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From Hormones to Powerhouse: The Mitochondrial Dimension of Thyroid Disease

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Abstract: Thyroid disorders are among the most common hormone diseases, affecting 200 million people. Understanding their cell-level actions is crucial. Thyroid hormones are key to cell energy and balance. New evidence shows that mitochondria support many of the metabolic functions of these hormones. Thyroid hormone signalling controls mitochondrial energy production and adaptation. It regulates the formation of new mitochondria, how cells use oxygen, and activity in the electron transport chain. If thyroid hormone levels change, it can disrupt mitochondrial breathing, increase reactive oxygen species, and weaken antioxidant defences. These disruptions lead to oxidative stress and impaired mitochondria. Such changes play a role in the development of thyroid disorders.

Recently, people have become more interested in how thyroid hormones and mitochondria are connected. This review covers new findings on thyroid hormone signalling, mitochondrial energy, metabolic control, and cellular balance. Studying this link may help us better understand diseases and identify new ways to treat mitochondrial dysfunction in thyroid-related metabolic diseases.

Keywords: Thyroid hormones, Thyroid-mitochondrial axis, PGC-1α, Reactive oxygen species, Hypothyroidism, Hyperthyroidism, Metabolic regulation.

1. INTRODUCTION

Thyroid hormones are central regulators of cellular energy metabolism and systemic metabolic homeostasis. Their effects span multiple physiological processes, including growth, development, and metabolic adaptation across nearly all tissues. While traditionally viewed as modulators of basal metabolic rate, accumulating evidence indicates that many of their metabolic actions are mediated through mitochondria, the principal sites of cellular energy production (1).

The thyroid gland synthesizes thyroxine (T4) and triiodothyronine (T3) through iodination of tyrosine residues within thyroglobulin. Although T4 is the predominant circulating form, T3 represents the biologically active hormone responsible for most cellular effects. T3 exerts its classical actions via nuclear thyroid hormone receptors, regulating the transcription of genes involved in metabolism, differentiation, and growth. In addition to these genomic effects, thyroid hormones also initiate rapid non-genomic signalling pathways that directly influence cellular organelles, including mitochondria, thereby modulating metabolic flux and energy production (2, 3).

Mitochondria are not only the primary source of adenosine triphosphate (ATP) but also critical regulators of redox signalling, apoptosis, and metabolic integration. Thyroid hormones play a key role in maintaining mitochondrial function by regulating mitochondrial biogenesis, oxidative phosphorylation, and substrate utilisation. Through

these mechanisms, they adjust cellular energy output to meet physiological demands, particularly in metabolically active tissues such as the liver, skeletal muscle, adipose tissue, heart, and brain (4, 5).

Alterations in thyroid hormone levels profoundly affect mitochondrial activity. Hypothyroidism is characterised by reduced mitochondrial respiration, impaired ATP generation, and decreased metabolic rate, whereas hyperthyroidism enhances mitochondrial oxygen consumption and metabolic flux but often at the cost of increased reactive oxygen species production and oxidative stress. These changes highlight the dual role of thyroid hormones in coordinating energy production and redox balance (6, 7).

Emerging evidence further suggests that mitochondrial dysfunction is not merely a consequence but also a contributing factor in thyroid disorders. Disruption of the thyroid-mitochondrial axis can lead to impaired energy metabolism, oxidative damage, and altered cellular signalling, thereby contributing to the pathophysiology of metabolic diseases. Despite growing recognition of this interplay, the precise mechanisms linking thyroid hormone signalling to mitochondrial function remain incompletely understood (8, 9).

This review aims to integrate current knowledge on thyroid hormone signalling and mitochondrial regulation, with a focus on bioenergetics, redox homeostasis, and metabolic dysfunction. It further examines how disruption of this axis contributes to thyroid disease and explores emerging therapeutic strategies targeting mitochondrial pathways.

2. THYROID HORMONE HOMEOSTASIS - SYNTHESIS, TRANSPORT, AND DEIODINATION

Thyroid hormone homeostasis is tightly regulated by the hypothalamus-pituitary-thyroid (HPT) axis, which maintains circulating hormone levels in accordance with physiological demand. The hypothalamus secretes thyrotropin-releasing hormone (TRH), stimulating the anterior pituitary to release thyroid-stimulating hormone (TSH). TSH, in turn, acts on thyroid follicular cells to promote the synthesis and secretion of thyroxine (T4) and triiodothyronine (T3). Circulating thyroid hormones exert negative feedback on both the hypothalamus and pituitary, thereby maintaining endocrine balance (10, 11).

Thyroid hormone synthesis occurs within thyroid follicular cells and involves several coordinated steps. Iodide is actively transported into thyrocytes via the sodium-iodide symporter (NIS) and subsequently oxidised and organified by thyroid peroxidase (TPO). This process enables the iodination of tyrosine residues within thyroglobulin, forming monoiodotyrosine and diiodotyrosine, which are coupled to generate T3 and T4. Upon TSH stimulation, iodinated thyroglobulin is internalised and proteolytically cleaved, releasing T3 and T4 into the circulation (12).

In the bloodstream, the majority of thyroid hormones are bound to carrier proteins, including thyroxine-binding globulin, transthyretin, and albumin. This binding regulates hormone distribution, prolongs half-life, and maintains a stable reservoir of circulating hormone, while only the free fraction remains biologically active. Cellular uptake of thyroid hormones is mediated by specific membrane transporters, notably monocarboxylate transporters (MCT8 and MCT10) and organic anion transporting polypeptides (OATPs). These transport systems are critical for tissue-specific hormone availability. Mutations in MCT8, for example, impair intracellular transport of T3 and are associated with Allan-Herndon-Dudley syndrome, highlighting the importance of transporter-mediated hormone distribution (13).

Intracellular activation and inactivation of thyroid hormones are controlled by iodothyronine deiodinases. Type 1 deiodinase contributes to circulating T3 production, primarily in the liver and kidney. Type 2 deiodinase generates T3 locally within tissues such as the brain, skeletal muscle, and brown adipose tissue, thereby ensuring adequate intracellular hormone signalling. In contrast, type 3 deiodinase inactivates thyroid hormones by converting T4 to reverse T3 and degrading T3, thus reducing thyroid hormone activity. This local regulation of hormone activation allows precise, tissue-specific control of metabolic processes. Collectively, these mechanisms ensure that thyroid hormone availability is finely tuned at both systemic and cellular levels. Disruption at any stage-synthesis, transport, or intracellular activation-can alter hormone signalling and contribute to metabolic dysfunction, underscoring the importance of tightly regulated thyroid hormone homeostasis in maintaining cellular energy balance (14).

3. MECHANISMS OF THYROID HORMONE ACTION - GENOMIC AND NON-GENOMIC PATHWAYS

Thyroid hormones regulate cellular metabolism through both genomic and non-genomic mechanisms, enabling coordinated control of gene expression and rapid modulation of cellular function. These complementary pathways allow precise regulation of energy homeostasis, particularly in metabolically active tissues. The genomic actions of triiodothyronine are mediated by nuclear thyroid hormone receptors (TRα and TRβ), which function as ligand-activated transcription factors. These receptors bind to thyroid hormone response elements (TREs) in the promoter regions of target genes, typically as heterodimers with retinoid X receptors. In the absence of ligand, TRs recruit corepressor complexes that suppress gene transcription. The binding of T3 induces conformational changes that release corepressors and recruit coactivators, thereby activating transcription. This process regulates genes

involved in mitochondrial biogenesis, oxidative phosphorylation, lipid metabolism, and glucose utilisation. Key transcriptional coactivators, including peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α), play a central role in linking thyroid hormone signalling to mitochondrial function (15).

In addition to these classical genomic effects, thyroid hormones exert rapid non-genomic actions that are independent of direct gene transcription. These effects are mediated through interactions with plasma membrane-associated receptors, particularly integrin αvβ3, as well as cytoplasmic signalling pathways. Activation of these pathways triggers intracellular cascades such as phosphatidylinositol 3-kinase (PI3-K)/Akt and mitogen-activated protein kinase (MAPK) signalling, leading to rapid modulation of cellular metabolism, ion transport, and mitochondrial activity (16).

Non-genomic signalling also influences mitochondrial function directly. Thyroid hormones have been reported to modulate mitochondrial membrane potential, respiratory chain activity, and substrate utilisation within minutes, suggesting a direct role in the acute regulation of bioenergetics. These rapid effects complement the slower genomic actions, together ensuring both immediate and sustained adaptation of cellular energy metabolism. The integration of genomic and non-genomic pathways is essential for maintaining metabolic flexibility. Disruption of these signalling mechanisms can impair mitochondrial function, alter energy production, and contribute to the development of metabolic and endocrine disorders. Thus, thyroid hormone action represents a multi-layered regulatory system linking endocrine signalling to mitochondrial bioenergetics and cellular homeostasis (17).

4. MITOCHONDRIAL BIOENERGETICS AND OXIDATIVE PHOSPHORYLATION

Mitochondrial oxidative phosphorylation is the principal mechanism by which cells generate adenosine triphosphate, linking substrate oxidation to energy production. This process is mediated by the electron transport chain, a series of multi-subunit protein complexes (Complex I–IV) embedded in the inner mitochondrial membrane, along with ATP synthase (Complex V). Electrons derived from NADH and $FADH_2$ are transferred through the ETC via mobile carriers, including ubiquinone and cytochrome C, ultimately reducing molecular oxygen to water. The energy released during electron transfer drives proton translocation across the inner mitochondrial membrane, establishing an electrochemical gradient that powers ATP synthesis (18).

Thyroid hormones play a critical role in regulating mitochondrial bioenergetics by modulating both the expression and activity of ETC components. Triiodothyronine enhances the transcription of nuclear and mitochondrial genes encoding respiratory chain proteins, thereby increasing mitochondrial respiratory capacity. In particular, T3 has been shown to stimulate Complex I activity, leading to increased electron flux and improved ATP production. Additionally, thyroid hormones regulate cytochrome c oxidase (Complex IV), the terminal enzyme of the ETC, primarily through transcriptional control, thereby influencing the efficiency of oxygen utilisation (19).

Thyroid hormone signalling also affects ATP synthase (Complex V), contributing to increased ATP turnover in hyperthyroid states. This upregulation of oxidative phosphorylation is associated with increased oxygen consumption and elevated basal metabolic rate. Conversely, hypothyroidism is characterised by reduced expression and activity of ETC complexes, leading to diminished electron transport, impaired proton gradient formation, and decreased ATP synthesis. Beyond direct effects on respiratory complexes, thyroid hormones influence the coupling efficiency of oxidative phosphorylation. Alterations in proton gradient utilisation can shift the balance between ATP production and heat generation, thereby affecting overall metabolic efficiency. These regulatory effects ensure that mitochondrial energy production is dynamically matched to cellular energy demands. Overall, thyroid hormones act as key modulators of mitochondrial oxidative phosphorylation, coordinating electron transport, ATP synthesis, and oxygen consumption. Disruption of these processes under altered thyroid states contributes to impaired bioenergetics and plays a central role in the metabolic dysfunction observed in thyroid disorders (20).

5. REGULATION OF MITOCHONDRIAL BIOGENESIS AND DYNAMICS

Thyroid hormones are key regulators of mitochondrial biogenesis, coordinating the expansion of mitochondrial mass and function in response to metabolic demand. This process is primarily governed by the transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator-1 alpha, which integrates endocrine and metabolic signals to regulate mitochondrial gene expression. Triiodothyronine enhances PGC-1α expression and activity through upstream signalling pathways, including AMP-activated protein kinase and cAMP response element-binding protein, thereby linking thyroid hormone signalling to cellular energy status (1, 6).PGC-1α coactivates nuclear respiratory factors, which regulate the transcription of nuclear genes encoding mitochondrial proteins involved in oxidative phosphorylation. These factors also induce the expression of mitochondrial transcription factor A, a key regulator of mitochondrial DNA replication and transcription. Through this coordinated nuclear-mitochondrial interaction, thyroid hormones promote the synthesis of respiratory chain components and support the maintenance of mitochondrial genome integrity (3, 16).

In addition to biogenesis, thyroid hormones regulate mitochondrial dynamics, a set of processes that control mitochondrial morphology, distribution, and quality. Mitochondrial fusion, mediated by mitofusin proteins (MFN1 and MFN2) and optic atrophy protein 1 (OPA1), facilitates the mixing of mitochondrial contents, thereby maintaining functional integrity. In contrast, mitochondrial fission, primarily regulated by dynamin-related protein 1 (DRP1), enables the segregation and removal of damaged mitochondria through mitophagy (17, 18).

Thyroid hormone signalling influences the balance between fusion and fission, thereby maintaining mitochondrial network homeostasis. In euthyroid conditions, this balance supports efficient energy production and cellular adaptation. Hypothyroidism is associated with reduced mitochondrial biogenesis, decreased expression of regulatory proteins such as PGC-1α and TFAM, and impaired mitochondrial turnover. These changes contribute to reduced mitochondrial density and compromised bioenergetic capacity. Conversely, hyperthyroidism promotes mitochondrial proliferation and enhances metabolic activity, although excessive stimulation may disrupt mitochondrial quality control mechanisms. The integration of mitochondrial biogenesis and dynamics is essential for maintaining mitochondrial efficiency and cellular energy balance. Disruption of these processes under altered thyroid states contributes to mitochondrial dysfunction, linking thyroid hormone signalling to metabolic disease and tissue-specific pathology (19, 20).

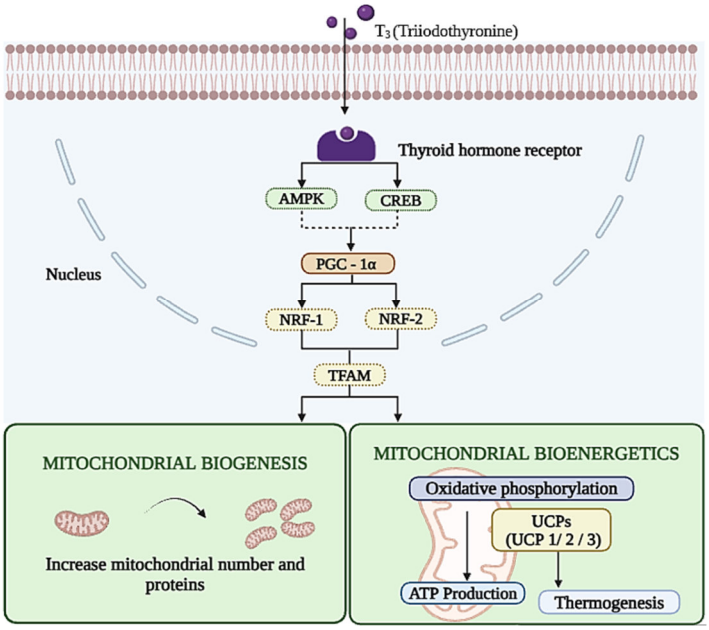

Figure 1: *Regulation of Mitochondrial Function and Bioenergetics by Thyroid Hormones.*

T3 (Triiodothyronine), TR (thyroid hormone receptor), PGC-1α (peroxisome proliferator-activated receptor gamma coactivator-1 alpha), AMPK (AMP-activated protein kinase), CREB (cAMP response element-binding protein), NRF-1/NRF-2 (Nuclear Respiratory Factors 1 and 2), TFAM (mitochondrial transcription factor A), ETC (electron transport chain), ATP (adenosine triphosphate), UCP (uncoupling protein).

6. THERMOGENESIS AND UNCOUPLING MECHANISMS

Thyroid hormones play a central role in thermogenesis by modulating the coupling efficiency of mitochondrial oxidative phosphorylation. Under normal conditions, the proton gradient generated by the electron transport chain is utilised by ATP synthase to produce ATP. However, this gradient can be partially dissipated as heat through the action of uncoupling proteins (UCPs), thereby reducing ATP yield while increasing thermogenesis (21, 22).

Triiodothyronine upregulates the expression of uncoupling proteins, particularly UCP1 in brown adipose tissue and UCP2 and UCP3 in skeletal muscle. UCP1 mediates thermogenesis by facilitating proton leak across the inner mitochondrial membrane, converting stored energy into heat. This mechanism is especially important in maintaining body temperature and energy expenditure in response to environmental and metabolic stimuli (23).

In hyperthyroid states, elevated thyroid hormone levels enhance UCP expression and activity, leading to increased proton leak, increased heat production, and reduced ATP synthesis efficiency. This contributes to the characteristic features of hyperthyroidism, including heat intolerance, increased basal metabolic rate, and weight loss despite normal or increased caloric intake (23, 24).

Conversely, hypothyroidism is associated with reduced expression of uncoupling proteins, resulting in more tightly coupled oxidative phosphorylation. While this may preserve ATP production efficiency, it leads to

diminished heat generation and reduced energy expenditure, contributing to cold intolerance, weight gain, and decreased metabolic rate (21, 24).

By regulating mitochondrial coupling and uncoupling, thyroid hormones finely balance ATP production and heat generation to meet physiological needs. Disruption of this balance under altered thyroid states contributes to metabolic inefficiency and thermoregulatory abnormalities, reinforcing the role of mitochondria as key mediators of thyroid hormone action (25).

7. REDOX HOMEOSTASIS AND REACTIVE OXYGEN SPECIES

Mitochondria are the principal intracellular source of reactive oxygen species, generated as by-products of oxidative phosphorylation. During electron transport, a small proportion of electrons prematurely reduce molecular oxygen, primarily at Complex I and Complex III, forming superoxide anions. These reactive intermediates are rapidly converted to hydrogen peroxide by mitochondrial manganese superoxide dismutase and subsequently detoxified by antioxidant systems, including glutathione peroxidase, catalase, and the thioredoxin–peroxiredoxin network (26).

At physiological levels, ROS function as signalling molecules that regulate gene expression, cellular adaptation, and metabolic homeostasis. They participate in redox-sensitive signalling pathways that influence mitochondrial biogenesis, substrate utilisation, and stress responses. Thus, ROS are integral components of normal mitochondrial function rather than merely harmful by-products (27).

Thyroid hormones play a critical role in maintaining mitochondrial redox balance by modulating both ROS production and antioxidant defence mechanisms. Through their effects on mitochondrial respiration, thyroid hormones influence the rate of electron flow through the electron transport chain, thereby indirectly regulating ROS generation. In parallel, thyroid hormone signalling regulates the expression and activity of key antioxidant enzymes, enabling cells to adapt to changes in metabolic demand (28).

Alterations in thyroid hormone levels disrupt this balance. In hyperthyroid states, increased mitochondrial respiration elevates electron flux, leading to enhanced ROS production that may exceed the capacity of antioxidant defence. In contrast, hypothyroidism is associated with reduced mitochondrial activity and altered antioxidant enzyme expression, which can impair redox signalling and cellular adaptation. In both conditions, dysregulation of redox homeostasis contributes to mitochondrial dysfunction (29).

Maintaining redox equilibrium is therefore essential for preserving mitochondrial integrity and function. An imbalance between ROS generation and antioxidant capacity leads to oxidative stress, which can damage mitochondrial lipids, proteins, and DNA, ultimately impairing cellular energy metabolism and contributing to the pathogenesis of thyroid-related disorders (30, 31).

8. OXIDATIVE STRESS IN THYROID DYSFUNCTION

Oxidative stress arises when the production of reactive oxygen species exceeds the capacity of cellular antioxidant defence, leading to disruption of redox homeostasis and cellular damage. In thyroid disorders, altered hormone levels significantly perturb this balance, linking endocrine dysfunction to mitochondrial injury and metabolic impairment (31).

In hypothyroidism, reduced thyroid hormone signalling diminishes mitochondrial respiration and impairs oxidative phosphorylation. This is accompanied by decreased activity of respiratory chain enzymes and reduced ATP synthesis. In parallel, downregulation of key regulators of mitochondrial biogenesis, including PGC-1α and mitochondrial transcription factor A, contributes to reduced mitochondrial turnover and functional capacity. These changes are often associated with altered antioxidant enzyme activity, resulting in impaired redox signalling and increased susceptibility to oxidative damage despite lower overall metabolic flux (32).

In contrast, hyperthyroidism is characterised by enhanced mitochondrial respiration and increased oxygen consumption, which elevate electron leakage from the electron transport chain and promote excessive ROS generation. This overproduction of ROS is associated with lipid peroxidation, protein oxidation, and mitochondrial DNA damage, particularly in metabolically active tissues such as the liver, heart, and skeletal muscle. Persistent oxidative stress can compromise mitochondrial membrane integrity, disrupt electron transport chain function, and further amplify ROS production (33).

Structural alterations in mitochondria also contribute to oxidative stress in thyroid dysfunction. Imbalances in mitochondrial dynamics, including reduced fusion and increased fission, promote mitochondrial fragmentation and impair membrane potential. In addition, defective mitophagy may lead to the accumulation of damaged mitochondria, exacerbating oxidative injury and impairing cellular energy metabolism (34).

Excessive ROS can induce the opening of the mitochondrial permeability transition pore, leading to loss of membrane potential, release of pro-apoptotic factors, and activation of cell death pathways. These mechanisms are particularly relevant in the cardiac complications associated with thyrotoxicosis, where sustained oxidative stress contributes to tissue damage and functional decline (35).

Overall, oxidative stress represents a central mechanism linking altered thyroid hormone signalling to mitochondrial dysfunction. While hypothyroidism is associated with reduced metabolic activity and impaired redox regulation, hyperthyroidism is characterised by increased but inefficient mitochondrial activity and heightened oxidative damage. This imbalance plays a critical role in the pathophysiology of thyroid disorders and their systemic complications (36).

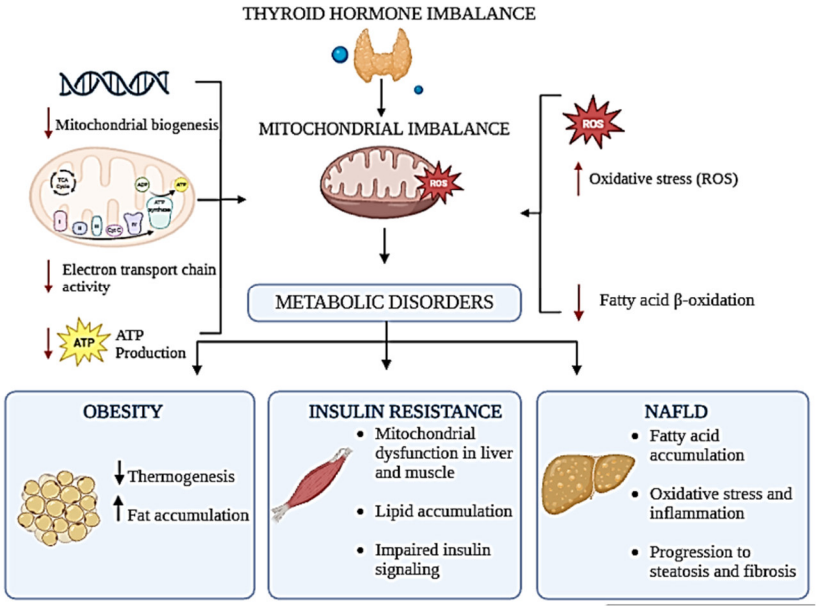

Figure 2: *Thyroid–Mitochondrial Axis in Oxidative Stress and Metabolic Dysfunction*

9. MITOCHONDRIAL DNA ALTERATIONS IN THYROID DISEASE

Mitochondrial DNA (mtDNA) encodes essential subunits of the oxidative phosphorylation system, and its integrity is critical for maintaining mitochondrial function and cellular energy metabolism. Unlike nuclear DNA, mtDNA is more susceptible to damage due to its proximity to the electron transport chain and limited DNA repair capacity. Consequently, alterations in mtDNA can directly impair respiratory chain function and contribute to metabolic dysfunction (37).

Thyroid hormones regulate mitochondrial biogenesis and thereby influence mtDNA copy number in metabolically active tissues. Hyperthyroid states are generally associated with increased mitochondrial density and elevated mtDNA copy number, reflecting enhanced biogenesis and metabolic demand. In contrast, hypothyroidism is linked to reduced mtDNA content, consistent with decreased mitochondrial proliferation and diminished bioenergetic capacity. These variations in mtDNA copy number have been explored as potential biomarkers of mitochondrial function and thyroid hormone activity (38).

In addition to quantitative changes, qualitative alterations in mtDNA, including somatic mutations and deletions, have been implicated in thyroid pathology, particularly thyroid cancer. Mutations affecting genes encoding components of the electron transport chain can disrupt oxidative phosphorylation, increase reactive oxygen species production, and promote metabolic reprogramming. Such mitochondrial alterations may contribute to tumorigenesis by favouring glycolytic metabolism and enhancing oxidative stress (39).

Furthermore, oxidative damage to mtDNA represents a key link between redox imbalance and mitochondrial dysfunction in thyroid disorders. Accumulation of mtDNA lesions can impair transcription and replication, leading to defective respiratory chain assembly and further amplification of oxidative stress. This creates a self-perpetuating cycle of mitochondrial damage and functional decline. Overall, alterations in mtDNA play a significant role in mediating the effects of thyroid hormone imbalance on mitochondrial function. These changes not only reflect underlying metabolic disturbances but may also contribute directly to the progression of thyroid-related diseases (40, 41).

10. MITOCHONDRIAL MECHANISMS IN THYROID DISORDERS

Thyroid disorders are characterised by distinct alterations in mitochondrial function, reflecting the central role of thyroid hormones in regulating cellular bioenergetics. Both hypothyroidism and hyperthyroidism disrupt mitochondrial homeostasis, but through fundamentally different mechanisms that converge on impaired energy metabolism and increased cellular stress (42).

10.1. Hypothyroidism

Hypothyroidism is associated with a global reduction in mitochondrial activity, leading to impaired energy production and metabolic slowing. Decreased thyroid hormone signalling suppresses key regulators of mitochondrial biogenesis, including PGC-1α, nuclear respiratory factors and mitochondrial transcription factor A. This results in reduced mitochondrial content and diminished expression of oxidative phosphorylation components (43).

Functionally, these changes manifest as decreased electron transport chain activity, reduced proton gradient formation, and lower ATP synthesis. Mitochondria in hypothyroid states also exhibit reduced membrane potential and impaired tricarboxylic acid cycle activity, further limiting energy output. These bioenergetic deficits contribute to clinical features such as fatigue, cold intolerance, weight gain, and reduced exercise capacity. In addition, impaired mitochondrial fatty acid oxidation promotes lipid accumulation in tissues such as the liver and skeletal muscle, contributing to dyslipidaemia and metabolic dysfunction. Alterations in mitochondrial dynamics and reduced mitophagy may further exacerbate the accumulation of dysfunctional mitochondria, reinforcing energy deficits (44).

10.2. Hyperthyroidism

In contrast, hyperthyroidism induces a hypermetabolic state characterised by increased mitochondrial biogenesis, elevated oxygen consumption, and enhanced electron transport chain activity. Thyroid hormone excess stimulates the expression of respiratory chain components and increases substrate oxidation, thereby accelerating metabolic flux. However, this heightened activity is often accompanied by reduced efficiency of oxidative phosphorylation. Increased proton leak across the inner mitochondrial membrane, partly mediated by uncoupling proteins, diverts energy from ATP synthesis toward heat production. As a result, despite increased metabolic rate, ATP generation may be relatively inefficient (45).

Moreover, excessive mitochondrial respiration increases reactive oxygen species production, which can overwhelm antioxidant defences and cause oxidative damage to lipids, proteins, and mitochondrial DNA. This contributes to tissue injury, particularly in high-energy-demand organs such as the heart and skeletal muscle, and is implicated in complications such as thyrotoxic cardiomyopathy (46).

10.3 Metabolic Disorders Associated with Thyroid Dysfunction

Mitochondrial dysfunction under altered thyroid states also contributes to broader metabolic disorders. In hypothyroidism, reduced mitochondrial oxidative capacity impairs fatty acid β-oxidation, promoting triglyceride accumulation and increasing the risk of non-alcoholic fatty liver disease. Similarly, decreased mitochondrial function in skeletal muscle and liver interferes with insulin signalling pathways, contributing to insulin resistance (47).

Conversely, although hyperthyroidism increases energy expenditure, persistent oxidative stress and mitochondrial inefficiency may disrupt metabolic homeostasis over time. Dysregulation of mitochondrial pathways, including those governed by PGC-1α, further exacerbates alterations in glucose and lipid metabolism. Overall, thyroid disorders exert profound and differential effects on mitochondrial function. Hypothyroidism is characterised by reduced mitochondrial activity and impaired energy generation, whereas hyperthyroidism involves increased but inefficient mitochondrial metabolism accompanied by oxidative stress. These mitochondrial alterations provide a mechanistic basis for the systemic metabolic disturbances observed in thyroid disease (48).

11. THERAPEUTIC TARGETING OF MITOCHONDRIAL DYSFUNCTION IN THYROID DISEASE

Conventional management of thyroid disorders primarily focuses on normalising circulating hormone levels. However, persistent symptoms in a subset of patients despite biochemical euthyroidism suggest that restoration of systemic hormone levels does not fully correct intracellular metabolic and mitochondrial dysfunction. This has prompted increasing interest in therapeutic strategies that directly target mitochondrial pathways and redox balance (49).

11.1. Thyroid Hormone Replacement

Levothyroxine (L-T4) remains the standard treatment for hypothyroidism, restoring circulating hormone levels and, indirectly, mitochondrial function through conversion to triiodothyronine (T3). Adequate replacement

therapy improves mitochondrial biogenesis, enhances oxidative phosphorylation, and restores antioxidant capacity. Nevertheless, incomplete peripheral conversion of T4 to T3 or impaired tissue-level responsiveness may limit full recovery of mitochondrial function in some patients, contributing to residual symptoms such as fatigue and reduced exercise tolerance. Combination therapy with levothyroxine and liothyronine (T3) has been explored to better mimic physiological hormone balance, although clinical outcomes remain variable and evidence for routine use is inconclusive. These observations underscore the importance of tissue-specific thyroid hormone signalling in regulating mitochondrial activity (50).

11.2. Mitochondria-Targeted Antioxidants

Given the central role of oxidative stress in thyroid-related mitochondrial dysfunction, mitochondria-targeted antioxidants have emerged as a potential adjunct therapeutic approach. Compounds such as mitoquinone (MitoQ), a derivative of coenzyme Q10, selectively accumulate in mitochondria driven by the mitochondrial membrane potential. Experimental studies indicate that such agents can reduce reactive oxygen species production, improve electron transport chain efficiency, and protect against oxidative damage. However, robust clinical evidence in thyroid disorders remains limited (51).

11.3. Coenzyme Q10 Supplementation

Coenzyme Q10 (CoQ10) functions both as an essential electron carrier within the electron transport chain and as a lipid-soluble antioxidant. Reduced CoQ10 levels have been reported in hypothyroid states, suggesting impaired mitochondrial function. Supplementation has been associated in some studies with improvements in fatigue and exercise tolerance, as well as reductions in oxidative stress markers. However, data are heterogeneous, and large-scale controlled trials are required to establish efficacy and optimal dosing strategies (52).

11.4. Selenium and Redox Regulation

Selenium is a critical micronutrient involved in thyroid hormone metabolism and antioxidant defence. It is a cofactor for iodothyronine deiodinases and for antioxidant enzymes such as glutathione peroxidases. Selenium supplementation has shown potential benefits in reducing oxidative stress and modulating immune responses, particularly in autoimmune thyroid diseases. Nonetheless, its therapeutic value remains context-dependent, and indiscriminate supplementation is not universally recommended (52, 53).

11.5. Thyromimetics and Targeted Therapies

Selective thyroid hormone receptor (TR) agonists, particularly TRβ-selective agents such as resmetirom, represent a promising strategy for targeting metabolic pathways without systemic thyrotoxic effects. By preferentially acting on hepatic thyroid hormone receptors, these agents enhance lipid metabolism and mitochondrial function while minimising adverse effects on the heart and bone. This approach highlights the potential of tissue-specific modulation of thyroid hormone signalling to correct mitochondrial and metabolic dysfunction (53).

11.6. Critical Perspective

While multiple therapeutic approaches targeting mitochondrial dysfunction are under investigation, most remain adjunctive and lack definitive clinical validation in thyroid disease. A major limitation is the incomplete understanding of tissue-specific mitochondrial responses to thyroid hormone signalling. Future therapeutic strategies will likely require integration of endocrine, metabolic, and mitochondrial targets to achieve optimal clinical outcomes (54).

12. EMERGING DIRECTIONS AND FUTURE PERSPECTIVES

Despite substantial advances, the mechanistic interplay between thyroid hormone signalling and mitochondrial function remains incompletely resolved, particularly at the level of tissue-specific regulation and disease progression. Emerging research is beginning to refine this axis and may offer new diagnostic and therapeutic opportunities (55).

12.1. Microbiome-Mitochondria Interactions

The gut microbiome has been increasingly recognised as a modulator of host metabolism, with potential influence on thyroid–mitochondrial signalling. Microbial metabolites, particularly short-chain fatty acids, can activate key metabolic regulators such as AMP-activated protein kinase (AMPK) and PGC-1α, thereby influencing mitochondrial biogenesis and energy homeostasis. Alterations in gut microbiota composition reported in autoimmune thyroid diseases suggest a possible link between microbial dysbiosis, mitochondrial function, and metabolic phenotype. However, causal relationships and therapeutic implications remain to be clearly established (55, 56).

12.2. Epigenetic Regulation of Mitochondrial Function

Epigenetic mechanisms, including DNA methylation, histone modification, and non-coding RNAs, are emerging as important regulators of thyroid hormone signalling and mitochondrial gene expression. These modifications can influence the activity of key metabolic regulators such as PGC-1α and nuclear respiratory factors, thereby

modulating oxidative metabolism and mitochondrial biogenesis. Epigenetic alterations may also contribute to long-term metabolic reprogramming in thyroid disorders, offering potential biomarkers and targets for intervention (56).

12.3. Advances in Therapeutics and Drug Delivery

Recent developments in thyroid hormone formulations, including liquid and soft-gel levothyroxine, have improved absorption and bioavailability, particularly in patients with gastrointestinal disorders. In parallel, combination therapies involving levothyroxine and liothyronine continue to be explored to address persistent symptoms, although their clinical benefit remains uncertain. Targeted drug delivery systems and mitochondria-specific therapeutics are also under investigation to enhance treatment specificity and efficacy. These approaches aim to directly modulate mitochondrial pathways involved in energy production and oxidative stress, potentially overcoming the limitations of systemic hormone replacement (57).

12.4. Multi-Omics and Precision Medicine

The integration of genomics, transcriptomics, metabolomics, and proteomics is enabling a more comprehensive understanding of thyroid–mitochondrial interactions. Multi-omics approaches can identify novel biomarkers reflecting mitochondrial activity and metabolic status, facilitating earlier diagnosis and improved disease monitoring. Coupled with advances in computational modelling and artificial intelligence, these strategies may support the development of personalised therapeutic interventions tailored to individual metabolic profiles (58).

13. FUTURE DIRECTIONS

Future research should prioritise elucidating the precise molecular mechanisms linking thyroid hormone signalling to mitochondrial function across different tissues. Identification of reliable, tissue-specific biomarkers of mitochondrial activity will be critical for translating mechanistic insights into clinical practice. In addition, therapeutic strategies targeting mitochondrial biogenesis, redox balance, and metabolic regulation hold promise but require rigorous clinical validation (59).

14. CONCLUSION

Thyroid hormones are key regulators of mitochondrial bioenergetics, integrating endocrine signalling with cellular energy production and redox balance. Disruption of this axis underlies thyroid disorders, with hypothyroidism impairing ATP generation and hyperthyroidism promoting oxidative stress and inefficient metabolism. Targeting mitochondrial dysfunction represents a promising adjunct strategy, but requires stronger clinical validation and a better understanding of tissue-specific mechanisms.

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