



QUALITY IN SPORT

eISSN 2450-3118 · Open Access · Peer-reviewed

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MATYAS, Anna, ZIAJKA, Piotr, ZWOLIŃSKA, Agnieszka, GAUDYNEK-SOWAŁA, Aleksandra, ŁAPOT, Monika, SZCZEPANEK, Gabriela, LURKA, Hubert, ZYSKOWSKA, Anna, STARCZEWSKI, Michał, TOMCZAK, Adam, and KOROLCHUK, Anhelina. Primary Hypothyroidism in Older Adults: Do Current Guidelines Need an Update? *Quality in Sport*. 2026;77;76055. <https://doi.org/10.12775/QS.2026.77.76055>

ARTICLE TIMELINE

Received: 13.09.2026. Revised: 15.09.2026 Accepted: 16.09.2026. Published: 29.09.2026.

The journal has been awarded 20 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32553). Unique Journal Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).

Punkty Ministerialne z 2019 – aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych). © The Authors 2026.

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Primary Hypothyroidism in Older Adults: Do Current Guidelines Need an Update?

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ABSTRACT

Background. Hypothyroidism is one of the most common endocrine disorders in the geriatric population. However, diagnosing this condition in older adults presents significant challenges due to the overlap of non-specific symptoms with the normal aging process and comorbidities. Furthermore, physiological aging is associated with an upward shift in the thyrotropic axis set-point, resulting in naturally higher serum thyroid-stimulating hormone (TSH) levels, which are frequently misinterpreted as a pathological state.

Aim. The aim of this narrative review is to evaluate the current state of knowledge regarding primary hypothyroidism in patients aged 65 years and older, with a particular emphasis on the oldest-old, to ascertain whether recent scientific evidence warrants an update to prevailing clinical guidelines.

Material and Methods. A narrative review of the current medical literature was conducted. The analysis included guidelines from international endocrine societies (European Thyroid Association ETA, American Thyroid Association ATA, American Association of Clinical Endocrinology AACE), observational studies, meta-analyses, and pivotal multicenter randomized controlled trials evaluating the efficacy and safety of levothyroxine therapy in the geriatric population.

Results Mildly elevated serum TSH levels in older adults often normalize spontaneously and may represent an adaptive physiological mechanism predisposing to longevity. Evidence from large-scale randomized controlled trials conclusively demonstrates a lack of clinically significant benefits from routine levothyroxine (L-T4) treatment in older patients with subclinical hypothyroidism (SCH) regarding symptom alleviation, quality of life, or cardiovascular outcomes. Conversely, inappropriate hormone replacement carries a higher risk of iatrogenic complications.

Conclusions. Current scientific evidence does not justify the routine treatment of subclinical hypothyroidism in the elderly. The preferred management strategy is watchful waiting, strict individualization of therapeutic decisions, and adherence to the "start low and go slow" principle. Further large-scale randomized clinical trials involving the oldest age cohorts are urgently needed to update current guidelines, particularly to establish and implement age-specific serum TSH reference ranges.

Keywords: primary hypothyroidism, subclinical hypothyroidism, thyroid-stimulating hormone, levothyroxine, older adults, oldest-old, clinical practice guidelines

1. Introduction

Hypothyroidism is one of the most common endocrine disorders in the geriatric population, and its prevalence increases with age [1,2]. However, diagnosing this condition in older adults presents significant challenges. The clinical presentation in the elderly is often oligosymptomatic, and non-specific complaints are frequently misattributed to physiological aging processes [1,3]. Furthermore, advancing age is associated with alterations in the hypothalamic-pituitary-thyroid axis, a key manifestation of which is a shift in the set-point and the occurrence of higher serum TSH levels [1,2]. Misinterpretation of this phenomenon as a pathological state carries a high risk of disease overdiagnosis [3].

Therapeutic management in the oldest patients is also a subject of vigorous debate. Long-term observations suggest that mildly elevated serum TSH levels may represent a physiological adaptive mechanism, protecting the body against excessive metabolism and predisposing to longer survival [1,4,5]. Moreover, multicenter randomized controlled trials have demonstrated a lack of significant benefits from L-T4 treatment in older patients in terms of symptom alleviation, quality of life improvement, or reduction in cardiovascular mortality [6,7]. These findings have also been corroborated by comprehensive meta-analyses [8].

Given the identified distinct characteristics of the geriatric population, contemporary literature strongly advocates for the implementation of age-specific TSH reference ranges to minimize false diagnoses of hypothyroidism [2,9]. Current European and American guidelines emphasize the individualization of therapeutic goals and favor a watchful waiting approach when

considering treatment initiation in the oldest patients [10,11]. However, there is still a lack of precise and fully validated recommendations dedicated specifically to the oldest-old [12,13]. This paper is a narrative review aimed at summarizing the current knowledge regarding the clinical presentation, diagnosis, and treatment of primary hypothyroidism in patients aged 65 years and older. The primary intention of this article is to answer the question of whether, in light of the latest clinical trial results, current guidelines for the management of hypothyroidism require the development of more precise recommendations for geriatric patients.

2. Material and Methods

The present study was conducted as a narrative review of the current medical literature. The objective of this approach was to summarize the current state of knowledge regarding the clinical presentation, diagnosis, and management of primary hypothyroidism in patients aged 65 years and older. The conducted analysis aimed to determine whether, in light of the latest evidence from clinical trials, the currently prevailing clinical guidelines necessitate the development of more precise recommendations tailored to the geriatric population. As part of this review, the following materials were subjected to detailed evaluation: clinical guidelines established by leading international endocrinological societies (ETA, ATA and AACE), recent observational studies, comprehensive meta-analyses, and key multicenter randomized controlled trials assessing the efficacy and safety of levothyroxine therapy in the geriatric population (including the Thyroid Hormone Replacement for Untreated Older Adults with Subclinical Hypothyroidism Trial and the study protocol for the Institute for Evidence-Based Medicine in Old Age 80-plus Thyroid Trial).

3. Definitions

Old age is the final stage of human life; this process is continuous, individually variable, and multidimensional. The World Health Organization (WHO) establishes the threshold age as 60 years for individuals residing in developing countries and 65 years for those in developed countries. Due to the vast heterogeneity in the health status and functional capacity of older adults, the period of old age is subdivided into the young-old (60-74 years old), the old-old (75-89 years old), and the oldest-old (aged 90 years and older; including centenarians aged 100 years and older) [14,15].

Primary hypothyroidism is a disorder resulting from direct damage to or failure of the thyroid gland itself, leading to insufficient synthesis and secretion of thyroid hormones relative to tissue demands. In accordance with European and American guidelines, overt primary

hypothyroidism is biochemically defined as an elevated serum TSH level above the upper limit of the reference range, accompanied by a decreased serum free thyroxine (FT4) level below the lower limit of the normal range. A distinct stage of the disease is subclinical hypothyroidism, which is diagnosed when the serum TSH level is elevated while the serum FT4 level remains within the normal reference range [10,11].

4. Clinical Presentation of Primary Hypothyroidism in Older Adults

The prevalence of hypothyroidism increases with age [1,2]. The development and pathogenesis of thyroid disorders in older patients are influenced by a variety of physiological and clinical factors. These include a decrease in lean body mass, impaired thyroxine absorption, and disturbances in the deiodination process [1]. Furthermore, the burden of comorbidities and the phenomenon of polypharmacy play a significant role [1,3]. Moreover, the presence of antithyroid antibodies is an important prognostic factor. Scientific studies demonstrate that elevated titers of thyroid peroxidase antibodies (anti-TPO) constitute a predisposing factor for the progression of SCH to overt disease [12,16,17]. It is estimated that in patients with diagnosed mild SCH, the risk of such transition ranges from 2 to 4% annually [12].

The most common clinical manifestations of hypothyroidism include chronic fatigue, unexplained weight gain, cold intolerance, excessive skin dryness, constipation, bradycardia, and cognitive decline, including memory impairment [11]. In contrast to younger individuals, older adults present with the aforementioned symptoms less frequently, and the disease course itself is often non-specific and oligosymptomatic [1–3]. Non-specific complaints reported by patients are often mistakenly attributed to physiological aging processes, which can complicate establishing a diagnosis [1,3]. It should be noted that elderly patients carry a significantly higher risk of developing one of the most severe complications of untreated hypothyroidism, namely myxedema coma [3].

5. Age-Related Changes in Serum TSH Levels

With age, the thyroid gland undergoes natural involutional processes, including atrophy and fibrosis. Consequently, fluctuations in the serum TSH and free thyroid hormones levels occur [1].

A key aspect in older adults is the physiological shift of the set-point of the hypothalamic-pituitary-thyroid axis, which manifests as higher serum TSH levels [2]. The exact etiology of this phenomenon remains a subject of investigation; however, it is known that the thyrotropic axis set-point is highly individual and largely genetically determined [16]. Due to these

changes, a mild elevation in serum TSH levels in elderly patients often represents a variant of the body's physiological adaptation to aging rather than a glandular pathology [10]. The necessity of considering this phenomenon was already recognized in the joint AACE and ATA guidelines. This document explicitly indicated that in older individuals, the TSH distribution curve shifts towards higher values, calling into question the rationale and benefits of routine treatment for mild SCH in this population [11]. It should also be noted that the intra-individual reference range for serum TSH and FT4 levels is typically narrower than standard population-based intervals [12]. Furthermore, current serum TSH levels are influenced by circadian variations, environmental factors, polypharmacy, and the burden of comorbidities [1]. Misinterpretation of physiologically elevated serum TSH levels may result in the overdiagnosis of hypothyroidism, as well as the erroneous classification of healthy individuals as diseased [3]. In light of these reports, contemporary literature even more strongly advocates the use of age-specific TSH reference ranges in clinical practice, which allows for minimizing the rate of false diagnoses and enhancing patient safety [2].

6. Serum TSH Levels and Longevity

Observational studies and population-based analyses provide evidence suggesting that higher serum TSH levels, with concurrently normal or decreased serum FT4 levels, may exert a beneficial effect on the body, including predisposing to longer survival [4]. From a physiological perspective, thyroid hormones act as a key modulator of the basal metabolic rate, which directly determines the intensity of tissue aging processes. Decreased biological activity of FT4 translates into a reduction in the resting metabolic rate, which hypothetically leads to a deceleration of catabolic processes and a reduction in the depletion of the body's energy reserves [5].

In light of these mechanisms, it is postulated that an isolated, progressive age-related increase in serum TSH levels does not necessarily represent a manifestation of thyroid disease. This phenomenon may be an expression of adaptation and a protective mechanism of the body that promotes longevity [1,5].

Understanding this relationship is of fundamental importance for clinical practice, as it radically alters the approach to pharmacotherapy in older patients. This highlights the necessity of adjusting treatment depending on the patient's age [3]. Striving to lower serum TSH levels to reference ranges typical for younger individuals may disrupt these natural adaptive mechanisms and increase the risk of adverse events, morbidity, and mortality [2].

7. Non-Thyroidal Illness Syndrome in Older Adults

Another challenge in the diagnostic evaluation of elderly patients is the proper interpretation of laboratory test results in the course of the so-called non-thyroidal illness syndrome (NTIS), also referred to as euthyroid sick syndrome (ESS). This phenomenon involves the occurrence of transient disturbances in the thyroid hormone profile in individuals with severe systemic diseases, malnutrition, or in a state of severe physiological stress, in whom no primary pathology of the gland itself is identified [3].

The typical laboratory picture in NTIS includes decreased serum triiodothyronine (T3) level, normal or mildly decreased serum TSH level, and normal or elevated serum FT4 level. This phenomenon is commonly observed in older patients hospitalized for non-endocrinological reasons. Interestingly, studies demonstrate that it is the severity of the underlying acute illness, rather than the patient's age itself, that constitutes the primary factor determining the magnitude of the reduction in serum T3 levels [3].

Currently, there is a lack of convincing evidence and clear guidelines that would justify the use of hormone replacement therapy in patients diagnosed with NTIS. Clinical guidelines generally advise against the routine measurement of thyroid parameters in acutely ill patients, as these results can be highly misleading (unless there is a strong clinical suspicion of primary thyroid dysfunction) [11]. Furthermore, attempts to correct thyroid hormone levels during the acute phase of a systemic illness typically do not provide clinical benefit. Follow-up laboratory investigations should be conducted during the convalescence period, usually about 2 weeks after the patient's discharge from the hospital. Based on these results, a decision can be made as to whether thyroid hormone replacement therapy is required [3].

8. Spontaneous Normalization of Serum TSH Levels

Clinical observations and long-term population-based studies provide strong evidence that a significant proportion of elderly patients diagnosed with SCH experience spontaneous disease remission without the need for treatment. Studies involving large cohorts of primary care patients have demonstrated that over a 5-year follow-up period, more than half of the patients with a mildly elevated serum TSH level experience a spontaneous return to euthyroidism [18]. These observations were corroborated by the results of the large-scale British Birmingham Elderly Thyroid Study. The authors of this analysis demonstrated that thyroid function in older adults is generally highly stable over the years, and in cases of mild deviations from the norm, the probability of spontaneous serum TSH levels normalization is significantly higher than the risk of progression to overt hypothyroidism [19].

The likelihood of spontaneous remission is determined by a range of clinical and demographic factors. This phenomenon is more frequently observed in patients with negative anti-TPO antibody titers [12]. Furthermore, factors predisposing to the normalization of thyroid parameters include a lower baseline serum TSH level, younger age, female sex, and serum FT4 levels remaining in the upper limits of the reference range. It has also been noted that serum TSH level measurements performed during the summer months more frequently show a tendency toward normal values [13].

Due to the high prevalence of this phenomenon, a watchful waiting approach is recommended in elderly patients with SCH. Prior to making a decision to initiate treatment, it is recommended to perform multiple verifications of the abnormal serum TSH levels (up to 3 times over a period of several months) [1,12]. The ETA guidelines recommend repeating the tests after 2-3 months [10]. Such a strategy may reduce the rate of SCH diagnoses and protect patients from initiating unjustified treatment.

Nevertheless, to precisely formulate criteria for completely withholding therapy in this age group, the scientific community still requires further prospective analyses evaluating the natural history of subclinical hypothyroidism in the older adult population [13].

9. Diagnosis of Primary Hypothyroidism

In accordance with the ETA and AACE/ATA guidelines, the cornerstone of the biochemical diagnosis of hypothyroidism is the measurement of serum TSH and FT4 levels. Additionally, to confirm the autoimmune etiology of the disease, measurement of anti-TPO antibody titers is recommended [10,11].

The diagnostic criteria for hypothyroidism (both overt and subclinical) are consistent across the European and American guidelines. Overt hypothyroidism is diagnosed based on an elevated serum TSH level with a concurrent decrease in serum FT4 level below the lower limit of the normal range. In turn, the SCH is characterized by an elevated serum TSH level with a normal serum FT4 level (typically at the lower end of the reference range) [10,11]. Furthermore, the ETA guidelines stratify SCH into a mild form (TSH levels ranging from 4.0 to 10.0 mIU/L) and a severe form (TSH >10.0 mIU/L) [10].

Both European and American guidelines place a strong emphasis on the distinct interpretation of laboratory findings in geriatric patients. Both documents highlight the influence of the aging process on TSH values [10,20]. The ETA recommendations advocate the necessity of utilizing age-specific TSH reference ranges, provided such data are available for the specific population [10]. ATA/AACE experts emphasize that the diagnosis in older adults must be highly

individualized to avoid erroneously categorizing natural age-related changes as pathology [11,20].

10. Treatment of Primary Hypothyroidism

Current expert consensus statements (both European and American) agree that the gold standard in the treatment of hypothyroidism is levothyroxine sodium (L-T4). This recommendation applies to all patients, regardless of age [20,21].

10.1. Treatment of Overt Hypothyroidism

In the event of a diagnosis of overt primary hypothyroidism, the initiation of pharmacotherapy is strictly indicated in every patient, regardless of baseline serum TSH levels. However, a significant difference in the geriatric population is the treatment initiation strategy itself. Guidelines unanimously recommend initiating therapy with very low doses of the drug, followed by a slow, gradual dose titration (in accordance with the "start low and go slow" principle) [11,21].

10.2. Treatment of Subclinical Hypothyroidism

The decision to initiate treatment depends on the patient's age and serum TSH levels. According to the ETA guidelines, in patients <65-70 years with a serum TSH levels >10 mIU/L, treatment initiation is recommended even in the absence of clinical symptoms. In the same age group, for serum TSH levels between 4.0-10.0 mIU/L, a therapeutic trial may be considered. Conversely, in patients >80-85 years with a serum TSH levels ≤10 mIU/L, continued observation of the patient and routine withholding of treatment are recommended in accordance with a "wait and see" strategy [10].

The American societies ATA/AACE present a very similar position. They recommend initiating therapy in individuals with a serum TSH levels >10 mIU/L, while exercising great caution in older patients. However, when the serum TSH level is <10 mIU/L, the decision regarding further management should be highly individualized, and routine treatment initiation is discouraged in the majority of older adults. In patients >80-85 years and older with a serum TSH levels ≤10 mIU/L, treatment is generally not indicated [11].

11. Levothyroxine Requirements and Dosing Regimens in Older Adults

The standard, full replacement dose of L-T4 for an adult patient is approximately 1.5 µg/kg/day according to the ETA, and approximately 1.6 µg/kg/day according to the ATA [20,21]. These

requirements decrease significantly in older individuals, primarily due to a physiological decline in lean body mass. Additionally, the drug's absorption and metabolism are influenced by malabsorption syndromes, comorbidities, dietary factors, and drug-drug interactions. Consequently, clinical guidelines indicate distinct regimens for the initiation of therapy. The ETA recommends initiating treatment in older patients at doses of 25-50 µg/day; the dose may be increased by 25 µg every 2-3 weeks based on laboratory test results [21]. Conversely, the ATA guidelines propose an even more conservative approach, suggesting a starting dose of 12.5-25 µg/day, with potential dose escalation at 4-6 week intervals [11,20].

12. Target Serum TSH Levels During Levothyroxine Therapy

According to the ETA, in individuals <65–70 years, the goal should be to maintain the serum TSH levels in the lower half of the reference range (i.e., approximately 0.4-2.5 mIU/L). For patients >70-75 years, this target range is accordingly 1.0-5.0 mIU/L. For the oldest patient cohort, exceeding 80-85 years, the guidelines refrain from establishing rigid boundaries, placing emphasis primarily on the avoidance of chronically suppressed TSH values [10].

The ATA and AACE recommendations stipulate that in the majority of adults, the serum TSH levels should fall within the range of 0.4-4.0 mIU/L. In individuals aged 70-80, it is acceptable to maintain higher values, in the range of 4.0-6.0 mIU/L. The American guidelines also do not specify a strict upper limit for the oldest-old [11,20].

Both societies (European and American) emphasize the need for the individualization of target serum TSH levels depending on the patient's age [10,20].

13. Monitoring Levothyroxine Therapy

According to the ETA guidelines, verification of serum TSH levels should take place 6-8 weeks after initiating treatment. In the event of a L-T4 dose adjustment, follow-up testing should be performed after approximately 2 months. Once the optimal medication dose is established and the patient achieves the target TSH level, routine monitoring of laboratory parameters on an annual basis is recommended [21].

The American guidelines suggest evaluating serum TSH levels 4-6 weeks following drug initiation or any dose modification. The first follow-up assessment after serum TSH stabilization should be conducted at 4-6 months, with subsequent evaluations performed annually [11,20].

14. Impact of Thyroid Hormones on Selected Organ Systems in Older Adults

Thyroid hormones play a fundamental role in modulating metabolic pathways and maintaining homeostasis. Their action determines the proper functioning of key organs and systems, including the cardiovascular system, the central nervous system, and the musculoskeletal system, as well as the regulation of the body's lipid and energy metabolism. A deficiency of these hormones can lead to widespread dysfunctions. In the geriatric population, assessing the actual impact of hypothyroidism on the body's functioning poses a significant diagnostic challenge. This is due to the fact that the symptoms of thyroid disorders frequently overlap with physiological aging processes or the clinical manifestations of comorbidities [1,3].

A breakthrough in verifying the rationale for treating SCH in older adults was provided by 2 large, randomized clinical trials: the Thyroid Hormone Replacement for Untreated Older Adults with Subclinical Hypothyroidism Trial (TRUST trial) and the study protocol for the Institute for Evidence-Based Medicine in Old Age 80-plus Thyroid Trial (IEMO 80-plus thyroid trial). The TRUST trial evaluated the impact of L-T4 replacement therapy on clinical outcomes in older adults with SCH. It was a multicenter, randomized, double-blind, placebo-controlled trial. A total of 737 participants aged 65 years and older with persistent SCH (defined as a serum TSH level ranging from 4.60 to 19.99 mIU/L, confirmed by at least 2 measurements taken 3 months to 3 years apart, with a normal serum FT4 level) were enrolled. In the levothyroxine group, the drug dose was titrated to achieve serum TSH levels within the reference range of 0.40–4.59 mIU/L. The follow-up period for participants ranged from 1 to 3 years. The efficacy of the treatment, both for L-T4 and placebo, was assessed using the Thyroid-Related Quality-of-Life Patient-Reported Outcome (ThyPRO) questionnaires, which included an evaluation of hypothyroid symptom severity and tiredness. Levothyroxine treatment did not yield a significant improvement in disease-related symptoms compared to placebo. Furthermore, no differences were demonstrated regarding secondary endpoints (general and thyroid-related quality of life, handgrip strength, executive functions, blood pressure values, body weight, body mass index, waist circumference, performance in basic and instrumental activities of daily living, and the incidence of cardiovascular events). The study results indicate a lack of significant clinical benefits derived from L-T4 treatment in older adults with SCH. There was also no observed increase in the incidence of hyperthyroid symptoms following the initiation of L-T4 therapy, nor a significant increase in the incidence of severe adverse events, such as atrial fibrillation, heart failure, fractures, or a new diagnosis of osteoporosis [6].

The IEMO 80-plus trial protocol was designed as a randomized, double-blind, placebo-controlled study aimed at evaluating the effects of L-T4 treatment in patients aged 80 years and

older with SCH. It served as a complementary study to the TRUST trial. Due to the highly similar methodology of both projects, a pooled analysis of the results was planned, encompassing the largest cohort studied to date of patients aged 80 years and older with SCH. Participants were to be randomly assigned to receive either L-T4 or placebo, with a follow-up period ranging from 1 to 3 years. The primary endpoint was defined as the assessment of changes in quality of life and the severity of thyroid-related symptoms using the ThyPRO questionnaire. Secondary endpoints included the evaluation of general and thyroid-related quality of life, cognitive function, handgrip strength, functional capacity, gait speed, the ability to live independently, and the incidence of falls. Furthermore, the analysis was planned to include changes in blood pressure values, body weight, height, waist circumference, and body mass index, as well as all-cause and cardiovascular mortality, and the incidence of fatal and non-fatal cardiovascular events [7].

Pooling the data from both of these studies (the TRUST trial and the IEMO 80-plus thyroid trial) enabled the largest analysis to date evaluating the effects of L-T4 treatment in patients aged 80 years and older. The obtained results conclusively demonstrated that L-T4 administration in this age group does not yield a significant improvement in hypothyroid-related symptoms or overall quality of life compared to placebo [22]. These conclusions are strongly supported by a comprehensive meta-analysis evaluating the effects of L-T4 therapy in a broader population of patients with SCH, which similarly failed to demonstrate clinically significant benefits of the treatment regarding muscle strength, body weight, blood pressure values, or the reduction of chronic fatigue [8].

14.1. Cardiovascular System

The association between SCH and cardiovascular risk in older adults remains inconclusive. On the one hand, it is hypothesized that thyroid hormone deficiency predisposes to cardiac complications. Conversely, a pooled analysis of individual patient data from the TRUST and IEMO 80-plus trials failed to demonstrate that L-T4 treatment in older adults reduces the risk of cardiovascular events or cardiovascular mortality [23]. Moreover, investigators warn that inappropriately managed hormone replacement therapy (both under- and overtreatment) may paradoxically induce complications, such as the exacerbation of heart failure symptoms or the onset of cardiac arrhythmias. For this reason, initiating L-T4 treatment solely for the purpose of cardiovascular prevention is currently not justified; however, concerns regarding potential complications should not preclude therapy in patients with clear clinical indications. It should be noted that despite the significance of the TRUST and IEMO 80-plus trials, there remains a

lack of multicenter trials with adequate statistical power to definitively determine the impact of treatment on hard cardiovascular endpoints [12,23].

14.2. Cognitive Function, Mood and Frailty Syndrome

Thyroid axis disturbances frequently coexist with neurocognitive deficits and mood disorders. Despite numerous neuropsychological assessments conducted in patients without baseline dementia, medical interventions to date have failed to demonstrate that the initiation of L-T4 treatment in patients with SCH completely reverses these deficits. Furthermore, in the population of individuals aged 75 years and older, a definitive causal relationship between mildly elevated serum TSH levels and the incidence of depression or dementia has not been established. This raises questions regarding the extent to which the observed changes result from thyroid pathology versus being an inherent component of the aging process [12]. Conversely, emerging reports suggest that the persistence of SCH in the oldest-old may constitute a physiological, protective adaptive mechanism, which is associated with better preservation of physical function and a reduced risk of developing frailty syndrome [1].

15. Management of Primary Hypothyroidism in Older Adults

15.1 Diagnostic Principles and the Watchful Waiting Approach

In the event of a diagnosis of SCH in older patients, prior to making a final decision regarding the initiation of pharmacotherapy, a reassessment of serum TSH and FT4 levels, along with the measurement of anti-TPO antibodies, is recommended. This approach is clinically justified by the high probability of spontaneous remission of the abnormalities and a return to euthyroidism. Follow-up laboratory testing should be conducted after a period of 2-3 months. An exception is made for patients with a baseline serum TSH level >15 mIU/L; in these individuals, testing should typically be repeated within 1-2 weeks [10,13].

Given the low risk of progression from SCH to the overt form of the disease, the preferred and safest approach in older adults is close observation without the initiation of L-T4 treatment [1]. A potential therapeutic trial may be considered only in selected patients presenting with overt clinical symptoms. Conversely, in patients with a severe form of SCH (TSH >10 mIU/L), the risk of progression to overt hypothyroidism increases, which generally justifies the necessity of initiating treatment [10].

15.2. Individualization of Therapy and the "Start Low and Go Slow" Principle

Therapy for hypothyroidism in the geriatric population requires a highly individualized approach. Clinical decisions must take into account the patient's age, the etiology of the disorder, the degree of serum TSH level, lean body mass, the presence of comorbidities, the phenomenon of polypharmacy, and the risk of developing frailty syndrome [3]. The initiation of treatment should be based on the "start low and go slow" principle: initiating therapy with minimal doses followed by slow and cautious up-titration. Such a strategy is particularly crucial in the oldest-old and in patients with a history of cardiovascular disease. It must be emphasized that elderly patients are characterized by a significantly higher susceptibility to adverse effects resulting from iatrogenic thyroid hormone excess [20].

15.3. The Need to Update Guidelines Based on New Research Findings

With regard to SCH in older adults, definitive criteria for the initiation of replacement therapy have yet to be established. The results of randomized clinical trials to date have failed to demonstrate significant benefits of treating SCH in patients aged 65 years and older; conversely, complications associated with overtreatment are more frequently observed in this cohort [1,6,12,13]. There remains a paucity of large-scale randomized controlled trials necessary to determine optimal target serum TSH levels, appropriate L-T4 dosages, potential therapeutic benefits, and the impact of patient age on treatment goals [1,12,13].

A fundamental issue raised in the literature, highlighting the urgent need for guideline revision, is the lack of routine implementation of age-specific serum TSH reference ranges. Large-scale epidemiological analyses in the American population have conclusively demonstrated that the upper limit of normal for serum TSH level naturally shifts toward higher values in successive decades of life [9]. Unfortunately, there is still a lack of large, long-term randomized controlled trials that would allow for the definitive establishment of optimal and safe therapeutic targets accommodating this physiological process [12]. Given these numerous controversies, regular monitoring of thyroid parameters in older adults remains a crucial tool in preventing the iatrogenic complications of pharmacotherapy [3].

16. Conclusions

With the progressive aging of populations, hypothyroidism is becoming an increasingly common clinical challenge in geriatric practice. As unequivocally indicated by the guidelines of scientific societies, the diagnostic and therapeutic management of elderly patients requires individualization. This is due to the high prevalence of comorbidities, polypharmacy, and an

increased susceptibility to adverse effects of treatment. A key diagnostic challenge is the phenomenon of the age-related increase in serum TSH levels. The application of universal serum TSH reference ranges for all adults leads to overdiagnosis of the disease, erroneously categorizing the body's natural adaptive processes as pathology.

A review of the current literature demonstrates that routine L-T4 replacement therapy in older patients with SCH does not yield significant clinical benefits. Furthermore, in this age group, hormonal overtreatment carries a greater risk of iatrogenic complications. Therefore, the routine implementation of pharmacotherapy in this subpopulation currently lacks sufficient justification.

Despite a growing body of research, widely accepted, age-validated serum TSH reference ranges and target TSH values during L-T4 therapy have yet to be established. This issue is of fundamental importance, as adopting the appropriate normal range determines the rate of diagnosis and directly influences the decision to initiate treatment.

In conclusion, current scientific evidence does not allow for the establishment of a fully optimized and universal management strategy for older adults with hypothyroidism, particularly within the oldest-old cohort. Further large-scale randomized controlled trials involving this specific population are warranted. These would enable the evaluation of the impact of L-T4 treatment on hard endpoints and the determination of age-adjusted serum TSH reference ranges. There is also still a lack of precise clinical criteria to identify the narrow subset of patients who could derive genuine benefit from hormone replacement therapy.

Until new scientific evidence is acquired and recommendations are subsequently updated, therapeutic decisions should remain highly individualized and based on current international guidelines.

Disclosures

Author's contribution:

Conceptualization: AM, MS, PZ; Methodology: AM, AZ, AGS, GS; Software: AK, AT, HL; Check: AZY, MŁ; Formal analysis: AM, AZY, MŁ; Investigation: MS, AT, HL; Resources: GS, AGS, AZ; Data curation: AM, PZ, MS; Writing-rough preparation: AK; Writing -review and editing: AM, PZ, AZ, AGS; Visualization: AZY, GS, AT; Supervision: AK, HL, MŁ; Project administration: AM, HL, AZY

Funding Statement: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: Not applicable.

Conflict of Interest Statement: The authors declare no conflicts of interest.

All authors have read and agreed with the published version of the manuscript.

Declaration of the use of generative AI and AI-assisted technologies in the writing process. In preparing this work, the authors used ChatGPT and Gemini Pro for the purpose of improving language and readability. After using this tool, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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