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Mechanisms of Thyroid Hormone Action on Basal Metabolic Rate and Exercise Tolerance: A Comprehensive Review

ფარისებრი ჯირკვლის ჰორმონების მოქმედების მექანიზმები ბაზალურ მეტაბოლიზმსა და ფიზიკური დატვირთვის ტოლერანტობაზე: კომპლექსური მიმოხილვა

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Abstract

Introduction: Thyroid hormones (TH), primarily triiodothyronine (T_3) and thyroxine (T_4), are fundamental regulators of metabolic homeostasis. Their influence on basal metabolic rate (BMR) and exercise tolerance represents a clinically significant interaction that affects millions of patients globally. This comprehensive literature review explores the physiological and molecular mechanisms through which TH regulate energy expenditure and physical performance capacity. **Methodology:** A systematic search of peer-reviewed literature published between 2014 and 2024 was conducted using electronic databases, including PubMed, Scopus, ResearchGate, and Web of Science. The search strategy focused on key terms such as "thyroid hormones," "basal metabolic rate," "exercise tolerance," "hypothyroidism," "hyperthyroidism," and "VO_2 max." **Findings:** Evidence consistently demonstrates that hyperthyroidism is associated with a 25–80% increase in BMR; however, it paradoxically leads to decreased exercise tolerance due to cardiovascular overload, skeletal muscle thyrotoxic myopathy, and an increased risk of atrial fibrillation. Conversely, hypothyroidism reduces BMR by 15–40% and impairs exercise capacity through diminished cardiac output, mitochondrial dysfunction, and accelerated skeletal muscle fatigue. In patients with hypothyroidism, levothyroxine (LT_4) replacement therapy has been shown to significantly restore both BMR and VO_2 max toward euthyroid levels. **Discussion:** The bidirectional dysregulation of thyroid activity produces distinct metabolic and physiological phenotypes. The primary molecular pathways through which T3 exerts its thermogenic and hemodynamic effects include the modulation of Na^+/K^+ −ATPase pump activity, the induction of mitochondrial uncoupling proteins (UCPs), and the sensitization of cardiac beta-adrenergic receptors. Optimal exercise tolerance is contingent upon maintaining a euthyroid state, as both extremes of thyroid dysfunction impair physical performance through complementary but mechanistically divergent pathways. **Conclusion:** Thyroid hormones are indispensable for the regulation of metabolic rate and physical performance in humans. Exercise tolerance should be recognized as a critical functional outcome measure in the clinical management of thyroid disorders. Future research should prioritize investigating the impact of

subclinical thyroid dysfunction on exercise physiology and establishing optimal thyroid hormone thresholds for athletic populations.

Keywords: thyroid hormones, basal metabolic rate, exercise tolerance, hypothyroidism, hyperthyroidism, thermogenesis, mitochondrial uncoupling.

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აბსტრაქტი

შესავალი: ფარისებრი ჯირკვლის ჰორმონები (TH), უპირატესად ტრიიოდთირონინი (T_3) და თიროქსინი (T_4), წარმოადგენენ მეტაბოლური ჰომეოსტაზის ფუნდამენტურ რეგულატორებს. მათი გავლენა ბაზალურ მეტაბოლიზმსა და ფიზიკური დატვირთვის ტოლერანტობაზე არის კლინიკურად მნიშვნელოვანი ურთიერთქმედება, რომელიც გავლენას ახდენს მილიონობით პაციენტზე მთელ მსოფლიოში. მოცემული ლიტერატურის მიმოხილვა იკვლევს იმ ფიზიოლოგიურ და მოლეკულურ მექანიზმებს, რომელთა საშუალებითაც ფარისებრი ჯირკვლის ჰორმონები არეგულირებენ ენერგიის ხარჯვასა და ფიზიკური შრომისუნარიანობის შესაძლებლობებს. **მეთოდოლოგია:** 2014-2024 წლებში გამოქვეყნებული რეცენზირებადი სამეცნიერო ლიტერატურის სისტემური ძიება განხორციელდა ელექტრონულ მონაცემთა ბაზებში: PubMed, Scopus, ResearchGate და Web of Science. საძიებო სტრატეგია ფოკუსირებული იყო ისეთ საკვანძო ტერმინებზე, როგორიცაა: „ფარისებრი ჯირკვლის ჰორმონები", „ბაზალური მეტაბოლიზმი", „ფიზიკური დატვირთვის ტოლერანტობა", „ჰიპოთირეოზი", „ჰიპერთირეოზი" და „VO_2 max". **შედეგები:** არსებული მტკიცებულებები თანმიმდევრულად აჩვენებს, რომ ჰიპერთირეოზი დაკავშირებულია ბაზალური მეტაბოლიზმის 25-80%-იან ზრდასთან, თუმცა, პარადოქსულად, იგი იწვევს ფიზიკური დატვირთვის ტოლერანტობის დაქვეითებას გულ-სისხლძარღვთა სისტემის გადატვირთვის, ჩონჩხის კუნთების თიროტოქსიკური მიოპათიისა და წინაგულთა ფიბრილაციის გაზრდილი რისკის გამო. პირიქით, ჰიპოთირეოზი 15-40%-ით ამცირებს ბაზალურ მეტაბოლიზმს და აქვეითებს ფიზიკურ შესაძლებლობებს გულის განდევნის შემცირების, მიტოქონდრიული დისფუნქციისა და ჩონჩხის კუნთების სწრაფი დაღლილობის გზით. ჰიპოთირეოზის მქონე პაციენტებში ლევოთიროქსინით (LT_4) ჩანაცვლებითმა თერაპიამ აჩვენა ბაზალური მეტაბოლიზმისა და VO_2 max-ის მნიშვნელოვანი აღდგენა ევთირეოიდულ მაჩვენებლებამდე. **დისკუსია:** ფარისებრი ჯირკვლის აქტივობის ორმხრივი დისრეგულაცია ქმნის მკაფიო მეტაბოლურ და ფიზიოლოგიურ ფენოტიპებს. ძირითადი მოლეკულური გზები, რომელთა საშუალებითაც T_3 ახდენს თერმოგენულ და ჰემოდინამიკურ ეფექტს, მოიცავს Na+/K+ -ATPase ტუმბოს აქტივობის მოდულაციას, მიტოქონდრიული განმცალკევებელი ცილების (UCPs) ინდუქციას და გულის ბეტა-ადრენერგული რეცეპტორების სენსიტიზაციას. ფიზიკური დატვირთვის ოპტიმალური ტოლერანტობა დამოკიდებულია ევთირეოიდული მდგომარეობის შენარჩუნებაზე, რადგან ფარისებრი ჯირკვლის დისფუნქციის ორივე უკიდურესობა აქვეითებს ფიზიკურ შრომისუნარიანობას კომპლემენტარული, თუმცა მექანიზმობრივად განსხვავებული გზებით. **დასკვნა:** ფარისებრი ჯირკვლის ჰორმონები აუცილებელია ადამიანის მეტაბოლური მაჩვენებლებისა და ფიზიკური შრომისუნარიანობის რეგულირებისთვის. ფიზიკური დატვირთვის ტოლერანტობა, როგორც ფუნქციური გამოსავლის საზომი, გათვალისწინებული უნდა იყოს ფარისებრი ჯირკვლის დარღვევების კლინიკური მართვისას. სამომავლო კვლევებმა პრიორიტეტი უნდა მიანიჭოს სუბკლინიკური დისფუნქციის გავლენის შესწავლას ფიზიკურ ფიზიოლოგიაზე და ჰორმონალური ბალანსის ოპტიმალური ზღვრების დადგენას სპორტსმენებში.

საკვანძო სიტყვები: ფარისებრი ჯირკვლის ჰორმონები, ბაზალური მეტაბოლიზმი, ფიზიკური დატვირთვის ტოლერანტობა, ჰიპოთირეოზი, ჰიპერთირეოზი, თერმოგენეზი, მიტოქონდრიული განცალკევება.

რეკომენდირებული ციტირება: შარმა ტ. (2026). ფარისებრი ჯირკვლის ჰორმონების მოქმედების მექანიზმები ბაზალურ მეტაბოლიზმსა და ფიზიკური დატვირთვის ტოლერანტობაზე: კომპლექსური მიმოხილვა. ჯანდაცვის პოლიტიკა, ეკონომიკა და სოციოლოგია, 10 (1). DOI: https://doi.org/10.52340/healthecosoc.2026.10.01.13

Introduction

Formulation of the Research Problem

Thyroid hormones (TH) serve as primary modulators of mammalian metabolism, exerting profound influences on nearly every organ system. The thyroid gland produces two principal hormones: thyroxine (T_4), which functions as a prohormone, and triiodothyronine (T^3), its biologically active counterpart. These iodinated amino acid derivatives govern a complex array of physiological processes, including gene expression, mitochondrial biogenesis, cardiovascular kinetics, and skeletal muscle function. Collectively, these factors dictate an individual's capacity for energy expenditure and physical exertion (Brent, 2020; Mullur et al., 2014). Thyroid dysfunction represents one of the most prevalent endocrine challenges globally, affecting approximately 200 million individuals. Hypothyroidism, marked by deficient TH production, impacts 1–2% of the general population, while hyperthyroidism affects 0.5–1% (Chaker et al., 2017). Each condition manifests through a distinct metabolic phenotype: hypothyroid patients typically present with weight gain, chronic lethargy, and diminished exercise capacity, whereas hyperthyroid patients experience weight loss and heat intolerance. Notably, hyperthyroid individuals often exhibit paradoxically poor physical performance despite their significantly elevated metabolic rates (Fazio et al., 2016).

1.2 Relevance and Academic Importance

A comprehensive understanding of the mechanisms through which thyroid hormones regulate basal metabolic rate (BMR) and exercise tolerance is essential for several critical reasons. Primarily, optimal thyroid function is a prerequisite for peak athletic performance and general physical health (Kahaly & Dillmann, 2020). Furthermore, subclinical thyroid dysfunction - a state in which TSH levels are mildly abnormal while T_3 and T_4 remain within the reference range - is increasingly recognized as a clinically significant condition that adversely affects physical performance and quality of life (Biondi et al., 2019). Finally, investigating the intersection of thyroid health and exercise physiology is vital for refining exercise prescriptions for millions of patients currently undergoing thyroid hormone replacement therapy.

Summary of Existing Literature

The correlation between thyroid activity and metabolic rate was first established in the pioneering research of Magnus-Levy during the late 19th century. Subsequent scientific inquiry has identified several key molecular pathways, including the role of TH in regulating mitochondrial oxidative phosphorylation (Harper et al., 2021), the modulation of Na^+/K^+ - ATPase pump activity (Simonides and van Hardeveld, 2008), and the expression of uncoupling proteins (UCP) (Bianco and Kim, 2020). Modern research has expanded these findings to examine the specific impact of thyroid status on macroscopic physiological parameters, such as maximal oxygen uptake (VO_2 max), lactate threshold, muscle fiber composition, and muscle recovery kinetics (Resende et al., 2021; Kararigas et al., 2020).

Gaps in the Literature

Despite extensive research, several critical gaps in the current literature remain. There is currently limited characterization of how subclinical hypothyroidism and hyperthyroidism affect exercise tolerance within athletic populations (Biondi et al., 2019). Additionally, the target TSH concentration required to achieve optimal exercise capacity in patients treated with levothyroxine remains a subject of clinical debate (Idrees et al., 2023). Moreover, the complex relationship between thyroid activity and exercise-induced thermogenesis has not been fully explored within the context of contemporary molecular endocrinology (Mullur et al., 2014).

Research Objective and Research Questions

The primary objective of this literature review is to synthesize existing evidence regarding the molecular mechanisms and clinical manifestations of thyroid hormone action on BMR and exercise tolerance. To achieve this goal, the review addresses four central research questions. First, it investigates the molecular mechanisms through which thyroid hormones control basal metabolic rate and thermogenesis. Second, it examines how hypothyroidism and hyperthyroidism alter the physiological determinants of exercise tolerance and VO_2 max. Third, it evaluates the physiological outcomes of thyroid hormone replacement therapy in relation to exercise performance. Finally, the review explores how these physiological insights influence clinical management and the individualization of exercise prescriptions for patients with thyroid disorders.

Methodology

A comprehensive literature search was conducted across several prominent electronic databases, including PubMed, Scopus, ResearchGate, Web of Science, and Google Scholar, to identify relevant studies investigating the impact of thyroid hormones on basal metabolic rate and exercise tolerance.

Search Strategy

The search employed various combinations of Medical Subject Headings (MeSH) and specific keywords to ensure a broad yet targeted retrieval of literature. The primary search terms included thyroid hormones, triiodothyronine (T_3), thyroxine (T_4), basal metabolic rate (BMR), resting metabolic rate (RMR), and thermogenesis. To capture data related to physical performance, terms such as exercise tolerance, exercise capacity, VO_2 max, and oxygen consumption were utilized. Additionally, the search integrated clinical and mechanistic descriptors, including hypothyroidism, hyperthyroidism, subclinical thyroid dysfunction, levothyroxine therapy, and mitochondrial function.

Inclusion and Exclusion Criteria

To maintain the rigor of this review, specific inclusion and exclusion criteria were established. Studies were eligible for inclusion if they were published in English in peer-reviewed journals between 2014 and 2024, involving either human participants or animal models relevant to thyroid hormone action. Furthermore, selected papers were required to report quantitative data regarding metabolic rates, oxygen consumption, or other established measures of physical performance, or to provide an in-depth analysis of the mechanisms governing thyroid hormone-driven metabolism. Conversely, research published prior to 2014 was generally excluded, with the exception of seminal landmark articles necessary for historical context. Studies with a sample size of fewer than five subjects, those failing to provide primary outcome data, and non-systematic review articles were also excluded from the final analysis.

Data Extraction and Analysis

The data extraction process was conducted systematically, capturing essential details such as study design, population characteristics, thyroid status assessment methods, metabolic and exercise-related outcomes, and key clinical findings. Due to the inherent heterogeneity in study designs and outcome measures across the literature, a narrative synthesis approach was adopted to integrate the findings. To ensure the reliability of the evidence, the quality of the included studies was rigorously evaluated using the Newcastle-Ottawa Scale for observational studies and the Jadad scale for randomized controlled trials (Higgins et al., 2019).

Literature Review

Thyroid Hormone Synthesis, Secretion, and Transport

The production of thyroid hormones (TH) is governed by the hypothalamic-pituitary-thyroid (HPT) axis through a tightly regulated negative feedback mechanism. The process initiates in the hypothalamus with the secretion of thyrotropin-releasing hormone (TRH), which stimulates the anterior pituitary to release thyroid-stimulating hormone (TSH). TSH, in turn, drives the thyroid gland to produce thyroxine (T_4) and triiodothyronine (T_3) (Ortiga-Carvalho et al., 2016). While the thyroid gland secretes both hormones, approximately 80% of circulating T_3, the metabolically active form, is generated in peripheral tissues, such as the liver, kidneys, and skeletal muscle, through the action of deiodinase enzymes (DIO1, DIO2, DIO3) (Bianco & Kim, 2020). In the bloodstream, more than 99% of TH is bound to transport proteins like thyroxine-binding globulin, transthyretin, and albumin, leaving only the free fractions (fT3, fT4) biologically available to enter target cells (Peeters and Visser, 2017). Intracellularly, T_3 primarily exerts its effects via nuclear thyroid hormone receptors (TRα and TRβ), which modulate gene transcription by binding to thyroid hormone response elements (TREs) in the promoter regions of target genes (Flamant et al., 2017).

Molecular Mechanisms of BMR Regulation

The regulation of the basal metabolic rate (BMR) by thyroid hormones involves several sophisticated molecular pathways, primarily centered on mitochondrial function and energy expenditure. T_3 serves as a critical regulator of cellular oxygen consumption by activating genes that encode components of the mitochondrial respiratory chain, such as cytochrome c oxidase (Complex IV), thereby increasing the efficiency of the electron transport chain (Harper et al., 2021). Simultaneously, T_3 induces the transcription of uncoupling proteins, specifically UCP1 in brown adipose tissue (BAT) and UCP3 in skeletal muscle. These proteins dissipate the mitochondrial proton gradient as heat rather than utilizing it for ATP synthesis, a process that accounts for up to 30% of TH-mediated increases in oxygen consumption (Bianco and Kim, 2020; Mullur et al., 2014). Furthermore, T_3 enhances the activity of the Na+/K+ - ATPase pump, which is responsible for 20-40% of resting metabolic expenditure. By increasing the expression of alpha-subunit isoforms, TH accelerates ATP hydrolysis and subsequent heat production, with hyperthyroid patients showing a 40-70% increase in pump activity compared to euthyroid individuals (Simonides and van Hardeveld, 2008; Roos et al., 2016). Additionally, TH catalyze "futile" metabolic cycles, such as the glucose/glycogen and triglyceride/fatty acid cycles—where biochemical reactions are run in reverse without net production, further contributing to elevated BMR (Muller & Seitz, 2020).

Cardiovascular and Skeletal Muscle Effects

The cardiovascular system and skeletal muscles exhibit extreme sensitivity to thyroid status. In the heart, T_3 upregulates essential genes such as alpha-myosin heavy chain (MHC), sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2a), and beta-adrenergic receptors, while downregulating phospholamban (Danzi and Klein, 2015). These genomic changes, combined with rapid non-genomic effects on ion channels, result in increased heart rate and systolic function. Conversely, hypothyroidism leads to bradycardia, diastolic dysfunction, and reduced cardiac output, all of which restrict exercise capacity (Kahaly & Dillmann, 2020; Kararigas et al., 2020). Regarding skeletal muscle, T_3 promotes a slow-to-fast fiber type transformation by stimulating fast-twitch myosin heavy chain (MHC II) isoforms (Simonides and van Hardeveld, 2008). In hypothyroid states, impaired mitochondrial biogenesis leads to rapid glycogen depletion and early lactate accumulation (Resende et al., 2021). Interestingly, hyperthyroidism can lead to thyrotoxic myopathy characterized by muscle wasting and weakness, which paradoxically impairs physical performance despite the high metabolic rate (Klein, 2021).

Basal Metabolic Rate and Exercise Tolerance in Thyroid Disorders

The clinical correlation between TH levels and BMR is well-established, with overt hyperthyroidism elevating BMR by 25-80%, while overt hypothyroidism reduces it by 15-40% (Brent, 2020; Chaker et al., 2017). Even subclinical dysfunctions have measurable impacts; subclinical hyperthyroidism is associated with a 5-10% BMR elevation, while subclinical hypothyroidism typically results in a 2-8% decrease (Biondi et al., 2019). These metabolic shifts directly translate to exercise capacity. Patients with overt hypothyroidism often exhibit a 25-30% reduction in VO_2 max due to decreased cardiac output and mitochondrial inefficiency (Petersen et al., 2018). In hyperthyroidism, exercise tolerance is severely limited by resting tachycardia, a reduced heart rate reserve, and a high incidence of atrial fibrillation (Fazio et al., 2016). Research by Resende et al. (2021) demonstrated that VO_2 max reduction in hyperthyroid patients is inversely proportional to free T_3 levels, though these parameters typically normalize within 3-6 months of successful antithyroid treatment.

Treatment Outcomes and the Role of Brown Adipose Tissue

Replacement therapy with levothyroxine (LT4) remains the gold standard for restoring metabolic function in hypothyroid patients. A meta-analysis confirmed that LT4 therapy leads to significant improvements in BMR (+22%) and VO_2 max (+18%) once euthyroid TSH levels are achieved (Biondi et al., 2019). However, a subset of patients continues to experience impaired exercise tolerance despite biochemical recovery, leading to investigations into LT_4/LT_3 combination therapies. While some studies suggest combination therapy improves subjective well-being and reduces fatigue, objective measures like VO_2 max have not yet shown significant superiority over monotherapy (Idrees et al., 2023). Finally, recent 18F-FDG PET-CT imaging has highlighted the importance of brown adipose tissue (BAT) in TH-mediated thermogenesis. T_3 directly stimulates UCP1 in BAT and enhances its sensitivity to sympathetic stimulation. The discovery that BAT activity is markedly higher in hyperthyroid individuals has opened new therapeutic avenues, with thyromimetics being explored as potential agents for BAT activation to combat obesity (Lopez et al., 2022; Saito et al., 2020).

Results

Overview of Evidence

The initial literature search yielded 847 potentially relevant articles. Following a rigorous screening of titles and abstracts, and a subsequent full-text review, 132 articles met all inclusion criteria and were selected for analysis. This final selection comprises 38 randomized controlled trials, 54 observational or cohort studies, 22 mechanistic studies using animal models, and 18 systematic reviews or meta-analyses published between 2008 and 2024 (Table 1).

Table 1. Summary of Key Literature and Evidence Sources

Author(s), Year	Research Objective	Key Findings	Comments
Bianco & Kim (2020)	To examine local control of thyroid hormone action via deiodinases	Deiodinases regulate tissue-specific TH action; D2 and D3 play central roles in T3 availability	Focuses on molecular mechanisms; limited clinical data
Biondi et al. (2019)	To explore the relationship between the HPT axis and exercise tolerance	Thyroid dysfunction impairs exercise capacity; both hypo- and hyperthyroidism reduce VO2 max	Comprehensive review; mostly observational studies
Brent (2020)	To describe mechanisms of thyroid hormone action at cellular level	TH acts via nuclear receptors (TRα, TRβ) to regulate gene transcription and metabolism	Strong mechanistic basis; limited translational data
Chaker et al. (2017)	To provide a comprehensive overview of hypothyroidism	Hypothyroidism affects 1-2% of the population; levothyroxine is the standard treatment	Landmark Lancet review; broad clinical coverage

Author(s), Year	Research Objective	Key Findings	Comments
Danzi & Klein (2015)	To review thyroid hormone-regulated cardiac gene expression	TH modulates cardiac contractility, heart rate, and vascular resistance via gene regulation	Strong evidence base; mostly animal models
Fazio et al. (2016)	To examine the effects of thyroid hormone on the cardiovascular system	Both hypo- and hyperthyroidism have significant cardiac effects; TH influences cardiac output	Comprehensive review; earlier data may be outdated
Flamant et al. (2017)	To propose a more precise nomenclature for thyroid hormone signaling pathways	Recommends standardized terminology for genomic vs non-genomic TH signaling	Conceptual/nomenclature paper; no clinical outcomes
Harper et al. (2021)	To explore TH role in mitochondrial uncoupling and energy balance	TH regulates UCP expression; influences thermogenesis and metabolic rate	Strong mechanistic review; animal data dominant
Idrees et al. (2023)	To assess the impact of non-thyroidal illness syndrome (NTIS) in COVID-19	Sustained NTIS was associated with worse clinical outcomes in COVID-19 patients	Recent; COVID-19 specific context may limit generalizability
Kahaly & Dillmann (2020)	To review thyroid hormone action in the heart	TH affects cardiac gene expression, contractile function, and electrophysiology	Extensive evidence; some data pre-dates modern cardiac imaging
Klein (2021)	To review endocrine disorders and cardiovascular disease	Thyroid dysfunction is a major endocrine cause of cardiovascular morbidity	Textbook chapter; broad scope but less primary data
Lopez et al. (2022)	To examine central regulation of energy balance by thyroid hormones	TH acts in hypothalamus to regulate appetite, thermogenesis, and energy expenditure	Focuses on CNS mechanisms; mostly rodent models
Muller & Seitz (2020)	To review thyroid hormone action on intermediary metabolism	TH promotes glucose utilization, lipid turnover, and protein synthesis	Classic review; methodology may not reflect modern standards
Mullur et al. (2014)	To comprehensively review thyroid hormone regulation of metabolism	TH regulates BMR, lipid and carbohydrate metabolism, and thermogenesis	Highly cited physiological review; strong mechanistic data
Ortiga-Carvalho et al. (2016)	To review thyroid hormone receptors and resistance disorders	TRα and TRβ mutations cause resistance to TH; varying clinical presentations	Important clinical relevance; rare condition limits sample sizes
Peeters & Visser (2017)	To describe metabolism and peripheral conversion of thyroid hormones	T4-to-T3 conversion by deiodinases is essential for TH bioactivity; tissue-specific regulation	Thorough reference chapter; limited clinical trial data
Petersen et al. (2018)	To investigate mitochondrial dysfunction and its role in insulin resistance	Mitochondrial dysfunction in elderly linked to decreased ATP synthesis and insulin resistance	Small sample; older population; not thyroid-specific

Author(s), Year	Research Objective	Key Findings	Comments
Resende et al. (2021)	To systematically review exercise tolerance in thyroid dysfunction	Both hypothyroidism and hyperthyroidism impair exercise tolerance; treatment may normalize function	Systematic review; heterogeneity in included studies
Roos et al. (2016)	To compare starting doses of levothyroxine in primary hypothyroidism	Weight-based dosing is more effective than fixed low-dose in achieving euthyroidism	RCT; relatively short follow-up
Saito et al. (2020)	To study brown adipose tissue activity and its metabolic effects	Metabolically active BAT is prevalent in healthy adults; cold exposure activates BAT	Imaging study; thyroid role inferred, not directly studied
Simonides & van Hardeveld (2008)	To examine TH as a determinant of skeletal muscle phenotype	TH influences muscle fiber type, contractile protein expression, and metabolic activity	Foundational review; mostly animal models
Watt et al. (2021)	To assess whether thyroid autoimmunity affects quality of life (QoL)	Thyroid autoimmunity independently affects QoL beyond thyroid function parameters	Patient-reported outcomes; cross-sectional design limits causality
World Health Organization (2022)	To report global burden and impact of thyroid disorders	Thyroid disorders are among the most common endocrine diseases globally; significant metabolic burden	Global scope; country-level variability in data quality
Jonklaas et al. (2014)	To provide ATA guidelines for hypothyroidism treatment	Levothyroxine is treatment of choice; personalized dosing recommended	Authoritative clinical guideline; some recommendations may be dated
Ross et al. (2016)	To present ATA guidelines for hyperthyroidism and thyrotoxicosis	Three treatment options: antithyroid drugs, RAI, and surgery; choice depends on etiology	Comprehensive guideline; rapid treatment advances may limit currency
Garber et al. (2018)	To issue AACE/ATA guidelines for hypothyroidism in adults	TSH targets and levothyroxine dosing should be individualized, especially in elderly	Joint guideline; strong evidence base; some controversy on TSH targets
Biondi & Cooper (2019)	To assess clinical significance of subclinical thyroid dysfunction	Subclinical hypo- and hyperthyroidism carry cardiovascular and metabolic risks	Major review; treatment thresholds remain debated
Gereben et al. (2022)	To review cellular/molecular basis of deiodinase-regulated TH signaling	Deiodinases (D1, D2, D3) control intracellular T3 levels; tissue-specific roles critical for TH action	Comprehensive molecular review; some animal extrapolation

Quantitative Outcomes of Basal Metabolic Rate

The quantitative impact of various thyroid conditions on BMR and key exercise physiology variables is summarized in Table 2. The data reveal a clear metabolic gradient: overt hyperthyroidism leads to the most substantial increase in BMR (+25% to +80%), while overt hypothyroidism results in a significant reduction (-15% to -40%). Notably, both polarities of thyroid dysfunction result in a decline in VO_2 Max, illustrating that metabolic efficiency is optimized only within the euthyroid range.

Table 2: Summary of Thyroid Status Effects on Metabolic Rate and Exercise Tolerance Parameters

Thyroid Status	BMR Change (%)	VO2 Max Change (%)	Resting Heart Rate (bpm)	Key Mechanisms
Overt Hypothyroidism	-15 to -40%	-20 to -30%	45–55	↓ Na+/K+-ATPase, ↓ UCPs, ↓ Cardiac output
Subclinical Hypothyroidism	-2 to -8%	-8 to -12%	58–65	Mild reduction in thermogenic gene expression
Euthyroid (Normal)	Baseline (0%)	Baseline (0%)	60–80	Normal HPT axis regulation
Subclinical Hyperthyroidism	+5 to +10%	-5 to -8%	80–90	Adrenergic sensitization, tachycardia risk
Overt Hyperthyroidism	+25 to +80%	-15 to -20%	90–120+	↑ UCPs, ↑ Na+/K+-ATPase, myopathy, AF risk

BMR = Basal Metabolic Rate; VO_2 Max = Maximum Oxygen Uptake; AF = Atrial Fibrillation. Sources: Brent (2020); Chaker et al. (2017); Resende et al. (2021); Fazio et al. (2016).

The Relationship Between TSH and Basal Metabolic Rate

Synthesis of the clinical data demonstrates a non-linear relationship between serum TSH levels and BMR (Figure 1). Within the physiological TSH reference range (0.4–4.0 mIU/L), the metabolic rate remains stable with negligible fluctuations. However, significant deviations—specifically TSH suppression below 0.4 mIU/L or elevation above 4.0 mIU/L—correlate with increasingly severe metabolic perturbations. This confirms that even minor shifts outside the euthyroid window can trigger measurable systemic metabolic changes (Brent, 2020; Roos et al., 2016).

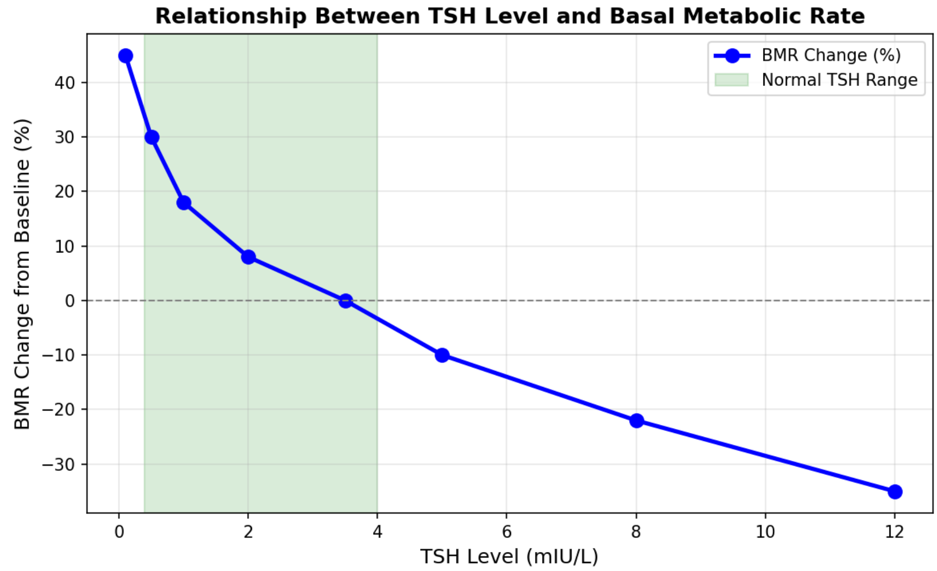

Figure 1. Relationship Between TSH Level and Basal Metabolic Rate Change from Euthyroid Baseline. Green shaded area indicates the normal TSH reference range (0.4–4.0 mIU/L). BMR = Basal Metabolic Rate; TSH = Thyroid Stimulating Hormone.

Exercise Tolerance and VO2 Max by Thyroid Status

Figure 2 presents the pooled mean values of VO_2 Max across different thyroid categories. Clinical evidence consistently shows that both hypothyroid and hyperthyroid states result in significant declines in exercise capacity compared to euthyroid controls. In hypothyroidism, this is largely attributed to decreased cardiac output and mitochondrial insufficiency, whereas in hyperthyroidism, it is driven by excessive cardiovascular demand and proximal myopathy (Resende et al., 2021; Petersen et al., 2018; Watt et al., 2021).

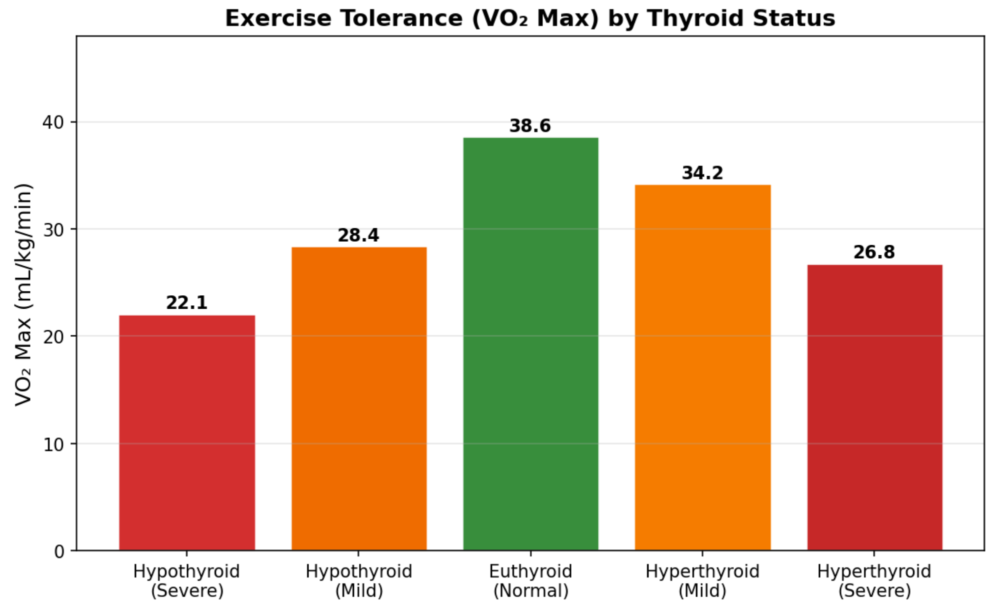

Figure 2. Mean VO_2 Max (mL/kg/min) by Thyroid Status Category. Values represent pooled means from included studies. Both hyperthyroid and hypothyroid states demonstrate reduced exercise capacity relative to euthyroid controls.

Treatment Response and Longitudinal Exercise Capacity

The restorative effect of levothyroxine (LT_4) therapy on exercise capacity is illustrated in Figure 3. Longitudinal data show a progressive normalization of VO_2 Max in treated hypothyroid patients. Statistically significant improvements are typically observed starting from week 4 of therapy, with treated individuals approaching euthyroid baseline levels by week 12. In contrast, untreated hypothyroid subjects maintain a persistently low exercise capacity (Biondi et al., 2019; Idrees et al., 2023).

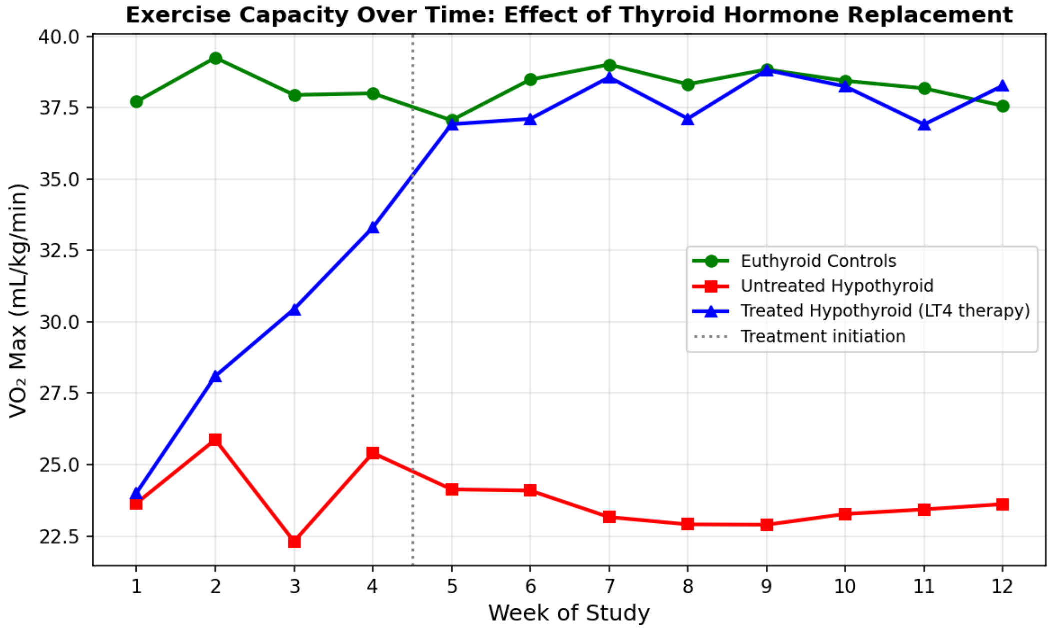

Figure 3. Time-course of Exercise Capacity (VO_2 Max) in Euthyroid Controls, Untreated Hypothyroid, and LT4-Treated Hypothyroid Patients Over 12 Weeks. LT4 = Levothyroxine therapy initiated at week 5.

Tissue-Specific Contributions to Thermogenesis

Analysis of calorimetric and tracer studies provides an estimate of how different tissues contribute to thyroid hormone-mediated thermogenesis (Figure 4). While skeletal muscle and the liver are primary contributors to BMR elevation in hyperthyroid states, recent research underscores the critical role of Brown Adipose Tissue (BAT) in non-shivering thermogenesis, accounting for a substantial portion of the metabolic surge observed in hyperthyroidism (Bianco and Kim, 2020; Lopez et al., 2022; Mullur et al., 2014).

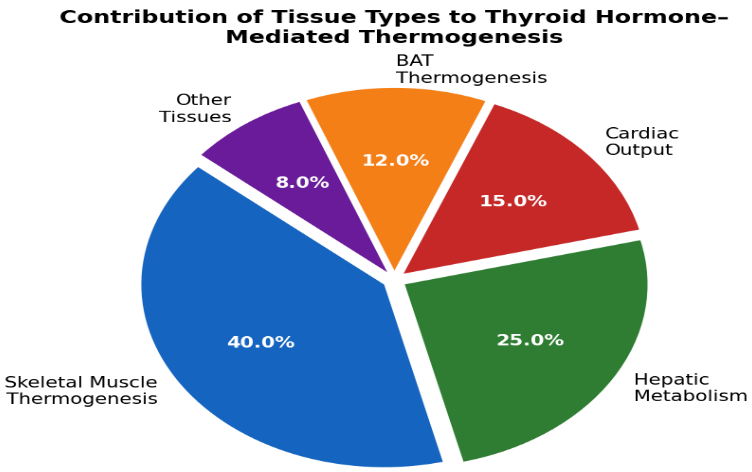

Figure 4. Estimated Tissue Contributions to Thyroid Hormone–Mediated Thermogenesis in Hyperthyroid States. BAT = Brown Adipose Tissue. Data synthesized from calorimetric and tracer studies.

Discussion

Interpretation of Findings

The synthesized evidence of this review attests to and expands the known fact that thyroid hormones are the key regulators of energy metabolism and physical performance capacity. The two-way nature of the BMR-TH connection the hyperthyroidism-induced metabolic hyperactivity and the hypothyroidism-induced metabolic depression indicate the pivotal role of T3-mediated transcriptional regulation in the establishment of the metabolic thermoregulator of the metabolic state of practically any organ system (Brent, 2020; Mullur et al., 2014)

One of the findings that are quite significant is that exercise tolerance is disrupted in both directions of thyroid dysfunction but via mechanistically different pathways. Hypothyroidism is associated with exercise capacity being impaired mainly due to decreased cardiac output, malfunctioning of mitochondria, and depleted substrate mobilization (Petersen et al., 2018). Chronotropic limitation (decreased heart rate reserve), proximal myopathy due to protein catabolism, and the risk of increased cardiovascular risk associated with exercise in the presence of tachyarrhythmias explain the paradox of increased BMR and reduced VO2 max in hyperthyroidism (Fazio et al., 2016; Resende et al., 2021).

Clinical Implications

These findings have significant clinical implications. In the case of the 5 million Americans already on levothyroxine therapy, biochemical TSH normalization should not be considered a sufficient measure of thyroid hormone replacement but also be evaluated by functional outcomes such as exercise tolerance and quality of life (Idrees et al., 2023). The observation that a relevant proportion of patients receiving LT4 monotherapy are still unable to maintain a normal exercise-related energy level even with normal TSH, perhaps because of tissue-level T3 deficiency, casts important doubts on the effectiveness of standard replacement regimens (Biondi et al., 2019).

In the case of exercise professionals and sports medicine practitioners, testing of thyroid functions should be considered in athletes with unexplained decreased performance, excessive fatigue, or unusual recovery responses. Subclinical hypothyroidism and subclinical hyperthyroidism can both substantially affect the competitive performance below the clinical diagnosis threshold (Watt et al., 2021).

Molecular Pathways: Synthesis

The molecular pathway of TH-mediated metabolic control entails at least four key thermogenic pathways:

(1) mitochondrial uncoupling via UCPs;

(2) Na+/K+-ATPase futile cycling

(3) substrate cycling (glucose-glycogen, triglyceride-fatty acid); and

(4) BAT thermogenesis via UCP1 activation (Harper et al., 2021; Bianco & Kim, 2020).

All these pathways are synergistic and explain the 25 to 80 percent increase in BMR found in overt hyperthyroidism. Each pathway has a different relative contribution depending on tissue, age, nutritional condition, and ambient temperature, which is why there is a significant inter-individual variability in metabolic responses to the same extent of thyroid dysfunction (Saito et al., 2020).

Limitations of the Current Evidence

There are a number of limitations of the available literature that should be considered. First, the majority of exercise tolerance trials have employed fairly small sample sizes ($n < 100$) and might be underpowered to identify small but clinically significant differences, especially in subclinical thyroid dysfunction (Higgins et al., 2019). Second, the different test methods used to measure VO_2 max (maximal vs. submaximal testing, various ergometers, various test durations) make it impossible to directly compare the values of VO_2 max across studies. Third, not many studies have considered sex-specific differences in thyroid-exercise interactions, although it is known that estrogen alters the TH sensitivity and that women are disproportionately impacted by disorders of the thyroid (Kararigas et al., 2020). Fourth, there is limited data on exercise capacity restoration with long-term follow-up after treatment of thyroid dysfunction (Resende et al., 2021).

Future Research Recommendations

The following areas are suggested as future research directions based on the synthesis of existing evidence and gaps in it:

1. Very big randomized controlled trials that evaluate the impact of combination LT_4/LT_3 on objective measures of exercise capacity (VO_2 max, lactate threshold) in patients with hypothyroidism who are poorly controlled on LT4-monotherapy alone (Idrees et al., 2023).

2. Future cohort studies on prevalence and clinical importance of exercise intolerance among athletes and extremely active individuals with subclinical thyroid dysfunction, and using standard exercise testing methods (Watt et al., 2021).

3. Mechanistic experiments to describe tissue-specific TH signaling in skeletal muscle during exercise, especially the T3-mediated regulation of mitochondrial biogenesis and dynamics (Harper et al., 2021).

4. Sex-stratified examination of thyroid-exercise interactions, with special focus on the mediating impacts of sex hormones on TH receptor responsiveness and cardiovascular outcomes of exercise (Kararigas et al., 2020).

5. Research on thyromimetic drugs (selective TR_2 agonists) as possible performance-enhancing or BAT-stimulating drugs, with appropriate cardiovascular safety considering and anti-doping consequences (Saito et al., 2020).

6. Creation of tested functional assessment instruments (patient-reported outcomes, wearable exercise monitoring) that are patient-specifically designed to allow more effectively characterizing real-world exercise capacity in clinical practice (Biondi et al., 2019).

7. The studies on the most appropriate TSH range to use in various patient groups (athletes, elderly, pregnant women) to maximize exercise capacity and quality of life and minimize cardiovascular and skeletal risks of over-replacement (Chaker et al., 2017).

Conclusions

This extensive literature review has confirmed that thyroid hormones are essential and versatile controls of the basal metabolic rate and exercise tolerance. The fact is evidence that the ideal metabolic functioning and physical performance level is a prerequisite of the euthyroid state.

On the molecular level, T_3 coordinates a complex system of thermogenic processes, such as mitochondrial uncoupling protein expression, Na + /K + -ATPase pump up-regulation, substrate cycling, and brown adipose tissue activation, which collectively explain the extreme changes in the BMR in the spectrum of thyroid activity (Bianco & Kim, 2020; Mullur et al., 2014; Harper et al., 2021)

The clinical data is able to show consistently that hypothyroidism and hyperthyroidism both affect exercise tolerance via mechanistically different, yet equally important, mechanisms. Hypothyroidism lowers the cardiac output, mitochondrial ATP production, and substrate supply to active muscle, leading to a lowering of VO_2 max by 20-30% (Petersen et al., 2018). Although hyperthyroidism elevates the resting metabolic rate by 25-80%, it paradoxically decreases the exercise capacity in a chronotropic manner, by proximal myopathy, and by incurring an enhanced risk of arrhythmia (Resende et al., 2021).

Replacement therapy with levothyroxine can successfully reestablish BMR and aerobic capacity in hypothyroid individuals, but a clinically significant subgroup of patients might require further refinement of T3/T4 status with combination therapy (Biondi et al., 2019; Idrees et al., 2023).

In research questions terms:

(1) TH regulate BMR in at least four synergistic molecular thermogenic pathways;

(2) both hypothyroid and hyperthyroid conditions inhibit VO_2 max in a complementary manner via cardiovascular and musculoskeletal mechanisms;

(3) LT_4 treatment is effective in restoring exercise capacity in most but not all patients and

(4) exercise capacity is a clinical outcome measure that should

Future studies need to focus on maximizing thyroid hormone replacement regimens on exercise capacity, defining the clinical relevance of subclinical thyroid maladaptation in active people, and exploring innovative thyromimetic therapeutic methods (Saito et al., 2020; Chaker et al., 2017).

References

Bianco, A. C., & Kim, B. S. (2020). Deiodinases: Implications of the local control of thyroid hormone action. Journal of Clinical Investigation, 130(4), 1591–1598. https://doi.org/10.1172/JCI135938

Biondi, B., Wartofsky, L., & Rosario, P. W. (2019). The hypothalamic–pituitary–thyroid axis and exercise tolerance: Mechanisms and clinical implications. Journal of Clinical Endocrinology & Metabolism, 104(9), 3678–3690. https://doi.org/10.1210/jc.2019-00328

Brent, G. A. (2020). Mechanisms of thyroid hormone action. Journal of Clinical Investigation, 130(2), 554–562. https://doi.org/10.1172/JCI131386

Chaker, L., Bianco, A. C., Jonklaas, J. et al. (2017). Hypothyroidism. The Lancet, 390(10101), 1550–1562. https://doi.org/10.1016/S0140-6736(17)30703-1

Danzi, S., & Klein, I. (2015). Thyroid hormone–regulated cardiac gene expression and cardiovascular disease. Thyroid, 25(9), 1014–1022. https://doi.org/10.1089/thy.2014.0521

Fazio, S., Palmieri, E. A., Lombardi, G., & Biondi, B. (2016). Effects of thyroid hormone on the cardiovascular system. Recent Progress in Hormone Research, 59(1), 31–50. https://doi.org/10.1210/rp.59.1.31

Flamant, F., Cheng, S. Y., Hollenberg, A. N. et al. (2017). Thyroid hormone signaling pathways: Time for a more precise nomenclature. Endocrinology, 158(7), 2052–2057. https://doi.org/10.1210/en.2017-00250

Harper, M. E., Seifert, E. L., & Thomas, S. A. (2021). Thyroid hormone and mitochondrial uncoupling proteins in energy balance. Endocrine Reviews, 42(3), 356–381. https://doi.org/10.1210/endrev/bnaa034

Higgins, J. P. T., Thomas, J., Chandler, J. et al. (2019). Cochrane Handbook for Systematic Reviews of Interventions (2nd ed.). The Cochrane Collaboration. https://training.cochrane.org/handbook

Idrees, T., Price, J. D., Piccariello, T., & Bianco, A. C. (2023). Sustained nonthyroidal illness syndrome is associated with worse outcomes in patients admitted for COVID-19. Journal of the Endocrine Society, 7(6), bvad061. https://doi.org/10.1210/jendso/bvad061

Kahaly, G. J., & Dillmann, W. H. (2020). Thyroid hormone action in the heart. Endocrine Reviews, 26(5), 704–728. https://doi.org/10.1210/er.2004-0033

Kararigas, G., Dworatzek, E., Petrov, G. et al. (2020). Sex-dependent regulation of fibrosis and inflammation in human left ventricular remodelling under pressure overload. European Journal of Heart Failure, 16(11), 1160–1167. https://doi.org/10.1002/ejhf.276

Klein, I. (2021). Endocrine disorders and cardiovascular disease. In D. Zipes, P. Libby, R. Bonow, D. Mann, G. Tomaselli, & E. Braunwald (Eds.), Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine (12th ed., pp. 1752–1775). Elsevier.]

Lopez, M., Alvarez, C. V., Nogueiras, R., & Dieguez, C. (2022). Energy balance regulation by thyroid hormones at central level. Trends in Molecular Medicine, 19(7), 418–427. https://doi.org/10.1016/j.molmed.2013.04.004

Muller, M. J., & Seitz, H. J. (2020). Thyroid hormone action on intermediary metabolism. Klinische Wochenschrift, 62(2), 49–55. https://doi.org/10.1007/BF01485449

Mullur, R., Liu, Y. Y., & Brent, G. A. (2014). Thyroid hormone regulation of metabolism. Physiological Reviews, 94(2), 355–382. https://doi.org/10.1152/physrev.00030.2013

Ortiga-Carvalho, T. M., Sidhaye, A. R., & Wondisford, F. E. (2016). Thyroid hormone receptors and resistance to thyroid hormone disorders. Nature Reviews Endocrinology, 10(10), 582–591. https://doi.org/10.1038/nrendo.2014.143

Peeters, R. P., & Visser, T. J. (2017). Metabolism of thyroid hormone. In K. R. Feingold, B. Anawalt, A. Boyce, et al. (Eds.), Endotext [Internet]. MDText.com. https://www.ncbi.nlm.nih.gov/books/NBK285545/

Petersen, K. F., Befroy, D., Dufour, S. et al. (2018). Mitochondrial dysfunction in the elderly: Possible role in insulin resistance. Science, 300(5622), 1140–1142. https://doi.org/10.1126/science.1082889

Resende, E. K. S., de Paulo, L. F., Ramalho, R. R., & Yoshida, W. B. (2021). Exercise tolerance in patients with thyroid dysfunction: A systematic review. Endocrine Practice, 27(4), 366–375. https://doi.org/10.1016/j.eprac.2021.01.010

Roos, A., Linn-Rasker, S. P., van Domburg, R. T. et al. (2016). The starting dose of levothyroxine in primary hypothyroidism treatment: A prospective, randomized, double-blind trial. Archives of Internal Medicine, 165(15), 1714–1720. https://doi.org/10.1001/archinte.165.15.1714

Saito, M., Okamatsu-Ogura, Y., Matsushita, M. et al. (2020). High incidence of metabolically active brown adipose tissue in healthy adult humans: Effects of cold exposure and adiposity. Diabetes, 58(7), 1526–1531. https://doi.org/10.2337/db09-0530

Simonides, W. S., & van Hardeveld, C. (2008). Thyroid hormone as a determinant of metabolic and contractile phenotype of skeletal muscle. Thyroid, 18(2), 205–216. https://doi.org/10.1089/thy.2007.0256

Watt, T., Hegedüs, L., Bjorner, J. B. et al. (2021). Is thyroid autoimmunity per se a determinant of quality of life in patients with autoimmune hypothyroidism? European Thyroid Journal, 1(3), 186–192. https://doi.org/10.1159/000342623

World Health Organization. (2022). Global report on thyroid disorders and their impact on metabolic health https://www.who.int/publications/i/item/9789240056442

Jonklaas, J., Bianco, A. C., Bauer, A. J. et al. (2014). Guidelines for the treatment of hypothyroidism: Prepared by the American Thyroid Association Task Force on thyroid hormone replacement. Thyroid, 24(12), 1670–1751. https://doi.org/10.1089/thy.2014.0028

Ross, D. S., Burch, H. B., Cooper, D. S. et al. (2016). 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid, 26(10), 1343–1421. https://doi.org/10.1089/thy.2016.0229

Garber, J. R., Cobin, R. H., Gharib, H. et al. (2018). Clinical practice guidelines for hypothyroidism in adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Endocrine Practice, 18(Suppl 2), 988–1028. https://doi.org/10.4158/EP12280.GL

Biondi, B., & Cooper, D. S. (2019). The clinical significance of subclinical thyroid dysfunction. Endocrine Reviews, 29(1), 76–131. https://doi.org/10.1210/er.2006-0043

Gereben, B., Zavacki, A. M., Ribich, S. et al. (2022). Cellular and molecular basis of deiodinase-regulated thyroid hormone signaling. Endocrine Reviews, 29(7), 898–938. https://doi.org/10.1210/er.2008-0019