

## SELENIUM SUBSTITUTION – EFFECT ON THYROID FUNCTION

Milica Pešić<sup>1,2</sup>, Danijela Radojković<sup>1,2</sup>

Clinic of Endocrinology, Clinical Center Niš, Serbia<sup>1</sup>  
University of Niš, Faculty of Medicine, Niš, Serbia<sup>2</sup>

The understanding of the essential role of selenium (Se) in thyroid hormone synthesis, metabolism and action, as well as normal thyroid function, increased during the past decades. The thyroid gland is among the human tissues with the highest Se content per mass unit, similar to other endocrine organs and brain.

Biological actions of Se are mediated, in most cases, through the expression of at least 30 selenoproteins coded by 25 selenoprotein genes in the human. Via the selenoproteins, selenium can influence the cell function through antioxidant activities, modifying redox status and thyroid hormone synthesis and metabolism. Selenoproteins iodothyronine deiodinases are present in most tissues and have a role to increase the production of bioactive tri-iodothyronine.

Furthermore, Se has been shown to be important in the regulation of immune function. Se deficiency is accompanied by the loss of immune competence. The links between Se deficiency, altered immune function and inflammation have prompted studies in humans to examine if Se supplementation can modify auto-antibodies production in patients with chronic autoimmune thyroiditis. Until now, several randomised prospective clinical trials have been performed in patients with established chronic autoimmune thyroiditis. The clinical endpoint of each study was the decrease in TPO antibodies concentration after 3-12 months of treatment. Usually, the dosage of daily Se supplementation was 200µg. Selenium supplementation had no significant effect on the concentration of TSH or thyroid hormone concentrations. These studies indicate that Se treatment result in reduced inflammatory activity, but it does not cure chronic autoimmune process. *Acta Medica Medianae 2015;54(1): 56-59.*

**Key words:** thyroid gland, trace element, selenium

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Contact: Milica Pešić  
Clinic of Endocrinology, Clinical Center Niš, Serbia  
Bul. Zorana Đinđića 48, 18000 Niš  
E mail: mimapesic@gmail.com

### Introduction

Selenium (Se) is an essential trace element with many biological roles such as: prevention of cancer, cardiovascular diseases and viral mutations. In addition, this trace element is required for optimal endocrine and immune function. The dietary intake of Se in humans, recommended by FDA, is between 55 and 75µg per day. It is present in the variety of food as well as in the breast milk. High Se concentration can be found in the brewer's yeast, liver, butter, fish and lamb meat. Natural selenium-rich sources include garlic, broccoli, tomato, mushrooms and specially Brazil nuts.

Selenium deficiency is associated with a predisposition for diseases such as destructive

osteoarthritis (Kashin-Beck) and lethal myocarditis (Keshan), both characteristic for selenium deficient region of China. The first data about relationship between selenium deficiency and thyroid disease were from Central Africa. It was reported that in the children with myxoedematous cretinism, in region with endemic iodine and selenium deficiency, iodine supplementation alone is not enough effective in the thyroid status improvement. Since selenium plays an important role in the metabolism of thyroid hormones, this trace element is an important prognostic factor of conditions caused by iodine deficiency (1). In the last few decades there has been a growing interest for essential selenium role in the synthesis, metabolism and function of thyroid hormones. In the mid-eighties, one of the first hypotheses about association between selenium and thyroid function was raised. These biological actions are mediated in most cases through the expression of at least 30 selenoproteins coded by 25 genes in humans. Thyroid gland tissue is considered to be one with highest selenium concentration similar to other endocrine organs and brain. High selenium concentration in

thyroid tissue is present thanks to selenoenzymes expression: glutathione peroxidases (GPXs) and thioredoxin reductases (TRs) – enzymes capable to prevent thyrocyte damage by oxidative stress and iodothyronine deiodinases (Ds) – enzymes needed for normal thyroid hormone metabolism and function.

#### Selenium as an antioxidant in the thyroid

Until now, three deiodinases have been identified - D1, D2 and D3. Deiodinase are integral membrane proteins with selenium-cysteine residue which ensures high catalytic activity of the enzyme. Their tissue distribution is different. These enzymes have important regulator role in the activation and inactivation of thyroid hormones in all tissues.

The deiodinase D1 is the major isoform in liver, kidney, thyroid and pituitary. It can catalyse 5 or 5' monodeiodination and thus can convert T4 to the inactive rT3 or the active isomer T3. In Se-sufficient rats, hepatic D1 provides an important source of circulating T3. On the other hand, in Se-deficient animals with decreased hepatic D1 expression to 10%, additional mechanisms have to be switched on in order to maintain optimal T3 concentrations. The maintenance of plasma T3 is managed by adaptive rise in TSH which leads to increased de novo synthesis of T3 on thyroglobulin and also increased expression of thyroidal D1 that promotes T4-to-T3 conversion (3).

Expression of deiodinase D2 occurs in thyroid, heart, brain, skeletal muscle, placenta, and pituitary where is involved in the local thyroid hormones activation. The enzyme has a short half-life (<1 h) and can only perform 5' deiodination reactions.

Deiodinase D3 is found in the plasma membrane of the brain, placenta and foetal liver. There are no reliable data about thyroid expression of D3. This enzyme only catalyses 5 monodeiodination.

#### Selenium and autoimmune thyroid disease

It is well known that selenium has an important role in the regulation of the immunological system. Deficiency in Se is associated with diminished immunological response. This may be related to the selenium antioxidant effects. Experimental studies results demonstrated that in the conditions with Se deficiency, thyroid gland becomes infiltrated with T lymphocytes and activated macrophages with high expression of transforming growth factor  $\beta$  (TGF- $\beta$ ). It is precisely TGF  $\beta$  which is considered to be responsible for fibroblast proliferation and inhibition of thyroid cells proliferation. Chronic inflammation leads to thyroid destruction and atrophy. Selenium supplementation in the experimental animals prevents oxidative damage, necrosis and fibrosis (4).

Today, there is a hypothesis that even mild to moderate nutritional selenium deficiency may

be responsible for the initiation and progression of autoimmune thyroid disorders in people with a genetic predisposition to autoimmune disease.

The link between Se deficit, altered immune response and inflammation raised interest to investigate whether Se supplementation can modify antibody production. Many randomised prospective clinical studies have been conducted in patients with autoimmune thyroiditis (4,5). Majority have been conducted in the European countries where mild to moderate Se deficiency was present. Daily dose of Se was usually 200  $\mu\text{g}$  using supplements such as selenium methionine or sodium selenite. Selenium dose necessary to suppress thyroid peroxidase antibodies (TPO Ab) was greater than 100  $\mu\text{g}$  what is also required for maximal activation of glutathione peroxidase (6).

Outcome in all studies was decreased TPO Ab in the 3-12 months. When the Se supplementation was stopped, increased concentration of the TPO Ab occurred after 3-6 months follow-up period. It is not quite clear if decreased TPO Ab reflects decreased thyroid inflammation or improved function of the immune system. Unlike TPO Ab, thyroglobulin antibodies (TgAb) were not decreased during Se supplementation. Since TgAb are much less specific for the inflammatory autoimmune process in the thyroid, in comparison with TPO Ab, it could be concluded that Se supplementation has effect on thyroid inflammation (5).

There are no reported side effects with Se supplementation in this recommended dose. Selenium overdose can occur if higher doses are taken (400-800  $\mu\text{g}$ ) for a longer time. Side effects of Se are numerous: nausea, vomiting, abdominal pain, metallic taste in the mouth, weight loss, facial redness, hair loss, irritability, and even heart failure.

In these reported studies, patients also received L-thyroxin substitution, but significant alteration in thyroid status and TSH concentration was not reported. It was suggested that Se deficit in study patients was not big enough to decrease deiodinase activity.

In some patients with chronic autoimmune thyroiditis, an improved ultrasound echogenicity of the thyroid was noticed during Se supplementation period (7). The same authors pointed out that Se could protect and prevent thyroid goiter formation.

#### Selenium in the benign and malignant thyroid disease

Several studies have revealed a lower level of Se (serum and erythrocyte) in patients with Graves' disease, especially in those who are not adequately treated. The authors also suggested that hyperthyroidism can cause Se deficit. Increased tissue activity of deiodinase D1 and D2 was noticed both in patients with Graves' disease and toxic nodular goiter, which presume involvement of selenoproteins in pathogenesis of this

thyroid disorders (8). Significantly decreased Se concentration has also been reported in the patients with subacute and silent thyroiditis.

The association between thyroid carcinoma and selenium concentration has not been clarified yet. Moncayo et al. in their study showed high percent of the patients having thyroid carcinoma and Se concentration lower than one recommended for optimal glutathione peroxidase activity. This authors further revealed that 64,3% of patients with follicular carcinoma and 63,6% of patients with papillary carcinoma (164 patients with malignant thyroid disease) had suboptimal Se concentrations. The same study results showed significantly decreased Se in all thyroid diseases (2). However, the recent studies have not confirmed the relationship between thyroid

malignant tumors and selenium alterations (neither thyroid, nor plasma Se) (9).

### Conclusion

Trace element selenium is necessary for the thyroid hormones synthesis and metabolism. Selenoprotein-enzymes glutathione peroxidases, thioredoxin reductases and deiodinases have an important role in the thyroid hormones synthesis, antioxidative defence and thyrocyte redox control, as well as in the thyroid hormones' metabolism. Selenium supplementation benefit is revealed in the patients with chronic autoimmune thyroiditis (Hashimoto). However, mechanism of this selenium effect is still unclear, as well as the association between selenium deficit and thyroid cancer. So far, there have not been evidence about selenium influence on plasma thyroid hormone and TSH concentration.

### References

1. Arthur JR, Beckett GJ, Mitchell JH. The interactions between selenium and iodine deficiencies in man and animals. *Nutr Res Rev* 1999; 12(1): 55-73. [\[CrossRef\]](#) [\[PubMed\]](#)
2. Moncayo R, Kroiss A, Oberwinkler M, Karakolcu F, Starzinger M, Kapelari K, et al. The role of selenium, vitamin C, and zinc in benign thyroid diseases and of selenium in malignant thyroid diseases: Low selenium levels are found in subacute and silent thyroiditis and in papillary and follicular carcinoma. *BMC Endocr Disord* 2008; 8:2. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Beckett GJ, Arthur JR. Selenium and endocrine systems. *J Endocrinol* 2005; 184(3): 455-65. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Köhrle J, Gärtner R. Selenium and thyroid. *Best Pract Res Clin Endocrinol Metab* 2009; 23(6): 815-27. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Gärtner R, Gasnier BC, Dietrich JW, Krebs B, Angstwurm MW. Selenium supplementation in patients with autoimmune thyroiditis decreases thyroid peroxidase antibodies concentrations. *J Clin Endocrinol Metab* 2002; 87(4): 1687-91. [\[CrossRef\]](#) [\[PubMed\]](#)
6. Turker O, Kumanlioglu K, Karapolat I, Dogan I. Selenium treatment in autoimmune thyroiditis: 9-month follow-up with variable doses. *J Endocrinol* 2006; 190(1): 151-6. [\[CrossRef\]](#) [\[PubMed\]](#)
7. Derumeaux H, Valeix P, Castetbon K, Bensimon M, Boutron-Ruault MC, Arnaud J, Hercberg S. Association of selenium with thyroid volume and echostructure in 35- to 60-year-old French adults. *Eur J Endocrinol* 2003; 148(3): 309-15. [\[CrossRef\]](#) [\[PubMed\]](#)
8. Beckett GJ, Peterson FE, Choudhury K, Rae PW, Nicol F, Wu PS, Toft AD, Smith AF, Arthur JR. Interrelationships between selenium and thyroid hormone metabolism in the rat and man. *J Trace Elem Electrolytes Health Dis* 1991; 5(4): 265-7. [\[PubMed\]](#)
9. Zagrodzki P, Nicol F, Arthur JR, Słowiaczek M, Walas S, Mrowiec H, Wietecha-Postłuszny R. Selenoenzymes, laboratory parameters, and trace elements in different types of thyroid tumor. *Biol Trace Elem Res* 2010; 134(1): 25-40. [\[CrossRef\]](#) [\[PubMed\]](#)

## SUPSTITUCIJA SELENOM – EFEKAT NA TIROIDNU FUNKCIJU

Milica Pešić<sup>1,2</sup>, Danijela Radojković<sup>1,2</sup>

Klinika za endokrinologiju Klinički centar Niš, Srbija<sup>1</sup>  
Univerzitet u Nišu, Medicinski fakultet, Srbija<sup>2</sup>

Poslednjih decenija postignut je napredak u razumevanju esencijalne uloge selena (Se) u sintezi, metabolizmu i delovanju tiroidnih hormona, kao i u normalnoj tiroidnoj funkciji. Tiroidna žlezda spada u humana tkiva sa najvećim sadržajem selena u odnosu na jedinicu mase, slično kao i kod drugih endokrinih organa i mozga.

Biološko dejstvo selena je najčešće posredovano ekspresijom bar 30 selenoproteina, kodiranih sa 25 selenoproteinskih gena. Posredstvom selenoproteina, selen može uticati na ćelijsku funkciju kroz antioksidativne procese, modifikaciju redoks statusa i posredstvom uticaja na sintezu i metabolizam tiroidnih hormona. Selenoproteini jodotironin dejodinaze prisutni su u brojnim tkivima i imaju ulogu u produkciji bioaktivnog trijoditironina.

Pokazano je takođe da je selen značajan u regulaciji imunološkog odgovora. Deficit selena povezan je sa gubitkom imuno-kompetencije. Veza između deficita selena, izmenjenog imunološkog odgovora i inflamacije uslovlila je klinička ispitivanja sa ciljem da se ispita da li nadoknada selena može izmeniti produkciju antitela kod bolesnika sa hroničnim autoimunim tireoiditisom. Do sada je sprovedeno nekoliko prospektivnih kliničkih studija kod bolesnika sa dijagnozom hroničnog autoimunog tireoiditisa. Rezultati svih kliničkih studija pokazali su pad TPO antitela nakon tri do 12 meseci tretmana. Dnevna doza selena najčešće je bila 200 µg. Nadoknada selena nije imala značajnog efekta na koncentraciju TSH, niti na nivoe tiroidnih hormona. Rezultati studija pokazuju da tretman selenom rezultira redukcijom inflamatorne aktivnosti, ali ne leči hronični autoimuni tireoiditis. *Acta Medica Medianae 2015; 54(1):56-59.*

**Ključne reči:** tiroidna žlezda, oligoelement, selen