**Thyroid Optimization: A Data-Driven Guide to Resolving Thyroid Dysfunction.**

**Abstract:**
Thyroid dysfunction remains a pervasive clinical challenge, affecting between 1% and 10% of the global population and significantly impacting cardiovascular, metabolic, and mental health. Despite the prevalence of these disorders, conventional management continues to rely on a TSH-centric model and levothyroxine (L-T4) monotherapy, leaving a dissatisfaction gap where 15% to 20% of patients remain symptomatic despite having normal laboratory values. This work explores the paradigm shift toward personalized and functional medicine, which moves beyond population-based averages to address individual biochemical variability and systemic root causes. Central to this framework is the recognition of cellular hypothyroidism, often driven by genetic polymorphisms like DIO2 that impair the peripheral conversion of T4 to active T3. By integrating expanded diagnostic panels, including free T3, reverse T3, and ferritin, clinicians can identify metabolic bottlenecks and hormonal resistance at the tissue level. Furthermore, the study emphasizes the critical gut-thyroid-immune axis, where chronic inflammation and nutrient insufficiencies in selenium, zinc, iron, and vitamin D sabotage thyroid function. Ultimately, this data-driven guide advocates for precision therapeutic strategies, such as combination L-T4/L-T3 therapy and targeted nutritional repletion, to restore the body's unique homeostatic set point. By moving from reactive symptom management to proactive, personalized optimization, the medical community can achieve true tissue-level euthyroidism and mitigate long-term metabolic complications.

- **Background: Prevalence and complexity of thyroid disorders**

The prevalence of thyroid dysfunction in adults in the general population ranges from 1 to 10 percent, and is even higher in selected groups. Reasons for the variation include the testing site (community, health fair, medical clinic), age and sex of people tested, and method of assessment. In addition, it is not always clear whether people with known thyroid disease, those taking thyroid hormone or antithyroid therapy, or those who had other disorders that might affect thyroid function were included or excluded from the study group.

The thyroid gland is one of the most vital organs that plays a critical role in the normal growth, differentiation, metabolism, and physiological functioning of the human body. Thyroid dysfunction is one of the most common problems in clinical practice and has become more prevalent throughout the world in recent decades; therefore, its associated risk factors have received much attention. It can be caused by oversecretion or undersecretion of thyroid hormones and abnormalities in thyroid hormone receptors. The prevalence of thyroid disorders depends on sex, age, and geographical location, and dietary variation of iodine intake. It is easily identifiable and treatable, but it can have severe consequences if left undiagnosed or untreated. Thyroid dysfunction significantly impacts health outcomes, including cardiovascular and metabolic dysfunction, metabolic disorders, mental and bone health.

Females are 10 times more prone to develop thyroid dysfunction and associated anemia and other diseases than males. Little information is available about the prevalence of thyroid disorder and associated anemia in the Kingdom of Saudi Arabia (KSA). Minimal studies have been conducted in a primary setting, whereas none are carried out among the general population

While the global prevalence of thyroid dysfunction fluctuates between 1% and 10% based on geography and diet, these numbers often mask a deeper, more personal reality for patients. In regions like the Asir province of Saudi Arabia, the data reveals a significant overlap between thyroid health and systemic issues like anemia, particularly among women who are ten times more likely to struggle with these imbalances. Conventional research has long relied on the TSH test as the gold standard, yet emerging clinical evidence suggests this one-size-fits-all approach leaves a massive gap.

We are now seeing that a significant cohort of non-responders aren't just imagining their symptoms; rather, they are often dealing with genetic variations, such as DIO2 polymorphisms, which prevent their bodies from effectively converting standard T4 medication into the active T3 their cells crave. Furthermore, the functional model has identified a critical Gut-Thyroid-Immune Axis, where the presence of inflammation or nutrient deficiencies specifically in selenium, zinc, and Vitamin D can sabotage thyroid function even when serum levels appear normal on a lab report.

The future of thyroid care lies in a paradigm shift from population-based averages to personalized biological optimization. It is no longer enough to achieve a normal TSH while the patient still suffers from debilitating fatigue, brain fog, and metabolic resistance. Clinical relevance in the modern era demands a broader diagnostic lens that includes Free T3, Reverse T3, and ferritin levels to ensure that hormones are actually reaching and activating the tissues.

Moving forward, the medical community must embrace a root cause philosophy that prioritizes gut health and genetic screening alongside traditional hormone replacement. By integrating these personalized strategies, we can move beyond mere symptom management and toward true tissue-level euthyroidism. This approach not only resolves the persistent complaints of the individual but also serves as a preventative shield against the long-term cardiovascular and metabolic complications associated with untreated thyroid dysfunction.

## 5. Thyroid Physiology Through a Systems Biology Lens

- **Hypothalamic-pituitary-thyroid (HPT) axis**

The Hypothalamic-Pituitary-Thyroid (HPT) axis functions as the body's primary metabolic thermostat, operating through a sophisticated and tightly regulated communication loop. The process begins in the hypothalamus, which acts as the command center by monitoring circulating thyroid hormone levels. When the body requires an energy boost or detects a hormone deficit, the hypothalamus releases Thyrotropin-Releasing Hormone (TRH). This signal travels directly to the anterior pituitary gland, which serves as a relay station, responding by secreting Thyroid-Stimulating Hormone (TSH) into the bloodstream.

Once TSH reaches the thyroid gland, it stimulates the production of two main hormones: thyroxine (T4), which is the relatively inactive storage form, and triiodothyronine (T3), the active form that drives cellular metabolism. To prevent the system from over-revving, the HPT axis utilizes a negative feedback mechanism. As levels of T4 and T3 rise, they signal the hypothalamus and pituitary to throttle back the production of TRH and TSH, ensuring the body maintains a state of euthyroidism, or perfect hormonal balance.

However, the HPT axis only tells part of the story. While the brain and thyroid manage production, the majority of the active T3 your body uses is actually created through peripheral conversion. This occurs outside the thyroid gland, primarily in the liver, gut, and kidneys, where enzymes called deiodinases strip an iodine molecule from T4 to turn it into T3. In functional medicine, this is a critical focal point; if stress, illness, or nutrient deficiencies interfere with this conversion, a patient can feel hypothyroid even if their HPT axis and TSH levels appear perfectly normal on a standard lab test.

- **Peripheral thyroid hormone metabolism**

Peripheral thyroid hormone metabolism is the critical process where the pro-hormone thyroxine (T4) is transformed into the biologically active triiodothyronine (T3) or the inactive reverse T3 (rT3). While the thyroid gland produces the bulk of T4, it serves primarily as a circulating reservoir. The actual metabolic work occurs in the peripheral tissues, mainly the liver, kidneys, and skeletal muscle, regulated by a family of selenium-dependent enzymes known as deiodinases (D1, D2, and D3). These enzymes are the body's way of fine-tuning metabolism at the local level, allowing specific organs to increase or decrease thyroid activity without changing the overall output of the thyroid gland itself. The direction of this metabolism is a major focal point in functional medicine. Under normal conditions, D1 and D2 strip an iodine atom from the outer ring of T4 to create active T3, which then binds to nuclear receptors to stimulate energy production and protein synthesis. However, during periods of systemic stress, chronic illness, or significant caloric restriction, the body may shift its preference toward the D3 enzyme. This enzyme removes an iodine from the inner ring, producing rT3. Because rT3 is metabolically inactive and competes with active T3 for receptor sites, an elevation in rT3 can lead to cellular hypothyroidism , a state where a patient feels symptomatic despite having normal TSH and T4 levels.

Several clinical factors act as switches for these metabolic pathways. Optimal peripheral metabolism requires a specific suite of micronutrients, most notably selenium, which is a structural component of the deiodinase enzymes, and zinc, which facilitates the binding of T3 to its receptors. Conversely, factors like high cortisol (stress), systemic inflammation (cytokines like IL-6), and heavy metal toxicity can inhibit D1 and D2 activity while promoting D3. This explains why many patients with chronic inflammatory conditions or gut dysbiosis continue to experience symptoms like brain fog and cold intolerance; their machinery is simply shifting thyroid hormone into an inactive storage state rather than an active metabolic fuel.

- **Tissue-level thyroid hormone action**

While serum hormone levels provide a snapshot of what is circulating in the bloodstream, the true measure of thyroid health is tissue-level thyroid hormone action. This refers to the ability of the active hormone, T3, to enter a cell, reach the nucleus, and successfully bind to thyroid hormone receptors (TRs) to trigger gene expression. In this final stage of the thyroid journey, the hormone acts like a key entering a lock, turning on the engines that regulate everything from heart rate and body temperature to the rate at which we burn fat and repair skin cells.

The effectiveness of this action depends on two critical hurdles: cellular transport and receptor sensitivity. Even if the body has sufficient T3, the hormone must be ushered into the cell by specific transporter proteins, such as MCT8 and OATP1C1. Once inside, T3 must navigate through the cytoplasm to the nucleus to find its receptor. If these transporters are inhibited by high levels of toxins, certain medications, or systemic inflammation, the hormone remains stuck in the lobby of the cell, unable to perform its metabolic duties. This explains the hypothyroid symptoms of fatigue and weight gain seen in patients whose blood tests suggest they have plenty of hormones available. Finally, the lock itself the thyroid hormone receptor must be sensitive enough to respond. Functional medicine highlights that receptor sensitivity is highly dependent on the cellular environment. Factors such as Vitamin A, which is a co-factor for the retinoid X receptor (RXR) that pairs with the thyroid receptor, and Zinc, which is essential for the structural integrity of zinc fingers that allow the receptor to bind to DNA, are non-negotiable for success. When these nutrients are lacking, or when high cortisol levels block the receptor sites, the genomic switch isn't flipped. This emphasizes that thyroid optimization is not just about the gland’s output but about ensuring the cellular environment is prepared to receive and execute the hormone's instructions.

- **Genetic and epigenetic variability**

The biological blueprint for thyroid function is far from a universal standard; it is a unique settings menu shaped by inherited genetic markers and the environmental volume knobs of epigenetics. While standard medicine often treats patients as a statistical average, genetic variations, specifically Single Nucleotide Polymorphisms (SNPs) explain why two people with the same TSH level can feel worlds apart. The most notable example is the DIO2 gene polymorphism. This genetic glitch affects the enzyme responsible for converting T4 to active T3 within the brain and tissues. For those carrying this variant, the local conversion is sluggish, meaning their brain may be starved for thyroid hormone even if their bloodwork looks pristine. Other variations in transport genes, like MCT8 or OATP1C1, can further complicate how efficiently hormones move from the blood into the cells where they are needed.

Beyond the fixed code of our DNA, epigenetics introduces a dynamic layer of control that responds to the world around us. Epigenetic modifications, such as DNA methylation, don't change your genetic sequence, but they do determine which genes are loud and which are silenced. Life events like chronic stress, exposure to endocrine-disrupting chemicals like BPA, or even significant nutritional deficiencies can leave tags on our genes. In the thyroid context, these shifts can permanently alter how sensitive the pituitary gland is to feedback or how many receptors your cells produce to catch T3. This is why a period of intense physiological stress can seemingly break someone's metabolism long after the stressor is gone; the body has epigenetically dialed down its metabolic thermostat as a survival mechanism. This intersection of nature and nurture is the ultimate argument for a personalized and functional approach. By acknowledging that our genes load the gun but our environment and epigenetics pull the trigger, we can move away from the frustration of normal labs towards high-precision care. For example, knowing a patient's DIO2 status allows a clinician to bypass the conversion hurdle entirely by prescribing T3 alongside T4 from day one. Understanding these variables allows us to decode the unique signature of an individual's metabolic health, turning a guessing game into a targeted strategy for optimization.

- **Interactions with metabolic, immune, and stress-response systems**

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### 6.1 Standard Diagnostic Paradigms

- **TSH-Centric Evaluation**

The prevailing clinical model for thyroid assessment relies almost exclusively on the Thyroid-Stimulating Hormone (TSH) as the definitive diagnostic gold standard. This approach operates on the top-down logic that the pituitary gland is the most sensitive sensor in the human body, capable of accurately reflecting the thyroid status of every peripheral tissue. In a standard screening, if the TSH falls within the laboratory's predetermined range, the diagnostic journey typically ends, leaving active hormones like Free T3 and Free T4 unmeasured. This TSH-first gatekeeping is designed for clinical efficiency, aiming to catch overt disease while minimizing the costs of broader hormone panels.

However, this reliance on the pituitary as a proxy for the rest of the body creates a significant biological blind spot. The pituitary gland is uniquely efficient at converting T4 into the active T3 hormone, often far more so than the liver, kidneys, or brain. This means that even if a patient's peripheral tissues are effectively starving for thyroid hormone due to poor conversion or systemic inflammation, the pituitary may remain perfectly satisfied and continue to pump out a normal TSH signal. By treating the pituitary as the body's only thermostat, clinicians risk ignoring a state of cellular hypothyroidism where the blood levels appear stable, but the metabolic engines of the patient's cells are failing to turn over.

Furthermore, the TSH-centric model often fails to account for the time-lag between the onset of symptoms and the manifestation of biochemical disease. Patients frequently experience debilitating fatigue, weight gain, and cognitive fog for years while their TSH levels slowly drift toward the upper limit of normal. Because the current paradigm prioritizes a single laboratory marker over the patient's clinical presentation, these individuals are often dismissed or misdiagnosed with depression or age-related decline. This highlights a critical disconnect in modern endocrinology: a lab test that was designed to identify end-stage failure is being used as the sole tool to evaluate a complex, multi-organ metabolic system.

- **Population reference ranges**

The concept of normal thyroid function is currently defined by population-based reference ranges, which are derived from a statistical bell curve of the general population. Typically spanning from roughly 0.45 to 4.5 mIU/L, these ranges are intended to capture 95% of the healthy population. While this statistical framework is helpful for identifying severe pathology like Graves' disease or overt myxedema, it is inherently flawed because it treats health as the absence of extreme disease rather than the presence of optimal function.

The primary issue with these broad ranges is that they fail to account for the narrow, genetically determined set point unique to each individual. Research suggests that a person's healthy TSH level typically fluctuates very little throughout their adult life. If an individual's personal baseline is 1.0 mIU/L, and their TSH rises to 4.0 mIU/L, they have experienced a massive 300% shift in their hormonal balance. To a laboratory technician, this patient is still normal because they haven't crossed the 4.5 threshold, but to the patient's biology, they are in a state of significant metabolic distress. Standard ranges turn a highly personal biological metric into a generic average, often gaslighting symptomatic patients whose numbers remain technically within range. Moreover, the data used to build these reference ranges is often polluted by including individuals who may have undiagnosed subclinical thyroid issues, nutrient deficiencies, or age-related shifts. For example, a TSH of 4.2 might be perfectly physiological for an 80-year-old, but it could signal early-stage thyroid failure in a 25-year-old woman struggling with infertility. By relying on a static, one-size-fits-all window, conventional medicine misses the opportunity for early intervention. This is why the shift toward personalized medicine is so vital; it moves the focus away from a statistical average and toward finding the specific optimal range that allows an individual to actually thrive.

### 6.2 Standard Treatment Strategies

- **Levothyroxine monotherapy**

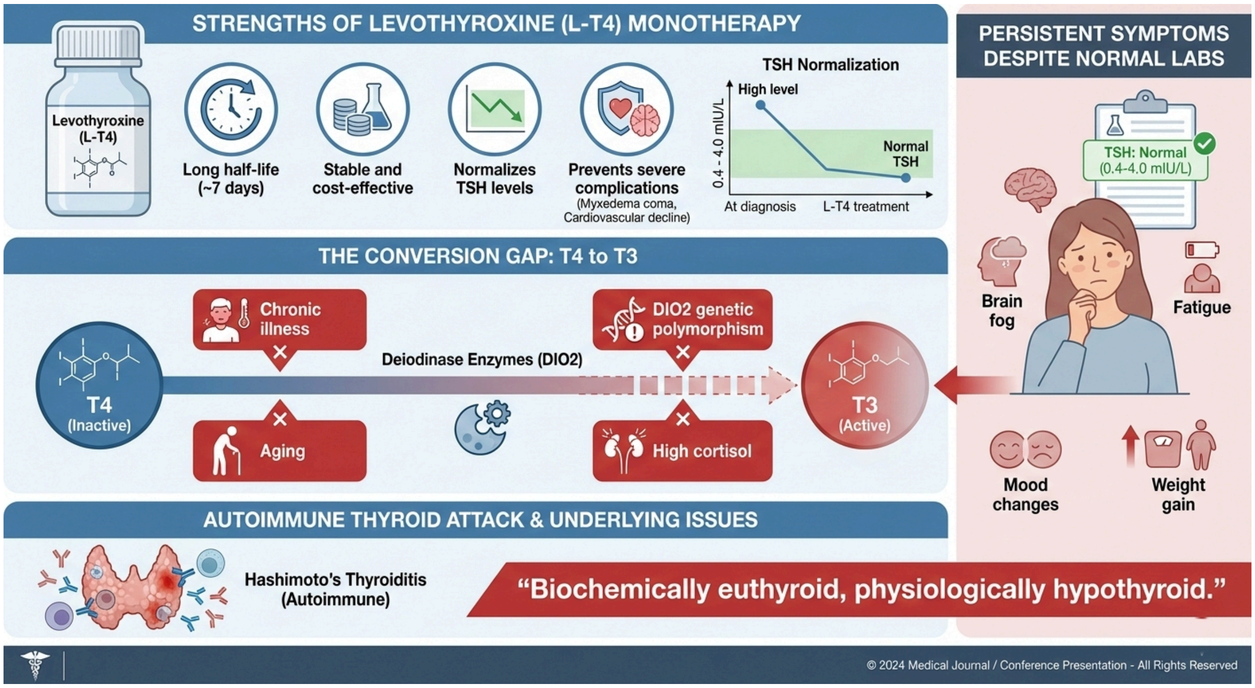
Levothyroxine (L-T4) monotherapy has served as the undisputed gold standard for treating hypothyroidism for decades, favored by clinicians for its long half-life, cost-effectiveness, and the biochemical stability it brings to laboratory results. The clinical logic is elegantly simple: by providing a synthetic version of the storage hormone thyroxine, the body is given a steady reservoir from which it can theoretically draw. The medical community relies on the body's internal machinery , specifically the deiodinase enzymes in the liver, kidneys, and brain to convert this inactive T4 into the active T3 hormone on an as-needed basis, mimicking the natural rhythm of a healthy thyroid gland.

However, this one-size-fits-all strategy rests on the critical assumption that every patient possesses the enzymatic efficiency to perform this conversion effectively. In practice, a significant portion of the population suffers from what is often called a conversion ceiling. Factors such as chronic stress, systemic inflammation, or genetic variations like DIO2 polymorphisms can hinder the body's ability to turn the medication into its active form. For these individuals, standard treatment provides the raw materials but fails to deliver the finished product, resulting in a clinical paradox where a patient's TSH levels look perfect on paper, yet they remain trapped in a state of metabolic famine at the cellular level. Furthermore, the conventional reliance on L-T4 monotherapy often overlooks the systemic nature of thyroid dysfunction, particularly in autoimmune cases like Hashimoto's thyroiditis. Because the primary goal is to normalize the TSH, the treatment is largely reactive rather than proactive. It replaces a missing hormone but does little to address the underlying immune fire or the nutrient deficiencies such as low selenium or zinc that caused the dysfunction in the first place. This leads to a management style where the lab numbers are successfully managed, but the person's quality of life, marked by persistent fatigue and brain fog, continues to decline because the root causes of their symptoms remain unaddressed.

- **Strengths, limitations, and real-world outcomes**

The historical success of levothyroxine (L-T4) monotherapy is rooted in its undeniable practical strengths. From a public health perspective, it is a highly stable medication with a long half-life of approximately seven days, making it forgiving if a dose is occasionally missed. Its cost-effectiveness and the ease with which it normalizes the TSH (Thyroid-Stimulating Hormone) have made it a reliable tool for preventing the most severe complications of hypothyroidism, such as myxedema coma or significant cardiovascular decline. For the majority of patients, this simple replacement of the pro-hormone provides a sufficient reservoir that the body can successfully convert into active T3 to maintain metabolic health. However, the limitations of this one-size-fits-all model become evident when looking at the quality of life for a significant minority of patients. The most glaring weakness is the conversion gap. Standard treatment assumes that every human body possesses the enzymatic machinery, specifically the deiodinase enzymes, to transform inactive T4 into active T3 at an optimal rate. Clinical reality suggests otherwise; factors like chronic illness, aging, DIO2 genetic polymorphisms, and even high levels of cortisol can sabotage this process. Consequently, a patient may be biochemically euthyroid (normal TSH) while remaining physiologically hypothyroid at the cellular level, leading to the frustrating phenomenon of being told you are fine while feeling anything.

Surveys consistently show that roughly 15% to 20% of patients on L-T4 monotherapy report persistent symptoms such as cognitive impairment (brain fog), mood disturbances, and an inability to manage weight despite having perfect lab results. Furthermore, the standard model's reactive nature means that in autoimmune cases like Hashimoto's, the root cause of the immune system attacking the gland is often ignored until the gland is sufficiently destroyed to trigger a TSH rise. This reliance on a single laboratory marker as the sole metric of success often overlooks the multi-systemic nature of the disease, leaving many patients trapped in a cycle of dose adjustments that never quite resolve their lived experience of the illness.




## 7. Rationale for Personalized Medicine in Thyroid Care

The rationale for personalized medicine in thyroid care stems from the clinical recognition that a normal lab result does not always equate to a healthy patient. While the current medical system is built on population averages, personalized care acknowledges that every individual possesses a unique biochemical and genetic signature. This transition is driven by the fact that nearly 20% of patients treated with standard levothyroxine continue to experience debilitating symptoms like brain fog, fatigue, and depression despite having perfect TSH levels. The personalized model seeks to close this dissatisfaction gap by moving beyond the pituitary-centric view and investigating why the hormone is failing to work at the cellular level.

A primary driver for this approach is the identification of genetic variability, particularly in the DIO2 and MCT8 genes. These genetic blueprints determine how well an individual converts storage hormone (T4) into active hormone (T3) and how effectively that hormone enters the cells. In a personalized framework, a patient's genetic predisposition is used to tailor their prescription potentially moving them to a combination T4/T3 therapy or a desiccated thyroid extract (DTE) right from the start. This bypasses the traditional trial and error method, saving the patient months or even years of sub-optimal health by respecting their specific biological requirements. Furthermore, the personalized approach views the thyroid not as an isolated organ but as a critical node in a larger interconnected system. It recognizes that thyroid function is intimately tied to gut health, adrenal function, and nutrient status. For instance, chronic inflammation or a leaky gut can trigger autoimmune flares in Hashimoto's patients, while high cortisol from stress can block thyroid receptors. By addressing these root causes rather than just replacing the missing hormone, personalized medicine aims to restore the entire system to a state of balance. This comprehensive view allows for a more proactive and precise form of care that treats the whole person rather than just their lab numbers.

Finally, the rationale for this model is rooted in the concept of Optimal vs. Normal. Functional medicine practitioners argue that the goal of treatment should be to return a patient to their personal set point where they feel their best, rather than simply moving them into a broad statistical range. By utilizing more sensitive markers like the free T3 to reverse T3 ratio and optimizing levels of selenium, zinc, and vitamin D, personalized nutrition ensures that the key (the hormone) actually fits and turns the lock (the receptor). This shifts the focus of thyroid management from mere survival to true metabolic thriving.

- **Inter-individual variability in thyroid hormone sensitivity**

The concept of inter-individual variability in thyroid hormone sensitivity challenges the traditional assumption that a specific concentration of hormone in the blood produces the same metabolic effect in every person. While the key (the thyroid hormone) might be present in the lock, the sensitivity of that lock determines whether the door to metabolic activity actually opens. This variability explains why some individuals feel energetic and mentally sharp with a TSH of 3.5 mIU/L, while others suffer from classic hypothyroid symptoms like weight gain and brain fog even when their levels are technically within the same range. This hormonal resistance at the cellular level is a primary focal point for personalized medicine.

Beyond transport, the sensitivity of the thyroid hormone receptors (TRs) themselves plays a decisive role. These receptors, primarily the Alpha and Beta isoforms, require specific cofactors to bind effectively to DNA and trigger gene expression. For instance, the receptor must pair with the Retinoid X Receptor (RXR), a process that is highly dependent on adequate levels of Vitamin A. Furthermore, zinc within the receptor structure must be intact for the hormone to successfully flip the switch on metabolism. When a patient is deficient in these critical nutrients, or when high levels of cortisol from chronic stress block the receptor sites, the body becomes effectively deaf to the thyroid's signals, regardless of how much medication is prescribed.

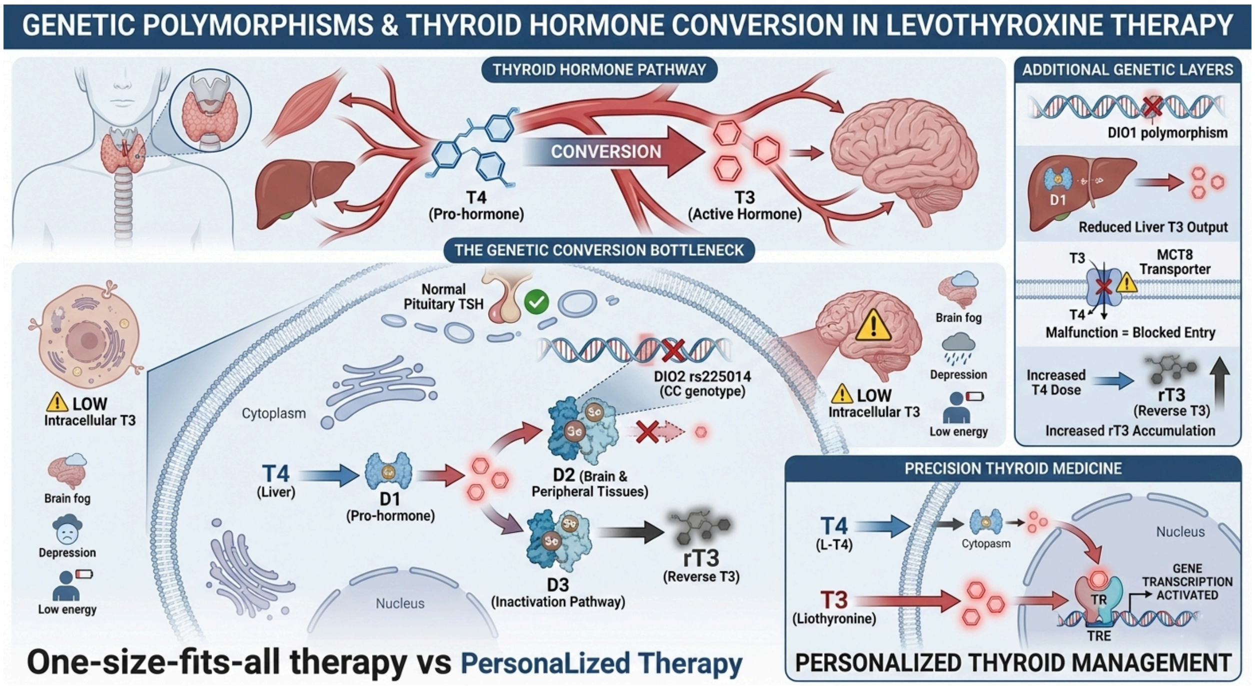
Finally, acquired factors such as systemic inflammation and environmental toxins can epigenetically dial down the body's sensitivity to thyroid hormones. Pro-inflammatory cytokines, like IL-6 or TNF-alpha, have been shown to reduce the expression of thyroid receptors and interfere with the nuclear binding process. Similarly, exposure to endocrine-disruptors like bisphenol A (BPA) can act as competitive inhibitors, sitting in the receptor lock and preventing the real hormone from doing its job. By acknowledging this vast landscape of inter-individual variability, clinicians can move toward a more sophisticated model of care that prioritizes cellular response over mere laboratory averages.

- **Genetic polymorphisms (e.g., deiodinase activity)**

Genetic polymorphisms, particularly those affecting the deiodinase family of enzymes, represent a critical layer of individual variability that can fundamentally alter a person's response to standard thyroid therapy. While the thyroid gland primarily secretes T4, the pro-hormone, the body's metabolic engine runs on the active version, T3. The bridge between these two states is maintained by three selenium-dependent enzymes (D1, D2, and D3). However, subtle variations in the genetic code known as Single Nucleotide Polymorphisms (SNPs) can result in enzymes that are less efficient, essentially creating a conversion bottleneck that is invisible to traditional TSH-only screening.

The most clinically significant of these is the DIO2 (rs225014) polymorphism. This specific genetic variation impacts the Type 2 deiodinase enzyme, which is responsible for converting T4 to T3 within the brain and peripheral tissues. Research has consistently shown that individuals who carry the CC genotype for this polymorphism often struggle on standard Levothyroxine (L-T4) monotherapy. Because their intracellular conversion is impaired, their brain and tissues remain in a localized state of hypothyroidism, leading to persistent symptoms like brain fog, depression, and low energy. Interestingly, the pituitary gland follows different conversion rules, so these patients often have a perfectly normal TSH despite their cellular suffering.

Beyond DIO2, polymorphisms in the DIO1 and MCT8 genes add further complexity. Variations in DIO1 can lower the overall circulating levels of T3 by reducing the liver's capacity for conversion, while MCT8 polymorphisms affect the transport of thyroid hormones into the cells. These genetic predispositions mean that the one-size-fits-all model of thyroid care is biologically flawed for a significant subset of the population. For a carrier of these SNPs, the most effective clinical solution is often the introduction of combination T4/T3 therapy, which bypasses the genetic conversion hurdle by providing the active hormone directly. Understanding these polymorphisms allows for a move toward high-precision thyroid management. In a personalized medicine framework, testing for these specific genetic markers can explain why a patient remains symptomatic despite optimal lab results. It shifts the clinical focus from simply increasing the T4 dose which may actually increase levels of inactive Reverse T3 (rT3) in these individuals to a more nuanced strategy that respects the patient's unique enzymatic capacity. By decoding these genetic hurdles, clinicians can finally resolve the dissatisfaction gap and help patients achieve true metabolic optimization.




- **Optimal Ranges**

The transition from population-based averages to personalized reference ranges is a cornerstone of the shift toward precision thyroid care. Conventional medicine typically defines normal as any value falling within a broad bell curve, usually a TSH between 0.45 and 4.5 mIU/L representing the middle 95% of a largely heterogeneous population. However, functional medicine argues that normal is not synonymous with optimal. A personalized range is based on the biological reality that every individual has a unique, genetically determined homeostatic set-point.

Establishing these personalized parameters requires a more expansive diagnostic lens. Rather than relying on a single TSH data point, a personalized profile incorporates Free T3, Free T4, and Reverse T3 (rT3) to assess the flow of hormones through the system. For example, a personalized optimal Free T3 is often targeted in the upper 25% of the laboratory range (e.g., >3.5 pg/mL) to ensure adequate cellular fuel, while rT3 is monitored to ensure the hormone isn't being shunted into an inactive storage form due to stress or inflammation. By looking at these ratios, clinicians can identify cellular hypothyroidism, a state where blood levels look acceptable by population standards, but the ratio of active-to-inactive hormone is insufficient for that specific patient's metabolic needs.

Furthermore, personalized reference ranges account for life stage and comorbidities, recognizing that optimal range changes with context. By moving away from a static, one-size-fits-all window, this approach ends the clinical gaslighting of symptomatic patients who are told they are fine because they are one decimal point away from a diagnostic threshold.

Instead, it prioritizes symptomatic resolution and metabolic thriving as the ultimate metrics of success.

- **Patient-reported outcomes and symptom heterogeneity**

The clinical reality of thyroid management is often defined by a profound dissatisfaction gap , a phenomenon where roughly 15% to 20% of patients continue to struggle with debilitating symptoms despite achieving biochemically perfect lab results. This symptom heterogeneity means that two patients with identical TSH levels can experience vastly different qualities of life; while one may feel entirely restored, another may remain trapped in a cycle of persistent fatigue, cognitive brain fog, and emotional instability. This disconnect highlights the limitation of using a single laboratory marker to define a patient's health, as the subjective experience of thyroid disease is often far more complex than a numerical value on a report.

To capture this lived experience, modern personalized medicine increasingly relies on Patient-Reported Outcome Measures (PROMs), such as the validated ThyPRO questionnaire. These tools move beyond the blood test to evaluate a broad spectrum of symptoms, including physical stamina, social functioning, and mental health. By systematically tracking these metrics, clinicians can identify specific clusters of symptoms, such as the mental fatigue associated with low T3 that standard protocols often miss. This shift recognizes that the patient's voice is an essential diagnostic tool, providing a more granular view of how thyroid dysfunction ripples through the cardiovascular, neurological, and gastrointestinal systems.

The biological drivers of this symptom variety are often hidden at the cellular and systemic levels. Beyond the thyroid gland itself, factors such as gut microbiome dysbiosis, insulin resistance, and localized nutrient deficiencies (like low selenium or zinc) can sabotage how a patient feels. For instance, chronic inflammation can trigger a metabolic braking system, shunting thyroid hormone into its inactive reverse T3 form. This creates a state of cellular hypothyroidism that is invisible to a TSH test but deeply felt by the patient. By acknowledging these hidden culprits, a personalized approach seeks to treat the whole person, integrating physiological data with the patient's unique symptom profile to achieve a state of true metabolic thriving.

- **Longitudinal data vs single time-point testing**

In traditional clinical settings, thyroid health is often determined by single time-point testing, which captures a static snapshot of a highly dynamic system. Because thyroid hormones are subject to circadian rhythms, seasonal shifts, and acute physiological stressors such as an overnight fast or an intense workout a single blood draw may not accurately reflect a patient's true baseline. This snapshot approach can lead to misdiagnosis or premature treatment, as a TSH level that appears slightly elevated on a Tuesday morning might naturally resolve to the center of the range just a week later.

The move toward longitudinal data analysis represents a fundamental shift toward more accurate, personalized care. By tracking thyroid markers over weeks, months, or years, clinicians can identify a patient's unique hormonal signature and detect subtle trends before they cross the threshold into overt disease. This time-series approach allows for the differentiation between a transient dip in thyroid function caused by a recent viral illness and a genuine, progressive decline in gland output. Longitudinal tracking turns the lab report from a pass/fail grade into a narrative, revealing how a patient's lifestyle, stress levels, and nutritional status impact their metabolic stability over time.

Furthermore, longitudinal data is essential for assessing the efficacy of interventions. In a personalized medicine framework, the goal is not just to normalize a number, but to find the level at which the patient feels their best. By correlating long-term laboratory trends with subjective symptom tracking (such as temperature, heart rate, and mood logs), clinicians can pinpoint a patient's optimal window. This data-driven approach reduces the need for the aggressive dose-chasing often seen in conventional medicine, replacing it with a nuanced strategy that respects the body's natural fluctuations and focuses on long-term systemic stability rather than reactive adjustments based on a single, isolated lab result.

## 8. Functional Medicine Framework in Thyroid Dysfunction

The Functional Medicine framework for thyroid dysfunction represents a fundamental shift from treating a single organ to addressing the interconnected web of a patient's unique biology. Rather than focusing solely on the thyroid gland's output, this systems-biology approach investigates the upstream triggers such as chronic inflammation, gut dysbiosis, and adrenal stress that can sabotage thyroid hormone production, conversion, and cellular action long before laboratory markers cross into the diagnostic range of pathology. By viewing the thyroid as a sensitive indicator of systemic health, clinicians can move beyond the one-pill-fits-all model and prioritize the restoration of foundational processes, such as the gut-immune barrier and micronutrient status. This holistic lens ensures that the thyroid is not just supported in isolation, but is optimized within the context of a thriving, balanced internal environment.

### 8.1 Root-Cause Analysis

- **Immune dysregulation (autoimmunity)**

Immune dysregulation is a key driver of thyroid dysfunction, particularly in autoimmune thyroid diseases, where loss of immune tolerance leads to inappropriate immune responses against thyroid tissue. Rather than being an isolated glandular disorder, thyroid dysfunction often reflects broader disturbances in immune regulation and inflammatory balance. This systems-based understanding is central to personalized and functional medicine approaches, which emphasize upstream mechanisms contributing to disease onset and progression. Conditions such as Hashimoto's thyroiditis and Graves' disease exemplify immune-mediated thyroid dysfunction. In Hashimoto's thyroiditis, immune cell infiltration and autoantibody production result in progressive thyroid tissue damage and hypothyroidism, whereas Graves' disease is characterized by stimulatory antibodies that cause excessive thyroid hormone production. Pro-inflammatory cytokines and impaired regulatory immune pathways can further disrupt thyroid hormone synthesis, peripheral hormone conversion, and tissue-level signaling, contributing to symptoms even when standard thyroid hormone levels appear normal.

The development of immune-related thyroid disorders is influenced by a combination of genetic predisposition and modifiable environmental factors. Nutrient deficiencies, gut barrier dysfunction, chronic stress, infections, and exposure to environmental toxins may all contribute to immune imbalance and autoimmunity in susceptible individuals. Clinically, immune markers such as thyroid autoantibodies may precede hormonal abnormalities, and persistent symptoms despite biochemical euthyroidism may reflect unresolved immune dysfunction, underscoring the importance of integrating immune assessment into personalized, data-driven thyroid care.

- **Nutrient insufficiencies**

Nutrient insufficiencies play a significant role in the development and progression of thyroid dysfunction by impairing both thyroid hormone synthesis and immune regulation. The thyroid gland has a high demand for specific micronutrients that support hormone production, antioxidant defense, and protection against immune-mediated damage. Inadequate nutrient availability can therefore contribute to reduced thyroid hormone output, altered peripheral hormone conversion, and increased vulnerability to autoimmune processes.

Several nutrients are particularly critical for optimal thyroid function. Iodine is essential for thyroid hormone synthesis, yet both deficiency and excess can disrupt thyroid activity and trigger autoimmune responses in susceptible individuals. Selenium supports the activity of deiodinase enzymes responsible for converting thyroxine (T4) to the biologically active triiodothyronine (T3) and plays a key role in reducing oxidative stress within thyroid tissue. Iron deficiency can impair thyroid peroxidase activity, limiting hormone production, while zinc is involved in thyroid hormone receptor function and intracellular signaling. Vitamin D also contributes to immune modulation, and low levels have been associated with increased prevalence and severity of autoimmune thyroid disease.

From a personalized and functional medicine perspective, nutrient insufficiencies often coexist and interact with other physiological stressors such as inflammation, gut dysfunction, and chronic stress. Subclinical deficiencies may not be evident on routine testing yet can meaningfully affect thyroid physiology and symptom burden. Addressing nutrient status through individualized assessment and targeted repletion may therefore support thyroid hormone metabolism, immune balance, and overall treatment responsiveness as part of a comprehensive, data-driven approach to thyroid optimization.

- **Chronic inflammation**

Chronic low-grade inflammation is a key underlying factor in the development and progression of thyroid disorders, particularly autoimmune thyroid diseases. Persistent activation of the immune system can disrupt thyroid tissue integrity, alter hormone synthesis, and promote the production of thyroid autoantibodies. Pro-inflammatory cytokines interfere with thyroid hormone signaling and reduce peripheral conversion of T4 to the active hormone T3, contributing to functional hypothyroidism even when serum hormone levels appear normal.

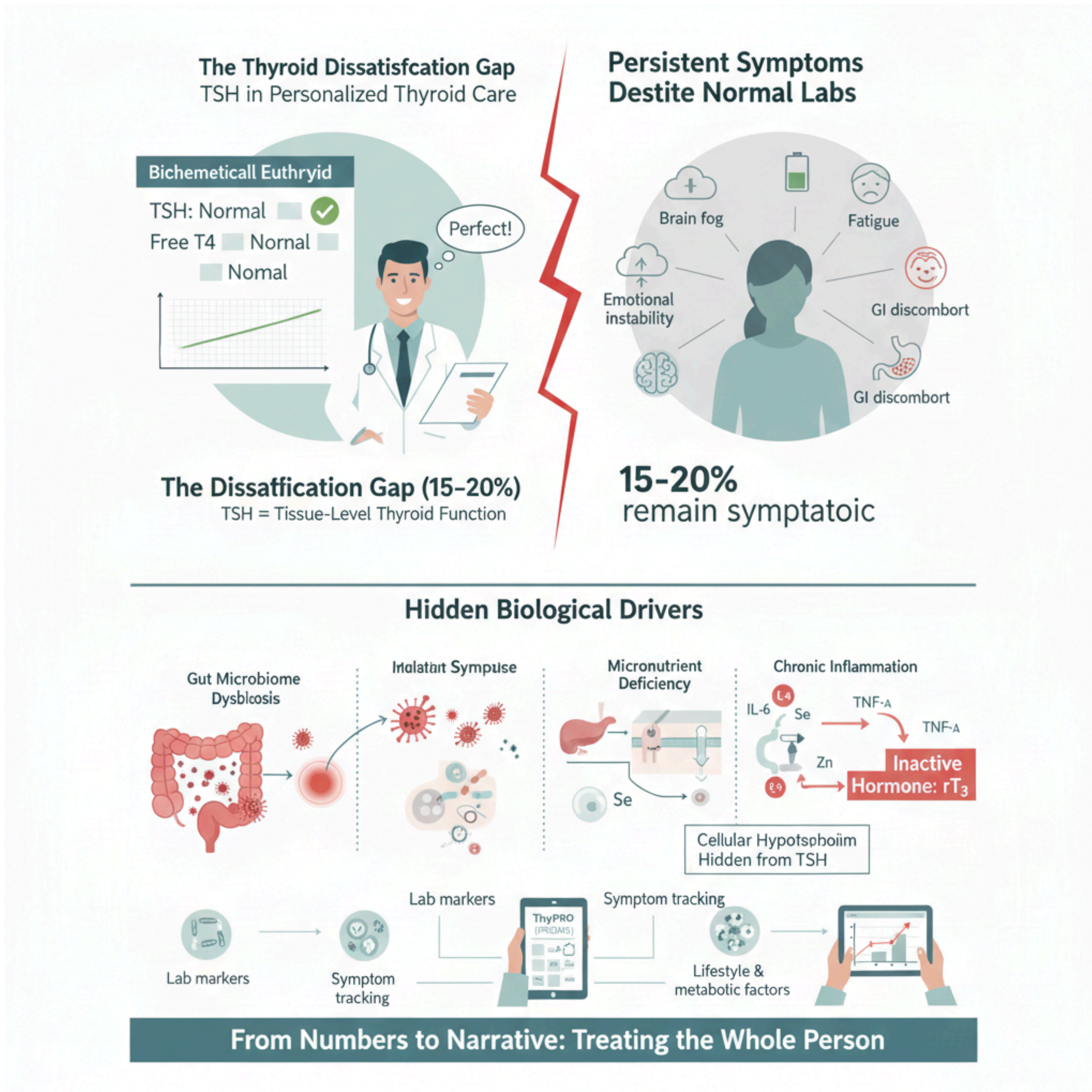
Several lifestyle and environmental factors can sustain chronic inflammation, including poor dietary patterns, micronutrient deficiencies, obesity, physical inactivity, sleep disturbances, psychological stress, and exposure to environmental toxins. Increased intestinal permeability, oxidative stress, and immune dysregulation further amplify inflammatory pathways, creating a self-perpetuating cycle. Addressing chronic inflammation through anti-inflammatory Diet, optimized lifestyle habits, and targeted management of metabolic and immune stressors is therefore central to restoring thyroid balance and improving long-term outcomes.

- **Gut-thyroid axis**

The intestinal microbiota plays a central role in metabolic regulation, immune homeostasis, and nutrient absorption, and growing evidence supports the existence of a thyroid-gut axis. Gut microorganisms influence thyroid function by modulating the absorption of key micronutrients required for thyroid hormone synthesis, including iodine, selenium, zinc, and iron, as well as participating in thyroid hormone metabolism. Iodothyronine deiodinase activity within the intestinal wall contributes to the conversion of thyroxine (T4) to triiodothyronine (T3) or reverse T3, thereby affecting systemic thyroid hormone availability. Alterations in gut microbiota composition have been consistently observed following dietary changes, reinforcing the role of nutrition in shaping thyroidmicrobiota interactions.

Exposure to endocrine-disrupting chemicals (EDCs) further complicates this relationship by altering gut microbial composition and metabolic function. Early-life exposure is particularly relevant, as breast milk represents a major source of EDC transfer during the first 1,000 days of life through the entero-mammary pathway. Common contaminants such as phthalates and bisphenol A have been detected in breast milk, with maternal exposure influenced by lifestyle, environment, occupation, and personal care products. Increased EDC exposure may promote dysbiosis by stimulating pathogenic microbial species, impairing intestinal barrier function, and enhancing immune dysregulation, thereby increasing susceptibility to inflammatory and autoimmune thyroid diseases.

Diet also links the gut microbiota, epigenetic regulation, and thyroid function. Microbial metabolites, such as short-chain fatty acids, can influence epigenetic mechanisms, including DNA methylation and histone modification, thereby indirectly affecting thyroid hormone metabolism and signaling. Nutrients involved in one-carbon metabolism, such as folate and vitamin B12, support epigenetic stability and may contribute to optimal thyroid health. Additionally, dietary polyphenols from fruits, vegetables, and tea exhibit epigenetic and anti-inflammatory effects that may offer protective benefits. Conversely, thyroid hormones themselves influence gut epithelial function and microbial composition, highlighting a dynamic, bidirectional interaction between thyroid physiology, diet, and the intestinal microbiome.




**Environmental Toxins:**

Environmental toxin load represents a biologically plausible upstream driver of thyroid dysfunction, affecting not only free triiodothyronine (FT3), but also thyroxine (T4), thyroid-stimulating hormone (TSH), thyroid autoimmunity, and peripheral thyroid hormone metabolism. Human epidemiological data have demonstrated associations between exposure to heavy metals including mercury, arsenic, cadmium, and lead and alterations in thyroid hormone parameters. Population-based studies report inverse relationships between blood mercury concentrations and circulating T3 measures, along with broader disturbances in T4 and TSH dynamics. Occupational exposure studies further support the association between chronic metallic mercury exposure and altered thyroid hormone profiles.

Mechanistically, heavy metals exert multiple thyroid-disrupting effects. These include oxidative stress within thyroid tissue, inhibition of thyroid peroxidase activity, interference with iodide uptake, disruption of hormone transport proteins, and impairment of 5′-deiodinase enzymes responsible for peripheral conversion of T4 to T3. Such interference can result in reduced active hormone availability, altered feedback signaling to the hypothalamic-pituitary-thyroid (HPT) axis, and compensatory shifts in TSH secretion.

Halogenated environmental exposures, including chlorine- and bromine-derived compounds, may further contribute to thyroid disruption. Because halogens share structural similarity with iodine, they may competitively inhibit iodine uptake and organification within the thyroid gland. Chronic exposure to chlorine and bromide compounds, including disinfection by-products such as trihalomethanes, has been associated in human studies with altered thyroid hormone levels. Impaired iodine utilization can disrupt hormone synthesis, alter T4 and T3 production, and potentially contribute to goitrogenesis or subclinical hypothyroid patterns.

Collectively, cumulative environmental toxin burden may disrupt thyroid physiology at multiple levels: glandular synthesis, iodine regulation, peripheral hormone activation, transport, receptor signaling, and HPT axis regulation.

**Biological Toxins:**

Biological toxin load, particularly exposure to mycotoxins, represents an additional and often underrecognized contributor to thyroid dysregulation. Mycotoxins such as aflatoxins and ochratoxin A are fungal secondary metabolites detectable in human biological samples. These compounds are recognized endocrine-disrupting agents with documented effects on hepatic metabolism, immune regulation, mitochondrial function, and inflammatory signaling.

Thyroid hormone homeostasis is highly dependent on hepatic function, as the liver plays a central role in thyroid hormone metabolism, conjugation, clearance, and peripheral conversion of T4 to T3. Mycotoxin-induced hepatic stress may therefore impair deiodination efficiency and alter circulating levels of FT3 and reverse T3. Additionally, biological toxins promote oxidative stress and chronic immune activation, which can suppress type 1 and type 2 deiodinase activity while increasing type 3 deiodinase expression, favoring inactivation of T3.

Beyond hormone conversion, chronic inflammatory signaling triggered by biological toxins may also influence thyroid autoimmunity. Immune dysregulation and sustained cytokine activity are mechanistically linked to autoimmune thyroid conditions, including Hashimoto thyroiditis. Inflammatory stress may therefore contribute not only to altered hormone levels but also to structural and immunologic thyroid pathology.

Taken together, total toxin load encompassing environmental toxicants such as mercury, chlorine, and bromide, as well as biological toxins such as mycotoxins may function as a systemic root contributor to thyroid dysfunction. Through oxidative stress, iodine antagonism, hepatic impairment, immune dysregulation, and disruption of peripheral hormone metabolism, toxin burden has the potential to affect multiple dimensions of thyroid physiology beyond FT3 alone. While further prospective human studies are required to clarify causal relationships, existing epidemiological and mechanistic evidence supports toxin load as a biologically plausible upstream factor in thyroid dysregulation.

### 8.2 Functional Assessment Tools

- **Comprehensive thyroid panels**

Functional assessment of thyroid health increasingly relies on comprehensive thyroid panels that go beyond basic TSH and free T4 measurements. These panels typically include free T3, reverse T3, and thyroid autoantibodies (TPOAb and TgAb), providing a deeper understanding of hormone production, conversion efficiency, and autoimmune activity. By examining both peripheral and central thyroid function, clinicians can detect subclinical dysfunction, identify impaired T4-to-T3 conversion, and uncover early autoimmune responses that might be missed by standard tests. Such detailed profiling enables more precise diagnosis, informs individualized treatment strategies, and helps monitor therapy effectiveness over time.

- **Inflammatory and metabolic markers**

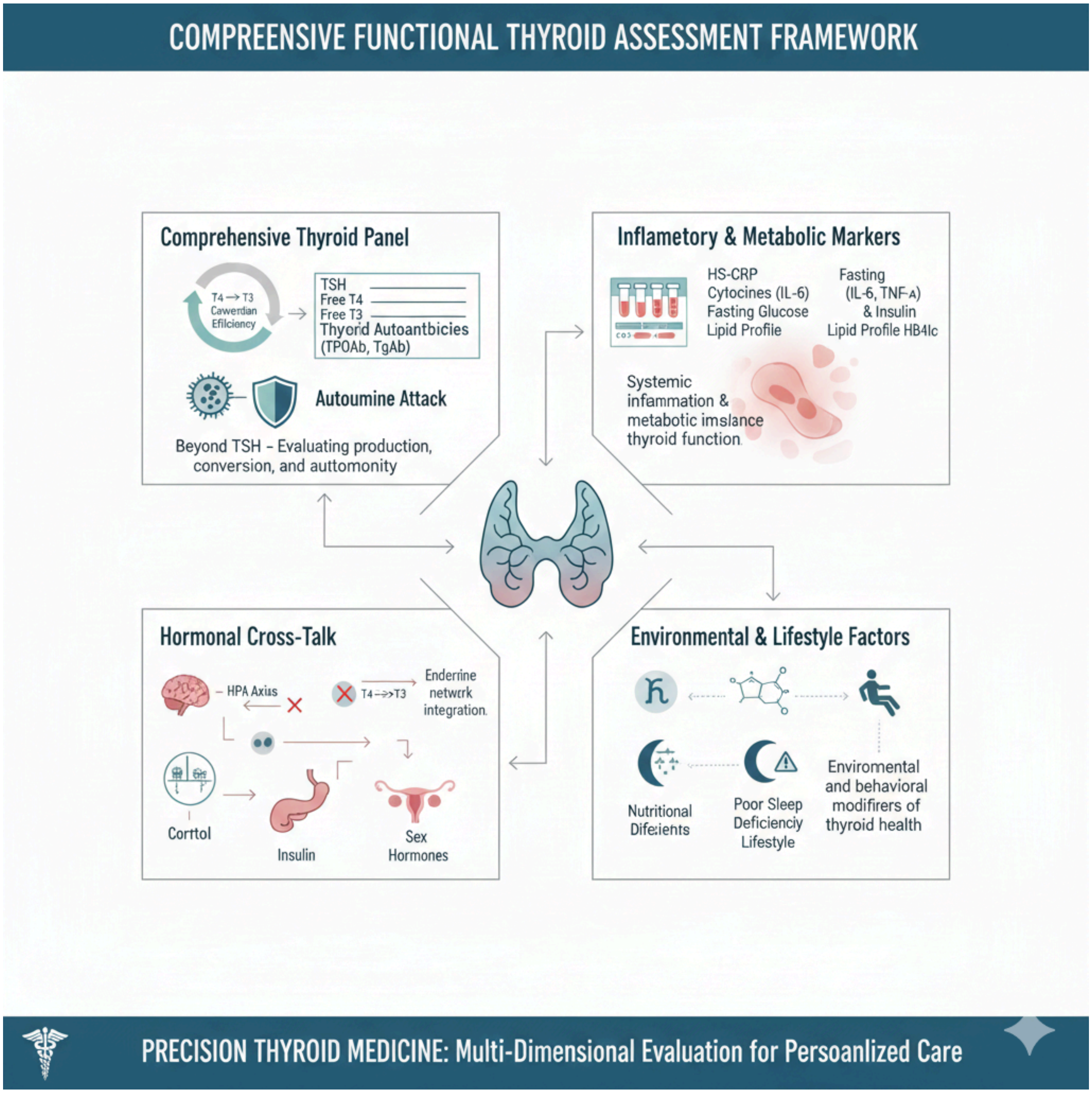
Thyroid disorders are closely linked with systemic inflammation and metabolic imbalance. Functional assessment often incorporates inflammatory markers such as HS-CRP, interleukins, and tumor necrosis factor-alpha (TNF-α), alongside metabolic indicators like fasting glucose, insulin, lipid profile, and HbA1c. Monitoring these biomarkers helps identify underlying contributors to thyroid dysfunction, such as chronic inflammation, insulin resistance, or oxidative stress. Tracking these markers can guide interventions aimed at reducing systemic inflammation, improving metabolic efficiency, and supporting thyroid hormone activity at the tissue level.

- **Hormonal cross-talk (cortisol, insulin, sex hormones)**

Thyroid function is influenced by complex interactions with other endocrine systems, making assessment of hormonal cross-talk critical. Cortisol, insulin, and sex hormones (estrogen, progesterone, and testosterone) all affect thyroid hormone synthesis, conversion, and receptor sensitivity. Chronic stress and elevated cortisol can suppress TSH and impair T4-to-T3 conversion, while insulin resistance and hormonal imbalances can exacerbate hypothyroid or hyperthyroid states. Evaluating these interactions allows clinicians to identify secondary contributors to thyroid dysfunction and design integrated interventions targeting multiple hormonal pathways simultaneously.

- **Environmental and lifestyle contributors**

Functional thyroid assessment also considers environmental and lifestyle factors that impact endocrine health. Exposure to endocrine-disrupting chemicals, heavy metals, and pollutants, as well as poor sleep, sedentary lifestyle, and dietary insufficiencies, can compromise thyroid function directly or indirectly through immune and metabolic pathways. Collecting information on these contributors enables a holistic understanding of each patient’s thyroid health, allowing for targeted lifestyle modifications and environmental interventions that complement conventional therapy and optimize long-term outcomes.




### 9.1 Expanded Thyroid Biomarkers

- **Free T3, Free T4**

Free T3 (triiodothyronine) and free T4 (thyroxine) are the biologically active forms of thyroid hormones circulating in the bloodstream. Assessing free hormone levels, rather than total hormone concentrations, provides a more accurate reflection of thyroid activity at the tissue level. Free T4 is primarily produced by the thyroid gland and serves as a precursor to T3, while free T3 represents the active hormone responsible for regulating metabolism, energy production, and cellular function. Measuring both hormones helps detect subtle imbalances, impaired conversion of T4 to T3, and subclinical thyroid disorders that may not be evident through TSH testing alone.

- **Reverse T3**

Reverse T3 (rT3) is an inactive form of T3 produced from T4 during periods of stress, illness, or impaired metabolic function. Elevated rT3 can block thyroid hormone receptors, reducing tissue-level thyroid activity even when circulating T4 and T3 appear normal. Assessing rT3 alongside free T3 and T4 allows clinicians to identify conditions such as low T3 syndrome or tissue hypothyroidism, offering insight into metabolic stress, chronic illness, or nutrient deficiencies that interfere with proper hormone utilization.

- **Thyroid autoantibodies**

Thyroid autoantibodies, including thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb), are critical markers of autoimmune thyroid disease. Their presence indicates immune-mediated damage to thyroid tissue, as seen in Hashimoto's thyroiditis or Graves' disease. Quantifying autoantibody levels helps assess disease activity, predict progression, guide therapy decisions, and monitor response to interventions. Together with expanded hormone panels, autoantibody testing provides a comprehensive view of both functional and immunological aspects of thyroid health.

### 9.2 Metabolic and Nutritional Modifiers: Stress, Inflammation, and Mitochondrial Function

- **Iron and ferritin**

Iron and ferritin are critical components for optimal thyroid function because iron is an essential cofactor for thyroid peroxidase (TPO), the enzyme responsible for iodination of thyroglobulin during thyroid hormone synthesis. Low iron levels or iron deficiency anemia can impair TPO activity, reduce thyroid hormone production, and exacerbate hypothyroid symptoms such as fatigue, cold intolerance, and cognitive slowing. Measuring both serum iron and ferritin, the primary iron storage protein, provides a more accurate assessment of iron status, as ferritin reflects total body iron reserves even before anemia develops.

Iron deficiency is particularly relevant in populations with autoimmune thyroid disease, chronic gastrointestinal conditions, or dietary restrictions, where impaired absorption or chronic blood loss can further compromise thyroid health. Optimizing iron status through dietary intake, supplementation, or addressing underlying absorption issues enhances thyroid hormone synthesis, supports peripheral conversion of T4 to T3, and improves energy metabolism. Monitoring iron and ferritin alongside thyroid function tests is therefore essential for comprehensive thyroid care.

- **Iodine status**

Iodine plays an essential role in the synthesis of thyroid hormones (TH). It is absorbed in the small intestine, primarily in the form of iodide ions (I-), transported via the bloodstream to the thyroid gland, where it is actively taken up by thyroid follicular cells. Within the thyroid follicular cells, iodine is enzymatically incorporated into tyrosine residues on thyroglobulin, a large glycoprotein synthesized by the thyroid gland. This process results in the formation of monoiodotyrosine (MIT) and diiodotyrosine (DIT), which then undergo further iodination to produce triiodothyronine and thyroxine, the active thyroid hormones. These iodinated tyrosine residues are part of the thyroglobulin molecule, and when the hormone is required, thyroglobulin is broken down, releasing T3 and T4 into the bloodstream. Therefore, adequate iodine intake is necessary for maintaining normal thyroid function. The European Food Society Authority (EFSA) proposes age-specific intakes of iodine ranging from 70 μg/24 h for children to 150 μg/24 h at the end of adolescence. These are intakes calculated to ensure a urinary iodine concentration (UIC) ≥ 100 μg/L, which is the cut-off associated with the lowest prevalence of iodine-deficient goiter in school-aged children. It is calculated that in healthy children, the body contains around 15 to 20 mg of iodine, with the majority found in the thyroid gland.

Adequate iodine intake is necessary during the weaning period. In infants, it changes from exclusive breastfeeding to a mixed diet. While breastfeeding is an excellent source of iodine for infants, the amount of iodine depends on the mother's iodine intake. Iodine deficiency in pregnancy can severely impact the cognitive development of the offspring. As both maternal and fetal thyroid functions are affected

- **Selenium, zinc**

Selenium deficiency has been associated with multiple thyroid disorders, including overt and subclinical hypothyroidism, thyroid cancer, and autoimmune thyroid diseases such as Hashimoto's thyroiditis and Graves' disease. Evidence in pediatric populations is limited, but studies in children with phenylketonuria (PKU) suggest altered thyroid hormone profiles. Van Bakel et al. reported significantly higher free T4 and free T3 levels in children with PKU compared to controls, indicating a potential relationship between selenium status and thyroid hormone metabolism.

Calomme et al. demonstrated that selenium supplementation in severely deficient individuals significantly increased plasma selenium levels and glutathione peroxidase activity while reducing circulating T4 and reverse T3 concentrations. Discontinuation of supplementation reversed these changes, whereas TSH and T3 levels remained unaffected, suggesting that selenium primarily influences peripheral thyroid hormone metabolism rather than pituitary feedback mechanisms. These findings are consistent with animal studies showing that selenium deficiency impairs hepatic deiodinase activity, elevates T4 and reverse T3 levels, and does not result in clinically apparent hypothyroidism.

Zinc deficiency can disrupt thyroid hormone signaling by impairing thyroid hormone receptor function, reducing hormone binding and gene regulation, and potentially decreasing thyroid hormone synthesis, thereby contributing to the development of hypothyroidism [8991]. Numerous studies and systematic reviews have reported an association between zinc deficiency and hypothyroidism. Acquired zinc deficiency has also been implicated in hair-related manifestations commonly observed in hypothyroid patients, including hair loss, dryness, brittleness, and pigment changes, reflecting zinc's role as a cofactor for multiple metalloenzymes. Diets rich in zinc have been suggested as supportive in achieving euthyroidism and improving alopecia; however, robust randomized clinical trials are still required to clarify the therapeutic role of zinc supplementation in hypothyroid-associated hair loss.

Evidence regarding the relationship between zinc and hyperthyroidism remains limited and inconsistent. While some studies have suggested a role for zinc in papillary thyroid cancer and follicular carcinoma, a recent Mendelian randomization analysis found no causal association, underscoring the need for further investigation. Zinc deficiency has also been associated with thyroid enlargement in both children and adults. In pediatric populations, an inverse correlation between serum zinc levels and thyroid size has been reported, potentially due to impaired triiodothyronine action and reduced nuclear receptor binding. Similar associations have been observed in adults, including those with nodular goiter, particularly in iodine-deficient regions. Low zinc status has additionally been linked to autoimmune thyroid disease, although findings remain controversial. Some studies report a positive association between zinc deficiency and thyroid autoimmunity, while others have found no significant differences in zinc levels between individuals with Hashimoto's thyroiditis and healthy controls. These conflicting results highlight the need for further well-designed studies to clarify the role of zinc in thyroid autoimmunity and thyroid disease progression.

- **Insulin resistance**

Thyroid hormones play a critical role in the regulation of glucose metabolism through both direct and indirect mechanisms. They directly influence the expression of thyroid hormone responsive genes in target tissues and indirectly modulate glucose homeostasis via hypothalamic pathways that regulate sympathetic nervous system activity. Thyroid hormones may exert insulin-agonistic effects in tissues such as skeletal muscle while acting antagonistically in the liver, highlighting their tissue-specific metabolic actions. In hyperthyroidism, disruption of this balance frequently leads to glucose intolerance, primarily driven by hepatic insulin resistance. In hypothyroidism, metabolic effects on glucose regulation are less pronounced; however, existing evidence suggests the presence of insulin resistance predominantly in peripheral tissues, potentially due to impaired mitochondrial oxidative metabolism and reduced blood flow in muscle and adipose tissue.

- **Cortisol dynamics**

The effects of hypercortisolism on HPT axis activity are complex and involve different mechanisms. The most evident consequence of the inappropriate cortisol secretion on thyroid axis activity is a central hypothyroidism, which is due to the inhibitory effects of glucocorticoids on TRH and TSH secretion. Peripheral actions of thyroid hormones can be altered by an impaired function of deiodinases, which is related to the inappropriate cortisol secretion. However, the clinical interpretation and significance of dynamic changes in HPT function during active CS syndrome is still debated. The studies are mainly retrospective and included small and heterogeneous groups of patients. Furthermore, in clinical practice, the possible effects of some drugs used for the control of hypercortisolism should be considered. Based on recent findings, the evaluation of thyroid function in CS patients both during active disease and after the remission of hypercortisolism represents a reasonable approach. In fact, some dynamic changes in HPT axis activity are recovered after successful surgery. Furthermore, the increased prevalence of autoimmune thyroid disease observed after hypercortisolism remission must be considered. Probably, in patients with underlying autoimmune thyroid disease, the inappropriate cortisol secretion guarantees an immunologic tolerance masking the overt thyroid dysfunction, which develops after the cure of CS.

Notably, 52.5% of patients exhibited subclinical hypothyroidism, highlighting the limitations of routine thyroid function tests, including TSH, FT4, and FT3, in identifying early-stage thyroid dysfunction. These findings suggest that cortisol dysregulation may impair thyroid function by disrupting peripheral conversion of thyroxine to triiodothyronine, underscoring the close interplay between the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid axes under chronic stress conditions. Incorporating advanced diagnostic measures, such as reverse T3 assessment to evaluate peripheral thyroid hormone metabolism and dynamic cortisol testing (e.g., diurnal cortisol profiling or ACTH stimulation), may enhance detection of subclinical thyroid and adrenal dysfunction in chronically stressed populations. Such integrated testing approaches may facilitate earlier identification and more precise management of stress-related endocrine disturbances. Future research should investigate targeted interventions, including strategies to modulate cortisol levels and individualized thyroid hormone therapies for subclinical cases, to mitigate the metabolic consequences of chronic stress. Additionally, longitudinal studies are needed to elucidate the causal mechanisms underlying cortisol-thyroid interactions and their contribution to the progression of stress-associated endocrine disorders.

- **Chronic low-grade inflammation**

The relationship between inflammation and thyroid function is complex and bidirectional, as inflammatory processes can disrupt thyroid hormone homeostasis while thyroid hormones themselves modulate inflammatory responses. During severe illness or infection characterized by marked inflammation, circulating thyroid hormone levels typically decline, with or without a concomitant reduction in TSH, a phenomenon referred to as euthyroid sick syndrome. This response has been observed not only in humans but also in animal models, including mice, rats, and rabbits. Reduced triiodothyronine levels are largely attributed to altered activity of iodothyronine deiodinases, whereas decreased thyroxine concentrations are commonly linked to suppression of TSH secretion.

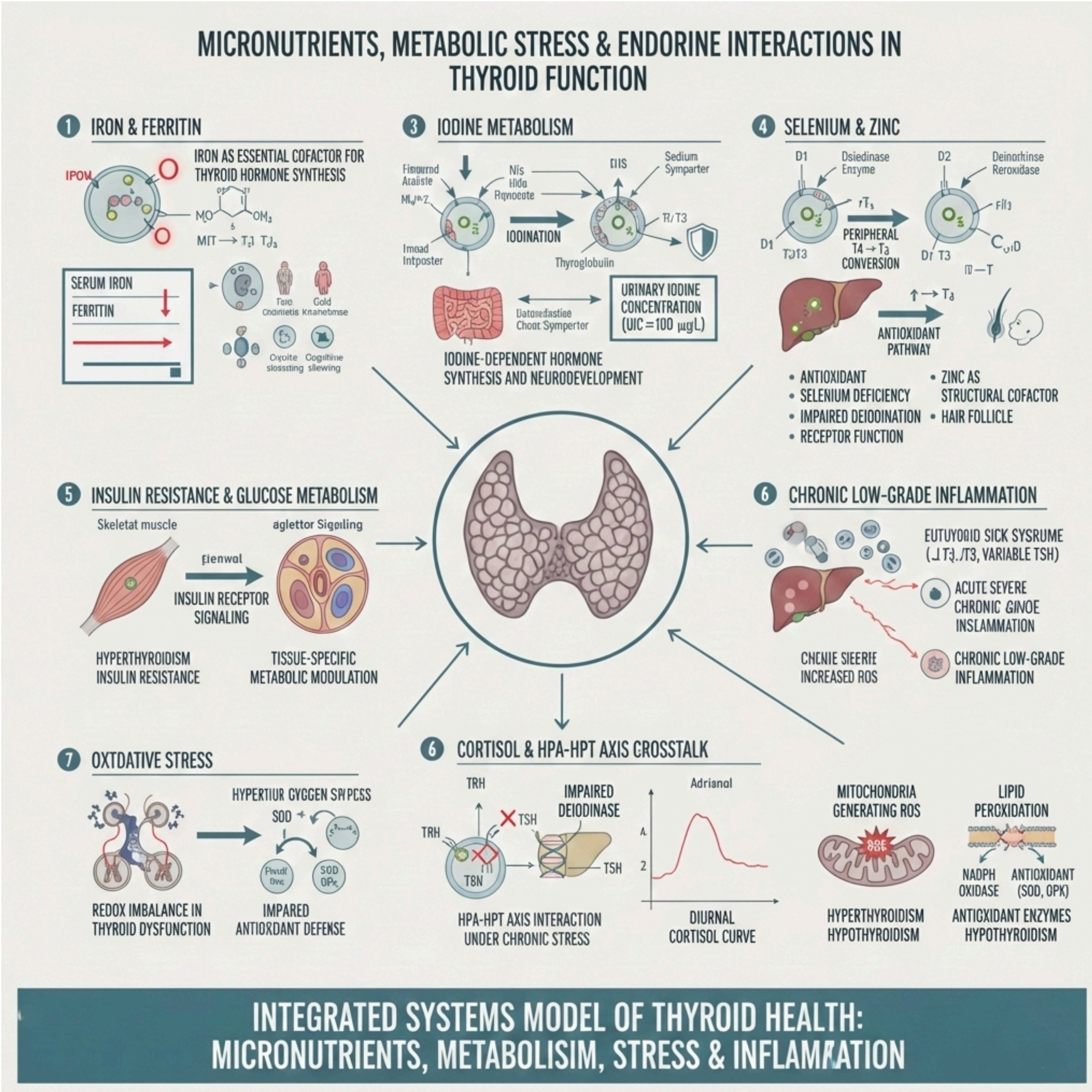
In cases where TSH remains within the normal range despite reduced T4 levels, additional mechanisms must be considered. Bioinformatic and experimental evidence suggests that inflammatory mediators may directly suppress T4 levels independent of pituitary regulation. In severe inflammatory states, the normal negative feedback response of the hypothalamic-pituitary-thyroid axis appears to be blunted, preventing the expected compensatory rise in TSH. In contrast, this feedback mechanism remains functional in subclinical, chronic, and low-grade inflammatory conditions.

Supporting this distinction, Moura Neto et al. compared thyroid function in type 1 diabetes mellitus, an autoimmune inflammatory disorder, and type-2-diabetes mellitus, a metabolic condition associated with chronic low-grade inflammation. They observed reductions in serum T3 and T4 in both conditions; however, TSH levels were decreased in type 1 diabetes and increased in type-2-diabetes, highlighting inflammation-dependent differences in hypothalamic-pituitary-thyroid axis regulation.

- **Oxidative stress**

Elevated malondialdehyde levels have been reported in individuals with hypothyroidism, including subclinical forms, compared with healthy controls, indicating increased oxidative stress. In addition to impaired antioxidant defenses, these changes may be partly attributable to alterations in lipid metabolism within thyroid cells. Although treatment of hypothyroidism has been shown to reduce lipid peroxidation, serum malondialdehyde concentrations often remain higher than those observed in euthyroid individuals, while superoxide dismutase activity may increase significantly following therapy. The association between hypothyroidism and oxidative stress is therefore thought to reflect reduced efficiency of endogenous antioxidant systems, resulting in insufficient protection against free radical accumulation and subsequent oxidative damage. Moreover, genetic variations affecting NADPH oxidase activity may further enhance reactive oxygen species production, potentially inhibiting thyroid peroxidase activity and disrupting thyroid hormone synthesis, thereby contributing to the development of hypothyroidism.

Thyroid hormones stimulate mitochondrial respiration, which can increase reactive oxygen species generation within the respiratory chain. Excess thyroid hormone production therefore promotes oxidative stress through enhanced free radical formation, whereas in hypothyroidism, redox imbalance is more commonly attributed to impaired antioxidant defense mechanisms.. As a result, hyperthyroidism is frequently associated with oxidative damage to cellular structures. Individuals with hyperthyroidism exhibit higher levels of lipid peroxidation compared with euthyroid controls, reflecting oxidative injury to membrane lipids. Furthermore, studies examining the effects of lead exposure on thyroid function and antioxidant markers have demonstrated positive correlations between thyroid hormone levels and malondialdehyde, as well as associations between TSH and glutathione levels, further supporting a close link between hyperthyroidism and increased oxidative stress.




### 10. Lifestyle and Environmental Determinants

- **Dietary patterns and macronutrient adequacy**

Vitamin B12 is essential for thyroid hormone synthesis, energy metabolism, and immune function and is obtained primarily from animal-based foods. Deficiency is common in autoimmune thyroid disorders, particularly Hashimoto's thyroiditis (HTs), often due to coexisting autoimmune conditions that impair absorption. Low vitamin B12 levels have been associated with anemia, increased thyroid autoimmunity, and higher thyroid antibody levels. Although findings across studies are inconsistent, individuals with overt hypothyroidism tend to have lower vitamin B12 levels than healthy adults, supporting routine screening for vitamin B12 deficiency and anemia in these patients.

Vitamin A plays an important immunomodulatory role in thyroid homeostasis by influencing regulatory T cells, cytokine signaling, and gut barrier integrity. Immune dysregulation and gut microbiota alterations, frequently observed in HTs, may impair nutrient absorption and promote autoimmunity. Genetic variations affecting vitamin A metabolism have been linked to disease severity, suggesting that vitamin A status may influence immune polarization and thyroid disease progression. However, the interactions between vitamin A transport proteins and thyroid hormone distribution remain incompletely understood, and further research is needed to define the therapeutic potential of supplementation.

Magnesium is essential for mitochondrial function and oxidative balance. Deficiency may impair energy metabolism and promote inflammation and oxidative stress, potentially contributing to hyperthyroidism and thyroid carcinogenesis. Lower magnesium levels have been observed in patients with papillary thyroid cancer, while higher levels appear protective. Magnesium concentrations decline after menopause and are indirectly associated with thyroid hormone regulation, suggesting a role in postmenopausal thyroid dysfunction. However, excessive magnesium intake may overstimulate thyroid activity and disrupt hormone metabolism, emphasizing the importance of balanced intake.

Copper is involved in redox regulation and thyroid hormone metabolism, though its role in thyroid disease remains unclear. Elevated copper levels have been associated with increased circulating thyroid hormones and may contribute to thyroid tissue proliferation and cancer progression through angiogenic mechanisms. Alterations in the copperselenium balance may influence thyroid hormone requirements in hypothyroid patients. While copper-targeted therapies show promise in certain thyroid malignancies, evidence regarding copper status in HTs is limited and inconsistent.

Zinc is required for thyroid hormone action, receptor binding, and immune regulation. Zinc deficiency has been associated with thyroid enlargement and nodular goiter in both children and adults, particularly in iodine-deficient regions. Some evidence links low zinc levels with autoimmune thyroid disease, although findings are inconsistent. Supplementation does not appear to significantly alter thyroid hormone or antibody levels but may reduce the need for increasing levothyroxine doses over time, suggesting a supportive role in hypothyroid management.

Vitamin D deficiency is frequently observed in thyroid disorders and may reflect reduced sun exposure, malabsorption, or lifestyle changes rather than causality. Low vitamin D status has been associated with an increased risk of thyroid cancer and greater autoimmune activity. Supplementation has been shown to reduce thyroid autoantibody levels and modestly improve thyroid hormone profiles, likely through immunomodulatory effects, though long-term benefits remain uncertain.

Iron is essential for thyroid hormone synthesis through its role in thyroid peroxidase activity, while thyroid hormones stimulate erythropoiesis, creating a bidirectional relationship. Iron deficiency and anemia are common in hypothyroidism, particularly in HTs patients with comorbid autoimmune gastrointestinal disorders. Optimizing iron status alongside thyroid hormone replacement improves treatment efficacy and should be routinely considered in clinical practice.

Selenium is critical for antioxidant defense and thyroid hormone metabolism. Low selenium status has been associated with an increased risk of autoimmune thyroiditis, particularly in women. Supplementation may reduce thyroid antibody levels and improve thyroid function in selected patients, although benefits vary and excessive intake carries toxicity risks. Supplementation should therefore be individualized and monitored.

- **Physical activity and recovery**

Physical activity is an important lifestyle factor influencing thyroid function, metabolic regulation, and overall health. Regular, moderate exercise improves energy balance, insulin sensitivity, cardiovascular fitness, and body composition, all of which are commonly affected in thyroid disorders. In individuals with hypothyroidism, physical activity may help reduce fatigue, weight gain, and mood disturbances while enhancing peripheral thyroid hormone action and tissue responsiveness, even when circulating hormone levels remain unchanged.

The impact of exercise differs according to thyroid status. In hyperthyroidism, increased metabolic rate, muscle catabolism, and cardiovascular strain can reduce exercise tolerance, making high-intensity or prolonged training inappropriate during active disease. Low-impact and moderate activities are generally better tolerated until thyroid function is stabilized, after which gradual progression to resistance and aerobic training supports muscle recovery, bone health, and metabolic normalization. In autoimmune thyroid diseases, regular physical activity may help reduce systemic inflammation and improve immune balance, while also alleviating stress, a known contributor to disease exacerbation.

Adequate recovery is essential for maintaining thyroid health and preventing hormonal dysregulation. Excessive training, insufficient rest, or chronic sleep deprivation may increase cortisol levels and impair thyroid hormone signaling, particularly in individuals with hypothyroidism. Ensuring sufficient sleep, incorporating rest days, managing stress, and aligning exercise intensity with individual tolerance are critical components of a balanced lifestyle. Overall, a consistent, moderate approach to physical activity combined with appropriate recovery supports thyroid stability and improves long-term well-being.

- **Sleep, circadian rhythm, and stress**

Sleep, circadian rhythm, and stress are closely interconnected regulators of thyroid function and overall endocrine health. The hypothalamic-pituitary-thyroid (HPT) axis follows a circadian pattern, with thyroid-stimulating hormone (TSH) exhibiting a nocturnal peak that is strongly influenced by sleep duration and timing. Chronic sleep deprivation, irregular sleep schedules, or circadian misalignment such as shift work or frequent jet lag can disrupt this rhythm, leading to alterations in TSH secretion and impaired peripheral thyroid hormone signaling. Over time, these disturbances may contribute to fatigue, metabolic dysregulation, and worsening of thyroid-related symptoms. Psychological and physiological stress also exerts a significant impact on thyroid homeostasis through activation of the hypothalamic-pituitary-adrenal (HPA) axis. Elevated and sustained cortisol levels can suppress TSH release, reduce the conversion of T4 to the active hormone T3, and promote a shift toward inactive reverse T3, thereby diminishing thyroid hormone availability at the tissue level. In individuals with autoimmune thyroid diseases, chronic stress may further exacerbate immune dysregulation, increase inflammatory activity, and potentially trigger disease onset or flares.

Restorative sleep and effective stress management are therefore essential components of thyroid health. Consistent sleep wake schedules, adequate sleep duration, and alignment with natural lightdark cycles help maintain circadian integrity and support normal thyroid hormone regulation. Stress-reduction strategies such as mindfulness practices, relaxation techniques, moderate physical activity, and psychological support may help normalize cortisol levels and improve thyroid hormone sensitivity. Together, optimizing sleep, circadian rhythm, and stress resilience contributes to improved metabolic stability, immune balance, and overall well-being in individuals with thyroid disorders.

- **Endocrine-disrupting chemicals**

Endocrine-disrupting chemicals (EDCs) are exogenous compounds that interfere with hormonal signaling and have been increasingly implicated in thyroid dysfunction. These substances can disrupt thyroid hormone synthesis, transport, metabolism, and receptor binding by mimicking or antagonizing endogenous hormones or by altering regulatory enzymes involved in thyroid homeostasis. Common EDCs associated with thyroid disruption include bisphenols, phthalates, polychlorinated biphenyls (PCBs), pesticides, flame retardants, and per- and polyfluoroalkyl substances (PFAS). Exposure occurs through food packaging, plastics, personal care products, contaminated water, household dust, and occupational environments, often resulting in chronic, low-dose accumulation.

EDCs can impair iodine uptake, inhibit thyroid peroxidase activity, alter deiodinase enzymes responsible for T4-to-T3 conversion, and disrupt thyroid hormone transport proteins, leading to altered circulating and tissue-level hormone availability. Early-life exposure, particularly during pregnancy and infancy, is of special concern, as thyroid hormones are essential for neurodevelopment and metabolic programming. Additionally, EDC-induced alterations in immune function, oxidative stress, and gut microbiota composition may increase susceptibility to autoimmune thyroid diseases and thyroid cancer. Reducing exposure through lifestyle choices, regulatory policies, and public health interventions is therefore critical to mitigating EDC-related thyroid dysfunction and supporting long-term endocrine health.

## 11. Personalized Therapeutic Strategies

Personalized therapeutic strategies are essential for effectively managing thyroid dysfunction, as thyroid disorders arise from diverse etiologies including autoimmunity, nutrient deficiencies, hormonal dysregulation, gut imbalance, and environmental exposures. A precision-based approach begins with identifying the individual root causes driving thyroid dysfunction, such as autoimmune activity, impaired hormone conversion, chronic inflammation, or altered hypothalamic-pituitary-thyroid axis signaling. Comprehensive assessment may include thyroid function tests, antibody profiling, micronutrient status, metabolic markers, lifestyle factors, and comorbid conditions to guide targeted interventions.

Therapy should be tailored to the patient's physiological and clinical profile. Hormone replacement or antithyroid therapy remains foundational when indicated, but outcomes are optimized when combined with individualized nutritional support, including correction of deficiencies in iodine, selenium, iron, zinc, vitamin D, and vitamin B12. Dietary patterns emphasizing anti-inflammatory, gut-supportive foods, along with stress management, sleep optimization, and appropriately dosed physical activity, can enhance thyroid hormone sensitivity and immune regulation. In autoimmune thyroid disease, strategies aimed at modulating immune responses such as addressing gut dysbiosis, reducing endocrine-disrupting chemical exposure, and managing chronic stress may help reduce antibody activity and disease progression.

Long-term management requires continuous monitoring and adaptation of therapy based on clinical response and life-stage changes. Genetic predisposition, sex, age, reproductive status, and environmental exposures all influence treatment needs and therapeutic response. Patient education and shared decision-making are central to successful personalization, empowering individuals to actively participate in lifestyle modifications alongside medical therapy. Ultimately, integrating conventional treatments with individualized lifestyle and nutritional interventions offers the greatest potential for restoring thyroid balance, improving quality of life, and achieving sustainable disease control.

### 11.2 Non-Pharmacological Interventions

- **Targeted nutrition**
  Targeted nutrition is a cornerstone of non-pharmacological management of thyroid dysfunction. Individualized dietary strategies aim to correct nutrient deficiencies that impair thyroid hormone synthesis, conversion, and immune regulation, including iodine, selenium, iron, zinc, magnesium, vitamin D, and vitamin B12. Anti-inflammatory dietary patterns rich in whole foods, lean proteins, healthy fats, fiber, and phytonutrients support metabolic health and immune balance, while minimizing ultra-processed foods may reduce oxidative stress and autoimmune activity. Tailoring nutrition to life stage, thyroid status, gut health, and comorbid conditions enhances therapeutic effectiveness and supports long-term thyroid stability.
- **Stress modulation**
  Chronic psychological and physiological stress plays a significant role in thyroid dysregulation by activating the hypothalamic-pituitary-adrenal axis and elevating cortisol levels, which can suppress thyroid hormone signaling and impair T4-to-T3 conversion. Stress modulation strategies such as mindfulness practices, relaxation techniques,

breathwork, yoga, and cognitive behavioral approaches help restore neuroendocrine balance and reduce inflammatory burden. Improving sleep quality and circadian alignment further supports stress resilience and thyroid hormone regulation, particularly in autoimmune thyroid conditions.

- **Lifestyle medicine interventions**
  Lifestyle medicine interventions integrate physical activity, sleep optimization, environmental health, and behavioral modification to address root causes of thyroid dysfunction. Regular, moderate exercise improves metabolic efficiency, insulin sensitivity, and quality of life, while adequate recovery prevents hormonal imbalance. Reducing exposure to endocrine-disrupting chemicals, supporting gut health, maintaining healthy body composition, and fostering social connection are additional pillars of lifestyle medicine. Together, these interventions complement medical therapy, promote individualized care, and support sustainable improvements in thyroid function and overall well-being.

**14. Future Directions**

- **Precision diagnostics**

Precision diagnostics are poised to transform thyroid care by moving beyond standard blood tests to a more holistic understanding of disease mechanisms at the individual level. Traditional assessments, such as TSH, free T4, and T3 measurements, provide limited insight into the underlying causes of thyroid dysfunction, particularly in autoimmune or subclinical cases. Emerging approaches integrate genomic, epigenomic, and proteomic data, as well as immune profiling, micronutrient status, and gut microbiome composition, to identify patient-specific disease drivers. For example, genetic polymorphisms affecting deiodinase enzymes, thyroid hormone receptors, or immune regulation can inform personalized risk assessments and predict therapeutic responsiveness. Additionally, epigenetic markers and metabolomic profiles can provide early warning signs of thyroid stress or dysregulation before clinical symptoms manifest. By capturing this multi-dimensional data, clinicians can stratify patients more accurately, anticipate disease progression, and develop interventions tailored to each individual’s biological context.

Implementing precision diagnostics also enables proactive and preventive thyroid care. For instance, identifying subtle nutrient deficiencies, early autoimmune activation, or environmental toxin exposure allows for targeted interventions before irreversible thyroid damage occurs. Integration with electronic health records and clinical decision support systems can facilitate rapid analysis and interpretation of complex data sets, guiding individualized treatment plans. Over time, precision diagnostics may reduce the trial-and-error approach often seen in thyroid therapy, improve patient outcomes, and enhance quality of life by addressing root causes rather than solely managing symptoms. The ultimate goal is a paradigm shift from reactive to proactive thyroid management, with interventions guided by comprehensive, patient-specific biological insights.

- **Digital health and longitudinal tracking**

Digital health technologies are revolutionizing the way thyroid disorders are monitored and managed, enabling continuous, real-world tracking of patient health. Wearable devices, mobile applications, and remote monitoring platforms can capture vital signs, sleep patterns, activity levels, stress markers, and medication adherence in real time. This longitudinal data provides clinicians with a dynamic view of thyroid function and disease impact, far beyond what occasional laboratory tests can offer. For patients with autoimmune thyroid disorders, such continuous monitoring allows for early detection of flare-ups, identification of lifestyle or environmental triggers, and more precise adjustment of hormone therapy or supplemental interventions. Digital platforms also empower patients to actively participate in their care by tracking symptoms, setting personalized goals, and visualizing progress, enhancing engagement and adherence to therapy. Furthermore, digital health enables population-level insights and predictive modeling. Aggregated longitudinal data can identify patterns in disease progression, response to therapy, and the influence of lifestyle, stress, and environmental factors. Artificial intelligence and machine learning algorithms can analyze this complex information to predict individualized treatment responses, optimize dosing schedules, and identify patients at risk of complications. Telemedicine integration also allows for timely intervention and remote support, which is particularly valuable for patients in underserved or geographically isolated areas. Overall, digital health and longitudinal tracking offer the potential for continuous, personalized, and preventive thyroid care, bridging the gap between episodic clinical visits and day-to-day disease management.

- **Systems-based clinical trials**

Conventional thyroid research often evaluates single interventions in isolation, which may not fully capture the multifactorial nature of thyroid disorders. Systems-based clinical trials address this limitation by studying integrated, multi-component interventions that combine pharmacological therapy with nutrition, lifestyle modifications, stress management, and environmental exposure reduction. These trials adopt a holistic, patient-centered approach that reflects real-world management of thyroid disorders, where multiple physiological and environmental factors interact simultaneously to influence disease progression and treatment response. By evaluating combinations of interventions, researchers can better understand synergistic effects, identify the most effective multi-modal strategies, and optimize personalized care protocols.

Additionally, systems-based trials can incorporate advanced biomarkers and longitudinal outcome measures to capture complex responses at molecular, physiological, and functional levels. For example, tracking thyroid autoantibody titers, inflammatory markers, micronutrient status, gut microbiome composition, and patient-reported outcomes allows for a comprehensive evaluation of intervention impact. This approach also facilitates adaptive trial designs, where interventions can be adjusted dynamically based on real-time patient data, enhancing efficiency and relevance. Ultimately, systems-based clinical trials aim to provide robust, evidence-based guidance for integrative thyroid management, moving beyond symptom control to address underlying disease mechanisms and improve long-term health outcomes.

**15. Conclusion**

The transition from a standardized, TSH-centric model to a personalized, functional framework represents a necessary evolution in thyroid care. Conventional diagnostic paradigms often fail to account for the deep inter-individual variability in hormone metabolism and receptor sensitivity. By moving beyond broad population reference ranges and prioritizing a patient's unique biochemical set-point, clinicians can begin to resolve the dissatisfaction gap that leaves many patients symptomatic despite achieving technically normal laboratory values. A primary driver of this shift is the recognition that thyroid health is a multi-systemic endeavor, involving the intricate Gut-Thyroid-Immune Axis. Chronic low-grade inflammation, gut dysbiosis, and nutrient insufficiencies particularly in selenium, zinc, iron, and Vitamin D act as critical upstream triggers that sabotage metabolic function. Addressing these root causes, rather than merely replacing missing hormones, allows for a more proactive and sustainable approach to endocrine health.

Furthermore, the integration of precision diagnostics, such as screening for DIO2 genetic polymorphisms, allows for more targeted therapeutic interventions. Identifying patients who possess an impaired ability to convert T4 to T3 at the cellular level can transform treatment outcomes, moving them toward combination L-T4/L-T3 therapies that bypass genetic conversion hurdles. This data-driven precision turns a conventional guessing game into a sophisticated, personalized strategy for metabolic optimization.

The inclusion of patient-reported outcomes and longitudinal data further humanizes and refines thyroid management. Moving away from single time-point snapshots allows clinicians to identify a patient's unique hormonal signature and detect subtle trends before they manifest as overt disease. By honoring the patient's lived experience alongside their biochemical data, medical providers can ensure that the ultimate metric of success is not just a stabilized lab value, but a significant improvement in quality of life. Ultimately, the future of thyroid optimization lies in a holistic, root-cause philosophy that integrates conventional medicine with nutritional and lifestyle modifications. As we move toward an era of digital health and precision diagnostics, the ability to treat the whole person becomes increasingly achievable. Embracing these personalized strategies not only resolves persistent complaints like fatigue and brain fog but also serves as a preventative shield against long-term cardiovascular and metabolic complications.

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