

ORIGINAL ARTICLE

Subclinical Thyroid Dysfunction: When to treat and when to observe. A comprehensive clinical review

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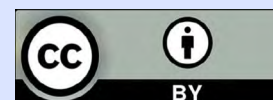
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relevant publications not captured by the database search.

Inclusion and Exclusion Criteria

Publications were considered eligible if they met the following criteria: (1) primary study, systematic review, meta-analysis, or evidence-based guideline addressing the diagnosis, natural history, or management of subclinical thyroid dysfunction in adults; (2) use of biochemical definitions consistent with current standards (TSH outside the reference range with normal FT4 and FT3); (3) reporting of clinically relevant outcomes including cardiovascular events, mortality, bone mineral density, quality of life, symptom burden, or obstetric outcomes. Exclusion criteria included: case reports and case series with fewer than ten participants; studies conducted exclusively in paediatric populations; publications addressing overt thyroid dysfunction as the primary condition; non-peer-reviewed opinion pieces without reference to primary evidence; and duplicate publications reporting the same dataset as a previously identified article.

KEYWORDS

subclinical hypothyroidism; subclinical hyperthyroidism; TSH; thyroid-stimulating hormone; levothyroxine; anti-TPO antibodies; atrial fibrillation; osteoporosis; pregnancy; watchful waiting

ABSTRAKT

Subclinical thyroid dysfunction (STD) - encompassing subclinical hypothyroidism (SCH) and subclinical hyperthyroidism (SHT) - represents one of the most prevalent and clinically nuanced endocrine conditions encountered in general practice. Defined by abnormal serum thyroid-stimulating hormone (TSH) levels in the presence of normal free thyroxine (FT4) and free triiodothyronine (FT3), these conditions affect an estimated 5-10% of the general adult population, with disproportionately higher prevalence among women and individuals over the age of 65. The fundamental clinical dilemma lies in determining when pharmacological intervention is warranted versus when a strategy of watchful waiting is more appropriate. Premature or indiscriminate treatment carries its own risks - iatrogenic hyperthyroidism, bone loss, and cardiovascular strain - while untreated dysfunction may progress to overt disease or silently contribute to metabolic, cardiac, or cognitive morbidity.

This review synthesizes current evidence and reconciles the recommendations of major international bodies - the American Thyroid Association (ATA), the European Thyroid Association (ETA), and the Polish Society of Endocrinology (PTE) - to present a practical, patient-centered decision framework. Special emphasis is placed on age-adapted TSH reference ranges, the distinct risks posed by each form of STD, and the clinical circumstances that should guide individualized management. The overarching conclusion is that rigid, threshold-based decision-making is insufficient; instead, treatment decisions must integrate TSH magnitude, clinical symptoms, comorbidities, patient age, reproductive status, and serological markers such as anti-thyroid peroxidase (anti-TPO) antibodies.

This narrative review pursues five principal objectives:

- (1) To critically evaluate the clinical significance of subclinical thyroid dysfunction - encompassing both subclinical hypothyroidism (SCH) and subclinical hyperthyroidism (SHT) - as defined by current biochemical and clinical criteria, with particular attention to the limitations of TSH-based diagnosis.
- (2) To synthesize and compare the recommendations of three major international guideline bodies - the American Thyroid Association (ATA), the European Thyroid Association (ETA), and the Polish Society of Endocrinology (PTE) - identifying points of consensus and areas of divergence that have direct implications for clinical practice.
- (3) To identify and characterize the patient subgroups most likely to derive clinically meaningful benefit from pharmacological intervention, distinguishing these from populations in whom watchful waiting constitutes the more appropriate evidence-based strategy.
- (4) To present a patient-centered, individualized decision framework that integrates TSH magnitude, symptom burden, comorbidity profile, anti-TPO antibody status, patient age, and reproductive status into coherent and actionable clinical guidance.
- (5) To address the specific management challenges posed by high-priority subpopulations - including pregnant women, individuals planning conception, and the very elderly - in whom standard algorithms require substantial modification to reflect underlying physiology and outcome data.

Search Strategy and Information Sources

This review was conducted in accordance with the PRISMA-ScR framework for narrative review methodology. A systematic search of three major biomedical databases was performed: MEDLINE (via PubMed), EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search covered publications from database inception through December 2024. Reference lists of included systematic reviews and practice guidelines were hand-searched to identify additional

Chapter 1 - Introduction

Definition of Subclinical Thyroid Dysfunction

Thyroid function is classically assessed through a triad of hormonal measurements: TSH (thyroid-stimulating hormone), FT4 (free thyroxine), and FT3 (free triiodothyronine). In overt thyroid disease, all three markers deviate from their reference ranges in a clinically predictable pattern. Subclinical thyroid dysfunction, however, occupies an intermediate state: TSH is outside the normal range, while FT4 and FT3 remain within laboratory reference limits - typically 0.8–1.8 ng/dL for FT4 and 2.3–4.1 pg/mL for FT3.

Subclinical Hypothyroidism (SCH) is characterized by an elevated TSH, most commonly defined as exceeding 4.5 mIU/L, in the context of normal FT4 and FT3. The degree of TSH elevation further stratifies SCH into mild (TSH 4.5–10 mIU/L) and severe (TSH >10 mIU/L) forms, with important therapeutic implications.

Subclinical Hyperthyroidism (SHT) is defined by a suppressed TSH, typically below 0.4 mIU/L, with normal FT4 and FT3. A distinction is drawn between mild suppression (TSH 0.1–0.4 mIU/L) and severe suppression (TSH <0.1 mIU/L), the latter carrying substantially greater risk for adverse outcomes. SHT may be endogenous - arising from multimodular goiter or early Graves' disease - or exogenous, caused by over-replacement with levothyroxine.

It bears emphasis that the laboratory definition of STD, while diagnostically precise, does not automatically imply clinical significance. TSH values are subject to biological variation, pulsatile secretion, circadian rhythm, and assay-dependent differences, making a single measurement insufficient for diagnosis. International guidelines consistently recommend confirmation of STD with a repeated TSH measurement after a minimum of 2–3 months before initiating any therapeutic decision.

Epidemiology - Why It Matters

Subclinical thyroid dysfunction is not a clinical rarity. Large cross-sectional studies, including the landmark NHANES III survey and the Whickham Cohort Study from the United Kingdom, have established that SCH affects approximately 4–8% of the general population in iodine-sufficient regions, with prevalence rising sharply to 15–20% among women aged 60 and above. SHT is somewhat less common, present in approximately 1–2% of the adult population, though estimates vary based on iodine intake and assay sensitivity.

The sex disparity in thyroid pathology is well-documented: women are 5–10 times more likely than men to develop autoimmune thyroid disease, including the subclinical forms. This excess risk is driven by the interplay of hormonal, immunological, and genetic factors. Estrogen modulates immune tolerance, and transitions such as the postpartum period, perimenopause, and menopause are recognized as windows of vulnerability for thyroid dysfunction.

The aging population presents a distinct epidemiological challenge. Thyroid axis physiology changes with age: TSH levels naturally increase in older adults, partly due to altered iodothyronine metabolism and pituitary set-point recalibration. Consequently, what qualifies as subclinical hypothyroidism in a 35-year-old may represent a physiological variant in an 80-year-old. This observation has critical implications for the application of population-derived reference ranges to elderly patients.

From a public health standpoint, the sheer prevalence of STD mandates clarity in clinical guidance. A physician seeing 30 patients per week will encounter subclinical thyroid conditions several times monthly - often in asymptomatic individuals found on routine screening. The cost of universal treatment would be enormous and potentially harmful; the cost of universal neglect could be equally problematic for high-risk subgroups.

The Diagnostic Dilemma

The clinical tension surrounding subclinical thyroid dysfunction can be summarized succinctly: treating carries risk, not treating also carries risk. This bidirectional uncertainty is what distinguishes STD from more clear-cut clinical scenarios.

On the hypothyroid side, the physician's reluctance to treat stems from concerns about iatrogenic hyperthyroidism - a state that can accelerate atrial fibrillation, reduce bone density, and paradoxically increase cardiovascular mortality in the very patients one aims to protect. In elderly patients with borderline TSH elevation, the risks of over-treatment may outweigh any potential benefit.

On the hyperthyroid side, the risk of aggressive intervention with antithyroid drugs or radioiodine must be balanced against the spontaneous resolution rate of SHT, which can reach 30–40% within 12 months for mild endogenous cases. Premature treatment forecloses the possibility of natural remission.

Simultaneously, undertreatment carries its own burden. Subclinical hypothyroidism - particularly at TSH >10 mIU/L - has been associated with elevated LDL cholesterol, impaired myocardial function, and increased cardiovascular event rates in meta-analyses.

Subclinical hyperthyroidism carries a well-quantified risk of atrial fibrillation, with relative risk estimates ranging from 1.5 to 3.1 in prospective studies, and of osteoporotic fractures, particularly in postmenopausal women.

This review is structured to navigate that dilemma systematically - by condition type, by TSH severity, by patient age, and by comorbidity profile - ultimately arguing for a model of individualized, evidence-based clinical judgment over algorithmic uniformity.

Chapter 2 - Subclinical Hypothyroidism - To Treat or to Observe?

The „Rule of 10”: TSH >10 mIU/L as an Absolute Indication

A widely adopted clinical heuristic - informally termed the „Rule of 10” - holds that a confirmed TSH exceeding 10 mIU/L constitutes an absolute indication for levothyroxine (LT4) therapy, regardless of patient age, symptom burden, or anti-TPO status. This threshold is supported by the convergent recommendations of the ATA, ETA, and PTE, and is grounded in a substantial body of evidence linking severe subclinical hypothyroidism to adverse cardiovascular outcomes.

A 2010 meta-analysis by Rodondi and colleagues, published in JAMA, pooled individual patient data from 55,287 adults across 11 prospective cohorts. The analysis demonstrated a statistically significant and graded association between increasing TSH and the risk of coronary heart disease events and coronary mortality, with the most pronounced risk in patients with TSH >10 mIU/L. Relative risks for coronary heart disease events in this group were comparable to those associated with traditional cardiovascular risk factors.

Mechanistically, the cardiovascular harm of severe SCH is multifactorial. Thyroid hormone exerts direct inotropic and chronotropic effects on the myocardium, regulates vascular smooth muscle tone, and modulates lipid metabolism. In the hypothyroid state, systemic vascular resistance increases, cardiac output decreases, and LDL cholesterol rises - a constellation that accelerates atherogenesis and predisposes to heart failure. Echocardiographic studies have documented diastolic dysfunction and impaired left ventricular relaxation even in patients with TSH values between 5 and 10 mIU/L.

For TSH >10 mIU/L, the evidence base is sufficiently robust that therapeutic intervention is recommended across all major guidelines, with the target of

restoring TSH to the age-appropriate reference range. Levothyroxine initiation is typically at low doses (25–50 mcg/day) with titration every 6–8 weeks until the therapeutic target is achieved.

The Grey Zone: TSH Between 4.5 and 10 mIU/L

The most contested territory in the management of SCH lies within the range of TSH 4.5–10 mIU/L - a zone where the absolute cardiovascular risk is lower, spontaneous normalization is common (occurring in up to 40% of cases within 2 years), and the evidence for treatment benefit is heterogeneous. Clinical decision-making in this range must be tailored to the individual patient.

When to Treat

Several clinical profiles within the mild SCH range provide grounds for initiating LT4 therapy:

- **Young patients (<45 years):** The longitudinal risk of progression to overt hypothyroidism is highest in this group, particularly those with detectable anti-TPO antibodies. The benefits of treatment in terms of symptom relief, fertility optimization, and cardiovascular risk reduction outweigh the risks of iatrogenic hyperthyroidism when therapy is carefully monitored.
- **Patients planning pregnancy or currently pregnant:** The thyroid axis is uniquely critical during gestation. Maternal hypothyroxinemia - even subclinical - has been linked to reduced fertility, increased miscarriage rates, gestational hypertension, preterm delivery, and impaired neurodevelopmental outcomes in offspring. This population warrants early treatment initiation (see Section 4.1).
- **Symptomatic patients:** Fatigue, cold intolerance, constipation, weight gain, myalgia, and depressive symptoms - when attributable to thyroid dysfunction after excluding other causes - justify a therapeutic trial of LT4. Response to treatment, assessed at 3–6 months, serves both therapeutic and diagnostic purposes.
- **Elevated anti-TPO antibodies:** The presence of high-titer anti-TPO antibodies indicates active autoimmune thyroiditis (Hashimoto's disease) and dramatically increases the annual risk of progression to overt hypothyroidism (from approximately 2% to 4–5% per year). Some guidelines recommend treatment in anti-TPO-positive patients even with TSH in the 4.5–7 mIU/L range.
- **Patients with dyslipidemia or established cardiovascular risk:** Given the lipid-modulating effects of thyroid hormone, SCH in patients with concurrent

hypercholesterolemia, coronary artery disease, or heart failure may benefit from LT4 therapy as an adjunct to lipid-lowering treatment.

When to Observe

Conversely, a strategy of watchful waiting - active, structured monitoring without pharmacological intervention - is appropriate in the following scenarios:

- **Elderly patients (>65–70 years):** As discussed in Section 2.3, TSH reference ranges shift upward with age. In older adults, mildly elevated TSH may represent adaptive physiology rather than pathology. The TRUST trial (2017), a randomized placebo-controlled trial in patients over 65 with SCH, found no significant improvement in fatigue, quality of life, or cognitive function with LT4 therapy over placebo. This landmark study has substantially tempered enthusiasm for treating mild SCH in the elderly.
- **Asymptomatic patients:** In the absence of symptoms attributable to hypothyroidism, the risk-benefit calculus favors observation, particularly given the high rate of spontaneous normalization. Annual TSH retesting is sufficient to identify patients who progress.
- **Fluctuating TSH values:** TSH has substantial intra-individual variability. A TSH value marginally above the upper limit of normal that normalizes on repeat testing 3 months later does not represent true SCH and should not trigger treatment. Only confirmed, persistent elevation warrants clinical response.
- **Recent acute illness or medication changes:** TSH can be transiently disrupted by intercurrent illness, caloric restriction, glucocorticoid use, or iodine-containing contrast media. Repeating the measurement after recovery is essential before concluding that SCH is present.

Age-Specific TSH Reference Ranges

One of the most important yet underappreciated aspects of subclinical hypothyroidism management is the recognition that the „normal” TSH range is not fixed - it shifts systematically across the lifespan. The population-derived reference interval of 0.4–4.5 mIU/L was established primarily from studies of middle-aged adults and may not be appropriate for applying to other age groups.

In children and adolescents, TSH values are naturally higher during infancy and early childhood, gradually declining to adult levels by late adolescence. In neonates,

TSH may normally exceed 20 mIU/L in the first 48 hours of life before falling rapidly.

In adults under 45, the standard reference range applies with confidence. The upper limit of normal in this age group is approximately 4.0–4.5 mIU/L in most high-quality population studies excluding those with thyroid autoimmunity.

In adults aged 45–55, the TSH distribution shifts incrementally upward. The 97.5th percentile of TSH in healthy adults aged 60–70 is approximately 5.8–6.2 mIU/L in iodine-sufficient populations. This shift reflects a combination of decreased metabolic clearance of TSH, altered feedback sensitivity, and subclinical autoimmune thyroid burden accumulated over decades.

In adults over 70, the physiological TSH upper limit may approach 6–7 mIU/L. In the oldest-old (85+), several studies have documented a paradoxical relationship between TSH and mortality: higher TSH values are associated with better survival outcomes - a finding consistent with data from supercentenarian cohorts showing that exceptional longevity is associated with mildly elevated TSH (see Section 4.2).

The practical implication is straightforward: a TSH of 5.8 mIU/L in a 78-year-old asymptomatic woman should not automatically trigger levothyroxine initiation. Rather, the clinician must apply age-adjusted interpretation and resist the temptation to treat a number rather than a patient.

Chapter 3 - Subclinical Hyperthyroidism - Managing the Risks

Thresholds of Suppression - Mild vs. Severe

Subclinical hyperthyroidism is defined by a suppressed TSH with normal FT4 and FT3. Its clinical significance depends critically on the degree of TSH suppression, which serves as a surrogate marker of the intensity of thyroid hormone excess at the tissue level - even when circulating hormone concentrations remain nominally within the reference range.

Mild suppression, defined as TSH 0.1–0.4 mIU/L, carries a substantially lower risk profile than severe suppression. The pituitary TSH signal remains partially intact, thyroid hormone production is only modestly above homeostatic requirements, and the rate of progression to overt hyperthyroidism is low. Spontaneous resolution occurs in approximately 30–40% of cases within 12–18 months, particularly in young patients with no structural thyroid disease.

Severe suppression, defined as TSH <0.1 mIU/L, is associated with a markedly different risk trajectory. At this degree of suppression, clinically significant thyroid hormone excess is more likely, the probability of progression to overt hyperthyroidism is higher, and the risks of cardiac and skeletal complications are substantially elevated. This distinction drives the fundamentally different management approaches recommended for the two subgroups.

Etiological classification is also relevant. Endogenous SHT (arising from multinodular goiter, toxic adenoma, or early Graves' disease) is distinguished from exogenous SHT (over-treatment with levothyroxine in patients with hypothyroidism or thyroid cancer). Exogenous SHT requires dose adjustment of LT4 rather than antithyroid medication, though the systemic risks are similar.

Primary Concerns - Atrial Fibrillation and Osteoporosis

The two principal adverse outcomes of subclinical hyperthyroidism are atrial fibrillation (AF) and osteoporosis - both of which can cause irreversible harm before overt symptoms develop. Understanding these risks is essential for individualizing treatment decisions.

Atrial Fibrillation

The association between SHT and AF is well-established. Thyroid hormone exerts potent chronotropic and pro-arrhythmic effects on the myocardium, including shortening of the atrial effective refractory period, enhancement of adrenergic sensitivity, and up-regulation of beta-adrenergic receptors. Even marginally elevated FT3 and FT4 within the normal reference range may produce cumulative electrophysiological changes.

The Cardiovascular Health Study, a prospective observational study of 3,233 adults aged 65 and over, found that patients with TSH <0.1 mIU/L had a three-fold higher risk of incident AF compared to euthyroid controls over a 10-year follow-up period. The risk was attenuated but still statistically significant for mild SHT. The absolute risk increase was greatest in patients over 60 - reinforcing age as a paramount risk modifier.

Once AF is established, its management becomes substantially more complex, requiring anticoagulation, rate or rhythm control, and long-term follow-up. Prevention through timely management of SHT is therefore not merely a symptomatic strategy but a clinically meaningful intervention to reduce overall morbidity.

Osteoporosis

Thyroid hormone stimulates osteoclast activity, accelerating bone resorption and reducing bone mineral density (BMD). In premenopausal women and men, skeletal homeostasis can compensate for mild thyroid hormone excess through increased osteoblast activity. However, in postmenopausal women - who lack estrogen's protective effect on bone - SHT can tip the balance decisively toward net bone loss.

Multiple meta-analyses have demonstrated that postmenopausal women with SHT (TSH <0.1 mIU/L) have significantly lower BMD at both the femoral neck and lumbar spine, and a relative risk of hip fracture approximately 1.4–2.0 times higher than euthyroid controls. The magnitude of BMD loss correlates with the duration and severity of TSH suppression.

In clinical practice, this means that bone densitometry (DEXA scan) should be considered in postmenopausal women with confirmed SHT, and that the finding of established osteopenia or osteoporosis substantially strengthens the case for therapeutic intervention.

Decision Matrix - Treatment vs. Monitoring

The decision to initiate antithyroid therapy versus monitoring should integrate SHT severity, patient age, and the presence of risk factors for AF or osteoporosis. The following matrix reflects the synthesis of current guidelines:

Severe SHT (TSH <0.1 mIU/L). Treatment is generally recommended for all patients aged over 65, for younger patients with cardiac disease, arrhythmia, or osteoporosis, or for any patient with symptoms suggestive of hyperthyroidism. The therapeutic modality depends on etiology: antithyroid drugs for Graves' disease, radioiodine ablation for autonomous nodular disease, and dose reduction for exogenous SHT.

Mild SHT (TSH 0.1–0.4 mIU/L). For patients over 65 with TSH below 0.4 mIU/L, the ATA and ETA recommend treatment if one or more risk factors are present (age >65 , osteoporosis, cardiac disease, or symptoms). Younger, asymptomatic patients without risk factors may be monitored with TSH, FT4, and FT3 every 3–6 months, with treatment initiated if TSH declines below 0.1 mIU/L or symptoms develop.

Monitoring protocol. For patients in the observation arm, standardized follow-up is mandatory. TSH should be retested at 3-month intervals during the first year, and 6-monthly thereafter if stable. Any deterioration - worsening TSH suppression, new symptoms, de-

velopment of cardiac arrhythmia, or significant BMD change - should prompt reassessment of the treatment decision.

Chapter 4 - Special Populations

Pregnancy and Fertility - The Most Rigorous Standards

No clinical context demands more rigorous thyroid hormone management than pregnancy and the periconceptional period. The developing fetus depends entirely on maternal thyroid hormones during the first trimester, before its own thyroid gland becomes functional (approximately at 10–12 weeks of gestation). Even mild maternal hypothyroxinemia during this critical window can impair fetal neural migration, myelination, and cognitive development - effects that may not be clinically apparent until later childhood.

The thyroid axis undergoes substantial physiological adaptation during normal pregnancy: hCG (human chorionic gonadotropin), which surges in the first trimester, has TSH-like agonist activity and physiologically suppresses TSH. Simultaneously, thyroxine-binding globulin (TBG) levels increase due to estrogen-stimulated hepatic synthesis, raising total thyroid hormone levels while FT4 may fall slightly. These changes necessitate trimester-specific TSH reference ranges rather than the application of standard population norms.

Both the ATA (2017 guidelines) and the ETA advocate the following TSH targets during pregnancy: First trimester: 0.1–2.5 mIU/L; Second trimester: 0.2–3.0 mIU/L; Third trimester: 0.3–3.0 mIU/L. Women with TSH exceeding 2.5 mIU/L in the first trimester who are anti-TPO-positive are recommended to initiate LT4 therapy, given the substantially elevated risk of adverse obstetric outcomes in this subgroup.

For women with pre-existing SCH who are planning conception, preconception optimization of TSH is strongly advised. LT4 doses typically require an increase of 25–30% upon confirmed pregnancy, and TSH monitoring should occur every 4 weeks throughout the first half of pregnancy and at 26–28 weeks.

Subclinical hyperthyroidism in pregnancy presents a different challenge. Mild first-trimester SHT, often driven by gestational hCG stimulation, is frequently transient and does not require treatment. Persistent SHT beyond 16–20 weeks, or severe suppression (TSH <0.1 mIU/L) attributable to Graves' disease, requires careful evaluation given the risks of antithyroid drugs

to the fetus, particularly propylthiouracil (PTU) in the first trimester and methimazole thereafter.

The Elderly (80+) - Rethinking the TSH Paradigm

The management of subclinical thyroid dysfunction in the very elderly - particularly those aged 80 and above - represents perhaps the most significant departure from conventional thyroid guidelines. Emerging evidence suggests that for this population, the conventional approach to TSH normalization may not only be unnecessary but potentially harmful.

The Leiden 85-Plus Study, a prospective observational study of 599 Dutch individuals followed from age 85, found that high-normal and mildly elevated TSH values were associated with better physical performance, lower all-cause mortality, and superior cognitive function at 10-year follow-up. Participants in the highest TSH quartile had survival curves strikingly superior to those with lower TSH, even after adjustment for confounders.

Similarly, studies of centenarians and supercentenarians across multiple populations - including Italian, Danish, and Japanese cohorts - have consistently reported that extreme longevity is associated with mildly elevated TSH (typically 3–8 mIU/L) and modestly lower FT3 levels. This phenotype appears to represent an adaptive metabolic slowing that reduces oxidative stress, preserves mitochondrial function, and mitigates the wear-and-tear of high metabolic rates associated with normal or low TSH.

The mechanistic hypothesis is that mild thyroid hormone restriction in late life activates conserved longevity pathways - including FOXO transcription factors, sirtuins, and mTOR inhibition - that are associated with extended lifespan in multiple model organisms.

The clinical implication is clear: in asymptomatic individuals aged 80 or above with TSH values up to 7–8 mIU/L, watchful waiting is not merely acceptable - it may be actively beneficial. The risks of LT4 therapy in this group, including precipitation of AF, acceleration of bone loss, and the not-insignificant risk of over-treatment errors in frail patients taking multiple medications, argue strongly against treatment in the absence of compelling symptoms or very high TSH (>10 mIU/L).

For patients in this age group already established on LT4 therapy, it is appropriate to reassess the indication and, if necessary, carefully reduce the dose to allow TSH to rise into the age-appropriate physiological range. This „de-prescribing” approach is increasingly recognized as an important component of geriatric pharmacological stewardship.

Chapter 5 - Guidelines Synthesis

Comparison of International Standards: ATA, ETA, and PTE

The management of subclinical thyroid dysfunction is governed by guidelines from several authoritative organizations, each reflecting the evidence base, healthcare system context, and expert consensus at the time of publication. While the fundamental principles are broadly concordant, meaningful differences exist in specific thresholds, populations prioritized, and the emphasis placed on individualized decision-making versus algorithmic guidance.

The table below provides a structured comparison of the key recommendations from the American Thyroid Association (ATA), the European Thyroid Association (ETA), and the Polish Society of Endocrinology (Polskie Towarzystwo Endokrynologiczne, PTE): Despite these differences, several principles are universally endorsed: the requirement for confirmation of STD with repeated testing before treatment initiation; the use of age-adapted TSH interpretation; the recognition of pregnancy as a high-priority indication for early intervention; and the legitimacy of watchful waiting as an active, structured clinical strategy in appropriate patients.

The PTE guidelines are notable for their explicit acknowledgment of the Polish epidemiological context - historically mild iodine deficiency in parts of Poland increases the prevalence of nodular thyroid disease,

which is a common cause of endogenous SHT. Polish guidelines therefore give particular attention to thyroid ultrasound evaluation in the workup of SHT to identify structural causes amenable to definitive treatment.

Chapter 6 - Conclusions

Individualization Over Rigidity

The central conclusion of this review is that subclinical thyroid dysfunction demands individualized clinical reasoning, not algorithmic uniformity. The patient population affected by STD spans the full spectrum of age, comorbidity, reproductive status, and symptom burden - and a single management protocol cannot serve all of them equally well.

The evidence robustly supports treatment for: TSH >10 mIU/L (in virtually all patients); any degree of SCH or SHT in pregnancy; mild SCH in young, symptomatic, or anti-TPO-positive patients; and SHT with TSH <0.1 mIU/L in patients over 65 or with cardiac or skeletal risk factors.

Conversely, the evidence supports watchful waiting for: mild SCH in asymptomatic patients over 70; fluctuating TSH at marginally abnormal levels; mild SHT in asymptomatic young patients without structural thyroid disease; and all STD in the context of acute illness or recent medication changes.

Table 1. Comparison of ATA, ETA, and PTE recommendations for subclinical thyroid dysfunction management. SCH = subclinical hypothyroidism; SHT = subclinical hyperthyroidism; AF = atrial fibrillation; anti-TPO = anti-thyroid peroxidase antibodies; T1/T2/T3 = first/second/third trimester

Parameter	ATA (USA)	ETA (Europe)	PTE (Poland)
SCH treatment threshold	TSH >10 mIU/L (absolute); consider if TSH 5-10 + symptoms/risk factors	TSH >10 mIU/L absolute; TSH 4-10 if age <65, positive anti-TPO, or symptoms	TSH >10 mIU/L; individualized decision for TSH 4.5-10 based on clinical profile
SHT treatment threshold	TSH <0.1 with age >65 or AF/osteoporosis risk; mild SHT: watchful waiting	TSH <0.1; treat in >65 y/o or if high AF/bone fracture risk. TSH 0.1-0.4: monitor	Consistent with ETA; emphasize risk stratification before initiating treatment
Pregnancy TSH targets	T1: <2.5 mIU/L; T2-T3: <3.0 mIU/L; treat if TSH >2.5 + anti-TPO+	T1: 0.1-2.5 mIU/L; T2: 0.2-3.0; T3: 0.3-3.0; anti-TPO+ lowers threshold	Follows ATA/ETA; strong recommendation to screen all pregnant women
Elderly TSH targets (>70 y/o)	Accept TSH up to 6-7 mIU/L; avoid over-treatment; reassess annually	Age-adjusted upper limit; TSH up to 7 mIU/L in >80 y/o considered physiological	Cautious approach; higher TSH tolerance; monitor for CV symptoms
Monitoring interval (observation)	Every 6-12 months for stable SCH; 3-6 months for SHT or recent change	6-12 months SCH; 3-6 months for SHT; repeat testing if borderline results	6 months initial; annually if stable; 3 months if symptomatic or changing

„Watchful Waiting” as an Active Medical Strategy

„Watchful waiting” is sometimes mischaracterized as clinical inaction - a failure to commit. In the context of subclinical thyroid dysfunction, it is precisely the opposite. Structured observation is an active, evidence-based strategy that requires the clinician to: define the monitoring protocol (interval, tests); communicate clearly with the patient about the rationale for observation; identify predefined trigger criteria that would warrant reassessment; and follow through with scheduled re-evaluation.

The TRUST trial demonstrated that watchful waiting in older patients with mild SCH is not inferior to LT4 therapy in terms of patient-reported outcomes. This evidence should embolden clinicians to resist the societal and systemic pressures toward over-treatment, and to have clear, reassuring conversations with patients about why observation is the appropriate choice for them at this time.

At the same time, watchful waiting must never become passive neglect. A patient placed in the observation arm without a follow-up plan is not receiving watchful waiting - they are receiving no care. The structured nature of the observation is its defining feature and its therapeutic value.

Future Directions

Several important questions in the management of subclinical thyroid dysfunction remain unresolved and require further investigation. Large randomized controlled trials are needed to evaluate the effect of LT4 therapy on cardiovascular outcomes in younger adults with mild SCH and elevated anti-TPO - a population in which the TRUST trial provides limited guidance. The TEMPO and TRUST-2 trials currently in progress may address some of these gaps.

The development and validation of age-specific, sex-specific, and potentially ethnicity-specific TSH reference ranges remains an important priority. Adoption of such ranges in clinical laboratories would substantially reduce the number of patients incorrectly categorized as having subclinical dysfunction.

Finally, biomarker research into predictors of spontaneous normalization versus progression - incorporating genetic markers such as HLA haplotypes, epigenetic thyroid autoimmunity signatures, and metabolomic profiling - may eventually allow clinicians to stratify patients far more precisely than current TSH-based thresholds permit.

Summary Statement

Subclinical thyroid dysfunction sits at the intersection of endocrinology, cardiology, geriatrics, and reproductive medicine. Its management challenges clinicians to integrate biochemical data with clinical context, to resist the impulse to treat a laboratory value rather than a patient, and to recognize that the most sophisticated medical decisions are often those that choose judicious observation over reflexive intervention.

The framework presented in this review - grounded in the convergent guidance of ATA, ETA, and PTE, enriched by the latest evidence on age-specific physiology, and anchored in the principle of patient-centered individualization - provides a foundation for confident, defensible, and compassionate clinical practice in this complex and prevalent condition.

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