the same line, a cross-sectional study of adult populations was conducted in 10 cities of China including 15,008 individuals [9]. The aim was, among others, to establish an age-specific serum TSH reference range. By using an age-specific serum TSH reference range, the prevalence of SCH in older adults was 3.3%, which was significantly lower than that based on the reference range of the general population (3.3 vs. 19.87%). Meanwhile, the prevalence rates of overt hypothyroidism and hyperthyroidism as well as of subclinical hyperthyroidism did not differ much [9].

Symptoms and signs of hypothyroidism might be mild or even absent in the elderly, while some older individuals present atypical symptoms, rendering the diagnosis still more difficult. Nevertheless, since even mild symptoms of hypothyroidism may have a profound impact on overall health and wellbeing in this population, timely identification of the symptoms and signs of the disease are essential for the diagnosis and for implementation of optimal treatment. The most common symptoms of hypothyroidism in the old are depicted in Fig. 1. Given that elevated cholesterol might be the only sign of thyroid insufficiency in an older person, its presence always warrants a thyroid evaluation. Hypothyroidism leads to reduction of blood volume, systolic dysfunction, and slower heart rate, which may all contribute to heart failure. Some elderly patients present with constipation due to infrequent bowel movements, while in others, the only symptom of hypothyroidism may be vague joint pain. Depression can frequently affect older

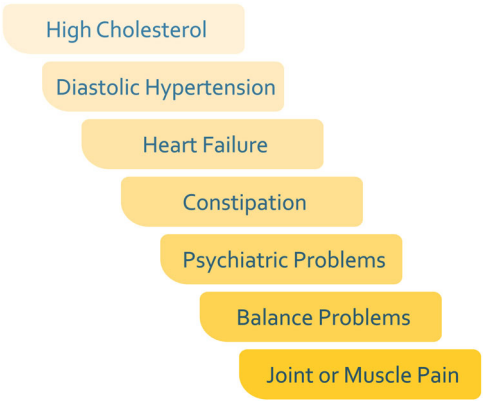

Fig. 1 Signs and symptoms commonly presented in hypothyroidism

hypothyroid patients, while debilitating memory loss, often accompanied by depression or psychosis, can be the only symptom. Hypothyroidism can lead to abnormalities in the cerebellum causing balance problems in walking in older people (Fig. 1). Hypothyroidism in the elderly may cause or exacerbate macrocytic anemia, hypercholesterolemia, and kidney dysfunction, therefore careful clinical and biochemical assessment is necessary [10]. Transient profound hypothyroidism, which is characterized by such neurologic disorders as depression, diminished fine motor performance, slow reaction times, and reduced processing speed, has been shown to be an important public health risk with wide-ranging implications, for example, with regard to driving vehicles [11].

While clinical signs associated with SCH are clearly identifiable in patients <60 years, they are not conclusive in older subjects, in whom, as a result, TSH measurements should not be solely evaluated on the basis of clinical signs but also of reference range set according to age [12].

The hypothalamic–pituitary–thyroid axis in the elderly

It is established that, up until the age of 40, for each increasing quartile of TSH, free T3 (FT3) and the FT3:FT4 ratio increase, while FT4 decreases significantly. However, this process does not occur in the old, which probably reflects a decrease in T4 to T3 conversion with age as part of the aging process [13]. Thyroid function is preserved in healthy aging adults, while FT3 levels decline, leading to reduced FT3:FT4 ratio. Meanwhile, there is a tendency to higher basal TSH concentrations particularly in women, whereas a decreased nocturnal TSH surge in basal overnight and TRH-stimulated TSH release with age is more often demonstrated in men [14, 15]. A decline in T3 levels with concomitantly low normal but detectable TSH levels may

reflect either illness or medication-induced inhibition of both TSH secretion and 5′-deiodinase activity [15].

In the very old (85+), reductions in mean and 24 h rhythmic (nychthemeral) TSH concentrations are more prominent, probably due to the decreased hypothalamic synthesis of TRH together with reduced outer ring deiodination of T4 and resetting of the thyrotroph threshold of TSH feedback suppression [16]. In aging individuals reduced serum T3 concentrations occur in both sexes and are particularly low in patients with organ failure, undernutrition, systemic inflammation, or debilitating illness [16]. With regard to neuropsychiatric diseases in the elderly, uncertainty remains concerning the extent to which low T3 levels are involved in manifestation of such conditions [17].

Serum TSH was lower among older individuals for the same degree of thyroid dysfunction [16], this probably caused by a drop in hypothalamic–pituitary response to low serum T4. Meanwhile, among this population, a rise in serum TSH could point to more severe hypothyroidism than would be found in a young patient [18].

A longitudinal study recruiting 1100 participants found an association between aging and higher serum TSH concentrations, not accompanied, however, by any change in FT4 concentrations [19]. The fact that the greatest TSH increase occurs in individuals with the lowest baseline TSH levels indicates that the TSH increase stems not from occult thyroid disease but instead from either age-related alteration in the TSH set point or reduced TSH bioactivity. With regard to the latter, the hypothesis is that each individual has a specific set point for the hypothalamic–pituitary–thyroid (HPT) axis, which is, to a large extent, genetically determined [20]. Other studies also showed that the upper limits for serum TSH at the 95% for individuals 80–90 years old was 6.0 mIU/L, and for individuals of 90 years or older it was 8.0 mIU/L [21], further supporting the notion that TSH levels rise physiologically with aging, independently of any accompanying thyroid conditions.

Thyroid status and longevity

There is good evidence that thyroid status is associated with longevity. In an analysis of TSH, FT4, and TSH frequency distribution curves in thyroid disease-free Ashkenazi Jews with exceptional longevity (centenarians; median age 98 years), it was shown that while, as is normally the case, TSH shifts to higher concentrations with age, it also appears as a continuum among this group, extending even to people of very great age [22]. The inverse correlation registered between TSH and FT4 in this study population points to changes in negative feedback, which could well contribute to these individuals' exceptional longevity [22].

In a prospective, observational, population-based follow-up study within the Leiden 85-Plus Study, a total of 599 participants were followed up from age 85 to 89 years [23]. Plasma levels of TSH and FT4 were not associated with disability in daily life and were, moreover, linked to a lower mortality rate, which persisted even after adjustments were performed for baseline disability and health status. It thus seems apparent that in the general population of the oldest old, individuals with abnormally high levels of TSH usually do not experience adverse effects and may, in fact, enjoy a prolonged and relatively healthy life [23].

In an extension of this study, 805 nonagenarians from the Leiden Longevity Study and 259 nonagenarians from the Leiden 85-plus Study were followed up to assess mortality data [24]. No association was found between parameters of thyroid function and the study population in relation to mortality. It is noteworthy that a higher FT3/FT4 ratio, higher FT3 values, and lower FT4 values were related to lower mortality in both long-lived families and in the general population.

These results are corroborated by those of a cross-sectional study including 859 nonagenarian siblings (median age 92.9 years) from 421 long-lived families, in whom a lower family mortality history score of the subjects' parents was associated with higher serum TSH levels and lower FT4 and FT3 levels [25]. While the biological mechanism has not as yet been clarified, these findings combined suggest that low thyroid activity in humans may comprise a heritable human phenotype contributing to exceptional familial longevity, as was determined in the Leiden Longevity Study.

The available data thus, suggest that slightly higher TSH concentrations may be normal in the elderly, implying that age modifies the pituitary set point and that a lower TSH response to hypothyroxinemia in older adults may be protective [26], a hypothesis that would be in concert with the findings that higher TSH concentrations are associated with longevity in older individuals.

Hypothyroidism and lipids

Hypothyroidism is accompanied by changes in lipid metabolism, increasing the risk for nonischemic cardiomyopathy [27, 28]. The impact of thyroid insufficiency on the lipid profile is briefly discussed below.

According to the third National Health and Nutrition Examination Survey (NHANES III), the prevalence of hypothyroidism was 1.4–13% in patients with hyperlipidemia [6, 29]. Similar findings were observed in other studies from Europe [30, 31]. Hypothyroidism is characterized by increased serum LDL-C and triglyceride levels, while a strong correlation exists between TSH values and the

severity of dyslipidemia in hypothyroid patients [31]. Indeed, when the TSH levels were between 5.1 and 10 mIU/L, patients had significantly higher mean total cholesterol (TC) and LDL-C levels than euthyroid individuals. In a retrospective cohort study, TSH was elevated in 5.2% of patients who were diagnosed with hyperlipidemia, 3.5% had TSH levels between 5 and 10 mIU/L, 1.7% had TSH levels >10 mIU/L and only about 50% of patients with newly diagnosed hyperlipidemia were monitored for thyroid dysfunction [32]. Taken together these studies suggest that not only hypothyroidism but also SCH could generate hypercholesterolemia and increase the risk for coronary heart disease [33]. In particular, the increase in LDL-C could lead to an accumulation in the arterial intima, where it undergoes lipid peroxidation by reactive oxygen species and causes oxidative stress, inflammation, and recruitment of macrophages, this leading to the development and progression of atherosclerotic plaque formation [34]. It also is possible that tissue -associated hypothyroidism can occur within the liver even when serum thyroid hormone and TSH values are normal, and thereby contribute to the development of hypercholesterolemia, hypertriglyceridemia and/or non-alcoholic fatty liver disease (NAFLD).

In a seminal paper, Pihlajamaki et al. analyzed transcriptomes from liver samples obtained from patients undergoing bariatric surgery and found the most prominent gene set that was altered and was related to TH action [35]. TH plays an important role in hepatic autophagy, β-oxidation of fatty acids, mitophagy, and mitochondrial biogenesis [36].

The fact that thyroid failure has deleterious genomic and nongenomic effects on lipid metabolism, as briefly depicted in this short section, needs to be taken into account when treatment decisions are made in older patients with TSH at least >7 mIU/L and concomitantly high plasma TC and LDL concentrations. Furthermore, thyroid function testing is recommended in elderly subjects with high lipid levels.

Hypothyroid treatment with LT4 in the elderly

While thyroxine is used in the elderly as first line treatment for hypothyroidism [37], caution should prevail. For example, when high TSH is confirmed in the old and very old by a second exam within a few weeks after the first, LT4 should be started at a dose of about 50 µg/day, or 25 µg/day when the patient is underweight or cardiovascular disease is detected, while the general condition of the patient, comorbidities, and medication must also be taken into consideration [38]. It is recommended that a stepwise approach be taken by increasing the dosage by 25 µg within 2–3 weeks in accordance with the patient's complaints or improvements while informing family members about possible reactions and/or symptoms.

Generally, hormone replacement with LT4 in patients with hypothyroidism requires patient-specific therapy. LT4 is available in the form of tablets at various doses, but also in liquid form as an oral solution, thus enabling a customized dose titration.

However, because of the high prevalence of abnormal thyroid function test results in older people under LT4 treatment, particularly in underweight patients or those with diabetes mellitus and a high risk of adverse cardiovascular and skeletal effects from overreplacement, frequent TSH monitoring of therapy is essential [39].

Reasons for patients needing high-dose LT4 replacement include poor compliance, medication interference, parietal cell antibodies (as a marker of atrophic/autoimmune gastritis), and celiac disease. Doses can be decreased following advice regarding medication or after management of underlying conditions [40].

Recently, the association between TSH and FT4 levels and mortality in hypothyroid patients was assessed in 611 patients aged 60–80 years treated with LT4. The study reported increased mortality in patients with median TSH levels of 5–10 IU/L, but no adverse effect was related to FT4 levels. The authors proposed that treatment should aim at achieving euthyroidism to improve survival [41].

In the elderly, >65 years old, as well as in younger patients with hypothyroidism and severe dyslipidemia or with familiar hypercholesterolemia, statin add-on therapy, by suppressing 3-hydroxy-3-methylglutaryl coenzyme A activity, decreases TC and LDL-C [42]. In addition, ezetimibe (EZE) and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, in conjunction with LT4 therapy, may have a synergistic effect and produce an even more favorable lipid profile [42]. EZE blocks the intestinal absorption of cholesterol, while in patients with heterozygous familiar hyperlipidemia, PCSK9 inhibitors suppress PCSK9, thereby promoting LDL-C degradation.

A common condition among elderly people is SCH [43]. However, as serum TSH levels rise physiologically with aging, independent of any accompanying thyroid conditions, the TSH levels may exceed the upper limit of the reference range of 4–5 mIU/L in the elderly patients. [44]. Treatment recommendations of SCH are based on the degree to which TSH hormone concentrations have deviated from normal as well as in the presence of comorbidities [44, 45].

In the Cardiovascular Health Study including 3996 participants of at least 65 years old, estimates of persistence, resolution, and progression of SCH were assessed over a period of 4 years and stratified by baseline TSH, antithyroid peroxidase antibody (TPOAb) status, age, and sex [46]. SCH was detected at baseline in 459 untreated individuals, and persisted for 4 years in just over half of older individuals. It is

noteworthy that high rates of reversion to euthyroidism in individuals with lower TSH concentrations and TPOAb negativity were registered. The results indicate that in advanced age, treatment of SCH should be carefully considered following re-evaluation of TSH in conjunction with biomarkers of autoimmunity, biochemical analyses, and the general health condition of the patient. In a randomized, double-blind, placebo-controlled trial (within the Thyroid Hormone Replacement for SCH trial), LT4 treatment did not induce any change in carotid intima media thickness or in carotid atherosclerosis in elderly individuals with SCH [47]. Baseline mean TSH ± SD was 6.35 ± 1.95 mIU/L and decreased to 3.55 ± 2.14 mIU/L under treatment with LT4, as compared with the placebo mean TSH 5.29 ± 2.21 mIU/L. Moreover, among well-functioning community-dwelling elderly recruited to the PROSPER study, no evidence was found that SCH decreased self-reported functional capacity [48]. However, in a final analysis of 1956 individuals with SCH, average age 83 years, who were followed up for 10 years, SCH (HR, 1.75; confidence interval [CI], 1.63–1.88) was associated with significantly increased mortality, which persisted in multivariate analysis [49]. A threshold TSH value of >6.35 mIU/l in the setting of SCH appears to be associated with higher mortality.

In a recent double-blind, randomized, placebo-controlled, parallel-group trial involving 737 adults (mean age was 74.4 years) with persistent SCH (TSH: 4.60–19.99 mIU/l), 368 patients received LT4 and 369 patients were assigned to receive placebo [50]. No differences in the mean change at 1 year in the Hypothyroid Symptoms Score or the Tiredness Score or on secondary outcome measures was found between groups. The study by Stott et al. is, nevertheless, of significance as no adverse effect of LT4 treatment in older patients with SCH was observed. On the other hand, a major criticism of the latter study is that FT4 levels were reported as pretreatment levels at baseline and no posttreatment values were available, while, in addition, the lipid levels were not included in the cardiovascular risk assessment [51]. Of interest, however, is a case-control study that enrolled patients aged 65 years or older with TSH levels 4.2–10 mIU/L and compared those who expired during the period 2012–2016 ("cases") with matched controls who remained alive during the same timeframe [52]. It was observed that though atrial fibrillation and femoral fractures following initiation of LT4 therapy were not more prevalent in the above group who died during the follow-up period, LT4 treatment was, nevertheless, strongly associated with increased mortality, as assessed by multivariate analysis.

There is certainly the need for appropriately designed and powered RCTs to evaluate the risk/benefit of treatment of mild SCH in older patients and to guide clinical management. However, until this is achieved, it is rational to aim for a higher TSH target when treating older hypothyroid patients, since their TH requirements may be lower, while, in general, a conservative policy in the management of SCH in older individuals is advocated. Furthermore, additional variants, such as unexplained TC and LDL-C levels as well as concomitant nonalcoholic fatty liver disease and T2D, must be considered before decision for treatment is made, due to the potential positive effect of LT4 treatment on lipids and lipid accumulation in the liver [53]. The ongoing combined analysis of the participants in the Institute for Evidence-Based Medicine in Old Age with participants aged over 80 in the TRUST trial will provide the firmest evidence base to date on multimodal effects of levothyroxine treatment in 80-plus persons [54].

Treatment of SCH in the old and very old should be individualized and guided by the degree of SCH, with a TSH higher than 10 mIU/L most likely being a reasonable threshold. The European Thyroid Association recommends treatment in patients above 70 years old who have a TSH >10 mUI/L and signs and/or symptoms of hypothyroidism, or who are at high risk of CVD [55]. However, the LT4 dose needs to be tailored, aiming for a TSH level between 4 and 10 mIU/L, while the patient's health condition and the potential presence of dyslipidemia and other metabolic derangements should be considered. In fact, even when therapy is started, not all treated patients are maintained at the original treatment target. Moreover, because of the well-known poor consistency between TSH and thyroid function testing [56], it is advisable that each patient's thyroid function be periodically assessed on an individual basis, with the subject's entire clinical picture kept in mind, while TSH monitoring at regular intervals is recommended to avoid overtreatment.

To conclude, hypothyroidism is widespread among the elderly population and steadily increases with age, while symptoms can be extremely varied and even atypical. In the face of this challenge, efforts should be made to maintain optimal thyroid function, individualizing treatment in accordance with the subject's age, degree of SCH, comorbidities, and other essential factors, while lifelong follow-up is strongly indicated.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Population Division. U.S. Census Bureau, The Census Bureau on prospects for US population growth in the twenty-first century.

Popul. Dev. Rev. **26**, 197–200 (2000). https://doi.org/10.1111/j.1728-4457.2000.00197.x
2. W. Lutz, W. Sanderson, S. Scherbov, The coming acceleration of global population ageing. Nature **451**, 716–719 (2008). https://doi.org/10.1038/nature06516
3. P. Laurberg, S. Andersen, I. Bülow Pedersen, A. Carle, Hypothyroidism in the elderly: pathophysiology, diagnosis and treatment. Drugs Aging **22**, 23–38 (2005). https://doi.org/10.2165/00002512-200522010-00002
4. J.V. Hennessey, R. Espaillat, Diagnosis and management of subclinical hypothyroidism in elderly adults: a review of the literature. J. Am. Geriatr. Soc. **63**, 1663–1673 (2015). https://doi.org/10.1111/jgs.13532
5. W.M. Tunbridge, D.C. Evered, R. Hall, D. Appleton, M. Brewis, F. Clark, J.G. Evans, E. Young, T. Bird, P.A. Smith, The spectrum of thyroid disease in a community: the Whickham survey. Clin. Endocrinol. **7**, 481–493 (1977)
6. J.G. Hollowell, N.W. Staehling, W.D. Flanders, W.H. Hannon, E. W. Gunter, C.A. Spencer, L.E. Braverman, Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J. Clin. Endocrinol. Metab. **87**, 489–499 (2002). https://doi.org/10.1210/jcem.87.2.8182
7. T. Vadiveloo, P.T. Donnan, M.J. Murphy, G.P. Leese, Age- and gender-specific TSH reference intervals in people with no obvious thyroid disease in Tayside, Scotland: the thyroid epidemiology, audit, and research study (TEARS). J. Clin. Endocrinol. Metab. **98**, 1147–1153 (2013). https://doi.org/10.1210/jc.2012-3191
8. O. Leng, S. Razvi, Hypothyroidism in the older population. Thyroid Res. **8**(12), 22 (2019). https://doi.org/10.1186/s13044-019-0063-3
9. X. Zhai, L. Zhang, L. Chen, X. Lian, C. Liu, B. Shi, L. Shi, N. Tong, S. Wang et al. An age-specific serum thyrotropin reference range for the diagnosis of thyroid diseases in older adults: a cross-sectional survey in China. Thyroid (2018). https://doi.org/10.1089/thy.2017.0715
10. L.H. Duntas, Thyroid function in aging: a discerning approach. Rejuvenation Res **21**, 22–28 (2018). https://doi.org/10.1089/rej.2017.1991
11. C.D. Smith, R. Grondin, W. LeMaster, B. Martin, B.T. Gold, K.B. Ain, Reversible cognitive, motor, and driving impairments in severe hypothyroidism. Thyroid **25**, 28–36 (2015). https://doi.org/10.1089/thy.2014.0371
12. R. Gourmelon, S. Donadio-Andréi, K. Chikh, M. Rabilloud, E. Kuczewski, A.S. Gauchez et al. Subclinical hypothyroidism: is it really subclinical with aging? Aging Dis. **10**, 520–529 (2019). https://doi.org/10.14336/AD.2018.0817
13. D. Strich, G. Karavani, S. Edri, D. Gillis, TSH enhancement of FT4 to FT3 conversion is age dependent. Eur. J. Endocrinol. **175**, 49–54 (2016). https://doi.org/10.1530/EJE-16-0007
14. J.D. Veldhuis, Changes in pituitary function with aging and implications for patient care. Nat. Rev. Endocrinol. **9**, 205–215. https://doi.org/10.1038/nrendo.2013.38
15. F. Monzani, P. Del Guerra, N. Caraccio, L. Del Corso, A. Casolaro, S. Mariotti, F. Pentimone, F. Age-related, modifications in the regulation of the hypothalamic-pituitary-thyroid axis. Horm. Res. **46**, 107–1012 (1996). https://doi.org/10.1159/000185005
16. S. Mariotti, G. Barbesino, P. Caturegli, L. Bartalena, P. Sansoni, F. Fagnoni, D. Monti, U. Fagiolo, C. Franceschi, A. Pinchera, Complex alteration of thyroid function in healthy centenarians. J. Clin. Endocrinol. Metab. **77**, 1130–1134 (1993). https://doi.org/10.1210/jcem.77.5.8077303
17. S. Volpato, J.M. Guralnik, L.P. Fried, A.T. Remaley, A.R. Cappola, L.J. Launer, Serum thyroxine level and cognitive decline in euthyroid older women. Neurology **58**, 1055–1061 (2002). https://doi.org/10.1212/wnl.58.7.1055
18. A. Carlé, P. Laurberg, I.B. Pedersen, H. Perrild, L. Ovesen, L.B. Rasmussen, T. Jorgensen, N. Knudsen, Age modifies the pituitary TSH response to thyroid failure. Thyroid **17**, 139–144 (2007). https://doi.org/10.1089/thy.2006.0191
19. A.P. Bremner, P. Feddema, P.J. Leedman, S.J. Brown, J.P. Beilby, E.M. Lim, S.G. Wilson, P.C. O'Lear, J.P. Walsh, Age-related changes in thyroid function: a longitudinal study of a community-based cohort. J. Clin. Endocrinol. Metab. **97**, 1554–1562 (2012). https://doi.org/10.1210/jc.2011-3020
20. P.S. Hansen, T.H. Brix, T.I. Sørensen, K.O. Kyvik, L. Hegedüs, Major genetic influence on the regulation of the pituitary-thyroid axis: a study of healthy Danish twins. J. Clin. Endocrinol. Metab. **89**, 1181–1187 (2004). https://doi.org/10.1210/jc.2003-031641
21. J.V. Hennessey, R. Espaillat, Subclinical hypothyroidism: a historical view and shifting prevalence. Int. J. Clin. Pract. **69**, 771–782 (2015). https://doi.org/10.1111/ijcp.12619
22. G. Atzmon, N. Barzilai, J.G. Hollowell, M.I. Surks, I. Gabriely, Extreme longevity is associated with increased serum thyrotropin. J. Clin. Endocrinol. Metab. **94**, 1251–1254 (2009). https://doi.org/10.1210/jc.2008-2325
23. J. Gussekloo, E. van Exel, A.J. de Craen, A.E. Meinders, M. Froehlich, R.G. Westendorp, Thyroid status, disability and cognitive function, and survival in old age. JAMA **292**, 2591–2599 (2004). https://doi.org/10.1001/jama.292.21.2591
24. N.A. van Vliet, E. van der Spoel, M. Beekman, P.E. Slagboom, G. J. Blauw, J. Gusseklo, R.G.J. Westendorp, D. van Heemst, Thyroid status and mortality in nonagenarians from long-lived families and the general population. Aging **9**, 2223–2234 (2017). https://doi.org/10.18632/aging.101310
25. M.P. Rozing, J.J. Houwing-Duistermaat, P.E. Slagboom, M. Beekman, M. Froelich, A.J. de Craen, Familial longevity is associated with decreased thyroid function. J. Clin. Endocrinol. Metab. **95**, 4979–4984 (2010). https://doi.org/10.1210/jc.2010-0875
26. R. Over, S. Mannan, H. Nsouli-Maktabi, K.D. Burman, J. Jonklaas, Age and thyrotropin response to hypothyroxinemia. J. Clin. Endocrinol. Metab. **95**, 3675–3683 (2010). https://doi.org/10.1210/jc.2010-0281
27. L.H. Duntas, G.A. Brenta, A renewed focus on the association between thyroid hormones and lipid metabolism. Front. Endocrinol. **9**, 511 (2018). https://doi.org/10.3389/fendo.2018.00511
28. G.A. Sigal, T.M. Tavoni, B.M.O. Silva, R. Kalil Filho, L.G. Brandão, R.C. Maranhão, Effects of short-term hypothyroidism on the lipid transfer to high-density lipoprotein and other parameters related to lipoprotein metabolism in patients submitted to thyroidectomy for thyroid cancer. Thyroid **29**, 53–58 (2019). https://doi.org/10.1089/thy.2018.0190
29. T. Tagami, H. Kimura, S. Ohtani, T. Tanaka, T. Tanaka, S. Hata, M. Saito, Y. Miyazaki, R. Araki, M. Tanaka, K. Yonezawa, M. Sawamura, T. Ise, A. Ogo, T. Shimbo, A. Shimatsu, M. Naruse; PHPH study group, Multi-center study on the prevalence of hypothyroidism in patients with hypercholesterolemia. Endocr. J. **58**, 449–4457 (2011)
30. P.N. Taylor, D. Albrecht, A. Scholz, G. Gutierrez-Buey, J.H. Lazarus, C.M. Dayan, O.E. Okosieme, Global epidemiology of hyperthyroidism and hypothyroidism. Nat. Rev. Endocrinol. **14**, 301–316 (2018). https://doi.org/10.1038/nrendo.2018.18
31. B.O. Asvold, L.J. Vatten, T.I. Nilsen, T. Bjoro, The association between TSH within the reference range and serum lipid concentrations in a population-based study. The HUNT Study. Eur. J. Endocrinol. **156**, 181–186 (2007). https://doi.org/10.1530/eje.1.02333
32. D.L. Willard, A.M. Leung, E.N. Pearce, Thyroid function testing in patients with newly diagnosed hyperlipidemia. JAMA Intern. Med. **174**, 287–289 (2014). https://doi.org/10.1001/jamainternmed.2013.12188

33. L.H. Duntas, L. Wartofsky, Cardiovascular risk and subclinical hypothyroidism: focus on lipids and new emerging risk factors. What is the evidence? Thyroid **17**, 1075–1084 (2007). https://doi.org/10.1089/thy.2007.0116
34. V. Arnao, A. Tuttolomondo, M. Daidone, A. Pinto, Lipoproteins in atherosclerosis process. Curr. Med. Chem. **26**, 1525–1543 (2019). https://doi.org/10.2174/0929867326666190516103953
35. J. Pihlajamaki, T. Boes, E.Y. Kim, F. Dearie, B.W. Kim, J. Schroeder, E. Mun, I. Nasser, P.J. Park, A.C. Bianco, A.B. Goldfine, M.E. Patti, Thyroid hormone-related regulation of gene expression in human fatty liver. J. Clin. Endocrinol. Metab. **94**, 3521–3529 (2009). https://doi.org/10.1210/jc.2009-0212
36. R.A. Sinha, S.H. You, J. Zhou, M.M. Siddique, B.H. Bay, X. Zhu, M.L. Privalsky, S.Y. Cheng, R.D. Stevens, S.A. Summers, C.B. Newgard, M.A. Lazar, P.M. Yen, Thyroid hormone stimulates hepatic lipid catabolism via activation of autophagy. J. Clin. Investig. **122**, 2428–2438 (2012). https://doi.org/10.1172/JCI60580
37. J. Jonklaas, A.C. Bianco, A.J. Bauer, K.D. Burman, A.R. Cappola, F.S. Celi, D.S. Cooper, B.W. Kim, R.P. Peeters, M.S. Rosenthal, A.M. Sawka, Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement. Thyroid **24**, 1670–1751 (2014). https://doi.org/10.1089/thy.2014.0028
38. D.S. Cooper, Thyroid disease in the oldest old: the exception to the rule. JAMA **292**, 2651–2654 (2004). https://doi.org/10.1001/jama.292.21.2651.
39. L.L. Somwaru, A.M. Arnold, N. Joshi, L.P. Fried, A.R. Cappola, High frequency of and factors associated with thyroid hormone over-replacement and under-replacement in men and women aged 65 and over. J. Clin. Endocrinol. Metab. **94**, 1342–1345 (2009). https://doi.org/10.1210/jc.2008-1696
40. H.M. Robertson, A.K. Narayanaswamy, O. Pereira, S.A. Copland, R. Herriot, A.W. McKinlay, J.S. Bevan, P. Abraham, Factors contributing to high levothyroxine doses in primary hypothyroidism: an interventional audit of a large community database. Thyroid **24**, 1765–1771 (2014). https://doi.org/10.1089/thy.2013.0661
41. A. Akirov, H. Gimbel, A. Grossman, T. Shochat, I. Shimon, Elevated TSH in adults treated for hypothyroidism is associated with increased mortality. Eur. J. Endocrinol. **176**, 57–66 (2017). https://doi.org/10.1530/EJE-16-0708
42. L.H. Duntas, G. Brenta, Thyroid hormones: a potential ally to LDL-cholesterol-lowering agents. Horm. (Athens) **15**, 500–510 (2016). https://doi.org/10.14310/horm.2002.1707
43. B. Biondi, A.R. Cappola, D.S. Cooper, Subclinical Hypothyroidism: a review. JAMA **322**, 153–160 (2019). https://doi.org/10.1001/jama.2019.9052
44. B. Biondi, D.S. Cooper, The clinical significance of subclinical thyroid dysfunction. Endocr. Rev. **29**, 76–131 (2008). https://doi.org/10.1210/er.2006-0043
45. D.S. Cooper, B. Biondi, Subclinical thyroid disease. Lancet **379**, 1142–1154 (2012). https://doi.org/10.1016/S0140-6736(11)60276-6
46. L.L. Somwaru, C.M. Rariy, A.M. Arnold, A.R. Cappola, The natural history of subclinical hypothyroidism in the elderly: the cardiovascular health study. J. Clin. Endocrinol. Metab. **97**, 1962–1969 (2012). https://doi.org/10.1210/jc.2011-3047
47. M.R. Blum, B. Gencer, L. Adam, M. Feller, T.H. Collet, B.R. da Costa, E. Moutzouri, J. Dopheide, M. Depairon, G.P. Sykiotis, P. Kearney, J. Gussekloo, R. Westendorp, D.J. Stott, D.C. Bauer, N. Rodondi, Impact of thyroid hormone therapy on atherosclerosis in the elderly with subclinical hypothyroidism: a randomized trial. J. Clin. Endocrinol. Metab. **103**, 2988–2997 (2018). https://doi.org/10.1210/jc.2018-00279
48. V.S. Virgini, L.W. Wijsman, N. Rodondi, D.C. Bauer, P.M. Kearney, J. Gussekloo, W.P. den Elzen, J.W. Jukema, R.G. Westendorp, I. Ford, D.J. Stott, S.P. Mooijaart, PROSPER study group: subclinical thyroid dysfunction and functional capacity among elderly. Thyroid **24**, 208–214 (2014). https://doi.org/10.1089/thy.2013.0071
49. A. Grossman, A. Weiss, N. Koren-Morag, I. Shimon, Y. Beloosesky, J. Meyerovitch, Subclinical thyroid disease and mortality in the elderly: a retrospective cohort study. Am. J. Med. **129**, 423–430 (2016). https://doi.org/10.1016/j.amjmed.2015.11.027.
50. D.J. Stott, N. Rodondi, P.M. Kearney, I. Ford, R.G.J. Westendorp, S.P. Mooijaart et al. Trust study group. thyroid hormone therapy for older adults with subclinical hypothyroidism. N. Engl. J. Med. **376**, 2534–2544 (2017). https://doi.org/10.1056/NEJMoa1603825
51. N.A. van Vliet, R. Noordam, D. van Heemst, Thyroid hormone therapy for older adults with subclinical hypothyroidism. N. Engl. J. Med. **377**, e20 (2017). https://doi.org/10.1056/NEJMc1709989
52. A. Grossman, I. Feldhamer, J. Meyerovitch, Treatment with levothyroxine in subclinical hypothyroidism is associated with increased mortality in the elderly. Eur. J. Intern. Med. **50**, 65–68 (2018). https://doi.org/10.1016/j.ejim.2017.11.010
53. E. Bruinstroop, R. Dalan, Y. Cao, Y.M. Bee, K. Chandran, L.W. Cho, S.B. Soh, E.K. Teo, S.A. Toh, M.K.S. Leow, R.A. Sinha, S. A. Sadananthan, N. Michael, H.M. Stapleton, C. Leung, P.W. Angus, S.K. Patel, L.M. Burrell, S.C. Lim, C.F. Sum, S.S. Velan, P.M. Yen, Low-dose levothyroxine reduces intrahepatic lipid content in patients with type 2 diabetes mellitus and NAFLD. J. Clin. Endocrinol. Metab. **103**, 2698–2706 (2018). https://doi.org/10.1210/jc.2018-00475
54. R.S. Du Puy, I. Postmus, D.J. Stott, M.R. Blum, R.K.E. Poortvliet, W.P.J. Den Elzen, R.P. Peeters, Study protocol: a randomised controlled trial on the clinical effects of levothyroxine treatment for subclinical hypothyroidism in people aged 80 years and over. BMC Endocr. Disord. **18**, 67 (2018). https://doi.org/10.1186/s12902-018-0285-8
55. S.H. Pearce, G. Brabant, L.H. Duntas, F. Monzani, R.P. Peeters, S. Razvi, J.L. Wemeau, 2013 ETA guideline: management of subclinical hypothyroidism. Eur. Thyroid J. **2**, 215–228 (2013). https://doi.org/10.1159/000356507
56. J. Jonklaas, S. Razvi, Reference intervals in the diagnosis of thyroid dysfunction: treating patients not numbers. Lancet Diabetes. Endocrinol. **7**, 473–483 (2019). https://doi.org/10.1016/S2213-8587(18)30371-1