The role of selenium in autoimmune thyroiditis

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Abstract

Selenium (Se) is an essential trace element of fundamental importance for human health. Se is incorporated into selenoproteins (SPs) which are endowed with pleiotropic effects including antioxidant and anti-inflammatory effects and active production of thyroid hormones. It has also been suggested that Se plays a crucial role in the pathogenesis of various human diseases. The therapeutic effects of supplementation with Se have already been described in various thyroid diseases. However, there are still conflicting results regarding the optimal dose of Se to administer and the duration of treatment, efficacy, and safety. The highly beneficial effects of supplementation with Se have been observed in subjects with thyroid disease in the hyperthyroid phase. In line with these observations, clinical studies have shown that in patients with Basedow's disease (BD) and autoimmune thyroiditis (AT), treatment with a combination of antithyroid drugs and Se restores the euthyroid state faster than administration of antithyroid drugs alone. However, the efficacy of this therapeutic approach remains to be better evaluated.

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Introduction

Growing clinical evidence suggests that nutraceuticals may be considered effective and preventive therapeutic agents in the treatment of different pathological conditions, including thyroid diseases. Iodine is recognized as the main dietary component which is essential for the proper functioning of the thyroid. However, other molecules including selenium (Se), l-carnitine, myo-inositol, melatonin, and resveratrol, appear to play important roles in thyroid physiology.[1] The thyroid gland contains the highest amount of Se per mg of tissue than other organ tissues.[2] Se is a non-metallic element that can be found in soil and groundwater. It enters the food chain through plants' roots and is taken up by aquatic organisms.[3] Se is involved in the regulation of many biological functions and biochemical processes in humans.[4] On the other hand, Se deficiency has been associated with the development of various pathological conditions, including heart diseases,[5] neuromuscular disorders,[6] neoplastic diseases,[7] male infertility,[8] inflammation[9], and other pathological conditions. Se appears to play a role in mammalian development,[10] immune functions,[11] inhibition of viral gene expression[12], and in delaying the progression of AIDS in HIV-positive patients.[13] Moreover, Se has been suggested to play an important role in cancer prevention, due to the incorporation of this element into proteins.[14] Se is a component of the amino acid selenocysteine (SeC) and of selenoproteins (SPs) which have an antioxidant activity, as regulators of redox reactions and as regulators of metabolism. Se may function as a cofactor for several important human enzyme systems.[15] Se is incorporated into polypeptide chains as part of the 21st amino acid, SeC. Proteins that contain SeC are called SPs. The key metabolic function of Se has therefore been attributed to its role as SeC.[16] The role of Se was elucidated following the discovery of an enzyme containing Se, namely glutathione peroxidase (GPx).[17] The most important selenium-containing enzymes belong to the GPx family which includes several isoforms.[18]

The importance of Se and SPs in health and disease is gaining increasing interest,[19] and the potential therapeutic effects of Se have

been investigated in various diseases such as hemorrhagic pancreatitis, cardiovascular diseases, stroke, and severe sepsis.[20,21] Several studies have also provided evidence of the inhibiting effects of Se on the growth of thyroid cancer cells.[22,23] Furthermore, altered expression levels of SPs have been reported to be associated with altered levels of thyroid hormones. These findings further support the importance of the role of Se in the homeostasis of thyroid hormones and its beneficial effects in the ophthalmopathy associated with autoimmune thyroiditis (AT), a condition that represents the most common extra-thyroid manifestation of thyroid disease.[24,25] In line with these observations, it has been reported that physiological levels of Se hinder excessive inflammation. These effects are explained by the capability of SPs to modulate the immunoregulatory expression of cytokines and lipid mediators (Figure 1).[26]

Absorption, metabolism, and physiological effects of selenium

All the inorganic and organic forms of Se are readily absorbed, mainly in the lower end of the small intestine, and taken up by the liver, where most of the SPs are synthesized. Once produced, SPs are then released into the systemic circulation and distributed to several organs where, in turn, other types of SPs can be synthesized. The local uptake of Se from the plasma occurs through endocytosis mediated by apolipoprotein receptors. In this manner, the liver regulates the distribution of Se throughout the body through the synthesis of SPs and the metabolism of compounds that will be excreted.[27] The excretion of Se in excess occurs via two metabolic pathways both resulting in the production of methylated species. In the presence of toxic levels of Se, trimethylselenium is mainly produced by a methyltransferase, which generates trimethylselenium and dimethylselenium, both excreted rapidly, one by the kidney and the other by the pulmonary route. Conversely, in the presence of low levels of Se selenide is converted into a seleno-sugar, then methylated and transformed into selen methylene acetylgalactosamide, which is excreted only with the urine.[28]

Glutathione peroxidase (GPx) and thioredoxin reductase (TxR) are the two main seleno-enzymes that foster the production of reactive oxygen species (ROS).[29] Se deficiency leads to a reduced production of SPs, including GPx. This phenomenon is responsible for the accumulation of hydrogen peroxide (H_2O_2) that may account for inflammation and tissue disease.[30] In addition, SPs play a key role in regulating human immune system functions. In line with these findings, several reports have shown that Se deficiency is accompanied by dysregulation of both cell-mediated immunity and B-cell functions[31] (Table 1).

H_2O_2 is a product of the inflammatory cascade along with other peroxides, such as hydroperoxide-phospholipids.[32]

Therefore, these hydroperoxides, which are intermediates of cyclooxygenase (COX) and lipoxygenase pathways, are effectively neutralized with a consequent decreased production of pro-inflammatory prostaglandins (PGs) and leukotrienes.[33] Ultimately, these effects may minimize further tissue injuries. Selenoprotein P (SePP) produced in the liver, is the major circulating form of Se and is endowed with high antioxidant activity.[34] A confirmation of a close link between the thyroid gland and Se is provided by thyroperoxidase (TPO), a key enzyme involved in the biosynthesis of thyroid hormones. However, the chemical reactions needed for the synthesis of thyroid hormones which are mediated by thyroid peroxidase, may favor the production of ROS. These effects might be dangerous and harmful if the antioxidant defense system is not able to protect the thyroid cell from oxidative damage. This intrathyroid defense system is largely represented by the selenium-dependent GPx enzyme.

Glutathione peroxidase

Glutathione peroxidase (GPx) belongs to a family of enzymes with antioxidant activity. Their main biological role is to protect the organism from oxidative damage by reducing the toxic effects induced by ROS, H_2O_2, and/or to protect cells from apoptosis and

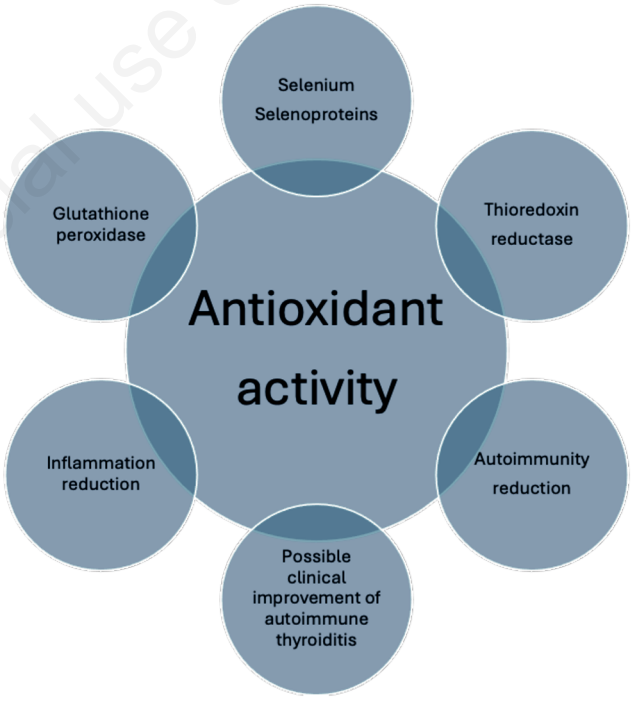

Figure 1. Scheme of the probable mechanism of selenium in autoimmune thyroiditis.

Table 1. Some studies on selenium supplementation in patients with Hashimoto's thyroiditis.

Reference	Number of patients	Duration of integration	Daily dose supplement	Thyroid antibody
Gartner, R. *et al. J Clin Endocrinol Metab*. 2002, 87, 1687-1691[31]	71	90 days	200 µg Na_2SeO_3	Reduction
Karanikas, G. *et al. Thyroid* 2008, 18, 7-12[102]	36	90 days	200 µg Na_2SeO_3	No reduction
Nacamulli, D. *et al. Clin Endocrinol* 2010, 73, 535-539[70]	76	6 months-1 year	80 µg SeMet	Reduction
Anastasilakis, A.D. *et al. Int J Clin Pract* 2012, 66, 378-383[106]	86	3-6 months	200 µg SeMet	Reduction

SeMet, selenomethionine.

to modulate the synthesis of thyroglobulin (Tg) and thyroid hormones (T4, T3). There are eight isoforms of this enzyme in mammalian cells. However, only five of them contain SeC residues and may efficiently catalyze the reduction of H_2O_2 and lipid hydroperoxides by using GSH as a cofactor.[35] The SeC residue is oxidized by the peroxide with the formation of selenic acid and reduced again to selenolate by thiols. The selenolic group of the active site of GPx is part of a catalytic triad of SeC, thiamine pyrophosphate, and glutamine, which may undergo stabilization and activation by the formation of hydrogen bonds.[36]

Each GPx isoform is characterized by the amount of Se incorporated, which is thought to be related to their biological importance: GPx2> GPx4> GPx3 = GPx1. Glutathione-peroxidase 1 is the enzyme of the GPx family which is most susceptible to the variation of Se concentrations in the body and to oxidative stress conditions. However, when under stress conditions total protein synthesis is reduced, GPx1 appears to recover more quickly in terms of functionality than other SPs to preserve cell resources.[37]

Glutathione-peroxidase 2 (GPx2) is mainly expressed in the gastrointestinal mucosa and esophagus. It protects the intestinal epithelium from oxidative stress and ensures intestinal mucosal homeostasis. The expression of GPx2 is much more resistant than GPx1, following a condition of seleno-deficiency status. Its resistance and position suggest that this selenoprotein can be regarded as the first line of defense against oxidative stress caused by the ingestion of pro-oxidant molecules.[38] Glutathione-peroxidase 3 (GPx3) is the only extracellular enzyme of this family. The presence of GPx3 in the plasma accounts for about 15-20% of the total Se. GPx3 is mainly expressed in the gastrointestinal tract, lung tissues, male reproductive tissues, and the thyroid gland, where it exerts antioxidant activity.

Glutathione-peroxidase 4 (GPx4) is an intracellular enzyme, whose expression and activity have been observed in different tissues, in particular at the endocrine level and in the mitochondria of spermatozoa; GPx4 is regulated by hormones. Furthermore, Imai *et al.* and Chabory *et al.* provided evidence that GPx4 exerts an important protective role against oxidative stress in photoreceptor cells.[39,40] Interestingly, some studies have shown that natural SePP dependent Se-transport by auto-antibodies is prevalent in patients with thyroid disease and appears to be likely responsible for alterations in Se transport and downregulation of GPx3 biosynthesis. It has been also observed that SePP auto-antibodies were prevalent in Hashimoto's thyroiditis (HT) compared to healthy subjects. These findings indicate that patients with impaired Se transport could be considered at health risk for autoimmune thyroid disease.[41]

Iodothyronine deiodinase

Iodothyronine deiodinases represent a family of enzymes, also known as deiodinases (D1, D2, D3) (Figure 2).[42] Each isoform has a different tissue distribution and determines the activation, or inactivation, of the thyroid hormones in different organs.[42] D1 is an integral plasma membrane protein with the greatest distribution in the body, mainly in the liver, kidney, and thyroid.[42] It converts T4 to T3 by deiodinating T4 in position 5. The enzymatic activity of D1 is the main source of circulating T3. D1 also possesses 5-deiodase activity and catalyzes the transformation of T4 into rT3. A distinctive peculiarity of D1, compared to other deiodinases, is that this isoform can be inhibited by propylthiouracil (PTU). The enzyme activity of D1 is stimulated by thyroid hormones. This phenomenon may account for its reduced activity in hypothyroidism or an increased activity in hyperthyroidism. D1 expression

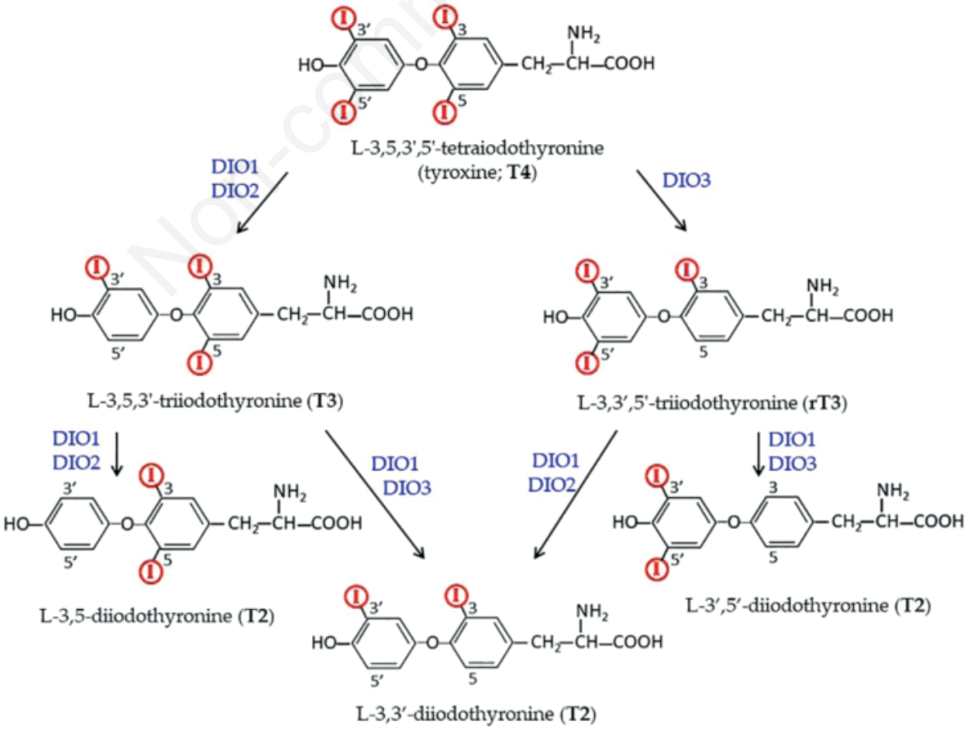

Figure. 2. Deiodinases involved in metabolic pathways leading from prohormone T4 to active hormone T3 and other derivatives. Giammanco *et al.* Int J Mol Sci 2020;21:4140.[42]

can be also down-regulated by various cytokines such as interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNF-α). D1 also catalyzes the reaction of deiodination in positions 3' and 3, which are important in the catabolism of thyroid hormones.

The D2 isoform is mainly localized in the pituitary gland, central nervous system (CNS), brown adipose tissue, and skeletal muscle. D2 has only a 5'-deiodase activity and is not susceptible to the inhibiting effects of propylthiouracil (PTU).

On the other hand, D3 is mainly present in the CNS, placenta, and skin. It has only a 5-deiodase activity and is the main source of circulating rT3. The function of deiodinases is to modulate the activity of thyroid hormones in a target organ, through the regulation of the amount of active hormone (T3) synthesized according to the needs of the organ. In fact, in physiological conditions, about 35% of T4 is deiodinated to T3 by D1 or D2 activity, 45% is deiodinated into rT3 by D1 or D3 activity while about 10% is secreted in the bile as a glucuronate metabolite or sulfate and then excreted with feces. The process of sulfation is a key step in the metabolic pathways of thyroid hormones as it increases the affinity of the substrate for deiodinases and consequently the efficiency of the hepatic deiodation processes. The amount of T4 that is deiodated to T3 or rT3 depends on the conditions of the organism and is influenced by the nutritional status (e.g. hyper- or hypo-alimentation) and health conditions (well-being, fever, or diseases). This explains why a reduction of D1 activity can be observed during illness and fasting. The function of rT3 in humans is not known even though experimental evidence has highlighted the fact that it inhibits 5-deiodase activity, thus suggesting its involvement in regulating the production of thyroid hormones.[43]

Thioredoxin and thioredoxin reductase

Thioredoxin (Trx), thioredoxin reductase (TrxR), and nicotinamide adenine dinucleotide phosphate (NADPH) are part of the thioredoxin system. Trx was identified in 1964 as a hydrogen donor for the enzymatic synthesis of cytidine deoxyribonucleoside diphosphate by the ribonucleotide reductase from *Escherichia coli*. This protein exerts a wide number of functions in several biological processes such as DNA synthesis, defense against oxidative stress, and apoptosis or redox signaling in the pathogenesis of many diseases.[44]

Thioredoxin reductases (TrxR) are homodimeric enzymes belonging to the flavoprotein family. Each TrxR monomer contains flavin adenine dinucleotide (FAD) as a prosthetic group, a binding site for NADPH, and an active site consisting of a disulfide that acts on redox reactions. TrxRs specifically reduce oxidized thioredoxins, a group of small ubiquitous peptides that can interact with DNA, causing alterations in gene transcription, and exert inhibitory effects on apoptosis, thus facilitating cell proliferation. These enzymes are shown to have oxidation-reductive effects and therefore hinder oxidative stress. The importance of this system is demonstrated by the shortened lifespan of the Methionine sulfoxide reductase (MsrA) gene knockout mice.[45] In line with this study, transgenic mice overexpressing human Trx1 were shown to have a longer lifespan and to be protected against oxidative stress-related diseases.[46,47]

Food sources

Although Se is distributed in soils all over the world, different factors such as soil composition, plant species and physiological conditions of the plant, environmental conditions, and agricultural practices may markedly influence Se content of vegetables, fruit, meat, fish, and water.[48] Se content in normal adult subjects may undergo wide variations. It has been estimated that about fifteen percent of the world's population is Se-deficient. In some parts of the world, including the Middle East, India, China, and some European countries such as Finland, there are considerably low levels of Se in the soil. This phenomenon may account for the deficiency of Se observed in the population of these countries.[49-51] Conversely, in those countries whose soil is rich in Se a significant percentage of the local population who consume locally grown food may exhibit signs of Se toxicity.[52,53] For instance, lentils grown in Canadian soils are extremely rich in Se (425-673 µg /kg).[54] A wide geographical variation in Se content can be also observed between subjects living in different areas of the same country. For example, one of these studies reported that Se intake in adults in Se-deficient areas and seleniferous areas in China was 2.6-5.0 and 1338 µg/day, respectively.[55] Vegetables such as onions and asparagus grown on seleniferous soil can accumulate up to 17 µg/g of Se. Garlic, cabbages, broccoli, and mustard are also rich in Se. Other commonly consumed vegetables and fruits generally contain only small amounts, that rarely exceed 10 µg/kg. Brazil nuts also have very high concentrations of Se.[56,57] On the other hand, several studies have reported that the content of Se in fish may widely vary in a range of concentrations comprised between 0.1 and 5.0 mg/kg.[58] Some sea fish, mainly those with large size, contain high amounts of Se in their body.[59,60]

Determination of selenium in the body and supplementation

There are several laboratory methods for measuring Se content in humans. By these methods, Se can be determined in plasma, serum, and also in the kidney and liver, hair and nails, or in urines.[48] The plasma level of Se reflects the amount of circulating SPs and selenoenzymes.[61] The Se status of an organism can be also indirectly assessed by determining the activity of GPx in erythrocytes.[48] Furthermore, some authors have described a procedure for the determination of Se by atomic absorption spectroscopy (AAS) in whole blood, serum, and urine.[62]

Several studies have shown that the concentrations of Se in the blood of citizens of several European countries are lower than the concentrations required for optimal plasma GPx activity in humans.[11] On the other hand, Se intake in Europe is lower than in the United States.[63] The highest level of intake was observed in individuals consuming a diet rich in whole-grain foods and seafood such as crabs, shellfish, and fish.[63] Some clinical investigations have reported an increase in free T3 in a cohort of patients in response to Se supplements with daily supplementation of 100 µg of L-selenomethionine.[64,65] Conversely, other studies have shown the absence of a significant influence of Se on the levels of free T3, free T4, and TSH.[66,67] In addition, some randomized controlled trials in healthy adults have shown a statistically significant decrease in serum T4 after supplementation with Se.[68,69]

In this setting, Gärtner *et al.* indicated that a significant reduction in the mean concentration of anti-peroxidase antibodies (TPO-Ab) can be reached following 3 months of supplementation with 200 µg of oral sodium selenite. The study also reported that 25% of patients showed complete normalization of both TPO-Ab concentrations and ultrasonographic echogenicity of the thyroid.[31]

Nacamulli *et al.* demonstrated that dietary supplementation with physiological doses of Se for up to 12 months was effective in reducing both anti-TPO-Ab and anti-thyroglobulin (Tg-Ab) autoantibodies [70] (Table 1). In this setting, Combs *et al.* reported that a period of 9 months is required to achieve an increase in plas-

ma Se concentrations in 28 healthy subjects supplemented with 200 µg of Se/day as selenomethionine. However, in these subjects, Se supplementation did not produce clinically significant changes in the concentrations of thyroid hormone. Only in men, there was a slight statistically significant increase in T3 concentrations, without any decrease in TSH.[66]

Other studies have evaluated the effects of Se supplementation on thyroid volume regression in AT. These investigations showed that low Se serum concentrations were associated with higher thyroid volume and a higher prevalence of thyroid enlargement.[71,72] Moreover, some authors recommend a 6-month course of Se in patients with mild Basedow's orbitopathy although to date there is no convincing scientific evidence regarding the optimal duration of Se supplementation in Basedow's Disease (BD).[73] Se status in healthy subjects should be investigated before or during the period of Se integration to integrate in a targeted manner deficiency states in subjects with autoimmune thyroid diseases.[74] A systematic review and meta-analysis of the clinically relevant effects of Se supplementation in patients with chronic AT showed no influence of Se supplementation on thyroid stimulating hormone, health-related quality of life, or thyroid ultrasound and in subjects treated or not treated with levothyroxine replacement.[75,76]

Selenium deficiency

Seleno deficiency appears to be directly associated with two endemic diseases, namely, Kashin-Beck disease and Keshan disease, that are widespread in China and Russia where the soils are poor in Se content.[78] The first is osteoarthritis characterized by atrophy, degeneration, and necrosis of the cartilage tissue, which occurs mainly in children and can lead to joint enlargement, shortening of the fingers and toes, and in extreme cases, even dwarfism.[77] The second one is a juvenile endemic multifocal cardiomyopathy, discovered in the Chinese province of Keshan, where the soil is deficient in Se. This pathological condition is characterized by cardiac enlargement, abnormalities in the electrocardiogram, cardiogenic shock, and congestive heart failure associated with multifocal myocardial necrosis.[78]

It is well known that Se deficiency does not show clinical signs characterized by many disorders. Consequently, this may explain the reason why Se deficiency appears in pathological forms, including thyroid autoimmunity, which is not related to Se deficiency.[79,80]

Se deficiency is mainly caused by a low dietary intake or poor intestinal absorption while a genetically inherited Se and SP deficiency is a rare condition.[81] On the other hand, subjects with hereditary defects in protein 2 binding the insertion sequence of selenocysteine (SBP2), present a syndrome of selenoprotein-related defects including abnormal thyroid hormone metabolism.[81]

SBP2 is considered a key transaction factor for the co-translational insertion of SeC into SPs. In subjects with SBP2 deficiency due to *SBP2* gene mutations the dietary intake of Se is not the limiting factor when regular daily intake of Se is provided.[82] Total serum Se concentrations in subjects with SPs biosynthesis defects respond to selenomethionine supplementation. A recent cross-sectional survey carried out in the Shaanxi Province, China, evidenced a higher prevalence of thyroid disease in a county with low usual consumption of Se compared to a neighboring county with higher consumption of Se.[83]

Selenium and thyroid ophthalmopathy

Lower Se serum levels have been observed in patients with thyroid disease while in Se-deficient areas a higher incidence of thyroid ophthalmopathy has been reported. Low Se levels have also been noted in infants born from mothers with thyroid disease.[84]

H_2O_2 is an essential co-substrate for thyroid peroxidase (TPO). During the oxidation of inorganic iodine, the number of H_2O_2 molecules produced is proportional to the intensity of stimulation on TSH receptors while GPx and TxR neutralize excesses of H_2O_2. The hyperactivity of the thyroid gland causes a greater production of H_2O_2 and ROS. Therefore, a greater amount of Se is needed to protect the glandular tissues from damage induced by superoxide. Several other agents such as superoxide dismutase, and vitamins C and E may also contribute to neutralizing H_2O_2.[85,86]

Basedow's disease (BD) is the most common cause of thyrotoxicosis while Hashimoto's thyroiditis (HT) is the most common cause of hypothyroidism: 90% of patients with thyroid ophthalmopathy are affected by BD and 10% are affected by HT. These autoimmune thyroid diseases are caused by an abnormal immune response to thyroid auto-antigens. In this context, a key role is played by T lymphocytes when antigen recognition is mediated by cell surface receptors. This disrupts tolerance for suppressor T cell deficiency and aberrant expression of the D-related (DR) region of the Human Leukocyte Antigen (HLA) (HLA-DR), absent in normal thyroid cells.[87]

Se exerts a dose-dependent inhibitory effect on the expression of interferon-γ-induced thyrocyte HLA-DR molecules. This may explain one of the beneficial effects of Se in reducing the severity of autoimmune thyroid disease.[88,89] The mechanisms responsible for the loss of tolerance of T cells towards the thyroid stimulating hormone receptors (TSHR) that trigger autoimmunity in BD are still unknown. This pathological condition is associated with an excessive secretion of antibodies to the TSH receptor (TSHR-Ab) by activated B cells. These antibodies bind to TSHR on thyroid cells and fibroblasts of the orbit. This antigen-antibody reaction on thyroid cells mimics the action of TSH which stimulates the function of thyrocytes with excessive production of thyroid hormones and therefore thyrotoxicosis.[90] This also stimulates H_2O_2 production which requires a higher SPs quantity to neutralize H_2O_2 in excess and to reduce oxidative stress and thyrocyte injury. In a population-based study, Pedersen *et al.* demonstrated significantly lower serum Se concentrations in BD than in normal subjects.[91]

Xu *et al.* in 2011 investigated the effect of Se on the thyroid glands of patients subjected to excessive iodine intake. These authors concluded that supplementation of Se could alleviate the toxic effect of excessive iodine on the thyroid as well.[92]

Although thyroid hormone synthesis is compartmentalized in the lumen of the follicles and both Dual Oxidase (DUOX) enzymes and TPO are located in the apical membrane of thyroid cells, H_2O_2 can diffuse freely into the cytoplasm and nucleus, where it can trigger aberrant oxidation and iodination of proteins and lipids thus promoting apoptosis and inducing DNA damage. Therefore, H_2O_2-induced tissue damage can release thyroid hormone stored as a colloid in the follicle lumen and enter the circulation, worsening the severity of hyperthyroidism. In severe Se deficiency, the breakdown of peroxide within the thyroid cells is reduced.[31]

The nutritional deficiency of Se therefore causes an increase in necrosis of thyroid cells and invasion of macrophages and a further increase in the levels of thyroid hormones in the blood due to the release of stored thyroid hormones.[93,94]

Like iodine, Se also affects the size of the thyroid gland. Rasmussen *et al.* showed an inverse relationship between Se serum concentration and thyroid gland volume.[71]

Se deficiency can also exacerbate the effects of iodine deficiency; a similar effect can be observed in vitamin A or iron deficiency.[95]

Basedow's ophthalmopathy is caused by inflammation of the extraocular muscles and orbital adipose tissue. Serum TSHR-Ab is

present in 70-100% of patients with BD and 1-2% of normal individuals.[96]

In addition to the thyrocytes, TSH receptors are also expressed in fibroblasts and orbital pre-adipocytes. When bound by TSHR-Abs they trigger a chronic inflammatory cascade with consequent swelling of the orbital tissues as seen in Basedow's ophthalmopathy.[97] Thus, the ophthalmic manifestations of BD are the result of a close interaction between orbital fibroblasts and T-cell lymphocytes; polymorphisms in immunomodulatory genes can alter the interaction between T-cells and orbital fibroblasts and influence disease susceptibility and progression.[98]

Although anti-peroxidase antibodies (TPO-Ab) are more commonly associated with HT and TSHR-Ab is more commonly associated with BD, there is an overlap.[99]

TPO-Abs are specific for auto-antigenic TPO and are approximately 90% of HT, 75% of BD, and 10-20% of nodular goiter or thyroid cancer. Additionally, 10-15% of normal individuals may have high-level TPO-Ab titers.[100]

There is clear evidence that the benefits of Se supplementation in patients with AT are more pronounced when administered at an early phase.[101] Some authors have suggested that the beneficial effects of Se supplementation in subjects with AT may vary in relation to the activity of the disease and the degree of inflammation (Table 1).[102]

Toulis *et al.* reported a significant lowering of TPO-Ab titers in patients with HT in response to Se supplementation.[103]

A blind prospective placebo-controlled study highlighted the fact that the mean anti-TPO antibody concentration fell by 49.5% in the group receiving a daily dose of 200 µg oral sodium selenite compared with a 10.1% reduction in the control group.[93] Another study showed a reduction of 36% of TPO-Ab in the group treated with Se. An analysis of the sub-groups of patients with TPO-Ab greater than 1200 UI/mL highlighted a median reduction of 40% in patients treated with Se when compared to a 10% increase in TPO-Ab in the placebo group.[31]

Other authors observed a significantly higher response to oral sodium selenite in hyperthyroid patients compared to euthyroid or hypothyroid patients. A subgroup analysis of these patients revealed a reduction of TPO-Ab titer of up to 64.42% in the subclinical hyperthyroid group of patients, while the reduction of TPO-Ab titer in the euthyroid, hypothyroid, and subclinical hypothyroid groups was still significant (41.13%, 47.18% and 42.64%, respectively).[93]

Another prospective placebo-controlled study including 132 patients with autoimmune thyroiditis reported a decreased inflammatory activity associated with a decreased quantity of TPO-Ab in response to Se supplementation. Furthermore, an inverse correlation between antioxidant capacity and TPO-Ab level has been also described.[104] However, it is still not clear whether Se deficiency alone could be responsible for the worsening of thyroid disease. In a woman with HT Zagrodzki and Ratajczak observed an increase in serum Se by 45%, an increase in plasma GPx3 by 21%, and a 76% reduction of TPO-Ab following Se supplementation.[105] However, other investigations have reported opposite results, since they failed to demonstrate a significant benefit of Se supplementation on serum levels of thyroid autoantibodies (Table 1).[106] On the other hand, Bonfig *et al.* demonstrated that the supplementation of Se in a population of children and adolescents did not cause a reduction of TPO-Ab concentrations.[107]

The pathogenesis of Basedow's ophthalmopathy relies on the infiltration of inflammatory cells, mainly activated T cells, that produce cytokines and activate the orbital production of glycosaminoglycan by fibroblasts.[108] A retrospective study of 83 patients with BD highlighted higher serum levels of Se in the group of patients in remission. These findings indicate a positive effect of Se levels on the regression of BD. Furthermore, in the relapsed group the levels of anti-thyroid stimulating hormone receptor autoantibodies (TRAb) and serum Se values were positively correlated, while a negative correlation was observed in the group of patients in remission with a significantly low concentration of the levels of TRAb and elevated Se levels in serum.[109]

In line with these observations, it has been shown that patients with BD treated with a mixture of vitamin C, vitamin E, beta-carotene, and Se in combination with anti-thyroid drugs, achieved euthyroidism faster than those treated with anti-thyroid drugs alone.[110,111] ROS production increases pro-inflammatory cytokine expression through the up-regulation of Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activity.[112] Lymphocytes, macrophages, and mainly neutrophils require ROS and pro-inflammatory molecules for activation, differentiation, and phagocytosis.[113] Experimental studies have shown that mice with autoimmune thyroiditis receiving Se supplementation had lower serum thyroglobulin antibody (TgAb) titers and reduced lymphocyte infiltration into the thyroid compared to mice with untreated thyroiditis.[114] GPx and TxR decrease the formation of ROS and reduce H_2O_2 and lipid hydroperoxides and phospholipids. The key enzymes of prostaglandin and leukotriene synthesis require specific concentrations of peroxide to be activated. Consequently, GPx plus reduced glutathione prevents any metabolic transformation of arachidonate by cyclooxygenase, 5-lipoxygenase, and 15-lipoxygenase.[17]

Conclusions

Selenium is an essential trace element endowed with several important protective functions in human health. Se deficiency is a key environmental factor that, when associated with genetic variants, may cause an increase in the incidence of autoimmune thyroid diseases, especially in those regions in the world with a deficiency of Se in the soil.[115] Se deficiency has been associated with several adverse thyroid conditions, including hypothyroidism, subclinical hypothyroidism, goiter, thyroid cancer, HT, and BD.[116-118]

Some authors have highlighted, in male mice, the protective effects of seleno-L-methionine (Se) against thyroid damage caused by cadmium (Cd) administration.[119] Cd is an extremely toxic heavy metal known to interfere with antioxidant enzymes, energy metabolism, gene expression, and cell membranes.[120]

SPs have been shown to protect thyroid cells from superoxide-mediated damage. In addition, these proteins modulate the effects of those thyroid auto-antibodies which are responsible for the ophthalmic manifestations. Furthermore, SPs are shown to possess anti-inflammatory activity, lower hydroperoxides in tissues, and inhibit the production of inflammatory prostaglandins and leukotrienes. Based on these observations, it has been hypothesized that even a slight Se deficiency may contribute to the development and maintenance of autoimmune thyroid diseases.[31]

References

1. Benvenga S, Feldt-Rasmussen U, Bonofiglio D, Asamoah E. Nutraceutical supplements in the thyroid setting: health benefits beyond basic nutrition. Nutrients 2019;11:2214.
2. Duntas LH. The role of iodine and selenium in autoimmune thyroiditis. Horm Metab Res 2015;47:721-6.
3. Weeks BS, Hanna MS, Cooperstein D. Dietary selenium and selenoprotein function. Med Sci Monit 2012;18:127-132.

4. Vyacheslav M, Labunskyy, Dolph L et al. Selenoproteins: molecular pathways and physiological roles. Physiol Rev 2014;94:739-77.
5. Shimada BK, Alfulaij N, Lucia A. Seale LA. The impact of selenium deficiency on cardiovascular function. Int J Mol Sci 2021;22:10713.
6. Moghadaszadeh B, Petit N, Jaillard C, et. al. Mutations in SEPN1 cause congenital muscular dystrophy with spinal rigidity and restrictive respiratory syndrome. Nature Genet 2001;29:17-8.
7. Cai X, Wang C, Yu W, et al. Selenium exposure and cancer risk: an updated meta-analysis and meta-regression. Sci Rep 2016;6:19213.
8. Qazi IH, Angel C, Yang H, et al. Role of selenium and selenoproteins in male reproductive function: A review of past and present evidences. Antioxidants 2019;8:268.
9. Hariharan S, Selvakumar Dharmaraj S. Selenium and selenoproteins: it's role in regulation of inflammation. Inflammopharmacology 2020;28:667-95.
10. Kohrle J. The deiodinase family: selenoenzymes regulating thyroid hormone availability and action. Cell Mol Life Sci 2000;57:1853-63.
11. Rayman MP. Selenium and human health. Lancet 2012;379: 1256-68.
12. Beck MA, Levander OA, Handy J. Selenium deficiency and viral infection. J Nutr 2003;133:1463S-7S.
13. Stone CA, Kawai K, Kupka R, Fawzi WW. Role of selenium in HIV infection. Nutr Rev 2010;68:671-81.
14. Steinbrenner H, Speckmann B, Sies H. Toward understanding success and failures in the use of selenium for cancer prevention. Antioxid Redox Signal 2013;10;181-91.
15. Przybylik-Mazurek E, Zagrodzki P, Kuźniarz-Rymarz S, Hubalewska-Dydejczyk A. Thyroid disorders-assessments of trace elements, clinical, and laboratory parameters. Biol Trace Elem Res 2011;141:65-75.
16. Schomburg L. Selenium, selenoproteins and the thyroid gland: interactions in health and disease. Nat Rev Endocrinol 2011;8:160-71.
17. Flohé L, Andreesen JR, Brigelius-Flohé R, et al. Selenium, the element of the moon, in life and earth. IUBMB Life 2000;49: 411-20.
18. Bierl C, Voetsch B, Jin RC, et al. Determinants of human plasma glutathione peroxidase (GPx-3) expression. J Biol Chem 2004;279:26839-45.
19. Schomburg L, Köhrle J. On the importance of selenium and iodine metabolism for thyroidhormone biosynthesis and human health. Mol Nutr Food Res 2008;52:1235-46.
20. Tsuji PA, Santesmasses D, Lee BJ, et al. Historical roles of selenium and selenoproteins in health and development: The good, the bad and the ugly. Int J Mol Sci 2022;23:5.
21. Kuklinsky B, Schweder R. Acute pancreatitis, a free radical disease; reducing lethality with the sodium selenite and other antioxidants. J Nutr Environ Med 1996;6:393-4.
22. Kato MA, Finley DJ, Lubitz CC, et al. Selenium decreases thyroid cancer cell growth by increasing expression of GADD153 and GADD34. Nutr Cancer 2010;62:66-73.
23. Glattre E, Nygard JF, Aaseth J. Selenium and cancer prevention: observations and complexity. J Trace Elem Med Biol 2012;26:168-9.
24. Mittag J, Behrends T, Hoefig CS, et al. Thyroid hormones regulate selenoprotein expression and selenium status in mice. PLoS One 2010;5:e12931.
25. Gillespie EF, Smith TJ, Douglas RS. Thyroid eye disease: towards an evidence base for treatment in the 21st century. Curr Neurol Neurosci Rep 2012;12:318-24.
26. Wolfram T, Weidenbach LM, Adolf J, et al. The trace element selenium is important for redox signaling in phorbol ester-differentiated THP-1 macrophages. Int J Mol Sci 2021;22:11060.
27. Burk RF, Hill KE. Selenoprotein P-Expression, functions, and roles in mammals. Biochim Biophys Acta 2009;1790:1441-7.
28. Ohta Y, Suzuki KT. Methylation and demethylation of intermediates selenide and methylselenol in the metabolism of selenium. Toxicol Appl Pharmacol 2008;226:169-77.
29. Köhrle J, Brigelius-Flohé R, Böck A, et al. Selenium in biology: facts and medical perspectives. Biol Chem 2000; 381:849-64.
30. Duntas LH. Environmental factors and thyroid autoimmunity. Ann Endocrinol 2011;72:108-13.
31. Gärtner R, Gasnier BC, Dietrich JW, et al. Selenium supplementation in patients with autoimmune thyroiditis decreases thyroid peroxidase antibodies concentrations. J Clin Endocrinol Metab 2002;87:1687-91.
32. Taylor EW. Selenium and cellular immunity. Evidence that selenoproteins may be encoded in the +1 reading frame overlapping the human CD4, CD8, and HLA-DR genes. Biol Trace Elem Res 1995;49:85-95.
33. Cheng W, Fu YX, Porres JM, et al. Selenium-dependent cellular glutathione peroxidase protects mice against a pro-oxidant-induced oxidation of NADPH, NADH, lipids, and protein. FASEB J 1999;13:1467-75.
34. Hill KE, Burk RF. Selenoprotein P: recent studies in rats and in humans. Biomed Environ Sci 1997;10:198-208.
35. Gromer S, Eubel JK, Lee BL, Jacob J. Human selenoproteins at a glance. Cell Mol Life Sci 2005;62:2414-37.
36. Roy G, Sarma BK, Phadnis PP, Mugesh G. Selenium-containing enzymes in mammals: Chemical perspectives. J Chem Sci 2005;117:287-303.
37. Sunde RA, Raines AM, Barnes KM, Everson JK. Selenium status highly-regulates selenoprotein mRNA levels for only a subset of the selenoproteins in the selenoproteome. Biosci Rep 2009;29:329-38.
38. Brigelius-Flohé R, Kipp A. Glutathione peroxidases in different stages of carcinogenesis. Biochim Biophys Acta 2009;1790:1555-68.
39. Imai H, Nakagawa Y. Biological significance of phospholipid hydroperoxide glutathione peroxidase (PHGPx, GPx4) in mammalian cells. Free Radical Biol Med 2003;34:145-69.
40. Chabory E, Damon C, Lenoir A, et al. Mammalian glutathione peroxidases control acquisition and maintenance of spermatozoa integrity. J Anim Sci 2010;88:1321-31.
41. Sun Q, Mehl S, Renko K, et al. Natural autoimmunity to Selenoprotein P impairs selenium transport in Hashimoto's thyroiditis. Int J Mol Sci 2021;22:13088.
42. Giammanco M, Di Liegro CM, Schiera G, Di Liegro I. Genomic and non-genomic mechanisms of action of thyroid hormones and their catabolite 3,5-diiodo-L-thyronine in mammals. Int J Mol Sci 2020;21:4140.
43. Bianco AC, Reed Larsen P. Intracellular pathways of iodothyronine metabolism, in Wener and Ingbar's The Thiroyd: a Fundamental and Clinical Text, 9th Ed., Braverman L.E., Utiger R.D. Eds, Lippincot Williams and Wilkins, Philadelphia, 2005, pp. 109.
44. Holmgren A, Lu J. Thioredoxin and thioredoxin reductase: Current research with special reference to human disease. Biochem Bioph Res Com 2010;396:120-4.
45. Moskovitz J, Bar-Noy S, Williams WM, et al. Methionine sulfoxide reductase (MsrA) is a regulator of antioxidant defense

and lifespan in mammals, Proc Natl Acad Sci USA 2001;23:12920-5.
46. Mitsui A, Hamuro J, Nakamura H, et al. Overexpression of human thioredoxin in transgenic mice controls oxidative stress and life span. Antioxid Redox Signal 2002;4:693-6.
47. Lillig CH, Holmgren A. Thioredoxin and related molecules: from biology to health and disease. Antioxid Redox Signal 2007;9:25-47.
48. Mehdi Y, Hornick JL, Istasse L, Dufrasne I. Selenium in the environment, metabolism and involvement in body functions. Molecules 2013;18:3292-311.
49. Das S, Bhansali A, Dutta P, et al. Persistence of goitre in the post-iodization phase: micronutrient deficiency or thyroid autoimmunity? Indian J Med Res 2011;133:103-9.
50. Aydin K, Kendirci M, Kurtoğlu S, et al. Iodine and selenium deficiency in school children in an endemic goitre area in Turkey. J Pediatr Endocrinol Metab 2002;15:1027-31.
51. Xia Y, Hill KE, Byrne DW, et al. Effectiveness of selenium supplements in a low-selenium area of China. Am J Clin Nutr 1998;81:829-34.
52. Hira CK, Partal K, Dhillon KS. Dietary selenium intake by men and women in high and low selenium areas of Punjab. Public Health Nutr 2004;7:39-43.
53. Fairweather-Tait SJ, Bao Y, Broadley MR, et al. Selenium in human health and disease. Antioxid Redox Signal 2011;14: 1337-83.
54. Thavarajah D, Thavarajah P, Wejesuriya A, et al. The potential of lentil (Lens culinaris L.) as a whole food for increased selenium, iron, and zinc intake: preliminary results from a 3 year study. Euphytica 2011;180:123-8.
55. Tan J, Zhu W, Wang W, et al. Selenium in soil and endemic diseases in China. Sci Total Environ 2002;284:227-35.
56. Navarro-Alarcon M, Cabrera-Vique C. Selenium in food and the human body: a review. Sci Total Environ 2008;400:115-41.
57. Dumont E, Vanhaecke F, Cornelis R. Selenium speciation from food source to metabolites: a critical review. Anal Bioanal Chem 2006;385:1304-23.
58. Rayman MP, Infante HG, Sargent M. Food-chain selenium and human health: spotlight on speciation. Br J Nutr 2008;100: 238-53.
59. Zou C, Yin D, Wang R. Mercury and selenium bioaccumulation in wild commercial fish in the coastal East China Sea: Selenium benefits versus mercury risks. Mar Poll Bull 2022;180:113754.
60. Fairweather-Tait SJ, Collings R, Hurst R. Selenium bioavailability: current knowledge and future research requirements. Am J Clin Nutr 2010;91:1484-91S.
61. Gärtner R. Selenium and thyroid hormone axis in critical ill states(?): an overview of conflicting view points. J Trace Elem Med Biol 2009;23:71-4.
62. Tiran B, Tiran A, Rossipal E, Lorenz O. Simple decomposition procedure for determination of selenium in whole blood, serum and urine by hydridegeneration atomic absorption spectroscopy. J Trace Elem Electrolytes Health Dis 1993;7:211-6.
63. Patterson P, Levander OA. Naturally occurring selenium compounds in cancer chemoprevention trials: a workshop summary. Cancer Epidemiol Biomarkers Prev 1997; 6:63-9.
64. Thomson CD, Campbell JM, Miller J, Skeaff SA. Minimal impact of excess iodate intake on thyroid hormones and selenium status in older New Zealanders. Eur J Endocrinol 2011;165:745-52.
65. Thomson CD, Campbell JM, Miller J, et al. Selenium and iodine supplementation: effect on thyroid function of older New Zealanders. Am J Clin Nutr 2009;90:1038-46.
66. Combs GF, Midthune DN, Patterson KY, et al. Effects of selenomethionine supplementation on selenium status and thyroid hormone concentrations in healthy adults. Am J Clin Nutr 2009;89:1808-14.
67. Rayman MP, Thompson AJ, Bekaert B, et al. Randomized controlled trial of the effect of selenium supplementation on thyroid function in the elderly in the United Kingdom. Am J Clin Nutr 2008;87:370-8.
68. Duffield AJ, Thomson CD, Hill KE, Williams S. An estimation of selenium requirements for New Zealanders. Am J Clin Nutr 1999;70:896-903.
69. Olivieri O, Girelli D, Azzini M, et al. Low selenium status in the elderly influences thyroid hormones. Clin Sci (Lond) 1995;89:637-42.
70. Nacamulli D, Mian C, Petricca D, et al. Influence of physiological dietary selenium supplementation on the natural course of autoimmune thyroiditis. Clin Endocrinol (Oxf) 2010;73: 535-9.
71. Rasmussen LB, Schomburg L, Köhrle J, et al. Selenium status, thyroid volume, and multiple nodule formation in an area with mild iodine deficiency. Eur J Endocrinol 2011;164:585-90.
72. Onal H, Keskindemirci G, Adal E, et al. Effects of selenium supplementation in the early stage of autoimmune thyroiditis in childhood: an open-label pilot study. J Pediatr Endocrinol Metab 2012;25:639-44.
73. Marcocci C, Altea MA, Leo M. Treatment options for Graves' orbitopathy. Expert Opin Pharmacother 2012;13:795-806.
74. Giammanco M, Giammanco MM. Selenium: A cure for autoimmune thyroiditis. Endoc Metab Immune Disord Drug Targets 2021;21:1377-8.
75. Winther KH, Wichman JEM, Bonnema SJ, Hegedüs L. Insufficient documentation for clinical efficacy of selenium supplementation in chronic autoimmune thyroiditis, based on a systematic review and meta-analysis. Endocrine 2017;55:376-85.
76. Winther KH, Rayman MP, Bonnema SJ, Hegedüs L. Selenium in thyroid disorders - essential knowledge for clinicians. Nat Rev Endocrinol 2020;16:165-76.
77. Li N, Gao Z, Luo D, et al. Selenium level in the environment and the population of Zhoukoudian area, Beijing, China. Sci Total Environ 2007;381:105-11.
78. Chen JS. An original discovery: selenium deficiency and Keshan disease (an endemic heart disease) Asia Pac J Clin Nutr 2012;21:320-6.
79. Wu Q, Rayman MP, Lv H, et al. Low Population selenium status is associated with increased prevalence of thyroid disease. J Clin Endocrinol Metab 2015;100:4037-47.
80. Winther KH, Bonnema SJ, Cold F, et al. Does selenium supplementation affect thyroid function? Results from a randomized, controlled, double-blinded trial in a Danish population. Eur J Endocrinol 2015;172:657-67.
81. Schweizer U, Dehina N, Schomburg L. Disorders of selenium metabolism and selenoprotein function. Curr Opin Pediatr 2011;23:429-35.
82. Schomburg L, Dumitrescu AM, Liao XH, et al. Selenium supplementation fails to correct the selenoprotein synthesis defect in subjects with SBP2 gene mutations. Thyroid 2009;19:277-81.
83. Wu Q, Wang Y, Chen P, et al. Increased incidence of

Hashimoto's thyroiditis in selenium deficiency: a prospective six-year cohort study. J Clin Endocr Metab 2022;107:e3603-11.
84. Kazi TG, Kandhro GA, Sirajuddin, et al. Evaluation of iodine, iron, and selenium in biological samples of thyroidmother and their newly born babies. Early Hum Dev 2010;86:649-55.
85. Di Majo D, La Guardia M, Leto G, et al. Flavonols and flavan-3-ols as modulators of xanthine oxidase and manganese superoxide dismutase activity. Int J Food Sci Nutr 2014;65:886-92.
86. Köhrle J, Jakob F, Contempré B, Dumont JE. Selenium, the thyroid, and the endocrine system. Endocr Rev 2005;26:944-84.
87. Stazi AV, Trinti B. Selenium status and over-expression of interleukin-15 in celiac disease and autoimmune thyroid diseases. Ann Ist Super Sanità 2010;46:389-99.
88. Petricca D, Nacamulli D, Mian C, et al. Effects of selenium supplementation on the natural course of autoimmune thyroiditis: a short review. J Endocrinol Invest 2012;35:419-24.
89. Balázs C, Kaczur V. Effect of selenium on HLA-DR expression of thyrocytes. Autoimmune Dis 2012:374635.
90. Morshed SA, Latif R, Davies TF. Delineating the autoimmune mechanisms in Graves' disease. Immunol Res 2012;54:191-203.
91. Pedersen IB, Knudsen N, Carlé A, et al. Serum selenium is low in newly diagnosed Graves' disease: a population-based study. Clin Endocrinol (Oxf) 2013;79:584-90.
92. Xu J, Liu XL, Yang XF, et al. Supplemental selenium alleviates the toxic effects of excessive iodine on thyroid. Biol Trace Elem Res 2011;141:110-18.
93. Bhuyan AK, Sarma D, Saikia UK. Selenium and the thyroid: A close-knit connection. Indian J Endocrinol Metab 2012;16: S354-5.
94. Contempre B, Le-Moine O, Dumont JE, et al. Selenium deficiency and thyroid fibrosis. A key role for macrophages and transforming growth factor β (TGF-β). Mol Cell Endocrinol 1996;124:7-15.
95. Doupis J, Stavrianos C, Saltiki K, et al. Thyroid volume, selenium levels and nutritional habits in a rural region in Albania. Hormones 2009;8:296-302.
96. Orgiazzi J. Anti-TSH receptor antibodies in clinical practice. Endocrinol Metab Clin North Am 2000;29:339-355.
97. Kloprogge SJ, Frauman AG. Expression of TSH-R in normal human extraocular muscles. Br J Ophthalmol 2006;90:124-5.
98. Khalilzadeh O, Noshad S, Rashidi A, Amirzargar A. Graves' ophthalmopathy: a review of immunogenetics. Curr Genomics 2011;12:564-75.
99. Saravanan P, Dayan CM. Thyroid autoantibodies. Endocrinol Metab Clin North Am 2001;30:315-37.
100. Chardès T, Chapal N, Bresson D, et al. The human anti-thyroid peroxidase autoantibody repertoire in Graves' and Hashimoto's autoimmune thyroid diseases. Immunogenetics 2002;54:141-57.
101. Gärtner R, Duntas LH. Effects of selenium supplementation on TPOAb and cytokines in acute autoimmune thyroiditis. Thyroid 2008;18:669-70.
102. Karanikas G, Schuetz M, Kontur S, et al. No immunological benefit of selenium in consecutive patients with autoimmune thyroiditis. Thyroid 2008;18:7-12.
103. Toulis KA, Anastasilakis AD, Tzellos TG, et al. Selenium supplementation in the treatment of Hashimoto's thyroiditis: a systematic review and a meta-analysis. Thyroid 2010;20: 1163-73.
104. Balázs C, Fehér J. The effect of selenium therapy on autoimmune thyroiditis. Clin Experimenta Med J 2009;3:269-77.
105. Zagrodzki P, Ratajczak R. Selenium supplementation in autoimmune thyroiditis female patient-effects on thyroid and ovarian functions (case study). Biol Trace Elem Res 2008;126:76-82.
106. Anastasilakis AD, Toulis KA, Nisianakis P, et al. Selenomethionine treatment in patients with autoimmune thyroiditis: a prospective, quasi-randomised trial. Int J Clin Pract 2012;66:378-8.
107. Bonfig W, Gärtner R, Schmidt H. Selenium supplementation does not decrease thyroid peroxidase antibody concentration in children and adolescents with autoimmune thyroiditis. Sci World J 2010;10:990-6.
108. Weetman AP. Graves' disease. New Engl J Med 2000;343: 1236-48.
109. Wertenbruch T, Willenberg HS, Sagert C, et al. Serum selenium levels in patients with remission and relapse of Graves' disease. Med Chem 2007;3:281-84.
110. Duntas LH. Selenium and the thyroid: a close-knit connection. J Clin Endocrinol Metab 2010;95:5180-8.
111. Vrca VB, Skreb F, Cepelak I, Mayer L. Supplementation with antioxidants in the treatment of Graves' disease: the effect on the extracellular antioxidative parameters. Acta Pharm 2004;54:79-89.
112. Tolando R, Jovanovic A, Brigelius-Flohé R, et al. Reactive oxygen species and proinflammatory cytokine signaling in endothelial cells: effects of selenium supplementation. Free Radic Biol Med 2000;28:979-86.
113. Hardy G, Hardy I, Manzanares W. Selenium supplementation in the critically iII. Nutr Clin Pract 2012;27:21-33.
114. Xue H, Wang W, Li Y, et al. Selenium upregulates CD4(+) CD25(+) regulatory T cells in iodine-induced autoimmune thyroiditis model of NOD.H-2(h4) mice. Endocr J 2010;57: 595-601.
115. Duntas LH. Environmental factors and autoimmune thyroiditis. Nat Clin Pract Endocrinol Metab 2008;4:454-60.
116. Rayman MP. Multiple nutritional factors and thyroid disease, with particular reference to autoimmune thyroid disease. P Nutr Soc 2019;78:34-44.
117. Rua RM, Nogales F, Carreras O, Ojeda ML. Selenium, selenoproteins and cancer of the thyroid. J Trace Elements Med Biol 2023;76:127115.
118. Giammanco M, Mazzola M, Giammanco MM, et al. Selenium and autoimmune thyroiditis. Euro Mediter Biomed J 2023;18:54-8.
119. Benvenga S, Marini HR, Micali A, et al. Protective effects of myo-inositol and selenium on cadmium-induced thyroid toxicity in mice. Nutrients 2020;12:1222.
120. Morabito R, Remigante A, Arcuri B, et al. Effect of cadmium on anion exchange capability through Band 3 protein in human erythrocytes. J Biol Res 2018;91:7203.