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Selenium and the Thyroid Gland

More Good News for Clinicians

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Abstract and Introduction

Abstract

The thyroid is the organ with the highest selenium content per gram of tissue because it expresses specific selenoproteins. Since the discovery of myxoedematous cretinism and thyroid destruction following selenium repletion in iodine- and selenium-deficient children, data on links between thyroid metabolism and selenium have multiplied. Although very minor amounts of selenium appear sufficient for adequate activity of deiodinases, thus limiting the impact of its potential deficiency on synthesis of thyroid hormones, selenium status appears to have an impact on the development of thyroid pathologies. The value of selenium supplementation in autoimmune thyroid disorders has been emphasized. Most authors attribute the effect of supplementation on the immune system to the regulation of the production of reactive oxygen species and their metabolites. In patients with Hashimoto's disease and in pregnant women with anti-TPO antibodies, selenium supplementation decreases anti-thyroid antibody levels and improves the ultrasound structure of the thyroid gland. Although clinical applications still need to be defined for Hashimoto's disease, they are very interesting for pregnant women given that supplementation significantly decreases the percentage of postpartum thyroiditis and definitive hypothyroidism. In Graves' disease, selenium supplementation results in euthyroidism being achieved more rapidly and appears to have a beneficial effect on mild inflammatory orbitopathy. A risk of diabetes has been reported following long-term selenium supplementation, but few data are available on the side effects associated with such supplementation and further studies are required.

Introduction

Selenium is an essential trace mineral that was discovered in 1817 by the Swedish chemist Berzelius. Its fundamental role was established in the 1980s when it was discovered that sodium selenite supplementation prevented or reversed the clinical signs of severe selenium deficiencies, that is, chondrodystrophy (Kashin-Beck disease) and juvenile cardiomyopathy (Keshan disease).

The thyroid is one of the organs with the highest selenium content because it expresses several specific selenoproteins of which some are implicated in thyroid hormone metabolism and others play an antioxidant defence role. The link between severe selenium deficiency and thyroid dysfunction was only established in the 90s when children with iodine and selenium deficiencies in a region of Central Africa were supplemented with selenium alone, which led to thyroid destruction and myxoedematous cretinism.[1] Since then, researchers have gained a better understanding of the links between thyroid metabolism and selenium, and it has been suggested that selenium supplementation might be useful for the treatment of autoimmune thyroid disorders.

General Points

Synthesis of Specific Selenoproteins

Selenium is an indispensible trace mineral for humans because of its antioxidant and antiinflammatory properties. Selenium is present in specific selenoproteins as selenocysteine. Selenocysteine, which is essential for enzyme activity,[2] is considered to be the 21st amino acid because it is encoded by a UGA codon, which is normally a stop codon and is co-translationally incorporated into proteins by specific tRNA; that is, the ribosomes are directed to translate the stop codon as selenocysteine by a particular stem-loop mRNA structure that is located in the 3′-untranslated region. The stem-loop structure (selenocysteine insertion sequence [SECIS] element) forms part of complex including a binding protein (SBP2) and a specialized elongation factor (EFsec), which donates the selenocysteine tRNA to a vacant ribosomal site, transforming the stop codon into a selenocysteine codon.[3]

The Principal Selenoproteins and their Functions

The principal selenoproteins, including glutathione peroxidase (GPXs) (seven genes), thioredoxin reductases (TRs) (three genes) and deiodinases (three genes), are expressed in the thyroid gland in large quantities. The main function of glutathione peroxidases is to protect the body against damage caused by oxygen free radicals, with each enzyme having a specific location.[4, 5] Thioredoxin reductases play an essential role in antioxidant processes but are also implicated in the regulation of certain transcription factors (NF-K β, Ref-1, P53) and in gene expression. Finally, there are three deiodinase isoforms (D1, D2, D3) and their localization and functions vary depending on the tissues where they are found in humans ( ).[5]

Table 1. The principal selenoproteins and their functions in humans (according to Beckett GJ and Arthur JR)

Selenoproteins	Proposed functions

Gluthatione peroxidases (GPXs)	
GPX1	Cytosolic antioxidant, type of reserve?
GPX 2	Digestive tract antioxidant
GPX 3	Plasma and extracellular space antioxidant, significant thyroid expression
GPX 4	Mitochondrial membrane antioxidant, structural protein of sperm, apoptosis?
GPX 5	Unknown
GPX 6	GPX1 homologue?
Thioredoxin reductase (TRs)	Sustain the oxidation-reduction systems within the body, regulates certain transcription and cell growth factors
TR1	Principally cytosolic, ubiquitous
TR2	Testes expression
TR3	Principally mitochondrial, ubiquitous
Deiodinases	
Type 1 deiodinase (D1)	Conversion of T4 into T3 and rT3, and T3 into rT3 or T2 Localisation: liver, kidneys, thyroid gland, pituitary gland
Type 2 deiodinase (D2)	Conversion of T4 into T3, and T3 into T2 Localisation: thyroid gland, CNS, pituitary gland, skeletal and heart muscles
Type 3 deiodinase (D3)	Conversion of T4 and T3 into rT3 and T2 Localisation: gravid uterus, placenta, foetal liver, foetal and neonatal brain, skin of newborns
Other selenoproteins	
Selenoprotein P	Transportation of selenium, endothelial antioxidant
Selenoprotein W	Heart and skeletal muscle antioxidant
Selenophosphate synthetase	Synthesis of selenophosphate for selenoproteins
15-kDa selenoprotein	Protection against cancer?
Selenoproteins H, I, K, M, N, O, R, S, T, V	Function unknown

Selenium Sources and Recommendations

Proteinaceous foods (meat, fish, shellfish, offal, eggs, cereals, etc.) are the richest in selenium, but bioavailability of the selenium they contain is variable, i.e. 20–50% for seafood against more than 80% for cereals or brewer's yeast. However, the selenium content of cereals is highly dependent on the selenium content of the soil where they are grown. The soils of most European countries have a low selenium content, which explains the mild to moderate selenium deficiencies observed in Europe compared to North America where the selenium content of the soils is high. Severe deficiencies causing *myxoedematous cretinism* are observed in large parts of Central Asia.

Standard plasma selenium concentrations range between 60 and 120 µg/l or 0·8 ± 0·36 µmol/l. Indeed, plasma selenium concentration is related to dietary selenium, whereas selenoprotein P reflects selenium stocks in the body and appears a better marker of selenium status.[6] It is not recommended to carry out plasma selenium assays in routine practice because true selenium deficiencies are rare and essentially related to severe undernourishment or to the daily ingestion of very low doses due to geographic location. However, plasma assays may be useful to screen for patients in whom supplementation should be undertaken with caution or even avoided. In a cancer prevention study, an increase in the risk of type 2 diabetes was reported in patients long-term treated (average of 7·7 years) with 200 µg of selenium per day (relative risk of 2·7 compared with placebo).[7] The diabetogenic effect mainly affected patients whose plasma selenium concentrations were in the upper third of the normal range.

Thus, daily dose recommendations vary from one country to another, i.e. 55 µg/day in the United States, 75 µg/day for men and 60 µg/day for women in England, 1 µg/kg/day in France. In any event, doses should not exceed 400 µg/day[8] and may require decreasing if the potentially harmful effects of selenium are confirmed metabolically.

Very little information is currently available on the chemical nature of selenium contained in food. Selenomethionine has been identified as a major component of certain cereals (wheat, soybeans), yeasts and meat. Inorganic selenium (sodium selenite, selenate) has been identified in drinking water in small amounts. It is also used in food supplements. The bioavailability of sodium selenite is excellent, and it is used directly for the synthesis of specific selenoproteins. Given that synthesis is highly regulated, the

risk of acute intoxication is only associated with very high doses (1000 µg/day).[9] The clinical signs of intoxication are asthenia, gastrointestinal disorders such as diarrhoea, bronchial or skin irritation, or hair loss and nail discoloration. Conversely, selenomethionine is not directly available for the synthesis of specific selenoproteins but is nonspecifically incorporated into proteins, essentially selenoalbumin, depending on its source. Metabolism of these nonspecific selenoproteins releases selenium, which may then be used for the synthesis of specific selenoproteins.[10] Use of selenomethionine appears to be safer and devoid of direct toxicity, even at high doses.[11]

Essential Role of Selenium in the Physiology of the Thyroid

Selenium: Its Role in the Synthesis of Thyroid Hormones

Synthesis of thyroid hormones requires iodination of thyroglobulin at the apical pole, in the follicular lumen under the action of thyroperoxidase (TPO) and in the presence of hydrogen peroxide (H_2O_2) (Fig. 1). Synthesis of H_2O_2, potentially dangerous for thyrocytes, is regulated by TSH via a complex system of second messengers[12] and appears to be the step that limits thyroid hormone synthesis when sufficient iodine is available. This organization enables the H_2O_2 formed at the surface of thyrocytes to be rapidly used for iodination reactions, while the intracellular H_2O_2 is degraded by antioxidant enzymes such as GPXs, TRs and catalases.[12]

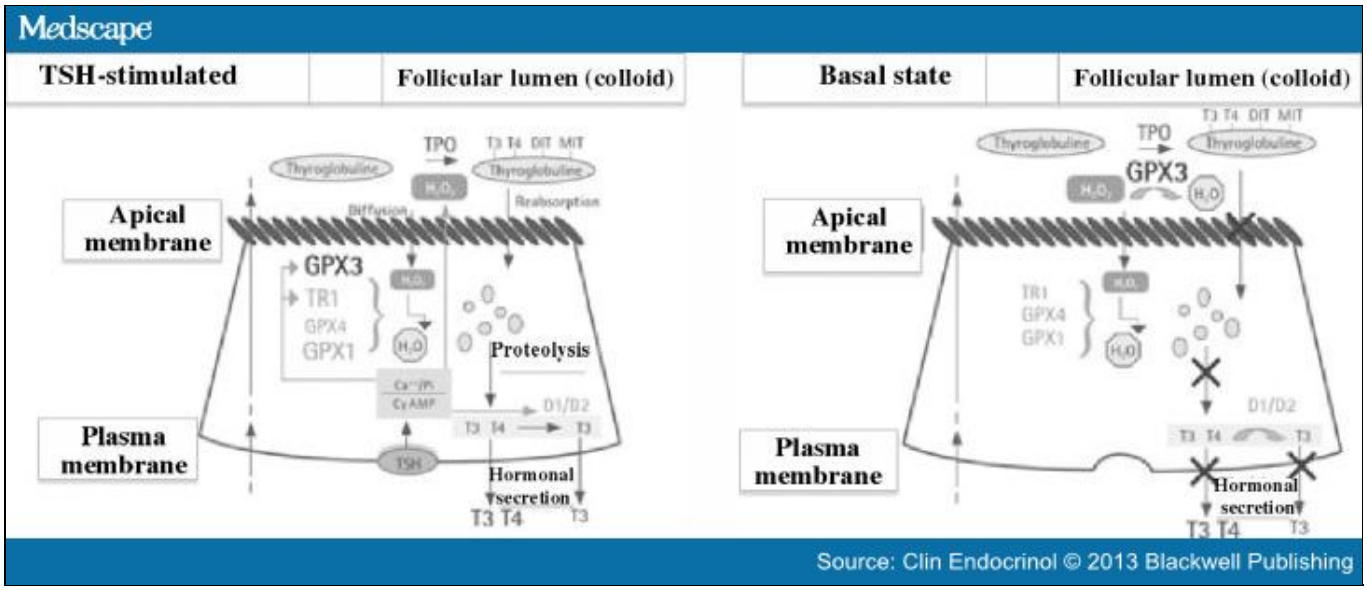

Figure 1.

Role of specific selenoproteins in the synthesis of thyroid hormones in humans (adapted from Beckett GJ and Arthur JR).

Role of GPX3 In human thyrocytes, GPX3 (extracellular or plasmatic GPx) is one of the selenoproteins that is the most expressed and consequently, it contributes to the high selenium content of the thyroid.[10] It appears to be a direct regulator of thyroid hormone synthesis.

In the absence of TSH, GPX3 secretion at the apical pole of the thyrocyte decreases the amount of H_2O_2 available for iodination reactions. Conversely, in the presence of TSH, which is responsible for increased calcium ionophore levels, the decrease in GPX3 at the apical pole results in more H_2O_2 being available for TPO. GPX3 concentrations thus increase within the thyrocytes, thereby increasing the protection against oxidative stress induced by the synthesis of thyroid hormones (Fig. 1).[5]

Role of the Deiodinases Only D1 and D2 have been identified in human thyrocytes.[13] The expression of deiodinases in different tissues varies depending on the species, which makes it difficult to extrapolate the results of animal studies to humans. While less expressed than GPX3, D1 and D2 are responsible for the local activation of thyroid hormones. Although many mechanisms regulate the synthesis of deiodinases (TSH, thyroid hormones, cyclic AMP), selenium content also directly affects their activity,[14, 15] and therefore, indirectly affects T3 synthesis. Selenium distribution in tissues is variable and selenoprotein synthesis is priortorized based on sources. Deiodinases appear to occupy a special place in the hierarchy in cases of selenium deficiencies thanks to the existence of a selenium accumulation and/or redistribution system in the thyroid gland.[16] More specifically, D2 and D3 appear to be more readily preserved than D1, but with organ-dependant particularities.[17, 18]

Several mechanisms appear to be implicated in the maintenance of the synthesis of various selenoproteins in cases of deficient intake. So far, two distinct types of stem-loop structures (SECIS) have been identified in the 3′ region of mRNA encoding selenoproteins, with each very probably displaying different features at the time of translation of specific mRNA.[19] Although no

particular affinities have been identified *in vivo* between the SBP2-binding protein (indispensible to translation) and either of the two SECIS variants, special interactions have been identified between SBP2 and the SECIS structures of GPX4 or selenoprotein P.[20] Furthermore, mRNAs encoding selenoproteins have different half-lives, particularly in cases of selenium deficiency.[21]

Finally, variable and relative contents of selenoproteins in cells and tissues also contribute to hierarchizing synthesis: deiodinases expressed at very low concentrations may recruit and use the selenium released during turnover of the selenoproteins present in much higher concentrations such as GPX1 or selenoprotein P. These two selenoproteins therefore represent a stock of accessible selenium in cases where intake is reduced.[25]

Selenium as an Antioxidant

Selenoproteins play a role in the regulation of the immune system. The role GPXs play in the maintenance of cell integrity and protein iodination has been clearly demonstrated, namely through the use of thyrocyte cultures of animal origin.

In pigs, selenium deficiency causing a decrease in intracellular GPX activity leads to cytoplasmic iodination of proteins following exposure to H_2O_2, whereas when sufficient selenium is available, iodination is limited to the apical pole of the thyrocytes.[12] Thus, alteration of the defence mechanisms used to fight the oxidative stress related to selenium deficiency results in aberrant iodination of certain proteins leading to cell apoptosis or the exposure of unusual epitopes possibly recognized by the immune system. In cultures of human thyroid follicles, apoptosis is induced by high doses of d' H_2O_2, iodine or TGF-β. Preincubation with low doses of selenium increases GPX activity and reduces cell death.[22]

Selenium and Thyroid Diseases

Myxoedematous Cretinism

The first clinical data establishing a link between selenium levels and thyroid metabolism were collected in Central Africa. The prevalence of myxoedematous cretinism is very high in this region where the population suffers from severe iodine and selenium deficiencies. Myxoedematous cretinism is characterized by the persistence of hypothyroidism despite supplementation with iodine alone.[23] Physical examination of subjects shows the thyroid gland to be firm and atrophic, suggestive of cell damage and secondary fibrosis. Conversely, selenium supplementation without prior iodine repletion may aggravate hypothyroidism and may even result in myxoedematous coma,[1] which suggests that selenium deficiency may play a protective role in subjects with combined iodine and selenium deficiency.

Several hypotheses can explain the pathogenesis of myxoedematous cretinism. Iodine deficiency leads to increased production of H_2O_2 through an increase in TSH, and selenium deficiency results in a decrease in GPX activity, namely GPX3. The excess of H_2O_2 cannot be neutralized by GPXs resulting in cell destruction and fibrosis due to macrophage infiltration. The macrophages synthesize TGF-β, which blocks the proliferation of epithelial cells and stimulates that of fibroblasts. These pathogenic mechanisms seem to commence shortly after birth and lead to the total destruction of the thyroid gland over a few years. In parallel, the activity of type 1 and type 3 deiodinases decreases, which reduces the turnover of the thyroid hormones, and limits loss of iodine through the urine. Conversely, hypothyroidism increases the activity of type 2 deiodinase, namely in the brain, thereby maintaining local production of sufficient T3 (at least during the prenatal and early postnatal periods), which is indispensible for neurological development. Thus, selenium repletion without prior iodine repletion aggravates the consequences of iodine deficiency.[24]

Similar iodine and selenium deficiencies may be observed in other regions of the world, namely in Tibet and China, but they are not associated with a high prevalence of myxoedematous cretinism. Additional environmental factors appear to promote thyroid disorders such as thiocyanate intake related to the consumption of manioc.[25] This worsens the iodine deficit because of competition between iodine and the iodine symporter or TPO.

Selenium and Thyroid Metabolism

Several studies have assessed the impact of selenium repletion on thyroid function in different population groups from industrialized countries ( ).[26] Selenium supplements between 10 and 300 µg/day were administered on a daily basis to populations in good apparent health over 3 months,[27] 5 months,[28, 29] 6 months[30] or 12 months.[31] In some of the studies, the subjects had selenium deficiencies;[32–34] while in others, they did not.[34–36]

Table 2. Impact of selenium repletion on thyroid metabolism in controlled, randomised clinical trials carried out in industrialised countries (according to Hess SY *et al*.)

Reference of the study	Characteristics of the study population	Study duration	Groups studied and sample sizes	Final levels of total T4 (nmol/l)a	Final levels of TSH (mUl/l)	Final levels (or change/start of study) of plasma selenium levels (µg/l)	Final levels of plasma erythrocyte GPX levels (Ul/g Hb)

Olivieri *et al*.[27] 1995 Italy	Elderly subjects in good health (86 years ± 7)	3	Placebo = 17 100 μg Se/day = 19	68·5 + 10·4 62 + 10 (*P* < 0·005)	0·99 + 0·71 1·18 + 0·58 (NS)	60·0 + 15·8 105·8 + 23·7 (*P* < 0·05)	4·1 + 1·1 7·78 + 2 (*P* < 0·05)
Rayman *et al*.[30] 2008 England	Elderly subjects in good health (60–74 years)	6	Placebo = 90 100 μg Se/day = 99 200 μg Se/day = 95 300 μg Se/day = 84	87·2 + 18 87·0 + 16·4 83·5 + 14·5 81·6 + 14·4 (NS)	1·23 + 0·72 1·23 + 0·70 1·27 + 0·69 1·18 + 0·69 (NS)	−2·6 (95% CI: −5·9 to 0·6) 54·9 (95% CI: 49·5–60·4) (*P* < 0·001) 99·0 (95% CI: 91·6–106·4) (*P* < 0·001) 133·2 (95% CI: 123·1–143·3) (*P* < 0·001)	ND ND ND ND
Duffield *et al*.[28] 1999 New Zealand	Selenium-deficient adult subjects (19–59 years)	5	Placebo = 10 10 μg Se/day = 10 20 μg Se/day = 11 30 μg Se/day = 10 40 μg Se/day = 11	99 + 30 93 + 10 (*P* < 0·05) 88 + 15 (NS) 90 + 17 (NS) 89 + 19 (NS)	ND ND ND ND ND	66·3 + 12·6 83·7 + 17·4 (*P* < 0·005)	ND ND ND ND ND
Thomson *et al*.[29] 2005 New Zealand (Study A)	Selenium-deficient adult subjects (19–52 years)	5	Placebo = 30 100 μg Se/day = 30	91 + 32 98 + 33 (NS)	ND ND	79·7 + 12·6 105·0 + 11·8 (*P* < 0·001)	ND ND
Thomson *et al*.[29] 2005 New Zealand (study B)	Healthy adults (18–65 years)	5	Placebo = 81 200 μg Se/day = 82	88 + 23 84 + 22 (NS)	ND ND	90 + 14·2 172·9 + 23·7 (*P* < 0·001)	ND ND
Hawkes *et al*.[31] 2008 United States	Men (18–45 years)	12	Placebo = 20 300 μg	92 + 18 92 + 22 (NS)	2·21 + 1·1 2·0 +	ND ND	ND ND

			Se/day = 22		0·9 (NS)		

[a] To convert total T4 to pmol/l (total T4 in nmol/l × 1000).

Four studies demonstrated a significant increase in plasma selenium levels in subjects benefiting from selenium repletion compared with the control group. However, only two studies demonstrated changes in thyroid hormone concentrations and/or in TSH levels.

The first study[27] that included a small number of elderly subjects in good health showed a significant decrease in T4 levels in the group given 100 µg of selenium per day for 3 months compared with the control group. In another study, the same author demonstrated that the elderly euthyroidal subjects presented with disrupted thyroid parameters with a decreased T3/T4 ratio, higher TSH values that were associated with a decrease in plasma selenium levels and erythrocyte GPX activity.[32] In reality, the abnormalities appear to be related to a decrease in peripheral deiodinase activity and therefore to decreased T3 production. Similar results were observed in phenylketonuric subjects,[33] in patients with cystic fibrosis[34] or in subjects nourished exclusively by the parenteral route[35] and who are at a risk of selenium deficiency due to restricted or inadequate protein intake.

In the second study that included patients aged between 60 and 90 years presenting with low plasma levels of selenium, subjects were supplemented with 10–40 µg of selenium per day for 5 months.[28] Plasma concentrations of selenium increased in all supplemented groups. Levels of T4 decreased in all the groups, but the decrease was only significant in the group receiving 10 µg of selenium per day or when the results of all the groups were combined and compared with the control group.

Other studies found no significant changes in thyroid parameters in elderly subjects in good health following selenium supplementation,[36] particularly the study by Rayman *et al*.[30] The authors assessed the effects of selenium repletion with different doses of selenium (100, 200 and 300 µg/day) in a population of 501 elderly euthyroidal subjects over a 6-month period. No changes in thyroid function (TSH concentration, total T4, free T4, total T3, free T3, total T3/T4 ratio, free T3/T4 ratio) were observed in the subjects receiving supplementation compared with the control group despite an increase in the plasma levels of selenium. It should be noted, however, that no significant selenium deficiencies were observed following assay of plasma levels of the patients prior to inclusion in the study (91 µg/l). Similarly, other authors found no change in thyroid parameters following selenium supplementation in deficient[29] or nondeficient populations.[31]

Thus, clinical data concerning the effects of selenium intake on thyroid function have not demonstrated a clear link between deiodinase expression and activity and selenium status. Finally, only very severe selenium deficiencies appear to affect thyroid function, and namely T3 synthesis. These clinical observations are consistent with fundamental data showing that small selenium concentrations are sufficient for satisfactory deiodinase expression.

Selenium, Goitres and Nodules

In addition to the role it plays in the metabolism of thyroid hormones, selenium appears to have an impact on thyroid volume. In children with a goitre living in areas where there are iodine and selenium deficiencies, iodine repletion alone does not reduce the volume of the goitre and does not improve thyroid function. In reality, the more severe the selenium deficiency, the less iodine supplementation helps to reduce thyroid volume.[37] In the French SUVIMAX study, the correlation between thyroid volume and selenium status was only established in women. So far, the molecular mechanism making women more sensitive to low selenium intake has not been elucidated.

Recently, Rasmussen *et al*.[38] published the results of a study on the correlations between selenium status, thyroid volume and nodule formation. Similarly to the French SUVIMAX study, the population presented with moderate iodine deficiency. A negative correlation was found between thyroid volume and plasma selenium levels, but the result was only statistically significant for the general population or for subjects supplemented with iodine. Therefore, the effect of selenium status on thyroid volume does not appear to be related to iodine deficiency. Finally, in the study, low plasma selenium concentrations were correlated with a risk of formation of multiple nodules over 10 mm in size, but did not impact the risk of development of solitary nodules. Similarly, Samir *et al*.[39] found low plasma selenium concentrations in 22 subjects presenting with multinodular goitre compared with a control group of 15 subjects. Conversely, Derumeaux *et al*.[40] did not find that the global risk of developing nodules was increased in selenium-deficient patients.

There are numerous hypotheses relating to the molecular mechanisms responsible for the increase in the risk of development of a goitre and nodules in selenium-deficient patients and they mainly concern GPX abnormalities.

Selenium and Thyroid Cancer

It is difficult to formally establish a link between selenium and thyroid cancer based on current data. The 'Janus Serum Bank' Norwegian study demonstrated a reverse correlation between the incidence of thyroid carcinomas and plasma selenium

concentrations.[41] Moreover, tissue concentrations were lowest in patients presenting with cancer.[42] Thus, the decrease in plasma or thyroid selenium concentrations appears to lead to defence mechanism and cell protection changes, particularly in the presence of activating mutations of the RAS oncogene, mutations which appear to be the cause of the increased production of reactive oxygen species.[43]

Selenium and Autoimmune Thyroid Diseases

Chronic Lymphocytic Thyroiditis

Chronic lymphocytic thyroiditis (CLT) is the most commonly observed autoimmune thyroid disease in cases where iodine supply is sufficient. Genetic predisposition or certain environmental factors including selenium deficits appear to be implicated in the pathogenesis of the disease.[44, 45] Between 2002 and 2007, six prospective studies carried out in countries where selenium supply was lower than the normal limit assessed the effects of systematic selenium supplementation in patients with CLT.[46] In all studies, patients received levothyroxine substitution therapy so their TSH levels were within normal limits. Selenium was administered as selenomethionine or as sodium selenite at the dose of 200 µg/day for 3–12 months.

All the studies[48–50] except one[47] demonstrated a significant decrease in anti-TPO antibody levels at 3 months. Continued supplementation led to an additional decrease of anti-TPO antibody titres at 6 months,[49, 50] 9 months[51] and 12 months[52] (Fig. 2). Recently, a study carried out in patients presenting with Hashimoto's thyroiditis with normal T4 levels and normal or slightly elevated TSH levels because of the absence of levothyroxine therapy demonstrated a significant decrease in anti-TPO antibody levels following 12 months supplementation with sodium selenite administered at physiological doses (80 µg/day).[53] It should be noted that the decrease in anti-TPO antibody levels was more important the higher their initial titre. In fact, Karanikas *et al*.[54] demonstrated a correlation between anti-TPO antibody levels and the production of inflammatory cytokines by thyroid lymphocytes, suggesting that the efficacy of selenium could be more marked during episodes of inflammation.

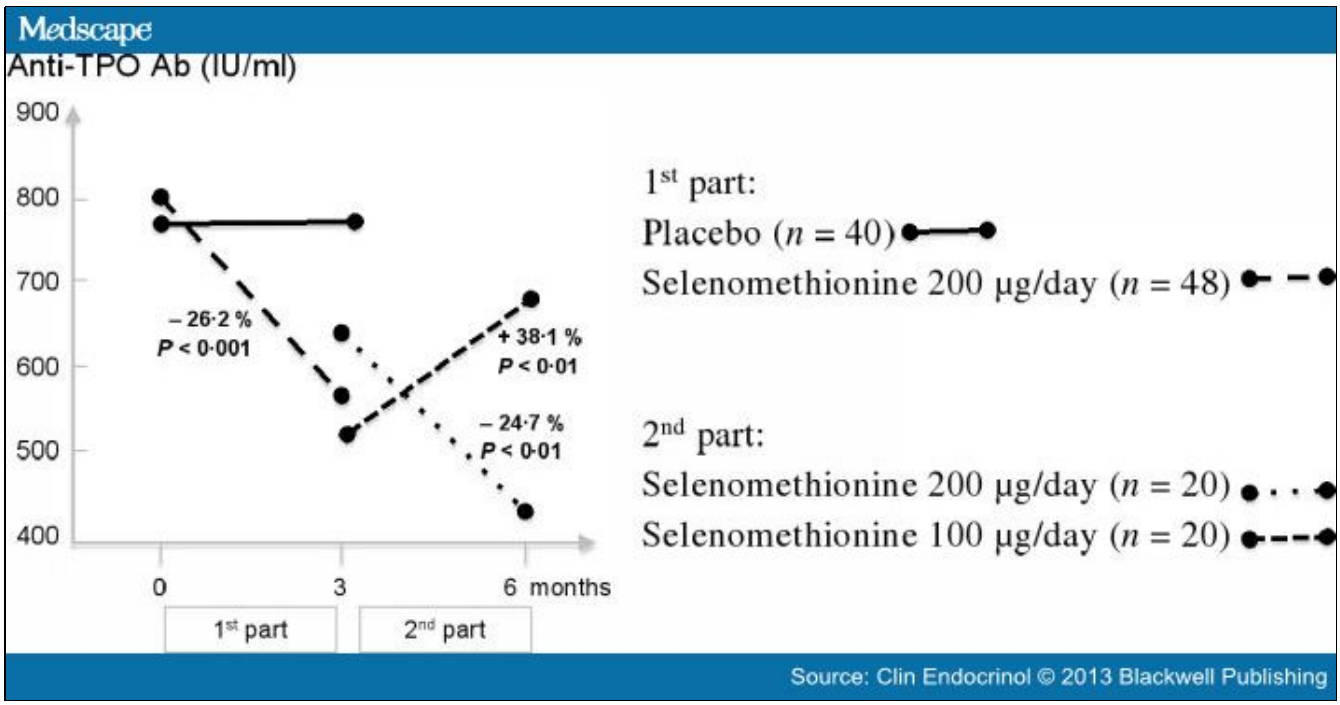

Figure 2.

Changes in anti-TPO antibody titres following selenium supplementation in patients presenting with chronic lymphocytic thyroiditis. The second part of the study, only included patients previously treated with selenium (according to Turker *et al*.).

Only one study demonstrated improvement in thyroid gland ultrasound structure in patients whose anti-TPO antibody levels had decreased to below 50 mUI/l,[48] with no hormonal changes (TSH, T4, T3) or changes in treatment with levothyroxine being observed. Finally, smoking has been identified as a resistance factor to selenium supplementation.[52]

On discontinuation of selenium supplementation, one study found that antibody levels increased to their initial levels after 3–6 months,[51] while another study found that the antibody levels remained stable.[52] In three studies, supplemented patients reported improved well-being, independently of the effect on anti-TPO antibodies. The positive effect appears to be related to a direct effect of selenium on cerebral and cognitive functions. Safety was found to be excellent in most patients except in a few rare cases where gastrointestinal disorders were reported.

Most authors consider that selenium affects the immune system through regulation of the production of the reactive oxygen species and their metabolites. Selenium supplementation appears to reinforce intrathyroidal GPX and TR activity, probably by increasing the concentration of selenium within the thyroid.[49] Recent data have also shown that a link exists between selenium and immune cells, namely T cells. Xue *et al*.[55] demonstrated a significant reduction in antithyroglobulin antibodies associated with decreased lymphocyte infiltration of the thyroid following selenium supplementation of mice with iodine-induced autoimmune thyroiditis. Finally, other data seem point to the participation of other selenoproteins, namely in macrophages. In mice with the tRNA (Ser) Sec gene specifically deleted in myeloid cells, aberrant migration of macrophages is observed, which perturbs the maintenance of tissue integrity in the body.[56]

Thus, the beneficial effects of selenium on thyroid autoimmune parameters appear to be interesting but currently, very few data are available on clinical applications. It is indispensible to carry out new studies assessing changes in levothyroxine dosages, thyroid ultrasound or cytologic and even histologic data to determine the efficacy of selenium supplementation in prevention and reversal of thyroid damage. Similarly, it would be interesting to be able to establish a relationship between the efficacy of selenium treatment, the initial titre of anti-TPO antibodies and/or early supplementation with respect to disease onset.

Autoimmunity and Pregnancy

Fifty per cent of women with anti-TPO antibodies are at a risk of developing postpartum thyroiditis in the 1st year after delivery and among them, 40% develop definitive hypothyroidism. In a prospective, randomized, placebo-controlled study, Négro *et al*.[57] studied variations in thyroid, ultrasound and autoimmune parameters in pregnant women with or without selenium supplementation.

The plasma selenium levels of all the women were in the lower range of normal at inclusion. Three groups were studied from the 10th week of amenorrhoea until the end of the 1st year postpartum: 77 TPO-positive women were given 200 µg/day of selenomethionine (group S1), 74 TPO-positive women did not receive supplementation (group S0) and a control group of TPO-negative women (group C) did not receive supplementation. During pregnancy, a significant decrease in anti-TPO antibodies was observed in both test groups, but the decrease was higher in the S1 group (62·4%) compared with the S0 group (43·9%) ($P < 0·01$). In the postpartum period, an increase in anti-TPO antibody titres was also observed in both groups, but the mean level and peak were lower in group S1 compared with group S0. During pregnancy, as many women in the S1 group (19·4%) as in the S0 group (21·6%) were treated with levothyroxine (mean dose of 52 µg/day, identical for both groups). Only 2·5% of the women in C group required levothyroxine. Ultrasound monitoring showed that the thyroid appearance remained stable in the S1 group throughout follow-up while marked degradation was observed in the S0 group. Postpartum thyroiditis was observed in 28·6% of patients from the S1 group of which 11·7% developed definitive hypothyroidism at the end of the study *vs* 48·6% in the S0 group, of which 20·3% developed definitive hypothyroidism. Thus, the percentage of patient presenting with postpartum thyroiditis and permanent hypothyroidism was significantly lower in the S1 group compared with the S0 group ($P < 0·01$ and $P < 0·01$, respectively). These study results are the first to demonstrate the clinical benefits of selenium supplementation in pregnant women presenting with thyroid autoimmunity.

Graves' Disease

Several studies have demonstrated an increase in oxidative stress during Graves' disease related to increased production of reactive oxygen species (excessive consumption of ATP and oxygen). Guerra *et al*.[58] found that urinary excretion of malondialdehyde content was increased in patients with hyperthyroidism compared with control subjects. Treatment with antithyroid drugs corrects these symptoms.[59]

In Graves' disease, the balance between intracellular and extracellular oxidants and antioxidants appears to be disturbed. Despite an increase in intracellular antioxidant enzymes such as GPX1 or TRs,[60] there is an overall decrease in the activity of GPXs[61] and other enzymes (superoxide dismutase, catalase)[59] or molecules (vitamin E, coenzyme Q10).[62] Based on these findings, several authors decided to study the benefits that could potentially be derived from selenium supplementation in patients with Graves' disease. Bacic-Vrca *et al*.[63] compared the efficacy of treatment with methimazole *vs* methimazole and a set combination of antioxidants (vitamin E, C, β carotene and selenium at the dose of 60 µg/day) in subjects presenting Graves' disease. The study was conducted in Croatia, a country where nutritional selenium levels are among the lowest in Europe. Plasma selenium concentrations increased in subjects receiving selenium and erythrocyte GPX activity increased in both groups, but significantly more markedly in the methimazole and antioxidant group (at day 30 and day 60). Finally, euthyroidal status was attained more rapidly in the methimazole and antioxidant group. A more recent study compared plasma selenium concentrations in Graves' disease patients in remission or with persistent or recurrent disease following discontinuation of treatment with antithyroid drugs. Although no significant differences were observed, it was in the group of patients in remission that selenium levels were the highest (>120 µg/l), and a negative correlation was demonstrated between TSH antireceptor antibody and plasma selenium levels in this group.[64] These data have boosted the interest for the 'selenium analogues' of synthetic antithyroid drugs. The first of these, methylselenoimidazole, was developed about 15 years ago,[65] but it was found to be less effective in terms of *in vivo* iodination inhibition than methimazole.[66] Other molecules offering new treatment perspectives are currently being developed.[67]

Graves' Orbitopathy

Orbitopathy is a common complication of Graves' disease. It may be severe, requiring treatment with glucocorticosteroids, radiotherapy or surgery, or more moderate and treated symptomatically (eye drops, sunglasses), but without really improving the patients' comfort.

A recent study of the EUGOGO (European Group of Graves' Orbitopathy) assessed the effects of selenium (sodium selenite, 200 µg/day) for the treatment of patients with mild inflammatory orbitopathy.[68] The randomized, double-blind, placebo-controlled study lasted 12 months (6 months of treatment and 6 months follow-up) and included 159 patients. The primary end-points at 6 and 12 months were assessed based on a full eye examination and on orbitopathy-specific quality of life questionnaire scores. Secondary end-points were assessed using Graves' orbitopathy clinical activity and severity score.

At 6 months, compared with placebo, selenium significantly improved the patients' quality of life ($P < 0{\cdot}001$), decreased eye lesions ($P = 0{\cdot}01$) and significantly slowed orbitopathy progression ($P = 0{\cdot}01$). More than 70% of patients treated with selenium reported an improvement in quality of life *vs* 22% of patients receiving placebo. Orbital lesions were improved in 61% of patients receiving selenium *vs* 35% of patients treated with placebo. They worsened in 7% of patients treated with selenium *vs* 26% of patients receiving placebo (Fig. 3).

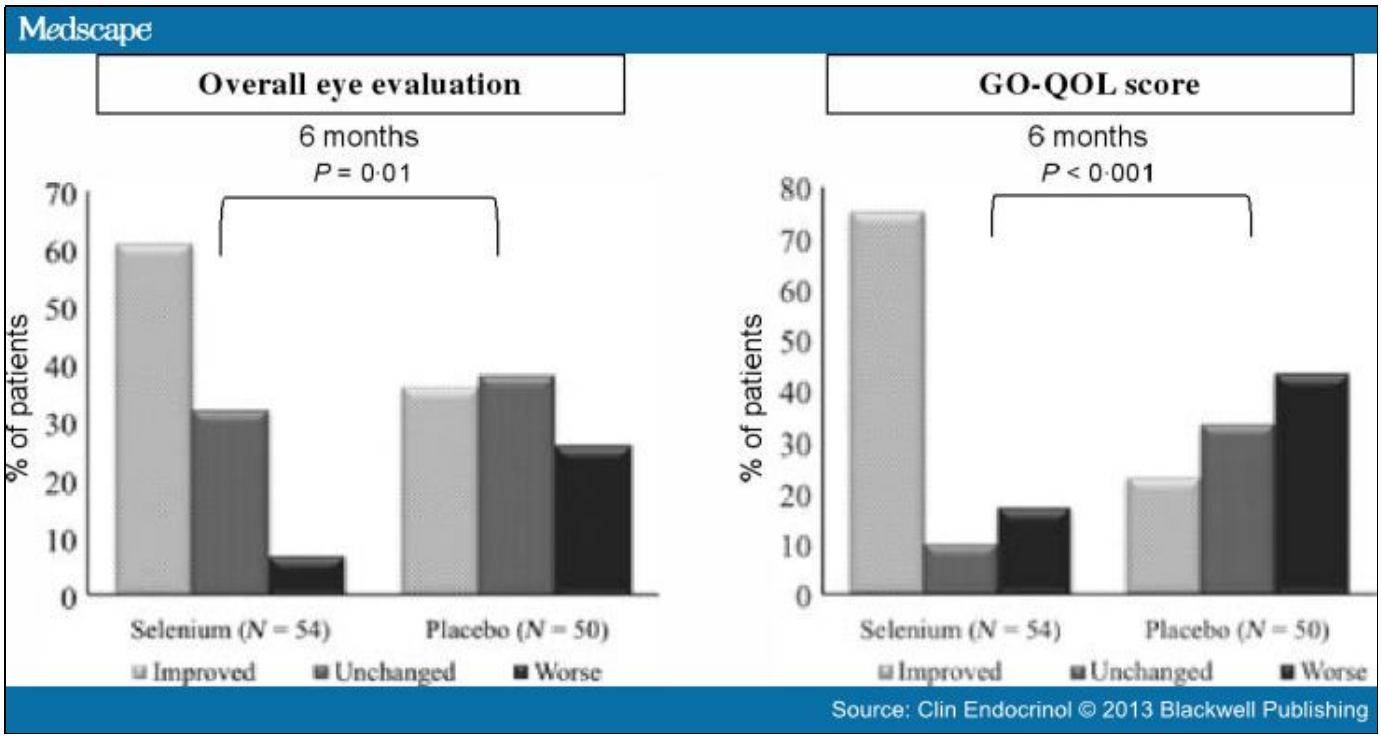

Figure 3.

Comparison of the effects of selenium (200 µg/day for 6 months) with placebo in the management of patients with mild to moderate Graves' orbitopathy (modified from Marcocci C *et al*.).

The clinical activity score decreased in all groups, but more significantly in the patients treated with selenium. The 12-month results were similar to the 6-month results. No side effects were observed in any of the 54 patients treated with selenium.

It should be noted, however, that in this study, plasma selenium concentrations were neither determined before supplementation nor during the study, which limits result interpretation. Most patients included were from selenium-deficient areas, which might explain the supplementation benefits observed. However, very little information was provided on the smoking habits of the patients.

Conclusion

Selenium is an essential trace mineral. It is the active centre of many selenoproteins implicated in antioxidant defence mechanisms, thyroid metabolism and the immune function.

Several studies have demonstrated the benefits of selenium supplementation in the management of autoimmune thyroid disorders. In Hashimoto's disease, selenium supplementation appears to potentiate the activity of selenoproteins, thereby decreasing local inflammatory reactions, which decrease anti-TPO antibody production and improves thyroid morphology. In Graves' disease, administration of selenium could help to promote euthyroidism and appears to have a beneficial effect on the development of at least moderate or mild orbitopathy.

Several points, however, need clarification. Plasma or serum selenium concentrations do not reflect intrathyroid concentrations, and assay of selenium levels is therefore not recommended in routine practice. It is indispensible to identify a reliable marker of thyroidal selenium status or thyroidal oxidative stress to backup the value of selenium supplementation in the management of thyroidal disorders and so that treatment doses and durations may be better defined. Furthermore, treatment cost/benefit studies must also be performed on a larger scale.

Currently, progression of Hashimoto's disease cannot be avoided but levothyroxine treatment is perfectly tolerated and inexpensive. Selenium supplementation can only be considered as an option and justified if, at the lowest cost, it truly improves the quality of life of patients by the selenium itself stopping or slowing down thyroid destruction.

The same applies to postpartum thyroiditis. However, the expected benefits of selenium supplementation appear to be superior in indications such as Graves' disease or Graves' orbitopathy as current treatment options for these disorders are sometimes ineffective, insufficient or poorly tolerated.

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