



Selenium in Hyperthyroidism

Shiela Stefani¹, Lukman Halim^{1,2}, Diyah Eka Andayani¹, Fiastuti. Witjaksono¹

^{1.} Department of Nutrition, Faculty of Medicine, Universitas Indonesia – Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia

^{2.} Sumber Waras Hospital, Jakarta, Indonesia

Received 20 April 2019,
Accepted 06 November 2019

Link to DOI:
10.25220/WNJ.V03.i2.0004

Journal Website:
www.worldnutrijournal.org

Abstract

Introduction: Thyroid gland has the highest selenium content compare with other endocrine organs. Enzyme that catalyzing thyroid hormone activation, iodothyronine deiodinases, were identified as selenocysteine-containing proteins. Selenium levels in soil and rice consumed in Indonesia were lower than in several other countries, which can increase the risk of selenium deficiency that has been associated with various type of thyroid diseases.

Methods: This is an article review of the current literatures published up to November 2018 about the role of selenium in hyperthyroid.

Result: Several studies have shown that selenium supplementation can be beneficial in patients with Graves disease and autoimmune thyroiditis. Selenium has an important immunomodulatory effect, but the effects of selenium supplementation in hyperthyroid has not been conclude. Data regarding selenium intake, prevalence of deficiency, and the relationship between selenium and thyroid disease in Indonesia are limited. Various study of selenium supplementation in thyroid disease provide controversial results, so there are no guidelines that include selenium as standard therapy hyperthyroid. Selenium supplementation can enhance the restoration of biochemical euthyroidism in Graves disease and was associated with a significant decrease in the levels of thyroid peroxidase antibodies in autoimmune thyroiditis.

Conclusions: Micronutrients that play a role in thyroid hormone synthesis and maintain thyroid function in addition to selenium are iodine, iron, zinc, and vitamin A. By correcting the deficit of selenium, and meeting other micronutrient requirements may provide health benefits in patient with hyperthyroid.

Keywords selenium, hyperthyroid, Graves disease, autoimmune thyroiditis

Introduction

Hyperthyroidism or thyrotoxicosis is a clinical condition due to inappropriately high synthesis and secretion of thyroid hormones by the thyroid gland. In the United States, the prevalence of hyperthyroidism is around 1.2%; 0.5% overt, and 0.7% subclinical. The most common cause of hyperthyroidism is Grave's disease, toxic multinodular goiter, and toxic adenoma.¹ Riset

Corresponding author:

Dr. dr. Fiastuti Witjaksono, MKM, MS, SpGK(K)
Jl. Salemba Raya No. 6 Central Jakarta, 10430,
Indonesia
Email: fiastuti.dr@gmail.com

Kesehatan Dasar (Riskesdas) 2013 in Indonesia, stated that the prevalence of hyperthyroidism in the Indonesian population aged 15 years or older was 0.4% or more than 700,000 persons.² Thyroid abnormalities occur very frequently in the population, located around 10-15% of the total population.³

The thyroid is a gland that contains high selenium compared to other endocrine organs. Selenium in the form of selenoprotein is important to maintain thyroid function.⁴ Selenoproteins (glutathione peroxidase and thioredoxin reductase) also act as cellular antioxidants and protect the thyroid gland from damage caused by hydrogen peroxide and reactive oxygen species. The most important enzymes and are directly involved in thyroid hormone activation, iodothyronin deiodinases, are also selenoproteins. Selenium deficiency, especially those that occur in conjunction with iodine deficiency, will interfere with the synthesis and metabolism of thyroid hormones and contribute to the incidence of goiter, hypothyroidism, and autoimmune thyroid disease. Lower selenium levels were observed in newly diagnosed Graves disease and autoimmune hypothyroidism, but correlations of selenium with serum thyroid peroxidase (TPO) and thyroglobulin autoantibodies (TgAb) are less consistent. The exact molecular, cellular and systemic mechanisms contributing to the obvious relationships among Se status, iodine availability and handling, and thyroid function and the maintenance of its integrity remain to be studied.⁵

In Indonesia, previous studies was found that selenium levels in soil was low, likewise the selenium intake and selenium content in rice consumed by Indonesian people were lower than some other countries, which could increase the risk of selenium deficiency.^{6,7} Selenium is most commonly found on the ground and a balanced diet should provide enough selenium for thyroid hormone synthesis. Selenium deficiency occurs in patients with impaired gastrointestinal absorption or receiving long-term parenteral nutrition therapy, as well as people living in areas where selenium content in their soil is very low. Providing selenium supplementation is very important in these patients to prevent dysfunction of the thyroid.⁸

In Graves disease, several studies have shown that selenium supplementation can enhance the restoration of biochemical euthyroidism.⁹ Selenium supplementation has also been shown to reduce thyroid peroxidase antibodies (TPOAb) in autoimmune thyroiditis.¹⁰ Immunomodulatory effects of selenium may causing a decrease in the release of proinflammatory cytokines,¹¹ but the effects of selenium supplementation that clinically relevant are still unclear. Research on selenium and its relationship to hyperthyroidism in Indonesia is still very limited. This paper will explain the role of selenium in hyperthyroidism, so that it is expected to increase knowledge about micronutrients that might help in prevention or therapy.

Hyperthyroidism

Hyperthyroidism or thyrotoxicosis can appear if (i) the thyroid is excessively stimulated (Graves disease); (ii) constitutive activation of thyroid hormone synthesis and secretion, that is cause autonomous release of excess thyroid hormone (toxic multinodular goitre, solitary toxic nodule, and familial non-autoimmune hyperthyroidism); (iii) thyroid are released in excessive amounts owing to autoimmune, infectious, chemical, or mechanical insult; or (iv) there is exposure to extrathyroidal sources of thyroid hormone (struma ovarii, metastatic differentiated thyroid cancer) or exogenous (factitious thyrotoxicosis).^{1,12}

The common causes of hyperthyroidism are Graves disease, toxic multinodular goitre, toxic adenoma, and painless thyroiditis. Graves disease is an autoimmune disease in which thyroid-stimulating antibodies (*thyrotropin receptor antibodies*, TRAb) will activate thyroid-stimulating hormone (TSH) receptors and triggering thyroid hormone synthesis.^{1,13} In addition to TRAb, TgAb and TPOAb can also be detected in patients with Graves disease.¹⁴ Risk factors for Graves disease are female and personal or family history of an autoimmune disorder. Toxic multinodular goitre is the most common cause hyperthyroidism in older persons who are living in iodine deficient areas. Nodules arise from replication of clonogenic cells that leads to a mutation of TSH receptors, if a single nodule detected, it is called a toxic adenoma.¹³ Other etiology is painless or silent thyroiditis. It is an

autoimmune that causes a destruction of thyroid follicles and leading to release of preformed thyroid hormones into the circulation.¹⁵ Gestational hyperthyroidism can occur in the first trimester of pregnancy. Placental beta human chorionic gonadotropin (β -hCG), which shares structural features with TSH, has stimulatory action on the

proximal muscles), psychiatric symptoms (range from anxiety to frank psychosis), atrial fibrillation (10% to 15% of patients), or heart failure (5.8% of patients).¹³

If there is clinical suspicion of hyperthyroidism, then laboratory testing should be done (Figure 1). Serum TSH has the highest

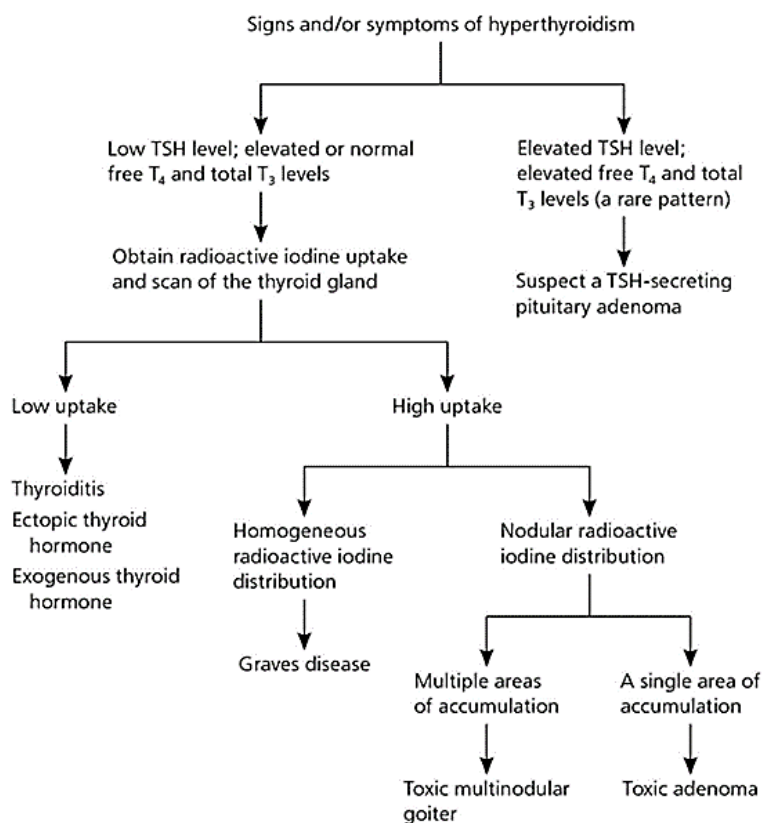


Figure 1. Algorithm for hyperthyroidism diagnosis
T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone
Source: reference no ¹³

thyroid gland. β -hCG mediated hyperthyroidism can also be caused by hyperemesis gravidarum or gestational trophoblastic tumor.¹⁶

The clinical manifestations of hyperthyroidism range from asymptomatic to thyroid storm. Increasing of thyroid hormone amplifies catecholamine signaling through increased numbers of beta-adrenergic receptors, and resulting adrenergic symptoms (palpitations, heat intolerance, diaphoresis, tremor, stare, lid lag, hyper defecation) are the most common clinical manifestations of hyperthyroidism.¹⁰ Despite of an increased appetite, hypermetabolism will induce weight loss in hyperthyroid patients. Other symptoms that can occur are neuromuscular symptoms (weakness of

sensitivity and specificity for hyperthyroidism. Free thyroxine (T4) and total triiodothyronine (T3) levels need to be tested if the TSH level is low (free T3 assays are poorly validated). The physicians can also order all three tests in one time to make the diagnosis more efficiently. To diagnose Graves disease, serum level of thyroid-stimulating immunoglobulins or TSH receptor antibodies helps distinguish from other causes of hyperthyroidism in patients who lack clinical signs and symptoms of Graves disease that are pathognomonic and have a contraindication to radioactive iodine uptake and scan.¹³

Metabolism, Daily Requirement, and Food Sources of Selenium

Selenium is a micronutrient that was first discovered in 1817. Selenium from the Greek, would be the “moon”, because selenium a sheen similar to that of the moon.¹⁷ Selenium is available both in organic compounds (selenomethionine and selenocysteine) and inorganic compounds (selenite and selenate).¹⁸ Selenium is present in food especially in organic forms, and probably absorbed in the small intestine especially by transcellular diffusion. The inorganic form of selenium, which is selenite or selenate are only found in small amounts in foodstuffs. There is a difference in absorption efficiency and bioavailability of selenium depending on the form (selenomethionine > selenocysteine > selenate > selenite).¹⁹ The biological activity of selenium depends on absorption, retention, and excretion. Selenomethionine is absorbed more quickly and completely (98%) than sodium selenite (84%) and uptake by the liver occurs faster after administration of organic selenium rather than inorganic. In addition, selenomethionine is excreted less than sodium selenite, faecal excretion: 4 versus 18%, urinary excretion: 11 versus 17%, and total excretion: 15 versus 35%. Selenomethionine is retained in the body for 363 days, while sodium selenite 147 days, this slower turnover allows an efficient reutilization of selenomethionine. Because of these properties, high doses of selenomethionine or uncontrolled long-term supplementation should be avoided because this can cause tissue accumulation and selenium toxicity.¹⁷ In other studies, increased selenite absorption occurs when given together with glutathione rather than given alone, this is probably due to formation of selenodiglutathione, which may be absorbed differently from selenite.²⁰ Selenium excretion is mostly via urine (in the form of selenosugars and methylated as trimethylselenonium) which is about 60% of total excretion of selenium, 35% is excreted through feces, and in small amounts excreted through sweat, breathing, and saliva.^{21,22}

Recommended dietary allowance of selenium in America and from European Commission (Scientific Committee on Food) for both male and female adults is 55 mcg/day. In United Kingdom and Belgium, recommendation for

selenium intake is between 60-75 mcg/day. Based on the World Health Organization/Food and Agriculture Organization/International Agricultural Exchange Association, recommendation of selenium intake is only 40 mcg/day in men and 30 mcg/day in women.⁶ The maximum recommendation of selenium based on the World Health Organization is 400 mcg/day, and the minimum intake is 10 mcg/day.⁷

Data of selenium intake and selenium content in food ingredients in Indonesia are very limited. The study of Untoro et al.²³ in East Java showed that selenium content in egg yolks (0.15-1.52 mcg/g) and egg white (0.2-2.97 mcg/g) were lower than 1 mcg/g, and that values are below the data from Belgium, Venezuela, and Chile. Eggs contribute about 8% of the estimated daily selenium intake (50 mcg/day for healthy adults).²³ In a study in Bandung that assess selenium levels in rice as the main staple food consumed by populations, the results showed that the mean selenium levels in rice consumed were 0.035 mcg/g, lower than other countries, as can be seen in Figure 2.⁶ In another study in East Java, it was found that the mean selenium levels in the soil in the area of the goitre group were lower compared to the control group, respectively 3.2 and 4.6 mcg/kg, but not significantly different.²⁴ The most recent study showed that selenium levels in the soil in Indonesia is around 0.24-1.31 mg/kg of soil, with the highest content in the Papua area, and the lowest found in Kalimantan area, as can be seen in Table 1.⁷

Until now it is still unknown the reference values of selenium levels that can be use as a parameters to detect the risk of disease caused by selenium deficiency.²⁵ Large studies are limited because it is difficult to estimate selenium intake from questionnaires due to significant variations of selenium content in the same food ingredients. Measuring the content of selenium in food ingredients is also limited due to the large geographic variability.²⁶ Food source of selenium and its content can be seen in Table 2.²⁷

The greatest selenium concentration (>1 mg/kg) was found in Brazil nuts and offal.²⁸ In Europe, the average daily intake of selenium is estimated at 40 mcg/day (range 32-62 mcg/day), whereas in America it is 93 mcg/day in women and 134 mcg/day in men.¹ The mean selenium intake in

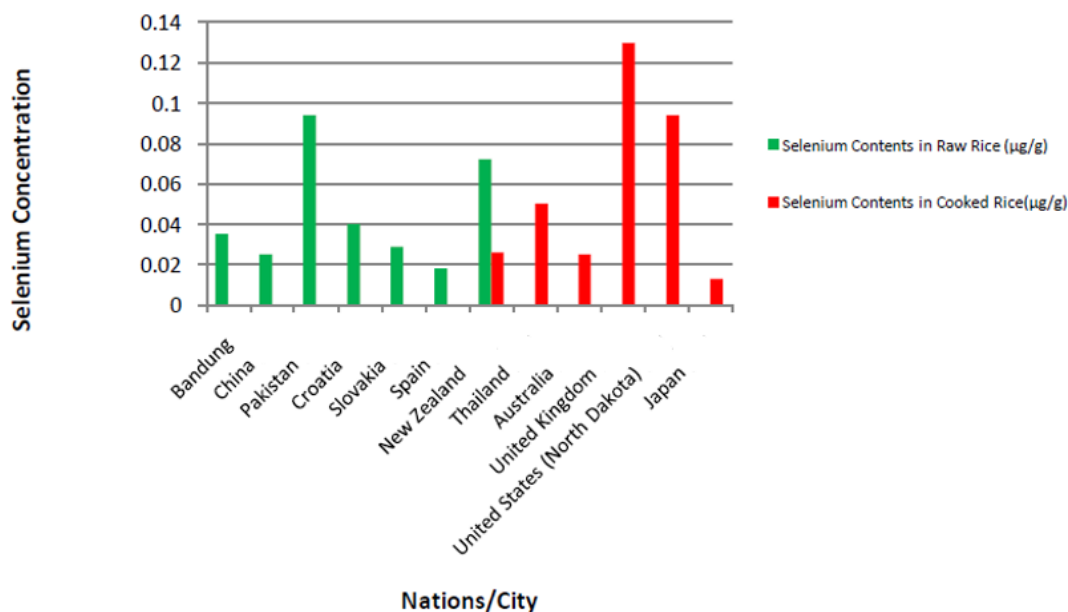


Figure 2. Comparison chart levels of selenium in raw rice or cooked rice in some countries
Source: reference no⁶

Table 1. Selenium concentration in the soil and rice by location in Indonesia

Area	Selenium	
	Soil	Rice
Papua	1.31±0.07	0.068±0.0015
Lampung	1.25±0.08	0.101±0.0059
Kalimantan	0.18±0.03	0.007±0.0012
Java	0.44±0.11	0.022±0.0040
Bali	0.24±0.03	0.007±0.0040
Sulawesi	0.24±0.03	0.024±0.0006

Source: reference no⁷

diabetic patients in several hospitals in Bandung was 74.62 ± 15.46 mcg/day, with a minimum intake was 41 mcg and a maximum was 104 mcg.²⁹

The content of selenium in vegetables can be lost during processing and cooking. Refining grains also will reduce selenium content by 50-75%, while boiling can reduce 45% selenium.³⁰ There are differences in the retention and distribution of selenium derived from broccoli or beef / pork, but administer of foods that is containing high selenium (1.5 mcg selenium/gram diet) did not cause significant changes in selenium bioavailability compared to adequate amounts (0.1 mcg selenium/gram diet).³¹

Selenium Function in Thyroid Gland

Selenium is work actively in the form of selenocysteine amino acids known as a group of

proteins known as selenoproteins. The main selenoprotein group is glutathione peroxidase (GPx), thioredoxin reductase (TXNRD), and iodothyronine deiodinase (DIO) as can be seen in Table 3.¹⁷ GPx which have oxidoreductase function and also regulates immune response, it is plays a role in the defense system of the cell against reactive oxygen species and maintains lipid constituents of cell membranes.²⁵ TXNRD can modulate transcription and signal transduction functions. DIO which catalyzes the conversion of T4 to T3, and rT3 which are very important for thyroid hormone metabolism.¹⁷ Although glutathione peroxidase acts in neutralizing oxidants, other antioxidants such as vitamin E and vitamin C, and Vitamin B2 which is needed by the glutathione reductase also plays a role in synergistic action in oxidative stress neutralization.^{32,33}

Table 2. Food sources and content of selenium

Food Source	mcg/portion	%needs/day
Brazil nuts, 1 ounce (6-8 nuts)	544	777
Tuna, yellow fin, cooked, dry heat, 3 ounces	92	131
Halibut, cooked, dry heat, 3 ounces	47	67
Sarden, canned in oil, dried with bone, 3 ounces	45	64
Ham, baked, 3 ounces	42	60
Shrimp, canned, 3 ounces	40	57
Steak, grilled, 3 ounces	33	47
Cow liver, pan fried, 3 ounces	28	40
Chicken, thigh, grilled, 3 ounces	22	31
Brown rice, cooked, 1 cup	19	27
Minced meat, 25% fat, grilled, 3 ounces	18	26
Egg, cooked, 1 egg	15	21
Wheat bread, 1 slice	13	19
Oatmeal cooked with water, 1 cup	13	19
Spinach, frozen, boiled, 1 cup	11	16
Milk, 1% fat, 1 cup	8	11
Yogurt, plain, low fat, 1 cup	8	11
White bread, 1 slice	6	9
Banana, 1 cup	2	3
Potato, baked, with skin, 1 piece	1	1
Carrot, raw, 1 cup	0	0

Source: reference no ²⁷

Table 3. Main selenoproteins and their function that are found in the thyroid gland

Selenoproteins	Abbreviation	Function
Glutathione peroxidase	GPX	Catalyzes the reduction of H ₂ O ₂ ; Protects against oxidative stress
Cytosolic GPx1	GPX1	Antioxidative defence
Extracellular GPx	GPX3	Anti-inflammatory action
Phospholipid GPx	GPX4	Reduces the phospholipids's hydroperoxides; Regulates apoptosis
Iodothyronine deiodinase	DIO	Catalyzes the conversion of T ₄ and T ₃
Type I DIO	DIO1	Conversion T ₄ to T ₃
Type II DIO	DIO2	Local production (intracellular) of T ₃ from T ₄
Type III DIO	DIO3	Production of rT ₃ from T ₄ , and T ₂ from T ₃
Thioredoxin reductase	TXNRD	Oxidoreductase activity having the NADPH as a cofactor
TXNRD cytosolic	TXNRD1	Main antioxidant "weapon" at the cellular level
TXNRD mitochondrial	TXNRD2	Regulates cell proliferation
Selenoprotein P	SEPP	Selenium transporter
Selenoprotein K	SELK	Endoplasmic reticulum-associated degradation and immune response
Selenoprotein N	SEP15	Degradation of H ₂ O ₂
Selenoprotein S	SELS	Transmembrane protein, putative role in endoplasmic reticulum stress
Selenoprotein T	SELT	Calcium mobilization
Selenoprotein V	SELV	Testes-specific expression
Selenoprotein W	SELW	Antioxidant role

NADPH = nicotinamide adenine dinucleotide phosphate (reduced form of the redox coenzyme nicotinamide adenine dinucleotide phosphate)

Source: reference no ¹⁷

Selenoprotein P (SEPP) is a source of more than 50% plasma selenium, which is the main plasma transport and distribution system of selenium. SEPP circulates in various forms with different glycosylation patterns. SEPP is produced by hepatocytes and it is very important for maintaining selenium homeostasis as it sustains retention of selenium in the body and increase distribution from the liver to other tissues, especially in selenium deficiency.³⁴ Inactivation of the SEPP gene in mice actually reduces selenium content in the plasma, kidneys, testis, brain, and the activity of selenoenzyme in various organs drastically.³⁵ SEPP deficiency can actually trigger neurological disorders (ataxia and seizures), indicating an important role of SEPP to transport selenium in the brain.³⁶ The thyroid affects the mRNA levels of several enzymes involved in selenoprotein biosynthesis and SEPP concentrations, suggesting that the thyroid hormones can have a positive effect on serum selenium status and regulates the expression of several selenoproteins. Recent data show that single-nucleotide polymorphisms in selenoproteins can increase selenium utilization and effectiveness.¹⁷

Selenium also has the ability to increase T cell activity and cytotoxicity from natural killer cells, so that it may be effective in viral infections.¹⁷ Selenium supplementation can stimulate the immune system by increasing the differentiation of CD4 + cells into T helper (Th) 1 cells, enhance expression of interleukin-2 and also lymphocyte proliferation.³⁷ This effect might be effective to eradicate the virus that considered to be involved in autoimmune thyroid diseases.³⁸ Further, selenium supplementation can also reduce production from CD4+ CD25+ T cells by increasing the regulation of forkhead box P3 (FOXP3) expression and increasing the percentage of regulatory T cells, thereby suppressing excessive inflammation.¹¹ This studies showed that selenium might have reduce the excessive immune responses in autoimmune thyroid disease.

Selenium in Hyperthyroidism

In the thyroid gland, selenium concentration is very high (0.2-2 mcg/g). In adults, selenium concentration in the thyroid gland (0.72 ± 0.44

mcg/g) was significantly higher than in liver (0.45 ± 0.11 mcg/g).³⁹ The association of selenium with the functioning of DIO was identified as an enzyme containing selenocysteine, and DIO activity depending on selenium availability. Thyrocytes produce hydrogen peroxide (H_2O_2), which is important for the activity of TPO and iodide oxidation.¹⁷ The formation of H_2O_2 is regulated through the action of TSH via a complex network of second-messenger systems. The iodination of thyroglobulin and formation of H_2O_2 occur on the apical membrane of the thyrocyte. The H_2O_2 formed on the surface of the thyrocyte are available for iodination of thyroglobulin.⁴⁰ H_2O_2 will be reduced to H_2O , but if H_2O_2 is present in large quantities, it will cause radical oxygen species damage.⁴¹ In the process of thyroid hormone synthesis, GPX1, GPX3, and TXNRD1 up-regulated, and by acting as antioxidants and modifying redox status, they can protect the thyroid from peroxidation damage.^{5,17} In hyperthyroidism, there is significantly increased of malondialdehyde (MDA) levels in erythrocytes, plasma, and urine patients.⁴² Selenoprotein protects the thyrocyte from oxidative damage and modulates thyroid hormone biosynthesis, so it is crucial for maintaining the function and integrity of the thyroid gland, although it might not be essential for survival of the thyrocyte.^{5,17}

Selenium supplementation (even in non-deficient subjects) can induce immune stimulatory effects such as an increase in the number of activated T lymphocytes and regulates of Th1/Th2 cytokine expression.⁴³ Combined iodide and selenium deficiency can cause H_2O_2 accumulation; selenium deficiency can reduced cell defense, increasing transforming growth factors β , and fibrosis of thyroid tissue. This will cause thyroid destruction.^{44,45} In iodine and selenium deficiency, selenium supplementation can aggravate hypothyroidism due to stimulation of thyroxine metabolism by DIO type I, so selenium supplementation is not indicated without iodine supplementation or thyroid hormone.⁴⁶

In euthyroid healthy subjects with marginal selenium deficiency, selenium supplementation has little and no clinically significant effect on thyroid function.⁴⁷ From previous studies it was found that selenium levels were inversely related to thyroid size,⁴⁸ and several diseases that might have an effect

on Selenium supplementation is Graves disease and autoimmune thyroiditis.⁴⁹

Selenium in Graves Disease

In a study by giving of 300 mcg/day of selenium supplementation, it was increasing levels of serum selenium and SPP significantly compared to placebo. The serum level of fT3, TRAb, and TPOAb were markedly lower in subject who received selenium supplementation for 24 weeks. Serum levels of SPP correlated with serum selenium and TSH, but negatively correlated with serum fT3 and TPOAb. Serum selenium levels negatively correlated with serum TPOAb. This results indicated that SPP was the more meaningful biomarker of selenium status rather than serum selenium. Although there were a significant increase of the serum levels of selenium and SPP in the selenium group, it did not increase the response or decrease the recurrence rate. There were no significant differences between two groups pertaining to efficacy and clinical course of the thyroid disease. The results obtained in the above study support that there is a relationship between Grave's disease and selenium status, because selenium and SPP concentrations are negatively related to TPOAb, and SPP is positively associated with serum TSH.¹¹

Previous study by Leo, et al.⁵⁰ there was an increase in serum selenium levels after supplementation 166 mcg/day for 45 days without a difference in serum fT3, fT4, and MDA levels compared to the control group. In this study, the research subjects were selenium-sufficient. From the results of this study concluded that selenium supplementation does not provide short-term benefits in hyperthyroidism, but may be useful in patients with selenium deficiency, so it is necessary to evaluate the selenium status of patients before giving antithyroid therapy, to assess whether the patient might get beneficial effects from selenium.⁵⁰

The study by Calissendorff et al.³⁷ in patients Graves thyrotoxicosis was found that fT4 levels decreased more in the selenium supplementation (200 mcg/day) group after 18 and 36 weeks, and increase TSH levels after 18 weeks. The concentration of SPP also increased in the selenium group. FT4 and TSH might imply a reduction in disease activity in patients with Graves disease with

the addition of selenium. There was no change in TRAb levels in the two groups probably due to other indirect mechanisms. Some factors could be mediated by the immune system, by effects on oxidative stress in the thyroid gland or by deiodinase enzymes. Selenium is important for initiation and enhancing immunity, but it is also being involved in the regulation of excessive immune responses. This is very important to prevent responses that can lead to autoimmunity or chronic inflammation.³⁷ Selenium supplementation also has a stimulating effects on the immune system by promote the differentiation of CD4 + cells into Th1 cells.⁵¹ The supplementation of selenium also shows an association between enhanced expression of interleukin-2 receptors and lymphocyte proliferation, but whether the immune system can be modulated through selenium in Graves disease remains speculative. In this study there were no significant changes in TRAb or TPOAb during selenium supplementation.³⁷ Serum selenium levels that increased significantly in selenium supplementation were not accompanied by decreased levels of autoantibodies, indicating a lack of adjuvant effects of selenium supplementation in antithyroid treatment. These results were contrary to Hashimoto's thyroiditis disease, where there was a decrease in TPOAb after selenium.⁵² Selenium did not appear to affect immunoglobulins in Graves disease.³⁷

The results of meta-analysis of selenium supplementation can enhance the restoration of biochemical euthyroidism and might be useful in Graves disease with selenium deficiency.^{9,49} Positive results of the study should be carried out in a larger methodology study before selenium can be included in international guidelines as standard therapy.⁹ European Group On Graves Orbitopathy (EUGOGO) provides selenium supplementation in mild and inactive Graves orbitopathy patients in initial management.⁵³ This is due to the potential efficacy of supplementation 200 mcg/day selenium for 6 months in Graves Orbitopathy. Giving selenium supplementation was significantly improves quality of life, reduces ocular involvement, and slows disease progression in patients with mild Graves orbitopathy.⁵⁴

Selenium in Autoimmune Thyroiditis

In patients with euthyroid autoimmune thyroiditis, supplementation of 166 mcg selenium/day for 6 months did not change concentrations of TSH, fT4, fT3, TPOAb, thyroid echogenicity, and CXCL-10 (chemotactic cytokines that seems to have a major role in thyroid autoimmunity) levels compared to the control group. Short-term selenium supplementation has a limited effect on euthyroid autoimmune thyroiditis patients. In this study, there was an increase in fT3 levels and a decrease in fT4 in the group given selenium, but not in the control group after 3 and 6 months. This may be due to an increased action of deiodinase induced by L-selenomethionine.⁵⁵

This study is different from the results obtained by Nacamulli et al.¹⁰ that 80 mcg selenium supplementation/day may be effective in preventing a decrease in thyroid echogenicity and reducing levels of TPOAb and TgAb, although there were no changes in TSH and fT4 levels for 12 months. This difference in results may be due to differences in the timing of selenium supplementation associated with low selenium intake. The study area where the study subjects lived only had soil with lower selenium levels.⁵⁵ Another study with selenomethionine 80 mcg and 160 mcg for 12 months in euthyroid autoimmune thyroiditis patients did not provide changes in TPOAb levels, but there was a significant increase in TPOAb in the group who got a placebo. This shows the potential for selenium effects to protect the progression of the disease in selenomethionine supplementation.⁵⁶

Other studies showed a significant reduction in TPOAb levels after 3 months supplementation of 200 mcg selenomethionine/day.⁵⁷ Chemokine CXCL-9 levels decreased significantly after 12 months supplementation of 80 mcg of selenomethionine/day, whereas with supplementation 160 mcg selenomethionine/day, a significant decrease was seen in the 6 month and remain stable. CXCL-10 levels decreased significantly after 12 months of supplementation both in the group that given selenomethionine 80 mcg and 160 mcg. The chemokines are involved in the pathogenesis of autoimmune thyroiditis. The results of that study showed a positive effect of

selenomethionine as an immunomodulator by reducing some cytokine regulation.⁵⁶

Study by Farias et al.⁵² showed a decrease in TPOAb by giving selenium supplementation for 3 months that occurred after 6 months. Low selenium levels are associated with poor immune function, and it has been hypothesized that mild selenium deficiency may promote the progression of thyroid autoimmunity. Selenium supplementation is associated with decreased levels of serum concentration of thyroid autoantibodies and stabilized the autoimmune response in various variables in different studies and different groups of patients.⁵² The decreases in TPOAb may be due to an increase in intra-thyroid selenium levels that will reduce reactive oxygen species damage through enhanced expression of glutathione peroxidase and improvement of redox status in thyrocyte through increasing thioredoxin reductase activity. Selenium supplementation may also reduce the production of CD4 + CD25 + T cells by up-regulating of Fox3p mRNA and increasing the percentage of T regulatory cells, which will decrease some immune responses and restore them to approach normal levels. Selenium requirements are not only influenced by selenium status, but also by selenoprotein gene polymorphisms including SEPP, therefore it is better to rule out the presence of gene polymorphisms before drawing conclusions about activity of selenoprotein in response to therapy. The positive effects of selenium supplementation on chronic thyroiditis autoimmune are obtained both in deficiency and adequacy due to pharmacologic activity.⁵²

Meta-analysis by Toulis et al.⁵⁸ found that supplementation 200 mcg selenium/day in chronic autoimmune thyroiditis was associated with a decrease in concentration of TPOAb within 3 months. Other systematic reviews of 4 studies showed that supplementation of 200 mcg selenium/day of in chronic autoimmune thyroiditis gave positive and statistically significant results, but the study have a high risk of bias, so evidence to support the efficacy of Hashimoto's thyroiditis is not reliable enough to help make clinical decisions.⁵⁹ The latest meta-analysis informs that there have been conflicting reports regarding selenium supplementation in autoimmune thyroiditis patients. With current evidence it is not possible to justify

selenium supplementation in autoimmune thyroiditis patients, but correcting of a selenium deficit might provide other health benefits.⁶⁰

Micronutrients that contribute to thyroid hormone synthesis and maintain thyroid function other than selenium is iodine, iron, zinc, and vitamin A.⁸ Study by Guerra et al.⁴² in Graves disease patients who were given methimazole and supplemented with antioxidant mixture (200 mg vitamin E, 3 mg β -carotene, 250 mg vitamin C, 1 mg Cu, 7.5 mg Zn, 1.5 mg Mn, and 15 mcg Se) associated with a better biochemical and clinical control of hyperthyroidism in patients given this mixture compared with methimazole alone. In this study, they only gave a small amount of selenium (15 mcg), but patients receiving the antioxidant mixture showed a significant improvement in their clinical score after the first 4 week. Methimazole and the antioxidant mixture affected both urinary and serum malondialdehyde contents.⁴² In other study, the fT4 and fT3 levels decreased more rapidly in Graves disease patients who received methimazole, antioxidants and 60 mcg selenium compared to methimazole alone after 30 and 60 days. In the group receiving antioxidants there is also significant increase of TSH after 60 days.⁶¹ This may be due either to the other antioxidative components (vitamin C, vitamin E, and β -carotene) or to selenium given in that study.

Conclusion

Selenium is a micronutrient that needed only in a small quantities by the human body. Amount of selenium in food ingredients depends on the content of selenium in the soil. Studies on selenium levels, intake, and prevalence of selenium deficiency in Indonesia are very limited. In Indonesia, some studies showed that selenium in the soil were low, which might increase risk of selenium deficiency. Selenium has an important function in various metabolisms in the body, especially in the thyroid gland. Selenium works in its active form, namely selenocysteine which is known in the selenoprotein group. Glutathione peroxidase, thioredoxin reductase, and iodothyronine deiodinase are the main selenoproteins that play a role in maintaining the function and regulation of the thyroid gland through antioxidant mechanisms, regulation of

immune responses, and signal transcription and transduction.

In hyperthyroidism, the administrations of selenium as supplementation were have different results and the benefits that are clinically relevant are still unclear. Selenium supplementation may improve biochemical hormone in patients with Graves' disease with selenium deficiency, whereas in mild inactive Graves orbitopathy, selenium supplementation might be beneficial. In several studies in patients with autoimmune thyroiditis, it was found that selenium supplementation can reduce autoimmune antibodies, but from the results of existing studies, it cannot be concluded that selenium supplementation can have a positive effect. Perhaps the administration of selenium in hyperthyroid patients with selenium deficiency can provide health effects, accompanied by meeting the needs of other micronutrients that play a role in maintaining the thyroid function such as iodide, iron, zinc, and vitamin A. The exact molecular, cellular, and systemic mechanisms contributing to the obvious relationships among selenium status and thyroid function and the maintenance of its integrity remain to be studied. Further research is needed on the role of selenium in hyperthyroid patients, selenium levels in various foods in Indonesia, as well as the prevalence of selenium deficiency to determine whether selenium supplementation should be given, especially in autoimmune hyperthyroid patients

Conflict of Interest

Authors declared no conflict of interest regarding this study.

Open Access

This article is distributed under the terms of the Creative Commons Attribution 4.0 International Licence

(<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

Reference

1. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. *Thyroid* 2016;26:1343-421. [Google Scholar]
2. Balitbang Kemenkes R. Riset Kesehatan Dasar; RISKESDAS. Jakarta: Balitbang Kemenkes RI 2013.
3. Das S, Bhansali A, Dutta P, Aggarwal A, Bansal M, Garg D, et al. Persistence of goitre in the post-iodization phase: micronutrient deficiency or thyroid autoimmunity. *The Indian journal of medical research* 2011;133:103. [Google Scholar]
4. Köhrle J. Pathophysiological relevance of selenium. *Journal of endocrinological investigation* 2013;36:1-7. [Google Scholar]
5. Kohrle J. Selenium and the thyroid. *Curr Opin Endocrinol Diabetes Obes* 2015;22:392-401. [Google Scholar]
6. Holik HA, Bianti H, Mutakin RA. Determination of selenium concentration in different species of rice consumed in Bandung Indonesia. *Int Res J Pharm App Sci* 2013;3:38-41. [Google Scholar]
7. Rivai IF, Setiawan A, Abdulah R, Kobayashi K, Yamazaki C, Kameo S, et al. A Study of the association between selenium and cardiovascular disease in Lampung, Indonesia. *Southeast Asian Journal of Tropical Medicine and Public Health* 2016;47:299. [Google Scholar]
8. Sharma R, Bharti S, Kumar KH. Diet and thyroid-myths and facts. *Journal of Medical Nutrition and Nutraceuticals* 2014;3:60. [Google Scholar]
9. Zheng H, Wei J, Wang L, Wang Q, Zhao J, Chen S, et al. . Effects of Selenium Supplementation on Graves' Disease: A Systematic Review and Meta-Analysis. *Evidence-Based Complementary and Alternative Medicine* 2018; 2018. [Google Scholar]
10. Nacamulli D, Mian C, Petricca D, Lazzarotto F, Barollo S, Pozza D, et al. Influence of physiological dietary selenium supplementation on the natural course of autoimmune thyroiditis. *Clinical endocrinology* 2010;73:535-9. [Google Scholar]
11. Kahaly GJ, Riedl M, König J, Diana T, Schomburg L. Double-blind, placebo-controlled, randomized trial of selenium in graves hyperthyroidism. *The Journal of Clinical Endocrinology & Metabolism* 2017;102:4333-41. [Google Scholar]
12. Taylor PN, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus JH, Dayan CM, et al. Global epidemiology of hyperthyroidism and hypothyroidism. *Nat Rev Endocrinol* 2018;14:301-16. [Google Scholar]
13. Kravets I. Hyperthyroidism: diagnosis and treatment. *Am Fam Physician* 2016;93:363-70. [Google Scholar]
14. Smith TJ, Hegedüs L. Graves' disease. *New England Journal of Medicine* 2016;375:1552-65. [Google Scholar]
15. Pearce EN, Farwell AP, Braverman LE. Thyroiditis. *New England Journal of Medicine* 2003;348:2646-55. [Google Scholar]
16. Carney LA, Quinlan JD, West JM. Thyroid disease in pregnancy. *American family physician* 2014;89.
17. Duntas LH, Benvenga S. Selenium: an element for life. *Endocrine* 2015;48:756-75. [Google Scholar]
18. Ventura M, Melo M, Carrilho F. . Selenium and thyroid disease: From pathophysiology to treatment. *International journal of endocrinology* 2017; 2017. [Google Scholar]
19. Thiry C, Ruttens A, Pussemier L, Schneider YJ. An in vitro investigation of species-dependent intestinal transport of selenium and the impact of this process on selenium bioavailability. *British Journal of Nutrition* 2013;109:2126-34. [Google Scholar]
20. Gammelgaard B, Rasmussen LH, Gabel-Jensen C, Steffansen B. Estimating intestinal absorption of inorganic and organic selenium compounds by in vitro flux and biotransformation studies in Caco-2 cells and ICP-MS detection. *Biological trace element research* 2012;145:248-56. [Google Scholar]
21. Weekley CM, Harris HH. Which form is that? The importance of selenium speciation and metabolism in the prevention and treatment of disease. *Chem Soc Rev* 2013;42:8870-94. [Google Scholar]
22. Kobayashi Y, Ogra Y, Ishiwata K, Takayama H, Aimi N, Suzuki KT. Selenosugars are key and urinary metabolites for selenium excretion within the required to low-toxic range. *Proc Natl Acad Sci U S A* 2002;99:15932-6. [Google Scholar]
23. Untoro J, Ruz M, Gross R. Low environmental selenium availability as an additional determinant for goiter in East Java, Indonesia. *Biological trace element research* 1999;70:127-36. [Google Scholar]
24. Bachtiar H. Faktor Determinan Kejadian Gondok di Daerah Pantai Jawa Timur. *Jurnal*

- Kesehatan Masyarakat Andalas 2009;3:62-7. [Google Scholar]
25. Wasowicz W, Gromadzinska J, Rydzynski K, Tomczak J. Selenium status of low-selenium area residents: Polish experience. *Toxicology Letters* 2003;137:95-101. [Google Scholar]
 26. Park K, Rimm E, Siscovick D, Spiegelman D, Morris JS, Mozaffarian D. Demographic and lifestyle factors and selenium levels in men and women in the US. *Nutrition research and practice* 2011;5:357-64. [Google Scholar]
 27. Waegeneers N, Thiry C, Temmerman L, De Ruttens A. Predicted dietary intake of selenium by the general adult population in Belgium. *Food Additives & Contaminants: Part A* 2013;30:278-85. [Google Scholar]
 28. Widiastuti IKSJY. Aspek Molekuler Hubungan Asupan Zinc dan Selenium dengan Hemoglobin Glikosilasi pada Pasien Diabetes Mellitus Tipe 2. *Journal of Biota* 2016;1. [Google Scholar]
 29. Finley JW, Grusak MA, Keck AS, Gregoire BR. Bioavailability of selenium from meat and broccoli as determined by retention and distribution of ⁷⁵Se. *Biological trace element research* 2004;99:191. [Google Scholar]
 30. Ilkhani F, Hosseini B, Saedisomeolia A. Niacin and oxidative stress: a mini review. *Journal of Nutritional Medicine and Diet Care* 2016;2:2-14. [Google Scholar]
 31. Chauhan S, Liu F, Leury B, Cottrell J, Celi P, Dunshea F. Functionality and genomics of selenium and vitamin E supplementation in ruminants. *Animal Production Science* 2016;56:1285-98. [Google Scholar]
 32. Hill KE, Wu S, Motley AK, Stevenson TD, Winfrey VP, Capecchi MR, et al. Production of selenoprotein P (Sepp1) by hepatocytes is central to selenium homeostasis. *Journal of biological chemistry* 2012 Nov;287(48):40414-24. [Google Scholar]
 33. Renko K, Werner M, Renner-Müller I, Cooper TG, Yeung CH, Hollenbach B, et al. Hepatic selenoprotein P (SePP) expression restores selenium transport and prevents infertility and motor-incoordination in Sepp-knockout mice. *Biochemical Journal* 2008;409:741-9. [Google Scholar]
 34. Hill KE, Zhou J, McMahan WJ, Motley AK, Burk RF. Neurological dysfunction occurs in mice with targeted deletion of the selenoprotein P gene. *The Journal of nutrition* 2004;134:157-61. [Google Scholar]
 35. Calissendorff J, Mikulski E, Larsen EH, Möller M. A prospective investigation of Graves' disease and selenium: thyroid hormones, auto-antibodies and self-rated symptoms. *European thyroid journal* 2015;4:93-8. [Google Scholar]
 36. Janegova A, Janega P, Rychly B, Kuracinova K, Babal P. The role of Epstein-Barr virus infection in the development of autoimmune thyroid diseases. *Endokrynologia Polska* 2015;66:132-6.
 37. Aaseth J, Frey H, Glatte E, Norheim G, Ringstad J, Thomassen Y. Selenium concentrations in the human thyroid gland. *Biological trace element research* 1990;24:147-52. [Google Scholar]
 38. Beckett GJ, Arthur JR. Selenium and endocrine systems. *Journal of endocrinology* 2005;184:455-65.
 39. Flohé L, Aumann KD, Steinert P. Role of selenium in the enzymatic reduction of hydroperoxides. *Phosphorus, Sulfur, and Silicon and the Related Elements* 1998;136:25-42. [Google Scholar]
 40. Guerra LN, MdCR dM, Miler EA, Moiguer S, Karner M, Burdman JA. Antioxidants and methimazole in the treatment of Graves' disease: effect on urinary malondialdehyde levels. *Clinica chimica acta* 2005;352:115-20. [Google Scholar]
 41. Tan L, Sang ZN, Shen J, Wu YT, Yao ZX, Zhang JX, et al. Selenium supplementation alleviates autoimmune thyroiditis by regulating expression of TH1/TH2 cytokines. *Biomed Environ Sci* 2013;26:920-5. [Google Scholar]
 42. Contempéré B, Escobar G.M. De , Denef JF, Dumont JE, Many MC. Thiocyanate induces cell necrosis and fibrosis in selenium-and iodine-deficient rat thyroids: a potential experimental model for myxedematous endemic cretinism in central Africa. *Endocrinology* 2004;145:994-1002. [Google Scholar]

43. Contempre B, Moine, O. Le , Dumont JE, Deneff JF, Many MC. Selenium deficiency and thyroid fibrosis. A key role for macrophages and transforming growth factor β (TGF- β). *Molecular and Cellular Endocrinology* 1996;124:7-15. [Google Scholar]
44. Vanderpas JB, Contempre B, Duale NL, Deckx H, Bebe N, Longombé AO, et al. Selenium deficiency mitigates hypothyroxinemia in iodine-deficient subjects. *The American journal of clinical nutrition* 1993;57:271. [Google Scholar]
45. Winther KH, Bonnema SJ, Cold F, Debrabant B, Nybo M, Cold S, et al. Does selenium supplementation affect thyroid function? Results from a randomized, controlled, double-blinded trial in a Danish population. *European journal of endocrinology* 2015;172:657-67. [Google Scholar]
46. Rasmussen LB, Schomburg L, Kohrle J, Pedersen IB, Hollenbach B, Hog A, et al. Selenium status, thyroid volume, and multiple nodule formation in an area with mild iodine deficiency. *Eur J Endocrinol* 2011;164:585-90. [Google Scholar]
47. Marinò M, Marcocci C, Vitti P, Chiovato L, Bartalena L. Selenium in the Treatment of Thyroid Diseases. *European thyroid journal* 2017;6:113-4. [Google Scholar]
48. Leo M, Bartalena L, Dottore GR, Piantanida E, Premoli P, Ionni I, et al. Effects of selenium on short-term control of hyperthyroidism due to Graves' disease treated with methimazole: results of a randomized clinical trial. *Journal of endocrinological investigation* 2017;40:281-7. [Google Scholar]
49. Hoffmann FW, Hashimoto AC, Shafer LA, Dow S, Berry MJ, Hoffmann PR. Dietary Selenium Modulates Activation and Differentiation of CD4+ T Cells in Mice through a Mechanism Involving Cellular Free Thiols-3. *The Journal of nutrition* 2010;140:1155-61. [Google Scholar]
50. Farias, C. De , Cardoso B, Oliveira, G. de , de Mello Guazzelli I , Catarino R, Chammas M, et al. A randomized-controlled, double-blind study of the impact of selenium supplementation on thyroid autoimmunity and inflammation with focus on the GPx1 genotypes. *Journal of endocrinological investigation* 2015;38:1065-74. [Google Scholar]
51. Perros P, Žarković M, Azzolini C, Ayvaz G, Baldeschi L, Bartalena L, et al. PREGO (presentation of Graves' orbitopathy) study: changes in referral patterns to European Group On Graves' Orbitopathy (EUGOGO) centres over the period from 2000 to 2012. *British Journal of Ophthalmology* 2015;99:1531-5. [Google Scholar]
52. Marcocci C, Kahaly GJ, Krassas GE, Bartalena L, Prummel M, Stahl M, et al. Selenium and the course of mild Graves' orbitopathy. *New England Journal of Medicine* 2011;364:1920-31. [Google Scholar]
53. Esposito D, Rotondi M, Accardo G, Vallone G, Conzo G, Docimo G, et al. Influence of short-term selenium supplementation on the natural course of Hashimoto's thyroiditis: clinical results of a blinded placebo-controlled randomized prospective trial. *Journal of endocrinological investigation* 2017;40:83-9. [Google Scholar]
54. Pilli T, Cantara S, Schomburg L, Cenci V, Cardinale S, Heid EC, et al. IFN γ -inducible chemokines decrease upon selenomethionine supplementation in women with euthyroid autoimmune thyroiditis: comparison between two doses of selenomethionine (80 or 160 μ g) versus placebo. *European thyroid journal* 2015;4:226-33. [Google Scholar]
55. Mazokopakis EE, Papadakis JA, Papadomanolaki MG, Batistakis AG, Giannakopoulos TG, Protopapadakis EE, et al. Effects of 12 months treatment with L-selenomethionine on serum anti-TPO Levels in Patients with Hashimoto's thyroiditis. *Thyroid* 2007;17:609-12. [Google Scholar]
56. Toulis KA, Anastasilakis AD, Tzellos TG, Goulis DG, Kouvelas D. Selenium supplementation in the treatment of Hashimoto's thyroiditis: a systematic review and a meta-analysis. *Thyroid* 2010;20:1163-73. [Google Scholar]
57. Zuuren, E.J. van , Albusta AY, Fedorowicz Z, Carter B, Pijl H. Selenium supplementation for Hashimoto's thyroiditis: summary of a Cochrane Systematic Review. *European thyroid journal* 2014;3:25-31. [Google Scholar]

58. Winther KH, Wichman JEM, Bonnema SJ, Hegedüs L. Insufficient documentation for clinical efficacy of selenium supplementation in chronic autoimmune thyroiditis, based on a systematic review and meta-analysis: Springer, 2017.
59. Vrca V, Mayer L, Škreb F, Rahelić D, Marušić S. Antioxidant supplementation and serum lipids in patients with Graves' disease: Effect on LDL-cholesterol. *Acta Pharmaceutica* 2012;62:115-22. [Google Scholar]