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Effect of nutrients and dietary substances on thyroid function and hypothyroidism

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Abstract

This article aims to develop a literature review of food nutrients and substances that can impact on thyroid function. A literature review using "hypothyroidism" associated with the descriptors iodine, selenium, zinc, soy, gluten and flavonoids was conducted on the Pubmed database in 2014. It was found 172 articles and 42 were selected, as well as other material needed to achieve the objective of this study. It was observed that iodide participates in the organification reaction and subsequently engages with tyrosyl residues to form the thyroid hormones. Excessive or deficient amounts of iodine contribute to thyroid dysfunction, including hypothyroidism. Selenium and zinc are co-factors for deiodination reactions, which convert thyroxine (T4) into triiodothyronine (T3) peripherally. Deficiency of these minerals can be developed on restrictive diets or unbalanced diet at any stage of life, collaborating with a decreased production of thyroid hormones. Furthermore, ingested substances, such as thiocyanate and isothiocyanate can compete with iodide for the entry in thyroid follicles and compromise hormones synthesis, as well as soy, which can inhibit thyroid peroxidase, enzyme responsible for the oxidation of iodide and formation of thyroid hormones, when there is iodine deficiency. In vivo studies that show the type and amount of flavonoids that may interfere with the conversion of T4 to T3 should be performed, as well as studies to elucidate the role of the exemption of gluten in the reversal of subclinical hypothyroidism.

Keywords: Thyroid Gland. Iodine Deficiency. Thyroxine. Selenium. Soybean.

Introduction

Among the most common endocrine alterations are disorders of the thyroid gland, especially hypothyroidism. The thyroid secretes two important hormones, thyroxine (T4) and triiodothyronine (T3), both with the effect of controlling growth, the metabolism and body development, acting in the production of structural proteins, enzymes and other hormones.[1] However, the major role of hormones is to stimulate the metabolism, because in general they enhance the proteins, lipids and carbohydrates metabolism. They also increase oxygen consumption and heat production, expressed by an increased basal metabolic rate. [2]

In order that the synthesis and proper functioning of thyroid hormones (THs) occur, many micronutrients are necessary such as iodine, selenium and zinc. Other substances provided by foods intake may have an effect on the thyroid functioning, among them glucosinolates, gluten, isoflavones, and flavonoids.[3]

Hypothyroidism, a clinical condition resulting from THs deficiency, is responsible for various body changes that may induce noncommunicable chronic diseases (NCD) such as obesity, dyslipidemias and even some neoplasias.[4] However, it should be emphasized that inappropriate diets are one of the risk factors for the emergence and aggravation of hypothyroidism. [1]

The influence of nutrients on thyroid functioning is still scientifically unclear, indicating the need for new researches to broaden the knowledge on this field so that preventive or treatment support measures can be taken and effectively help in an adequate thyroid functioning. Thus, the aim of this study was to conduct a literature review on the nutrients and food substances that may have an impact on the thyroid function, especially with respect to hypothyroidism.

Methods

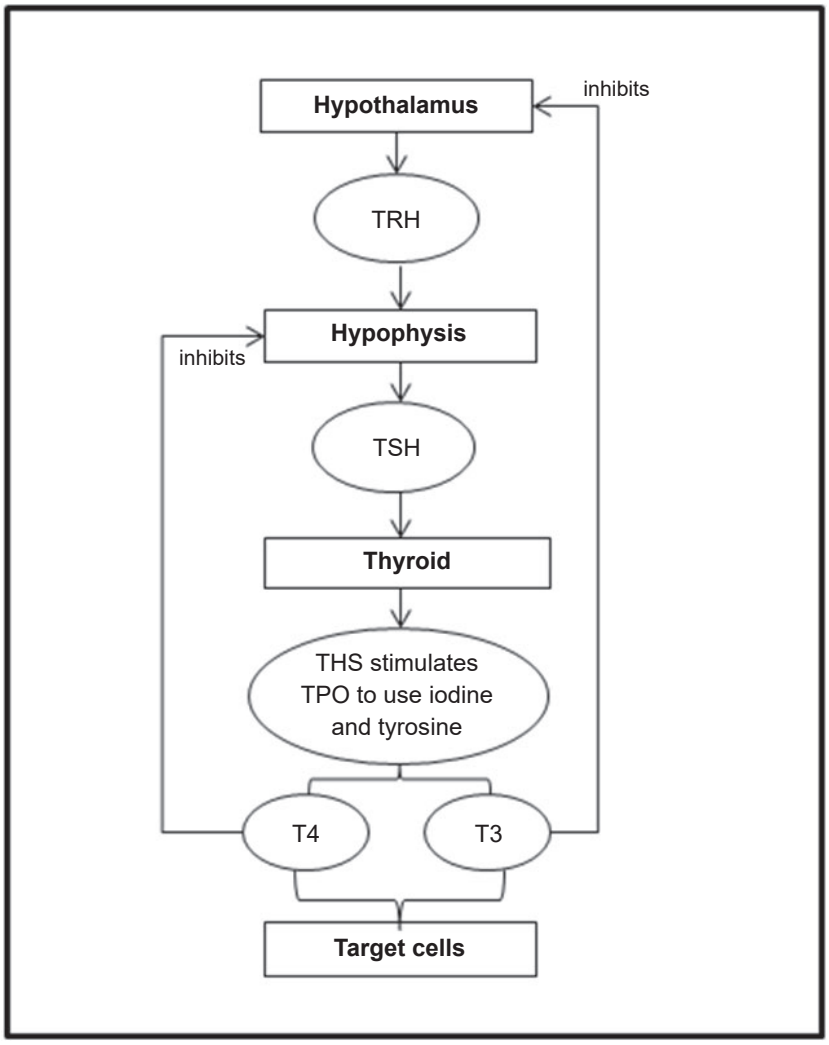
A literature survey was carried out based on scientific articles that associated the descriptor "hypothyroidism" with the following descriptors: iodine, selenium, soy, zinc, gluten and flavonoids. The search was conducted only on the Pubmed database via the National Library of Medicine, in 2014. A total of 172 articles were found.

The criteria used for the selection of the articles were approaches on hypothyroidism and thyroid diseases associated with the abovementioned descriptors. Literature not directly connected with the scope of this review, although showing the descriptors selected, were excluded from the survey.

Thus, 42 articles were eligible for this study. Four books, a Brazilian guideline, a Collegiate Board Resolution, a foods composition chart, a document on recommended dietary intake, a Household Budget Survey and seven other articles relating to the subject matter were added.

Synthesis, storage and secretion of thyroid hormones

The glandular secretion of THs is regulated by a feedback loop involving the hypothalamus, hypophysis and thyroid gland. The hypothalamic thyrotropin-releasing hormone (TRH) receptor induces the hypophysis production of the thyroid-stimulating hormone (TSH), which, in turn, stimulates the synthesis and secretion of the THs, as illustrated in Fig. 1. The THS secreted by the thyroid cells of adenohypophysis play a vital role in the control of the thyroid axis and acts as an extremely useful physiological marker in the THs action .[4]



TRH: thyrotropin-releasing hormone; TSH: thyroid-stimulating hormone; TPO: thyroid peroxidase; T4: thyroxine; T3: triiodothyronine.

Source: adapted from Goldfeder[10].

Figure 1. Production of thyroid hormones

Approximately 90% of the hormones secreted by the thyroid gland are T4 and only 10% are T3, the latter being a bioactive hormone. However, a considerable amount of T4 is converted into T3 in the peripheral tissues, so that both are functionally important. About 80% of T3 are produced in the liver and kidneys by the *5'-deiodinase (5'D) enzyme, which removes a iodine molecule from T4 to form T3 or rT3*.[5]

The roles played by these two hormones are qualitatively the same, but are different regarding the velocity and intensity of action. T3 is about four times more active than T4, but is present in the bloodstream in much smaller amounts and persists for less time than T4.[5]

Hypothyroidism

Hypothyroidism is defined as a clinical condition resulting from a deficient production of hormones by the thyroid gland. The most prevalent form is primary hypothyroidism caused by the destruction of the gland, but may also occur due to a hypothalamus or hypophysis disease, being then referred to as central hypothyroidism.[6]

Primary hypothyroidism is common and affects nearly 5% of individuals. It is more commonly diagnosed in old women although it occurs in men and younger individuals. Central hypothyroidism is rare, accounting for less than 1% of the cases.[2]

Dietary deficiency of iodine is the major cause of primary hypothyroidism in some underdeveloped regions of the globe. The most common cause of primary hypothyroidism in the United States and in the majority of other countries is autoimmune or chronic thyroiditis (AIT), called Hashimoto's disease, a condition in which the immunity alteration mediated by the T cells causes a destruction of the thyroid tissue and impairment of the gland function.[2] Other common causes of hypothyroidism include the surgical removal of the gland, thyroid radiation therapy, medications that damage the gland and genetic disorders affecting the THs.[6]

Subclinical hypothyroidism, also known as mild thyroid failure, is diagnosed when the TH levels are within the normal reference range but TSH is elevated. It may suggest an initial failure of the thyroid gland without symptoms. Prevalence of this disease increases with age and affects up to 18% of older persons, more common in women. [7]

Clinical symptoms of hypothyroidism appear gradually and include fatigue, bradycardia, hoarseness, cold intolerance, dry skin, muscle weakness, constipation, lethargy, impaired reproduction and memory problems. In metabolic changes, there is a subtraction in the oxygen intake rate and decreased heat production, causing a decline in the metabolic rate and, consequently, weight gain despite a decreased appetite.[5]

Foods and nutrients

Iodine

Iodine is a key element for the synthesis of THs and to the body growth and development, particularly of the brain and central nervous system.[8] Iodine deficiency is a global public health problem, affecting nearly 800 million of people.[3]

Dietary iodite is absorbed in the gastrointestinal system and retrieved by the thyrocytes from the blood stream by means of a specific transporter existing in the basolateral membrane of the thyrocytes, the Na+/ I- Symporter (NIS). The NIS activity is electrogenic and dependent on the Na+ gradient generated by the Na+/K+ATPase pump. The iodite transfer by NIS is induced by the TSH and regulated by the self-regulating mechanism of the thyrocyte, in which the NIS activity varies inversely to the iodine glandular content.[9]

After entering the thyroid, iodite is transported to the apical membrane, where it is oxidized in an organification reaction that involves thyroid peroxidase (TPO), thyroid oxidase (ThOx) and hydrogen peroxide (H_2O_2). The iodine reactive atom is added to the tyrosyl residues (Tyr) selected within the thyroglobulin (Tg), giving origin to the monoiodothyrosines (MIT) and diiodotyrosines (DIT). The iodotyrosines in Tg are then engaged by an ether link in a reaction also catalyzed by TPO. Two molecules of DIT engage to form T4, while T3 arises from the junction of MIT and DIT.[10] Therefore, the THs formation depends on the availability of iodine in the apical region of the follicular cell, an adequate Tg synthesis, and the enzymes involved in the incorporation of iodine into the Tyr residues of the Tg molecule, a phase called "iodine organification".[11]

In cases of low iodine intake (<100μg/d), the thyroid adjusts itself by increasing the secretion of TSH by hypophysis. Such TSH increase elevates the plasma purification of inorganic iodite by the thyroid through the stimulation of the NIS expression. Provided that the iodine daily intake remains above 50μg/d, even with a decrease of the inorganic iodine circulating in plasma, the absolute absorption by thyroid remains adequate, and the iodine content in the thyroid is within the normal range (approximately 10-20 mg). Below this threshold value, many individuals develop goiter, hypothyroidism and mental retardation at any stage of life .[12]

In situations of iodine deficiency, high TSH levels trigger the production of H_2O_2 by thyroid cells, which can induce fibrosis and destruction of the gland, preventing the cells repair.[13]

To prevent these problems, various government strategies have been developed to add this element to foods.[14] Since 1920, supplementation with salt and iodized vegetable oil has yielded significant improvements to the populations worldwide. However, some subpopulations such as vegetarians do not have an appropriate iodine intake, even in countries considered iodine-

sufficient. Furthermore, a dietary iodine reduction may be associated with an increased adherence to dietary recommendations for reduction of salt intake to prevent or be an adjuvant in high pressure treatment. So, lack of nutritional control of iodine, after eradication of endemic goiter, can lead to iodine-deficiency disorders.[3]

According to the Brazilian Ministry of Health, since the addition of iodine to cooking salt became mandatory in 1950, four researches were conducted to evaluate the impact of this intervention in Brazil. It was observed a significant reduction of goiter prevalence (20.7% in 1955; 14.1% and 1974; 1.3% in 1984; and 1.4% in 2000). However, it is worth noting that despite this considerable advance in the control of iodine-deficiency disorders (IDD), there still is the need for improvement of prevention and control actions, because a continuous monitoring of iodine deficiency is vital to prevent recurrence.[15]

On the other hand, excessive iodine intake (20mg/day) also lead to AIT and hypothyroidism.[16,17] Initially, there is an increased iodine uptake, resulting in an elevated iodine content in the gland and thyroid secretion, but then regulatory mechanisms begin to act to revert to normal conditions. Administration of high doses of iodine causes a rapid inhibition of the iodine organification and synthesis of ThOx and T4, followed by an inhibition of hormones secretion. [11,14] Such inhibition of iodine organification that occurs in the presence of high iodine concentrations is called "Wolff-Chaikoff effect".[9] Du et al.[18] reported that subclinical hypothyroidism is more prevalent in regions where there is ingestion of large amounts of iodine.

A study conducted by Carvalho et al.[19] showed that 67.1% of schoolchildren in the state of São Paulo exhibited very high levels of urinary secretion of iodine (over 300μg/L) and only 1.9% of the children had values lower than 100 μg/dL. Such high values show an exaggerated ingestion of dietary iodine, by either an excessive salt intake and/or excessive iodine in cooking salt, above the values recommended by ANVISA (between 20 and 60μg/day).[20]

The latest update of the recommended dietary allowance (RDA) of iodine is 150 μg/day for adults, 220 μg/day for pregnant women and 290 μg/day for breastfeeding women.[21] However, the World Health Organization (WHO) recommends at least 75 μg of iodine per day, which corresponds to 10g of iodized salt.[11]

According to the Household Budget Survey (2008-2009), Brazilians ingest an average of 8.2g of salt per day, and the amount recommended by WHO is 5g/day.[22] From the data presented, it can be inferred that Brazilians ingest on average 61.5μg of iodine/day, a value that maintains the thyroid activity at normal levels,[12] but does not conform to the WHO recommendation.[22]

Iodine is widely distributed in nature and is present in both organic and inorganic substances in very small amounts. The iodine level in water reflects the iodine content in rocks and soils in

the region and, consequently, in edible plants at this location.[23] However, the only iodine source for humans is food; therefore, there is a high risk of iodine deficiency in places where the foods consumed come from iodine-insufficient areas .[13]

The major food sources, in addition to iodized salt, are seafood (oyster, mollusk, shellfish and seawater fish), milk and dairy products (as long as they are from animals that have grazed on iodine-rich soils or animal fed rations containing this nutrient). Brazil nut, bread and vegetables grown in iodine-rich soils are also good sources.[14]

Selenium

Selenium is a major trace element in antioxidant mechanisms and the immune system and plays a key role in the homeostasis of the thyroid gland.[3] Given that this mineral, such as selenocyteine, is a co-factor for 5'D, it has attracted much attention because of the THs peripheral metabolism. As mentioned earlier, the 5'D hepatic enzyme converts T4 into T3r or in active T3. If there is a selenium deficiency, the deiodinase (ID) activity will be damaged.[5]

A normal thyroid gland holds high concentrations of selenium and expresses many of the selenocyteines. These are found in the catalytic center of enzymes that protect the thyroid from damages from free radicals. Among them are the selenoproteins glutathione peroxidase, ID and the family of thyoredoxin reductase enzymes.[24]

Deiodination is the first step of the TH action to confer biological activity to T4, which is the metabolic pathway that removes a iodine residue from the T4 molecule to produce T3, the most active short form of TH.[25] Three ID isoforms (types I, II and III) are known, all of them responsible for the activation of intracellular and circulating T3.[3] IDs I and II are enzymes that catalyze the conversion of T4 into T3 by 5'D, while the ID III inactivates T4 and T3 and transform them into inactive metabolites (T3r and T2, respectively).[25]

Selenium also participates in other mechanisms such as glutathione peroxidase (GPx), which has a function in the oxidation reduction, i.e., it protects the cell from oxidative stress. GSH-Px 3 (glutathione peroxidase 3), produced and secreted by the thyrocytes, regulates the concentration of H_2O_2 in the follicular lumen. During the synthesis process of T3 and T4 in the thyroid, GSH-Px3 suffers a direct influence of TSH, which in turn stimulates the production of H_2O_2 in the apical membrane. GSH-Px3 has an antioxidant action, preventing further oxidative damages to the thyrocytes. In case of selenium deficiency, the apoptotic response to H_2O_2 is increased. In case of normal amounts of selenium, the thyoredoxin reductase system and SH-Px protect the thyrocytes from the peroxides action.[14]

Selenium deficiency has been a common finding in thyroid gland diseases.[26] In case of selenium deficiency, there is a reduction of selenoproteins, a decrease in the GSH-PX3 activity, increased deiodination, for aiding the H_2O_2 action in this process, intoxicating the thyrocytes in the long term, and a decrease of the ID I activity, leading to a peripheral reduction of T3 synthesis and its degradation.[27] Also, selenium deficiency and THs reduced production can be developed under special dietary conditions such as in long-term total parenteral nutrition, in phenylketonuria diet, cystic fibrosis, or can be the result from an unbalanced diet in children, the elderly or the sick. [5]

In regions with heavy iodine deficiency, combined with selenium deficiency, normalization of the iodine provision is mandatory before starting selenium supplementation in order to prevent hypothyroidism.[12] Thus, it can be seen that selenium plays a key part in the regulation of the thyroid function, as well as in the THs homeostasis, through the action of the selenocyteines and, ultimately protects the gland from damages caused by excessive exposure to iodite.[28]

Conversely, the intake of large amounts of selenium may also have adverse effects. Studies have demonstrated that a dietary intake of 300μg/day of selenium can have a toxic effect on the growth rate, similar to insulin (IGF-1), and on the THs synthesis as well. The major adverse effects include anorexia, diarrhea, depression, liver hemorrhage, kidney necrosis, blindness, ataxia, breathing disorders, dermatitis, and deficiencies of the central nervous system.[29]

Drutel, Archambeaud & Caron[27] report that in patients with AIT and pregnant women with thyroperoxidase antibodies (anti-TPO), selenium supplementation diminishes the levels of anti-thyroid antibodies and improves the thyroid structure. Also, Pizzulli & Ranjbar[30] report that children with hypothyroidism and selenium deficiency present an improvement of the thyroid metabolism after selenium supplementation, improving significantly all clinical symptoms, which is likely due to the selenium ability to restore the 5´D function. On the other hand, Rayman et al.[31] did not find evidences that the effect of selenium supplementation may aid T4 conversion into T3 in the elderly. Likewise, selenium supplementation did not diminish the concentrations of anti-TPO antibodies.[32,33]

Kandhro et al.[34] observed that selenium deficiency in hypothyroideans can play a key role in the severity of hypothyroidism associated to iodine deficiency.

Current selenium RDA for adults is 55 μg/day. Pregnant and breastfeeding women should have their selenium ingestion increased to 60 and 70 μg/day, respectively.[21]

Studies show that selenium intake by the Brazilian population ranges from 18.5 to 114.5 μg/day, mainly depending on the region, particularly in Mato Grosso and São Paulo, where there is the highest nutrition deficiency of this micronutrient.[35]

Meats and seafood are excellent sources of selenium as well as Brazil nut. However, selenium contents in nuts vary according to the tree absorption capacity and soil composition. The average selenium concentration in one average Brazil nut unit is 27.4μg; therefore, an intake of two daily units is sufficient to meet the RDA.[36] Selenium contents in meat and fish ranges from 2.8 to 80.9 μg/100g of food, fishes (particularly tuna and sardine) being the food with the largest amount of this mineral.[37] Black bean and whole wheat flour also have important amounts of selenium, 11.9 μg/100g and 13.6 μg/100g, respectively.

Routine serum test for selenium is not recommended, because food deficiencies are rare and primarily associated with severe malnutrition or according to the geographic location.[27] However, health professionals should be attentive to a deficiency of this micronutrient in low-income population because these foods are considered expensive. Also, public policies should be implemented to ensure food and nutrition security for the vulnerable population.

Zinc

There are reports in the literature that zinc deficiency is one of the causes of subclinical hypothyroidism, [38] because this mineral enhances the ID II activity.[1] In studies with animals, zinc deficiency resulted in an approximate reduction of 30% of the levels of free T3 and T4.[39]

In humans, zinc supplementation brought the thyroid function back to normality in hypothyroidean patients. In study conducted by Nishiyama et al.,[40] a 12-month zinc sulfate supplementation was provided to individuals with low T3, normal free T4 and moderate zinc deficiency. Oral zinc supplementation diminished the serum levels of T3 and free T3 and rT3, and the TRH-induced TSH reaction normalized.

Kuriyama et al.[41] demonstrated that erythrocyte zinc serum concentrations are lower in patients with transient thyroiditis than in patients with permanent thyroiditis. The authors suggested that serum dosage of erythrocyte zinc may be useful to distinguish these pathologies and, so, prevent the T4 unnecessary supplementation. Still about the study, patients whose erythrocyte zinc levels are lower than 12mg/L can revert the hypothyroidism condition.

The RDA of zinc is 15mg/day,[21] and this amount can be found in meat and fish, with amounts varying from 4 and 7.7mg/100g of food and in all kinds of nuts with concentrations from 2.1 to 4.7mg/100g of food.[42] According to the 2008-2009 Household Budget Survey, 19.9% of children and adolescents and 29% of adults and older people have an inadequate intake of this nutrient. [22]

Further studies are needed to clarify the role of zinc in the thyroid function.

Soy

Studies show the potential human health benefits of soy in the prevention of cancer, cardiovascular diseases, reduction of menopause symptoms, increased bone-mineral density and decreased insulin resistance. Conversely, soy has raised concern about the thyroid gland function.[43]

Patients with subclinical hypothyroidism are three times more likely to develop hypothyroidism with a daily supplementation of 16mg of soy phytostrogens.[44] In a study conducted with menopausal women,[45] 75mg of isoflavones reduced the levels of free T3 and alleviated menopause symptoms.

Researches also report soy interferences on children's thyroid. Babies fed soy-based formulas had their TSH levels increased compared to those who were fed soy-free formula.[46] Other authors refer to the emergence of goiter in babies fed soy-based formulas; however, this condition reverts to normality with the replacement of the formula with cow's milk or iodine-supplemented diets.[47]

In vitro and in animal studies demonstrated that isoflavones (particularly genistein and daidzein) present in soy has the ability to inhibit the TPO enzyme, which promotes iodation of thyroglobulin, important to the THs synthesis. Inhibition of this enzyme causes a decrease in the production of THs, an increase of production of endogenous TSH and may lead to the development of goiter and hypothyroidism.[48] On the other hand, Bitto et al.[49] demonstrated that 54mg/day of aglycone genistein for three years did not affect the production of thyroid hormones or anti-TPO antibodies in menoupausal and osteopenic women.

According to Messina & Redmond,[50] literature findings provide little evidence that euthyroid individuals with iodine deficiency have adverse effects with the ingestion of soy foods or isoflavones. However, there is a theoretical concern based in *in vitro* and animal studies that individuals with impaired thyroid function and/or whose iodine intake is marginal are more likely to develop hypothyroidism with soy consumption. Thus, it is vital that consumers of soy-based foods be sure that their ingestion of iodine is adequate.

In addition, soy may hinder the absorption of thyroid drugs.[50] Thus, individuals with a high soy consumption should be monitored, and new researches addressing the damages and benefits of soy to THs are necessary.

Gluten

The literature shows that the celiac disease is associated with an increased prevalence of AIT and vice-versa, with a prevalence around 9%.[13,51] In celiac disease patients, prevalence of hypothyroidism is 2 to 5%. [52]

It has been speculated that selenium deficiency, by reducing the GPX activity, allows the oxidation of structures such as TPO, which, modified, could be recognized as antigen, thus stimulating the emergence and proliferation of anti-TPO antibodies.[1] Prevalence of anti-TPO antibodies is higher in celiac individuals than in healthy ones.[53]

Sategna et al.[54] observed that a gluten-free diet can revert the abnormality of subclinical hypothyroidism, although they did not find a correlation between the time of exposure to gluten in celiac disease individuals and the risk for autoimmune diseases. Other authors also reported that gluten-free diet has a protective effect against thyroid diseases and recommend that a gluten-free diet should begin early, before autoimmune disorders are established, in order to prevent or minimize their development.[55] However, other authors disagree with these findings arguing that there is little evidence to support gluten-free diet to reduce the development of autoimmune thyroiditis, or AIT.[13]

Based on the data presented, gluten-free diet is still controversial as to its effectiveness in preventing AIT and hypothyroidism. However, for treatment of the celiac disease, it is mandatory to follow a gluten-free diet. So, more studies are necessary for a better understanding of the role of gluten in thyroid diseases.

Flavonoids

Flavonoids, either synthetic or natural, have a potential to interfere in the *in vitro* metabolism of THs. Flavonoids synthetic derivatives reduced serum concentrations of T4 and inhibited both the conversion of T4 to T3 and metabolic clearance of T3r by Se. Natural flavonoids seem to have a similar inhibitory effect.[56] Luteolin, a natural flavonoid, showed to be the most active inhibitor of the 5'D activity when tested *in vitro*; quercetin and myricetin also exhibited an *in vitro* inhibitory activity. [39]

Catechins, flavonoids found in large amounts in green tea, diminish the TPO and 5'D activities and the T3 and T4 levels, along with a significant raise of TSH.[57]

It still remains unclear whether similar effects occur *in vivo*, or if they occur, whether they are restricted to specific flavonoids and at which dosage. Either isolated or concentrated, flavonoids have been increasingly used in therapeutic interventions, but additional studies on the potential influence of these substances on the TH metabolism are desirable. Special care should be taken especially with regard to individuals with iodine nutritional deficiency because it can contribute to the development of hypothyroidism and goiter.[39,56]

Examples of food sources include beans, soybean, maize, pine nut, broccoli and canola, which potentially can hinder the iodine incorporation by TPO inhibition, as described earlier in the "soy" topic.[23]

Brassicas

Brassicas, broccoli, cauliflower, brussels sprouts, kale, turnip, radish, cabbage, and garlic and onion are sources of glucosinolates. When these foods are cut raw, an interaction occurs between the glucosinolates and the enzyme myrosinase, which catalyzes the formation of thiocyanate, isothiocyanate and nitrile.[1]

Thiocyanate and isothiocyanate compete with iodite to enter into the thyroid follicles, which may compromise the THs synthesis and induce the onset of goiter and hypothyroidism in patients with low iodine intake.[1]

Cyanogenic glycosides can be metabolized to thiocyanates and also compete with iodine to be absorbed by the thyroid. They are present in tropical plants such as cassava, bean, flaxseed, bamboo sprouts and sweet potato. Tobacco is also a source of thiocyanate.[58]

Linamarin is a thioglucoside found in cassava, a staple food in many developing countries. Fortunately, heat inactivates linamarin and the enzyme myrosinase, impeding the formation of thiocyanate and isothiocyanate. [1,23]

Up to now, there are no studies that define the amount of brassicas that may affect significantly the hormone synthesis.[1]

Final considerations

Iodine plays a key role in the production of THs. Excessive or deficient amounts of iodine and selenium contribute to thyroid alterations, among which is hypothyroidism. Selenium and zinc act as co-factors in deiodination reactions of T4 in active hormone. Further studies are needed to assess the actual intake of iodine and selenium by the Brazilian population in order to prevent their deficiency or excess.

There are few evidences that thiocyanate, isothiocyanate and soy isoflavones change the production of hormones by the thyroid in the absence of iodine deficiency. *In vivo* studies showing the type and amount of flavonoids that can interfere in the conversion of T4 into T3 should be conducted, as well as studies to elucidate the role of gluten-free diet in reverting subclinical hypothyroidism.

This study was limited to using the *Pubmed* database. It is suggested that further research studies be conducted on other databases as well as studies addressing possible interference of other nutrients or dietary substances on the thyroid function.

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