

Selenium in the thyroid: physiology and pathology

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Summary

Selenium (Se) is a trace element that plays a critical role in several processes for human health. The thyroid is the organ with the highest Se content per gram of tissue; in thyroid follicular cells, Se acts as antioxidant by contrasting the production of the reactive oxygen species that are generated during thyroid hormones biosynthesis. In addition, Se is part of the active site of the deiodinases, the enzymes responsible for thyroid hormones activation and inactivation.

Herein, the effects of Se supplementation in patients with thyroid related disorders have been reviewed on the basis of the studies published on this issue.

KEY WORDS: thyroid, selenium, autoimmunity, antioxidant.

Introduction

Selenium (Se) (from the Greek word "Selene" meaning Moon) is an essential trace element, that was discovered in 1817 by the Swedish chemist Jons Jacob Berzelius (1). Two hundred years later, Se was recognized as a fundamental micronutrient that plays a critical role in several processes for human health (2-4): in 1957 Schwarz discovered that traces of Se can prevent liver necrosis in vitamin-E-deficient rats (5) and some years later, in 1973, Rothrock demonstrated the biological function of Se as a cofactor of glutathione peroxidase (GPX) (6).

Se is the most powerful antioxidant agent present in the human body (7), it acts as a growth factor, contributes to the regulation of thyroid hormone biosynthesis, it is a modulator of cardiovascular health, is important in the prevention of neurodegenerative diseases and cancer, and its optimal serum concentrations are required for a correct immune response and fertility (8, 9).

Se plays an important role in human physiology, and it is a basic element for many biological processes. Its most important function is likely to be as a fundamental component of the selenoproteins (4). Selenoproteins are a group of proteins, encoded by at least 25 human genes (10), presenting in their catalytic site in the amino acid selenocysteine (Se-Cys).

The functions of several of the selenoproteins are now known and approximately half of them have been shown to protect the cell against the action of reactive oxygen species (ROS) (10, 11). Selenocysteine-containing proteins influence several biological processes and exhibit a wide range of functions including free radical catabolism, immune response and carcinogenesis (9, 11).

A severe Se deficiency is associated with serious endemic diseases such as Kashin-Beck disease (an osteoarthropathy reported in north-east Asia and Tibet), Keshan disease (a cardiomyopathy encountered in some regions of China), but also mixed ematous cretinism as reported in some areas of central Zaire (12).

Se is present in nature in both inorganic and organic forms (13). Most of the human Se intake originates from diet, but other sources of Se are the drinking water, the environmental pollution, and dietary supplementation. In particular, cereals, organ meats and seafood contains considerable levels of Se in forms of selenocysteine and selenomethionine (14).

Se status varies significantly across different populations and different ethnic groups (4), ranging from severe deficiency to toxic levels (2, 4). The quantity and the type of Se in foods are not constant all over the world (15) and the high variability in Se intake is determined not only by the different Se concentration in the soil (i.e., volcanic grounds have lower Se content), but also by other factors that influence the availability of Se to the food chain or the presence of ions that can complex with Se (2, 4).

The optimal Se intake is still very debate (16) since it has been reported that if a low serum Se can contribute and worsen chronic diseases also Se excesses are associated with toxicity (17-21).

Currently, a definition of the optimal Se intake is based on its role in the modulation of anti-oxidase activity, and the optimal nutritional level are those necessary to maximize the activity of the glutathione peroxidase 1 (GPX1). The optimal intake should bring Se plasmatic

concentration around 95 $\mu\text{g/L}$. (range 89-114) (2, 16). This corresponds to an intake of 75 and 60 $\mu\text{g/day}$ for men and women, respectively (3, 16). In the US, selenium intake ranges from 60-220 $\mu\text{g/day}$ (21, 22). Se intake in Europe is lower than in the US, with large variability across different countries, ranging from adequate or marginally adequate intakes in Western and Central Europe (30-90 $\mu\text{g/day}$) to low or deficient intakes in Eastern European countries (7-30 $\mu\text{g/day}$) (22).

Role of selenium in thyroid physiology

The thyroid gland has the highest content of Se per mass unit (23) compared to all other endocrine organs and tissues (4, 10), and the understanding of the fundamental role of Se in the thyroid has been increased significantly during the past few years (10).

Several selenoproteins are expressed in thyroid follicular cells (24-26). Among these, two isoforms of iodothyronine 5'-deiodinase (type1 and type2, DIO1 and DIO2), which produce active thyroid hormone (4); the thioredoxin reductase type 1 (27); the selenoprotein P (27); and three isoforms of glutathione peroxidase, two of which (GPX1 and GPX4) protect thyroid follicular cells from hydrogen peroxide generated by thyroid peroxidase (4), and the third (GPX3) which is present into the lumen, where seems to modulate hydrogen peroxide levels (28).

It is well known that thyroid physiology is closely dependent from the oxidative changes (29): during thyroid hormone biosynthesis, H_2O_2 is constantly produced in a considerable amount, thus exposing the thyroid follicular cells to high concentrations of H_2O_2 and ROS (1). The peroxidative damage is decreased by the action of the selenoenzymes systems which may be involved in the regulation of hormone biosynthesis (30). Of note, the amount of H_2O_2 produced in thyrocytes is similar to the amount that can be produced in activated leukocytes (31), however, while an activated leukocyte's has a life of a few hours, adult human thyrocyte's life spans almost seven years (32). Such a long life requires a very efficient anti-oxidative response process against H_2O_2 excess and this protective system is represented by selenoproteins with GPX3 in first line (31, 33, 34). Intra thyroidal Se concentrations are critical for GPXs activity and unbalances in this process as consequence of reduced Se concentrations can increase the oxidative stress and produce damages to the thyroid follicular cells. These damages can determine, to the very end, cell death and hypothyroidism.

Selenium and autoimmune thyroiditis

Chronic autoimmune Hashimoto's thyroiditis (HT) is the most common thyroid disorder and it is the main cause of acquired hypothyroidism in iodine-sufficient areas (23). All over the world it has a very high prevalence, affecting about 3% of the population (35). HT is characterized by the presence of auto-antibodies directed to the thyroid epitopes (thyroglobulin and thyroperoxidase),

which are closely associated with thyroid dysfunction as consequence of a progressive thyroidal damage and lymphocytic inflammation (36).

HT etiology is still unknown but several aspects are involved in its pathogenesis including genetic predisposition, endogenous and environmental factors, including Se deficiency. A role of Se deficiency was hypothesized by the observation of an higher incidence of HT in areas with severe Se deficiency (37).

Several studies have investigated the possible therapeutic effects of Se administration in patients with HT (12). In 2002, Gartner et al. conducted a randomized, placebo-controlled, blinded trial on 70 female patients in Germany, an area with mild Se and iodine deficiency. The endpoint of the study was to investigate the effects of a short-term Se supplementation on the natural course of HT. The patients, all under T4 treatment at substitutive doses, were split in two groups: 36 patients received 200 μg of sodium selenite/day for 3 months, and 34 patients received placebo. In the supplemented patients, serum Se levels increased from 0,87 to 1,09 μM and at the same time anti-TPO antibodies levels dropped by 37% (37).

The same author followed up some of patients for a further 6 months with a further decrease of TPO-Ab levels (38).

In 2003, Duntas et al. reported a 46% drop in thyroid antibodies levels after administration for three months of 200 $\mu\text{g/day}$ of selenomethionine, and a 55,5% drop of antibodies levels after 6 months of treatment (39). Similar results have been reported by Mazokopakis in 2007 with the administration for one year of 200 $\mu\text{g/day}$ of selenomethionine (40).

In 2006, Turker et al. compared the efficacy of 100 μg and 200 μg of selenomethionine supplementation, concluding that a better effect in maximize GPX activities and suppress autoimmune activity is obtained using the higher dose (41).

In contrast with the previous studies, Karanikas et al. found no significant reduction in anti-TPO antibodies after 3 months of Se supplementation with 200 $\mu\text{g/day}$ of sodium selenite in a series of Austrian patients with HT (42).

In 2009, Nacamulli's study focused mainly on the effect of a year-long course of Se supplementation in Italian patients with early-stage HT and a normal thyroid function or mild hypofunction not receiving substitutive L-T4 therapy. 46 patients were treated with 80 $\mu\text{g/day}$ of sodium selenite for 12 months, while 30 patients were given no treatment. TPO-Ab or Tg-Ab level decreased significantly (30% and 19%, respectively) after 12 months in the Se-treated group, but not in the control group (43). More recently, Krysiak and Okopien conducted a randomized clinical trial involving a group of 170 euthyroid women with recently diagnosed and previously untreated Hashimoto's thyroiditis and 41 matched healthy subjects. The primary endpoint was to evaluate the effects of L-T4, Selenomethionine, or their combination on several inflammatory markers (TNF-alpha, IL-1B, IL-6, MCP-1, IL-2, INF-G, and high sensitivity CRP). The study demonstrated that L-T4 treatment reduces monocyte release of TNF- α , IL-1 β , IL-6, and MCP-1, whereas

selenomethionine inhibits lymphocyte release of IL-2, INF-G, TNF-alpha, and plasma CRP levels. The decrease in cytokines was even strongest when both drugs were administrated together (44).

In 2011, Balazs analyzed IFN- γ -induced HLA-DR expression in cultured human thyrocytes at various concentrations of sodium selenite. Se has a dose-dependent inhibitory effect on the expression of HLA-DR and this effect shows an inverse correlation with anti-oxidative capacity, suggesting that this can be one of the mechanisms associated with the efficacy of Se supplementation in HT (45).

Finally, very recently Anastasilakis et al. described 86 patients with HT and supplemented with 200 $\mu\text{g}/\text{day}$ of Se or placebo. No changes in TSH, FT4, FT3 and TPO-Ab levels were detected in Se supplemented patients, while a significant drop in Anti-Tg level ($p=0,001$) was observed after a 6 months treatment (46).

Results on efficacy of Se supplementation in HT are still not univocal, however it seems that Se may improve the inflammatory activity in patients with HT. Such effect is more evident in areas of mild Se deficiency, but whether this effect is specific for HT or may also be effective in other endocrine autoimmune diseases has yet to be investigated.

Selenium and post-partum thyroiditis

Pregnancy is a period characterized by profound alterations in the biochemical parameters of thyroid gland and thyroid gland, on the other hand, influences the pregnancy. Thyroid autoimmunity is associated with an increased risk of miscarriage, women with elevated TPO-Ab are prone to develop hypothyroxinemia during pregnancy and thyroid dysfunction after delivery (47-49).

Recurrent abortions have been associated with lower serum Se levels (50), and during the 3rd trimester of gestation plasma Se levels drop significantly, returning to baseline after delivery with a risk, for pregnant women of Se deficiency.

Negro et al. reported the effect of Se supplementation on postpartum thyroid status in TPO-Ab positive pregnant women (51). The results indicate that Se supplementation reduced the incidence of post-partum thyroiditis and permanent hypothyroidism, and treated patients showed a significant decrease in the titer of TPO-Ab in the postpartum period, suggesting that selenium administration is effective in prevention of postpartum thyroiditis (PPT). Nevertheless, no other studies so far reported similar results and study replications are required before confirming the efficacy of Se supplementation in prevention of PPT (52).

Selenium and Graves' disease

Graves' Disease (GD), similarly to HT, is organ-specific autoimmune-inflammatory disease with a complex pathogenesis. GD is characterized by lymphocytic infiltration of the thyroid gland with the production of antibodies that bind to the thyrotropin receptor, miming the TSH action (53). The hyperstimulation of the TSH

receptor causes an increase of thyroid hormone biosynthesis with H_2O_2 overproduction. This increases ROS production and oxidative stress of the thyroid follicular cell (3). It is now a common view that H_2O_2 is implicated in the pathogenesis of GD with an imbalance of the antioxidant/oxidant status, as suggested by several authors (3, 54, 55).

In this view, adequate serum Se levels are fundamental to contrast the inflammatory processes: low serum Se levels have been reported in patients with hyperthyroidism and Graves' disease (56) being associated with the hyperthyroidism, since the administration of antithyroid drugs can increase plasma Se (34, 57). The efficacy of Se supplementation in GD has been suggested by Vrca et al., that demonstrated that patients with GD receiving in addition to methimazole also a supplementation with and antioxidant mixture of Se, beta-carotene, and vitamins C and E, led to euthyroidism faster than patients treated with methimazole alone (58).

Selenium and Graves' ophthalmopathy

Graves' orbitopathy (GO) is caused by inflammation in the orbital connective tissue leading to an enhanced adipogenesis and overproduction of glycosaminoglycans. This causes an increase in orbital volume and fibrosis of the extra ocular muscles (59). Oxidative stress is involved in the pathogenesis of GO (60) as suggested by the results of studies reporting the efficacy of antioxidant treatment in GO.

In 2000, Bouzas et al. demonstrated that 9 of 11 (82%) patients treated with oral antioxidants showed an improvement of mild to moderately severe Graves' ophthalmopathy while improvement was observed only in 3 of 11 (27%) patients in the untreated group ($P < .05$) (61).

A recent study conducted by Marcocci et al. compared the effects on GO of Se administration compared to an anti-inflammatory agent, pentoxifylline, and placebo (62). The results demonstrated that Se treatment was associated with an improved quality of life, less eye involvement and slower progression of GO, compared to placebo and to pentoxifylline. In addition, Se supplementation is associated with less side effects. The study has two limitations: the authors did not measured the effects on plasma Se concentration of Se administration, and the study was conducted in areas of moderate Se deficiency, which may potentiate the effects of Se supplementation.

In addition, no confirmatory studies have been reported, and further trials are necessary to define Se supplementation in the treatment of mild and moderate GO (60).

Conclusions

In this review the role of the trace element Se was analyzed for its effects on thyroid metabolism and diseases.

Se supplementation seems to produce benefits in the management of autoimmune thyroid disorders (Tab. 1).

Table 1 - Clinical studies using selenium supplementation in patients with autoimmune thyroid disorders.

Disease	Country	Follow-up	Study Group	Se dose	Major outcome	Author
HT	Germany	3 months	70 patients (F)	200 µg/day (Se selenite)	Drop in TPO-Ab (-63.3%)	(37)
	Germany	6 months	47 patients (F)	200 µg/day (Se selenite)	Major decrease in TPO-Ab in patients continuing supplementation	(38)
	Greece	6 months	65 patients (56 F/9 M)	200 µg/day (SeMe)	Drop in TPO-Ab (-46% at 3 months; -55,5% at 6 months)	(39)
	Turkey	9 months	88 patients (F)	100 or 200 µg/day (SeMe)	Drop in TPO-Ab, major effects with 200 µg/day	(41)
	Greece	6 + 6 months	80 patients (F)	200 µg/day (SeMe)	Drop in TPO-Ab (-20% at 12 months)	(40)
	Austria	3 months	36 patients (F)	200 µg/day (Se selenite)	No effect on TPO-Ab	(42)
	Italy	12 months	76 patients (65 F/11 M)	80 µg/day (Se selenite)	Drop in TPO-Ab	(43)
	Poland	6 months	165 patients	200 µg/day (SeMe)	Reduction in cytokines production	(44)
	Greece	6 months	86 patients (53 F/33 M)	200 µg/day (SeMe)	Drop in TPO-Ab (not significant)	(46)
PPT	Italy	Pregnancy and post partum	232 patients (F)	200 mcg/day (Seme)	Evaluation of the prevalence of PPTD and hypothyroidism	(51)
GD	Croatia	3 months	57 patients	Vitamin C and E, Beta carotene and Selenium	Attainment of Euthyroidism	(58)
GO	Italy	6 + 6 months	159 patients	200 mcg/day (Selenium)	Improvement GO	(62)

HT: Hashimoto's thyroiditis; PPT: post-partum thyroiditis; GD: Graves' disease; GO: Graves' ophthalmopathy.

Se reduces anti-thyroid antibodies levels and improves thyroid morphology at ultrasound in patients with Hashimoto's thyroiditis, the administration of Se in addition to methimazole seems to be associated

with a faster normalization of hyperthyroidism in patients with Graves' disease, and, finally, Se has been proposed as treatment for mild or moderate Graves' ophthalmopathy.

However, the story is not completely clarified yet and additional studies are required to better define doses and modality of Se supplementation.

In addition, other limitations in understanding the role of Se in thyroid autoimmune diseases are associated with the observation that intrathyroidal Se levels not directly correlate with serum Se concentrations, and, in addition, it should be considered that serum Se assay are expensive and not recommended in routine practice.

Finally, it should be considered that selenium supplementation in subjects with normal selenium levels was associated with an increased risk of type 2 diabetes, and an elevated serum selenium levels were linked to peripheral vascular disease and all-cause mortality in several population studies (20, 21, 63). Although these findings need to be confirmed, long-term selenium supplementation should not be viewed as harmless and a possibly healthy way to prevent illness, at least in patients with normal/high Se income.

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