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REVIEW ARTICLE

Search for relevant indications for selenium supplementation in thyroid diseases

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Abstract

Selenium plays a significant role in the thyroid function and its deficiency is considered by some authors to be a cause of thyroid disorders. The potential therapeutic influence of selenium supplementation in thyroid disease was investigated in several studies and some results were encouraging, however results were inconsistent and did not allow conclusion to be drawn. For that reason, we have performed a review study on relevance of selenium supplementation in thyroid disease. Till now, there is no strong evidence that selenium supplementation leads to clinical improvement in the course of autoimmune thyroiditis, nodular goitre or thyroid cancer. On the other hand, there is some evidence that selenium is effective in the treatment of orbitopathy; thus, the European Group on Graves' Orbitopathy (EUGOGO) recommends selenium administration in mild active orbitopathy.

ROLE OF SELENIUM IN THE THYROID GLAND

Intracellular selenium is embedded in several peptides and proteins, mainly in selenomethionine and selenocysteine. Selenoproteins have various functions. So far, about 25 selenoproteins were described (Dharmasena 2014). The most important selenoproteins belong to glutathione peroxidase, thioredoxin reductase and iodothyronine deiodinase families.

Selenoproteins of iodothyronine deiodinase family contribute to thyroxine (T4) to triiodothyronine (T3) conversion, thereby controlling thyroid hormones concentration at the cellular level (Beckett and Arthur 2005). The deiodinase enzymes are dimeric integral membrane proteins with single transmembrane segments and large globular heads. They have active site including the rare selenocysteine amino acid and two histidine residues. In thyrocytes the deiodinase (DIO) isoenzymes (DIO1, DIO2, in contrast to DIO3) are all expressed and play particularly important roles. The DIO1 and DIO2 activate T4 by transforming it into T3 – by removal of iodine atom from external ring (5' position), while DIO1 and DIO3 prevent T4 from being activated by converting it to the inactive reverse T3, by disconnection of an iodine atom from the inner ring (5 position). Furthermore, DIO3 also inactivates T3 by 5-deiodination to T2. Outside the thyroid, DIO2 is mainly responsible for the local conversion of T4 to T3 in target tissues. DIO3 is found in fetal tissues, the placenta and central nervous system, where it pro-

tects sensitive cells from toxic concentration of active T3 (Kohrle *et al.* 2005).

Oxidative reactions, producing free radicals, occur at certain level in all biological structures and they are indispensable for numerous physiological processes. However, when free radicals are in excess, they can damage biological macromolecules such as DNA, lipids and proteins (Sagan *et al.* 2015). Selenoproteins of glutathione peroxidase and thioredoxin reductase families protect lipids, lipoproteins and DNA from destructive impact of free radicals (Kieliszek and Błażejak 2013). Glutathione peroxidases are responsible for thyroid protection, since they remove the excess of oxygen free radicals produced during normal synthesis of thyroid hormones (Schomburg 2011). In glutathione peroxidase, selenium is located in the catalytic site, being an essential component of antioxidant action of the enzyme (Schomburg 2011).

Recently, the physiological role of P and W families of selenoproteins has been elucidated. Selenoprotein P – that contains 60% of selenium present in plasma – acts as a transporting protein for selenium; in turn, selenoprotein W plays a role in antioxidative processes in muscles (Mehdi *et al.* 2013).

Additionally, selenium is involved, *via* variable selenoproteins in anti-inflammatory processes. Selenium enhances CD4+/CD25 FOXP3 and T regulatory cells activity while suppressing cytokine secretion, thus preventing apoptosis of cells including the thyroid follicular cells and providing protection from thyroiditis (Duntas 2015).

The data presented above confirm significant role of selenoproteins in antioxidative, endocrine and immune processes, as well as in regulation of inflammatory processes. Because of possible relevant role of selenium in the thyroid function and its implication into thyroid disorders pathogenesis, several authors tried to elucidate the problem in question. Although some results are encouraging, findings are inconsistent.

NATURAL SOURCES OF SELENIUM

The state of selenium supply is difficult to assess by analyzing only consumption of selenium-rich products. This is due to the influence of many factors on the presence of selenium in the food chain. The selenium content in the soil is not uniform, moreover there are other factors that affect the concentration of selenium in various foods, such as soil pH, rainfall, land formation or microbial activity. Therefore, evaluation of the selenium intake only on the basis of the consumption of the selenium containing products in the population may be unreliable.

The richest source of selenium are Brazil nuts – however they should not be recommended as a basic dietary source of selenium due to highly variable concentration of this element (0.03 to 512 mg/kg of fresh nuts) and due to high barium accumulation. Other selenium rich products include meat, seafood, and cereals. Selenium deficiency has been associated with consumption of eggs, white rice, alcohol, coffee, smoking and with advanced age (Park *et al.* 2011).

Selenium is absorbed mainly in small intestine (50–80%) and excreted by kidneys (60%), intestines (35%), and perspiration and saliva (5%) . Selenium can be available both in organic compounds (selenomethionine and selenocysteine) and inorganic compounds (selenite and selenate) (Duntas and Benvenga 2015). Considering that organic form has better absorption, it seems to be preferable formulation for supplementation treatment.

Thyroid tissue contains the largest amount of selenium (0.2–2 μg/g) – due to large amount of selenoproteinases (deiodinases) – in comparison with other tissues. Furthermore, selenium concentration in thyroid gland is relatively constant regardless of dietary selenium intake (Duntas and Benvenga 2015).

SELENIUM DEFICIENCY AND REQUIREMENTS

The studies revealed that selenium intake in Europe is low and reflects insufficient selenium concentration in soil, especially in Eastern Europe. Eastern European countries exhibit a tendency for lower selenium intake than Western Europe – this has been confirmed by Skibniewska *et al.* (2007). This study has included 30 students (males and females, aged from 19 to 25 years) from the University of Warmia and Mazury, Olsztyn, Poland, and average selenium dietary intake has been assessed at 25 μg. Subsequent study, evaluating blood selenium concentration in population of Upper Silesia, Poland (Kłapcińska *et al.* 2006), documented that an average serum selenium concentration was 63.5±18.1 μg/L. Furthermore, studies have demonstrated general tendency to lower selenium concentration in such conditions as multiple sclerosis (Socha *et al.* 2014), obesity (Błażewicz *et al.* 2015), diabetes mellitus (Salomonowicz *et al.* 2014) and neoplasms (Jaworska *et al.* 2013).

According to Rayman (2005), average selenium intake in Polish population is below 50 μg/d. Daily selenium requirement that provides normal enzymatic activity is 55–75 μg/day (Rayman 2005). The recommended supplementation dose for Polish population is unknown. In case of British population, characterised by similar daily selenium intake like in Poland, it has been demonstrated that selenium intake of 100 μg/day provides suboptimal blood selenium concentration – approximately 140 μg (Rayman 2008). The majority of multivitamin supplements contain about 50 μg of selenium, and it seems to be an adequate dose.

Recommended selenium dose in the United Kingdom is 60 μg/day for adult women and 75 μg/day for breastfeeding women and adult men (Dietary Reference Values For Food, Energy And Nutrients For The UK, 1991). In the United States, the recommended dose is 55 μg/day for women and men (Dietary Refer-

ence Intakes for Vitamin C, Vitamin E, Selenium and Carotenoids, 2000), for European Union countries recommended dose is 70 μg (Scientific Opinion on Dietary Reference Values for Selenium, 2014).

It should also be mentioned that excessive selenium intake may be toxic, but selenium supplements administered in the dose of 200 μg/day are generally believed to be safe. However, they can lead to adverse effects (alopecia, dermatitis, squamous cell carcinoma, type 2 diabetes), as observed in populations of higher selenium intake compared to Europe (e.g. in North America). Selenosis symptoms can occur when selenium dose is higher than 400 μg per day; they include vomiting, nausea, abdominal pain, diarrhoea, hair loss, onychorrhexis, peripheral neuropathy, and characteristic smell of sweat and exhaled air (smell of garlic). After drug withdrawal, the selenium concentration in urine and serum normalizes within 1–2 weeks and 6 weeks, respectively (Ventura *et al.* 2017).

Summing up, most of European countries are still an area of insufficient selenium intake. However, due to a very low range of selenium supplementary dose, decision to introduce supplementation should be supported by coexistence of diseases being unequivocal indication for such a treatment.

INDICATIONS FOR SELENIUM SUPPLEMENTATION IN THYROIDOLOGY

According to EUGOGO (European Group on Graves' Orbitopathy) recommendations (2016), patients with mild active Graves' orbitopathy of short duration (under 18 months) should take selenium 100 μg twice a day for 6 months (sodium selenite, the dose corresponds to 93.6 μg of elementary selenium per day), as such treatment significantly improves eye symptoms, quality of life, and inhibits progress of disease. A positive effect of selenium supplementation has been confirmed by a large, multi-centre (Netherlands, Germany, Switzerland, Italy, Greece) randomised, double-blinded, placebo-controlled study, including 152 patients with mild Graves' orbitopathy. No adverse effects of selenium supplementation have been observed in patients from regions of insufficient selenium intake. The data concerning safety of selenium supplementation in regions of normal selenium intake are unknown. Unfortunately, the quoted study does not present any data concerning selenium concentration in patients before and after treatment, which could explain the hypothesis whether the degree of selenium insufficiency in patients may correlate with improvement of eye symptoms (Marcocci *et al.* 2011, Bartalena *et al.* 2016).

Another studies have revealed that selenium reduces oxidative stress in orbital fibroblast cell culture, by suppressing their proliferation and excretion of proinflammatory cytokines. The study results facilitate understanding cellular mechanism of selenium treatment in Graves' orbitopathy (Rotondo Dottore *et al.* 2017).

In case of patients treated with antithyroid drugs (ATD) due to Graves' hyperthyroidism but without orbitopathy, the study performed by Leo *et al.* (2017) has not confirmed significant adjuvant role of 6-month selenium supplementation.

The ongoing GRASS study (GRAves' disease Selenium Suplementation trial) has included 492 patients with Graves' hyperthyroidism treated with ATD and selenium in a dose of 200 μg/day *vs placebo* for 24 and 30 months. The aim of the above study has been to evaluate whether selenium supplementation reduces percentage of ATD treatment failure (re-ocurrence), precipitates the remission and increases quality of life.

Autoimmune thyroid diseases arise due to complex interactions between environmental and genetic factors. Possible involvement of environmental insults (selenium deficiency), endocrine disruptors and duration of exposure are unquestioned risk factors for the development of diseases (Wojciechowska-Durczynska *et al.* 2016). Several hypotheses, assuming selenium supplementation as adjuvant therapy of L-thyroxine (L-T4) substitution in Hashimoto's disease, are also emerging. It has been reported that selenium supplementation is related to significant decrease of anti-TPO antibodies concentration and to improvement of patients' well-being (Toulis *et al.* 2010). The study has showed different results, depending on the basal anti-TPO concentration. Thus, anti-TPO concentration might be a qualifying parameter for selenium therapy and an evidence of beneficial impact of selenium supplementation on this particular patient.

Furthermore, it has recently been shown that selenium supplementation (83 μg daily for 4 months) in patients with subclinical hypothyroidism, due to Hashimoto disease, leads to TSH normalisation in a high percentage of patients, as measured *vs* control group (30/96 [31.3%] *vs* 3/96 [3.1%]; respectively $p<0.001$) (Pirola *et al.* 2016). The significant reduction of anti-TPO antibodies concentration due to selenium therapy has also been reported (Pirola *et al.* 2016). In previous study (Moncayo *et al.* 2005), the significant improvement of thyroid function following selenium treatment has been observed. In the similar study (Nordio and Pajalich 2013), the beneficial influence of selenium supplementation in patients with subclinical hypothyroidism in the course of Hashimoto disease has been found; in this study TSH concentration normalized in 33% of patients after 4 months of selenium therapy.

Next, beneficial impact of selenium supplementation on reduction of anti-TPO and anti-Tg concentrations, as well as normalisation of thyroid echogenicity after 12 and 6 months of treatment with selenium (80 μg/day) has been observed (Nacamulli *et al.* 2010). However, the authors failed to confirm the influence of selenium on TSH or T4 concentrations.

The beneficial influence of selenium therapy has also been confirmed in pregnant women. It has been documented that selenium supplementation of 200 μg/day

during pregnancy and postpartum period in anti-TPO positive women leads to reduction of antibodies concentration and reduction of frequency of thyroid function abnormalities (Negro *et al.* 2007). In contrast, in another study including pregnant women with autoimmune thyroiditis, the efficacy of selenium supplementation has not been confirmed (Mao *et al.* 2016). However, the strength of evidence is weak, as in the study in question selenium dose has been smaller (60 mg/day) and the median value of anti-TPO antibodies concentration has been lower, as well (Mao *et al.* 2016).

The aforementioned results on selenium efficacy have not been confirmed in a study reported by Esposito *et al.* 2017. The authors have observed that selenium supplementation (166 µg/day for 6 months) does not affect natural the course of Hashimoto's disease in euthyroid patients. In the meta-analysis of eleven (11) publications (9 controlled studies), (Winther *et al.* 2017), the authors reported no changes in TSH and no influence on quality of life, as well as no variations in thyroid echogenicity. It has been concluded that none of analysed reports provided sufficient evidence for recommendation of selenium supplementation in autoimmune thyroiditis. The above mentioned meta-analysis comprised relatively few studies – which influenced the quality of data presented (Winther *et al.* 2017). The earlier, much more extensive meta-analysis (Wichman *et al.* 2016) showed that selenium supplementation reduced anti-TPO concentration after 3, 6 and 12 months in patients with AITD treated with L-T4. However, the strength of evidence was assessed as weak.

As the significance of selenium supplementation in chronic autoimmune thyroiditis is still unproven, a randomised controlled the CATALYST trial (the Chronic Autoimmune Thyroiditis Quality Of Life Selenium Trial) is being conducted presently. It includes 472 patients with autoimmune thyroiditis treated with L-T4. The aim of the study is to evaluate influence of 12-months selenium supplementation in a dose of 200 µg/day *vs. placebo* and assessment of quality of life of patients, T3/T4 ratio, anti-TPO concentration, selenium concentration and oxidative stress biomarkers. In contrast to earlier studies, the conducted analysis evaluates serum selenium concentration during supplementation. According to the respective protocols, both GRASS and CATALYST trials are scheduled to finish in 2018.

Carcinogenesis is a multistage process, preceded by an initiation of neoplastic transformation at the level of single cell. Thyroid carcinoma is the most frequently observed neoplasm of endocrine glands (Lewinski and Wojciechowska 2006). In some studies, the lower selenium concentrations were associated with increased incidence of thyroid cancer diagnoses, although the specific mechanisms have not fully been understood; it seems that the antioxidant properties of selenoenzymes are relevant in carcinogenesis and tumour progression in the thyroid gland (Shen *et al.* 2015; Jinklaas *et al.* 2013).

In other study, the low serum selenium concentration was associated with higher risk of enlargement of thyroid gland and with the development of thyroid nodules (Rasmussen *et al.* 2011). Similar results were obtained by Wu *et al.* (2015). However, other authors failed to demonstrate any significant relationship between serum selenium levels and nodular thyroid disease in an iodine sufficient region (Sakiz *et al.* 2016). In the light of all above discussed results, further studies are required to assess the role of selenium in thyroid nodule formation.

CONCLUSIONS

Although nowadays there is no evidence that selenium supplementation leads to clinical improvement in autoimmune thyroiditis, nodular goitre or thyroid cancer, the correct selenium intake (diet, supplements) seems to be an important issue due to significant role of selenium in thyroid function regulation. In regions of iodine insufficiency or iodine excessive intake, an increased requirement for selenium probably exists – due to protective role of selenoproteins against free radicals (H_2O_2, reactive forms of oxygen) in the course of inflammatory processes. Also the role of selenium in enhancing of immune tolerance should not be neglected. Because of the increased risk of thyroid function abnormalities, women – especially during pregnancy – have probably higher selenium requirements.

Current EUGOGO recommendations (2016) suggest selenium supplementation at the level of 100 µg twice a day for 6 months in case of mild active Graves' orbitopathy of short duration (below 18 months). Till now, none of scientific societies recommend selenium supplementation in case of autoimmune thyroiditis.

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