EMBJ.ORG FOR YOUNG DOCTORS

EUROMEDITERRANEAN BIOMEDICAL JOURNAL
2023,18 (11) 54-58
(*FORMERLY: CAPSULA EBURNEA*)

Review

SELENIUM AND AUTOIMMUNE THYROIDITIS

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ARTICLE INFO

Article history:
Received 26 Dec 2022
Accepted 24 Feb 2023
Published 20 Apr 2023

Keywords:
selenium, nutrition, selenoproteins, autoimmune thyroiditis, Hashimoto's thyroiditis, Graves' disease, Graves' ophthalmopathy.

ABSTRACT

Selenium (Se) is an essential trace element of pivotal importance to human health. Se is incorporated into selenoproteins (*SePs*) which have pleiotropic effects, including antioxidant and anti-inflammatory effects, and in the production of active thyroid hormone. These findings may explain the relationship between Se deficiency and pathogenesis of various human diseases including thyroid disorder. In line with these observations, the therapeutic effectiveness of Se supplementation has already been reported in patients with various thyroid diseases. However, there are still controversial data about the optimal dose of Se to be administered, as well as the duration and efficacy of treatment and safety of this trace element. It is currently recommended to administer Se supplements following the assessment of any deficiency status of this element and, after that, its association with chronic autoimmune thyroid disease has been proven. Consistent with these observations, several clinical studies have highlighted the fact that Se supplementation in patients with chronic autoimmune thyroid disease was associated with a reduction of thyroid auto-antibodies, and with an improvement of the thyroid-associated ophthalmopathy**.** The beneficial effects of Se supplementation have been reported in subjects with thyroid disease during the hyperthyroid phase. The restoration of euthyroidism is a major goal in the management of thyrotoxicosis of Graves' disease. In line with these observations, clinical studies have shown that, in patients with Graves' disease and autoimmune thyroiditis, treatment with a combination of anti-thyroid drugs and Se restore the euthyroid status faster than the administration of anti-thyroid drugs alone. The review shows that the treatment of an autoimmune thyroid disease with ***Se*** may bring about beneficial effects.

1. Introduction

Selenium (Se) is a non-metallic chemical element that can be found in soil and groundwater. Se enters the food chain through plant roots and its uptake by aquatic organisms (1). The major route of Se intake in humans is through the diet. The total amount of Se in the diet can vary widely according to the type and composition of the food. The largest contribution to Se intake is provided by grains, meat, fish, eggs and milk/dairy products (2). As Se mediates important antioxidant effects, adequate bioavailable levels of this mineral are needed for a proper functioning of several important physiological processes (3).

Se appears to be an essential element for the central nervous system, male reproductive function, endocrine system, muscle function, cardiovascular system, and immune system (4). In this setting, a daily intake of Se is highly recommended in order to maintain metabolic homeostasis in humans (2). The levels of intake for the Italian population (LARN) elaborated by the Italian Society of Human Nutrition (SINU) has established an average daily intake for the adult population of 45µg of Se; 50 µg for pregnant women and 60 µg for breast-feeding women (5). Besides, the LARN has established 300 µg/day of Se, as a maximum tolerable dose (6).

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DOI: 10.3269/1970-5492.2023.18.11
 ISSN: 2279-7165 - Available on-line at www.embj.org

Skeletal muscle is the major site of Se storage, accounting for approximately 28-46% of the total Se pool (2). Unlike other minerals, in humans Se is incorporated into proteins as a component of the amino acid selenocysteine (*SeCys*) (the "21st amino acid" used for protein synthesis in the body) by co-translational mechanisms (4). Selenocysteine is encoded by the codon UGA. Although UGA normally functions as "stop codon", it may occasionally be translated to give selenocysteine through a process called "translational decoding" (2). The main form of Se ingested by humans is selenomethionine (3).

2. Selenoproteins

To date, 25 genes encoding selenoproteins (*SePs*) have been identified in humans, 24 in rodents, and 3 in the fruit fly *Drosophila* (2). However, few of these proteins have been functionally characterized so far (4). Most of *SePs* have antioxidant properties. Due to these properties, these proteins, in particular, glutathione peroxidase (*GPxs*) and thioredoxin reductase (*TRxRs*), appear to play a major role in the cellular antioxidant defense and in regulating redox homeostasis (4). *GPxs* belong to a broad family of proteins with antioxidant functions, whose main role is to protect cell membranes and lipid-containing organelles from oxidative damage by inhibiting oxidative stress and by degrading oxidised components (7). The *GPxs* family includes eight isoforms (Roman 2014). However, only five members have a *SeCys* moiety and can catalyze the reduction of hydrogen peroxide (H_2O_2) and lipid hydroperoxides by using glutathione (*GSH*) as a reducing cofactor (4). *GPxs*, in combination with Vitamin E, contribute to maintain the integrity of cell membranes by modulating redox reactions with *GSH* and hydrogen peroxide production. Therefore, *Se* deficiency may exacerbate redox byproduct toxicity and cell membrane-induced oxidative damage (7). Thioredoxin reductases (*TrxRs*) are homodimeric enzymes belonging to the flavoprotein family (8). Each *TrxR* monomer contains FAD as a prosthetic group, a binding site for NADPH, and a redox-active disulfide site. *TrxRs* reduce the oxidized disulfide form of the active sites of their major endogenous substrate thioredoxins (*Trxs*), a group of small ubiquitous peptides that may interact with DNA, causing alterations in gene transcription. *Trxs* may also exert inhibitory effects on apoptosis, thus facilitating cell proliferation (8). However, some *SePs* may play more specific and important roles. For instance, the enzymes of the iodothyronine deiodinases (*D*) family are involved in the metabolism of thyroid hormones (*THs*) (4). The three isoforms of these enzymes (*D1*, *D2*, *D3*) are homo-dimeric membrane-anchored *SePs* that share the folding structure of thioredoxin (10). Each isoform shows a different tissue distribution and determines the activation, or inactivation, of THs in different organs (11). These three enzymes, have different cellular localizations according to their functional role; in particular *D1* and *D3* are expressed in the plasma membrane, *D2* is present in the endoplasmic reticulum membrane. Thyroxine (*T4*), which is the major hormone produced by the thyroid gland, is converted into triiodothyronine (*T3*) by *D1* and *D2* through the de-iodination of the outer ring of *T4* molecules. While *T4* is primarily a pro-hormone, *T3* is considered the biologically active hormone. Both *T3* and *T4* can be inactivated by de-iodination of the inner ring by *D3* and, to a lesser extent, by *D1*, with formation of inactive reverse catabolic products of *T3* (*rT3*) and *T2*, respectively. In physiological conditions, these three enzymes contribute to regulating TH homeostasis and activity. In particular *D1* appears to be implicated in the regulation of *TH* levels in the circulation, while *D2* and *D3* are involved in the regulation of the intracellular concentration of *T3* (12).

Selenoproteins and thyroid function

There is convincing evidence that *SePs* are essential for a proper functioning of the thyroid gland. In fact, this endocrine gland is characterized by a high concentration of Se, which is incorporated into several *SePs* and which, in turn, regulate many key biological functions in the gland (13, 14). These proteins have a particularly important role in regulating hormonal metabolism. In addition, they are endowed with a powerful antioxidant activity directed against free radicals that are generated during the production of thyroid hormone (12). These findings may explain the correlation between Se deficiency and impairment of thyroid functions. Se is a crucial element for the function of the thyroid gland. These observations may explain the reason why variable dietary intake of Se may influence immunity. Consequently, dietary Se may contribute to the development of thyroid autoimmunity and may be of clinical use in the treatment of autoimmune thyroid dysfunction (15). Besides, the findings showing a correlation between altered levels of *SePs* expression and altered thyroid hormone levels, further support the pivotal role of Se in thyroid hormone homeostasis and its beneficial effects in autoimmune thyroiditis-associated ophthalmopathy, a condition that represents the most common extrathyroidal manifestation of thyroid disease (16, 17). In line with these observations, physiological levels of Se have been reported to thwart excessive immune response and chronic inflammation. These effects are explained by the ability of *SePs* to modulate the immuno-regulatory expression of cytokines and lipid mediators (18). Furthermore, Se deficiency has been shown to be associated with a number of pathological conditions of the thyroid gland, including hypothyroidism, subclinical hypothyroidism, goiter, thyroid cancer, Hashimoto's thyroiditis and Graves' disease (19). In this context, a growing number of experimental and clinical studies are currently undertaken with the aim to elucidate the possible mechanisms underlying the correlation between Se, *SePs*, and immune-mediated disorders of the thyroid gland (14).

3. Autoimmune thyroiditis

Autoimmune thyroiditis (AIT) is a pathological condition occurring in about 0.3-1.5/1000 subjects/year (20). AIT affects up to 5% of patients worldwide and is more frequent in middle-aged women than men (20). The most common forms of AIT are Hashimoto's thyroiditis (HT) and Graves' disease (GD) (12).

3.1 Hashimoto's thyroiditis

Hashimoto's thyroiditis (HT), also known as chronic lymphocytic thyroiditis or autoimmune thyroiditis (AIT), is a chronic inflammation of the thyroid gland whose etiopathogenesis remains to be fully elucidated (20). HT is the most common autoimmune disease and endocrine disorder. Its diagnosis is determined by biochemical tests (positive circulating thyroid autoantibodies) and imaging tests (showing an inhomogeneous, hypoechoic thyroid structure on ultrasound) with characteristic clinical features. HT is characterized by the production of anti-thyroid peroxidase antibodies (*TPOAb*) and anti-thyroglobulin antibodies (*TgAb*) (20-22). Circulating *TPOAbs* may be found in about 90% of HT patients while, *TgAbs* are less sensitive (positive in about 60-80% of patients) and less specific than *TPOAbs* (20). As a result of inflammation, the thyroid follicles are destroyed and replaced by small lymphocytes. These effects can be observed on ultrasound, as decreased echogenicity of the thyroid parenchyma (21).

The pathogenesis of HT is related to the intra-thyroid lymphocytic infiltration by T and B cells, in particular CD4+ Th1, and the production of anti-thyroid antibodies as well (20-22). These effects lead to chronic inflammation and, consequently, to gradual fibrosis and atrophy of the thyroid tissue (20, 23). Inflammation in chronic autoimmune thyroiditis may also result in an activation of T and B lymphocytes and, consequently, in an increased oxidative stress activity (reactive oxygen species-ROS) mediated by the enzyme nicotinamide adenine dinucleotide phosphate oxidase (*NOX*). These phenomena also lead to an increase of thyroid autoantibody titers (24). In the last decade, a growing number of studies have provided evidence on the involvement of Th17 cells and pro-inflammatory *IL-17* in the pathogenesis of HT. Notably, these studies have been identified in the *Th1*/*Th2 cells* and *Th17/Treg* imbalance as one of the causes fostering HT. Th17 lymphocytes mainly secrete *IL-17* and *IL-22*. *IL-17*, a critical pro-inflammatory cytokine that mediates chronic and autoimmune inflammation and neutrophil recruitment. On the other hand, *IL-17* promotes the expression of various inflammatory cytokines by acting on immune and non-immune cells including epithelial cells, endothelial cells, fibroblasts, and osteoclasts (25). HT is associated with various functional states of the thyroid gland ranging from euthyroid subclinical hypothyroidism to overt hypothyroidism (21). This last condition is associated with an increase in thyrotropin (*TSH*) and a decrease in free thyroid hormone levels (26). HT is also a very common condition in pregnancy, with 2-17% of pregnant women presenting with *TPOAb* or *TgAb* (27).

3.2 Graves' disease

Graves' disease (GD) is an autoimmune disease characterized by the production of thyroid-stimulating immunoglobulins (*TSIs*), also known as thyroid stimulating antibody (*TSAb*). TSIs bind to the *TSH* receptor on the thyroid gland resulting in unregulated production and release of TH (12). Graves' disease is the most common cause of hyperthyroidism, accounting for 60% to 80% of hyperthyroid cases (28). B-lymphocytes mainly promote the synthesis of TSIs within thyroid cells. However, TSIs can also be synthesized in lymph nodes and bone marrow. B-lymphocytes are stimulated by T-lymphocytes which have been sensitized by antigen in the thyroid gland (29). TSIs stimulate both the synthesis of thyroid hormone and the growth of the thyroid gland, thus causing hyperthyroidism (30). One third of GD patients develop peculiar ophthalmic signs, a condition known as Graves' ophthalmopathy (GO). It is an autoimmune inflammatory disease of the orbit and peri-orbital tissues (31).

4. Selenium and autoimmune thyroiditis

It is well known that patients with thyroid disease (including hypothyroidism, subclinical hypothyroidism, autoimmune thyroiditis, and enlarged thyroid) have decreased Se levels (12).

Current studies suggest that Se deficiency is a risk factor for thyroid gland enlargement, and AIT development.

Therefore, it is reasonable to recommend Se supplementation to those AIT patients living in Se-deficient geographic areas (12).

4.1 Hashimoto's Thyroiditis

To date there is no specific and effective therapeutic approach to suppress immune destruction.

Therefore, thyroxine replacement has been the generally accepted therapy for HT patients with hypothyroidism (32).

Very low or very high Se intake (47 and 297 μg/day) may alter TH concentrations by reducing or increasing *T3* levels, respectively (27). Numerous studies have highlighted the fact that Se supplementation can affect thyroid antibodies expression and influence *TSH*, *FT3*, *FT4*, *TPOAb* and *TgAb* serum levels in patients with autoimmune thyroid (32). In this context, some clinical studies, have demonstrated that Se supplementation reduced *TPOAb* and/or *TgAb* titers, thus improving glandular echogenicity and thyroid function in HT patients.

These findings suggest that Se may be useful in reducing the thyroid autoimmunity (32). Moreover, recent clinical observations have shown that at 6-months of 100 μg/day, Se (32) supplementation significantly reduced the circulating levels of anti-thyroid peroxidase antibodies in patients with newly diagnosed and/or previously untreated *HT* and in patients with euthyroidism or subclinical hypothyroidism (33). On the other hand, clinical observations have shown that a short-term supplementation with *SeMet* was associated with a normalization of TSH serum levels which, in 50% of patients with subclinical hypothyroidism due to chronic autoimmune thyroiditis, lasted up to 6 months after *Se* suspension (34). Besides, a randomized, placebo-controlled, double-blind study aimed at assessing the effect of *Se* supplementation, administered at a dose of 200 μg/day versus placebo in patients with elevated *TPOAb* (>300 IU/mL), showed that the *TPOAb* titer decreased by 10.0% at 3 months and by 10.7% at 6 months after *Se* supplementation. However, there was a moderate increase in *TPOAb* titers in patients treated with placebo (35). As the mean concentration required for an optimal *GPx activity* is approximately 90 μg/L, in subjects with low-normal plasma concentrations of *Se*, *GPx activity* results were impaired. In addition, as *TPOAb* reduction has been shown to be dose-dependent, doses of *Se* greater than 100 μg/day are required to maximize *GPx activity* (27). Clinical studies undertaken in pregnant women have demonstrated that, hypothyroid patients had significantly lower plasma levels of Se compared to healthy women and a positive correlation between Se and FT4.

These observations further support the hypothesis that hyperthyroidism is likely associated with a reduced antioxidant response (27). Furthermore, these studies have shown that Se supplement is effective in reducing TPOAb concentrations and the recurrence of postpartum thyroiditis during pregnancy (36). Besides, preclinical *in vivo* studies in transgenic mice have highlighted the fact that the biosynthesis of renal GPX3 depends on the supply of Se by the hepatic Se transporter selenoprotein P (*SELENOP*). There are several variants of *SELENOP* with a different incorporation efficiency of Se content. Quantitative immunoassays studies have shown that natural auto-antibodies against *SELENOP* were particularly prevalent in Hashimoto's thyroiditis compared to healthy subjects (6.6% vs 0.3%). Therefore, these findings indicate that a compromised Se transport may negatively affect the *GPX3* biosynthesis (37). Se deficiency can impair *CD4+ T cell* differentiation, leading to a dysregulation of cellular and humoral responses. Se deficiency has been suggested to be related with the inhibition of *SPs* and an impaired secretion of *IL-10*, *IL-12p40* and *IFN-γ*.

These effects may lead to a Th1/Th2 imbalance shifting towards *Th1* responses. Furthermore, glutathione peroxidase (*GPx*) 1-deficient Th lymphocytes demonstrate a shift towards Th1 cells and attenuate Th cell differentiation into the Th17 lineage (25).

Some clinical studies have reported that GD patients achieving disease remission during the follow-up period (median follow-up, 20.1 months) had elevated serum Se levels (>120 μg/L) that were inversely correlated with *TSH* receptor autoantibodies (*TRAb*).

These results are consistent with the observed beneficial effect of Se on the thyroid autoimmune process (12). In this setting, data from recent investigations indicate that, in patients with recurrent disease, Se supplementation may potentiate the effect of anti-thyroid drugs (e.g. triiodothyronine/free thyroxine-*fT3*/*fT4* ratio) by lowering the *TRAb* level toward the return to normal values. On the other hand, other studies failed to find beneficial effects of Se intake on the clinical outcome of patients or on serological parameters (e.g., free triiodothyronine/free thyroxine ratio*fT3*/*fT4*), *TRAb*, prevalence of moderate-to-severe Graves' orbitopathy and thyroid volume (12, 38). A recent systematic review and meta-analysis, including 10 randomized trials, have reported that that a 3- or 6-month Se supplementation period had statistically significant effects on *fT4*, *fT3*, *TSH*, and *TRAb* levels in patients with *GD*. However, a 9-month period of Se supplementation did not result to be more effective. *TSH* levels were more elevated in the group of patients taking selenium than in the control group at 3 and 6, but not 9 months. *TRAb* levels decreased at 6 months but not at 9 months (39).

5. Discussion and Conclusions

Despite the lack of official clinical guidelines, Se supplements are commonly prescribed to AIT patients by European endocrinologists (40). As low levels of Se appear to be associated with an increased risk of developing antithyroid antibodies, and that Se supplementation can reduce TPOAb titers, we can hypothesize that a reduction in levothyroxine doses is necessary for the treatment of hypothyroidism and/or a prevention in the progression of subclinical hypothyroidism with Se supplementation (12).

The administration of Se to AIT patients may relieve symptoms or prevent disease progression toward hypothyroidism and postpartum hypothyroidism. In patients with euthyroid, subclinical AIT or overt hypothyroidism, Se supplementation decreases the level of circulating thyroid auto-antibodies, and lowers or maintains *TSH* level within normal range values.

Se also reduced *fT4*/*fT3* ratio, the oxidative stress and the inflammatory status of patients. These effects may influence the quality of life of patients and the structure and volume of thyroid ultrasound (40). In pregnant women, Se status appears to influence thyroid function. These observations suggest a potential clinical benefit of Se supplementation. Although both the presence of AIT and low Se status can lead to adverse obstetric outcomes such as miscarriages, preeclampsia/hypertension, preterm delivery, and the birth of small-for-gestational-age infants, the 2017 American Thyroid Association had released a statement advising against Se supplementation in pregnant women with AIT (27, 40).

Although recent evidence suggests promising results following Se supplementation (27), further studies are needed of these patients. Furthermore, it has been reported that adequate Se supplementation to the elderly population reduced the risk of cardiovascular diseases including hypertension. However, a prolonged intake of excessive doses of Se increased the all-cause mortality rate (40).

There is wide geographic variation in the availability of Se in foods. The crucial factor that needs to be emphasized regarding the health effects is that, for people with a low Se content in the body, supplemental Se intake may be of benefit, but those with a high Se content may be negatively affected and should avoid the intake of Se supplements (41, 42).

Therefore, it is important to assess the amount of Se in the body before Se supplementation and, at regular intervals, during treatment period (43). However, the effectiveness of this therapeutic approach remains to be better assessed.

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