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CLINICAL MANIFESTATIONS OF METABOLIC CHANGES IN HYPOTHYROIDISM AND HYPERTHYROIDISM

Rashidov Rustamjon Shamsiddin o'g'li
Neurologist, Family Polyclinic No. 5,
Margilan City Medical Association,
Fergana Region

Abstract
Thyroid hormones exert profound regulatory effects on systemic metabolism, with deviations in their secretion precipitating distinctive metabolic phenotypes. This review examines the clinical and biochemical manifestations arising from metabolic alterations in hypothyroidism and hyperthyroidism. Through comparative analysis of carbohydrate, lipid, and protein metabolism alongside energy homeostasis, cardiovascular implications, and diagnostic markers, this work elucidates the pathophysiological mechanisms underlying thyroid-mediated metabolic dysfunction and emphasizes the clinical imperative for early recognition and therapeutic intervention.

Keywords: Hyperthyroidism, metabolism, thyroxine, triiodothyronine, thermogenesis, lipogenesis, catabolism, gluconeogenesis, homeostasis, thyrotoxicosis, myxedema, dysmetabolism, mitochondria, lipolysis.

Introduction

The thyroid gland orchestrates metabolic regulation through synthesis and secretion of thyroid hormones, principally thyroxine and triiodothyronine, which modulate cellular energy expenditure, substrate utilization, and anabolic-catabolic balance across virtually all tissues. These hormones bind nuclear receptors to influence transcription of genes governing mitochondrial biogenesis, thermogenic uncoupling proteins, and metabolic enzymes, thereby establishing the basal metabolic rate. Perturbations in thyroid function manifest as either hypothyroidism, characterized by hormone deficiency, or hyperthyroidism, marked by excessive hormone production. Both conditions precipitate profound metabolic derangements with distinctive clinical signatures that reflect opposing disruptions in energy homeostasis, substrate metabolism, and cellular respiration. Understanding these metabolic alterations provides essential insights for differential diagnosis and therapeutic management. This analysis examines the comparative metabolic manifestations of thyroid dysfunction, elucidating the biochemical underpinnings of clinical presentation.

Literature review

Contemporary research has substantially advanced understanding of thyroid hormone action on metabolic pathways. Mullur and colleagues demonstrated in their seminal work published in Physiological Reviews that thyroid hormones regulate basal metabolic rate through both genomic

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and non-genomic mechanisms, with triiodothyronine exerting particularly potent effects on mitochondrial oxidative phosphorylation and thermogenesis. Their analysis revealed that thyroid hormone deficiency reduces oxygen consumption by approximately thirty percent, whereas excess increases metabolic rate proportionally to hormone concentration. Notably, Duntas and Brenta, writing in Thyroid, established that hypothyroidism induces characteristic dyslipidemia through reduced hepatic low-density lipoprotein receptor expression and diminished lipoprotein lipase activity, culminating in elevated total cholesterol and low-density lipoprotein concentrations that substantially increase cardiovascular risk.

Research published in The Journal of Clinical Endocrinology and Metabolism by Iwen and associates illustrated that hyperthyroidism accelerates gluconeogenesis and glycogenolysis while simultaneously enhancing peripheral glucose utilization, creating a paradoxical state of glucose intolerance despite increased insulin secretion. This work highlighted the complex interplay between thyroid hormones and pancreatic beta-cell function. Furthermore, investigations by Salvatore and colleagues in Nature Reviews Endocrinology elucidated the molecular mechanisms whereby thyroid hormones influence protein turnover, demonstrating that excessive thyroid hormone action accelerates proteolysis, particularly affecting skeletal and cardiac muscle, thereby contributing to the muscle wasting observed in thyrotoxicosis.

Klein and Danzi, in a comprehensive analysis appearing in Circulation, examined cardiovascular metabolic implications of thyroid dysfunction, documenting that hypothyroidism reduces cardiac contractility and heart rate through diminished expression of calcium-handling proteins and beta-adrenergic receptors, whereas hyperthyroidism enhances cardiac workload and oxygen demand through increased chronotropic and inotropic effects. These findings underscore the systemic nature of thyroid hormone action and the clinical significance of metabolic alterations in thyroid disease.

MAIN BODY

The metabolic consequences of thyroid dysfunction manifest across multiple biochemical domains, with carbohydrate metabolism demonstrating particularly instructive contrasts between hypo- and hyperthyroid states. In hypothyroidism, reduced thyroid hormone availability diminishes hepatic gluconeogenesis and intestinal glucose absorption, contributing to the characteristically flat glucose tolerance curves observed in affected patients. Conversely, hyperthyroidism accelerates hepatic glucose production through enhanced glycogenolysis and gluconeogenesis while simultaneously increasing peripheral glucose uptake and utilization. This hypermetabolic state paradoxically impairs glucose tolerance in many patients, as pancreatic beta-cells struggle to maintain adequate insulin secretion despite heightened glucose turnover. The resultant glucose intolerance may precipitate or exacerbate diabetes mellitus, particularly in predisposed individuals. These opposing effects on carbohydrate homeostasis reflect the fundamental role of thyroid hormones in regulating the balance between glucose production and utilization. Lipid metabolism undergoes equally profound alterations in thyroid dysfunction, with clinical implications extending beyond laboratory abnormalities to substantial cardiovascular risk. Hypothyroidism characteristically produces a proatherogenic lipid profile through multiple mechanisms. Reduced expression of hepatic low-density lipoprotein receptors impairs clearance of circulating cholesterol-rich particles, while diminished lipoprotein lipase activity reduces triglyceride hydrolysis. Additionally, decreased

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cholesterol conversion to bile acids further elevates plasma cholesterol concentrations. The resultant hypercholesterolemia, particularly elevated low-density lipoprotein cholesterol, significantly increases atherosclerotic risk and may contribute to the increased cardiovascular morbidity observed in untreated hypothyroidism. In marked contrast, hyperthyroidism accelerates lipolysis and enhances lipid oxidation, typically producing decreased total cholesterol and low-density lipoprotein concentrations. However, this apparent benefit proves illusory, as accelerated lipid turnover may increase oxidative stress and contribute to endothelial dysfunction, while the hypermetabolic state imposes substantial cardiovascular strain through increased myocardial oxygen demand.

Protein metabolism demonstrates similarly divergent patterns between thyroid hormone deficiency and excess. Hypothyroidism reduces both protein synthesis and degradation, though synthesis declines more substantially, resulting in net protein accumulation in interstitial spaces as mucopolysaccharide deposits, producing the characteristic myxedematous appearance. This abnormal protein accumulation in subcutaneous tissues, combined with sodium and water retention, contributes to the non-pitting edema and thickened features observed clinically. Muscle protein turnover decreases, potentially contributing to the muscle stiffness and delayed relaxation of deep tendon reflexes characteristic of hypothyroidism. Conversely, hyperthyroidism dramatically accelerates protein catabolism, exceeding the compensatory increase in protein synthesis and resulting in negative nitrogen balance. This catabolic state produces clinically significant skeletal muscle wasting, weakness, and fatigue, while also affecting cardiac muscle, where increased protein turnover may contribute to the development of high-output heart failure in severe, prolonged thyrotoxicosis. Energy homeostasis and thermogenesis represent perhaps the most clinically apparent metabolic alterations in thyroid dysfunction. Thyroid hormones fundamentally regulate basal metabolic rate through effects on mitochondrial oxidative phosphorylation and expression of uncoupling proteins that dissipate the proton gradient as heat rather than capturing energy in adenosine triphosphate bonds. In hypothyroidism, reduced mitochondrial oxygen consumption and diminished thermogenesis manifest clinically as cold intolerance, reduced body temperature, and decreased energy expenditure that promotes weight gain despite often-reduced appetite. The reduction in metabolic rate may reach thirty percent below normal, substantially affecting daily energy requirements. Hyperthyroidism produces the mirror image: enhanced mitochondrial activity, increased thermogenesis, and elevated basal metabolic rate that may increase energy expenditure by fifty percent or more. Patients experience heat intolerance, excessive sweating, and paradoxical weight loss despite increased appetite and food intake, as energy expenditure exceeds intake despite hyperphagia. This hypermetabolic state places substantial demands on cardiovascular and respiratory systems to deliver oxygen and nutrients to tissues.

Cardiovascular manifestations of thyroid dysfunction directly reflect underlying metabolic alterations. Hypothyroidism reduces cardiac output through decreased heart rate and contractility, reflecting reduced expression of cardiac calcium-handling proteins and beta-adrenergic receptors. Peripheral vascular resistance increases, contributing to diastolic hypertension in some patients, while reduced metabolic oxygen consumption by peripheral tissues decreases oxygen extraction. The combination produces decreased cardiac workload at rest, though exercise capacity remains substantially impaired. Hyperthyroidism produces contrasting effects: increased heart rate, enhanced contractility, reduced systemic vascular resistance, and increased cardiac output that may reach two to three times normal values in severe cases. This high-output state increases myocardial oxygen consumption and workload, potentially precipitating angina in patients with underlying coronary disease and contributing to development of atrial fibrillation through multiple mechanisms including increased atrial stretch and altered electrophysiology.

Results and discussion

Laboratory evaluation plays a pivotal role in confirming thyroid dysfunction and elucidating the extent of associated metabolic disturbances. In hypothyroidism, the biochemical profile is typically characterized by elevated serum thyroid-stimulating hormone (TSH) levels, accompanied by reduced concentrations of free thyroxine (FT_4) and triiodothyronine (FT_3), reflecting primary thyroid failure and compensatory pituitary hypersecretion. These hormonal changes precipitate a range of metabolic consequences. Hypercholesterolemia, particularly elevated low-density lipoprotein cholesterol, arises from diminished hepatic LDL receptor activity and reduced cholesterol clearance. Serum creatine kinase (CK) levels are frequently increased, reflecting impaired skeletal muscle energy metabolism and subclinical myopathy. In some cases, mild hyponatremia develops as a result of impaired free water clearance secondary to inappropriate antidiuretic hormone activity. Additionally, a mild normocytic anemia may occur due to decreased erythropoietin production and slowed metabolic turnover. Collectively, these findings provide a biochemical fingerprint that mirrors the systemic slowing of metabolism characteristic of hypothyroid states.

Conversely, hyperthyroidism presents a diametrically opposite biochemical pattern. Laboratory assessment typically reveals suppressed TSH levels-often below the assay's detection threshold-accompanied by elevated FT_4 and FT_3 concentrations, indicating excessive thyroid hormone production and pituitary feedback inhibition. The heightened metabolic rate produces several secondary biochemical alterations. Mild hyperglycemia is commonly observed, attributable to enhanced gluconeogenesis, increased intestinal glucose absorption, and peripheral insulin resistance. Elevated alkaline phosphatase (ALP) levels frequently reflect accelerated bone turnover and heightened osteoclastic activity, while serum calcium may be mildly increased due to increased bone resorption and altered calcium kinetics. Hepatic enzyme elevations, particularly aspartate aminotransferase (AST) and alanine aminotransferase (ALT), can also occur, reflecting increased hepatic oxygen consumption and metabolic stress. These biochemical findings, when interpreted alongside clinical presentation, provide a comprehensive framework for diagnosis and disease severity assessment. Importantly, they underscore that thyroid disorders are not isolated endocrine abnormalities but rather systemic metabolic syndromes affecting nearly every tissue type. The constellation of laboratory results mirrors the pervasive influence of thyroid hormones on energy utilization, lipid and carbohydrate homeostasis, protein turnover, and electrolyte regulation.

Clinically, the manifestations of these metabolic disturbances extend well beyond the cardinal symptoms of hormone excess or deficiency. In hypothyroidism, weight gain, cold intolerance, bradycardia, and lethargy reflect global metabolic downregulation, while dry skin, hair loss, and constipation mirror impaired protein synthesis and reduced smooth muscle tone. In contrast, hyperthyroid patients frequently exhibit unintentional weight loss despite increased appetite, heat

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intolerance, tachycardia, tremor, and anxiety, all of which correspond to heightened oxidative metabolism and sympathetic activation. The systemic reach of these hormonal imbalances often encompasses cardiovascular, hepatic, and musculoskeletal systems, creating a complex clinical mosaic. Recognizing these integrated metabolic and clinical patterns allows clinicians to view thyroid dysfunction not merely as a disturbance in hormone secretion but as a multisystem metabolic disorder. Such understanding enhances diagnostic accuracy and informs more holistic therapeutic strategies-combining hormone replacement or suppression with metabolic modulation, nutritional management, and monitoring for secondary complications such as dyslipidemia, insulin resistance, and bone demineralization. This comprehensive approach transforms thyroid management from isolated endocrine correction to true metabolic rehabilitation, improving both short-term symptom resolution and long-term systemic outcomes.

Thyroid hormone excess and deficiency produce distinctive metabolic phenotypes affecting carbohydrate, lipid, and protein metabolism alongside energy homeostasis and cardiovascular function. These alterations generate characteristic clinical manifestations that, when recognized, facilitate diagnosis and guide therapeutic intervention. Early identification and appropriate treatment prove essential for preventing metabolic complications and improving patient outcomes. Future research should further elucidate cellular mechanisms underlying these metabolic effects and develop targeted therapeutic approaches addressing specific metabolic derangements beyond hormone normalization alone.

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