Dietary factors and thyroid dysfunction

Ivana Đuričić*, Vanja Todorović, Nevena Dabetić, Milica Zrnic Cirić, Nevena Ivanović, Bojana Vidović

University of Belgrade - Faculty of Pharmacy, Department of Bromatology,
Vojvode Stepe 450, 11221, Belgrade, Serbia

*Corresponding author: Ivana Đuričić, e-mail: ivana.djuricic@pharmacy.bg.ac.rs

Abstract

Besides iodine deficiency, autoimmune Hashimoto thyroiditis is the leading cause of hypothyroidism globally, characterized by the increased titer of thyroid autoantibodies and destruction of thyroid cells. Graves' disease is the most common etiology of hyperthyroidism worldwide. Patients with thyroid dysfunction often require dietary modifications. Popular interventions include supplementation with certain vitamins and minerals, as well as trace elements such as iodine and selenium. The intake of food containing goitrogens should be limited. Goitrogens are substances of plant origin that interfere with the production of thyroid hormones, increasing the risk for goiter and hypothyroidism. The primary dietary sources of goitrogens are cruciferous vegetables, soy products, starchy plants, and some fruits. Beyond essential nutrients, there has been an increasing interest in using specific nutraceuticals, including myoinositol, L-carnitine, melatonin, and resveratrol, as potential preventive and therapeutic agents in thyroid diseases. Even though current evidence promotes some beneficial outcomes of these nutraceuticals, further investigations are needed to clarify dose-dependent effects, duration of supplementation, combination in different clinical settings, and the exact mechanism of their action in thyroid disorders.

Key words: thyroid disease, diet, micronutrients, nutraceuticals, goitrogens

Introduction

Adequate thyroid hormone production is critical for normal human development and physiological functions. Alongside genetic and intrinsic influence, many environmental triggers, such as lifestyle and pollutants, can negatively affect thyroid function and disturb normal thyroid hormone levels (1). For example, factors that inhibit the proper production of thyroid hormones are stress, infections, medications, and toxins (e.g., pesticides, heavy metals) (2). On the other hand, nutrients like iodine, selenium, tyrosine, vitamins B, C, D, etc., taken from the diet in sufficient amounts, are necessary for the normal production of thyroid hormones (2, 3). Additionally, exercise appears to improve cellular sensitivity to thyroid hormones. Although iodine deficiency is considered to be the leading cause of hypothyroidism globally, there is rising evidence of autoimmune Hashimoto thyroiditis (HT), characterized by the increased titer of thyroid autoantibodies and destruction of thyrocytes. The pathophysiology of HT increases the risk for hypothyroidism (4). Higher levels of serum thyroid-stimulating antibodies are found in Graves' disease (GD), which presents the leading cause of hyperthyroidism worldwide (4). Patients with thyroid dysfunction often require dietary modifications alone or as an adjunct to standard medical care for reversal/treatment of their disease. More attention should be paid to potential interactions between conventional therapies and nutrients. For example, some foods such as soybean, grapefruit, papaya, and coffee may interfere with intestinal absorption of levothyroxine, commonly used as hormone replacement therapy (5). Beyond basic nutrition, there has been a growing interest in using nutraceuticals as potential preventive and therapeutic agents in various thyroid diseases (6). Some of them include myoinositol, L-carnitine, melatonin, and resveratrol. Therefore, this paper discusses the common nutrients related to thyroid function and the possible benefits of specific nutraceuticals in thyroid diseases.

Iodine

Iodine is an essential mineral for thyroid hormone production. The first step in thyroid hormone synthesis includes the active transport of iodide from the circulation to thyrocytes, where iodine is found in 20 to 50 times higher concentrations than in the blood (healthy adults have 15 to 20 mg of iodine) (7). In the thyroid gland, iodide is oxidized to iodine with hydrogen peroxide (H_2O_2) by the thyroperoxidase enzyme. In this form, iodine binds to tyrosine from thyroglobulin and leads to the production of precursor molecules, monoiodotyrosine and diiodotyrosine. Thyroxine (T4) and triiodothyronine (T3) are formed by combining precursor molecules (8).

The relationship between iodine consumption and thyroid disturbances in populations is U-shaped, since both iodine deficiency and excess intake can compromise thyroid function (9). Since iodine deficiency in early life impairs growth and development, it is a determinant of adult thyroid disorders such as goiter and hypothyroidism. Namely, despite increased thyroid activity to increase iodine uptake and recycling, iodine levels are still insufficient to promote thyroid hormone production (10). On the other hand, excessive iodine intake can also alter thyroid function, even though

higher doses of iodine are well tolerated by most individuals (7). After exposure to high levels of iodine, thyroid hormone synthesis is appropriately inhibited by the acute Wolff-Chaikoff effect (11). However, the application of additional iodine in people with endemic goiter followed by iodine deficiency can result in thyrotoxicosis. This response, called iodide-induced hyperthyroidism or the Iodine-Basedow effect, occurs only in a small number of individuals (12). Accordingly, the American Thyroid Association suggests taking supplements containing < 500 μg/day of iodine in those with a history of endemic iodine deficiency or pre-existing thyroid disease (13).

Patients who suffer from a mild form of autoimmune thyroid disease, such as HT, are susceptible to evolving iodine-induced hypothyroidism following several weeks of exposure (12). Additionally, sudden high iodine exposure in iodine-deficient patients can induce autoimmune thyroiditis (14).

Apart from iodized salt, other dietary sources of iodine are seafood (oysters, molluscs, shellfish and marine fish), milk and milk products (if they come from animals that grazed on iodine-containing soils), Brazil nuts, bread and vegetables from iodine-rich grounds (15). Most healthy adults are tolerant to iodine intakes of up to 1 mg/day, which is in line with the estimated tolerable upper level for iodine (1100 μg/day). It should be noted that the new EU tolerable upper intake level for iodine (600 μg/day) is lower than the USA upper level (1100 μg/day). The Recommended Dietary Intake (RDI) for iodine is 150 μg/day in adults (16).

Overall, iodine intake range should be relatively narrow, whereby disorders of iodine deficiency and excessive intake can be prevented. Monitoring and adjusting iodine intake in the population is an integral part of thyroid disease prevention.

Selenium

As an essential trace element, selenium plays a significant role in human health (17). The richest dietary sources are seafood, meat, and Brazil nuts. In living systems, selenium can be found as selenocysteine, selenomethionine, and methyl selenocysteine. Numerous clinical trials and epidemiological data reveal the strong relation between selenium metabolism, iodine homeostasis and thyroid function (18, 19). The thyroid gland contains the highest amount of selenium per gram of tissue (0.2 - 2 μg/g) (20).

Selenium is part of various selenoproteins, including glutathione peroxidases (GPx), thioredoxin reductases (TR) and iodothyronine deiodinases (DI). GPx, due to oxidoreductase activities, protects cells from oxidative damage by reducing reactive oxygen species generated during thyroid hormone production. TR is involved in creating a cellular redox system necessary for cellular development and proliferation. DI plays a crucial role in thyroid hormone metabolism (21). Selenium deficiency reduces the synthesis of thyroid hormones, especially DI, responsible for converting T4 into active T3. Decreased thyroid hormone levels stimulate the hypothalamic-pituitary axis due to a lack of negative feedback control, and increase thyroid-stimulating hormone (TSH) production. TSH further triggers DI to convert T4 to T3, with consequent H_2O_2

production. Because of reduced GPx activity, H_2O_2 is not adequately removed from thyroid tissue, thus leading to thyrocyte damage with subsequent fibrosis (22). Furthermore, a low concentration of selenium causes autoimmune reactions in the thyroid gland, so selenium deficiency is pivotal in the pathogenesis of autoimmune thyroiditis or GD. Reduced selenium concentration also raises the risk for thyroid cancer development (23).

A recent systematic review and meta-analysis have reported a reduction in thyroperoxidase (TPOAb) and thyroglobulin autoantibodies (TgAb) in patients with chronic autoimmune thyroiditis (AIT) after three months of selenium supplementation (24). Additionally, selenium supplementation in GD may cause remission of hyperthyroidism and improve the quality of life and the course of ocular disease in patients with mild Graves' orbitopathy (25). The dosage of selenium used in the clinical trials was up to 200 μg/day and supplementation lasted 3 to 12 months (25). The RDI of selenium is 55μg/day in adults (16). Selenium is the most efficient as yeast-based selenomethionine in treatment formulations, since the organic form has better absorption than inorganic selenite and selenate (26).

Goitrogenic foods

Goitrogens are specific compounds present in plants, drugs, and other chemicals, which may interfere with thyroid gland metabolism. The term "goitrogens" comes from "goiter", which refers to the enlargement of the thyroid gland. Goitrogens are basically classified into those acting directly on the gland and those acting indirectly, increasing the thyroid hormone metabolism rate (27). Iodine deficiency impairs the response of the thyroid gland to goitrogens, leading to abnormal thyroid functioning. Many studies showed that goitrogen consumption has adverse effects only in diets with low iodine intake and in vulnerable groups, such as patients with different thyroid disorders (5, 28).

The main dietary sources of goitrogens are cruciferous vegetables, followed by soy products, starchy plants, and some fruits (29). Cruciferous vegetables like broccoli, cauliflower, cabbage, rutabaga, radish, horseradish, and turnip, contain glucosinolates with sulfur and nitrogen in their structure. Glucosinolates are bioactive compounds that have antiproliferative, chemopreventive, anticholesterolemic, anti-inflammatory, and other health promotion effects (30). However, glucosinolate hydrolysis, by plant or intestinal myrosinase, can lead to a range of products, including thiocyanates, isothiocyanates, or epithionitriles. These breakdown products act as competitive inhibitors of sodium iodide symporter of follicular thyroid cells, thus preventing the synthesis of thyroid hormones and consequently leading to hypothyroidism (31, 32). Cyanogenic glycosides, present in starchy plants and some fruits, can also be metabolized to thiocyanate (33). Food processing significantly reduces the concentration of glucosinolate derivatives. Namely, myrosinase is temperature sensitive and can be inactivated by cooking (34). Nevertheless, the gut

microbiota composition and activity determine the bioavailability of glucosinolate derivatives (35).

Soy products, including soy milk, soy sauce, tofu, edamame, miso and tempeh, contain phytoestrogens, i.e., isoflavones. These compounds are also found in linseeds and red clover. Independently of estrogenicity, isoflavones genistein and daidzein can hinder thyroid peroxidase function, reducing thyroid hormone synthesis (33). The negative effect of soy isoflavones on thyroid function has been observed in numerous *in vitro* and *in vivo* studies (36). Soy products seem to have fewer harmful effects on the human thyroid gland compared to experimental animals. This could be explained by poorer intestinal absorption and more intense hepatic metabolism of flavonoids in the human population.

The anti-thyroid effects of cruciferous vegetables and soy products have been known for a long time. Numerous epidemiological studies have revealed a causal association between the consumption of these foodstuffs and the development of goiter, especially in iodine-deficient populations.

Moreover, other plant bioactive ingredients can affect thyroid function (37). For instance, flavonoids, such as quercetin, luteolin and apigenin, act as anti-thyroid agents by inhibiting thyroid peroxidase activity, with competitive or non-competitive mechanisms. In addition, some of them can interfere with thyroid hormone metabolism and action (37). Finally, resveratrol is the best-known stilbenoid, which causes numerous controversies, particularly regarding the thyroid gland. This bioactive compound is present in grapes, berries, and peanuts, and has many beneficial health effects due to its potent antioxidant properties. It is widely accepted that resveratrol has a protective role in states of increased production of reactive oxygen species, such as hyperthyroidism and autoimmune thyroiditis. Moreover, this compound represents a promising cytotoxic agent, as resveratrol might prevent the proliferation of thyroid cancer cells (38, 39). On the other hand, it can interfere with iodine trapping and act as a mediator of TSH regulation, becoming a strong anti-thyroid agent (40).

Inositol

Inositol, cyclic polyol, is a water-soluble substance related to the vitamin B complex family (also known as vitamin B8). Inositol may exist in nine geometrical isomers through the epimerization of its hydroxyl groups and is naturally stored in the brain, kidneys, liver, placenta and other tissues. Myoinositol (MI) is the most physiologically/clinically relevant stereoisomer. It constitutes almost all of the intracellular pool of inositol present in most tissues (41). Inositol requirements are partly met by dietary intake (roughly 1 g/day), while the rest is synthesized endogenously (up to 4 g/day), with kidneys being the major contributors. The main dietary sources of inositol are cereals with high bran content, citrus fruits (except for lemon), oil seeds, legumes, and nuts (42), but the absorption may be affected by age, other nutrients, or medications. Due to inadequate endogenous production, proper diet and/or supplements

intake becomes necessary. MI is incorporated into cell membranes as structural lipids phosphatidyl-inositol, phosphatidyl-inositol phosphate and other phosphates (43).

Phosphatidyl-inositol is the precursor of inositol triphosphate, acting as a second messenger essential in the transduction of endocrine signals, i.e., insulin, gonadotropins, and TSH. As a second messenger in the phospholipase C-dependent inositol phosphate Ca^{2+}/ diacylglycerol pathway, MI is essential for producing H_2O_2 required for thyroid hormone synthesis (41). Impaired MI homeostasis or reduced dietary intake may contribute to the pathogenesis of numerous diseases, e.g., thyroid disorders, polycystic ovary syndrome, diabetes, metabolic and neurological disorders (44). In the thyroid, altered MI metabolism can impair thyroid hormone synthesis, storage and secretion (41). MI has an important role in thyroid physiology by involvement in TSH regulation of iodination and increased thyrocytes' sensitivity to TSH (45). Clinical evidence has indicated that hypothyroid patients require a higher intake of MI than healthy individuals (46). Altered MI levels or impaired inositol-dependent TSH signalling pathways may contribute to the development of hypothyroidism, pointing out the role of MI in increasing iodine availability (47).

A growing interest in recovering thyroid dysfunctions has prompted investigation into MI supplementation in subclinical hypothyroidism (SCH) and AIT. Clinical studies have demonstrated that treatment with MI plus selenium (600 mg + 83 μg, respectively) has effectively restored euthyroidism in patients with SCH with or without AIT (48, 49). TSH reduction was accompanied by decreased concentrations of TPOAb and TgAb. Supplementation with selenium alone was effective only in reducing anti-thyroid autoantibodies levels, with no change in TSH levels. A recent study on patients with euthyroid AIT has shown that supplementation with MI and selenium can reduce the risk of progression to hypothyroidism. After treatment, anti-thyroid autoantibody level declined, as well as chemokine concentration. This study first showed an immune-modulatory effect of this combination (50). A retrospective study has demonstrated positive effects of the aforementioned combined treatment regarding the reduction of diameter and number of mixed thyroid nodules, as well as their elasticity in patients with SCH and AIT (51).

Given the complexity of mechanisms related to inositol, many of its beneficial effects are still under investigation. More extensive studies are needed to assess the optimal dosage, frequency, and timing of proper use and combination of inositol in different clinical settings, as well as its safety and long-term effects.

Carnitine

Carnitine is a non-essential amino acid found in all living cells. It is a quaternary amine (3-hydroxy-4-N-trimethylaminobutyrate) and exists as two stereoisomers: L-carnitine (biologically active form) and D-carnitine. L-carnitine is involved in fat metabolism and energy production, especially in skeletal and cardiac muscle cells, as these cells mainly depend on fatty acids as a primary energy source (52). Namely, L-carnitine carries long-chain fatty acids from the cytosol into the mitochondria to undergo

beta-oxidation for ATP production (53). L-carnitine plays a role in maintaining the cell membrane integrity, in the excretion of intermediate metabolism products, balancing the coenzyme A pool inside the mitochondria, and preventing the accumulation of fatty acids. It also exhibits antioxidant activity by increasing the activity of antioxidant enzymes, improving mitochondrial function, or improving the turnover of membrane phospholipid fatty acids (52, 54).

The human body contains around 300 mg/kg of L-carnitine, with the highest amount found in the muscles (about 80%), followed by the gastrointestinal tract (5-10%) and the liver (3%) (55). About 75% of the daily need for L-carnitine is met through dietary sources, primarily by consuming foods of animal origin, such as meat, fish and dairy products (mixed food of animal origin provides about 60-180 mg of carnitine per day). The remaining 25% is completed through endogenous synthesis from the amino acids lysine and methionine in the liver and partially in the kidneys (52, 55).

Several lines of evidence have pointed to a link between thyroid hormones and the carnitine system. In the hyperthyroid state, a significantly lower total carnitine level is observed in skeletal muscles compared to euthyroid individuals. At the same time, hypothyroid patients also tend to have lower carnitine levels (6). In both cases, reduced carnitine levels in skeletal muscle contribute to myopathy and fatigue (6). Some evidence indicates that carnitine acts as a peripheral antagonist of the action of thyroid hormones by inhibiting the entry of T3 and T4 into the cell nucleus of some tissues with specific nuclear receptors through which they mainly exert their action (56). These findings imply that the administration of L-carnitine can be beneficial in cases of thyroid disorders.

Nevertheless, there is limited clinical evidence for the beneficial effects of L-carnitine supplementation on thyroid hormone activity. A randomized, placebo-controlled study has shown that the supplementation with 2 g/day or 4 g/day L-carnitine for 2 or 4 months led to the reversal of hyperthyroid clinical and biochemical symptoms in a group of women on thyroid stimulating hormone suppressive therapy (n=10). Moreover, supplementation with L-carnitine could prevent or minimize the occurrence of these symptoms when L-carnitine is administered prophylactically (56). In another randomized trial, the effects of L-carnitine supplementation (990 mg, twice daily for 12 weeks) on mental and physical fatigue were investigated in sixty thyroid-hormone adequately replaced hypothyroid patients. The intervention with L-carnitine showed a significant improvement in the mental fatigue score compared to placebo. In a subgroup of patients aged < 50 years and those with serum levels of free T3 more than 4 pg/mL, supplementation with L-carnitine led to a significant improvement in both physical and mental scores compared to placebo (57).

A pilot study on the effects of L-carnitine and selenium (500 mg/day and 83 µg/day, respectively) in patients with TSH levels between 0.1-0.4 mIU/L and positive antibodies has shown favourable improvements in symptoms associated with subclinical hyperthyroidism and in the quality of life, but with no benefits on the endocrine profile (58). Although there is certain clinical evidence of the beneficial effects of L-carnitine supplementation on hormonal thyroid function, further larger-scale clinical trials are

required to clarify the effective dose, duration of supplementation, and the exact mechanism of action in thyroid diseases.

Melatonin

Melatonin (N-acetyl-5-methoxy-tryptamine) is a hormone primarily synthesized by the epiphysis (pineal gland) from L-tryptophan through enzymatic cascade reactions, following a circadian rhythm (59). Apart from epiphysis, melatonin synthesis was reported in other endocrine organs, neural structures, and immunocompetent cells (60). Beyond chronobiology functions, melatonin exerts antioxidant, antiproliferative, anti-inflammatory, immunomodulatory, metabolic, and other beneficial effects (61). However, melatonin synthesis is known to decline with age. A decreased level of melatonin in the blood is also reported in many age-associated diseases (59). Therefore, the rising trend of supplementation with synthetic melatonin is not surprising (62). Melatonin-containing supplements are assumed not only to regulate the sleep pattern and adaptation to time zone differences, but also to be adjuncts in treating many disorders (59).

Although mechanisms are not fully explained, *in vitro* and animal studies suggest that melatonin could directly or indirectly impact the thyroid gland and its function (63). There are findings showing that endogenous synthesis of melatonin in thyroid C-cells is under TSH control, and that melatonin, via the paracrine mode of action, influences thyroglobulin gene expression in follicular cells (61). In an experimental model of hypothyroidism, it has been demonstrated that melatonin could increase the level of thyroid hormones via regulating the neuroendocrine axis and upregulation of TSH, pointing out that exogenous melatonin differentially modulates the MT1 and MT2 receptor protein expression in the pituitary and thyroid gland (64). Additionally, it has been shown that melatonin can increase plasma thyroid hormone levels and enhance thyrocyte destruction and the T-cell proliferation capacity in the autoimmune thyroiditis mouse model (65). There is very limited evidence for the effects of supplemental melatonin on human thyroid function. In a double-blind placebo-controlled trial, 79 perimenopausal and menopausal women aged 42-62 years were randomly assigned to take 3 mg melatonin or placebo at bedtime (22:00-00:00). The results showed that six-month supplementation led to a significant increase of T3 and T4 levels, particularly in women with a low basal level of endogenous melatonin (66). In another study in peri- and menopausal women (n=139), the same authors confirmed that melatonin (3 mg), after six months, increased the levels of total T4 in women with a low basal level of melatonin in comparison to placebo-treated women (67). Both studies showed no effects of melatonin on TSH levels (66, 67). However, co-administration of 2g/day myoinositol plus 3mg/day melatonin before sleeping in women during the menopausal transition (45-55 years) did not alter thyroid hormone levels. Furthermore, in contrast to the group treated with myoinositol alone (2g/day), it was observed that the addition of melatonin increased the level of TSH over the six-month treatment period (68). In a recent study, daytime

acute melatonin ingestion (6 mg) before 50 min of submaximal exercise did not influence the responses of thyroid hormones to exercise (69).

Overall, additional clinical studies are required to explore the potential beneficial effects of melatonin intake for thyroid function improvement.

In summary, although dietary factors can alleviate a number of symptoms and signs of thyroid diseases, routine supplementation with certain micronutrients/nutraceuticals is not recommended in either hypothyroid or hyperthyroid patients. Furthermore, food containing goitrogens should be carefully consumed in hypothyroid states.

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Dijetarni faktori i tiroidna disfunkcija

Ivana Đuričić*, Vanja Todorović, Nevena Dabetić, Milica Zrnić Cirić, Nevena Ivanović, Bojana Vidović

Univerzitet u Beogradu - Farmaceutski fakultet, Katedra za bromatologiju, Vojvode Stepe 450, 11221, Beograd, Srbija

*Autor za korespondenciju: Ivana Đuričić, e-mail: ivana.djuricic@pharmacy.bg.ac.rs

Kratak sadržaj

Pored nedostatka joda, najčešća etiologija hipotireoze u razvijenim zemljama je Hašimoto tireoiditis, koji karakteriše povišen nivo serum autoantitela i limfocitna infiltracija štitaste žlezde. Grejvsova bolest je vodeći uzrok hipertireoza na globalnom nivou. Pacijenti sa oboljenjem štitaste žlezde često zahtevaju modifikaciju dijetarnog režima. Popularne intervencije uključuju suplementaciju određenim vitaminima, mineralima i mikroelementima kao što su jod i selen. Preporučuje se ograničen unos namirnica koje sadrže goitrogene supstance jer ometaju normalnu sintezu tiroidnih hormona, povećavajući rizik za nastanak strume i hipotireoze. Primarni izvori goitrogena u ishrani su kruciferno povrće, proizvodi od soje, skrobne biljke i pojedine vrste voća. Osim esencijalnih nutrijenata, postoji sve veće interesovanje za primenu specifičnih nutraceutika u prevenciji i koterapiji bolesti štitaste žlezde, kao što su mioinozitol, L-karnitin, melatonin i rezveratrol. Trenutni dokazi ukazuju na moguće promotivne efekte ovih jedinjenja u oboljenjima štitaste žlezde. Potrebna su dalja ispitivanja koja bi pratila uticaj doze i dužine suplementacije nutraceutika i potvrdila tačne mehanizme njihovog delovanja u poremećajima funkcije štitaste žlezde.

Ključne reči: bolesti štitaste žlezde, dijetarni faktori, nutraceutici, mikroelementi, goitrogeni