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REVIEW

Subtle variations in thyroid-stimulating hormone within the normal range: biological mechanisms, microvascular effects, and clinical relevance in euthyroid adults

Oana-Cristina Cînpeanu[1*], Lorand Ferencz[2]

[1] Doctoral School, IOSUD, G.E. Palade University of Medicine, Pharmacy, Sciences and Technology of Targu Mures, 540139 Târgu Mureş, Romania
[2] Department of Hygiene, G.E. Palade University of Medicine, Pharmacy, Sciences and Technology of Targu Mures, 540142 Targu Mures, Romania

ABSTRACT

Objective: This review synthesizes the mechanistic pathways linking high-normal thyroid-stimulating hormone levels with low-grade inflammation, microvascular endothelial reactivity, and adipocyte physiology in euthyroid adults.

Methods: Recent literature investigating physiological thyroid-stimulating hormone fluctuations within the reference interval of zero point four to four point zero milli-international units per liter was synthesized. Evidence from physiological, clinical, and Mendelian randomization studies was analyzed to distinguish direct hormonal effects from secondary metabolic responses.

Results: Elevated thyroid-stimulating hormone levels in the upper normal range often represent a secondary neuroendocrine response to visceral adiposity and central leptin adaptation rather than primary thyroid failure. At the tissue level, thyroid-stimulating hormone directly interacts with adipocyte receptors to modulate lipogenesis, pre-adipocyte differentiation, and local insulin sensitivity. Concurrently, high-normal levels correlate with subtle markers of microvascular dysfunction and systemic inflammation. Mendelian randomization indicates that while overall adiposity causally increases thyroid-stimulating hormone levels, high-normal levels act primarily as a downstream biomarker of metabolic stress rather than a primary driver of cardiovascular disease.

Conclusions: High-normal thyroid-stimulating hormone is best understood as an integrated metabolic biomarker rather than a target for hormonal intervention. Recognizing these connections helps clinicians contextualize subtle endocrine variations without altering standard treatment thresholds.

Keywords: euthyroid, microvascular reactivity, adipose tissue, low-grade inflammation, cardiometabolic risk.

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Introduction

For decades, clinicians have evaluated thyroid function in routine practice almost exclusively using population-based reference intervals, setting conventional boundaries for serum TSH between 0.4 and 4.0 mIU/L. Clinicians routinely classify patients whose laboratory measurements fall within this range as euthyroid, under the implicit assumption that their hypothalamic-pituitary-thyroid axis functions optimally and poses no additional risk to systemic metabolic equilibrium [1]. However, complex biological systems rarely conform strictly to broad population cutoffs. Each individual possesses a unique, genetically anchored physiological set-point for thyroid hormones that operates within a considerably narrower range than the reference interval established for the general population [2]. Consequently, a TSH level in the upper tertile or quartile of the normal reference range may substantially deviate from an individual's baseline, even if automated laboratory software flags the result as unremarkable [2].

Over the past few years, epidemiological research has documented consistent associations between high-normal TSH concentrations and unfavorable metabolic parameters [3,4]. Large-scale observational studies show that euthyroid individuals with TSH concentrations near the upper reference limit have higher body mass index, increased abdominal fat deposition, atherogenic lipid abnormalities, and impaired glucose tolerance [3,4]. While these observational links are well established, the underlying cellular and vascular mechanisms connecting subtle pituitary signaling to peripheral organ dysfunction remain under investigation.

Distinguishing these physiological intra-individual variations within the euthyroid range from pathological states such as subclinical hypothyroidism is clinically crucial. While previous literature has separately examined subclinical thyroid dysfunction or epidemiological correlations of TSH with metabolic syndrome, this narrative review provides a novel, integrated synthesis specifically focused on the strictly euthyroid range (0.4–4.0 mIU/L). Unlike existing reviews that focus on primary thyroid pathology, our work establishes a three-tiered conceptual framework distinguishing direct TSH receptor-mediated tissue effects (*in vitro*) from adaptive systemic responses to visceral adi-

* Correspondence to: Oana-Cristina Cînpeanu
E-mail: c.oana976@gmail.com

posity and central leptin dynamics. Furthermore, it explicitly delineates the therapeutic boundary between subclinical hypothyroidism and euthyroid metabolic adaptations, providing clear guidance against iatrogenic hormone replacement.

Methods

A comprehensive literature search was conducted across electronic databases including PubMed/MEDLINE, Scopus, and Google Scholar for studies published between January 2021 and October 2026 (date of last search: October 15, 2026), alongside foundational physiological literature.

Search Strategy: Search terms included Boolean combinations of free-text keywords and MeSH terms: ("thyrotropin" OR "TSH" OR "TSH within reference range" OR "high-normal TSH") AND ("euthyroid adults" OR "reference range") AND ("microvascular reactivity" OR "adipocyte TSH receptor" OR "leptin resistance" OR "low-grade inflammation" OR "cardiometabolic risk" OR "Mendelian randomization").

Selection criteria:

Inclusion criteria prioritized peer-reviewed original observational studies (cross-sectional, case-control, and prospective cohort studies), cellular and translational mechanistic studies, and Mendelian randomization investigations published in peer-reviewed journals. Eligible studies were restricted to adult euthyroid human populations, defined as having serum TSH concentrations within the standard population reference interval of 0.4–4.0 mIU/L.

Exclusion criteria comprised: pediatric populations, pregnant women, and individuals with diagnosed overt or subclinical thyroid disorders (e.g., TSH > 4.0 mIU/L) or receiving thyroid hormone replacement therapy; observational studies lacking adequate adjustment for major metabolic confounders, such as age, body mass index, or measures of insulin resistance; review articles without a systematic methodology and conference abstracts lacking peer-reviewed data. Studies primarily examining pathological subclinical hypothyroidism or overt thyroid disease were strictly excluded from the primary synthesis to prevent confounding physiological metabolic adaptation with primary endocrine failure.

Study Selection Flow: The initial electronic database search identified a total of 145 records (PubMed/MEDLINE: 55; Scopus: 60; Google Scholar: 30). Following the removal of 35 duplicates, 110 unique records underwent title and abstract screening. From these, 42 full-text articles were retrieved and evaluated against the pre-specified eligibility criteria. Ultimately, 20 studies met all inclusion criteria and were incorporated into the narrative synthesis and reference list of this review.

Ethical statement: Not applicable.

Results

Hierarchy of Evidence and Mechanistic Categorization

To prevent over-interpretation of subtle TSH variations, the synthesized literature was categorized into three distinct levels of biological evidence:

- Experimentally Supported Mechanisms (*In Vitro* & Cellular Models): Direct functional interactions, including TSH receptor (TSHR) activation on adipocytes (promoting lipogenesis and modulating GLUT-4 translocation) and vascular endothelial signaling (eNOS suppression and ROS generation).
- Observational Associations (Clinical Cohorts): Epidemiological correlations established in euthyroid adult populations, such as high-normal TSH co-occurring with elevated body mass index, visceral adiposity, hs-CRP, and altered flow-mediated dilation.
- Hypotheses Requiring Further Validation: Downstream translational claims, such as whether upper-normal TSH directly accelerates long-term clinical microvascular outcomes or if targeted non-hormonal metabolic interventions can completely reverse TSH receptor-mediated endothelial blunting in humans.

The Interplay Between Central Regulation and Peripheral Adipose Tissue

Understanding the physiological context of high-normal TSH requires moving beyond the classic paradigm in which the pituitary gland responds strictly to circulating free thyroid hormone concentrations [5]. In individuals with overweight or visceral obesity, the hypothalamic-pituitary-thyroid axis operates in a modified metabolic environment, exposed to continuous feedback from peripheral metabolic signals, most notably leptin. Leptin, an adipokine secreted by white adipose tissue in proportion to total fat mass, crosses the blood-brain barrier and binds to specific receptors on pro-opiomelanocortin and thyrotropin-releasing hormone neurons within the hypothalamus, enhancing thyrotropin-releasing hormone expression to increase thermogenesis and basal metabolic rate [6].

However, in states of chronic positive energy balance and progressive adiposity, sustained hyperleptinemia frequently leads to central leptin resistance. Hypothalamic signaling pathways become blunted, shifting the thyroid axis's homeostatic set point. The anterior pituitary compensates for this diminished hypothalamic sensitivity by maintaining TSH secretion at a slightly higher baseline, keeping peripheral free thyroxine and triiodothyronine levels within normal limits. Thus, an elevated TSH level within the normal reference range frequently reflects an adaptive neuroendocrine response to increased body fat mass rather than an intrinsic defect within the thyroid follicular cell itself [7].

Furthermore, the relationship between circulating TSH and adipose tissue is distinctly bidirectional. White and

brown adipocytes, particularly those located within visceral fat depots, express functional TSH receptors on their cell membranes. In experimental cellular models, when circulating TSH levels reside in the upper normal range, binding to these functional TSH receptors activates intracellular signaling pathways (such as the PI3K-Akt pathway), promoting pre-adipocyte survival and differentiation while upregulating downstream lipogenic enzymes that facilitate triglyceride accumulation [8].

Microvascular Reactivity and Low-Grade Systemic Inflammation

While macrovascular events such as ischemic heart disease and cerebrovascular accidents develop over decades through advanced atherosclerotic plaque formation, subtle endocrine and metabolic variations manifest much earlier within the microvascular bed. Microvascular reactivity reflects the capacity of small arterioles and capillaries to adjust vessel diameter in response to mechanical or chemical stimuli, a process heavily reliant on endothelial health. Experimental data demonstrate that vascular alterations are accompanied by blunted endothelial nitric oxide synthase activity, reduced nitric oxide bioavailability, and a simultaneous increase in intracellular reactive oxygen species production within the vascular wall [9]. In clinical cross-sectional evaluations, individuals with variations in thyroid function within the normal or mildly altered range exhibit subtle impairments in vascular reactivity, indicating early subclinical endothelial dysfunction before macrovascular disease becomes clinically evident [10].

In parallel with microvascular alterations, observational studies confirm that high-normal TSH levels co-occur with systemic low-grade inflammation. Visceral adipose tissue operates as an active endocrine organ infiltrated by pro-inflammatory macrophages that secrete cytokines, including interleukin-6 and tumor necrosis factor-alpha, directly into the portal circulation. Interleukin-6 acts on hepatocytes to stimulate the synthesis of high-sensitivity C-reactive protein, an established biomarker of vascular inflammation [3]. Euthyroid adults in the upper TSH tertile display higher circulating levels of inflammatory markers compared to those in lower tertiles, illustrating a persistent state of low-grade systemic stress [3].

Re-evaluating Causality: Insights from Mendelian Randomization

A central challenge in interpreting observational epidemiological data is disentangling true biological causality from secondary adaptation and residual confounding. Obesity independently promotes dyslipidemia, systemic hypertension, peripheral insulin resistance, and chronic inflammation while simultaneously elevating serum TSH through leptin-mediated pathways [11]. Consequently, standard statistical adjustments for body mass index in observational cohorts may not fully eliminate confounding from visceral fat distribution or subtle variations in body composition.

Recent Mendelian randomization studies have clarified the association by using single nucleotide polymorphisms associated with thyroid function as genetic instrumental variables. Because genetic alleles are randomly assigned at conception, Mendelian randomization minimizes postnatal environmental confounding and eliminates reverse causation [11].

Large-scale clinical and epidemiological evaluations demonstrate a clear association between serum TSH and metabolic parameters. Elevated body mass and adiposity are consistently linked to variations in serum TSH levels within the reference range, supporting the concept that high-normal TSH frequently accompanies excess adiposity in population-based cohorts [12]. Conversely, genetically determined variations in TSH within the normal range do not strongly affect overall body weight, type 2 diabetes risk, or major adverse cardiovascular events [13]. While Mendelian randomization indicates a modest causal effect of higher normal TSH on low-density lipoprotein cholesterol clearance through hepatic receptor regulation [14], this isolated effect accounts for only a minor fraction of overall cardiovascular risk compared to established metabolic risk factors.

Clinical Implications and Practical Perspective

Clinically, interpret the observed associations between high-normal TSH, inflammatory markers, and cardiometabolic risk with diagnostic caution [15]. Rather than treating the laboratory value in isolation, clinicians should recognize high-normal TSH as an integrated metabolic and inflammatory warning sign that reinforces the need for targeted lifestyle interventions. A serum TSH value in the upper reference range (e.g., 2.8–4.0 mIU/L) in a euthyroid patient with metabolic syndrome or visceral obesity should not trigger pharmacological intervention with exogenous thyroid hormones [16]. Current international clinical guidelines strongly advise against initiating levothyroxine therapy in euthyroid individuals solely for weight reduction, lipid management, or cardiovascular risk mitigation [16].

Controlled clinical trials have repeatedly shown that thyroid hormone replacement in individuals with subclinical hypothyroidism does not meaningfully improve thyroid-related symptoms or quality of life [17]. Furthermore, recent systematic reviews and meta-analyses of clinical trials indicate that thyroid hormone therapy in individuals with mild thyroid dysfunction yields little to no significant improvement in quality of life or thyroid-related symptoms, challenging the routine use of exogenous hormone administration in such populations [18].

Discussions

To ensure a balanced interpretation of the available evidence, we explicitly differentiate between established bio-

logical mechanisms, observed clinical associations, and proposed pathophysiological hypotheses:

- Established Mechanisms: Translational and *in vitro* models definitively establish that functional TSH receptors (TSHR) are expressed on human adipocytes and microvascular endothelial cells, where direct TSH binding stimulates lipogenesis and alters endothelial nitric oxide synthase (eNOS) signaling.
- Observed Associations: Observational population cohorts consistently report positive correlations between serum TSH within the upper-normal range (2.8–4.0 mIU/L) and markers of metabolic dysfunction, including elevated BMI, visceral adiposity, leptin levels, and subclinical vascular stiffness.
- Proposed Hypotheses: Genetic causal inference via Mendelian randomization supports the hypothesis that upper-normal TSH represents a downstream, adaptive neuroendocrine response to adipose-derived leptin signaling—functioning as a metabolic buffer rather than a primary driver of cardiovascular pathology.

This review highlights that upper-normal TSH levels often reflect an adaptive neuroendocrine response rather than primary thyroid failure. While cell models show that TSH directly influences adipocyte lipogenesis and endothelial tone [8,9], Mendelian randomization shows that elevated TSH is primarily a downstream consequence of visceral fat accumulation and central leptin resistance [12,13]. Consequently, high-normal TSH functions as an integrative marker of metabolic and inflammatory stress [3,10].

When interpreting tissue-level receptors and observational cohorts, causal claims must be framed with methodological precision. While cellular models demonstrate direct TSH receptor activation and Mendelian randomization supports a causal pathway from adiposity to elevated TSH, observational correlations between high-normal TSH and vascular markers do not inherently prove direct systemic causation in humans. Furthermore, clinical evidence evaluating levothyroxine intervention in subclinical hypothyroidism (TSH>4.0 mIU/L) cannot be extrapolated to euthyroid adults. In individuals with normal thyroid function (TSH within 0.4–4.0 mIU/L), high-normal TSH operates as a secondary metabolic biomarker rather than a primary disease state.

Importantly, while higher TSH values within the reference range consistently correlate with obesity, central leptin dynamics, and low-grade systemic inflammation, these associations do not equate to an independent predictive capacity for cardiometabolic risk. Rather than operating as an isolated, standalone prognostic marker or direct cardiovascular driver, upper-normal TSH reflects an integrated, downstream manifestation of underlying metabolic and adipose tissue adaptation. To address these epidemiological and biological complexities and guide clinical interpretation, a comprehensive synthesis of the evidence tiers, underlying mechanisms, and clinical boundaries is summarized in Table 1.

This distinction carries immediate clinical value. Because high-normal TSH reflects metabolic adaptation rather than primary endocrine disease, suppressing it with levothyroxine in euthyroid individuals provides no metabolic benefit and introduces iatrogenic risks [16-18]. Instead, clinicians should interpret high-normal TSH as a prompt to reinforce targeted lifestyle interventions that successfully reduce visceral adiposity, lower systemic inflammation, and naturally reset hypothalamic feedback dynamics [19,20]. Future prospective longitudinal studies incorporating direct microvascular assessments and broader cohorts will be necessary to confirm the utility of upper-normal TSH as an independent risk marker.

Rather than triggering hormone prescription, view a TSH level in the upper normal range as an integrative metabolic barometer. When clinicians identify a high-normal TSH result alongside visceral adiposity or dyslipidemia, the finding underscores underlying metabolic strain and systemic inflammation [19]. Management should focus entirely on evidence-based lifestyle modifications and conventional risk factor control. Structured exercise programs, dietary interventions to reduce refined carbohydrates, and moderate weight loss can reduce visceral fat mass, restore central leptin sensitivity, and lower circulating inflammatory cytokines, often bringing serum TSH toward the middle of the reference range [20].

While our analysis supports the clinical prudence that a serum TSH value within the upper normal range does not, in itself, constitute an indication for hormone re-

Table 1. Synthesis of Evidence on High-Normal TSH (0.4–4.0 mIU/L) in Euthyroid Adults

Evidence Tier	Study Types / Models	Key Findings & Biological Mechanisms	Clinical Implication / Boundary
Tier 1: Experimental & Translational	*In vitro* cell cultures, microvascular tissue models	Direct TSH receptor (TSHR) activation in adipocytes promotes lipogenesis; endothelial TSHR binding impairs eNOS signaling and increases ROS	Demonstrates tissue-level biological plausibility, but cannot be directly extrapolated to systemic causation in humans
Tier 2: Observational & Epidemiological	Cross-sectional cohorts, prospective population studies	High-normal TSH (2.8–4.0 mIU/L) co-occurs with elevated BMI, visceral adiposity, insulin resistance, and subclinical inflammation	TSH functions as an integrative biomarker; high-normal levels do not possess independent predictive capacity for cardiometabolic risk
Tier 3: Causal Inference & Genetic	Mendelian Randomization (MR) studies	Genetically driven increases in BMI and visceral fat causally elevate serum TSH via leptin-mediated hypothalamic axis resetting	Confirms that elevated TSH is primarily a downstream adaptive consequence of adiposity, not a primary driver of metabolic disease
Therapeutic Framework	RCTs & Guidelines (Subclinical Hypothyroidism vs. Euthyroid)	Levothyroxine provides no cardiometabolic benefit in euthyroid adults and carries iatrogenic risks (arrhythmias, bone loss).	Levothyroxine is strictly contraindicated; management should focus exclusively on targeted lifestyle optimization.

placement therapy, these conclusions must be interpreted with caution. Available evidence primarily highlights statistical associations between high-normal TSH levels and specific metabolic characteristics, rather than establishing TSH as a validated, independent biomarker of cardiometabolic stress. Furthermore, while experimental models provide valuable insights into potential cellular pathways, it remains to be fully elucidated whether these proposed mechanisms are entirely operative at physiological concentrations in humans, emphasizing the need for targeted prospective and mechanistic studies in clinical cohorts.

Clinical Utility, Limitations, and Future Prospective Directions

While recognizing upper-normal TSH (2.8–4.0 mIU/L) as an integrative metabolic barometer carries conceptual value, its direct clinical utility remains bounded by key physiological and diagnostic limitations. First, intra-individual TSH variability—influenced by circadian rhythmicity, seasonal fluctuations, acute sleep deprivation, and transient systemic stress—limits the reliance on a single TSH measurement for long-term cardiometabolic risk stratification. Second, upper-normal TSH lacks diagnostic specificity; it functions as a non-specific downstream responder to adiposity and low-grade inflammation rather than a pathognomonic marker of specific vascular damage.

Consequently, high-normal TSH should not be used as an isolated screening tool or an independent target for therapeutic manipulation. To translate these pathophysiological insights into clinical practice, prospective longitudinal studies are required to clarify several unresolved questions: (1) whether temporal changes in TSH within the reference range parallel metabolic recovery following targeted weight loss or anti-inflammatory interventions; (2) whether combining upper-normal TSH with established biomarkers (e.g., hs-CRP, HOMA-IR) improves multivariate risk prediction models; and (3) whether direct microvascular endpoints, such as flow-mediated dilation or capillary density, independently track with TSH dynamics in non-obese euthyroid cohorts over extended follow-up periods.

Conclusion

Fluctuations in serum TSH within the population reference range reflect complex connections across the neuroendocrine system, visceral adipose tissue, and vascular endothelium. Rather than signaling primary thyroid gland disease, a high-normal TSH level in the upper normal range (2.8–4.0 mIU/L) in euthyroid adults functions primarily as an adaptive, secondary biomarker of increased body mass, central leptin adaptation, and low-grade inflammatory stress.

Reflecting the clear boundaries of current evidence, these findings must be interpreted with diagnostic caution. Present data do not support using upper-normal TSH as a standalone predictor for cardiovascular risk or as a trigger for levothyroxine therapy. Recognizing the limitations of current evidence, clinicians should interpret high-normal TSH values not as an isolated pathology requiring hormonal correction, but as a contextual indicator that reinforces the need for comprehensive lifestyle management and conventional cardiovascular risk optimization, remaining strictly distinct from the treatment framework of subclinical hypothyroidism.

In conclusion, a serum TSH level in the upper normal range does not, in itself, warrant hormonal intervention. While current evidence demonstrates associations with specific metabolic parameters, high-normal TSH should not be considered a validated independent biomarker of cardiometabolic stress, and further translational research is required to confirm whether preclinical mechanisms operate at human physiological levels.

Authors' contributions

COC (Conceived the review, performed the literature search, and drafted the initial manuscript); TM (Critically revised the manuscript for key intellectual content, supervised the work, and provided final approval). FL (Performed the literature search, critically revised the manuscript, and provided final approval). All authors read and approved the final version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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