Selenium and Graves' Disease

Vahab Fatourechi, Hassan M. Heshmati

Emeritus Member, Division of Endocrinology, Diabetes, Metabolism and Nutrition (Fatourechi), Mayo Clinic, Rochester, Minnesota; and Endocrinology Metabolism Consulting, LLC (Heshmati), Anthem, Arizona

Received: 11 Sep. 2023; Accepted: 18 Jan. 2024

Abstract- Selenium, a trace element present in specific selenoproteins, is essential for thyroid hormone metabolism. Selenium is also an antioxidant with immunosuppressive properties and may help in managing thyroid autoimmune diseases, including Graves' (GD) hyperthyroidism and Graves' ophthalmopathy (GO). There were 320 clinical studies related to selenium and thyroid published in English and French between January 1, 2000, and June 1, 2023. Our focus was to identify studies reporting levels of serum selenium in patients with GD and studies that assessed the effect of selenium supplementation on outcomes of GD hyperthyroidism and GO. We also reviewed 20 systematic reviews and meta-analyses of randomized controlled trials that reported selenium levels in GD and the effects of supplementation on GD and GO outcomes. Our review showed that patients with GD had serum selenium levels lower than those of various control patients. In the short-term, a selenium supplement to antithyroid drugs showed benefit for GD hyperthyroidism in most studies, but long-term benefits and positive effects on remission rate were unclear. Some studies did not show benefit. The benefits may depend on baseline selenium deficiency. Two randomized controlled trials showed positive effects of supplementation for mild GO; however, studies about moderate and severe GO are still needed. There is evidence for benefit with short-term selenium supplementation for GD hyperthyroidism, but controlled studies are needed to assess long-term benefits, and benefits in selenium-sufficient areas.

Acta Med Iran 2024;62(Janyary-February):6-14.

Keywords: Autoimmunity; Graves' disease; Graves' ophthalmopathy; Hashimoto thyroiditis; Selenium; Thyroid function

Selenium is an essential trace element (1) with dietary sources from meat, seafood, eggs, and grains (2). Selenium is critical for thyroid function (3-5). In addition, selenium-containing selenoenzymes have antioxidant properties, therefore making selenium deficiency a potential contributor in the pathogenesis of autoimmune thyroid disorders such as Hashimoto thyroiditis and Graves' disease (GD) (4). Studies have shown that selenium supplementation decreased the levels of thyroid autoantibodies in Hashimoto thyroiditis (6) and GD (7), and randomized controlled trials have shown that selenium therapy improved mild Graves' ophthalmopathy (GO) (8,9). Studies have also shown that selenium supplementation enhanced the effect of antithyroid drugs and lowered the levels of thyroid-stimulating hormone receptor antibodies (TRAb) in GD, and patients with active GD had lower selenium levels than patients in remission (10,11). However, a randomized controlled trial from Germany reported no positive effect of selenium supplementation on GD (12). Thus, the issue of selenium supplementation for GD remains controversial.

In this mini review, we aimed to present the current understanding of the role of selenium in thyroid pathophysiology and thyroid autoimmunity and the evidence for selenium supplementation for patients with GD hyperthyroidism and/or GO. The relationship of selenium with other thyroid autoimmune conditions is not the subject of this review.

Data sources and search strategies

We performed a comprehensive search of Ovid

Corresponding Author: V. Fatourechi
Emeritus Member, Division of Endocrinology, Diabetes, Metabolism and Nutrition (Fatourechi), Mayo Clinic, Rochester, Minnesota; and Endocrinology Metabolism Consulting, LLC (Heshmati), Anthem, Arizona
Tel: +98 2142910700, E-mail address: fatourechi.vahab@mayo.edu

MEDLINE, PubMed and Epub Ahead of Print, In-Process & Other Nonindexed Citations, Ovid EMBASE, and Scopus between January 1, 2000, and June 1, 2023. The search strategy was designed and conducted by an experienced librarian at Mayo Clinic with input from the study's first author (V.F.) and limited to English and French languages. Controlled vocabulary supplemented with keywords was used to search, i.e., selenium, selenium and GD, selenium and autoimmunity, selenium and thyroid disease, selenium and GO, orbitopathy and selenium, selenium and thyroid function, and selenium levels thyroid disease.

Selenium deficiency

Selenium deficiency is a common worldwide problem (13). The selenium content of the soil, dietary habits, and consumed foods containing selenium (e.g., nuts, cereals, eggs, meat, fish) all contribute to serum selenium levels. Contributors to selenium deficiency include pregnancy and severe illness, which can result in very low concentrations of selenium biomarkers. Finland has added selenium to the food chain for decades to improve its population's selenium levels (14,15). Selenium has a narrow optimal serum reference range (90-120 µg/L), with the usual intake of 40 to 300 µg/day. Adverse effects can occur with both extremes of intake (16). Thus, although obtaining an optimal selenium level is desirable, harmfully high serum concentrations should be of equal concern (2,16).

A study in different counties in China associated low selenium levels with increased risk of autoimmune thyroid disease (17). Also, serum selenium measurements in 4 European countries, including Greece, Romania, Austria, and Italy showed selenium deficiencies in all, with Austria more and Italy less deficient. Plasma selenium levels were lower in patients with GD than in those without autoimmune thyroid disease. However, in contrast to the Chinese study, a relationship was not shown between the degree of deficiency and the prevalence of autoimmune thyroid disease (18). In an Austrian study, persons without an autoimmune thyroid disease had slightly higher serum selenium levels than those with an autoimmune thyroid disease, although the difference was not statistically significant or sufficient to support a link between inadequate selenium supply and autoimmune thyroid disease (5). In a 2016 review, the evidence for stopping the progression of subclinical hypothyroidism with selenium supplementation was inconclusive, even though low selenium intake was shown to be associated with a higher prevalence of thyroid autoimmunity (19).

Adverse effects of selenium toxicity

Adverse effects can occur with excess selenium intake. A Chinese study suggested that higher levels of serum selenium might increase. the risk of metabolic syndrome and increase the level of fasting plasma glucose (20). A randomized study of selenium supplementation (100, 200, or 300 µg/day) taken for 5 years by 491 Danish volunteers aged 60 to 73 years showed increased all-cause mortality at 10-year follow-up for the group receiving 300 µg/day, but this was not seen in 100- and 200-µg/day groups (21). Although the sample size was small, the findings indicate that it is advisable to limit selenium supplementation to less than 200 µg/day in clinical practice and in study populations. Other possible adverse effects, although controversial, include increased risk of squamous cell carcinoma of the skin and prostate cancer (2). Acute selenium toxicity has been reported after high oral intake (harmful levels >400 µg/d), and death has occurred with ingested doses greater than 1 mg selenium/kg body weight (22). Abdominal pain, nausea, vomiting, and diarrhea are symptoms of toxicity, and severe toxicity results in cardiac and pulmonary symptoms (22). Thus, harmfully high serum concentrations must be avoided (16).

Biologic actions of selenium and selenoproteins

In the 1990s, selenium was identified as a component of an enzyme involved in thyroid hormone metabolism. Selenium is present in specific selenoproteins including glutathione peroxidase, thioredoxin reductase, and iodothyronine deiodinase (23) and is essential for selenocysteine-containing selenoproteins, including the enzymes glutathione peroxidase 3 (GPX3) and the selenium-transporter, selenoprotein-P. Serum selenoprotein-P comes mainly from hepatocytes, whereas GPX3 is produced mainly by the kidneys (24).

The biologic functions of selenoproteins encompass a range of essential roles. These include antioxidant activities (25), regulation of the immune system (26), and regulation of thyroid hormone metabolism (27). Selenoproteins also have oxidation-reduction and anti-inflammatory activity, enhance CD4+/CD25, and suppress cytokine secretion, thus preventing apoptosis of thyroid follicular cells (28), and a selenium-dependent downregulation of interferon-γ–inducible chemokines has been reported (29). Selenium has been reported to have a role in the immune response and erythropoiesis (30). However, no specific hormonal regulation was identified for selenium in contrast to hormone regulation of calcium and phosphorus (31). Selenoproteins have been reported to protect thyroid cells and fibroblasts from

hydrogen peroxide–induced damage (23), as shown in in vitro studies of human thyrocytes and fibroblasts (32).

Effects of selenium on the thyroid gland

Selenoproteins are involved in thyroid hormone synthesis and deactivation, as well as in iodine release (2). Selenium acts as a cofactor for the deiodinases involved in thyroid hormone metabolism (33). During the synthesis of thyroid hormones, reactive oxygen species (ROS), which can damage cells, are produced. Selenium helps neutralize ROS by working with glutathione peroxidases, enzymes that are also selenoproteins. In patients with autoimmune thyroid disease, levels of ROS are elevated. Because selenoproteins enhance ROS clearance, selenium may help in inhibiting thyroid autoimmunity (34). Mitochondria also contain enzymes with selenium as a cofactor, and thyroid hormones have an important role on mitochondrial biogenesis. Thus, selenium deficiency or excess may be important in mitochondrial dysfunction in the setting of thyroid disorders (35). A meta-analysis that included 787 patients with autoimmune thyroid disease concluded that selenium decreases thyroperoxidase antibody (TPOAb) titers at 6 months and thyroglobulin antibody (TGAb) titers at 12 months (36). Benefits of selenium supplementation on TGAb may be by antioxidant activity, upregulating of the activated regulatory T cells (37), and reducing ROS (34).

Selenium levels in GD

A 2009 study from Europe showed reduced serum levels of selenium in GD and GO, and the levels correlated inversely with severity of GO, but it was not clear if the level of deficiency was a result or cause of severity (38). A 2010 study reported no difference in serum selenium levels in GD and controls (39) (Table 1). In 2013, it was reported that patients with a new diagnosis of GD had significantly lower serum selenium levels than control patients (40). In a 2014 Australian study, serum selenium levels in a population with borderline selenium status were lower in patients with GO than in patients with GD but without GO, indicating that selenium deficiency may be a risk factor for GO in patients with GD (41). Another report showed that the degree of low serum selenium levels of patients with GO did not corelate with the severity of GO (42). Results of this retrospective study neither supported nor discouraged adjuvant selenium supplementation.

In a 2022 Iranian study, the selenium level of 120 patients with GD (97.7 µg/L) was significantly lower than that in the 120 control patients with normally functioning thyroids (122.6 µg/L) (43). Patients with GO also had significantly lower serum selenium levels than patients with GD but without GO. In another Iranian study, however, no significant differences were shown for serum selenium levels of patients with GO and GD compared with a control group, and there was no difference in selenium levels for those with and without GO in the GD group (44). In a study of selenium supplementation in Greece, for patients with hyperthyroid GD vs controls, the increase in serum selenium levels for patients with GD was less than for control patients, indicating the possibility of lower selenium levels for patients with GD (45). In a 2022 study from South Korea, a selenium-sufficient geographic area, serum selenium levels of patients with GD with and without GO were significantly lower than those of control patients (4). Mean serum selenium levels were also slightly lower in patients with GO than for patients with GD without GO. The levels were lower in patients with GO and eyelid retraction.

Table 1. Studies of Serum Se Levels in GD and GO

Author	Year	Country	Patients, No.	Low Se level		Difference from controls
				GD	GO	
Dehina (38)	2009	Germany	NA	Yes	Yes	Yes
Karassas (39)	2010	Europe		No	No	No difference
Bülow Pedersen et al (40)	2013	Denmark	92 GD	Yes	NA	NA
Khong et al (41)	2014	Australia	97 GD 101 GO	NA	Yes	NA
Dehina et al (42)	2016	Germany	92 GO	NA	Yes	NA
Heidari and Sheikhi (43)	2022	Iran	120 GD 120 controls	Yes	NA	NA
Owji et al (44)	2022	Iran	60 GO 56 GD 58 controls	No	No	No difference
Kim et al (4)	2022	South Korea	33 GD 31 GO 27 controls	Yes	Yes	NA

Abbreviations: GD, Graves' disease; GO, Graves' ophthalmopathy; NA, not available; Se, selenium

Selenium supplementation as a therapy for GD hyperthyroidism

A 2007 retrospective study reported that patients in GD remission had higher serum selenium levels than those in relapse. In other reports, when selenium was given in addition to antithyroid drugs, patients with GD reverted to euthyroidism sooner than those treated with antithyroid drugs alone; there was no benefit in 2 studies (46), as described in Tables 2 and 3 (7,10-12,46-53). In an Italian trial, 42 patients with new-onset GD and marginal selenium and vitamin D levels were randomly assigned to treatment with either methimazole monotherapy or methimazole with selenium and vitamin D supplementation (11). The study showed that achieving optimal selenium and vitamin D levels increased the efficacy of methimazole therapy by achieving earlier euthyroidism.

Table 2. Randomized Studies of the Effect of Se Supplementation on GD Hyperthyroidism

Author	Year	Location	Patients, No.	Se status	Result	Overall effect
Calissendorff *et al* (48)	2015	Sweden	38	Sufficient	Earlier euthyroid. No significant reduction of TRAb	Benefit biochemical. Clinical benefit unclear
Wang *et al* (49)	2016	China	41	NA	Reduced TRAb. Earlier remission	Benefit
Leo *et al* (50)	2017	Italy	30	Sufficient	No short-term benefit	No benefit
Kahaly *et al* (12)	2017	Germany	70 (300 µg)	Sufficient	No difference for response or remission rate. Se levels normal at baseline	No benefit
Xu *et al* (51)	2019	China	103	NA	Better control. Lower TRAb	Benefit
Gallo *et al* (11)	2022	Italy	42	Marginally insufficient	Sooner euthyroid	Benefit
Zhang *et al* (7)	2022	China	103 (50 µg)	NA	Better results. Sooner euthyroid. Lower TRAb	Benefit

Abbreviations: GD, Graves' disease; NA, not applicable; Se, selenium; TRAb, thyroid-stimulating hormone receptor antibodies

A randomized trial of selenium supplementation in China included 103 patients with hyperthyroidism and GD randomized to 2 groups: methimazole and methimazole plus selenium (51). After 6 months of therapy, thyrotropin receptor antibody, TPOAb, and TGAb decreased significantly in both groups, with a greater reduction in the group taking the selenium supplement. In another study from China that included children with GD hyperthyroidism, methimazole combined with selenium reduced the levels of TPOAb, TRAb, and free thyroxine, augmenting the effect of methimazole (7). The Chinese studies should be considered in the light of regional variations in selenium intake.

In a meta-analysis of 10 trials involving 796 patients with GD hyperthyroidism taking antithyroid therapy, TRAb levels decreased at 6 months with selenium supplementation (10). In addition, patients taking selenium supplements were more likely than patients taking antithyroid agents alone to have improved thyroid function. However, the beneficial effect was not detected at 9 months (Table 3). Whether these effects have clinical significance was not clear from the study. Another meta-analysis of 6 studies also suggested benefit from selenium supplementation (7). A recent meta-analysis from China, published in 2020, included 7 controlled studies that suggested benefit for selenium supplementations, but results were not consistent in the studies (53).

Not all studies of selenium supplementation have had positive findings. An Italian study of patients with GD who had sufficient levels of selenium did not show short-term benefit for selenium supplements (50). In a randomized controlled trial conducted in Germany, patients with hyperthyroidism and GD received a 300 µg/day selenium supplement for 6 months (12). However, the addition of selenium to methimazole did not augment the response to antithyroid therapy or change recurrence rates for GD (12). In this study, baseline selenium and selenoprotein levels of study patients were within normal ranges.

These negative studies do not necessarily exclude the benefits of selenium supplementation for selenium deficiency (52). The available studies are not conclusive, however, regarding selenium supplementation for GD, owing to several important limitations. The long-term success rate of selenium supplementation with antithyroid drugs (e.g., in maintaining remission of GD) is not available. Also, there was a limitation because of

the small number of patients in randomized studies. More research is therefore needed to identify which persons with GD could benefit from selenium supplementation, possibly by using selenium sufficiency levels or genetic profiles (2,54). For example, selenium supplementation may confer benefit only if serum levels are insufficient at baseline. Geographic variation in selenium sufficiency may also help explain differences in results of studies. It is also advisable to measure serum selenium levels before and during selenium supplementation to avoid a potential iatrogenic selenium overdose (46).

Table 3. Reviews and Meta-Analyses of Se Supplementation in GD Hyperthyroidism

Author	Year	Location	Study type	Se supplementation with methimazole	Se effect
Dharmasena (46)	**2014**	**UK**	**Review of 137 papers on GO**	**Faster achievement of euthyroidism**	**Benefit**
Winther *et al* (52)	**2017**	**Denmark**	**Review article**	**No support for GD supplementation with Se sufficiency**	**No benefit if no Se deficiency**
Zheng *et al* (10)	**2018**	**China**	**Meta-analysis of 10 trials with 796 patients**	**Se group benefited at 6 months; no benefit at 9 months**	**Benefit at 6 months. Short-term benefit**
Wang and Yu (53)	**2020**	**China**	**Meta-analysis of 7 reports**	**Benefit in 5 of 7 studies of Se supplementation**	**Benefit not consistent**

Abbreviations: GD, Graves' disease; GO, Graves' ophthalmopathy; Se, selenium

Selenium and GO

Selenium has an effect in orbital fibroblast culture. As an antioxidant, selenium improves the remodeling of orbital tissues and has a protective effect against oxidative stress in fibroblasts (32). When selenium is added to cultured orbital fibroblasts from patients with GO, it suppresses hyaluronan and cytokine production, such as interleukin (IL)-1α, IL-8, and tumor necrosis factor (16). In a 2021 study of cultured orbital fibroblasts from GO patients, hyaluronan and inflammatory cytokine production were suppressed by selenium (55), and selenium protected orbital fibroblasts from the harmful effects of hydrogen peroxide (56).

Studies have also described selenium levels in GO (Table 1). Compared with control patients, patients with GO had lower levels of selenoprotein P. It was not clear whether this could be attributed to immune-related inflammatory reactions from selenium consumption (57). In a study of patients with newly diagnosed GD (20 with inactive GO, 18 with active GO), low selenium levels were associated with higher clinical activity scores (CAS), and selenium was an independent predictor for the diagnosis of active GO (58). A 2020 review concluded that selenium levels were significantly lower for patients with GD with or without GO, when the patients were compared with non-GD control groups (59). In this review, selenium levels were not associated with CAS, but low selenium levels were associated with eyelid retraction. In a study of 32 patients with mild GO and 68 with severe GO, selenium deficiency (low-level cutoff of 93 μg/L) was noted in 48.5% of patients with severe disease and 12.5% of patients with mild disease (60). The authors concluded that relative selenium insufficiency (serum level ≤93 μg/L) was a potential risk factor for development of severe GO, and they recommended measuring and monitoring serum selenium levels of patients with GO to predict disease progression and guide selenium- supplementation therapy.

Selenium supplementation for GO therapy

In a seminal paper from 2011, the European Group on Graves' Orbitopathy reported results of a randomized controlled trial of 159 patients with mild GO that showed a benefit for patients after 6 months of selenium selenite (has 25% selenium trace element) supplementation at 100 μg twice daily (8). Signs and symptoms of GO improved, and the progression of mild GO slowed for patients receiving selenium. There were significant improvements in CAS and quality of life at 6 months in the selenium group (vs the placebo and pentoxifylline groups). In this study from 6 countries in Europe, selenium levels were not measured before the study, but Europe is a relatively selenium-deficient continent (61). The authors concluded that in mild cases, selenium administration significantly improved GO and quality of life and slowed progression of disease (8). The study resulted in a recommendation for selenium supplements for mild GO by the European Group on Graves' Orbitopathy (62). In 2016, the European Thyroid Association/European Group on Graves' Orbitopathy published guidelines for managing GO that advised a 6-month course of selenium supplementation for mild GO, which had been shown to be effective in improving manifestations of GO and preventing progression to more

severe forms of disease (63). The protocol has been published for an ongoing multicenter, randomized, prospective, open-label controlled trial of mild to moderate GO in South Korea, a selenium-sufficient area, although results have not been reported yet (33).

A 2022 randomized controlled trial included 30 patients seen in an ophthalmology clinic in Mexico City who were given 100 µg of selenium twice daily and a control group given placebo tablets twice daily for 6 months (9). The patients in both groups were evaluated by CAS before and after the first, third, and sixth months of treatment. This was a small study, and baseline serum selenium status of the studied patients was unclear, although the authors stated that central Mexican soil is selenium deficient. At 6 months, selenium was associated with decreased CAS and slowing of progression of mild GO. As a result of these 2 studies, the European Group on Graves' Orbitopathy suggested that in mild and active GO, local treatments, supportive measures, and selenium supplementation are usually sufficient to manage GO (64).

Since the 2011 randomized trial, selenium supplements have been used for GO by 73% of European endocrinologists (65), which is substantially more than the 32% of North American endocrinologists who supplement selenium for GO (66). Results of another survey showed that 38.2% of European Thyroid Association members would give a selenium supplement for GD hyperthyroidism without GO, and most responders would use a selenium supplement for patients with mild to severe ocular involvement (67). This clinical practice is not evidence-based and disagrees with current European guidelines that recommend selenium as a 6-month treatment only for mild GO, as the effects of selenium supplementation for moderate to severe GO are unknown. Controlled studies of selenium supplementation in patients with severe GO are difficult to complete, and results will be difficult to interpret. Because patients with severe GO require immunosuppressive therapy and surgical reconstruction of the orbit, many factors influence the outcomes.

Although the long-term effectiveness of selenium for GD remains questionable, its use in the management of mild GO is beneficial and recommended (59,64,68). A consensus statement published in 2022 by the American Thyroid Association and the European Thyroid Association recommends use of 200 µg/day of selenium selenite for 6 months for mild GO and states that benefits for moderate and severe GO and benefits for supplementation beyond 6 months are lacking (69).

Selenium supplementation should also be a strong consideration for patients in selenium-deficient geographic areas (64). It should be noted that the 2 randomized trials of selenium supplementation for mild GO were in areas of possible selenium deficiency. Selenium supplementation for all patients with GO is not evidence-based. Evidence-based data are needed for moderate and severe cases of GO and for patients with selenium sufficiency.

Selenium and selenoproteins are essential for thyroid hormone metabolism and synthesis. Selenium is also an antioxidant with immunosuppressive action. Selenium deficiency is common and varies geographically, which may explain the different results for low and normal levels of serum selenium in studies of GD and GO. Not enough studies correlate selenium deficiency and pretherapy serum selenium levels on the response of hyperthyroid GD and GO to selenium supplementation. Two randomized studies (1 in Europe, 1 in Mexico) showed benefit for supplementation in mild GO. However, these 2 studies did not include baseline serum selenium levels. Europe is likely a selenium-deficient area (18), and Mexico City may be in a selenium-deficient area (9).

The addition of selenium supplements to drug therapy for GD hyperthyroidism in certain geographic areas has shown short-term benefit; however, its long-term benefits and benefits in selenium-sufficient areas are not known. It is reasonable to suggest measuring selenium levels for all patients with GD to optimize serum levels with supplementation. However, further studies are needed to evaluate the beneficial effects of selenium supplementation and the relationship of the effect of supplementation with baseline selenium levels. Additionally, research on the long-term effects and remission rate of GD hyperthyroidism is essential.

A scientometrics analysis of publications on the effect of selenium on thyroid disorders by Pakdel *et al*., in 2019, showed that most studies about relationship of thyroid and selenium were from Europe, particularly Germany (70). It is of note that most of the studies in present review were from Europe or China. We did not find any controlled studies from North America except a small study from Mexico City for GO. Therefore, more North American studies are needed as are studies of possible adverse effects of excessive selenium supplementation (e.g., on glucose metabolism). For mild GO, the current recommended dose is 200 µg/day of selenium selenite for 6 months. Selenium supplementation has not been studied for moderate and severe GO, and in these cases its use is not evidence-based, and benefits are unknown. When it is used for mild GO, occasional monitoring of serum

selenium levels should be considered, and the dose should be adjusted to avoid excess levels. Safety of supplemental doses above 300 µg/day is unknown.

Acknowledgments

Marianne Mallia, ELS, MWC, senior scientific/medical editor, Mayo Clinic, provided editorial suggestions on a previous draft of the manuscript.

The authors also thank Larry J. Prokop, MLIS, for providing library support (the search strategy and literature search).

References

1. Rayman MP. Selenium and human health. Lancet 2012;379:1256-68.
2. Winther KH, Rayman MP, Bonnema SJ, Hegedus L. Selenium in thyroid disorders - essential knowledge for clinicians. Nat Rev Endocrinol 2020;16:165-76.
3. Zhou Q, Xue S, Zhang L, Chen G. Trace elements and the thyroid. Front Endocrinol (Lausanne) 2022;13:904889.
4. Kim TH, Ko J, Kim BR, Shin DY, Lee EJ, Yoon JS. Serum Selenium Levels in Patients with Graves Disease: Associations with Clinical Activity and Severity in a Retrospective Case-control Study. Korean J Ophthalmol 2022;36:36-43.
5. Wimmer I, Hartmann T, Brustbauer R, Minear G, Dam K. Selenium levels in patients with autoimmune thyroiditis and controls in lower Austria. Horm Metab Res 2014;46:707-9.
6. de Farias CR, Cardoso BR, de Oliveira GM, de Mello Guazzelli IC, Catarino RM, Chammas MC, 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. J Endocrinol Invest 2015;38:1065-74.
7. Zhang XH, Yuan GP, Chen TL. Clinical effect of methimazole combined with selenium in the treatment of toxic diffuse goiter in children. World J Clin Cases 2022;10:1190-7.
8. Marcocci C, Kahaly GJ, Krassas GE, Bartalena L, Prummel M, Stahl M, et al. Selenium and the course of mild Graves' orbitopathy. N Engl J Med 2011;364:1920-31.
9. Almanza-Monterrubio M, Garnica-Hayashi L, Davila-Camargo A, Nava-Castaneda A. Oral selenium improved the disease activity in patients with mild Graves' orbitopathy. J Fr Ophtalmol 2021;44:643-51.
10. 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. Evid Based Complement Alternat Med 2018;2018:3763565.
11. Gallo D, Mortara L, Veronesi G, Cattaneo SA, Genoni A, Gallazzi M, et al. Add-On Effect of Selenium and Vitamin D Combined Supplementation in Early Control of Graves' Disease Hyperthyroidism During Methimazole Treatment. Front Endocrinol (Lausanne) 2022;13:886451.
12. Kahaly GJ, Riedl M, Konig J, Diana T, Schomburg L. Double-Blind, Placebo-Controlled, Randomized Trial of Selenium in Graves Hyperthyroidism. J Clin Endocrinol Metab 2017;102:4333-41.
13. Veisa V, Kalere I, Zake T, Strele I, Makrecka-Kuka M, Upmale-Engela S, et al. Assessment of Iodine and Selenium Nutritional Status in Women of Reproductive Age in Latvia. Medicina (Kaunas) 2021;57:1211.
14. Schomburg L. Selenium Deficiency Due to Diet, Pregnancy, Severe Illness, or COVID-19-A Preventable Trigger for Autoimmune Disease. Int J Mol Sci. 2021;22:8532.
15. Alfthan G, Eurola M, Ekholm P, Venalainen ER, Root T, Korkalainen K, et al. Effects of nationwide addition of selenium to fertilizers on foods, and animal and human health in Finland: From deficiency to optimal selenium status of the population. J Trace Elem Med Biol 2015;31:142-7.
16. Gorini F, Sabatino L, Pingitore A, Vassalle C. Selenium: An Element of Life Essential for Thyroid Function. Molecules 2021;26:7084.
17. Wu Q, Rayman MP, Lv H, Schomburg L, Cui B, Gao C, et al. Low Population Selenium Status Is Associated With Increased Prevalence of Thyroid Disease. J Clin Endocrinol Metab 2015;100:4037-47.
18. Krassas GE, Pontikides N, Tziomalos K, Tzotzas T, Zosin I, Vlad M, et al. Selenium status in patients with autoimmune and non-autoimmune thyroid diseases from four European countries. Expert Rev Endocrinol Metab 2014;9:685-92.
19. Wiersinga WM. Clinical Relevance of Environmental Factors in the Pathogenesis of Autoimmune Thyroid Disease. Endocrinol Metab (Seoul) 2016;31:213-22.
20. Yuan Z, Xu X, Ye H, Jin L, Zhang X, Zhu Y. High levels of plasma selenium are associated with metabolic syndrome and elevated fasting plasma glucose in a Chinese population: A case-control study. J Trace Elem Med Biol 2015;32:189-94.
21. Rayman MP, Winther KH, Pastor-Barriuso R, Cold F, Thvilum M, Stranges S, et al. Effect of long-term selenium supplementation on mortality: Results from a multiple-dose, randomised controlled trial. Free Radic Biol Med 2018;127:46-54.
22. Hadrup N, Ravn-Haren G. Acute human toxicity and

mortality after selenium ingestion: A review. J Trace Elem Med Biol 2020;58:126435.
23. Brodin O, Hackler J, Misra S, Wendt S, Sun Q, Laaf E, et al. Selenoprotein P as Biomarker of Selenium Status in Clinical Trials with Therapeutic Dosages of Selenite. Nutrients 2020;12:1067.
24. Sun Q, Mehl S, Renko K, Seemann P, Gorlich CL, Hackler J, et al. Natural Autoimmunity to Selenoprotein P Impairs Selenium Transport in Hashimoto's Thyroiditis. Int J Mol Sci 2021;22:13088.
25. Santos LR, Neves C, Melo M, Soares P. Selenium and Selenoproteins in Immune Mediated Thyroid Disorders. Diagnostics (Basel) 2018;8:70.
26. Schomburg L. Selenium, selenoproteins and the thyroid gland: interactions in health and disease. Nat Rev Endocrinol 2011;8:160-71.
27. Valea A, Georgescu CE. Selenoproteins in human body: focus on thyroid pathophysiology. Hormones (Athens) 2018;17:183-96.
28. Duntas LH. The Role of Iodine and Selenium in Autoimmune Thyroiditis. Horm Metab Res 2015;47:721-6.
29. Pilli T, Cantara S, Schomburg L, Cenci V, Cardinale S, Heid EC, et al. IFNgamma-Inducible Chemokines Decrease upon Selenomethionine Supplementation in Women with Euthyroid Autoimmune Thyroiditis: Comparison between Two Doses of Selenomethionine (80 or 160 mug) versus Placebo. Eur Thyroid J 2015;4:226-33.
30. Wang Y, Zhao F, Rijntjes E, Wu L, Wu Q, Sui J, et al. Role of Selenium Intake for Risk and Development of Hyperthyroidism. J Clin Endocrinol Metab 2019;104:568-80.
31. Kohrle J. Selenium in Endocrinology-Selenoprotein-Related Diseases, Population Studies, and Epidemiological Evidence. Endocrinology 2021;162:bqaa228.
32. Ruggeri RM, D'Ascola A, Vicchio TM, Campo S, Giani F, Giovinazzo S, et al. Selenium exerts protective effects against oxidative stress and cell damage in human thyrocytes and fibroblasts. Endocrine 2020;68:151-62.
33. Chung CW, Jung KY, Jung EH, Lee MJ, Park YJ, Lee JK, et al. Efficacy of selenium supplementation for mild-to-moderate Graves' ophthalmopathy in a selenium-sufficient area (SeGOSS trial): study protocol for a phase III, multicenter, open-label, randomized, controlled intervention trial. Trials 2023;24:272.
34. Chakrabarti SK, Ghosh S, Banerjee S, Mukherjee S, Chowdhury S. Oxidative stress in hypothyroid patients and the role of antioxidant supplementation. Indian J Endocrinol Metab 2016;20:674-8.
35. Gheorghiu ML, Badiu C. Selenium involvement in mitochondrial function in thyroid disorders. Hormones (Athens) 2020;19:25-30.
36. Fan Y, Xu S, Zhang H, Cao W, Wang K, Chen G, et al. Selenium supplementation for autoimmune thyroiditis: a systematic review and meta-analysis. Int J Endocrinol 2014;2014:904573.
37. Hu Y, Feng W, Chen H, Shi H, Jiang L, Zheng X, et al. Effect of selenium on thyroid autoimmunity and regulatory T cells in patients with Hashimoto's thyroiditis: A prospective randomized-controlled trial. Clin Transl Sci 2021;14:1390-402.
38. Dehina NE, Minich W, Behrends T, Morgenthaler NG, Kohrle J, Schomburg L. Circulating selenoprotein P concentrations are decreased in patients with Graves' disease and correlate inversely to severity of orbitopathy. Acta Med Port 2009;22:1.
39. Karassas G, Karras S, Boborides K, Spanos E. Selenium serum levels in patients with mild Graves' orbitopathy: Results of a controlled study. 12th European Congress of Endocrinology (Abstract) 2010;22:779.
40. Bülow Pedersen I, Knudsen N, Carlé A, Schomburg L, Köhrle J, Jørgensen T, et al. Serum selenium is low in newly diagnosed Graves' disease: a population-based study. Clin Endocrinol (Oxf) 2013;79:584-90.
41. Khong JJ, Goldstein RF, Sanders KM, Schneider H, Pope J, Burdon KP, et al. Serum selenium status in Graves' disease with and without orbitopathy: a case-control study. Clin Endocrinol (Oxf) 2014;80:905-10.
42. Dehina N, Hofmann PJ, Behrends T, Eckstein A, Schomburg L. Lack of Association between Selenium Status and Disease Severity and Activity in Patients with Graves' Ophthalmopathy. Eur Thyroid J 2016;5:57-64.
43. Heidari Z, Sheikhi V. Serum selenium status in Graves' disease and Hashimoto's thyroiditis in an iodine-sufficient area: A case-control study. J Res Med Sci 2022;27:87.
44. Owji N, Moradi F, Khalili MR, Jahanbani-Ardakani H. Serum Selenium Levels in Patients With Graves Disease With or Without Thyroid Ophthalmopathy. Endocr Pract 2022;28:1216-20.
45. Duntas LH, Boutsiadis A, Tsakris A. Impaired Metabolism of Selenomethionine in Graves' Disease: A Biokinetics Study of Soft Gel Capsule Formulation. Horm Metab Res 2017;49:589-94.
46. Dharmasena A. Selenium supplementation in thyroid associated ophthalmopathy: an update. Int J Ophthalmol 2014;7:365-75.
47. Wertenbruch T, Willenberg HS, Sagert C, Nguyen TB, Bahlo M, Feldkamp J, et al. Serum selenium levels in patients with remission and relapse of graves' disease. Med Chem 2007;3:281-4.
48. Calissendorff J, Mikulski E, Larsen EH, Moller M. A Prospective Investigation of Graves' Disease and

Selenium: Thyroid Hormones, Auto-Antibodies and Self-Rated Symptoms. Eur Thyroid J 2015;4:93-8.

49. Wang L, Wang B, Chen SR, Hou X, Wang XF, Zhao SH, et al. Effect of Selenium Supplementation on Recurrent Hyperthyroidism Caused by Graves' Disease: A Prospective Pilot Study. Horm Metab Res 2016;48:559-64.
50. Leo M, Bartalena L, Rotondo Dottore G, 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. J Endocrinol Invest 2017;40:281-7.
51. Xu B, Wu D, Ying H, Zhang Y. A pilot study on the beneficial effects of additional selenium supplementation to methimazole for treating patients with Graves' disease. Turk J Med Sci 2019;49:715-22.
52. Winther KH, Bonnema SJ, Hegedus L. Is selenium supplementation in autoimmune thyroid diseases justified? Curr Opin Endocrinol Diabetes Obes 2017;24:348-55.
53. Wang M, Yu Y. Therapeutic Effects of Combination Regimens Including Methimazole on Graves Hyperthyroidism: A Network Meta-Analysis of Randomized Controlled Trials. Endocr Pract 2020;26:675-87.
54. Bednarczuk T, Schomburg L. Challenges and perspectives of selenium supplementation in Graves' disease and orbitopathy. Hormones (Athens) 2020;19:31-9.
55. Kim BY, Jang SY, Choi DH, Jung CH, Mok JO, Kim CH. Anti-inflammatory and Antioxidant Effects of Selenium on Orbital Fibroblasts of Patients With Graves Ophthalmopathy. Ophthalmic Plast Reconstr Surg 2021;37:476-81.
56. Rotondo Dottore G, Chiarini R, De Gregorio M, Leo M, Casini G, Cestari L, et al. Selenium rescues orbital fibroblasts from cell death induced by hydrogen peroxide: another molecular basis for the effects of selenium in graves' orbitopathy. Endocrine 2017;58:386-9.
57. Federige MAF, Romaldini JH, Miklos A, Koike MK, Takei K, Portes ES. Serum selenium and selenoprotein-P levels in autoimmune thyroid diseases patients in a select center: a transversal study. Arch Endocrinol Metab 2017;61:600-7.
58. He M, Wang Y, Wang J, Sui J, Ding X, Chen Z, et al. The potential markers involved in newly diagnosed graves' disease and the development of active graves' orbitopathy. Cytokine 2020;127:154998.
59. Lanzolla G, Marino M, Marcocci C. Selenium in the Treatment of Graves' Hyperthyroidism and Eye Disease. Front Endocrinol (Lausanne) 2020;11:608428.
60. Lumyongsatien M, Bhaktikamala U, Thongtong P, Sintuwong S, Nimitwongsakul O, Kanokkantapong J, et al. Relative selenium insufficiency is a risk factor for developing severe Graves' orbitopathy: a case-control study. BMJ Open Ophthalmol 2021;6:e000713.
61. Rayman MP, Rayman MP. The argument for increasing selenium intake. Proc Nutr Soc 2002;61:203-15.
62. Perros P, Zarkovic 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. Br J Ophthalmol 2015;99:1531-5.
63. Bartalena L, Baldeschi L, Boboridis K, Eckstein A, Kahaly GJ, Marcocci C, et al. The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. Eur Thyroid J 2016;5:9-26.
64. Bartalena L, Kahaly GJ, Baldeschi L, Dayan CM, Eckstein A, Marcocci C, et al. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. Eur J Endocrinol 2021;185:G43-67.
65. Schuh A, Ayvaz G, Baldeschi L, Baretić M, Bechtold D, Boschi A, et al. Presentation of Graves' orbitopathy within European Group On Graves' Orbitopathy (EUGOGO) centres from 2012 to 2019 (PREGO III). Br J Ophthalmol 2024;108:294-300.
66. Brito JP, Nagy EV, Singh Ospina N, M Za, Dosiou C, Fichter N, et al. A Survey on the Management of Thyroid Eye Disease Among American and European Thyroid Association Members. Thyroid 2022;32:1535-46.
67. Negro R, Hegedus L, Attanasio R, Papini E, Winther KH. A 2018 European Thyroid Association Survey on the Use of Selenium Supplementation in Graves' Hyperthyroidism and Graves' Orbitopathy. Eur Thyroid J 2019;8:7-15.
68. Oeverhaus M, Stohr M, Moller L, Fuhrer D, Eckstein A. Graves' Orbitopathy: Current Concepts for Medical Treatment. Klin Monbl Augenheilkd 2021;238:24-32.
69. Burch HB, Perros P, Bednarczuk T, Cooper DS, Dolman PJ, Leung AM, et al. Management of Thyroid Eye Disease: A Consensus Statement by the American Thyroid Association and the European Thyroid Association. Thyroid 2022;32:1439-70.
70. Pakdel F, Ghazavi R, Heidary R, Nezamabadi A, Parvizi M, Haji Safar Ali Memar M, et al. Effect of Selenium on Thyroid Disorders: Scientometric Analysis. Iran J Public Health 2019;48:410-20.