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A 2016 Italian Survey about the Clinical Use of Selenium in Thyroid Disease

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Key Words
Selenium · Graves' disease · Orbitopathy · Thyroid · Pregnancy · Survey · Hypothyroidism · Chronic autoimmune thyroiditis · Hashimoto's thyroiditis

Abstract
Background: Selenium (Se) is a trace element that plays key roles in thyroid physiology. Se deficiency is associated with increased risk of thyroid disease. Some evidence suggests that Se supplementation may be beneficial in autoimmune thyroid disease (either hypo- or hyperthyroidism). ***Objectives:*** We sought to examine the use of Se in daily clinical practice among Italian endocrinologists. ***Methods:*** Members of the Associazione Medici Endocrinologi (AME) were invited to participate in a web-based survey investigating the use of Se in different clinical conditions. ***Results:*** A total of 815 individuals (43.2% of AME members) participated in the survey, 778 of whom completed all of the sections. Among these respondents, 85.2% considered using Se for thyroid disease (58.1% rarely/occasionally and 27.1% often/always), and 79.4% prescribed Se for chronic autoimmune thyroiditis (AIT) (39.1% sometimes and 40.3% often/always). About two thirds of the respondents considered Se use in cases of subclinical autoimmune hypothyroidism, and about 40% had suggested Se use for patients with AIT who were planning pregnancy or already pregnant. About one fourth of the respondents had used Se for mild Graves' orbitopathy. Regarding the suggested daily dosage of Se, 60% of the respondents answered 100–200 μg, 20–30% recommended <100 μg, and 10–20% recommended >200 μg. ***Conclusions:*** Se use is widely considered in daily clinical practice. Moreover, Se supplementation is often used or suggested for purposes extending beyond those supported by evidence-based medicine. Ongoing studies will better clarify how Se treatment can be properly utilized in thyroid disease management.

Introduction

An essential trace element, selenium (Se) is required for correct immune system function and plays a key role in thyroid physiology [1]. Se is incorporated into the mo-

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lecular structures of some proteins. These so-called selenoproteins include several enzymes that are functionally active in the thyroid gland, such as glutathione peroxidase, thioredoxin reductase, and iodothyronine deiodinases, which exert oxidoreductase functions and regulate thyroid hormone concentrations [2]. Se deficiency reportedly leads to reduced glutathione peroxidase and iodothyronine deiodinase enzymatic activity, with consequent H_2O_2 accumulation, thyroid gland damage, and impaired thyroid hormone metabolism [3]. Mice with inactivated selenoprotein biosynthesis exhibit intact gross thyroid morphology, suggesting that while selenoproteins may protect thyrocytes from oxidative damage and modulate thyroid hormone biosynthesis, they are not essential for thyrocyte survival [4].

A population-based study from China, including over 6,000 people, demonstrated that individuals with low serum Se concentrations exhibited increased risks of hypothyroidism, subclinical hypothyroidism (SH), autoimmune thyroiditis (AIT), and enlarged thyroid [5]. However, some evidence has challenged the hypothesis that Se plays a clinical role in these disorders, particularly AIT. Published findings are conflicting with regard to whether AIT patients show significantly reduced thyroid peroxidase antibody (TPOAb) titers [6–10]. Notably, one study showed a significantly reduced incidence of postpartum thyroiditis among TPOAb-positive pregnant women treated with Se 200 μg/day [11], while another study demonstrated that Se administration significantly improved quality of life, reduced ocular involvement, and slowed disease progression in patients with mild Graves' orbitopathy (GO) [12].

While Se supplementation is an intriguing option for the treatment of autoimmune thyroid disease, the current body of evidence does not support its routine implementation in clinical practice. Our present survey aimed to investigate the perception of Se therapy among Italian endocrinologists and its present use in clinical practice.

Materials and Methods

This study utilized a web-based survey constructed with LimeSurvey, an open-access platform that provides various question templates. The questionnaire included 23 questions. A total of 1,888 Associazione Medici Endocrinologi (AME) members were sent an initial e-mail including an electronic link to the questionnaire, followed by weekly reminders from the AME secretariat from January 15 to February 29 in 2016. Survey responses were anonymously collected and electronically stored by the survey service, where they were accessible by password. The survey service automatically blocked repeat submissions from the same IP address. The system also blocked contradictory answers – namely, if a respondent denied Se use in a particular situation, the system automatically skipped questions regarding details for that situation.

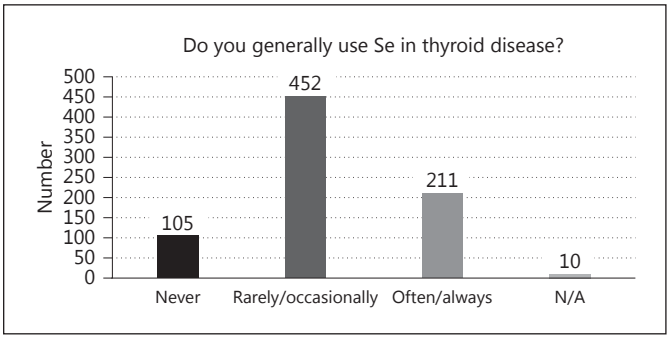

Fig. 1. Use of Se in thyroid disease.

Statistical Analysis

Summary statistics were prepared for responses to each question. Not every participant answered all of the questions. Thus, the percentage of the respondents providing a given answer was calculated individually for each question. A χ^2 test was used to evaluate the questionnaire response rates. Data were analyzed using IBM SPSS Statistics version 19 software (SPSS, Chicago, Ill., USA).

Results

Response Rate and Respondent Demographics

A total of 815 individuals (43.2% of AME members) participated in the survey, 778 (41.2%) of whom completed all of the sections. Among the respondents, 52.4% were female. The age distribution was as follows: 3.5%, 20–30 years; 23%, 31–40 years; 18.9%, 41–50 years; 36.6%, 51–60 years; 16.6%, 61–70 years, and 1.4%, >70 years. Of the respondents, 91.6% specialized in endocrinology, 5.1% in internal medicine, 0.9% in nuclear medicine, 0.8% in pediatric endocrinology, 0.4% in surgery, and 1.2% in other specialties ($p < 0.01$). Places of employment included referral hospitals (41.9%), private practice (33.8%), district hospitals (15.6%), and university hospitals (8.7%). Distributions of sex, age, specialty, workplace, and region were representative of the 1,888 AME members, with no significant differences in characteristics detected between respondents and the whole cohort of AME members.

Among the respondents, 74% were aware that Se was available as either a single-component supplement or a

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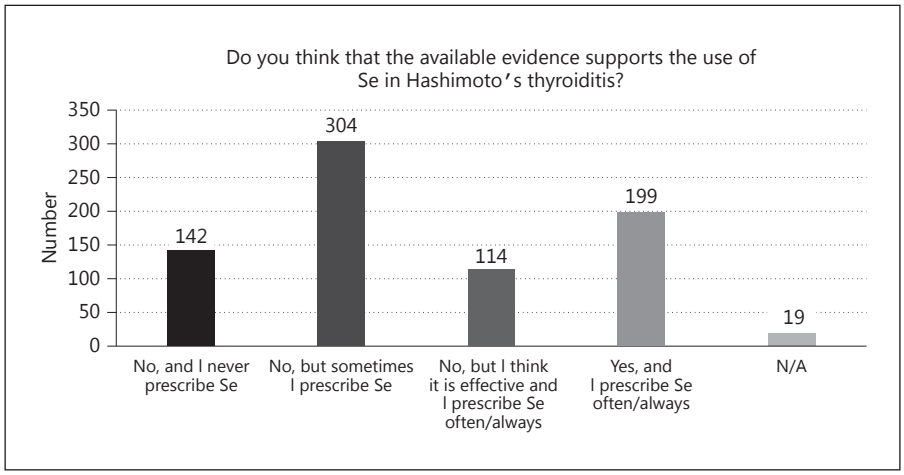

Fig. 2. Evidence-based medicine and use of Se in Hashimoto's thyroiditis.

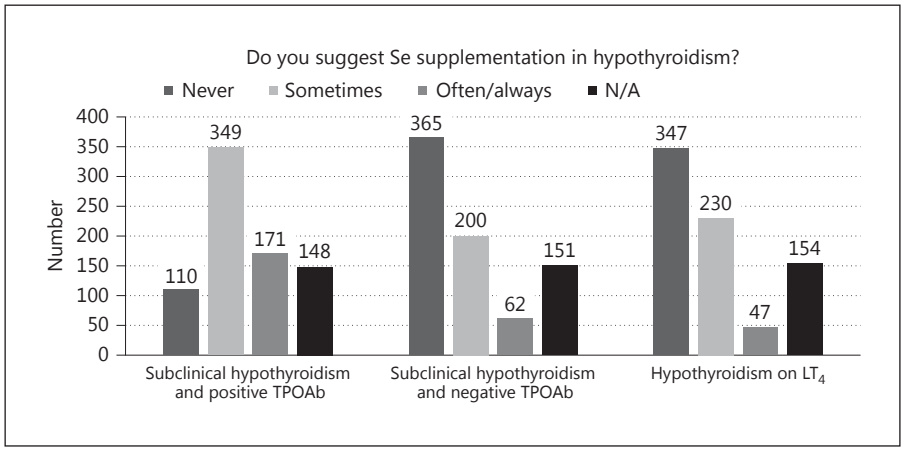

Fig. 3. Use of Se in hypothyroidism.

component in multivitamin pills ($p < 0.01$). The vast majority of the respondents stated that they had recommended Se use (rarely/occasionally or often/always), while only a minority denied ever using Se ($p < 0.01$) (fig. 1).

Chronic AIT (Euthyroidism)

With regard to patients suffering from AIT (euthyroidism), <20% of the respondents do not recommend Se use because there is no evidence showing its benefits. About half of the respondents prescribed Se (sometimes or often/always) in AIT despite a lack of supporting evidence. One fourth of the respondents believe that the evidence supports Se use and often/always prescribe Se. Overall, 72.1% of the respondents think there is a lack of evidence supporting Se use, while 25.6% think that the evidence supports Se use ($p < 0.01$); however, 79% prescribe Se, while only 18.3% do not (fig. 2). Among Se prescribers, 12.3% aim to ameliorate thyroid texture at ultrasound, 48.7% to prevent/slow TSH increase, and 39% to reduce thyroid antibody titers. Half of the respondents allow the patients to decide whether to use Se, while the other half convince the patients of its usefulness. If a patient requests treatment instead of inaction, ~80% suggest Se, while ~20% explain that Se supplementation is useless ($p < 0.01$). Among Se prescribers, 3.2% suggest >200 μg/day, 56.1% between 100 and 200 μg/day, and 40.5% <100 μg/day ($p < 0.01$).

Subclinical Hypothyroidism

In TPOAb-positive patients with SH, two thirds of the survey respondents suggest Se treatment (sometimes or often/always), while 14.1% never recommend Se use. In TPOAb-negative patients with SH, about one third of the respondents use Se (sometimes or often/always), while ~50% never recommend Se ($p < 0.01$). Similar response rates were obtained with regard to hypothyroid patients already treated with levothyroxine (LT_4) (fig. 3).

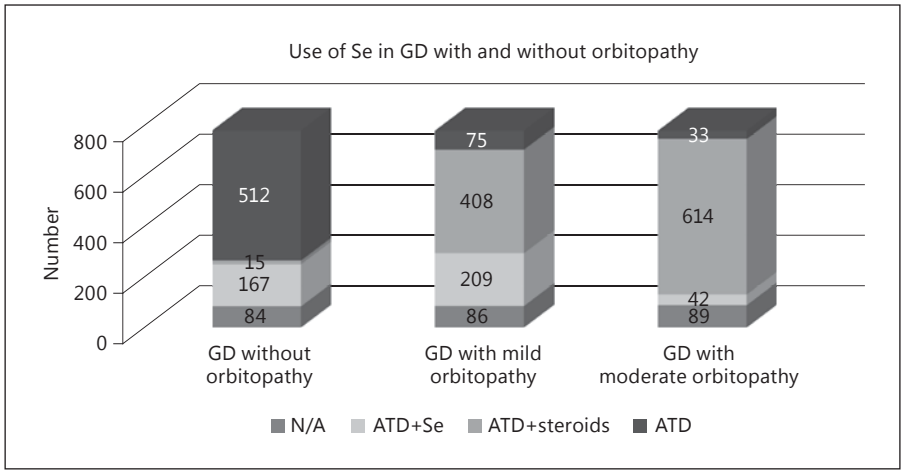

Fig. 4. Use of Se in patients with or without GO.

Chronic AIT and Pregnancy (Euthyroid)

In patients with AIT who are planning pregnancy or are already pregnant, ~40% of the respondents suggest Se use, 52% do not use Se ($p < 0.01$), and 8.0% did not respond. Among Se-recommending respondents, 39.9% aim to prevent hypothyroidism development, 24.7% to prevent postpartum thyroiditis, 30.7% to reduce TPOAb titers, and 4.7% gave other reasons. In this context, ~30% of the respondents suggested a Se amount of <100 μg/day, 60% recommended 100–200 μg/day, and 10% suggested >200 μg/day ($p < 0.01$).

Graves' Orbitopathy

Respondents were presented with the case of a 42-year-old woman newly diagnosed with Graves' disease (GD), showing suppressed TSH, doubled FT_4 concentration, enlarged thyroid, and no signs/symptoms of GO. After deciding on antithyroid drug (ATD) treatment, two thirds of the respondents would not give Se, about 20% would use Se, and few would add steroid treatment ($p < 0.01$). When the case was changed to include active GO – characterized by upper eyelid retraction, chemosis, and bilateral exophthalmos (20 mm right and 21 mm left eye) – the physicians' attitudes substantially changed, with over half of the respondents then recommending ATD plus steroids, one fourth suggesting ATD plus Se, and only a minority prescribing ATD only ($p < 0.01$). When the case was changed to include worsened GO – characterized by severe eyelid edema, chemosis, and bilateral exophthalmos (22 mm right and 23 mm left eye) – the vast majority of the respondents recommended ATD plus steroids, and few suggested ATD with Se or ATD alone ($p < 0.01$) (fig. 4). Among those suggesting Se in one of the abovementioned cases, the recommended dosage was <100 μg/day in 21% of cases, 100–200 μg/day in 60.2%, and >200 μg/day in 18.8% ($p < 0.01$). About half of the respondents would recommend Se supplementation for a patient in remission from hyperthyroidism for 18 months and with a clinical activity score of 2/7.

Discussion

This is the first survey to explore the perception and clinical use of Se supplementation in thyroid disease. Our results show that despite conflicting evidence supporting Se supplementation in thyroid disease, the vast majority of physicians consider its use (85.2%). Interpretation of the present results must take into account that decisions regarding Se supplementation are never based on serum Se concentration, as this test is not commonly available and is used only in research laboratories.

Autoimmune Thyroiditis

Since selenoproteins exert antioxidant activity, Se supplementation has been investigated as a possible intervention for slowing AIT progression, producing conflicting results. A 2010 meta-analysis reported that AIT patients receiving LT_4 treatment plus Se supplementation for 3 months showed significantly lower TPOAb titers (4 studies) and a significantly higher likelihood of improved well-being and/or mood (3 studies) compared with those without Se treatment, while demands in LT_4 replacement therapy and ultrasonographic thyroid morphology were unaltered or underreported [13]. Another review assessing the effects of Se supplementation in AIT reported that

4 included studies involving 463 participants exhibited an unclear to high risk of bias. Overall, the results showed no evidence clearly supporting or refuting the efficacy of Se supplementation in AIT [14]. Doubts regarding the usefulness of Se supplementation in AIT are supported by a recent randomized, placebo-controlled, double-blind study in which euthyroid women with TPOAb ≥100 kU/l were randomized to receive 200 μg/day sodium selenite or placebo for 6 months [9]. The treated group showed significant increases in Se and selenoprotein P, with no effect on serum TPOAb, TSH, or quality of life.

Our survey results showed that three fourths of the respondents are aware that the current evidence does not allow confident decision-making; however, over 80% of the respondents prescribe Se at least sometimes. This surprising result likely reflects the Italian endocrinologists' desire to slow Hashimoto's thyroiditis progression and to thereby slow hypothyroidism onset. Slightly less than 20% of the respondents do not prescribe Se due to the dearth of clear-cut evidence. Notably, when a patient seeks an active approach rather than inaction, about half of our respondents try to convince patients that Se supplementation is useful, while only a minority clearly explain this treatment. As the usefulness of Se supplementation is debatable, this prevalent attitude of the physicians toward their patients is disappointing. The lack of clear evidence necessitates an in-depth discussion to clearly explain the pros and cons of such supplementation to the patient.

Subclinical Hypothyroidism

To date, no randomized controlled trial has demonstrated the effectiveness of Se in TPOAb-positive or -negative SH patients. A double-blind placebo-controlled study of ~1,000 patients in the United Kingdom revealed no effect of Se supplementation (at 100, 200, or 300 μg/day) on thyroid function [15]. An ongoing multicenter randomized controlled trial involving adult patients with AIT receiving LT_4 treatment (CATALYST) will be completed in 2017 [16]. This study aims to investigate whether Se supplementation versus placebo adjuvant to standard LT_4 treatment in AIT patients will improve thyroid-specific quality of life and reduced autoimmune activity; investigators will also monitor LT_4 requirements.

We found that two thirds of the responding Italian endocrinologists consider Se use in TPOAb-positive SH patients compared to only one third in TPOAb-negative SH patients and patients already receiving LT_4 treatment. These proportions of physicians who would use Se treatment seem extremely high in light of the lack of evidence of any benefit deriving from Se supplementation in SH.

Pregnancy

Women of reproductive age are commonly TPOAb-positive, which is associated with complications, including infertility, miscarriage, and preterm delivery [17, 18]. Se has no proven benefit among patients planning pregnancy in terms of thyroid function, TPOAb titers, or fertility rate. However, one study showed significantly reduced postpartum thyroid dysfunction with the administration of Se 200 μg/day from midpregnancy onwards [10]. A double-blind, randomized, placebo-controlled study demonstrated that supplementation with Se 60 μg/day in pregnant women with mild-to-moderate Se deficiency did not impact TPOAb concentration, but it did tend to alter thyroid function in TPOAb-positive women [19].

Importantly, in pigs, sheep, and cattle, high Se consumption reportedly interferes with normal fetal development and leads to fetal malformations [20]. A randomized, double-blind, placebo-controlled trial of Se supplementation among 913 HIV-infected pregnant women in Tanzania demonstrated that 200 μg selenomethionine nonsignificantly increased the risk of fetal death [21]. Due to the lack of clear-cut benefits in cases of thyroid autoimmunity and pregnancy, and considering the potential side effects of Se supplementation, current guidelines do not endorse this treatment [22, 23].

For AIT patients planning pregnancy or already pregnant, more than 50% of the survey respondents do not suggest Se. Among those who prescribe Se, one third aim to prevent postpartum thyroiditis. These figures suggest that Italian physicians should be more prudent in suggesting Se to a woman with AIT who is planning pregnancy or is already pregnant. It is remarkable that 40% would use Se in such cases, and even more worrisome that 10% of those who recommend Se would prescribe over 200 μg/day.

Graves' Orbitopathy

Hyperthyroidism, especially when untreated, is associated with increases in several oxidative stress parameters, and serum Se concentration is reportedly lower in GD patients than in controls [24, 25]. Several studies have indicated that euthyroid patients with active GO show elevated oxidative status markers compared to GD patients without GO, suggesting the importance of the active orbital inflammatory process and the involvement of oxidative stress in GO pathogenesis. A study of ~200 patients

from Australia reported significantly lower mean serum Se levels in patients with GO (1.10 ± 0.18 μM) compared to GD and no GO (1.19 ± 0.20 μM) ($p = 0.001$) [26]. A recent retrospective study of 84 GO patients found that the majority showed relatively poor Se status. Moreover, neither Se nor selenoprotein P concentrations differed between GO patients with severe versus mild disease or active versus inactive disease, or were significantly associated with the clinical activity score or disease severity (NOSPECS) [27].

Marcocci et al. [12] performed a randomized, double-blind, placebo-controlled trial in 159 patients with mild GO to investigate the effects of Se (100 μg twice daily) or the anti-inflammatory agent pentoxifylline (600 mg twice daily) compared to placebo (twice daily) for 6 months. Compared with placebo, Se treatment, but not pentoxifylline treatment, was associated with improved quality of life ($p < 0.001$), reduced eye involvement ($p = 0.01$), and slower GO progression ($p = 0.01$). The clinical activity score decreased in all groups, with a significantly greater change among Se-treated patients. This study, however, lacks data regarding the patients' Se status before and after supplementation, which could have indicated whether positively responding patients were those with the strongest Se deficiencies, and thus who benefitted most from Se treatment. These results are incorporated in the recently published guidelines from the European Thyroid Association, suggesting 6-month Se supplementation in cases of mild GO [28].

Our survey results show that 21.5% of the respondents would recommend Se for GD without GO, 26.9% for mild GO, and 5.4% for severe GO. In parallel, steroid use progressively increased from 1.9% without GO, to 52.4% for mild GO, and up to 78.9% for moderate GO. Thus, only 25% of the respondents correctly utilized Se in cases of GD with mild GO. Se was misused in the other cases, especially in the case of remitted hyperthyroidism with inactive GO (about half of the respondents).

It also remains unclear what daily amount of Se should be suggested. Our survey results indicated that about 60% prescribe 100–200 μg, 20–30% <100 μg, and the remaining respondents >200 μg. Daily intake of 20 μg is considered the minimum required for good health, and 40–50 μg is the amount that maximizes glutathione peroxidase and selenoprotein activity [29]. Most studies involving thyroid patients have used 200 μg/day, obtaining conflicting results. A recent study tested 80 or 160 μg Se daily for 12 months in AIT patients, and reported no differences in TPOAb concentrations, thyroid echogenicity, thyroid volume, or quality of life; however, the authors observed Se-dependent downregulation of IFNγ-inducible chemokines [30]. If Se has beneficial effects in GD or AIT, the daily amount and treatment duration still must be ascertained.

Conclusions

There are still urgent research questions concerning the importance of baseline Se status for successful supplementation and about potential genetic/sex-specific differences in Se metabolism [31]. Ongoing studies will clarify how endocrinologists can appropriately determine Se treatment for thyroid disease management [16, 32]. Our present findings reveal that Se use is widely considered in daily clinical practice, and Se supplementation is often used or suggested beyond what is supported by evidence-based medicine. This surprisingly high Se use may be explained by patients with AIT requesting treatment to prevent hypothyroidism onset, physicians trying to provide satisfactory responses to demanding patients, and pressure from pharmaceutical companies. The scarcity of physicians who correctly use Se (e.g. in mild GO) indicates inadequate knowledge in this specific field. The present results can guide endocrine scientific societies in helping their members to provide a better quality of patient care.

Disclosure Statement

The authors have nothing to disclose.

References

1 Köhrle J, Jakob F, Contempré B, Dumont JE: Selenium, the thyroid, and the endocrine system. Endocr Rev 2005;26:944–984.

2 Kryukov GV, Castellano S, Novoselov SV, Lobanov AV, Zehtab O, Guigó R, Gladyshev VN: Characterization of mammalian selenoproteomes. Science 2003;300:1439–1443.

3 Zimmermann MB, Köhrle J: The impact of iron and selenium deficiencies on iodine and thyroid metabolism: biochemistry and relevance to public health. Thyroid 2002;12:867–878.

4 Chiu-Ugalde J, Wirth EK, Klein MO, Sapin R, Fradejas-Villar N, Renko K, Schomburg L, Köhrle J, Schweizer U: Thyroid function is maintained despite increased oxidative stress in mice lacking selenoprotein biosynthesis in thyroid epithelial cells. Antioxid Redox Signal 2012;17:902–913.

5 Wu Q, Rayman MP, Lv H, Schomburg L, Cui B, Gao C, Chen P, Zhuang G, Zhang Z, Peng X, Li H, Zhao Y, He X, Zeng G, Qin F, Hou P, Shi B: Low population selenium status is associated with increased prevalence of thyroid disease. J Clin Endocrinol Metab 2015;100: 4037–4047.

6 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: 1687–1691.

7 Duntas LH, Mantzou E, Koutras DA: Effects of a six month treatment with selenomethionine in patients with autoimmune thyroiditis. Eur J Endocrinol 2003;148:389–393.

8 Mazokopakis EE, Papadakis JA, Papadomanolaki MG, Batistakis AG, Giannakopoulos TG, Protopapadakis EE, Ganotakis ES: Effects of 12 months treatment with L-selenomethionine on serum anti-TPO levels in patients with Hashimoto's thyroiditis. Thyroid 2007;17:609–612.

9 Eskes SA, Endert E, Fliers E, Birnie E, Hollenbach B, Schomburg L, Köhrle J, Wiersinga WM: Selenite supplementation in euthyroid subjects with thyroid peroxidase antibodies. Clin Endocrinol (Oxf) 2014;80:444–451.

10 Bonfig W, Gärtner R, Schmidt H: Selenium supplementation does not decrease thyroid peroxidase antibody concentration in children and adolescents with autoimmune thyroiditis. ScientificWorldJournal 2010;10: 990–996.

11 Negro R, Greco G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H: The influence of selenium supplementation on postpartum thyroid status in pregnant women with thyroid peroxidase autoantibodies. J Clin Endocrinol Metab 2007;92:1263–1268.

12 Marcocci C, Kahaly GJ, Krassas GE, Bartalena L, Prummel M, Stahl M, Altea MA, Nardi M, Pitz S, Boboridis K, Sivelli P, von Arx G, Mourits MP, Baldeschi L, Bencivelli W, Wiersinga W; European Group on Graves' Orbitopathy: Selenium and the course of mild Graves' orbitopathy. N Engl J Med 2011;364:1920–1931.

13 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;20:1163–1173.

14 van Zuuren EJ, Albusta AY, Fedorowicz Z, Carter B, Pijl H: Selenium supplementation for Hashimoto's thyroiditis: summary of a Cochrane Systematic Review. Eur Thyroid J 2014;3:25–31.

15 Rayman MP, Thompson AJ, Bekaert B, Catterick J, Galassini R, Hall E, Warren-Perry M, Beckett GJ: Randomized controlled trial of the effect of selenium supplementation on thyroid function in the elderly in the United Kingdom. Am J Clin Nutr 2008;87:370–378.

16 Winther KH, Watt T, Bjørner JB, Cramon P, Feldt-Rasmussen U, Gluud C, Gram J, Groenvold M, Hegedüs L, Knudsen N, Rasmussen ÅK, Bonnema SJ: The chronic autoimmune thyroiditis quality of life selenium trial (CATALYST): study protocol for a randomized controlled trial. Trials 2014;15:115.

17 Thangaratinam S, Tan A, Knox E, Kilby MD, Franklyn J, Coomarasamy A: Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. BMJ 2011;342:d2616.

18 Krassas GE: Thyroid disease and female reproduction. Fertil Steril 2000;74:1063–1070.

19 Mao J, Pop VJ, Bath SC, Vader HL, Redman CW, Rayman MP: Effect of low-dose selenium on thyroid autoimmunity and thyroid function in UK pregnant women with mild-to-moderate iodine deficiency. Eur J Nutr 2016;55:55–61.

20 Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for Selenium (Update). Atlanta, Public Health Service, Department of Health and Human Services, 1996.

21 Kupka R, Mugusi F, Aboud S, Msamanga GI, Finkelstein JL, Spiegelman D, Fawzi WW: Randomized, double-blind, placebo-controlled trial of selenium supplements among HIV-infected pregnant women in Tanzania: effects on maternal and child outcomes. Am J Clin Nutr 2008;87:1802–1808.

22 Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce EN, Soldin OP, Sullivan S, Wiersinga W; American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum: Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 2011;21: 1081–1125.

23 De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, Eastman CJ, Lazarus JH, Luton D, Mandel SJ, Mestman J, Rovet J, Sullivan S: Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2012;97: 2543–2565.

24 Marcocci C, Leo M, Altea MA: Oxidative stress in Graves' disease. Eur Thyroid J 2012; 1:80–87.

25 Bülow Pedersen I, Knudsen N, Carlé A, Schomburg L, Köhrle J, Jørgensen T, Rasmussen LB, Ovesen L, Laurberg P: Serum selenium is low in newly diagnosed Graves' disease: a population-based study. Clin Endocrinol (Oxf) 2013;79:584–590.

26 Khong JJ, Goldstein RF, Sanders KM, Schneider H, Pope J, Burdon KP, Craig JE, Ebeling PR: Serum selenium status in Graves' disease with and without orbitopathy: a case-control study. Clin Endocrinol (Oxf) 2014;80:905–910.

27 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.

28 Bartalena L, Baldeschi L, Boboridis K, Eckstein A, Kahaly GJ, Marcocci C, Perros P, Salvi M, Wiersinga WM; European Group on Graves' Orbitopathy (EUGOGO): The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. Eur Thyroid J 2016;5:9–26.

29 Thomson CD: Assessment of requirements for selenium and adequacy of selenium status: a review. Eur J Clin Nutr 2004;58:391–402.

30 Pilli T, Cantara S, Schomburg L, Cenci V, Cardinale S, Heid EC, Kühn EC, Cevenini G, Sestini F, Fioravanti C, D'Hauw G, Pacini F: IFNγ-inducible chemokines decrease upon selenomethionine supplementation in women with euthyroid autoimmune thyroiditis: comparison between two doses of selenomethionine (80 or 160 μg) versus placebo. Eur Thyroid J 2015;4:226–233.

31 Santos LR, Durães C, Mendes A, Prazeres H, Alvelos MI, Moreira CS, Canedo P, Esteves C, Neves C, Carvalho D, Sobrinho-Simões M, Soares P: A polymorphism in the promoter region of the selenoprotein S gene (SEPS1) contributes to Hashimoto's thyroiditis susceptibility. J Clin Endocrinol Metab 2014; 99:E719–E723.

32 Watt T, Cramon P, Bjorner JB, Bonnema SJ, Feldt-Rasmussen U, Gluud C, Gram J, Hansen JL, Hegedüs L, Knudsen N, Bach-Mortensen P, Nolsøe R, Nygaard B, Pociot F, Skoog M, Winkel P, Rasmussen AK: Selenium supplementation for patients with Graves' hyperthyroidism (the GRASS trial): study protocol for a randomized controlled trial. Trials 2013;14:119.