REVIEW

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THE INFLUENCE OF MICRONUTRIENTS AND MACRONUTRIENTS EXCESS OR DEFICIENCY ON THYROID FUNCTION

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The thyroid gland's functionality is complex and is influenced by a variety of compounds, notably iodine, selenium, iron, calcium, thiamine (vitamin B_1), vitamin B_{12} and vitamin D. This study aims to elucidate the significance of micronutrients and macronutrients in the functioning of the thyroid gland and explore how nutrient imbalances may lead to various thyroid disorders, including thyroid cancer.

K e y w o r d s: thyroid functioning, micronutrients, macronutrients, thyroid carcinoma.

The thyroid gland, a singular endocrine organ, synthesizes and secretes the hormones thyroxine (T4), triiodothyronine (T3), and calcitonin [1]. Anatomically, it is positioned in the anterior-inferior region of the neck, comprising two lobes connected by an isthmus. The gland is encapsulated by a dense connective tissue sheath. The fundamental structural and functional unit of the thyroid is the thyroid follicle, consisting of follicular cells (thyrocytes) that encase a colloid-filled lumen. The principal component of the colloid is thyroglobulin, a glycoprotein that serves not only as a scaffold for the follicular cells but also as a precursor for thyroid hormone synthesis and storage. In addition to follicular cells, the thyroid gland contains parafollicular cells (C cells) that produce the hormone calcitonin, which plays a role in calcium homeostasis [2]. The gland is extensively vascularized, receiving blood supply predominantly from the superior and inferior thyroid arteries. Additionally, it is richly innervated, which is crucial for its regulatory functions.

The optimal functioning of the thyroid gland is contingent upon a multitude of regulatory factors. Foremost among these is thyrotropin (thyroid-stimulating hormone, TSH), which governs the gland's activity. TSH secretion is, in turn, regulated by the hypothalamus through the release of thyrotropin-releasing hormone (TRH). T4 and T3 exert extensive pleiotropic effects on a wide array of tissues and organ systems. The mechanism of their action is understood through observation and studies utilizing animal models. These hormones influence the musculoskeletal, circulatory, nervous, immune, respiratory, digestive systems, as well as the skin, and many other physiological processes [3].

Products of thyroid cell activity directly or indirectly interact with the skeletal system. In the case of thyroid hormone deficiency, there is a marked deceleration in the bone tissue remodeling process. This is evidenced by a significant reduction in both the activity of osteoblasts and osteoclasts and the number of bone remodeling units [4]. Conversely, an excess of thyroid hormones disrupts bone homeostasis and leads to increased bone turnover, especially in trabecular bone. This elevated turnover rate significantly raises the risk of fractures. Thyroid hormones also exert substantial effects on the circulatory system. They increase heart rate, enhance systolic function, improve myocardial relaxation, and reduce peripheral resistance. Hyperthyroidism results in heightened cardiac activity, whereas hypothyroidism leads to diminished cardiac function. Maintaining thyroid hormone homeostasis is crucial for reducing the risk of cardiovascular incidents [5]. Thyroid hormones are integral to the development of both the central and peripheral nervous systems.

They regulate gene expression by modulating the transcription of genes encoding growth factors and cell adhesion molecules [6]. Thyroid hormones also influence the respiratory system and the skin. Both hyperthyroidism and hypothyroidism can lead to edema in these tissues. The multifaceted effects of thyroid hormones underscore their critical role in maintaining various physiological functions.

Micronutrients, such as iodine, iron, copper, zinc, manganese, chromium, molybdenum, and selenium, occur in trace amounts in the human body but are vital for thyroid function. On the other hand, macronutrients, including calcium, sodium, magnesium, and potassium, are present in larger quantities. Mainly, elements such as selenium, zinc, iodine, iron, and vitamin D are particularly important for the metabolism and proper functioning of thyroid hormones [7].

The aim of the study is to elucidate the significance of both micronutrients and macronutrients in the functioning of the thyroid, and to describe how deficiencies or excesses of hormones can be causative factors in the development of thyroid disorders, including thyroid cancer.

The current review paper was constructed through a comprehensive analysis of scientific literature sourced from databases including PubMed, Google Scholar, Wiley Library, Web of Science, and the NCBI database. The majority of the reviewed articles were written in English, with the minority in Polish. Following an initial screening and subsequent detailed analysis of publications concerning the role of micronutrients in thyroid function, relevant materials were selected. The review was conducted employing a non-standardized literature review methodology, designed to offer a concise synthesis of the existing body of knowledge on this subject.

Description of the state of knowledge. For many years, extensive research has been conducted on the thyroid. Despite its relatively small size, the thyroid remains a complex organ with many undiscovered facets. To date, only a portion of its functions has been elucidated. The precise mechanisms of its interactions with other organs remain largely unclear [8, 9]. Although several theories have been proposed, certain mechanisms remain undiscovered, posing mysteries for researchers. The thyroid's processes are influenced by a multitude of factors, both genetic and environmental. Among these, micronutrients and macronutrients play critical roles. Disruptions in any metabolic process within the thyroid can result in significant clinical conditions, including hypothyroidism, hyperthyroidism, or the development of neoplastic disease. The primary micronutrients and macronutrients essential for thyroid function include iodine, selenium, iron, vitamin D, zinc, magnesium, vitamin B_{12}, omega-3, thiamine, vitamins C and E.

Iodine. Iodine is a crucial micronutrient essential for the optimal functioning of the thyroid gland. Its primary dietary sources include marine plants, fish, and seafood. As iodine cannot be synthesized endogenously in the human body, it must be obtained through dietary intake. The main role of iodine in the human body is its involvement in the biosynthesis of thyroid hormones. Nevertheless, its significance extends beyond this singular function, encompassing influence on cognitive processes such as concentration and memory retention. It plays a vital role in the cardiovascular system by modulating heart rate and myocardial contractility. Iodine is also involved in cellular respiration and energy production processes. It contributes to the regulation of inflammatory responses and supports the proper functioning of various bodily systems, including the reproductive system. Iodine influences the maturation of reproductive organs and is essential for reproductive health. Furthermore, iodine possesses antioxidant, anti-inflammatory, anti-carcinogenic, and detoxifying properties. Under physiological conditions, iodide functions as a cofactor for peroxidases, enzymes that catalyze the deactivation of hydrogen peroxide, thereby protecting cells from oxidative damage [10].

Iodine ingested through food is primarily absorbed in the small intestine, where over 90% of ingested iodide is taken up, predominantly in the form of iodides and iodates. Additionally, a portion of iodine is absorbed in the stomach, mainly as the inorganic iodide anion. Furthermore, a minimal amount is absorbed by the respiratory system and through the skin [11]. Once absorbed, iodine enters the bloodstream and is predominantly taken up by the thyroid gland, with smaller amounts stored in the salivary glands and the gastric mucosa. The active transport of iodine into the thyroid gland is facilitated by the sodium-iodide symporter located on the basal membrane of thyroid follicular cells. This transporter exploits the sodium concentration gradient maintained by the Na^+/K^+-ATPase pump to drive iodine uptake. As a result, the concentration of iodine within the thyroid gland is approximately

20-50 times higher than in the serum. Under conditions of adequate dietary iodine intake, the thyroid gland retains no more than 10% of the iodine absorbed from the gut. However, in chronic iodine deficiency, the gland can capture more than 80% of circulating iodide. Within the thyroid gland, iodide undergoes oxidation by the enzyme thyroperoxidase in the presence of hydrogen peroxide, leading to the formation of thyroid hormone precursors monoiodotyrosine and diiodotyrosine. These precursors are then coupled to form the thyroid hormones T4 and T3. As thyroid hormones degrade, iodine is released back into the bloodstream. There are two primary pathways for iodine following its release. The first pathway involves re-uptake by the thyroid gland and reuse for hormone synthesis. The second pathway involves excretion, primarily through the kidneys, which accounts for approximately 90% of iodine excretion. The remaining 10% is excreted via the feces. The urinary excretion of iodine serves as an important biomarker for assessing iodine status and identifying deficiencies, thereby facilitating the implementation of appropriate iodine prophylaxis [10].

The World Health Organization (WHO) provides specific guidelines for the optimal daily intake of iodine across different demographic groups, including age categories and physiological states such as pregnancy and lactation. According to WHO recommendations, the daily iodine intake for adults is set at 150 μg. For pregnant and lactating women, this requirement increases to 250 μg/day to support the heightened metabolic demands and developmental needs of the fetus and infant. Insufficient iodine intake, defined as consumption of less than 50 μg/day, can lead to inadequate thyroid function, as this level of intake is insufficient to support the synthesis of thyroid hormones [12].

On April 18, 2018, at the Jagiellonian University in Krakow, Poland, scientists from 27 countries convened to inaugurate the "EUthyroid" project [13]. This multinational initiative aims to devise comprehensive strategies for preventing iodine deficiency across Europe, emphasizing methodological proposals and monitoring protocols. Notably, the iodization of table salt has emerged as the foremost, cost-effective, and efficacious approach for iodine deficiency prevention. However, it is essential to emphasize the need to monitor this method to ensure its full effectiveness. Poland stands as one of the pioneering nations to have adopted iodized salt supplementation. Furthermore, under the National Health Program spanning 2016-2017, a project was launched with three primary objectives: conducting informational and educational campaigns elucidating the consequences of iodine deficiency in the diet, monitoring and regulating the iodine levels in the Polish population, with particular attention to vulnerable groups, and evaluating the effectiveness of the current preventive model in three groups: pregnant women, breastfeeding women, and school-age children [14].

Despite the widespread implementation of salt iodization programs globally, iodine deficiency remains a significant public health concern, with approximately 30% of the global population still at risk [1]. Iodine plays a pivotal role in thyroid function, and its deficiency can have profound repercussions on human health. Conversely, excessive iodine intake can also pose risks, underscoring the delicate balance required for optimal thyroid function. Prolonged consumption of iodine below 50 μg/day, for instance, has been associated with the development of hypothyroidism [15].

Pregnant women constitute a particularly vulnerable demographic with respect to iodine deficiency. The physiological demands for iodine increase significantly during pregnancy, heightening the risk of deficiency in this group. Insufficient iodine intake during pregnancy can lead to severe and irreversible consequences for the developing fetus, including brain damage, delayed mental development, and various neurological disorders. Low iodine levels during gestation are associated with neurodevelopmental deficits, which can manifest as intellectual impairments and cognitive delays. The most serious consequence for pregnant women exposed to iodine deficiency is fetal damage, which may present as miscarriage, stillbirth, congenital malformations, and intellectual impairment [16]. Congenital hypothyroidism is the most common preventable cause of intellectual disability worldwide, with an incidence of approximately 1 in 2000 to 1 in 4000 live births. Early detection and treatment through neonatal screening programs can effectively prevent the adverse outcomes associated with congenital hypothyroidism, thereby mitigating its impact on intellectual development [17].

Children and adolescents are particularly vulnerable to iodine deficiency. According to the WHO, the recommended daily iodine intake is approximately 90 μg for children under 5 years of age and 120 μg for children aged 6 to 12 years. In younger

children, the clinical manifestations of iodine deficiency are often nonspecific, making early detection challenging. Symptoms may include delayed teething, an underdeveloped nasal bridge, slowed growth, and disproportionate body build. Older children may exhibit more pronounced symptoms indicative of iodine deficiency, such as excessive lethargy and fatigue, increased sensitivity to cold, delayed pubertal development and physical growth, overweight, and difficulties with concentration. These symptoms reflect the broader systemic impacts of iodine deficiency, affecting metabolic rate, thermoregulation, and overall energy levels [18].

Iodine deficiency significantly increases oxidative stress and enhances lipid peroxidation in cell membranes, leading to the production of malondialdehyde, a compound with confirmed mutagenic properties in scientific studies [19]. Additionally, iodine exhibits pro-apoptotic and anti-proliferative effects on breast cancer cells. It induces mitochondrial apoptosis through the formation of iodolipids, which activate peroxisome proliferator-activated receptor gamma, thereby initiating apoptotic pathways. Several studies have reported a correlation between iodine deficiency and an increased incidence of breast diseases, including hyperplasia and hypertrophy hypertrophy of the breast gland [20]. The documented influence of iodine on breast cancer cells further supports this association. From various studies, we can conclude that high levels of iodine and selenium may reduce the risk of breast cancer, though further research is needed to fully elucidate the mechanisms involved [21]. In regions with prevalent iodine deficiency, such as Italy, there is a documented increase in gastric cancer incidence. This phenomenon is likely due to the antioxidative properties of iodine, which help protect cells from oxidative stress and prevent the promotion of inflammatory conditions that can lead to carcinogenic changes [22].

Iodine deficiency can lead to hypothyroidism by depleting the essential substrate required for the synthesis of thyroid hormones. Additionally, iodine deficiency is implicated in the development of nodular goiter, ultimately leading to toxic goiter, which can result in hyperthyroidism. Moreover, iodine deficiency is recognized as a risk factor for papillary thyroid cancer. The absence of iodine inhibits the cell cycle and apoptosis in malignant tumor cells. This disruption leads to thyroid hormone deficiency and subsequent elevation of TSH, a hormone that acts as a mitogen to stimulate thyroid growth. Elevated TSH levels promote thyroid cell proliferation, increasing the risk of neoplastic transformation and growth [23].

Both iodine deficiency and excess pose significant health risks. Excess iodine intake can arise from the consumption of large quantities of dietary supplements, excessively iodized salt, or overdose of iodine-rich medications such as amiodarone [8, 24]. The upper limit for safe iodine intake is approximately 1.1; milligrams per day; consumption above this threshold can lead to chronic and/or acute toxicity. Excessive iodine intake results in its accumulation in the body, which disrupts normal thyroid function. This dysregulation can manifest as thyroid inflammation, hyperthyroidism, hypothyroidism, or follicular thyroid cancer. Beyond the thyroid, excessive iodine can adversely affect other organs, leading to a range of systemic issues. Patients experiencing iodine overdose may present with various symptoms, including excessive salivation, allergies, and abdominal pain. These symptoms reflect the body's attempts to manage and expel the surplus iodine, highlighting the toxic effects of iodine excess on multiple physiological systems.

Indeed, the dual nature of iodine's impact on thyroid function, where excess iodine can induce both hyperthyroidism and hypothyroidism, is particularly intriguing. Excess iodine inhibits thyroid function through the Wolff-Chaikoff mechanism, a physiological phenomenon that temporarily halts uptake by the thyroid gland. This mechanism, first described by Jan Wolff and Israel L. Chaikoff in 1948, serves as a protective response against the potentially toxic effects of large iodine doses. The Wolff-Chaikoff effect operates by inducing a transient reduction in thyroid hormone synthesis when iodine levels are excessively high. This acute response involves the downregulation of thyroid peroxidase and other enzymes crucial for thyroid hormone biosynthesis, thereby preventing further iodine incorporation and mitigating the risk of thyroid hormone overproduction. However, when excess iodine exposure is sustained, the Wolff-Chaikoff mechanism can paradoxically lead to hypothyroidism. Persistent high iodine levels maintain the suppression of thyroid hormone synthesis, eventually resulting in a chronic deficiency of these hormones and the manifestation of hypothyroid symptoms. This adaptive response underscores the thyroid gland's complex regulatory mechanisms designed to maintain hormonal balance and protect against iodine toxicity [25].

In contrast to the Wolff-Chaikoff mechanism, the Jod-Basedow phenomenon represents an opposite response. Also known as iodine-induced hyperthyroidism, this phenomenon occurs when excessive iodine intake precipitates hyperthyroidism. Unlike the Wolff-Chaikoff effect, the Jod-Basedow phenomenon is not a physiological protective mechanism but rather a pathological response that develops in individuals with pre-existing thyroid conditions [26]. Excessive iodine can trigger hyperthyroidism in susceptible individuals, particularly those with underlying thyroid diseases such as multinodular goiter or latent Graves' disease. In these cases, the thyroid gland fails to appropriately regulate hormone synthesis in response to increased iodine availability, leading to an overproduction of thyroid hormones.

Excess iodine intake has been found to influence the level of antibodies against thyroglobulin, potentially serving as an independent risk factor for papillary thyroid cancer. A clinical-control study conducted in 2021 involved 500 healthy individuals and 446 individuals diagnosed with papillary thyroid cancer. The study confirmed a significant association between excessive iodine intake and the occurrence of papillary thyroid cancer [27,28]. In 2020, global reports indicated 586,202 cases of thyroid cancer, with 91% of these cases occurring in regions characterized by very high levels of social development. Among the WHO regions, the Western Pacific region exhibited the highest incidence of thyroid cancer, accounting for 47.6% of global cases. Projections estimate that by 2040, the incidence and mortality rates of thyroid cancer will increase by 29.9 and 67%, respectively [23].

Selenium. Selenium is a micronutrient primarily found in meat and its derivatives, present in minute quantities within the human body. This element is a constituent of over 20 enzymes, including glutathione peroxidase, which protects cells against peroxide damage. Selenium significantly influences the functioning of the thyroid gland as well as the immune system. Adequate dietary selenium intake reduces the risk of certain cancers and prevents inflammatory conditions [29]. It also enhances the functioning of the nervous and cardiovascular systems. Both selenium excess and deficiency can be detrimental to human health. Selenium deficiency can weaken the immune system, increasing the risk of cardiovascular and neurodegenerative diseases. Although rare, selenium excess, known as selenosis, leads to symptoms such as increased hair loss, diarrhea, depression, and damage to the kidneys and liver [30]. Selenium is a crucial component of iodothyronine deiodinases, enzymes that contain selenium in the form of selenocysteine. Deiodinases are essential for the activation and deactivation of thyroid hormones, converting T4 into the active form, T3 [31]. The thyroid gland contains the highest concentration of selenium per gram of tissue in the body. Selenium in the thyroid serves multiple functions, with two primary roles being the protection of the thyroid against hydrogen peroxide-induced damage and participation in the conversion of T4 to T3 [32].

Clinical studies have shown that selenium deficiency increases the frequency of thyroid diseases. In Hashimoto's disease, appropriate selenium supplementation reduces the level of antibodies that cause organ destruction. In Graves' disease, selenium delays disease progression. Additionally, selenium supplementation may reduce tumorigenic activity in thyroid cancer [33]. A meta-analysis assessing whether selenium supplementation can reduce the number of circulating thyroid autoantibodies in patients with autoimmune thyroiditis revealed significant findings. Patients treated with levothyroxine and supplemented with selenium had significantly lower levels of thyroid peroxidase antibodies (TPOAb) after three months (weighted mean difference in serum (WMD) = -271 [Confidence Interval (CI) -366 to -175]; $P < 0.0001$), six months (WMD = -469 [CI -617 to -322]; $P < 0.001$), and twelve months (WMD = -423 [CI -450 to -396]; $P < 0.0001$) compared to groups treated with levothyroxine alone. In newly diagnosed populations not yet treated with levothyroxine, the selenium-supplemented group showed significantly lower TPOAb levels after three months (three studies: WMD = -512 [CI -626 to -398]; $P < 0.0001$); but not after six or twelve months [34]. However, it should be noted that further research is needed to document the exact role of selenium in thyroid diseases.

Iron. This micronutrient is found in red meat, beans, broccoli, and pork liver. It is a critical component of hemoglobin, enzymes involved in DNA synthesis, neurotransmitter synthesis, myoglobin, and many other compounds crucial for proper body functioning. Both deficiency and excess of iron have adverse effects on the body. Elevated levels of iron lead to nausea, constipation, joint pain, and hormonal imbalances. Excess iron adversely affects the liver, promotes the development of insulin resistance and diabetes, and increases the risk of cardiovascular

incidents. Iron levels in the body can decrease due to inadequate consumption of iron-rich foods, heavy menstrual bleeding or surgical procedures. Symptoms of iron deficiency (ID) include pale skin, irregular heartbeat, hair loss, fatigue, drowsiness, and decreased immunity. Iron deficiencies are commonly observed in vegans, vegetarians, and chronically ill individuals [35].

Most cases of thyroid dysfunction are associated with autoimmune diseases. Both iron (Fe) and vitamin B12 play significant roles in the functioning of the immune system. Iron influences macrophage polarization and modulation of the inflammatory response. Elevated iron levels inhibit the lipopolysaccharide-induced pro-inflammatory response by reducing the nuclear translocation of NF-κB p65, leading to decreased expression of IL-1β, IL-6, IL-12, and TNF-α. A key enzyme for thyroid function is thyroid peroxidase (TPO), which is responsible for the iodination of thyroglobulin and the coupling of two tyrosine residues. TPO is a glycosylated heme enzyme that becomes active upon binding heme, a non-protein prosthetic group containing Fe^{2+}. ID is associated with an increased incidence of thyroid peroxidase antibodies, leading to reduced thyroid hormone production [36].

Iron plays a crucial role in the proper functioning of the thyroid gland. It is a structural component of thyroid peroxidase. This enzyme, along with other proteins, participates in the synthesis of thyroid hormones. Deficiencies in iron impair the conversion of T4 to T3. A decrease in thyroid hormone synthesis leads to an increase in TSH levels and enlargement of the thyroid organ, resulting in hypothyroidism. Conversely, excess, iron can accumulate in the thyroid, potentially causing damage to the gland [37].

A meta-analysis conducted within a population of women of reproductive age has unveiled a significant association between ID and the heightened risk of positive TPOAb (Odds Ratio [OR]: 1.89; 95% CI: 1.17, 3.06: $P = 0.01$), as well as concurrent positive TPOAb and thyroglobulin antibodies (TgAb) (OR: 1.48; 95% CI: 1.03, 2.11: $P = 0.03$) [38]. Furthermore, iron plays a crucial role in the thyroid function of pregnant women. The same meta-analysis conducted within this demographic revealed that pregnant women afflicted with ID demonstrated elevated serum TSH levels (Mean Difference (MD): 0.12; 95% CI: 0.07–0.17; $P < 0.00001$) and diminished free T4 levels (MD: -0.73; 95% CI: -1.04–-0.41; $P < 0.00001$). Moreover, there was a noteworthy escalation in the incidence of overt hypothyroidism (OR: 1.60; 95% CI: 1.17–2.19; $P = 0.004$) and subclinical hypothyroidism (OR: 1.37; 95% CI: 1.13–1.66; $P = 0.001$) among pregnant women grappling with ID.

In 2022, a comprehensive meta-analysis was undertaken focusing on pregnant women to elucidate the impact of ID on thyroid function. The study revealed that individuals afflicted with ID and iron deficiency anemia (IDA) exhibited significantly diminished levels of free T3 and free T4 compared to those with normal iron status ($P < 0.05$). Conversely, the level of TSH was markedly elevated in both the ID and IDA groups compared to individuals with normal iron status ($P < 0.05$). Moreover, the incidence of hypothyroidism was notably heightened in both the ID and IDA cohorts in contrast to the control group, whereas the occurrence of hyperthyroidism was diminished in both groups ($P < 0.05$). Serum ferritin and hemoglobin levels exhibited a positive correlation with FT3 and FT4, whereas they showed a negative correlation with TSH [39].

Vitamin D. Vitamin D, sourced from dietary staples such as eggs, milk, and plant oils, plays a pivotal role in calcium and phosphorus metabolism within the body. In many studies, a correlation has also been observed between autoimmune diseases and the increased incidence of certain cancers, for example, prostate cancer [40]. Both excess and deficiency carry consequences. Individuals susceptible to its deficiency include those suffering from civilization-related diseases such as obesity, cardiovascular diseases, allergies, kidney and liver diseases. Individuals deficient in vitamin D develop many symptoms such as lowered immunity, osteomalacia, and an increased risk of fractures. Conversely, in individuals experiencing vitamin intoxication, symptoms commonly reported include weakness, drowsiness, vomiting, constipation, and polyuria [41]. To prevent deficiency and excess of vitamin D in the diet, recommendations for prophylactic vitamin D dosage have been prepared, which are presented in Table [42].

The multifaceted influence of vitamin D extends to the thyroid, where it is regarded as a potential modulator of disease pathogenesis, including autoimmune thyroid diseases (AITD) and thyroid cancer. Both *in vitro* and *in vivo* studies have underscored the therapeutic potential of vitamin D in the treatment of thyroid cancer. Notably, calcitriol and its analog MART-10 have exhibited inhibitory effects on the proliferation of anaplastic thyroid can-

Table. Recommended prophylactic doses of vitamin D

Age group	Prophylactic dose
Infants 0-6 months old	400 IU, regardless of feeding method
Infants 6-12 months old	400-600 IU, depending on the amount of vitamin D obtained from food
Children 2-10 years old	600-1000 IU, depending on body weight and dietary intake of vitamin D
Children and adolescents 11-18 years old	800-2000 IU per day, depending on body weight and dietary intake of vitamin D
Obese children	double the recommended dose of vitamin D compared to peers with normal body weight

cer cells in experimental settings. Nevertheless, the extant literature on the relationship between vitamin D and thyroid health remains somewhat equivocal, necessitating large-scale investigations to delineate its precise impact [43].

At the molecular level, the vitamin D receptor (VDR) ubiquitously expressed across tissue types serves as a conduit for vitamin D's regulatory actions. Following binding with calcitriol, VDR, dimerizes with the retinoid X receptor (RXR), then translocates to the cell nucleus where it interacts to vitamin D response elements in DNA, thereby orchestrating the expression of over 1,000 genes crucial for cellular homeostasis. VDR plays a crucial role in regulating the expression of over 1,000 genes [44].

Human studies investigating the role of vitamin D in AITD have proliferated, shedding light on its potential therapeutic implications. Genetic inquiries have elucidated associations between polymorphisms in the VDR and other vitamin D signaling-related genes, and an elevated predisposition to autoimmune thyroid pathologies. Notably, clinical trials assessing vitamin D supplementation have yielded promising outcomes. In patients with Hashimoto's disease, such interventions have been shown to significantly attenuate levels of thyroid peroxidase antibodies (standardized mean difference [SMD] = -1.084, 95% CI = -1.624 to -0.545) and thyroglobulin antibodies (SMD = -0.996, 95% CI = -1.579 to -0.413) compared to control cohorts. Moreover, vitamin D supplementation has demonstrated efficacy in modulating thyroid function parameters. Specifically, supplementation has been associated with reductions in TSH levels (SMD = -0.167, 95% CI = -0.302 to -0.031) and enhancements in free T3 (SMD = 0.549, 95% CI = 0.077 to 1.020) and free T4 concentrations (SMD = 0.734, 95% CI = 0.184 to 1.285) compared to control groups. These findings underscore the potential utility of vitamin D supplementation as an adjunctive therapeutic approach in the management of AITD [44].

Zinc. Zinc is predominantly sourced from meat, eggs, nuts, and liver. It is a vital component of over 200 enzymes which are instrumental in regulating various biological processes such as DNA and RNA synthesis, as well as hormone production. Zinc exhibits similar effects to selenium and participates in the metabolism of lipids, proteins, and carbohydrates. Essential for proper growth and development in children, zinc also significantly impacts cardiovascular, immune and nervous systems functions. It plays a critical role in blood pressure regulation, bone mineralization, and hormonal balance. Zinc is indispensable for maintaining healthy hair, skin, and nails, as well as insulin levels. It reduces copper absorption, increases LDL level, and decreases HDL level. Both deficiency and excess of zinc can be harmful. Individuals at highest risk of zinc deficiency include those with insulin resistance, diabetes, and vegetarians. Zinc deficiency can lead to cognitive impairment, chronic fatigue, diminished libido, taste and smell disturbances. Zinc excess is extremely rare, typically resulting from overconsumption of dietary supplements. Patients may experience gastrointestinal discomfort, headaches, dizziness, weakness, excessive sweating, and psychotic symptoms [45, 46].

Thyroid tissues exhibit zinc transporter expression in both follicular and C cells. The expression levels of thyroid antigens have been positively correlated with the amount of ZnT8 expression in thyroid tissues ($P < 0.025$ for zinc; $P < 0.01$ for TPO) [47]. Advances in immunohistopathology have identified a zinc finger protein, crucial for domain stability due to the presence of zinc ions. Bioinformatics analysis and immunohistochemistry have shown that the expression level of Myc-Associated Zinc Finger Protein in thyroid cancer tissues is higher than in adjacent normal thyroid tissues ($P < 0.05$). Furthermore,

its expression level correlates with tumor size and the presence of a tumor capsule in thyroid cancer patients [48].

Zinc also exhibits antioxidant properties, similar to selenium, providing protection to the thyroid gland from oxidative damage caused by free radicals. It also participates in the conversion of T4 to T3 and is essential for the production of thyrotropin. Moreover, studies have shown that zinc transporters are present in the pituitary gland and hypothalamus. Zinc deficiency can lead to a reduction in thyroid hormones levels, potentially resulting in hypothyroidism. On the other hand, a study involving 98 women aged 20 to 50 years did not show a correlation between low zinc levels and thyroid hormone levels, indicating the need for further research to elucidate zinc's precise role in thyroid function [49, 50].

In another study, multivariate analysis revealed a statistically significant decrease in free T4 levels, $P < 0.01$) and total T4 levels ($P < 0.01$) with increasing serum zinc levels in men, though no such differences were observed in women . This highlights the complex and potentially sex-specific interactions between zinc and thyroid hormone metabolism, necessitating further investigation [51].

Vitamin B_{12}. Vitamin B_{12}, also known as cyanocobalamin, is a water-soluble vitamin primarily obtained from dietary sources such as milk, natural yogurts, blue cheeses, fish, and seafood. It is essential for various physiological processes, including growth, cell division, hematopoiesis, and myelin synthesis. Vitamin B_{12} functions as a coenzyme in the synthesis of compounds critical for the construction of genetic material [52]. Additionally, it facilitates protein metabolism and the maturation of epithelial cells, while also playing a role in regulating hematopoietic processes and the nervous system. Deficiency in vitamin B_{12} is prevalent among individuals adhering to vegetarian diets, those with alcohol dependency, and individuals with absorption disorders due to conditions like partial intestinal resection, non-specific intestinal inflammations, or chronic pancreatitis. Such deficiencies can lead to a range of hematologic, neurological, and psychiatric disorders [53]. Classic symptoms of deficiency include megaloblastic anemia, concentration disturbances, dizziness, shortness of breath, and palpitations. As the deficiency progresses, gastrointestinal symptoms such as diarrhea, constipation, and nausea may occur, along with neurological symptoms such as limb tingling, sensory and vibrational disturbances, and limb numbness. Similarly, an excess of vitamin B_{12} can also be detrimental, potentially leading to hematologic malignancies, solid malignant tumors, as well as liver and kidney failure[54].

Vitamin B_{12} is essential for the proper functioning of endocrine glands, including the thyroid. AITD are among the most common thyroid disorders, and vitamin B_{12} plays a pivotal role in immune system functioning. Numerous studies have demonstrated a correlation between vitamin B_{12} levels and thyroid diseases. It is involved in thyroid hormone synthesis processes, and its deficiency can result in decreased hormone levels and, consequently, hypothyroidism. Maintaining adequate vitamin B_{12} levels is thus crucial for patients exhibiting symptoms of hypothyroidism, such as those with Hashimoto's disease. A study conducted in 2020 investigated the relationship between AITD and vitamin B_{12} deficiency, involving 306 participants divided into groups based on the presence or absence of vitamin B_{12} deficiency and AITD. The study found that the mean concentration of vitamin B12 was significantly lower in patients with AITD (mean 200.70 ± 108.84) compared to the control group (mean 393.41 ± 150.78; $P < 0.0001$). Patients with vitamin B_{12} deficiency exhibited significantly higher mean values of anti-TPO antibodies (236.60 ± 455.74) compared to the control group (39.51 ± 165.57; $P < 0.0001$). An inverse correlation between vitamin B_{12} levels and anti-TPO antibody concentrations was observed ($P < 0.001$) [55]. On the other hand, a meta-analysis revealed no significant differences in vitamin B_{12} levels between healthy individuals and patients with AITD ($P = 0.22$) and hyperthyroidism ($P = 0.78$). However, patients with hypothyroidism had lower levels of vitamin B_{12} compared to healthy individuals ($P = 0.01$) [52].

Thiamine. The best sources of thiamine, also known as vitamin B_1, are cereal products and dry seeds of leguminous plants. Smaller amounts can also be found in fruits, vegetables, and milk. Vitamin B_1 performs several crucial functions in the human body, influencing the proper functioning of the nervous system, supporting the cardiovascular system, and exhibiting antioxidant properties similar to selenium.

Thiamine deficiency primarily affects older individuals or those involved in strenuous physical activities. Factors such as stress, alcohol consumption, and intake of coffee, and tea further exacerbate thiamine depletion. Patients may experience muscle

pains and cramps, decreased libido, fatigue, digestive disorders, symptoms of circulatory insufficiency, and neurological. Thiamine excess is exceptionally rare due to its efficient excretion through urine, with overdose typically resulting from excessive supplement consumption. Overdose symptoms may include heart rhythm disturbances, muscle tremors, dizziness, or allergic reactions [56].

Individuals with hypothyroidism are particularly susceptible to thiamine deficiency. Thiamine plays a role in the synthesis of thyroid hormones, making it a vital nutrient for the proper functioning of the thyroid gland. Therefore, monitoring thiamine levels in the blood is advisable, especially for individuals with Hashimoto's disease, to ensure adequate thyroid function and overall health [57].

Other. Magnesium, a micronutrient, is responsible for stabilizing nucleic acids and is involved in critical cellular processes such as DNA replication, transcription, and repair. It is essential for the proper functioning of the thyroid gland. Studies indicate that patients with thyroid cancer exhibit lower blood magnesium levels compared to healthy individuals. A meta-analysis conducted in 2015, which reviewed 1291 articles, identified a relationship between magnesium, copper, selenium levels and the incidence of thyroid cancer [58]. Inositol, also known as vitamin B_8, plays a significant role in thyroid function by enhancing the thyroid's sensitivity to thyrotropin and reducing thyroid antibody levels [59]. Additionally, vitamins A and C are vital for the proper functioning of the thyroid gland. Adequate levels of these vitamins have been shown to reduce the risk of subclinical hypothyroidism in premenopausal women. These vitamins contribute to the regulation of thyroid hormone metabolism and inhibit the secretion of TSH [57].

Thus, to summarize, the thyroid gland, a critical endocrine organ, is essential for maintaining systemic homeostasis. It exerts significant influence over various physiological systems, including the circulatory, skeletal, and nervous systems. The gland's multifaceted and complex functioning underscores its importance, with even minor disruptions potentially leading to adverse health outcomes.

Several factors impact the synthesis of thyroid hormones and the overall functionality of the thyroid gland. Key micronutrients regulating its activity include iodine, selenium, vitamin D, iron, vitamin B_{12} and thiamine (vitamin B_1). Imbalances in these micronutrients, whether due to excess or deficiency, can disrupt thyroid function, with both scenarios posing significant health risks. The most severe complication arising from abnormal levels of these micronutrients is the development of papillary, follicular, or other types of thyroid cancer.

Conflict of interest. The authors have completed the Unified Conflicts of Interest form at http://ukrbiochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

ВПЛИВ НАДЛИШКУ АБО ДЕФІЦИТУ МІКРОЕЛЕМЕНТІВ І МАКРОЕЛЕМЕНТІВ НА ФУНКЦІЮ ЩИТОВИДНОЇ ЗАЛОЗИ

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Функціонування щитовидної залози є складним і на нього впливають різноманітні сполуки, зокрема йод, селен, залізо, кальцій, тіамін (вітамін B_1), вітамін B_{12} і вітамін D. Це дослідження спрямоване на з'ясування значення мікроелементів і макроелементів у функціонуванні щитовидної залози та з'ясовує, як дисбаланс цих поживних речовин може призвести до різних захворювань щитовидної залози, включаючи рак щитовидної залози

Ключові слова: функціонування щитовидної залози, мікроелементи, макроелементи, карцинома щитовидної залози.

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