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REVIEW ARTICLE

Pathophysiological Processes Associated with Hypothyroidism and the Protective role of Polyphenols: Current Insights

**Mamadaliyeva Shohista Raviljon Qizi*, Karimova Iroda Ibrohimjonovna,
Yusupova Umidaxon Raxmonovna**

Department of Human and Animals Physiology,
National University of Uzbekistan named after Mirzo Ulugbek, Tashkent, Uzbekistan.

*Corresponding Author E-mail: mamadaliyevashohista849@gmail.com

ABSTRACT:

At present, thyroid-related disorders are increasing worldwide. In particular, hypothyroidism, which occurs when thyroid hormone levels fall below normal values, is one of the most frequently observed health problems among the population. Its main clinical manifestations include weight gain, fatigue, general weakness, chronic constipation, memory impairment, and cold intolerance. If hypothyroidism is not properly treated, it may lead to various metabolic disorders, such as diabetes mellitus and cardiovascular diseases. Although significant progress has been made in identifying the causes of hypothyroidism, understanding its clinical consequences, as well as in its diagnosis and treatment, a number of unanswered questions regarding its management still remain. Hypothyroidism is usually treated with synthetic pharmacological agents. However, long-term use of these drugs may cause adverse effects, including cardiac dysfunction, left ventricular hypertrophy, and oxidative stress-related liver damage¹. Therefore, the development of new therapeutic approaches with no or fewer side effects that can improve thyroid function and alleviate hypothyroidism-induced pathophysiological processes in the body is of great importance. Plant-based preparations are often considered promising alternatives, as they usually have minimal or no adverse effects and provide valuable therapeutic potential for various metabolic disorders. This review aims to summarize the role of the thyroid gland and its hormones, the systemic changes observed in hypothyroidism, as well as the modulatory effects of polyphenols on thyroid function and hypothyroidism-associated metabolic syndromes.

KEYWORDS: Thyroid gland, thyroxine, triiodothyronine, metabolism, nervous system, cardiovascular system, respiratory system, digestive system, excretory system, reproductive system, musculoskeletal system, polyphenols.

INTRODUCTION:

The thyroid gland is a bilobed organ located in the anterior region of the neck and is composed of two main types of cells: follicular and parafollicular cells. The fundamental morphofunctional and histological unit of the thyroid gland is the follicle. Thyroid follicles are spherical structures with an approximate diameter of 200 μm^2 . Follicular cells are responsible for the synthesis of thyroid hormones. Parafollicular cells, also known as C cells, secrete the hormone calcitonin, which plays a key role in calcium homeostasis³. The follicular wall is lined with follicular epithelium (thyrocytes), and the follicular lumen is filled with colloid, whose principal component is the protein thyroglobulin. Follicular cells possess a unique ability to actively uptake iodide anions from the

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bloodstream against a concentration gradient. This distinctive property of follicular cells enables the synthesis of thyroid hormones within the thyroid gland². Hormone synthesis occurs through the iodination of tyrosine residues within the glycoprotein thyroglobulin⁴. Furthermore, thyroid hormone biosynthesis requires active iodide transport mediated by the sodium/iodide symporter (NIS), synthesis of thyroglobulin (Tg), and iodination of Tg catalyzed by the enzyme thyroid peroxidase (TPO). Thyroid hormones, thyroxine (T₄) and triiodothyronine (T₃), are released following proteolysis of thyroglobulin. The thyroid gland secretes T₄ in significantly greater amounts than T₃, at a ratio of approximately 14:1⁵. In addition, thyroxine (T₄) is converted to triiodothyronine (T₃) in most target tissues through the action of type 1 and type 2 iodothyronine deiodinases (Dio₁ and Dio₂)⁶. Upon release into the circulation, the majority of thyroid hormones bind to plasma proteins, with more than 99.7% present in the bound form, while only a small fraction circulates as unbound or free hormones (fT₄ and fT₃). The free fractions of thyroid hormones represent the biologically active forms⁷. Thyroid hormones are essential for normal growth and development and are required for the proper functioning of multiple physiological systems. They influence numerous aspects of cellular physiology, including cell growth, differentiation, and apoptosis, and serve as key regulators of cellular energy metabolism and thermogenesis. Thyroid hormones stimulate oxygen consumption and heat production^{4,8}. During critical periods of development, thyroid hormone deficiency, such as that caused by maternal iodine deficiency or untreated congenital hypothyroidism may result in severe neurological impairments and growth retardation in the developing fetus⁹.

The biological actions of thyroid hormones (T₃ and T₄) are primarily mediated through the interaction of the biologically active hormone T₃ with thyroid hormone nuclear receptors (TRs), which regulate the activation or repression of target gene expression^{4,8}. In addition, the biosynthesis and metabolism of thyroid hormones are regulated by at least three key factors:

- The availability of the trace element iodine;
- Stimulation by pituitary-derived thyroid-stimulating hormone (TSH);
- The activity of deiodinase enzymes¹⁰.

The human body of a healthy individual contains approximately 15–20mg of iodine, of which about 70–80% is concentrated in the thyroid gland². All living organisms possess the ability to utilize iodine and incorporate it into proteins. Iodinated compounds are also considered essential in invertebrates lacking a thyroid gland, where they play important roles in the regulation of various physiological functions. In humans

and most vertebrates, the thyroid gland has evolved to store iodine and convert it into hormonally active forms. The thyroid gland synthesizes and stores iodinated molecules, including iodotyrosines, iodothyronines, and thyroid hormones (T₄ and T₃)¹¹. Iodine is an essential trace element that is absorbed primarily in the small intestine. This micronutrient is an integral component of thyroid hormones T₃ and T₄. Iodized salt, seafood, marine algae, and vegetables represent the main dietary sources of iodine. Insufficient iodine intake may result in iodine deficiency and a subsequent reduction in thyroid hormone synthesis. Iodine deficiency is a major etiological factor underlying disorders such as cretinism, myxedema, and hypothyroidism¹².

The levels of thyroid hormones in the blood plasma are regulated by the hypothalamic-pituitary-thyroid (HPT) feedback system, which, under the influence of the pituitary TSH and hypothalamic thyrotropin-releasing hormone (TRH), maintains stable thyroid hormone levels⁵. The hypothalamus is responsible for producing TRH, which reaches the pituitary gland through the venous system. In the pituitary, TRH binds to receptors on thyrotroph cells, inducing the production and secretion of TSH, also known as thyrotropin. TSH binds to its receptors on the thyroid gland, which are responsible for the synthesis of T₃ and T₄ hormones, accelerating the production and secretion of thyroid hormones in the follicular cells³. Thyroid hormone signaling is tightly regulated by the activity of iodothyronine deiodinase enzymes, which maintain the circulating levels of biologically active T₃ and locally control thyroid hormone homeostasis in a cell- and time-specific manner. The thyroid gland produces more inactive T₄ than active T₃. Consequently, the majority of intracellular T₃ arises from local regulation of thyroid hormone metabolism rather than direct secretion. Without altering plasma hormone concentrations, intracellular thyroid hormone levels can be modulated by a family of three deiodinase enzymes: type 1 (D₁), type 2(D₂), and type 3(D₃)⁶. All three enzymes are expressed in a tissue-specific manner during fetal development and adulthood, differentially catalyzing the activation or inactivation of thyroid hormones¹³.

Thyroid hormone receptors function as transcription factors that can bind both T₃ and T₄. However, they exhibit significantly higher sensitivity to T₃, while T₄ is relatively inactive compared to T₃. Deiodinases convert T₄ either to active T₃ or to inactive reverse T₃ (rT₃). The three types of deiodinases have specialized roles: type I (DIO₁) and type II (DIO₂) are located in the liver, kidneys, muscles, and thyroid gland, whereas type III (DIO₃) is predominantly found in the central nervous system and placenta. DIO₁ and DIO₂ convert T₄ into its active T₃ form, while DIO₃ transforms T₄ into inactive

rT₃^{4,14}. Deiodinases represent a dynamic system whose activity varies across different cells and tissues throughout life, reflecting their distinct functions and roles. Tissue-level deiodinase activity mediates the activation (DIO₁ and DIO₂) and inactivation (DIO₃) of thyroid hormones, allowing hormone homeostasis to be tailored to the functional requirements of each cell. These enzymes serve as a driving force for thyroid hormone homeostasis, enabling target cells to respond appropriately to thyroid hormone signaling while considering both circulating hormone levels and tissue-specific responses¹⁵.

MATERIALS AND METHODS:

We conducted a systematic review and analyzed previous studies related to the thyroid gland, the pathophysiological changes observed in the body during hypothyroidism, and the effects of polyphenols on these alterations. Electronic literature searches were conducted using the Scopus, Google Scholar, and PubMed databases. The search strategy included the following key terms: (1) the thyroid gland and its hormones, (2) pathophysiological changes occurring in hypothyroidism, and (3) polyphenols and their influence on thyroid function. All references included in this review were published between 2004 and 2025. During the preparation of this review article, studies published in earlier years were also consulted in certain cases, as these sources provide important fundamental scientific information on the topic in a detailed manner. The study selection process was conducted using the PRISMA method (Figure 1).

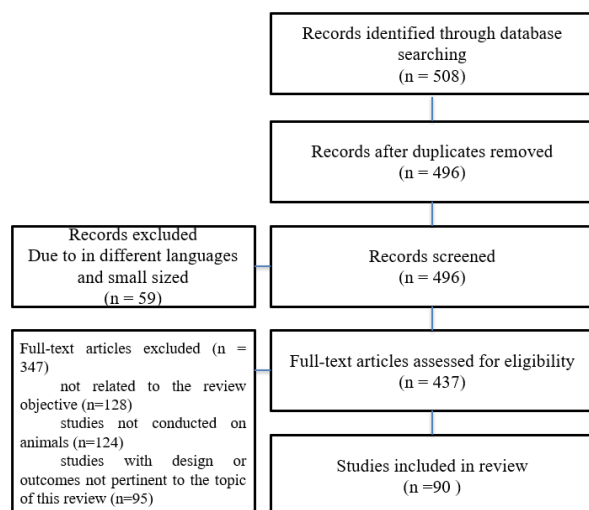


Figure 1. PRISMA flow diagram illustrating the identification, screening, eligibility assessment, and inclusion of studies.

RESULTS AND DISCUSSIONS:

The thyroid gland synthesizes the hormones T₃ and T₄, which play a crucial role in maintaining metabolism and homeostasis, through the following mechanism.

Iodide is actively transported into thyrocytes via the sodium–iodide symporter (NIS) located on the basolateral membrane and is subsequently transferred into the follicular lumen partly through pendrin (PDS/SLC26A4) situated on the apical membrane. In the presence of H₂O₂, iodide is rapidly oxidized by thyroid peroxidase (TPO) and covalently bound to tyrosine residues of the thyroglobulin (Tg) molecule located on the luminal side of the apical membrane. As a result of this step, monoiodotyrosine (MIT) and diiodotyrosine (DIT) are formed. Subsequently, only properly positioned MIT and DIT molecules within the Tg structure participate in coupling reactions to form thyroxine (T₄) and triiodothyronine (T₃); this reaction is also catalyzed by TPO in the presence of H₂O₂. The source of H₂O₂ in the thyroid gland is DUOX2 (dual oxidase 2), which is expressed on the apical plasma membrane in coordination with DUOXA2 (dual oxidase maturation factor 2), a factor required for the maturation of the dual oxidase enzyme. After thyroglobulin degradation, thyroid hormones are released into the bloodstream. MIT and DIT are deiodinated by the enzyme iodothyrosine dehalogenase 1 (DEHAL1). The synthesis of thyroid hormones is primarily regulated by thyroid-stimulating hormone (TSH). Binding of TSH to the TSH receptor (TSHR) activates Gs protein (stimulatory G protein) and Gq protein (phospholipase C-activating G protein). The first regulates growth, differentiation, and thyroid hormone secretion, whereas the second stimulates H₂O₂ generation and iodide organification through the inositol phosphate–Ca²⁺/diacylglycerol signaling pathway mediated by phospholipase C.¹⁶ (fig. 2).

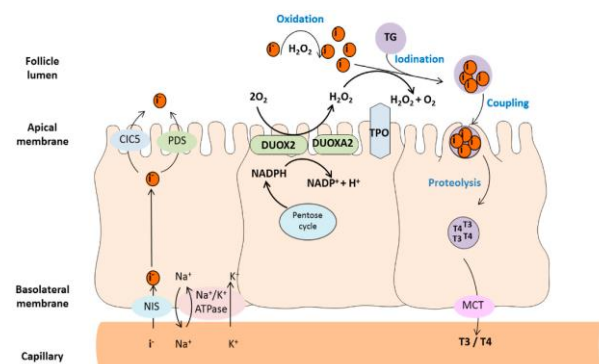


Figure 2. Synthesis of thyroid gland hormones¹⁷

Thyroid disorders are typically characterized based on the circulating levels of T₃, T₄, and TSH hormones. Accordingly, these disorders are classified into two main types: hyperthyroidism, which results from excessive production of thyroid hormones, and hypothyroidism, which is associated with insufficient hormone synthesis. Depending on the site of origin, thyroid disorders can further be categorized as primary, secondary, or tertiary. Primary disorders arise directly from intrinsic thyroid

gland abnormalities, secondary disorders result from pituitary gland dysfunction, and tertiary thyroid pathologies develop due to hypothalamic defects³. Hypothyroidism is a clinical syndrome resulting from a prolonged and persistent deficiency of thyroid hormones in the body or a reduced biological activity of these hormones at the tissue level. Its development can be attributed to multiple causes, and hypothyroidism is classified as primary, secondary, or tertiary. In primary hypothyroidism, the underlying process is localized directly within the thyroid gland. Secondary or tertiary hypothyroidism occurs when reduced thyroid function arises due to insufficient stimulation by TSH or TRH. Additionally, peripheral hypothyroidism can be distinguished, which is associated with resistance or decreased sensitivity of cellular and tissue receptors to thyroid hormones. Thyroid hormone deficiency in various forms of hypothyroidism leads to profound alterations across virtually all organs and systems. The primary mechanism underlying such damage is a marked reduction in the production of several cellular enzymes, which results in decreased metabolic activity, a significant reduction in oxygen demand, slower oxidation-reduction reactions, and ultimately a decline in overall metabolic indices³.

Metabolism:

In hypothyroid states, tissue oxygen consumption, energy expenditure, and utilization of energy substrates are reduced. Basal metabolic rate can decrease by as much as 35–40%, which, despite a reduction in appetite, may lead to moderate weight gain^{18,19}. Protein synthesis and metabolism are diminished in hypothyroidism, while many patients exhibit a positive nitrogen balance and increased plasma albumin levels. Additionally, glucose absorption through the intestines is impaired, leading to lower glycemic peaks during glucose tolerance tests. A hallmark of severe hypothyroidism is the development of myxedematous swelling, predominantly observed in connective tissue structures. These edematous changes arise due to the accumulation of hydrophilic protein degradation products (including proteins, glucuronides, and chondroitin derivatives) in mucous membranes, skin, subcutaneous tissue, and muscles, resulting from disrupted glycosaminoglycan metabolism¹⁸.

The cardiovascular, respiratory, renal, and central nervous systems, along with general homeostatic mechanisms, play critical roles in regulating the functions of various organ systems. These systems coordinate to control the organism's metabolic processes, with thyroid hormones produced by the thyroid gland acting as central regulators of metabolism²⁰.

Nervous system:

Thyroid hormones play a critical role in the development and maturation of the mammalian brain both prenatally and postnatally^{21,22}. Thyroid hormones are essential for the healthy development of the fetus's brain and nervous system during the first three months of pregnancy. During this period, the fetus is unable to produce its own hormones and relies on the mother's hormones, which are delivered through the placenta. Around the 12th week, the fetal thyroid gland begins to produce its own hormones independently²³. For many years, iodine deficiency has been considered a geographically restricted problem in certain regions of the world. Studies have shown that populations in these areas often exhibit cognitive impairments and lower IQ levels. Maternal thyroid dysfunction can arise from various causes, with iodine deficiency being one of the leading factors. Children born to hypothyroid mothers have been reported to show attention deficits and reduced activity levels. The primary factor responsible for long-term alterations in fetal neurological development is maternal hypothyroidism, characterized in early pregnancy by low plasma free thyroxine (fT₄) levels and elevated TSH concentrations. Therefore, normal maternal thyroid function during pregnancy is generally associated with a minimal risk of neurodevelopmental defects in the offspring. However, over the past two decades, epidemiological and experimental studies have indicated that fetal neurological development may be affected not only by maternal hypothyroidism but also by "hypothyroxinemia" in early pregnancy²¹. During fetal development, thyroid hormones significantly influence growth processes and the formation of central nervous system (CNS) cytoarchitecture. They are involved in neurogenesis, differentiation of neurons and glial cells, formation of the six-layered cortex, myelination and migration of neurons in the cortex, hippocampus, and cerebellum²⁴. Additionally, thyroid hormones play an essential role in synaptogenesis and in the regulation of GABAergic and noradrenergic neurotransmission. Thyroid hormone deficiency during pregnancy has been shown to lead to multiple structural abnormalities in the CNS. In congenital hypothyroidism, reductions are observed in the number of cells in the olfactory bulb, the granular layers of the CA1 and CA4 regions in the hippocampus and cerebellum, GABAergic neurons in the cerebellum, and interneurons in the cerebral cortex^{25,26,27}. Furthermore, dendritic structures of cholinergic and serotonergic neurons in the cerebellum, as well as Purkinje cells, may exhibit reduced neuropil, deformation, or permanent structural damage²⁷. In patients with prolonged and severe hypothyroidism, neuronal atrophy, gliosis, focal degeneration, as well as the accumulation of mucinous substances and rounded glycogen granules have been observed (fig. 3).

Hypothyroidism is also associated with disruptions in the metabolism and production of several mediators. Depression developing in subclinical and overt hypothyroidism has been linked to decreased 5-hydroxytryptamine (serotonin) activity in the central nervous system². Thyroid hormone deficiency can alter the chemical composition and properties of the brain. Studies have shown that insufficient thyroid hormones in the brain microenvironment can lead to reduced levels of monoamines, such as epinephrine and norepinephrine²⁸. Furthermore, metabolites of thyroid hormones, including 3'-iodothyronamine (T1AM), may exert significant effects on the central nervous system²⁹. T1AM can dose-dependently inhibit the activity of the organic anion transporting polypeptide 1C1 (OATP1C1) and monocarboxylate transporter 8 (MCT8), thereby blocking the passage of thyroid hormones across the blood-brain barrier and altering their effects within the CNS³⁰. Animal studies have demonstrated that T1AM contributes to the coordination of neural signaling, learning, and memory processes. These effects are mediated, at least in part, through the activation of mitochondrial ATP synthase and the trace amine-associated receptor 1 (TAAR1)^{31,32}. Thyroid hormones can influence the formation of myelin proteins, making them essential for proper myelination³³. In hypothyroidism, cognitive impairments such as memory decline and slower neural response times may occur³⁴. Additionally, researchers are investigating the relationship between Alzheimer's disease and Hashimoto's encephalopathy, as thyroid disorders have been associated with an increased risk of Alzheimer's and related cognitive deficits³⁵. Reduced production of thyroid hormones slows the brain cells' ability to utilize oxygen and glucose, which may contribute to chronic fatigue and memory impairment in affected patients. According to statistical data, approximately two-thirds of individuals with hypothyroidism experience problems related to memory and attention³⁶.

Cardiovascular system:

Thyroid hormones play a critical role in maintaining cardiovascular homeostasis, as thyroid hormone receptors are present both in the vascular endothelium and in the myocardium³⁷. Even subtle changes in circulating thyroid hormone levels can negatively affect cardiovascular function and are associated with an increased risk of cardiovascular disease and overall mortality. The main pathophysiological mechanisms linking hypothyroidism to cardiovascular disease include accelerated atherosclerosis and impaired myocardial function³⁸. Low levels of thyroid hormones contribute to endothelial dysfunction, abnormal lipid metabolism, blood pressure alterations, hemostatic abnormalities, and insulin resistance, all of which can accelerate the progression and severity of atherosclerosis³⁹. Endothelial dysfunction arises from an imbalance between vasoconstriction and vasodilation. Nitric oxide (NO) is a key mediator of endothelial function and vasodilation, and its release from vascular endothelial cells is primarily stimulated by shear stress, although other factors are also involved⁴⁰. Thyroid hormones can enhance endothelial NO production through non-genomic effects, particularly by activating phosphatidylinositol-3-kinase (PI3K) and serine/threonine-protein kinase signaling pathways. In patients with hypothyroidism, reduced NO production leads to endothelial dysfunction, which extends beyond vascular tone regulation. Endothelium also exerts anti-inflammatory and anti-atherogenic functions by modulating cytokine expression, vascular permeability, and platelet adhesion. Reduced NO levels contribute to impaired flow-mediated dilation and promote atherosclerosis through multiple mechanisms, including increased adhesion of platelets and monocytes, oxidation of low-density lipoproteins (LDL), expression of pro-thrombotic factors, and migration and proliferation of vascular smooth muscle cells⁴¹.

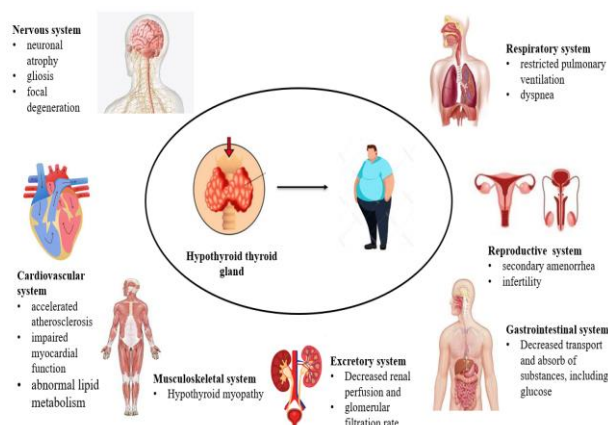


Figure 3. The effect of hypothyroidism on different organs.

Thyroid hormones (THs) play a crucial role in regulating lipid metabolism. Patients with TH deficiency often exhibit disrupted lipid homeostasis, as these hormones regulate the process through multiple mechanisms⁴¹. In the liver, THs stimulate the expression of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and low-density lipoprotein receptor (LDL-R) genes^{42,4}. When TH levels are low, hepatic cholesterol synthesis exceeds LDL-cholesterol (LDL-C) utilization, resulting in elevated circulating LDL levels⁴. In addition to hypercholesterolemia, patients often present with increased triglyceride (TG) concentrations due to the role of THs in activating lipoprotein lipase, which hydrolyzes TGs in circulating chylomicrons⁴³. Furthermore, hypothyroidism is associated with an unfavorable LDL-C to high-density lipoprotein cholesterol (HDL-C) ratio and increased LDL particle

oxidation, significantly raising the risk of atherogenesis⁴⁰. Thyroid hormones exert profound physiological effects on the heart and peripheral vasculature. Klein and Danzi have provided a comprehensive review of these mechanisms. Cardiac effects are primarily mediated by triiodothyronine (T_3), as cardiomyocytes lack significant deiodinase activity. T_3 regulates the transcription of key structural and functional genes via nuclear receptors. Specifically, T_3 activates the myosin heavy chain gene, essential for strong myocardial contraction, as well as sarcoplasmic reticulum Ca^{2+} -ATPase (SERCA) and its regulatory protein phospholamban, which control intracellular calcium cycling. These molecular actions enhance myocardial contractility and diastolic relaxation. T_3 also influences the expression of other genes, including Na^+/K^+ -ATPase, β_1 -adrenergic receptors, atrial natriuretic peptide, and several voltage-dependent potassium channels. In peripheral blood vessels, thyroid hormones reduce vascular resistance through both genomic and non-genomic effects on vascular smooth muscle cells. These mechanisms involve increased endothelial nitric oxide synthase activity and enhanced expression of adrenomedullin. Reduced vascular resistance activates the renin-angiotensin-aldosterone system (RAAS) and increases intravascular volume^{44,45}. Thyroid hormones exert positive inotropic and chronotropic effects on the heart, raising myocardial oxygen consumption. In hypothyroidism, bradycardia and mild arterial hypertension are observed, along with reduced stroke volume, heart rate, and myocardial contractility⁴⁶. However, heart failure typically occurs only in severe hypothyroidism, as the reduced cardiac output is balanced by decreased oxygen demand².

Respiratory system:

In hypothyroidism, both the maximal lung capacity and the ventilatory response to carbon dioxide (CO_2) are reduced. The primary cause of alveolar hypoventilation is diaphragmatic muscle weakness¹. Hypothyroidism can impair respiratory function, leading to conditions ranging from mild dyspnea to severe respiratory failure⁴⁰. Respiratory compromise in hypothyroidism is likely associated with restricted pulmonary ventilation, reduced cardiac reserve, and weakened inspiratory and expiratory muscles. Difficulties in weaning patients from mechanical ventilation in hypothyroid individuals are not solely due to respiratory muscle weakness but also reflect decreased central chemosensitivity to hypoxemia and hypercapnia²⁰.

Even asymptomatic patients with hypothyroidism may experience subclinical and potentially hazardous respiratory impairments. Numerous studies have investigated the impact of hypothyroidism on pulmonary function, as well as the beneficial effects of thyroid

hormone replacement therapy in mitigating these impairments⁴⁷.

Hypothyroid dermopathy and ectodermal disorders Syndrome:

Peripheral thyroid hormones (T_4 and T_3) influence the function of numerous organs and coordinate various physiological processes at the cellular level. The skin, in particular, is a key target organ for thyroid hormones, and these hormones exert significant effects on skin cells. Thyroid hormones are considered essential regulators of skin homeostasis, and dysregulation of these hormones is associated with multiple dermatological conditions. Hypothyroidism, hyperthyroidism, and thyroid cancer can manifest through various clinical signs in the skin⁴⁸. Thyroid hormone receptors have been identified in dermal fibroblasts, sebaceous glands, smooth muscle cells, Schwann cells, and many other skin cell types responsive to thyroid hormones. T_3 stimulates the proliferation of epidermal keratinocytes and dermal fibroblasts, and thyroid hormones enhance fibroblast proliferation, which subsequently modulates hyaluronate synthesis⁴⁹. During embryogenesis, thyroid hormones play a critical role in establishing the epidermal barrier by promoting the activity of the cholesterol sulfate cycle⁵⁰. Thyroid hormones accelerate the formation of skin barrier function, whereas hypothyroidism slows this process, potentially compromising epidermal barrier integrity⁵⁰. In myxedema, the primary accumulating glycosaminoglycan is hyaluronic acid, which can affect multiple organs. Extravasation of albumin into tissues leads to fluid accumulation in the extracellular space, exacerbated by inadequate lymphatic drainage. In hypothyroidism, the skin appears cold and pale due to increased dermal mucopolysaccharides and water content⁴⁸. This syndrome is associated with disrupted glycosaminoglycan metabolism in the context of thyroid hormone deficiency, resulting in increased tissue hydrophilicity. Characteristic features include firm myxedematous swelling of the face and extremities, enlarged lips, and dental impressions on the lateral edges of the tongue. The skin is thick, dry, cold, and pale yellow (due to impaired β -carotene metabolism), with scaling observed on the elbows. Hair becomes brittle, yellowish, slow-growing, and may be lost on the scalp, eyelashes, and extremities, with occasional total alopecia. Nails are thin and display horizontal or vertical ridging⁴⁶.

Gastrointestinal system:

THs affect nearly all organs in the body and regulate basal metabolism, and the gastrointestinal tract is no exception. In the interaction between the gut and thyroid hormones, the intestine may serve both as a reservoir for these hormones and as a modulator of their activity.

Excess or deficiency of thyroid hormones alters gastrointestinal function and metabolism, with hypothyroidism exerting a more profound effect than hyperthyroidism. Thyroxine influences the transport of substances, including glucose, across the small intestine⁵¹. Several studies have reported that glucose absorption increases following thyroxine therapy². Thyroid dysfunction can contribute to various gastrointestinal pathologies. In hyperthyroid patients, gastric volume is reduced, whereas in hypothyroidism, increased gastric mass, delayed gastric emptying, and muscular swelling may occur. Research conducted in Nigeria indicated that hypothyroid patients exhibit increased small intestinal weight and significant thickening of the intestinal wall, potentially due to myxedematous infiltration or fluid retention within the intestinal layers. Furthermore, intestinal infiltration and wall thickening in hypothyroidism may slow glucose transport, impairing nutrient absorption⁵². Reduced metabolism in hypothyroidism decreases the demand for energy substrates, leading to reduced appetite. Additional contributing factors include constipation, slowed intestinal peristalsis, and reduced food intake. Biliary motility is also diminished in hypothyroidism, which can result in dyskinesia and increase the risk of gallstone formation².

Excretory system and water-electrolyte balance:

Hypothyroidism can impair renal function through both direct and indirect mechanisms. First, hypothyroidism alters the production and activity of the renin-angiotensin-aldosterone system (RAAS), disrupting renal autoregulation⁵³. Second, hypothyroidism affects the expression and activity of several renal tubular ion transporters, including the $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransporter⁵⁴, Na^+ -phosphate cotransporter, $\text{Na}^+\text{-H}^+$ exchanger, and $\text{Na}^+\text{-K}^+\text{-ATPase}$. Changes in the expression of basolateral chloride channels further increase chloride delivery through distal tubules, activating the tubuloglomerular feedback mechanism. Third, hypothyroidism reduces cardiac output due to systolic and diastolic cardiac dysfunction and decreased erythrocyte production, further compromising renal perfusion⁵⁵. Fourth, intrarenal vasoconstriction occurs due to decreased synthesis and activity of renal vasodilators such as nitric oxide and adrenomedullin^{56,53}, exacerbating the decline in renal blood flow. Animal studies have demonstrated that hypothyroidism reduces single-nephron glomerular filtration rate (GFR), renal plasma flow (RPF), and glomerular transcapillary hydrostatic pressure⁵⁵. These observations have been corroborated in human clinical series, showing that severe hypothyroidism decreases GFR and RPF—findings confirmed by creatinine-based equations and isotopic standard methods—and can be restored with exogenous thyroid hormone replacement^{53,55,56}.

According to research conducted in India, women with untreated or inadequately treated hypothyroidism exhibited average serum creatinine levels close to the upper limit of the normal range and a reduced estimated glomerular filtration rate (eGFR)⁵⁷.

Furthermore, several large population-based studies have reported a correlation between elevated TSH levels and the risk and progression of chronic kidney disease (CKD)⁵⁵. Reduced cardiac output in hypothyroidism decreases renal blood flow and GFR, contributing to elevated serum creatinine. In addition, hypothyroidism leads to sodium retention due to binding with extracellular mucopolysaccharides, while serum sodium levels are often reduced due to inappropriate antidiuretic hormone (ADH) secretion, resulting in hyposmolar states². Therefore, patients with hypothyroidism should regularly monitor their kidney function as a precautionary measure.

Reproductive system:

Recent scientific evidence indicates that THs play a critical role in maintaining female reproductive system homeostasis. THs regulate reproductive functions through two primary mechanisms: genomic and nongenomic via thyroid hormone receptors (THRs). These processes occur either through binding of TH molecules to nuclear receptors (THRs or steroid hormone receptors) within the cell or to integrin receptors on the plasma membrane. Upon binding, THs recruit hormone response elements (HREs), activating gene expression or cellular signaling pathways. Moreover, THs interact in a complex, bidirectional manner with other reproductive hormones, including estrogen, progesterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). Due to structural similarities and shared DNA sequences, these hormones can influence each other through overlapping receptors or signaling pathways. THs not only affect the synthesis, secretion, and function of these reproductive hormones but are also themselves regulated by them. Such hormonal cross-regulation is a key factor in controlling normal reproductive processes as well as in the development of hormone-dependent pathological conditions, including reproductive system tumors and other endocrine disorders⁵⁸. Decreased levels of sex hormone-binding globulin result in lower circulating concentrations of total testosterone and estradiol. In primary hypothyroidism, excessive production of TRH leads to elevated secretion of TSH and prolactin. Clinical manifestations of primary hypothyroidism include galactorrhea in approximately 5% of patients, as well as secondary amenorrhea and infertility in up to 65% of affected women. The effects of thyroid hormone alterations on the reproductive system have been extensively studied in animal models, which generally

demonstrate that changes in normal thyroid function reduce sexual activity and fertility².

Musculoskeletal system:

Skeletal muscles are one of the primary target tissues of thyroid hormones, where they regulate cell proliferation, metabolism, differentiation, homeostasis, and growth. Under physiological conditions, thyroid hormones stimulate protein synthesis and degradation, and alterations in thyroid hormone levels often lead to characteristic myopathies. The intracellular concentration of thyroid hormones in muscle cells is modulated by a family of enzymes called deiodinases. In skeletal muscles, particularly, type 2 (Dio₂) and type 3 (Dio₃) deiodinases are present: Dio₂ converts the prohormone thyroxine (T₄) into its active form, triiodothyronine (T₃), while Dio₃ inactivates T₄ and T₃ by removing the inner-ring iodine⁵⁹. The expression and activity of deiodinases constitute a cell-autonomous pre-receptor mechanism that controls intracellular T₃ concentrations. Muscle contraction and relaxation rates depend on T₃-regulated myosin expression and mitochondrial substrate oxidation. The balance between Dio₂ and Dio₃ expression determines thyroid hormone levels, thereby influencing cell proliferation and differentiation, highlighting the critical role of thyroid hormones in muscle regeneration and myogenesis. During critical illness, alterations in thyroid hormone levels, receptor availability, and deiodinase activity adversely affect skeletal muscle function and recovery^{60,61}.

Thyroid hormones are also key regulators of cellular metabolism, thermoregulation, nervous system processes, cardiovascular function, and reproductive system activity. Consequently, thyroid disorders, including hypothyroidism, lead to systemic disturbances. Identifying new bioactive compounds that safely and effectively correct thyroid pathologies is of significant importance.

Thyroid gland and oxidative stress:

Reactive oxygen species (ROS) are crucial for thyroid function because they are required in the early stages of thyroid hormone synthesis, particularly during the oxidation of iodide. In addition, the reactions catalyzed by TPO during the synthesis of thyroxine T₄ and T₃ within thyroid follicles also occur with the participation of ROS. The dependence of normal thyroid function on ROS indicates that the thyroid gland is constantly exposed to ROS and is therefore particularly susceptible to oxidative damage. For this reason, in order to maintain the structural and functional integrity of the thyroid gland, its antioxidant defense system must effectively regulate and maintain a balance between ROS generation and their elimination⁶².

The Nrf2 (Nuclear factor erythroid 2-related factor 2) – Keap1 (Kelch-like ECH-associated protein 1) signaling pathway plays an important role in controlling oxidative stress in the thyroid gland. Nrf2 activates antioxidant defense mechanisms in thyroid cells by increasing the expression of antioxidant genes such as NQO1, GPX2, and TXNRD1. This system helps protect the thyroid gland from oxidative stress, particularly under conditions of excess iodide. In addition, Nrf2 also plays an important role in thyroid hormone synthesis, as it enhances the transcription of the thyroglobulin gene, which encodes the precursor protein of thyroid hormones⁶³. Selenium, which is present in relatively high concentrations in the thyroid gland, is an essential component of selenoproteins that play a crucial role in antioxidant defense. In particular, selenoprotein S encoded by SELENOS interacts functionally with Nrf2, forming an interconnected signaling system in which the two pathways may positively regulate each other. Studies have shown that Nrf2 deficiency leads to reduced expression of selenoprotein S, whereas decreased levels of selenoprotein S also suppress Nrf2 activity. This finding suggests the presence of a genetic interaction associated with the risk of Hashimoto thyroiditis⁶⁴.

Under hypothyroid conditions, increased oxidative stress in the thyroid gland may activate the Nrf2–Keap1 signaling pathway. Activated Nrf2 enhances cellular antioxidant defense by upregulating the expression of antioxidant genes such as NQO1, GPX2, and TXNRD1. In contrast, Keap1 normally acts as the main negative regulator that limits Nrf2 activity. However, when Keap1 function is reduced or disrupted, Nrf2 becomes activated and further increases the expression of antioxidant genes. Experimental studies using Keap1 models have demonstrated increased expression of Nrf2 target genes, as well as dilation of thyroid follicles and enlargement of the colloid compartment. These alterations may contribute to changes in thyroid function and, in some cases, to metabolic and structural alterations associated with hypothyroidism⁶⁵. Several antioxidant enzyme systems exist in the body to protect against oxidative stress (OxS). Enzymes that degrade ROS—such as catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione reductase (GR)—provide the primary antioxidant defense⁶⁶. However, the capacity of endogenous antioxidant systems is not always sufficient to prevent the damage caused by excessive ROS accumulation. Therefore, non-enzymatic mechanisms based on molecules with antioxidant properties—such as glutathione (GSH), thioredoxin, coenzyme Q10, and exogenous antioxidants including various polyphenolic compounds, ascorbic acid, tocopherol, retinol, and β -carotene—play a crucial role in supporting antioxidant

defense. Thyroid hormones also influence mitochondrial activity and modulate ROS production. Dysfunction of the mitochondrial respiratory chain caused by hypothyroidism has been reported to be associated with increased production of free radicals. Even in its subclinical form, hypothyroidism reduces the activity of antioxidant systems, thereby enhancing oxidative stress. This leads to oxidative damage in thyroid cells and alterations in lipid metabolism⁶⁷. Malondialdehyde (MDA), a by-product of lipid peroxidation triggered by ROS, has been found at elevated concentrations in patients with hypothyroidism. Although levothyroxine significantly reduces lipid peroxidation, serum MDA levels never reach those observed in healthy individuals⁶².

Therefore, the use of polyphenols as supplementary compounds capable of preventing the oxidation of cellular components may protect human organs—including the thyroid gland—from oxidative damage by increasing the overall antioxidant capacity of the body and may also exert corrective effects on metabolic alterations resulting from thyroid diseases.

Polyphenols and their thyroprotective effects:

Polyphenols are important secondary metabolites in plants. They play a crucial role in coloring flowers and fruits (primarily anthocyanins), enhancing the taste of fruits and vegetables, and protecting plant tissues from various biotic and abiotic stresses, such as herbivory, ultraviolet radiation, cold, heat, and salinity. These compounds also have significant implications for human health. Due to their antioxidant properties and free radical-scavenging activity, polyphenols contribute to protection against various diseases, including cancer, stroke, myocardial infarction, cardiovascular disorders, as well as certain immunological and neurological conditions. Additionally, polyphenols have beneficial effects in individuals with diabetes and obesity^{68,69,70}.

To date, nearly 8,000 polyphenolic structures have been identified and characterized in plants⁷¹. Polyphenols constitute a diverse group of compounds, including phenolic acids, flavonoids (such as flavonols, flavanones, flavan-3-ols, flavones, anthocyanins, and isoflavones), lignans, stilbenes, and, according to some classifications, tannins and coumarins⁷². Polyphenols are a crucial component of plant-derived foods that exert beneficial effects on human health. Due to their antioxidant, antithrombotic, and anti-inflammatory properties, polyphenols can prevent or mitigate symptoms associated with several metabolic syndromes, including type 2 diabetes, obesity, systemic hypertension, and atherogenic dyslipidemia⁷³, as well as cardiovascular diseases such as atherosclerosis, myocardial infarction, heart failure, and stroke⁷⁴.

Furthermore, polyphenols possess multiple functional groups, conjugated bonds, and aromatic rings, which provide an ideal structural framework for effective antioxidant activity⁷⁵. Consequently, they can inhibit lipid peroxidation, oxidative damage to proteins and carbohydrates, oxidative injury to nucleic acids, and the initiation of free radical reactions⁷¹. For many years, polyphenols have attracted considerable attention, particularly due to their antioxidant properties, which are widely utilized in the prevention and treatment of various diseases. Reactive oxygen species (ROS) play a critical role in numerous biological processes in the human body, including cell signaling, defense against pathogens, and regulation of blood pressure^{73,74}. ROS are naturally produced in animal tissues or plant cells during various physiological processes and can also have exogenous origins^{76,77}. However, an imbalance between ROS production, accumulation, and the capacity of cells or tissues to neutralize them results in oxidative stress. This imbalance may occur due to impaired antioxidant defense mechanisms or under various pathological conditions. Excessive ROS activity typically damages cells and contributes to the development of diverse diseases, making it generally harmful. Nonetheless, in some cases, deliberately induced oxidative stress can be employed therapeutically, for instance, in cancer treatment⁷⁸. Since thyroid hormones regulate mitochondrial oxidative metabolism, their deficiency can lead to mitochondrial dysfunction and a decrease in antioxidant system activity. As a result, excessive formation of reactive oxygen species (ROS) enhances lipid peroxidation, compromises membrane integrity, and reduces the availability of key biological molecules such as reduced glutathione (GSH) due to covalent binding with reactive intermediates, ultimately causing cellular damage. In an experimental model of hypothyroidism induced by methimazole (MMI), increased levels of thiobarbituric acid reactive substances (TBARS) were observed in the blood plasma, liver, and kidneys of hypothyroid animals. Additionally, elevated ROS levels were detected in the renal and hepatic tissues of these rats. The observed increase in lipid peroxidation and free radical generation in hypothyroid rats underscores the critical role of thyroid hormones in maintaining antioxidant system function and suggests that ROS may play a significant role in tissue damage associated with this disorder⁷⁹. Polyphenolic compounds isolated from plants exhibit a range of biological activities, including antibacterial, antiallergic, antimutagenic, antiviral, antithrombotic, and vasodilatory effects. Their most prominent feature is their antioxidant capacity, as these compounds can neutralize hydroxyl radicals, superoxide anions, and radicals generated during lipid peroxidation⁸⁰. Studies have shown that hypothyroidism is associated with a pro-oxidant state, which is

confirmed by increased lipid peroxidation and the generation of reactive oxygen species (ROS). Additionally, simultaneous increases in protein carbonyl (PCO) levels in liver tissue indicate that hepatocytes are under oxidative stress. It is plausible that increased lipid peroxidation and reactive oxygen species (ROS) generation in the liver play a role in causing protein damage within this tissue. Protein carbonyl formation, which arises from interactions with free radicals or reactive aldehydes like malondialdehyde (MDA) produced during lipid peroxidation, is the most widely employed indicator of protein oxidation^{81,82}.

Research conducted by Khasan Y. Kayumov and colleagues has shown that thamiflazid polyphenol can enhance the activity of the α -amylase enzyme and thereby help improve carbohydrate digestion⁸³. A study conducted in India demonstrated that *Alpinia galanga* (L.) rhizome extracts protect thyroid follicles under PTU-induced hypothyroidism. The results showed that, compared to untreated groups, treatment with rhizome extracts restored the follicles and reduced tissue damage in the thyroid⁸⁴. Red grape seed polyphenols, due to their antioxidant properties, have been shown to improve cognitive function in rats with Alzheimer's disease⁸⁵. Oral administration of a zinc-flavonol complex (5mg/kg body weight/day) for 30 days in diabetic rats significantly reduced blood glucose and glycated hemoglobin levels, and an increase in plasma insulin levels was observed⁸⁶.

Research has demonstrated that curcumin, a yellow-colored polyphenol, can reduce protein carbonylation in the renal cortex of hypothyroid rats⁸⁷. In a study conducted by A. Santi et al. in Brazil, quercetin flavonoid was administered at doses of 10 and 25mg/kg to hypothyroid animals for corrective purposes. The results showed that quercetin, at both concentrations, was able to protect hepatic cells from oxidative damage by reducing PCO levels. These findings suggest that quercetin, through its free radical scavenging activity, can prevent oxidative injury under hypothyroid conditions⁸⁸, and thereby potentially restore thyroid hormone levels and function.

Nevertheless, similar to other chemical substances, polyphenols can have detrimental effects depending on factors such as dosage, surrounding conditions, and environmental interactions. Specifically, some flavonoids are known to have either detrimental or beneficial effects on thyroid function. Consumption of certain flavonoids, particularly in regions with low iodine intake, may contribute to endemic goiter and hypothyroidism. Some flavonoids can influence thyroid hormone synthesis, their action on target tissues, and metabolism⁸⁹. According to recent evidence, natural

compounds such as resveratrol, catechins, curcumin, myricetin, quercetin, and apigenin may be beneficial in the treatment of thyroid cancer by slowing or blocking its development⁹⁰.

CONCLUSION:

Thyroid hormones play a crucial role in regulating metabolism, and their dysfunction can lead to various pathological changes. Natural compounds, such as plant-derived polyphenols, modulate thyroid function and protect tissues through their antioxidant, anti-inflammatory, and cytoprotective properties, making them promising agents against thyroid disorders. Currently, our team is conducting comprehensive studies on the positive and negative effects of polyphenol compounds on thyroid function, focusing on their role in correcting thyroid dysfunctions. The results of these studies may further clarify the potential effect of polyphenols in the prevention and treatment of thyroid diseases.

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation.

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