A 2018 European Thyroid Association Survey on the Use of Selenium Supplementation in Graves' Hyperthyroidism and Graves' Orbitopathy

Roberto Negro^a Laszlo Hegedüs^b Roberto Attanasio^c Enrico Papini^d
Kristian H. Winther^b

^aDivision of Endocrinology, V. Fazzi Hospital, Lecce, Italy; ^bDepartment of Endocrinology and Metabolism, Odense University Hospital, Odense, Denmark; ^cEndocrine Unit, IRCCS Istituto Galeazzi, Milan, Italy;

^dDepartment of Endocrinology and Metabolism, Ospedale Regina Apostolorum, Rome, Italy

Keywords

Selenium supplementation · Graves' disease · Graves' orbitopathy · Graves' disease treatment · Questionnaire · European Thyroid Association

Abstract

Objective: Selenium (Se) supplementation has been suggested in the treatment of Graves' disease (GD). We sought to investigate Se prescription patterns for GD across European countries. **Methods:** Members of the European Thyroid Association were invited to participate in an online survey investigating the use of Se in GD either without or with orbitopathy (GO). Of 872 invited members, 244 (28%) completed the survey. After exclusion of basic scientists and non-European members, 197 responses were retrieved out of clinical trials (nearly half of clinician members), of whom 61 do not use Se. Thus, 136 respondents remained for further analyses. **Results:** Among the 136 analyzed respondents, most (64.7%) were not aware of the Se status in their populations, did not assess Se levels (78.7%), nor considered iodine status (74.3%). In GD without GO, 38.2% recommend Se supplementation ("sometimes" [27.2%], "frequently" [5.9%] or "always" [5.1%]). When GO occurs, 94.1% recommend Se supplementation

("sometimes" [39%], "frequently" [30.1%] or "always" [25%]). Of these, 60.1% recommend Se as an alternative to watchful waiting in patients with mild ocular involvement and 44.9% as an adjuvant to the established treatment modalities in patients with moderate to severe ocular involvement. **Conclusions:** In Graves' hyperthyroidism without GO, 38.2% of ETA (European Thyroid Association) members recommend Se supplementation. Conversely, Se is recommended by the majority of respondents in GO, both in patients with mild and moderate to severe ocular involvement. This clinical practice is partially in disagreement with current European treatment guidelines that recommend Se as a 6-month treatment in mild GO only.

© 2018 European Thyroid Association
Published by S. Karger AG, Basel

Introduction

Graves' disease (GD), especially when accompanied by Graves' orbitopathy (GO), remains a conundrum both as for etiology and for treatment [1]. Genetic susceptibility in an elaborate and only partially understood interaction with a number of individual specific environmental variables, iodine intake and tobacco smoking being those

most studied, accounts for the final phenotype most likely unique to any individual [2, 3]. The disease has negative socioeconomic consequences [4] and is associated with excess morbidity and mortality [5, 6]. Questionnaires by American Endocrine Societies (The Endocrine Society, American Thyroid Association and American Association of Clinical Endocrinologists) and the European Thyroid Association (ETA) have previously dealt with diagnostic and therapeutic aspects of GD and GO, but not focused on the potential role of the trace element selenium (Se) [7, 8].

Se is a non-metal trace element, essential for the production of selenoproteins. The thyroid gland has an Se tissue concentration of 0.2–2 µg/g, which is the highest of any human tissue, and it contains a substantial number of identified selenoproteins [9, 10]. Selenoprotein families of particular interest include the glutathione peroxidases (GPxs), which protect thyrocytes from excess hydrogen peroxide during thyroid hormone synthesis, and iodothyronine deiodinases [11], which act as catalysts for the activation of thyroid hormone [12]. Adverse effects are clinically evident in severe Se and iodine-deficient areas [13], but may also be detectable in marginal Se deficiency countries [14], as is the case in most of Europe.

In patients with autoimmune thyroid disease, including GD, plasma Se and GPx concentrations have been reported to be lower than in those with goiter and non-autoimmune thyroid disease [15]. Indeed, GD is characterized by an increased oxidative stress that may result in the exhaustion of the antioxidant defense and the parallel decrease in Se and selenoproteins [16, 17]. Data from clinical trials offering Se supplementation are limited and have yielded equivocal results [18]. A recently published double-blind, placebo-controlled trial could not provide evidence of an effect of Se supplementation (300 µg/day) on either the response to treatment or the recurrence rate in GD [19]. Similarly, a trial with Se supplementation in an Se-sufficient cohort of patients failed to demonstrate an adjuvant role in the short-term control of hyperthyroidism [20]. On the other hand, two randomized studies, from China [21] and from Sweden [22], reported a faster remission of GD with Se treatment, and the Chinese trial additionally demonstrated a decrease in serum TSH receptor antibody (TRAb) concentrations.

The evidence for the efficacy of Se supplementation in patients with GO is very limited but less conflicting. A multicenter randomized, double-blind, placebo-controlled trial demonstrated that Se, but not the anti-inflammatory agent pentoxifylline, significantly improved quality of life, reduced ocular involvement, and slowed

progression of the disease in patients with mild GO [23]. In addition, an Australian case-control study showed that serum Se was lower in patients with GO than in those without, and that the mean Se levels decreased in parallel with the increasing severity of GO [24]. These results were only partially reinforced by a German study that did not demonstrate an association between Se levels and severity of GO, but confirmed that these patients are at an increased risk of Se deficiency and that Se levels are inversely associated with TRAb levels [25].

The insight into the role of Se in thyroid diseases has improved in recent years [26–28], and its therapeutic use in mild GO is recommended in current ETA guidelines [29, 30]. An Italian survey, published in 2016, investigated the clinical use of Se supplementation in the index case of a 42-year-old female patient with GD. In the absence of GO, only 20% of respondents suggested the use of Se supplementation, while the rate increased to 25% in the presence of mild GO and decreased to only about 5% for moderate GO [31]. Due to the lack of more comprehensive data concerning the use of Se supplementation in European countries, a dedicated questionnaire was developed and distributed to the members of the ETA, who remained anonymous throughout. The survey involved a spectrum of benign thyroid diseases. Here, we present the results regarding the use of Se in GD and GO.

Methods

We utilized a web-based survey constructed with Lime-Survey, an open-access platform that provides various question templates. The questionnaire included 56 questions. A total of 872 ETA members were sent an initial e-mail including an electronic link to the questionnaire, followed by two reminders, between April 1st and 30th, 2018. Survey responses were 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. For each disease group, standardized items regarding available evidence, attitude, aim, dosage, and duration of Se supplementation were used. The entire survey is available (online supplementary Appendix 1; see www.karger.com/doi/10.1159/000494837 for all online supplemental material).

Statistical Analysis

Summary statistics were prepared for responses to each question. We considered as valid for statistical evaluation only those questionnaires with complete demographic data from the respondents. Pearson's χ^2 test or Fisher's exact test were used to compare frequencies (percentages) between categorical variables. A two-sided *p* value of <0.05 was considered as statistically significant. Data were analyzed using IBM SPSS Statistics version 19 software (SPSS, Chicago, IL, USA).

Fig. 1. Countries of respondents. Absolute numbers and percentages are individually reported only for countries with at least 10 respondents. Other European countries include: Albania, Croatia, Finland, France, Hungary, Ireland, Latvia, Macedonia, Montenegro, Romania, Russia, Slovakia, Slovenia, Spain, Sweden, Switzerland, and Turkey. Non-European countries include: Armenia, Bahrain, Brazil, Canada, Georgia, India, Japan, Morocco, the Philippines, South Africa, and the USA.

In all analyses, respondents stating that they did not know the answer to a given question were pooled in the response category with respondents that did not provide an answer.

Answers from different countries were pooled and analyzed together, as the small number of respondent physicians from each single country did not allow any reliable comparison between countries.

Results

Data about the Survey Respondents

A total of 266 ETA members participated in the survey, 244 of whom provided complete personal data (28% of invited ones). Physicians from 34 countries answered the questionnaire, with Italy (15.6%) and Denmark (11.1%) providing the highest number of responses (Fig. 1).

Thirty-seven respondents (15.2%) were also members of the American Thyroid Association (ATA, $n = 32$), Latin American Thyroid Society (LATS, $n = 4$), or Asia and Oceania Thyroid Association (AOTA, $n = 1$).

Table 1. Characteristics of analyzed respondents ($n = 136$)

Sex	
Males	72 (52.9%)
Females	64 (47.1%)
Age	
≤40 years	24 (17.6%)
41–60 years	83 (61.1%)
>60 years	29 (21.3%)
Practicing medicine	
≤10 years	13 (9.6%)
11–30 years	79 (58.1%)
>30 years	44 (32.3%)
Specialization ^a	
Endocrinology	117 (86%)
Internal medicine	31 (22.8%)
Others ^b	23 (16.9%)
Place of employment ^d	
University	88 (64.7%)
Private clinic	36 (26.5%)
General hospital	33 (24.3%)

^a The sum of percentages exceeds 100% because 31 respondents (22.8%) have more than one specialty, and 23 respondents (16.9%) work in more than one place. ^b Nuclear Medicine, Surgery, Pediatric Endocrinology, Radiology, and Ophthalmology.

Figure 2 shows the selection of respondents, with the exclusion of incomplete response ($n = 22$), non-European members ($n = 32$), basic scientists ($n = 11$), and those not answering the questions about GD and GO ($n = 4$).

The milestone question was about the use of Se in patients with thyroid disease. Sixty-one participants who answered “never” or “only in the setting of clinical trials” were automatically driven to the end, ruling out the possibility to answer the following questions. The remaining 136 declared to use Se, namely 37 (27.2%) “frequently or always” and 99 (72.8%) “occasionally or rarely”, and represent the dataset for the subsequent analysis.

Characteristics of the 136 analyzed respondents are presented in Table 1. Demographic characteristics of the 61 respondents not using Se were not different from those of the 136 included (data not reported) except for country. Most Danish respondents (22/24; 92%) did not use Se at all or only in the setting of clinical trials, in contrast to all the other nationalities. Thus, the corresponding figures for Italian respondents were 7/35 (20%) and for all other countries pooled together 32/101 (31.7%) ($p < 0.001$).

General Data about Se Supplementation

The Se status in the general population of their own country was unknown to 88 respondents (64.7%). Nearly

Fig. 2. Flowchart over survey respondents.

all respondents (135; 99.3%) were aware of Se availability on the market, either as a mono-component in tablets or as a component of multivitamin supplements, but 24 (17.6%) were not aware of the chemical formulation of marketed Se (organic, i.e. selenomethionine, or inorganic, i.e. selenite).

One hundred and fourteen respondents (83.8%) asked their patients about the intake of dietary supplements containing Se before recommending Se treatment, 66 (48.5%) routinely and 48 (35.3%) occasionally.

For 82 respondents (60.3%), the decision to recommend Se supplementation was not influenced by the Se status of the general population. Only 29 physicians (21.3%) reported that they generally (5; 3.7%) or occasionally (24; 17.6%) measured a given patient's Se status before recommending supplementation, and 101 (74.3%) did not consider iodine status when deciding whether or not to recommend Se supplementation.

Only 76 of the respondents (55.9%) expressed a preference for one formulation over the other, among whom selenomethionine was the preferred formulation for 51 (67.1%). The majority of physicians (80; 58.9%) did not make a specific prescription, as Se is sold over-the-counter in their countries.

Se Supplementation in GD without GO (Fig. 3)

For patients with GD not associated with GO, 55 out of 136 respondents (40.4%) answered that the available evidence does not warrant the use of Se, and 84 (61.8%) affirmed that they never prescribed it. Fifty-two clinicians (38.2%) suggested the use of Se and 32 of them (61.5%)

gave the reduction of TRAb levels as the primary motivation for their recommendation. The second and third most frequent reasons for recommending Se in GD were the possibility of decreasing the risk of relapse and of improving the quality of life (20 and 16 respondents, respectively; note that more than one answer was allowed). The suggested doses for Se supplementation were nearly equally distributed between 100 and 200 µg/day (21 and 23 respondents, respectively, out of the 47 respondents who answered this question), whereas the recommended length of treatment was from a few weeks to months for 34 of 52 respondents (65.4%). The other respondents were evenly distributed among the other possible options: "as long as antithyroid medication is needed," "years," or "indefinitely."

Se Supplementation in GO (Fig. 4)

For Graves' patients with GO, 76 out of 136 respondents (55.9%) declared that the available evidence supports the use of Se supplementation. Only 6 (4.4%) answered that there is no evidence in favor of this treatment and 44 (32.3%) affirmed that they sometimes prescribed Se even if recognizing the available scientific evidence as insufficient (no answer was provided by 5; 3.6% of clinicians). Accordingly, the vast majority (128; 94.1%) of respondents recommended Se use in GO, namely 53 "sometimes" (39%), 41 "frequently" (30.1%), and 34 "always" (25%). Se supplementation was recommended by 83 ETA members (61%) as an alternative to surveillance alone in patients with mild ocular involvement and by 61 (44.9%) as a supplement to the established treatment modalities

Fig. 3. Distribution of respondents for Se supplementation in GD without GO. **a** The perceived quality of evidence about the use of Se in this setting. **b** The reasons supporting Se supplementation (note that more than one answer was allowed). **c** The declared use of Se supplementation.

in patients with moderate to severe GO (more than one answer was allowed). The preferred dose was ≤ 200 μg /day for 108 out of 119 (90.8%) clinicians who answered this question, and 102/128 (80%) recommended Se treatment for a period of a few weeks to months and a subsequent reassessment of the patient for evaluating the effect of Se supplementation.

Discussion

GD is an autoimmune thyroid disorder, characterized by a complex and only partially identified pathogenesis [1], which is associated with an increase in the oxidative stress of the thyroid tissue [16]. Due to the role of GPxs

in the synthesis of thyroid hormones, Se supplementation has been proposed as a potential adjuvant treatment both for accelerating the remission of hyperthyroidism and, when present, for improving the symptoms and signs of GO. Although the scientific evidence in favor of Se supplementation in patients with GD and GO is still limited, and somewhat controversial, its empirical use is not infrequently considered in clinical practice [31]. For these reasons, we have investigated the practice pattern in a large series of thyroid specialists across the different European countries.

As a main finding, a non-negligible minority (38.2%) of clinicians who prescribe Se recommend its use in GD not associated with symptoms or signs of GO. Conversely, the vast majority (94.1%) of clinicians recommend Se

Fig. 4. Distribution of respondents for Se supplementation in GO. **a** The perceived quality of evidence about the use of Se in this setting. **b** The reasons supporting Se supplementation (note that more than one answer was allowed). **c** The declared use of Se supplementation.

supplementation in mild GO – either always, frequently or sometimes – primarily as a therapeutic alternative to simple watchful waiting.

Differences among respondents from different countries would have been an interesting topic. Unfortunately, few experts answered from most countries, thus a complete comparison would have provided unreliable and meaningless information. The comparison between the two national groups with more respondents, namely Italians and Danes, showed a profound difference, with most of the Danes prescribing Se only within clinical trials (of note, none of Danes practices in a private setting vs. 21% of Italians). This finding points to a different consider-

ation of the same available scientific information by the experts, at least in these two countries.

The widely variable approaches of the European thyroidologists are probably the consequence of the limited and partly conflicting available clinical data. Although the majority of ETA members never use Se supplementation in the absence of GO, a considerable minority, as above reported, prescribe Se in this setting, and 5.2% even routinely. Notably, this clinical approach is not in accordance with current recommendations of recently published ETA guidelines [29]. It may be speculated that this surprisingly high number recommending Se use is based on a wish of offering complementary treatment to demand-

ing patients affected by a debilitating or even progressively worsening, disease. Further reasons could be pressure from pharmaceutical companies and the patients' request due to the widespread availability of web-based information on various, frequently uncontrolled, social media.

For more than half of those clinicians who recommend Se treatment, the main perceived benefit was the potential decrease in serum TRAb levels. For this purpose, the majority recommended a dose that did not exceed 200 µg/day and recommended to supplement Se for a few weeks to months and then to re-evaluate the patient. Interestingly, the reduction in TRAb levels was reported only in a single recent trial, limited to a series of 41 patients [21]. Thus, confirmatory data are needed before accepting the currently weak evidence of a favorable influence of Se on the autoimmune process. Such data may potentially be provided by an ongoing Danish trial, which aims at enrolling 492 patients with GD on a standard treatment with anti-thyroid drugs. The study addresses whether Se supplementation as opposed to placebo leads to a decrease in anti-thyroid drug treatment failure, a more rapid GD remission, and an improved quality of life [32].

Despite the limited data from clinical trials, the current ETA guidelines on management of GO and GD included Se supplementation as a suggested treatment for mild forms of GO [29, 30]. Interestingly, whereas only half of the clinicians stated that the available evidence warrants Se supplementation, the vast majority (over 90%) recommended this treatment in GO. Mostly, Se is used as an alternative therapeutic option to simple surveillance in patients with mild ocular involvement, in accordance with ETA guidelines. However, almost half of the clinicians state that they use Se as a therapeutic adjuvant to the established treatment modalities in moderate to severe GO, which is in conflict with the ETA guidelines [29, 30]. It is interesting to speculate, but unfortunately cannot be clarified by the present questionnaire, why recommendations have so rapidly been implemented, and why their use has been extended far beyond the GO phenotypes recommended in the ETA guidelines.

It remains unsettled which patients benefit the most, if at all, from Se supplementation. However, a U-shaped link between Se status and disease has been established, indicating that subjects who might benefit from supplementation are those with Se deficiency [33], possibly due to a relatively poor antioxidant activity. However, and surprisingly, for the majority of respondents Se status in the general population of their region was unknown and Se status was rarely evaluated before recommending sup-

plementation. However, most respondents asked the patients about their use of dietary, potentially Se-containing, supplements. Thus, overall, in many, if not most patients, it was unknown whether the patients had Se deficiency and, if treated, which Se level was reached. In published studies recruiting patients with GD and GO the Se dose mostly ranged from 200 to 300 µg/day. Notably, nearly no respondent suggested a dose exceeding 200 µg/day. This clinical approach appears sound. Whereas the recommended daily intake for adults is 70 µg/day for men and 60 µg/day for women [34], a daily amount exceeding 400 µg should be avoided due to its potential toxic effects (a condition defined as "selenosis"), characterized by diarrhea, fatigue, hair loss, and nail discoloration [35–37]. Further, in a recent randomized controlled trial, the safety of this upper limit has been questioned. A 300 µg/day dose of Se-enriched yeast taken for 5 years in Denmark, a region with a moderately low Se status, increased all-cause mortality 10 years later, as compared to placebo [38].

As both Se and iodine interact in thyroid hormone regulation [39], the combined assessment of their status should be considered when contemplating Se supplementation, at least at the population level. However, most clinicians do not take regional or, even better, individual iodine status into account, when deciding whether or not to recommend Se supplementation. The deterioration of thyroid function, which was observed after Se administration in severely iodine-deficient people in northern Zaire, for example, offers an important insight into the potential relevance of this interaction between these two deficiencies [13].

In accordance with the limited knowledge of Se status among respondents, almost half of the thyroid experts in this survey did not state any preference as to the formulation of Se. In most countries, it is available as both organic and inorganic compounds, and in both multivitamin tablets and single-component supplements. Significantly more respondents recommended an organic compound, such as selenomethionine, as compared to an inorganic compound, such as sodium selenite. In an animal model of laying hens, a higher antioxidant activity has been demonstrated for the organic versus the inorganic form [40], while in humans both the inorganic Se compounds and the organic derivatives gave rise to steady-state levels of GPx activity after 1 month of supplementation. However, the Se levels in the subjects receiving organic Se showed a steady rise during the whole period, whereas those supplemented with inorganic Se levelled off after a period of 1–3 months [41]. Important for clinical prac-

tice, it remains unknown whether one Se compound offers a significantly better therapeutic effect than another in GD and/or GO.

A strength of this survey is the relatively high number of respondents from 27 European countries. The exact number of European ETA members who routinely manage patients with GD or GO is presently unavailable, since not all the European thyroid experts responded to the questionnaire. However, extrapolating the data from a former ETA survey on GD management [8], the 136 clinicians who filled in the present questionnaire may represent approximately one-third of the clinicians usually involved in GD management. As a whole, the response rate of the present study is more representative than in former trials, accounting for 197 clinicians, since the 61 respondents who denied using Se at all were disregarded from further analyses.

On the other hand, the number of analyzed responses is somewhat small to draw firm conclusions and the small number of thyroidologists from each single country made any comparison between countries unreliable. The uneven distribution of answers, the high proportion of missing values, and the lack of both content and construct validation of the questionnaire are other limitations to the interpretation of the data. Evidently selection bias of respondents may skew the results towards both an over- and an underestimation of the recommendation of Se supplementation. Thus, we do not know whether these

physicians are representative of practice patterns in their countries. Also, the fact that Se is an over-the-counter product in most countries suggests that many patients are totally independent of the advice of their physicians, and may be easy targets of other sources of information.

In conclusion, the ETA members' self-reported use of Se supplementation in GD is partly in conflict with current ETA guidelines, where Se is only recommended for a 6-month period to improve mild and active GO and to prevent its progression to more severe forms. There is limited knowledge about local Se status among respondents, and, given the U-shaped association between Se status and thyroid disease, care must be taken because the empirical use may potentially have detrimental health effects. The present results also suggest that endocrine scientific societies should improve their educational activities in helping their members provide an evidence-based patient care.

Acknowledgment

We are indebted to all the members of the ETA who filled in the questionnaire.

Disclosure Statement

R.N., L.H., E.P., and K.H.W. declare no conflict of interest; R.A. received fees for scientific meetings from IBSA, Pfizer, and Novartis.

References

- 1 Smith TJ, Hegedüs L. Graves' Disease [Review]. *N Engl J Med*. 2016 Oct;375(16):1552–65.
- 2 Brix TH, Kyvik KO, Christensen K, Hegedüs L. Evidence for a major role of heredity in Graves' disease: a population-based study of two Danish twin cohorts. *J Clin Endocrinol Metab*. 2001 Feb;86(2):930–4.
- 3 Brix TH, Hegedüs L. Twin studies as a model for exploring the aetiology of autoimmune thyroid disease. *Clin Endocrinol (Oxf)*. 2012 Apr;76(4):457–64.
- 4 Brandt F, Thvilum M, Hegedüs L, Brix TH. Hyperthyroidism is associated with work disability and loss of labour market income. A Danish register-based study in singletons and disease-discordant twin pairs. *Eur J Endocrinol*. 2015 Nov;173(5):595–602.
- 5 Brandt F, Thvilum M, Almind D, Christensen K, Green A, Hegedüs L, et al. Graves' disease and toxic nodular goiter are both associated with increased mortality but differ with respect to the cause of death: a Danish population-based register study. *Thyroid*. 2013 Apr;23(4):408–13.
- 6 Schwensen CF, Brandt F, Hegedüs L, Brix TH. Mortality in Graves' orbitopathy is increased and influenced by gender, age and pre-existing morbidity: a nationwide Danish register study. *Eur J Endocrinol*. 2017 Jun;176(6):669–76.
- 7 Burch HB, Burman KD, Cooper DS. A 2011 survey of clinical practice patterns in the management of Graves' disease. *J Clin Endocrinol Metab*. 2012 Dec;97(12):4549–58.
- 8 Bartalena L, Burch HB, Burman KD, Kahaly GJ. A 2013 European survey of clinical practice patterns in the management of Graves' disease. *Clin Endocrinol (Oxf)*. 2016 Jan;84(1):115–20.
- 9 Duntas LH, Benavente S. Selenium: an element for life. *Endocrine*. 2015 Apr;48(3):756–75.
- 10 Dickson RC, Tomlinson RH. Selenium in blood and human tissues. *Clin Chim Acta*. 1967 May;16(2):311–21.
- 11 Köhrle J, Jakob F, Contempré B, Dumont JE. Selenium, the thyroid, and the endocrine system. *Endocr Rev*. 2005 Dec;26(7):944–84.
- 12 Kryukov GV, Castellano S, Novoselov SV, Lobanov AV, Zehtab O, Guigó R, et al. Characterization of mammalian selenoproteomes. *Science*. 2003 May;300(5624):1439–43.
- 13 Contempré B, Dumont JE, Ngo B, Thilly CH, Diplock AT, Vanderpas J. Effect of selenium supplementation in hypothyroid subjects of an iodine and selenium deficient area: the possible danger of indiscriminate supplementation of iodine-deficient subjects with selenium. *J Clin Endocrinol Metab*. 1991 Jul;73(1):213–5.
- 14 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-blind trial in a Danish population. *Eur J Endocrinol*. 2015 Jun;172(6):657–67.

- 15 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 Oct;79(4):584–90.
- 16 Marcocci C, Leo M, Altea MA. Oxidative stress in graves' disease. *Eur Thyroid J*. 2012 Jul;1(2):80–7.
- 17 Rotondo Dottore G, Leo M, Casini G, Latrofa F, Cestari L, Sellari-Franceschini S, et al. Antioxidant Actions of Selenium in Orbital Fibroblasts: A Basis for the Effects of Selenium in Graves' Orbitopathy. *Thyroid*. 2017 Feb;27(2):271–8.
- 18 Winther KH, Bonnema SJ, Hegedüs L. Is selenium supplementation in autoimmune thyroid diseases justified? *Curr Opin Endocrinol Diabetes Obes*. 2017 Oct;24(5):348–55.
- 19 Kahaly GJ, Riedl M, König J, Diana T, Schomburg L. Double-Blind, Placebo-Controlled, Randomized Trial of Selenium in Graves Hyperthyroidism. *J Clin Endocrinol Metab*. 2017 Nov;102(11):4333–41.
- 20 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 Mar;40(3):281–7.
- 21 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 Sep;48(9):559–64.
- 22 Calissendorff J, Mikulski E, Larsen EH, Möller M. A Prospective Investigation of Graves' Disease and Selenium: Thyroid Hormones, Auto-Antibodies and Self-Rated Symptoms. *Eur Thyroid J*. 2015 Jun;4(2):93–8.
- 23 Marcocci C, Kahaly GJ, Krassas GE, Bartalena L, Prummel M, Stahl M, et al.; European Group on Graves' Orbitopathy. Selenium and the course of mild Graves' orbitopathy. *N Engl J Med*. 2011 May;364(20):1920–31.
- 24 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 Jun;80(6):905–10.
- 25 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 Mar;5(1):57–64.
- 26 Marcocci C, Altea MA, Leo M. Treatment options for Graves' orbitopathy. *Expert Opin Pharmacother*. 2012 Apr;13(6):795–806.
- 27 Köhrle J. Selenium and the thyroid. *Curr Opin Endocrinol Diabetes Obes*. 2015 Oct;22(5):392–401.
- 28 Hegedüs L, Bonnema SJ, Winther KH. Selenium in the Treatment of Thyroid Diseases: An Element in Search of the Relevant Indications? *Eur Thyroid J*. 2016 Sep;5(3):149–51.
- 29 Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH. 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. *Eur Thyroid J*. 2018 Aug;7(4):167–86.
- 30 Bartalena L, Baldeschi L, Boboridis K, Eckstein A, Kahaly GJ, Marcocci C, et al.; 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 Mar;5(1):9–26.
- 31 Negro R, Attanasio R, Grimaldi F, Marcocci C, Guglielmi R, Papini E. A 2016 Italian Survey about the Clinical Use of Selenium in Thyroid Disease. *Eur Thyroid J*. 2016 Sep;5(3):164–70.
- 32 Watt T, Cramon P, Björner JB, Bonnema SJ, Feldt-Rasmussen U, Gluud C, et al. Selenium supplementation for patients with Graves' hyperthyroidism (the GRASS trial): study protocol for a randomized controlled trial. *Trials*. 2013 Apr;14:119.
- 33 Rayman MP. Selenium and human health. *Lancet*. 2012 Mar;379(9822):1256–68.
- 34 Kipp AP, Strohm D, Brigelius-Flohé R, Schomburg L, Bechthold A, Leschik-Bonnet E, et al.; German Nutrition Society (DGE). Revised reference values for selenium intake. *J Trace Elem Med Biol*. 2015 Oct;32:195–9.
- 35 Aguilar F, Charrondiere UR, Dusemund B, et al. L-selenomethionine as a source of selenium added for nutritional purpose to food supplements. *EFSA J*. 2009;1082:1–39.
- 36 MacFarquhar JK, Broussard DL, Melstrom P, Hutchinson R, Wolkin A, Martin C, et al. Acute selenium toxicity associated with a dietary supplement. *Arch Intern Med*. 2010 Feb;170(3):256–61.
- 37 Ventura M, Melo M, Carrilho F. Selenium and Thyroid Disease: From Pathophysiology to Treatment. *Int J Endocrinol*. 2017;2017:1297658.
- 38 Rayman MP, Winther KH, Pastor-Barriuso R, et al. Effect of long-term selenium supplementation on mortality: Results from a multiple-dose, randomised controlled trial. *Free Radic Biol Med*. 2018 Nov 1;127:46–54.
- 39 Schomburg L, Köhrle J. On the importance of selenium and iodine metabolism for thyroid hormone biosynthesis and human health. *Mol Nutr Food Res*. 2008 Nov;52(11):1235–46.
- 40 Jing CL, Dong XF, Wang ZM, Liu S, Tong JM. Comparative study of DL-selenomethionine vs sodium selenite and seleno-yeast on antioxidant activity and selenium status in laying hens. *Poult Sci*. 2015 May;94(5):965–75.
- 41 Clausen J, Nielsen SA. Comparison of whole blood selenium values and erythrocyte glutathione peroxidase activities of normal individuals on supplementation with selenate, selenite, L-selenomethionine, and high selenium yeast. *Biol Trace Elem Res*. 1988 Jan-Apr;15(1):125–38.