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TSH: Between Over-Reliance and Over-Avoidance: Toward Tissue-Level Thyroid Hormone Signaling

Angela D Mazza, DO, ABAARM, FAAMFM, ECNU*

Metabolic Center for Wellness, Oviedo, Florida, USA.

***Correspondence:**

Angela D. Mazza, DO, ABAARM, FAAMFM, ECNU, Metabolic Center for Wellness, Oviedo, Florida, USA, Tel: (407)542-0661.

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ABSTRACT

Thyroid-stimulating hormone (TSH) has long served as the primary biomarker guiding the diagnosis and management of hypothyroidism. Following the introduction of sensitive TSH assays in the 1970s and the recognition of peripheral conversion of thyroxine (T4) to triiodothyronine (T3), normalization of serum TSH became the central therapeutic target in thyroid hormone replacement therapy. This paradigm has improved treatment safety and standardization; however, a persistent clinical paradox has emerged: a subset of patients treated with levothyroxine achieve biochemical euthyroidism based on TSH criteria yet continue to experience symptoms suggestive of impaired thyroid hormone action.

In response, divergent clinical perspectives have developed. Conventional endocrine practice continues to prioritize TSH normalization as the principal indicator of adequate therapy, whereas some emerging approaches de-emphasize TSH in favor of symptom-based management. Both perspectives risk oversimplifying the complex, multi-level regulation of thyroid hormone physiology. While TSH reflects hypothalamic–pituitary–thyroid (HPT) axis feedback, it does not fully capture tissue-level thyroid hormone signaling, which is influenced by factors including hormone transport, deiodinase activity, receptor isoform distribution, inflammatory signaling, and metabolic context.

This review examines the physiologic role of TSH, the historical evolution of TSH-centric thyroid management, and the limitations of relying on TSH as a sole marker of thyroid hormone sufficiency. At the same time, it underscores the continued importance of TSH as a systemic safety signal, given well-established associations between suppressed TSH and adverse cardiovascular and skeletal outcomes. We propose a systems-based framework for interpreting thyroid function that integrates TSH with circulating thyroid hormone levels, metabolic and inflammatory markers, and clinical phenotype. This approach aims to reconcile current debates in thyroid medicine and support a more precise, physiology-informed model of thyroid hormone replacement.

Keywords

Thyroid-stimulating hormone, Hypothyroidism, Precision endocrinology, Thyroid hormone signaling, Levothyroxine, Tissue-level thyroid hormone activity, Deiodinases, Personalized medicine.

Introduction

Thyroid-stimulating hormone (TSH) has become the cornerstone of modern thyroid disease management, serving as the primary biomarker guiding both diagnosis and treatment of hypothyroidism. The widespread adoption of sensitive TSH assays in the 1970s, coupled with the recognition of peripheral conversion of thyroxine (T4) to triiodothyronine (T3), established a therapeutic paradigm in which normalization of serum TSH is considered synonymous with restoration of euthyroidism [1-3]. This approach has contributed significantly to improved safety, standardization, and population-level management of thyroid disease [4].

Despite these advances, a persistent and increasingly recognized clinical paradox remains. A subset of patients treated with levothyroxine achieve biochemical euthyroidism according to TSH-based criteria, yet continue to report symptoms including fatigue, weight gain, cognitive dysfunction, and impaired metabolic health [5-7]. These patients often exist in a gray zone—biochemically "normal" by conventional standards, yet clinically unwell. This discordance has prompted ongoing debate regarding the adequacy of TSH as a sole marker of thyroid hormone sufficiency.

In response, divergent clinical perspectives have emerged. Traditional endocrine practice continues to emphasize TSH normalization as the principal indicator of therapeutic success, prioritizing its role as a sensitive and well-validated marker of hypothalamic–pituitary–thyroid (HPT) axis feedback [4,8]. In contrast, some alternative or integrative approaches have shifted toward symptom-driven management, at times minimizing or disregarding TSH altogether. While each perspective reflects valid clinical concerns, both risk oversimplifying the complex and multi-level nature of thyroid hormone regulation.

Thyroid hormone signaling extends far beyond circulating hormone concentrations and pituitary feedback. At the tissue level, thyroid hormone activity is modulated by a network of processes including cellular transport, deiodinase-mediated activation and inactivation, receptor isoform distribution, mitochondrial function, and the influence of inflammatory and metabolic states [9-12]. As such, TSH provides an important but incomplete representation of thyroid hormone physiology, reflecting central regulation rather than peripheral tissue responsiveness.

At the same time, the clinical importance of TSH cannot be dismissed. Suppressed TSH levels have been consistently associated with adverse outcomes, including atrial fibrillation, bone loss, and increased fracture risk, underscoring its role as a critical physiologic safety signal [13-15]. The challenge, therefore, is not whether TSH should be used, but how it should be interpreted within a broader clinical and physiologic context.

The goal of this review is to examine the physiologic role and historical evolution of TSH in thyroid disease management, to explore its limitations as a surrogate for tissue-level thyroid hormone activity, and to propose a systems-based framework for interpreting thyroid function. By integrating TSH with circulating thyroid hormones, metabolic and inflammatory markers, and clinical phenotype, this approach aims to reconcile current debates and advance a more precise, individualized model of thyroid hormone replacement.

Historical Origins of TSH-Centric Thyroid Management

Pre-1970 Clinical Assessment

Prior to the development of sensitive biochemical assays, the diagnosis and management of hypothyroidism relied heavily on clinical assessment and indirect physiologic markers. Basal metabolic rate (BMR), serum cholesterol levels, and delayed relaxation of deep tendon reflexes—particularly the Achilles reflex—were commonly used to estimate thyroid function [16-18]. Treatment during this era frequently involved desiccated thyroid preparations, which contained both thyroxine (T4) and triiodothyronine (T3), often administered in doses titrated to symptomatic response rather than biochemical targets [19]. While this approach allowed for individualized care, it was limited by variability in potency, lack of standardization, and risk of overtreatment.

Discovery of Peripheral T4-to-T3 Conversion

A major paradigm shift occurred in the late 1960s and early 1970s with the discovery that T4 serves largely as a prohormone, undergoing peripheral conversion to the biologically active hormone T3 [1]. This finding, demonstrated in both animal and human studies, provided a physiologic basis for the use of levothyroxine (LT4) monotherapy, under the assumption that endogenous mechanisms would ensure appropriate tissue-level T3 production [20]. The recognition of this conversion pathway fundamentally reshaped the understanding of thyroid hormone physiology and therapeutic strategy.

Development of TSH Radioimmunoassays

The introduction of sensitive TSH radioimmunoassays in the 1970s revolutionized thyroid diagnostics [21]. For the first time, clinicians had access to a reliable and quantifiable marker of HPT axis activity. TSH measurement proved to be highly sensitive for detecting both overt and subclinical thyroid dysfunction, allowing for earlier diagnosis and more precise monitoring of therapy [22]. This technological advancement marked a turning point, shifting clinical practice from symptom-based assessment to laboratory-guided management.

Rise of Levothyroxine Monotherapy

With the combined insights of peripheral T4-to-T3 conversion and the availability of TSH assays, levothyroxine monotherapy emerged as the standard of care for hypothyroidism [7,23]. Compared to desiccated thyroid, LT4 offered greater stability, consistent potency, and ease of dosing. The ability to titrate therapy based on serum TSH further reinforced its adoption, aligning treatment with an objective biochemical target. Over time, combination therapies and desiccated thyroid preparations fell out of favor in mainstream practice, largely due to concerns regarding supraphysiologic T3 levels and variability in dosing [24,25].

Establishment of TSH Normalization as the Therapeutic Target

By the late 20th century, normalization of serum TSH had become the central therapeutic goal in the management of hypothyroidism. Clinical guidelines endorsed TSH as the primary biomarker for both diagnosis and dose adjustment, emphasizing its sensitivity, reproducibility, and association with clinical outcomes.[4,8] This TSH-centric model improved safety by reducing the risk of overtreatment and iatrogenic thyrotoxicosis, particularly in vulnerable populations such as older adults.

Key Takeaway

The dominance of TSH in thyroid disease management emerged from a convergence of physiologic discovery and technological advancement. While this paradigm has provided substantial clinical benefit, it also laid the foundation for a simplified model of thyroid hormone replacement that may not fully capture the complexity of tissue-level thyroid hormone signaling.

Physiologic Role of TSH Beyond a Laboratory Marker

Regulation of the Hypothalamic–Pituitary–Thyroid Axis

Thyroid-stimulating hormone plays a central role in the regulation of the hypothalamic-HPT axis, functioning as the primary mediator between central endocrine control and peripheral thyroid hormone production. TSH secretion from the anterior pituitary is stimulated by TRH and is tightly regulated through negative feedback by circulating thyroid hormones, particularly T3 [24,25].

Importantly, the pituitary gland exhibits a high degree of sensitivity to circulating T3 due to local expression of type 2 deiodinase (D2), which converts T4 to T3 within thyrotroph cells [3]. This allows for precise modulation of TSH secretion in response to subtle changes in circulating hormone levels. As a result, serum TSH has been widely regarded as a sensitive integrative marker of thyroid hormone status at the level of central regulation.

TSH Receptors Beyond the Thyroid

While TSH is classically understood for its role in stimulating thyroid hormone synthesis and secretion via the thyroid gland, TSH receptors (TSHR) are also expressed in multiple extrathyroidal tissues. These include bone, adipose tissue, and cells of the immune system, suggesting that TSH may exert direct biologic effects beyond its role in thyroid hormone regulation [26-28].

In adipocytes, TSH receptor activation has been associated with modulation of lipolysis and adipogenesis, implicating TSH in energy balance and metabolic regulation [27]. In bone tissue, TSH receptors are expressed on both osteoblasts and osteoclasts, supporting a role in skeletal remodeling independent of thyroid hormone levels [28]. These findings challenge the traditional view of TSH as solely a regulatory signal and instead position it as a hormone with broader systemic effects.

TSH and Immune Signaling

Emerging evidence suggests that TSH may play a role in immune modulation. TSH receptors have been identified on lymphocytes and other immune cells, and TSH signaling has been shown to influence cytokine production and immune cell activity [29,30]. This interaction is particularly relevant in the context of autoimmune thyroid disease, where bidirectional communication between the endocrine and immune systems contributes to disease pathogenesis and progression.

TSH may also act as a local signaling molecule within immune tissues, further supporting its role as part of a broader neuroendocrine–immune network. These observations highlight the complexity of TSH biology and suggest that alterations in TSH levels may have implications beyond thyroid hormone production alone.

TSH and Bone Remodeling

The relationship between TSH and skeletal health has gained increasing attention, particularly in light of clinical data linking suppressed TSH levels to increased fracture risk [14,15]. Experimental studies have demonstrated that TSH can directly inhibit osteoclastogenesis and bone resorption, suggesting a protective role in maintaining bone integrity [28].

These effects appear to be at least partially independent of circulating thyroid hormone levels, reinforcing the concept that TSH itself may function as a regulator of bone metabolism. Clinically, this has important implications for patients receiving thyroid hormone replacement, in whom iatrogenic TSH suppression may contribute to adverse skeletal outcomes.

Key Concept

TSH functions not only as a marker of hypothalamic–pituitary feedback, but also as a biologically active hormone with systemic effects across multiple tissues, including bone, adipose tissue, and the immune system. Its interpretation in clinical practice should therefore reflect both its regulatory role and its broader physiologic significance.

Limitations of TSH as a Marker of Tissue Thyroid Hormone Activity

While serum TSH is widely used as a surrogate marker of thyroid hormone sufficiency, it primarily reflects HPT axis feedback rather than tissue-specific thyroid hormone activity. As such, reliance on TSH alone may not fully capture the complexity of thyroid hormone signaling at the cellular level, where biologic effects are ultimately realized [9,10].

Tissue-Specific Thyroid Hormone Transport

The intracellular availability of thyroid hormones is regulated in part by membrane transporters, including monocarboxylate transporter 8 (MCT8) and organic anion transporting polypeptide 1C1 (OATP1C1) [31,32]. These transporters facilitate the entry of T4 and T3 into cells and exhibit tissue-specific expression patterns. Variability in transporter function—whether genetic, acquired, or influenced by illness—can result in discordance between circulating hormone levels and intracellular thyroid hormone availability [31]. As a result, normal serum TSH and free hormone levels do not necessarily ensure adequate hormone delivery to all tissues.

Deiodinase Regulation

Local thyroid hormone activation and inactivation are governed by a family of deiodinase enzymes, including type 1 (D1), type 2 (D2), and type 3 (D3) deiodinases [10]. These enzymes regulate the conversion of T4 to active T3 (via D1 and D2) or to inactive reverse T3 (via D3), thereby controlling tissue-specific thyroid hormone action independent of circulating levels.

Deiodinase activity is highly dynamic and influenced by factors such as inflammation, illness, caloric restriction, and metabolic stress [10,33]. For example, inflammatory cytokines have been shown to downregulate D1 and D2 while upregulating D3, leading to reduced intracellular T3 availability despite normal serum TSH—a pattern observed in non-thyroidal illness and other chronic conditions [33]. This adaptive or maladaptive shift further underscores the limitations of TSH as a reflection of tissue-level thyroid hormone activity.

Thyroid Hormone Receptor Isoform Distribution

Thyroid hormone effects are mediated through nuclear thyroid hormone receptors (TRs), primarily TRα and TRβ, which exhibit distinct tissue distributions and functional roles.[11] TRα is predominantly expressed in the heart, skeletal muscle, and central nervous system, whereas TRβ is more abundant in the liver, pituitary, and hypothalamus [11].

This differential expression contributes to tissue-specific sensitivity to thyroid hormones and may explain why certain organs or systems exhibit persistent dysfunction despite normalization of TSH. For example, the pituitary—rich in TRβ—may accurately sense circulating hormone levels and normalize TSH, while peripheral tissues with different receptor profiles may remain functionally hypothyroid.

Mitochondrial and Non-Genomic Thyroid Hormone Actions

In addition to classical genomic effects mediated through nuclear receptors, thyroid hormones exert important non-genomic actions, particularly at the level of the mitochondria. Thyroid hormone signaling influences mitochondrial biogenesis, oxidative phosphorylation, and energy expenditure, thereby playing a central role in metabolic regulation [12,34].

These mitochondrial effects are not fully captured by serum TSH measurements and may be influenced by factors such as nutrient status, oxidative stress, and overall metabolic health. As a result, patients may experience symptoms related to impaired energy production—such as fatigue or reduced exercise tolerance—despite "normal" TSH levels.

Effects of Metabolic and Inflammatory States

Systemic metabolic and inflammatory states further modulate thyroid hormone signaling at multiple levels. Conditions such as obesity, insulin resistance, chronic inflammation, and caloric restriction have been associated with alterations in thyroid hormone metabolism, transport, and receptor activity [12,33].

These states may produce patterns in which TSH remains within the reference range while tissue-level thyroid hormone action is altered. For example, low T3 states observed in chronic illness or active weight loss may reflect adaptive metabolic responses that are not appropriately captured by TSH alone [12]. This highlights the importance of interpreting thyroid function within the broader context of an individual's metabolic and physiologic environment.

Key Message

TSH reflects pituitary sensing of circulating thyroid hormone levels but does not fully represent tissue-level thyroid hormone signaling. Cellular thyroid hormone activity is shaped by a complex interplay of transport, activation, receptor sensitivity, mitochondrial function, and systemic metabolic context—factors that extend beyond the scope of TSH alone.

Risks of Dismissing TSH in Thyroid Hormone Therapy

While important limitations exist in using TSH as a sole marker of thyroid hormone sufficiency, dismissing TSH altogether in the management of hypothyroidism carries meaningful clinical risk. TSH remains a well-validated physiologic indicator of hypothalamic–pituitary–thyroid (HPT) axis regulation and serves as an important safety marker in thyroid hormone replacement therapy [4,8].

A substantial body of evidence has demonstrated associations between suppressed TSH levels and adverse cardiovascular outcomes. Subclinical hyperthyroidism, characterized by low or undetectable TSH with normal circulating thyroid hormone levels, has been consistently linked to an increased risk of atrial fibrillation, particularly in older adults [13,35]. In addition, low TSH levels have been associated with increased cardiovascular morbidity and mortality, including coronary heart disease events [14]. These findings underscore the importance of avoiding iatrogenic thyrotoxicosis in patients receiving thyroid hormone therapy.

Skeletal health is similarly affected by TSH suppression. Multiple studies have demonstrated an association between low TSH and reduced bone mineral density, as well as an increased risk of fractures, particularly in postmenopausal women [15,36]. Experimental data further suggest that TSH may exert direct inhibitory effects on bone resorption, providing a potential mechanistic explanation for these clinical observations.[28] Together, these data reinforce the role of TSH as a regulator of skeletal integrity.

Emerging evidence also suggests potential neurologic and cognitive implications of suppressed TSH, particularly in aging populations. Some studies have linked subclinical hyperthyroidism to cognitive decline and increased risk of dementia, although findings remain heterogeneous and may be influenced by comorbid conditions and duration of exposure [37]. These observations further highlight the systemic consequences of chronic TSH suppression.

It is important to distinguish between intentional and unintentional TSH suppression. In certain clinical contexts—such as differentiated thyroid cancer—TSH suppression is deliberately employed to reduce the risk of tumor recurrence, and the benefits may outweigh potential risks when carefully monitored [38]. In contrast, iatrogenic suppression resulting from overtreatment of hypothyroidism lacks therapeutic benefit and may expose patients to unnecessary harm.

Taken together, these data emphasize that TSH provides a critical physiologic safety signal in thyroid hormone therapy. While it may not fully reflect tissue-level thyroid hormone activity, it remains an essential component of risk stratification and treatment monitoring.

Key Message

TSH should not be dismissed in clinical practice. It serves as an important safety marker, with well-established associations between suppressed levels and adverse cardiovascular, skeletal, and potentially cognitive outcomes. The clinical challenge lies not in abandoning TSH, but in integrating it appropriately within a broader, physiology-informed framework.

Toward a Systems-Based Interpretation of Thyroid Function

The limitations of TSH as a standalone marker, combined with the risks of disregarding it entirely, highlight the need for a more integrated approach to thyroid function assessment. Thyroid hormone signaling is inherently multi-dimensional, influenced not only by circulating hormone levels, but also by cellular, metabolic, and inflammatory factors that determine tissue-level responsiveness [9-12,33]. A systems-based interpretation acknowledges this complexity and provides a more clinically actionable framework for individualized thyroid hormone replacement.

Integrating Multiple Biomarkers

A comprehensive evaluation of thyroid function should extend beyond TSH to include FT4 and FT3, which provide additional insight into hormone availability and peripheral conversion [4,8]. Patterns such as relatively low FT3 in the setting of normal TSH may suggest impaired T4-to-T3 conversion or altered deiodinase activity, particularly in the context of metabolic stress or chronic illness [6,33].

In addition, selected metabolic markers—including fasting insulin, glucose, lipid profile, and markers of hepatic function—can offer indirect insight into thyroid hormone action at the tissue level, particularly in metabolically active organs such as the liver and skeletal muscle [12]. These markers help contextualize thyroid hormone signaling within the broader metabolic environment, where thyroid hormone plays a central role in regulating energy expenditure, lipid metabolism, and insulin sensitivity [12].

Clinical Phenotype

Biochemical data must be interpreted alongside the patient's clinical presentation. Symptoms such as fatigue, weight gain, cold intolerance, cognitive dysfunction, and impaired exercise tolerance may reflect altered tissue-level thyroid hormone activity, even in the presence of a normal TSH [5-7].

Equally important are objective clinical parameters, including resting heart rate, lipid profile, body composition, and markers of metabolic health. Thyroid hormone has well-established effects on cardiovascular function, lipid metabolism, and thermogenesis, making these parameters clinically relevant indicators of thyroid hormone action [12]. A phenotype-based approach recognizes that thyroid hormone sufficiency is ultimately reflected in functional outcomes rather than laboratory values alone.

Contextual and Modifying Factors

Thyroid hormone signaling is highly sensitive to systemic context. Inflammatory states, micronutrient status, caloric intake, and mitochondrial function all influence the transport, activation, and utilization of thyroid hormones at the cellular level [12,33].

Micronutrients such as selenium and iron play essential roles in thyroid hormone metabolism, particularly in deiodinase activity and thyroid hormone synthesis [10,39]. Iron deficiency, for example, has been associated with impaired thyroid hormone production and altered peripheral conversion [39]. In parallel, chronic inflammation may shift deiodinase expression toward reduced T3 availability, contributing to low T3 states observed in both acute and chronic illness [33].

Caloric restriction and active weight loss—whether lifestyle-induced or pharmacologically mediated—may also result in adaptive reductions in T3, reflecting a physiologic attempt to conserve energy [12]. These changes are often not fully captured by TSH alone, further emphasizing the importance of interpreting thyroid function within the broader metabolic and physiologic context.

A Precision Endocrinology Framework

Taken together, these elements support a precision endocrinology approach to thyroid hormone replacement, in which TSH is interpreted as one component of a broader, integrated system. Within this framework, thyroid function is assessed across multiple domains:

- **Central regulation:** TSH as a marker of HPT axis feedback and safety
- **Hormone availability:** FT4 and FT3 as indicators of circulating hormone levels
- **Cellular signaling:** Influenced by transporters, deiodinases, receptor activity, and mitochondrial function [9-12]
- **Metabolic context:** Including insulin sensitivity, lipid metabolism, and energy balance [12]
- **Clinical phenotype:** Symptoms, functional status, and patient-reported outcomes [5-7]

This multi-dimensional model aligns with a systems-based view of endocrine physiology and reflects the interdependence of hormonal signaling, metabolic function, and inflammatory tone [9-12]. Conceptually, this approach parallels emerging models in precision medicine that emphasize individualized assessment across biologic systems rather than reliance on single biomarkers [40]. A conceptual overview of this systems-based framework is presented in Figure 1, with its principal domains summarized in Table 1.

Traditional management of hypothyroidism has emphasized normalization of serum thyroid-stimulating hormone (TSH) as the primary therapeutic target. While TSH remains an essential marker of hypothalamic–pituitary–thyroid (HPT) axis regulation

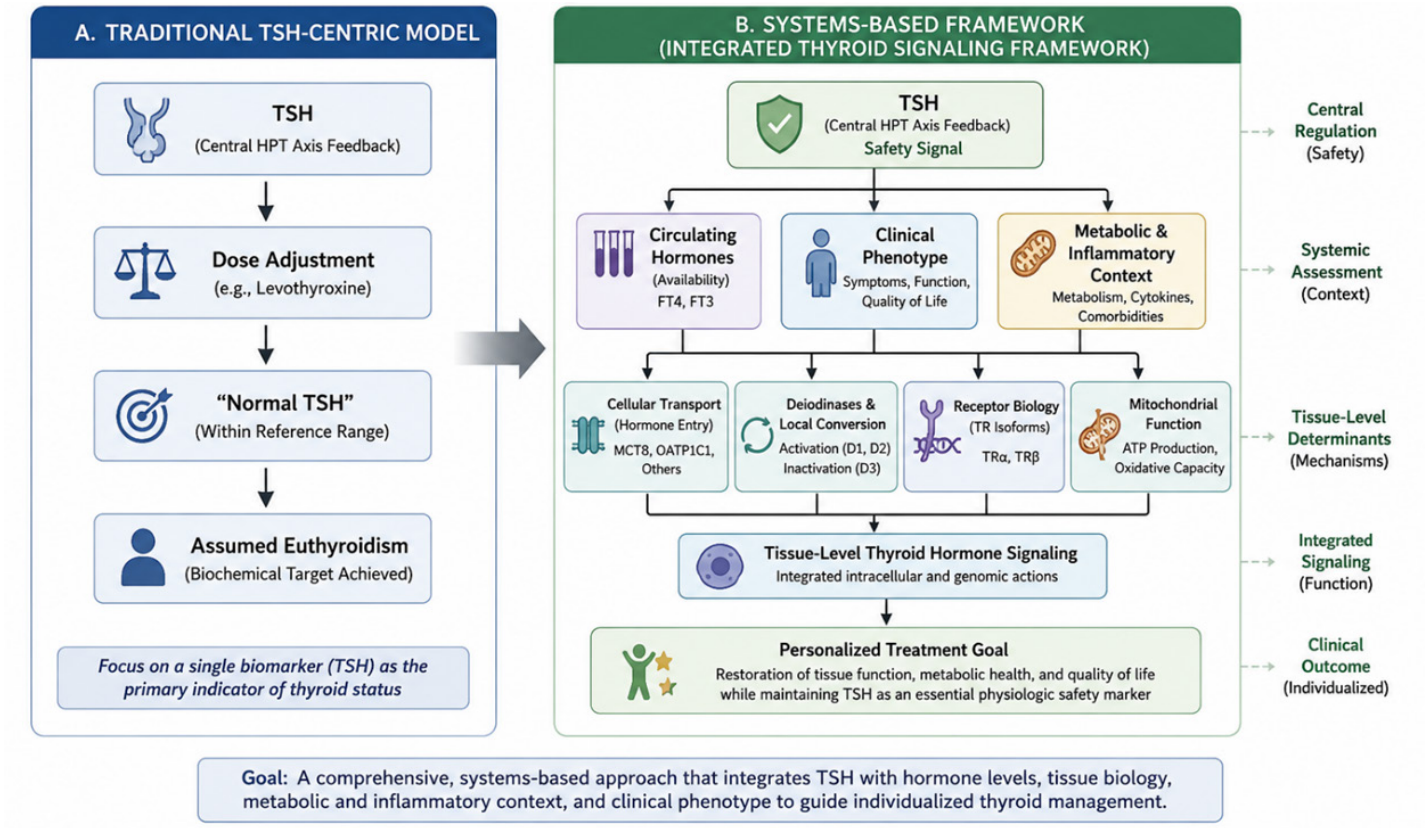

Figure 1: From TSH-centric management to a systems-based framework for thyroid hormone assessment.

Table 1: Components of a Systems-Based Assessment of Thyroid Function.

Domain	What it Represents	Examples	Clinical Relevance
TSH	Central HPT feedback	TSH	Safety marker; overtreatment risk
Circulating hormones	Hormone availability	FT4, FT3	Peripheral hormone supply
Cellular regulation	Intracellular signaling	MCT8, OATP1C1, D1/D2/D3	Tissue-specific hormone action
Receptor biology	Hormone responsiveness	TRα, TRβ	Organ-specific effects
Mitochondrial function	Cellular energy production	Oxidative phosphorylation, ATP generation	Fatigue, metabolism
Metabolic context	Whole-body physiology	Lipids, insulin resistance, obesity	Alters thyroid signaling
Inflammatory status	Cytokine effects	Chronic inflammation, illness	Alters deiodinases
Clinical phenotype	Functional outcomes	Symptoms, HR, exercise tolerance, QoL	Guides individualized care

and treatment safety, it does not fully reflect tissue-level thyroid hormone activity. A systems-based framework integrates TSH with circulating thyroid hormone levels (FT4 and FT3), clinical phenotype, metabolic and inflammatory context, cellular transport, deiodinase activity, receptor biology, and mitochondrial function to provide a more comprehensive assessment of thyroid hormone signaling and support individualized patient care.

Key Concept

A systems-based interpretation of thyroid function integrates TSH with circulating hormones, cellular signaling mechanisms, metabolic context, and clinical phenotype. This approach moves beyond a single-marker model toward a more precise and individualized understanding of thyroid hormone sufficiency.

Clinical Implications for Thyroid Hormone Replacement

The recognition that TSH alone does not fully capture tissue-level thyroid hormone activity has important implications for the clinical management of hypothyroidism. A systems-based approach supports more individualized treatment strategies that integrate biochemical markers, clinical phenotype, and underlying physiologic context, while preserving the safety framework provided by TSH [4,8].

Individualized Dosing Strategies

Levothyroxine monotherapy remains the standard first-line treatment for hypothyroidism due to its stability, predictable pharmacokinetics, and established safety profile [4]. However, interindividual variability in absorption, peripheral conversion, and tissue responsiveness may contribute to differences in clinical outcomes despite similar TSH levels [7,41].

Dosing should therefore be individualized, taking into account factors such as body weight, age, comorbid conditions, medication interactions, and clinical response [4,8]. In patients who achieve a normal TSH but continue to experience symptoms, further evaluation of FT4, FT3, and clinical context may provide additional insight into whether dose adjustment or alternative strategies should be considered [6].

Consideration of Combination Therapy

For select patients with persistent symptoms despite adequate LT4 therapy and normalized TSH, combination therapy with LT4 and LT3 may be considered [4,7]. While randomized controlled trials have shown mixed results at the population level, a subset of patients report symptomatic improvement, potentially reflecting interindividual differences in deiodinase activity or tissue-specific thyroid hormone requirements [7,41].

Current European Thyroid Association (ETA) guidelines acknowledge that a monitored trial of combination therapy may be appropriate in selected patients after careful discussion of risks and benefits [45]. Therapy should be initiated cautiously, with attention to dosing ratios and close monitoring to avoid TSH suppression and supraphysiologic T3 levels [4].

Avoiding Reflexive TSH Suppression

A key principle of thyroid hormone replacement is the avoidance of unnecessary TSH suppression. Suppressed TSH levels have been consistently associated with increased risks of atrial fibrillation, cardiovascular morbidity, and bone loss [13-15,35,36].

In the absence of a clear clinical indication—such as differentiated thyroid cancer—TSH suppression should not be used as a surrogate for improved symptom control [38]. Instead, clinicians should aim to maintain TSH within an appropriate reference range while addressing other contributors to persistent symptoms, including metabolic dysfunction, inflammation, and comorbid conditions.

Monitoring Beyond TSH

A systems-based approach supports the use of a broader panel of markers in selected patients, particularly those with persistent symptoms or complex metabolic profiles. In addition to TSH, measurement of FT4 and FT3 may provide insight into hormone availability and peripheral conversion [4,8].

Assessment of metabolic parameters—including lipid profile, glucose metabolism, and markers of cardiovascular risk—can further inform treatment decisions and help evaluate the physiologic impact of thyroid hormone therapy [12]. Thyroid hormone plays a central role in lipid metabolism, insulin sensitivity, and energy expenditure, making these markers clinically relevant adjuncts in patient assessment.

Emphasizing Patient-Centered Outcomes

The ultimate goal of thyroid hormone replacement is not solely biochemical normalization, but restoration of physiologic function and improvement in quality of life. Patient-reported symptoms, functional capacity, and overall well-being should therefore be considered integral components of treatment evaluation [5-7].

A patient-centered approach requires longitudinal assessment, careful clinical judgment, and a willingness to reassess treatment strategies when biochemical and clinical findings are discordant. This perspective aligns with broader principles of precision medicine, which emphasize individualized care based on both biologic and phenotypic variability [40].

Key Message

Effective thyroid hormone replacement requires a balance between biochemical targets and clinical outcomes. TSH remains an essential safety marker, but optimal management involves integrating TSH with free hormone levels, metabolic context, and patient-centered outcomes to guide individualized care.

Future Directions in Thyroid Physiology and Monitoring

Advances in thyroid physiology and systems biology are increasingly challenging traditional models of thyroid function assessment and creating new opportunities for more precise and individualized care. While TSH will likely remain a foundational component of thyroid evaluation, emerging tools and concepts may enhance the ability to assess tissue-level thyroid hormone activity and better align treatment with physiologic outcomes.

One important area of development is the identification of biomarkers that more directly reflect intracellular thyroid hormone signaling. Current research in metabolomics and transcriptomics has begun to identify patterns associated with thyroid hormone action at the tissue level, offering the potential to move beyond serum-based measurements toward a more functional assessment of thyroid status [42,43]. These approaches may help characterize interindividual variability in thyroid hormone responsiveness and identify patients who are less well served by conventional TSH-based strategies.

Another promising area involves a deeper understanding of mitochondrial thyroid hormone signaling. Thyroid hormones play a central role in mitochondrial biogenesis, oxidative phosphorylation, and cellular energy metabolism, yet these effects are not routinely assessed in clinical practice [12,34]. As tools to evaluate mitochondrial function become more accessible, they may provide additional insight into symptoms such as fatigue, reduced exercise tolerance, and metabolic inefficiency in patients with otherwise normal thyroid function tests.

The expanding field of genomics and personalized medicine also holds relevance for thyroid disease management. Genetic variation in deiodinase enzymes, thyroid hormone transporters, and receptors may influence tissue-level thyroid hormone activity and treatment response [9,19,44]. Incorporating genetic and molecular profiling into clinical decision-making may help identify subgroups of patients who are more likely to benefit from alternative therapeutic approaches, including combination therapy.

In parallel, evolving therapeutic strategies may further refine thyroid hormone replacement. These include modified-release T3 formulations, novel thyroid hormone analogs, and approaches designed to better mimic physiologic hormone delivery and circadian rhythm [45]. Such innovations may help address some of the limitations of current treatment paradigms, particularly in patients with persistent symptoms despite standard therapy.

Finally, the integration of multi-domain data—biochemical, metabolic, molecular, and clinical—into unified clinical models represents a key direction for the field. Advances in data analytics and systems medicine may enable more sophisticated interpretation of thyroid function, moving from static, single-point measurements toward dynamic, individualized profiles of endocrine health [40].

Key Message

The future of thyroid disease management lies in moving beyond single biomarkers toward integrated, systems-based models that more accurately reflect tissue-level thyroid hormone activity. Emerging tools in metabolomics, genomics, mitochondrial biology, and therapeutic innovation have the potential to support a more precise and individualized approach to thyroid hormone replacement.

Conclusion

Thyroid-stimulating hormone has served as a foundational biomarker in the diagnosis and management of hypothyroidism for decades, providing a reliable and standardized measure of hypothalamic–pituitary–thyroid axis regulation. Its widespread adoption has improved treatment safety and consistency, and its clinical value as a physiologic feedback signal remains firmly established.

Yet, as our understanding of thyroid hormone biology has evolved, so too has the recognition that TSH alone cannot fully capture the complexity of thyroid hormone action. Thyroid signaling is inherently multi-dimensional, shaped by tissue-specific transport, intracellular metabolism, receptor dynamics, mitochondrial function, and the broader metabolic and inflammatory environment. Within this context, the persistence of symptoms in a subset of patients despite normalization of TSH is not an anomaly, but rather a reflection of the limitations of a single-marker model.

The current divide in thyroid hormone management—between strict TSH-centric approaches and those that dismiss TSH altogether—represents an oversimplification on both ends of the spectrum. Moving forward requires not the rejection of TSH, but its integration into a more comprehensive and physiology-informed framework. TSH should be understood as both a regulator and a safety signal—necessary, but not sufficient.

A systems-based interpretation of thyroid function offers a path forward. By integrating TSH with circulating hormone levels, tissue-level determinants of hormone activity, metabolic context, and clinical phenotype, clinicians can move toward a more precise and individualized model of care. Such an approach aligns with broader shifts in medicine toward personalization and systems thinking, where complex biologic processes are interpreted within their full physiologic context.

Ultimately, the goal of thyroid hormone replacement is not simply biochemical normalization, but restoration of function, resilience, and quality of life. Achieving this requires a model of care that reflects the true complexity of thyroid physiology—one that honors the strengths of established paradigms while embracing the need for evolution.

Key Takeaways

- TSH remains a foundational biomarker in the diagnosis and management of hypothyroidism, reflecting hypothalamic–pituitary–thyroid (HPT) axis regulation and serving as an important safety signal.
- Normalization of TSH does not guarantee tissue-level euthyroidism. A subset of patients treated with levothyroxine continue to experience persistent symptoms despite biochemical targets being met.
- Thyroid hormone signaling is multi-dimensional, influenced by cellular transport, deiodinase activity, receptor distribution, mitochondrial function, and systemic metabolic and inflammatory states.
- TSH reflects central feedback, not peripheral tissue activity. As such, it provides an incomplete picture of thyroid hormone action at the cellular level.
- Dismissing TSH entirely introduces clinical risk, as suppressed TSH is associated with adverse cardiovascular, skeletal, and potentially cognitive outcomes.
- A systems-based approach to thyroid function is needed, integrating TSH with free hormone levels (FT4, FT3), metabolic markers, and clinical phenotype.
- Individualized thyroid hormone replacement is essential, recognizing interindividual variability in hormone metabolism, tissue responsiveness, and symptom expression.
- Combination LT4/LT3 therapy may benefit select patients, but should be used cautiously and within a monitored, evidence-informed framework.
- Clinical outcomes—not laboratory values alone—should guide management, with emphasis on symptom burden, functional status, and quality of life.
- The future of thyroid care lies in precision endocrinology, incorporating multi-domain data to better reflect tissue-level thyroid hormone activity and optimize patient-centered outcomes.

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