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Hypothyroidism in Older Adults: A Concise Review of the Recent Literature

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Abstract

Introduction Hypothyroidism (HypoT) is a common condition whose prevalence varies according to regional and ethnic factors, dietary iodine, gender, and age. The symptoms of HypoT are generally nonspecific, with considerable overlap with other conditions. These symptoms are not useful for diagnosing HypoT, and a thyroid function test is required for a final diagnosis.

Materials and methods We aimed to provide an overview of the recent global literature on HypoT in older adults. A narrative, nonsystematic review of the international literature from a single major medical online database (PubMed) for the past 5 years was performed. The relevant literature was narrated in a concise thematic account.

Results Most studies and expert opinions reiterated the benefit of replacement therapy in younger and middle-aged individuals. A good volume of literature also considered the interplay between thyroid hormones and (1) cardiovascular function and risk factors, (2) cognitive function, (3) mental health, and (4) quality of life. Most workers are cognizant of the important difference in normal ranges of thyroid-stimulating hormone (TSH) and the consequent TSH targets in older adults compared to younger age groups. Extra care is recommended for the initiation and titration of thyroid hormone replacement therapy to avoid cardiovascular and skeletal adverse effects of relative overtreatment.

Conclusion While clinical benefit is evident in patients under age 65 with overt and subclinical HypoT who are treated with levothyroxine, treatment may be harmful in older adults with subclinical HypoT. The 97th percentile of TSH distribution is 7.5 mIU/L for patients over age 80. Hence, TSH goals should be individualized in older adults to achieve any possible benefit and avoid unnecessary harm.

Keywords
- hypothyroidism
- subclinical hypothyroidism
- thyroid hormones
- older adults
- cardiovascular quality of life
- cognitive function

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Introduction

Hypothyroidism (HypoT) is one of the most common chronic endocrine conditions. Up to 60% of those with thyroid dysfunction are unaware of their condition, as symptoms of HypoT are insidious and nonspecific. However, this is counteracted by the increasing inclusion of thyroid function tests in routine health checks. Untreated HypoT may contribute to other chronic health conditions.[1] There has been much progress in the management of HypoT over the years. However, several important questions remain unanswered.[2] Among these concerns are the indications for treatment, dosing, and replacement targets in older adults.

Subclinical HypoT (SCH), defined as an elevated serum thyroid-stimulating hormone (TSH) level with normal levels of free thyroxine (fT4), affects up to 10% of the adult population. SCH is most often caused by autoimmune thyroiditis.[3,4] However, serum TSH levels rise as people without thyroid disease age; serum TSH concentrations may surpass the upper limit of the traditional reference range among older adult patients. This phenomenon has likely led to overestimating the true prevalence of SCH in persons older than 70 years. Patients with circulating thyroid peroxidase antibodies (TPO-Abs) have a greater risk of progression from SCH to overt HypoT. SCH may be associated with an increased risk of cardiovascular disease (CVD) and mortality. However, levothyroxine (L-T4) therapy may be associated with iatrogenic thyrotoxicosis, especially in older adults, and there is no evidence that it is beneficial in persons aged 65 years or older.[3,4] There are widely accepted international evidence-based guidelines for HypoT in adults. Also, regional guidelines take into consideration the ethnically and locally relevant considerations.[5]

It remains to be seen whether benefits from treatment of HypoT in younger people can be extrapolated to the not clear mildest form of HypoT. Furthermore, it is uncertain whether and to what extent the threshold for therapeutic intervention needs to be modified in older adults, in whom hypothalamic-pituitary regulation is increasingly insensitive to the negative feedback by thyroid hormones and the patient's response to thyroid hormone changes.[6] This is a focused review of the recent evidence and expert opinions regarding the burden, evaluation, and treatment of HypoT in old age, including the decision to initiate L-T4 therapy and setting the therapeutic TSH goals.

Materials and Methods

This is a narrative, nonsystematic review of the literature retrieved from a single major online database for 5 years up to April 11, 2024. The PubMed database (The National Center for Biotechnology Information, U.S. National Library of Medicine).was searched using a combination of search terms to identify the relevant records. The search combined terms were (Octagenarians OR "Old age" elderly "Older adults") AND (Hypothyroidism OR "Thyroid hormone replacement," OR "Thyroxine Replacement" OR "TSH goals" OR "TSH Targets"). Filters applied were clinical trial, meta-analysis, randomized controlled trial (RCT), review, systematic review, restricted for the last 5 years, and humans. Two hundred thirty-two records were identified, and retrieved articles were examined to confirm their relevance. The relevant articles were reviewed and were narrated thematically. One author performed the search and drafted an initial manuscript. All other authors reviewed and further developed it for intellectual content using a single version stored online using Google Docs. No statistical analysis was conducted on the data included in the original articles, and detailed numerical presentations were avoided. All types of original articles were included. The final product was refined through several multilateral rounds of discussion.

Results

Hypothyroidism in Older Adults in Context

Thyroid disease, particularly HypoT, is widespread among all age groups, and it is expected to increase as the population gets older steadily. Clinical diagnosis of HypoT is challenging, as the TSH reference range needs to be evaluated according to age. At the same time, when evaluating TSH levels, one must also consider body weight and other variants such as polypharmacy, comorbidities, and general health conditions. 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 HypoT has been confirmed, treatment requires caution, frequent cardiovascular monitoring, and individualized (precision) medicine.[7] Treatment of SCH in older adults should be undertaken with care, guided by age, symptoms, degree of TSH elevation, patient body weight, lean body mass, life expectancy, and the degree of SCH: a TSH higher than 10 mU/L seems a reasonable threshold, though it should be regularly reevaluated, while the L-T4 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.

L-T4 treatment of overt HypoT can be more challenging in older compared to young patients because of other comorbidity associations. The population of older adults is growing, and increasing incidence and prevalence of HypoT with age are observed globally. Older people have more comorbidities compared to young patients, complicating correct diagnosis and management of HypoT.[8] Most importantly, cardiovascular complications compromise the usual start dosage and upward titration of L-T4 due to a higher risk of decompensating cardiac ischemia and function. It, therefore, takes more effort and care from the clinician, and the maintenance dose may have to be lower to avoid cardiac manifestations

On the other hand, L-T4 has a beneficial effect on cardiac function by increasing performance. The clinical challenge should not prevent treatment with L-T4 should the patient develop cardiac ischemia. The endocrinologist must collaborate with the cardiologist on prophylactic cardiac measures by invasive cardiac surgery or medical therapy against cardiac ischemic angina. This usually allows subsequent successful treatment. Prevalent comorbidities in older adults complicate correct diagnosis since many concomitant morbidities can

result in nonthyroidal illness, resembling mild HypoT both clinically and biochemically.[8] The diagnosis is further complicated as methods for measuring thyroid function (serum TSH and fT4) vary immensely according to methodology and background population. It is thus imperative to ensure a correct diagnosis by etiology (e.g., autoimmunity) before deciding to treat. Even then, there is controversy regarding whether or not treatment of such mild forms of HypoT in older adults will improve mortality, morbidity, and quality of life. This should be studied in large cohorts of patients in long-term placebo-controlled trials with clinically relevant outcomes. Other cases of HypoT, for example, medications, iodine overload, or hypothalamus-pituitary-HypoT, each pose specific challenges to the management of HypoT; these cases are also more frequent in older adults. Finally, treatment adherence is generally challenging. This is also the case in older patients, which may necessitate measuring thyroid hormones at individually tailored intervals, which is important to avoid overtreatment with increased risk of cardiac morbidity and mortality, osteoporosis, cognitive dysfunction, musculoskeletal outcomes, and muscle weakness.

A literature appraisal regarding low-value thyroid care in older adults, summarizes recent findings about screening for thyroid dysfunction and managing HypoT, thyroid nodules, and low-risk differentiated thyroid cancer.[9] Despite a recent shift to a "less is more" paradigm for clinical thyroid care in older adults, current studies demonstrate that low-value care practices are still prevalent. Ineffective and potentially harmful services, such as routine treatment of SCH, can lead to overtreatment with thyroid hormone, inappropriate use of thyroid ultrasound, blanket fine-needle aspiration biopsies of thyroid nodules, and more aggressive approaches to low-risk differentiated thyroid cancers have been shown to contribute to adverse effects, particularly in comorbid older adults. Low-value thyroid care is common in older adults. It can trigger a cascade of overdiagnosis and overtreatment, leading to patient harm and increased health care costs, highlighting the urgent need for deimplementation efforts.

Subclinical Hypothyroidism in Older Adults

SCH is frequently found in older individuals. International guidelines differ in recommendations for managing SCH in older individuals.[10] Several data have been published during the past decade on SCH's clinical significance and treatment in individuals aged 65. Studies showed no significantly increased incidence of adverse cardiovascular, musculoskeletal, or cognitive outcomes in individuals aged 65 or older when serum TSH concentration was 4.5 to 7.0 mIU/L versus a euthyroid group. Moreover, in older individuals with SCH, symptoms of HypoT and cardiac and bone parameters did not improve after L-T4 treatment. These data suggest that treatment with L-T4 should be considered for individuals aged 65 years or older with SCH when TSH concentration is persistently 7 mIU/L or higher and in the presence of symptoms of HypoT and not to initiate treatment with TSH concentrations of less than 7 mIU/L.[10] L-T4 doses should be personalized according to age, comorbidities, and life expectancy.

The incidence and determinants of spontaneous normalization of TSH levels in older adults with SCH were investigated.[11] Pooled data were used from the (1) pretrial population and (2) in-trial placebo group from two randomized, double-blind, placebo-controlled trials (thyroid hormone replacement for untreated older adults with subclinical hypothyroidism trial and institute for evidence-based medicine in old age thyroid 80-plus thyroid trial), comprising of community-dwelling 65+ adults with SCH from the Netherlands, Switzerland, Ireland, and the United Kingdom. The pretrial population ($N = 2{,}335$) consisted of older adults with biochemical SCH, defined as ≥ 1 elevated TSH measurement (≥ 4.60 mIU/L) and a fT4 within the laboratory-specific reference range. Individuals with persistent SCH, defined as ≥ 2 elevated TSH measurements ≥ 3 months apart, were randomized to levothyroxine/placebo, of which the in-trial placebo group ($N = 361$) was included. Incidence of spontaneous normalization of TSH levels and associations between participant characteristics and normalization. In the pretrial phase, TSH levels normalized in 60.8% of participants in a median follow-up of 1 year. In the in-trial phase, levels normalized in 39.9% of participants after 1 year of follow-up. Younger age, female sex, lower initial TSH level, higher initial fT4 level, absence of TPO-Abs, and a follow-up measurement in summer were independent determinants for normalization. The authors suggested that a third measurement may be recommended before treatment because TSH levels spontaneously normalized in many older adults with SCH (also after confirmation by repeat measurement).

Evidence suggests that L-T4 treatment should be initiated, and the effects of therapy in SCH on symptoms such as weight, quality of life, vitality, cognition, and CVD should be studied. Calissendorff and Falhammar have recently considered the evidence for different thyroid hormone medications.[12] In addition, the option to withhold medication when there is an uncertain diagnosis or lack of clinical improvement is considered. A literature review suggested that available research supports the idea that levothyroxine should be initiated in patients with a TSH > 10 mIU/L. Treatment for HypoT is becoming more frequent. Symptoms related to vitality, weight, and quality of life in SCH often persist with L-T4 treatment, and other causes should be explored. Patients with cardiovascular risk factors may benefit from treatment, especially younger patients. Caution is necessary when treating older adult subjects with L-T4. The authors concluded that lifelong treatment with L-T4 should normally only be considered in manifest HypoT. However, in SCH with a TSH > 10 mIU/L, therapy is indicated. A wait-and-see strategy is advocated in milder subclinical forms to see if normalization occurs. Subgroups with cardiovascular risk and SCH may benefit from L-T4 therapy.

Treating HypoT is not always easy particularly deciding when to treat SCH, TSH goals in older adults, and alternatives to levothyroxine monotherapy.[13] Overzealous treatment of symptomatic patients with SCH may contribute to dissatisfaction among HypoT patients, as potential hypothyroid symptoms in patients with minimal HypoT rarely respond to treatment. Thyroid hormone prescriptions have increased

by 30% in the United States in the last decade. The diagnosis of SCH should be confirmed by repeat thyroid function tests, ideally obtained at least 2 months later, as 62% of elevated TSH levels may revert to normal spontaneously. Generally, treatment is unnecessary unless the TSH exceeds 7.0 to 10 mIU/L. In a double-blinded RCT, treatment did not improve symptoms or cognitive function if the TSH is less than 10 mIU/L. While cardiovascular events may be reduced in patients under age 65 with SCH who are treated with L-T4, treatment may be harmful in older patients with SCH. TSH goals are age-dependent, with a 97.5 percentile (upper limit of normal) of 3.6 mIU/L for patients under age 40 and 7.5 mIU/L for patients over age 80. In some HypoT patients who are dissatisfied with treatment, especially those with a polymorphism in type 2 deiodinase, combined therapy with L-T4 and L-T3 may be preferred.

A systematic review and meta-analysis evaluated whether L-T4 has a beneficial or harmful effect on older patients with SCH.[14] A total of 13 articles were included. Meta-analysis results showed that in older SCH patients, L-T4 could significantly reduce total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B (ApoB). In addition, L-T4 had no significant effect on bone mineral density (BMD), fatigue, HypoT symptoms, quality of life, body mass index (BMI), cognitive function, depression, blood pressure, etc. in older SCH patients. Also, it did not significantly increase the incidence of adverse events. The authors proposed that L-T4 treatment may reduce TC, TG, LDL-C, and ApoB among older SCH patients.

Sgarbi and Ward proposed a practical, contemporary approach to decision-making on SCH.[15] They underscored that the decision-making process needs to consider the risk of L-T4 overtreatment and the resulting adverse consequences, such as reduction of BMD, heart failure (HF), and atrial fibrillation (AFib). Hence, current evidence suggests that individuals with TSH $>$ 10 mU/L who test positive for TPO-Abs or are symptomatic may benefit from L-T4 treatment. However, a more cautious and conservative approach is required in older ($\geq$ 65 years of age) and oldest-old ($\geq$ 80 years) patients, particularly those with frailty, in which the risk of treatment can outweigh the potential benefits. The latter may benefit from a wait-and-see approach.

Pharmacology and Dosing

L-T4 is the standard therapy for patients with HypoT, a condition that affects up to 5% of people worldwide. While L-T4 therapy has substantially improved the lives of millions of HypoT patients since its introduction in 1949, the complexity of maintaining biochemical and clinical euthyroidism in patients undergoing treatment with L-T4 cannot be underestimated. Initial dosing of L-T4 can vary greatly and may be based on the amount of residual thyroid function retained by the patient, the body weight or lean body mass of the patient, and TSH levels.[16] As L-T4 is usually administered over a patient's lifetime, physiological changes throughout life will affect the dose of L-T4 required to maintain euthyroidism. Furthermore, dose adjustments may need to be made in patients with concomitant medical conditions, in patients taking certain medications, and in older adult patients. Patients undergoing any weight or hormonal changes may require dose adjustments, and most pregnant women need increased doses of L-T4. Optimal treatment of HypoT requires a partnership between patient and physician. The physician is tasked with a vigilant appraisal of the patient's status based on a thorough clinical and laboratory assessment and appropriate adjustment of their L-T4 therapy. The patient, in turn, is tasked with medication adherence and reporting symptomatology and any changes in their medical situation. The goal is consistent maintenance of euthyroidism without the patient experiencing the adverse events and negative health consequences of under- or overtreatment.

Whether L-T4 improves hypothyroid symptoms and tiredness among older adults with SCH and greater symptom burden was considered in a secondary analysis of the randomized, placebo-controlled trial TRUST (Thyroid Hormone Replacement for Untreated Older Adults with Subclinical Hypothyroidism Trial), conducted in patients from Switzerland, Ireland, the Netherlands, and Scotland.[17] Six hundred thirty-eight persons aged 65 years or older with persistent SCH (TSH level of 4.60N19.9 mIU/L for $>$ 3 months and normal fT4 level) and complete outcome data were included treated with L-T4 or matching placebo with mock dose titration. One-year change in hypothyroid symptoms and tiredness scores (range, 0–100; higher scores indicate more symptoms) on the Thyroid-Related Quality-of-Life Patient-Reported Outcome Questionnaire among participants with high symptom burden (baseline hypothyroid symptoms score $>$ 30 or tiredness score $>$ 40) versus lower symptom burden were measured. One hundred thirty-two participants had hypothyroid symptoms scores greater than 30, and 133 had tiredness scores greater than 40. The hypothyroid symptoms score improved among the group with a high symptom burden. Similarly, between those receiving L-thyroxine (mean within-group change, –12.3) and those receiving placebo (mean within-group change, –10.4 at 1 year; the adjusted between-group difference was –2.0, $p = 0.27$). Improvements in tiredness scores were also similar between those receiving L-T4 (mean within-group change, –8.9) and those receiving placebo (mean within-group change, –10.9; the adjusted between-group difference was 0.0, $p = 0.99$). There was no evidence that baseline hypothyroid symptoms score or tiredness score modified the effects of L-T4 versus placebo (p for interaction = 0.20 and 0.82, respectively). Post hoc analysis, small sample size, and examination of only patients with 1-year outcome data were done. In older adults with SCH and high symptom burden at baseline, L-thyroxine did not improve hypothyroid symptoms or tiredness compared with placebo.

Many hypothyroid patients start L-T4 treatment at a low dose (e.g. 25–50 mcg), especially older adults, those with residual thyroid function, those with low body weight, and those with significant (especially cardiac) comorbidities.[18] Almost half of the patients on L-T4 replacement therapy demonstrate either under- or overtreatment. Many L-T4 preparations have relatively large intervals between tablet strengths at the lower end of their dose ranges (providing 25, 50, and 75 mcg tablets), which may represent a barrier to

achieving the optimum maintenance treatment for some patients.[18] The availability of intermediate tablet strengths of L-T4 in the 25 to 75 mcg range may facilitate precise and effective dose titration of L-T4 and enable convenient maintenance regimens based on a single L-T4 tablet daily to support adherence to therapy.

On the other hand, Brun et al[19] developed a decision aid tool (DAT) that models L-T4 pharmacometrics and enables patient-tailored dosage. The aim of this was to speed up dosage adjustments for patients after total thyroidectomy. The DAT computer program was developed with a group of 46 patients postthyroidectomy, and it was then applied in a prospective randomized multicenter validation trial in 145 unselected patients admitted for total thyroidectomy for goiter, differentiated thyroid cancer, or thyrotoxicosis.[19] The L-T4 dosage was adjusted after only 2 weeks, with or without application of the DAT, which calculated individual fT4 targets based on four repeated measurements of fT4 and TSH levels. The individual TSH target was < 0.1, 0.1 to 0.5, or 0.5 to 2.0 mIU/L, depending on the diagnosis. Initial postoperative L-T4 dosage was determined according to a clinical routine without using algorithms. A simplified DAT with a population-based fT4 target was used for thyrotoxic patients who often went into surgery after prolonged TSH suppression. Subsequent L-T4 adjustments were carried out every 6 weeks until the target TSH was achieved. When clinicians were guided by the DAT, 40% of patients with goiter and 59% of patients with cancer satisfied the narrow TSH targets 8 weeks after surgery, compared with only 0 and 19% of the controls, respectively. The TSH was within the normal range in 80% of DAT/goiter patients 8 weeks after surgery compared to 19% of controls. The DAT shortened the average dosage adjustment period by 58 days in the goiter group and 40 days in the cancer group. Applying the simplified DAT did not improve the dosage adjustment for thyrotoxic patients. In conclusion, this application of the DAT in combination with early postoperative TSH and fT4 monitoring offers a fast approach to appropriate L-T4 dosage after total thyroidectomy for patients with goiter or differentiated thyroid cancer. Estimating individual TSH-fT4 dynamics was crucial for the model to work, as removing this feature in the applied model for thyrotoxic patients also removed the benefit of the DAT.

Cardiovascular Disease and Risk Factors

Excess adverse cardiovascular outcomes have been observed in certain patient populations with HypoT (►**Table 1**). Recent literature on the subject is reviewed below.[20–27] A worthwhile reading is that of Paschou et al who described the physiologic role of thyroid hormones on the cardiovascular system to present cardiovascular manifestations in patients with thyroid disorders, emphasizing molecular mechanisms and biochemical pathways and summarizing current knowledge of treatment options.[20] Thyroid hormone receptors are located both in the myocardium and vessels, and changes in their concentrations affect cardiovascular function. Hyperthyroidism or HypoT, both clinical and subclinical, without the indicated therapeutic management, may contribute to the progression of CVD. According to recent studies, even mild changes in thyroid hormone levels increase cardiovascular mortality from 20 to 80%. In more detail, thyroid disorders have serious effects on the cardiovascular system via a number of mechanisms, including dyslipidemia, hypertension, systolic and diastolic myocardial dysfunction, and endothelial dysfunction. On top of clinical thyroid disorders management, current therapeutics focus on younger patients with SCH. Huang et al explored the relationship between thyroid dysfunction, TSH levels, and risks of AFib in studies. They conducted a dose-response meta-analysis on the correlation between the TSH levels and the risk of AFib.[21] Thirteen studies from 5 databases with 649,293 subjects (mean age, 65.1 years) were included. The dose-response meta-analysis was conducted by comparing the risk ratios for incidental AFib associated with different levels of TSH across studies. Subclinical hyperthyroidism, SCH, and clinical hyperthyroidism were associated with an increased risk of AFib, whereas clinical HypoT was not associated with a significantly increased risk of AFib. A nonlinear relationship was observed in two models between the TSH levels and dangers of AFib. The study indicated that subclinical hyperthyroidism, SCH, and clinical hyperthyroidism were associated with the risk of AFib. The results for the TSH levels and risk of AFib were mixed, showing a U-shaped relationship.

Also, Delitala et al[22] reviewed the literature and found that although some studies have demonstrated that lipids are elevated in SCH, other studies did not confirm this. Clinical trials have also shown no clear evidence that L-T4 therapy in subjects with a milder form (TSH < 10 mU/L) of SCH could improve lipid status and other cardiovascular risk factors. Nevertheless, TSH level is the best predictor of CVD, particularly above 10 mU/L. They called for more prospective studies to clarify the cardiovascular risk in patients with mild SCH and assess the importance of treating older adults to improve or counteract the correlated risks. However, until clinical recommendations are updated, the decision to treat or not treat patients with SCH will still be based on clinical judgment, clinical practice guidelines, and expert opinion. Furthermore, Ettleson[23] concluded that CVD appears to be a major mediator of all-cause mortality in patients with SCH, in particular those aged at least 60 years of age. In contrast, pooled clinical trial results did not find that L-T4 reduced the incidence of cardiovascular events or mortality in this patient population. The impact of treatment of SCH on cardiovascular outcomes remains uncertain. He called for additional prospective and trial data to evaluate treatment effects on cardiovascular outcomes in younger populations.[23] Finally, a focused literature review was conducted from 38 papers with pertinent information.[24] The analysis of results from these papers indicated that the normal levels of TSH are increasing with the advancement of age from 4 up to 7.5 mIU/L for patients $\geq$ 75 years of age. Also, several reviewed studies have shown no benefits of treatment. In contrast, others have shown definite benefits of therapy with L-T4 supplementation on SCH's clinical and metabolic effects with reductions in CVD, HF, and mortality. They concluded that treatment is more effective in younger persons and less so in older persons. Thus, based on the overall evidence,

Table 1 Summary of recent data and contemporary expert opinion on the impact of hypothyroidism and thyroid hormone replacement therapy on cardiovascular disease and risk factors

Author, year [ref]	Study type	Setting	Conclusions
Paschou et al, 2022[20]	Literature review	Focused on physiologic & molecular mechanisms	Thyroid disorders have serious effects on the cardiovascular system via plenty of mechanisms, including dyslipidemia, hypertension, systolic and diastolic myocardial dysfunction, and endothelial dysfunction. On top of clinical thyroid disorders management, current therapeutics focus on younger patients with SCH
Huang et al, 2022[21]	Dose-response meta-analysis	13 studies on 649,293 patients	Subclinical hyperthyroidism, subclinical hypothyroidism, and clinical hyperthyroidism were associated with the risk of AF. The results for the TSH levels and risk of AF were mixed, showing a U-shaped relationship
Delitala et al, 2019[22]	Literature review (PubMed up to 2019)	Thyroid and cardiovascular risk factors	TSH level is the best predictor of cardiovascular disease, particularly above 10 mU/L. Whether to treat or not patients with SCH will still be based on clinical judgment, clinical practice guidelines, and expert opinion
Ettleson, 2023[23]	Narrative review (update)	Recent literature and opinion	The impact of treating SCH on cardiovascular outcomes remains uncertain. Additional perspectives and trial data are required to evaluate the effects of treatment on cardiovascular outcomes
Chrysant, 2020[24]	Focused literature review	Medline 2012–2019	In older subjects, treatment SCH should be individualized and based on symptoms at the level of TSH and initiated at TSH levels $\geq$ 10 mIU/L and at low doses to avoid adverse cardiovascular effects from overtreatment
Gluvic et al, 2022[25]	Literature review and analysis	Risk factors and atherosclerotic mechanism	This paper summarizes the recent literature on subclinical and clinical HypoT and atherosclerotic cardiovascular disease and discusses the effects of L-T4 replacement therapy on restoring biochemical euthyroidism and atherosclerosis processes
Gencer et al, 2020[26]	DB-PC trial nested within TRUST trial	185 subjects average age 74 years	Systolic and diastolic heart function did not differ after treatment with levothyroxine compared with placebo in older adults with mild SCH
Chahine et al, 2019[27]	Narrative review	Epidemiology, clinical and risk factors	HypoT-induced pericardial diseases are underdiagnosed. Initiating treatment early in the disease process and preventing complications relies on early diagnosis through systematic screening per guidelines

Abbreviations: AF, atrial fibrillation; HypoT, hypothyroid; L-T4, levothyroxine; SCH, subclinical hypothyroidism; TRUST trial, Multi-Modal Effects of Thyroid Replacement for Untreated Older Adults with Subclinical Hypothyroidism; TSH, thyroid-stimulating hormone.

treatment of SCH is indicated in younger persons with a TSH level $>$ 4.0 mIU/L. In older subjects, treatment should be individualized and based on the presence of symptoms and the level of TSH and initiated at TSH levels $\geq$ 10 mIU/L and at low doses to avoid adverse cardiovascular effects from overtreatment.[24]

The increased risk of acceleration and extension of atherosclerosis in patients with HypoT and SCH could be explained by dyslipidemia, diastolic hypertension, increased arterial stiffness, endothelial dysfunction, and altered blood coagulation.[25] The instability of atherosclerotic plaque in HypoT could cause excessive activity of the elements of innate immunity, which are characterized by the significant presence of macrophages in atherosclerotic plaques, increased nuclear factor kappa B expression, and elevated levels of tumor necrosis factor-α and matrix metalloproteinase-9, with reduced interstitial collagen; all of them together creates inflammation milieu, resulting in plaque rupture. Optimal substitution by L-T4 restores biochemical euthyroidism. In postmenopausal women and older adult patients with HypoT and associated vascular comorbidity, excessive L-T4 substitution could lead to atrial rhythm disorders and osteoporosis. Therefore, maintaining TSH levels in the reference range is of interest, thus eliminating the harmful effects of lower or higher TSH levels on the cardiovascular system.[25] Furthermore, Gencer et al[26] conducted a randomized,

double-blind, placebo-controlled trial nested within the TRUST trial. A total of 185 participants (mean age 74.1 years, 47% women) underwent echocardiography at the end of the trial. After a median treatment, the mean TSH decreased ($n = 96$) and remained elevated with placebo ($n = 89$). The adjusted between-group difference was insignificant for the mean left ventricular ejection fraction and the E/e ratio. No differences were found for the secondary diastolic function parameters or interaction according to sex, baseline TSH, preexisting HF, and treatment duration. Thus, systolic and diastolic heart function did not differ after treatment with levothyroxine compared with placebo in older adults with mild SCH.[26]

On a different front, HypoT causes pericardial effusion through increased permeability of the epicardial vessels and decreased lymphatic drainage of albumin, resulting in fluid accumulation in the pericardial space. Interestingly, autoimmunity does not play a major role in the pathophysiology, and most effusions are asymptomatic due to slow fluid accumulation.[27] The diagnosis is generally made when the pericardial disease is associated with an elevated TSH level and other secondary causes are excluded. Management consists of thyroid replacement therapy, along with pericardial drainage in case of tamponade.[27]

Skeletal Health

Both thyroid dysfunction and L-T4 therapy have been associated with bone loss, but studies on the effect of L-T4 for SCH on bone yielded conflicting results. Three studies on the subject were published recently.[28–30] The impact of L-T4 therapy for SCH on appendicular bone geometry and volumetric density was studied in a nested study within the TRUST trial by Büchi et al[28] assessing the effect of L-T4 therapy on bone geometry as measured by peripheral quantitative computed tomography. In the TRUST trial, community-dwelling adults aged $\geq$ 65 years with SCH were randomized to L-T4 with dose titration versus placebo with mock titration.[28] The 98 included participants had a mean age of 73.9 years, 45.9% were women, and 12% had osteoporosis. They were randomized to placebo ($n = 48$) or L-T4 ($n = 50$). Annual changes in bone mineral content and volumetric BMD (vBMD) were similar between placebo and L-T4-treated groups, without significant differences in bone geometry or vBMD changes, neither at the diaphysis nor the epiphysis. Similarly, Gonzalez Rodriguez et al[29] assessed the impact of L-T4 treatment on bone in older adults with SCH. Participants (196 community-dwelling adults over 65) with SCH were randomized to L-T4 with dose titration versus placebo with computerized mock titration. In conclusion, over 1 year levothyroxine did not affect bone health in older adults with SCH.[29] Netzer et al[30] reported an ancillary study within two RCTs conducted among adults aged $\geq$ 65 years with persistent SCH. Participants received daily levothyroxine with TSH-guided dose adjustment or placebo and mock titration. The mean age was 77.5 years, and 48.3% were women.[30] Compared to the placebo, participants in the L-T4 group had similar gait speed at the final visit (adjusted between-group mean difference, similar handgrip strength at 1 year, and similar yearly change in muscle mass). These findings suggest that the ancillary analysis of two RCTs and treatment of SCH did not affect muscle function, strength, and mass in individuals 65 years and older.[30]

Mental Health and Quality of Life

Several groups addressed the impact of HypoT on mental health and quality of life.[31–36] Recent studies and opinion pieces are briefly discussed below. Du et al[31] investigated the prevalence of abnormal thyroid function and depression in centrally obese participants and analyzed the relationship between thyroid hormones and depression with components of central obesity. They randomly selected 858 centrally obese participants and 500 nonobese controls in this study. For all participants, they measured serum markers of thyroid functions and metabolism. Centrally obese participants had a higher prevalence of HypoT and depression than nonobese controls. Serum fT4 levels negatively correlated with BMI and serum TSH levels and positively correlated with BMI, waist-hip ratio, and lipids. After excluding participants with HypoT and hyperthyroidism, serum fT4 levels showed a negative correlation, and serum TSH levels showed a positive correlation with BMI in the remaining centrally obese participants. Center for Epidemiological Studies Depression scores positively correlated with BMI. Therefore, a high prevalence of HypoT and depression among centrally obese participants was observed. FT4 and TSH are important in weight regulation.[31]

Moon et al[32] addressed the question of whether increasing the L-T4 dose confers additional mood benefits by a single-blinded before-and-after study of 24 patients with HypoT who were aged 65 years or older and undergoing L-T4 replacement therapy with stable doses. Korean version of Geriatric Depression Scale (GDS-K) and Hyperthyroid Symptom Scale (HSS-K) were assessed at baseline, 3 months after increasing the L-T4 dose by an additional 12.5 mcg/d, and 3 months after returning to the baseline dose. Serum TSH concentrations decreased at the higher L-T4 dose and recovered after returning to the baseline. Serum fT4 levels and HSS-K scores were unchanged during the study period. GDS-K scores improved on the increased dose ($p < 0.03$), and this improvement was maintained after returning to the baseline dose ($p = 0.01$). Higher serum TSH was independently associated with both higher GDS-K and depression risk among those with depressive mood (GDS-K > 10) at baseline. These data suggest that depressive mood improves with increased L-T4 dose, without significant hyperthyroid symptoms or signs, in older adults undergoing thyroid hormone replacement.[32] Also, Wildisen et al[33] assessed the effect of L-T4 on the development of depressive symptoms in older adults with SCH in the largest trial on this subject. It updated a previous meta-analysis, including the results of this study. This predefined ancillary study analyzed data from participants in the TRUST trial described above. This ancillary study included a subgroup of 472 participants from the Netherlands and Switzerland; after exclusions, 427 participants (211 randomized to levothyroxine and 216 to placebo) were analyzed. This analysis was conducted from

December 1, 2019 to September 1, 2020. Randomization was done to either levothyroxine or placebo. Depressive symptom scores after 12 months were measured with the GDS-15, with higher scores indicating more depressive symptoms (minimal clinically important difference = 2). A total of 427 participants with SCH (mean age, 74.5 years; 239 women) were included. They found that depressive symptoms did not differ after levothyroxine therapy compared with placebo after 12 months; thus, these results do not provide evidence in favor of levothyroxine therapy in older persons with SCH to reduce the risk of developing depressive symptoms.[33]

Stuber et al[34] reported a nested study within the randomized, placebo-controlled, multicenter TRUST trial described above. Interventions consisted of daily levothyroxine starting with 50 mcg (25 mcg if weight < 50 kg or known coronary heart diseases) and dose adjustments to achieve a normal TSH and mock titration in the placebo group. Among 230 participants, the mean TSH was 6.2 mIU/L at baseline and decreased to 3.1 with L-T4 ($n = 119$) versus 5.3 with placebo ($n = 111$, $p < 0.001$) after 1 year. After adjustment, no between-group difference was detected at 1 year on perceived physical or mental fatigability. In participants with higher fatigability at baseline, the adjusted between-group differences at 1 year were not significantly different. This suggests that L-T4 in older adults with mild SCH provides no change in physical or mental fatigability.[34] Danicic et al[35] discussed the impact of SCH on health-related quality of life (HRQoL) and the evidence for L-T4 therapy and exercise therapy to improve HRQoL in SCH. The prevalence of SCH in Australia is approximately 4 to 5% and is higher in females and older adults. Current evidence suggests thyroid hormone therapy is not associated with improving HRQoL. However, there appears to be a subgroup of those with SCH who experience an impairment in HRQoL and may benefit from treatment. Because the majority of research to date has been done in older adults, largely asymptomatic individuals, this may only be representative of some of the SCH population.[35] In addition, alternative treatments, such as exercise therapy, have yet to be explored in the literature despite exercise therapy's effects on HRQoL in other populations. Further research is required to define clearly which individuals with SCH are likely to experience an impaired HRQoL, as well as explore the effects of thyroid hormone therapy and exercise therapy in these individuals.[35]

A couple of years ago, Eslami-Amirabadi and Sajjadi[36] summarized the literature examining the relationship between thyroid hormonal dysregulation and cognition or behavior. They present the available imaging and pathological findings on structural and functional brain changes related to thyroid hormonal dysregulation. They also propose potential interaction mechanisms between thyroid hormones, autoantibodies, and cognition/behavior. Effects of gender, ethnicity, and environmental factors are also briefly discussed. This review highlights the need for long-term prospective studies to capture the course of brain functional changes associated with the incidence and progression of thyroid dysregulations and the confounding effects of nonmodifiable risk factors such as gender and ethnicity. Moreover, double-blind controlled clinical trials are necessary to devise appropriate treatment plans to prevent cognitive consequences of over- or undertreatment of thyroid disorders.[36]

Outcomes and Prognosis

Several reports of different types addressed the outcome of hyothyroidism.[37–41] Zhong et al[37] evaluated whether elevated endogenous thyrotropin levels contribute to an increased risk of adverse outcomes, such as all-cause mortality in older adults with SCH.[37] Eight electronic databases were searched for relevant articles from inception until March 23, 2022. Cohort studies assessing the association between thyrotropin levels and the risk of mortality among older adults aged $\geq$ 60 years with SCH were eligible. The outcomes of interest were either all-cause or cardiovascular-related mortality. Two independent researchers assessed the eligibility of the studies and collected data through a previously defined data extraction form. The Newcastle-Ottawa Scale was used to evaluate the quality of evidence, and multivariate-adjusted hazard ratios (HRs) were collected as the necessary risk estimate for synthesis. Random-effect models were applied for meta-analysis. Overall, 13 studies involving 44,514 participants were included in this meta-analysis. There were no significant differences in the risk of all-cause mortality and cardiovascular-related mortality between euthyroid older adults and older adults with SCH. The results remained the same when only older adults with thyrotropin $\geq$ 10 mIU/L were assessed. Therefore, high thyrotropin levels are not associated with increased risk for all-cause mortality as well as cardiovascular-related mortality in older adults aged $\geq$ 60 years with SCH, suggesting a superfluousness of initiating treatment.[37]

A meta-analysis aimed to determine the impact of HypoT on mortality in the older adult population.[38] Several databases were searched from inception until May 10, 2019. Studies evaluating the association between HypoT and all-cause and/or cardiovascular mortality in the older adult population were eligible. Two reviewers independently extracted data and assessed the quality of the studies. Relative risk was retrieved for synthesis. A random-effects model for meta-analyses was used. Twenty-seven cohort studies with 1,114,638 participants met the inclusion criteria. Overall, patients with HypoT experienced a higher risk of all-cause mortality than those with euthyroidism; meanwhile, no significant difference in cardiovascular mortality was found between patients with HypoT and those with euthyroidism. Subgroup analyses revealed that overt HypoT rather than SCH was associated with increased all-cause mortality. The heterogeneity primarily originated from different study designs (prospective and retrospective) and geographic locations. Based on the current evidence, HypoT is significantly associated with increased all-cause mortality instead of cardiovascular mortality among older adults. They observed considerable heterogeneity, so caution is needed when interpreting the results. Further prospective, large-scale, high-quality studies are warranted to confirm these findings.[38]

Thyroid hormones have vital roles in development, growth, and energy metabolism. Within the past two decades, disturbances in thyroid hormone action have been implicated in aging and the development of age-related diseases. van Heemst[39] reviewed the results from biomedical studies that have identified the importance of precise temporospatial regulation of thyroid hormone action for local tissue maintenance and repair. Age-related disturbances in the maintenance of tissue homeostasis are thought to be important drivers of age-related disease. In most iodine-proficient human populations without thyroid disease, the mean, median, and 97.5 centiles for circulating concentrations of the TSH are progressively higher in adults over 80 years of age compared with middle-aged (50–59 years) and younger (20–29 years) adults. This trend has been shown to extend into advanced ages (over 100 years). Here, potential causes and consequences of the altered thyroid status observed in old age and its association with longevity will be discussed. In about 5 to 20% of adults at least 65 years of age, TSH concentrations are elevated. Still, circulating thyroid hormone concentrations are within the population reference range, a condition called SCH. Results from randomized clinical trials that have tested the clinical benefit of thyroid hormone replacement therapy in older adults with mild SCH will be discussed, as well as the implications of these findings for screening and treatment of SCH in older adults.[39]

The associations between (sub-) clinical thyroid dysfunction and disability in daily living, cognitive function, depressive symptoms, physical function, and mortality in people aged 80 years and older were evaluated.[40] Four prospective cohorts participating in the Towards Understanding Longitudinal International Older People Studies (TULIPS) consortium were included. Outcome measures included disability in daily living (disability in activities of daily living [ADL] questionnaires), cognitive function (Mini-Mental State Examination [MMSE]), depressive symptoms (GDS), physical function (grip strength) at baseline and after 5 years of follow-up, and all-cause 5-year mortality. Of the total 2,116 participants at baseline (mean age 87 years, range 80–109 years), 105 participants (5.0%) were overtly HypoT, 6.4% had SCH, 85.6% euthyroid, 2.8% subclinically hyperthyroid, and 0.2% overtly hyperthyroid. Participants with thyroid dysfunction at baseline had nonsignificantly different ADL scores compared with euthyroid participants at baseline and had similar MMSE scores, GDS scores, and grip strength. During 5 years of follow-up, there was no difference in the change of any of these functional measures in participants with thyroid dysfunction. Compared with the euthyroid participants, no 5-year survival differences were identified in participants with overt HypoT (HR: 1.0), SCH (HR 0.9), subclinical hyperthyroidism (HR 1.1), and overt hyperthyroidism (HR 1.5). Results did not differ after excluding participants using thyroid-influencing medication. Therefore, in community-dwelling people aged 80 years and older, (sub-) clinical thyroid dysfunction was not associated with functional outcomes or mortality and may, hence, be of limited clinical significance.

The impact of thyroid hormone therapy on mortality in adults with SCH was summarized by searching several databases.[41] Studies comparing the effect of thyroid hormone therapy with that of placebo or no treatment in adults with SCH on all-cause and/or cardiovascular mortality were included. Five observational studies and 2 RCTs with 21,055 adults were included. Overall, thyroid hormone therapy was not significantly associated with all-cause or cardiovascular mortality. Subgroup analyses revealed that thyroid hormone therapy was significantly associated with lower all-cause and cardiovascular mortality in younger adults. However, no significant association between thyroid hormone therapy and mortality was observed in older adults. The use of thyroid hormone therapy does not provide protective effects on mortality in older adults with SCH.

Patient and Professional Perspectives

The lack of knowledge and understanding of HypoT and a tendency for many people to attribute the symptoms of HypoT to other causes have led to substantial unawareness and often late diagnosis of HypoT. Large observational studies and meta-analyses have shown that about 4 to 7% of community-derived populations in the United States and Europe have undiagnosed HypoT.[42] About four cases in five of these are SCH, with the remainder being overt HypoT. The prevalence of undiagnosed HypoT is higher in older subjects, in women, and in some ethnic groups, consistent with diagnosed disease. The authors suggested that more research is needed to quantify the clinical burden of undiagnosed HypoT around the world, with educational efforts aimed at the public and health care professionals aimed at identifying and managing these individuals. To this end, practice patterns regarding TSH goals and factors influencing physicians' decision-making when managing HypoT were evaluated using a case-based survey of a convenience sample of 286 physicians practicing in relevant disciplines in three developing regions.[43] Three-quarters of physicians stated they would consider patients' age when determining the TSH goal. The physicians targeted a higher TSH goal in octogenarians, which is still lower than the age-related reference, indicating awareness regarding inadequate benefits and an attempt to avoid iatrogenic hyperthyroidism. The authors suggested that consensus is needed on the role of patients' age in HypoT management, the complexity of managing HypoT in older adult patients, and the variability in practice patterns among physicians. They also proposed that addressing these challenges demands ongoing dialog and collaboration among health care providers to improve patient care and outcomes in HypoT management across different age groups.

Conclusion

The hypothalamic-pituitary-thyroid axis and its hormones undergo significant changes due to physiological aging. HypoT is more common among older subjects than their younger counterparts. For a correct diagnosis of HypoT in older adults, clinicians must consider such age-related

changes. The administration of replacement therapy in older adults should consider frailty, polypharmacy, and an increased risk of developing overtreatment symptoms. Recent studies have shown that levothyroxine treatment in milder forms rarely affects cognition, weight, muscle strength, or quality of life. Lifelong medication with levothyroxine should normally only be considered in manifest HypoT. In SCH with TSH $>$ 10 mIU/L, treatment is indicated. A wait-and-see strategy is advocated in milder SCH to see if normalization occurs. However, individuals with cardiovascular risk and SCH may benefit from levothyroxine treatment. Withholding levothyroxine could be advocated in mild forms when clinical improvement does not happen or if the diagnosis is uncertain, but follow-up is required. On the other hand, older patients with untreated or undertreated HypoT may develop a state of myxedema coma. Thyroid hormone therapy should be carefully individualized to achieve the potential benefit and avoid harm.

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All authors reviewed the whole document for intellectual content. All authors approved its final version.

Disclaimer
To the best of our abilities, we presented our perception of the published work in good faith. Original authors cannot be held responsible for any misrepresentation.

Conflict of Interest
None declared.

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