A 2018 European Thyroid Association Survey on the Use of Selenium Supplementation in Hashimoto's Thyroiditis

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Keywords

Selenium · Autoimmune thyroid disease · Hashimoto thyroiditis · Autoimmune thyroiditis · Hypothyroidism · European Thyroid Association · Questionnaire · Survey

Abstract

Objective: To investigate clinical practice regarding the use of selenium supplementation in patients with Hashimoto's thyroiditis (HT) among members of the European Thyroid Association (ETA). **Methods:** ETA members were invited to participate in an online survey investigating the use of selenium supplementation across the spectrum of benign thyroid diseases. Of 872 invited members, 242 (28%) completed the survey. After exclusion of basic scientists and non-European members, survey data from 212 respondents were eligible for further analyses. Responses from 65 (31%) individuals who did not at all recommend selenium, or only considered its use in the setting of a clinical trial, were not included in the final analysis of survey data from 147 respondents. **Results:** While only a minority of respondents (29 of 147, 20%) stated that the available evidence warrants the use of Se in patients with HT, a statistically significant majority (95

of 147; 65%, $p < 0.001$) used Se occasionally or routinely. Se was predominantly recommended for patients with HT not receiving LT4 (102 of 147; 69%) to reduce circulating thyroid autoantibody levels. Very few respondents routinely recommended Se to pregnant patients with HT. **Conclusions:** A minority of responding ETA members stated that the available evidence warrants the use of Se in HT, but a majority recommended it to some extent, especially to patients not yet receiving LT4. This is questionable, and selenium is not recommended to patients with HT according to current ETA guidelines. Ongoing and future trials may lead to the reversal of current medical practice.

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Introduction

Since 1991, when selenium was identified in type 1 deiodinase that catalyzes the conversion of thyroxine (T4) to triiodothyronine (T3) [1], the relevance of this trace element for thyroid health and disease has been extensively investigated [2, 3]. The first clinical intervention studies were published in populations with combined severe io-

Fig. 1. Flowchart of survey respondents.

dine and selenium deficiency [4, 5], and it was soon recognized that the importance of the selenium status for the thyroid is dependent on the status of other trace elements [6]. The interplay with iodine and iron has since been elaborated, in particular for Hashimoto's thyroiditis (HT) [7]. The clinical importance of selenium status for thyroid hormone metabolism may be limited in healthy adults [8]. Meanwhile, the independent importance of the selenium status for thyroid diseases was recently corroborated in a large cross-sectional study conducted in two counties of the Chinese Shaanxi Province, defined as adequate and low-selenium areas [9]. There, the prevalence of HT was significantly higher in the low-selenium county and attenuated in individuals with serum Se >70 µg/L. In the selenium and thyroid research field, HT has been the most frequently investigated disease over the course of the past 20 years, with more than 20 published trials, predominantly from Europe and China. One general conclusion from those trials, as summarized in several systematic reviews, is that Se supplementation decreases thyroid autoantibody concentrations [10, 11]. However, effects of Se on direct clinical outcomes have been sparsely evaluated. Thus, little can be deduced about disease progression or

remission, quality of life, or thyroid hormone substitution dose following Se supplementation, for example [12]. Finally, a relevant but still unsettled issue is the use of Se to prevent the occurrence of postpartum thyroiditis in pregnant women with elevated thyroid peroxidase autoantibodies (TPO-Ab) [13]. So, in light of the available and growing body of evidence from human trials, the role of Se supplementation in everyday clinical care for patients with HT has been debated in recent years. In 2016, a survey of the use of Se across the spectrum of benign thyroid diseases was carried out among members of the Italian Association of Clinical Endocrinologists (AME – Associazione Medici Endocrinologi) [14]. Out of 778 respondents, 72% replied that there is no evidence supporting Se use in HT. However, 79% did in fact prescribe Se sometimes, often, or always. The motivation to prescribe Se was primarily to prevent serum TSH increase (49%) or to decrease thyroid autoantibody levels (39%) [14].

This finding prompted us to develop a survey for distribution among the members of the European Thyroid Association (ETA). The survey covers the use of Se across benign thyroid diseases, and the results with respect to HT are reported here.

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 2 reminders between April 1 and 30, 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 as online suppl. Appendix 1; see www.karger.com/doi/10.1159/000504781.

Statistical Analysis

Summary statistics were prepared for responses to each question. We considered only those questionnaires with complete demographic data from the respondents as valid for statistical evaluation. The Pearson χ^2 test was used to compare frequencies (percentages) between categorical variables. A two-sided value of $p < 0.05$ was considered statistically significant. Data were analyzed using SAS 9.4.

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

Respondents from different countries were pooled and analyzed together, except where stated otherwise, as the small number of responding physicians from each single country did, in general, not allow for comparisons between countries.

Fig. 2. Evidence for Se in Hashimoto's thyroiditis. Distribution of respondents ($n = 147$). One option is allowed per respondent: yes, and I recommend it routinely (29 of 147; 20%); no, and I never recommend it (35 of 147; 24%); no, but I recommend it occasionally (60 of 147; 41%); no, but I think it is effective and I recommend it routinely (8 of 147; 5%); other, please specify (6 of 212; 4%), or don't know (9 of 212; 6%).

Results

Survey Respondents

A total of 266 ETA members (31% of 872 invited ETA members) participated in the survey, and 242 respondents provided complete demographic information. The respondent flow is illustrated in Figure 1. Physicians from 34 countries answered the questionnaire. Italy ($n = 38$; 16%) and Denmark ($n = 27$; 11%) provided the highest number of responses.

Non-European members ($n = 18$) and basic scientists ($n = 12$) were excluded from further analyses. Of the remaining 212 respondents, 52% were male, their median age was 51–60 years, and the median duration of practicing medicine was 21–30 years. The majority (84%) were specialists in endocrinology, and 65% worked at a university hospital, with 35% of respondents equally distributed between general hospitals and private clinics.

The initial key question in the survey was: “Do you use selenium supplements in patients with thyroid disease?” Respondents answering “Never” ($n = 34$), “Only in the setting of a clinical trial” ($n = 18$), or those that did not provide an answer ($n = 13$) were excluded from the survey at that junction. The remaining 147 respondents were analyzed for all other survey data. Demographic characteristics were similar for respondents that used Se versus those that did not (data not shown), except for country. Only a minority of Italian respondents (7 of 37; 19%) did not use Se, whereas most Danish respondents did not use Se (22 of 24; 92% $p < 0.001$). When respondent data from all other countries than Denmark were pooled and compared to Danish respondents, significantly more used Se (148 of 191; 77%, $p < 0.001$).

General Data about Se Supplementation

The Se status in the general population of their own country was unknown to 95 respondents (63%). Nearly all respondents (146; 99%) were aware of Se availability on the market, either as a mono-component in tablets or as a component of multivitamin supplements, but some (30 of 147; 20%) were not aware of the chemical formulation of marketed Se (organic, i.e., selenomethionine, or inorganic, i.e., selenite). Just above half of the respondents (80 of 147; 54%) expressed a preference for one formulation over the other, with selenomethionine being the more popular (69%). Most respondents (122 of 147; 83%) asked their patients about the intake of dietary supplements containing Se before recommending Se treatment.

For a slight majority of respondents (88 of 147; 60%), the decision to recommend Se supplementation was not influenced by the Se status of the general population. Only a few respondents (30 of 147; 20%) reported that they generally (4%) or occasionally (16%) measured Se status before recommending supplementation, and most (110 of 147; 75%) did not consider iodine status when deciding whether or not to recommend Se supplementation.

The majority of respondents (85 of 147; 58%) did not make a specific prescription, as Se is sold over the counter in their countries. Throughout the survey, respondents agreed about the recommended supplementation dose and duration. With little distribution variation across patient subpopulations, it was $\leq 200 \mu\text{g/day}$ with a duration of weeks to months followed by a re-evaluation of the treatment effects.

Fig. 3. Recommendations of Se supplementation in patients with Hashimoto's thyroiditis. Distribution of respondents ($n = 147$). One option is allowed per respondent: a: never (73 of 147; 50%); sometimes (57 of 147; 39%); frequently (15 of 147; 10%); or always (2 of 147; 1%). b: never (45 of 147; 31%); sometimes (65 of 147; 44%); frequently (28 of 147; 19%); or always (9 of 147; 6%).

Se Supplementation in HT

Only 29 of 147 respondents (20%) answered that the available evidence warrants the use of selenium supplementation and recommend Se routinely to this patient group. However, 68 respondents who answered that the available evidence does not warrant the use of Se also recommend Se occasionally (60 of 147; 41%) or routinely (8 of 147; 5%) (Fig. 2). A minority, (35 of 147; 24%) would never recommend Se. Finally, a few respondents specified other recommendations (6 of 147; 4%) or did not know (9 of 147; 6%) (for homogeneity across response categories: $p < 0.001$).

Patients with HT Receiving LT4

For this HT subgroup, half of the respondents (73 of 147; 50%) would never recommend Se. The other half recommended Se occasionally (57 of 147; 39%), frequently (15 of 147; 10%), or always (2 of 147; 1%) (Fig. 3) (for homogeneity across response categories: $p < 0.001$). Of the respondents recommending Se occasionally, frequently, or always, the majority (54 of 74; 73%) aimed at reducing thyroid autoantibodies. Other frequent motivations were to slow TSH increase (25 of 74; 34%), improve health-related quality of life (22 of 74; 30%), or thyroid morphology as determined ultrasonically (21; 28%). In pregnant patients, the majority (104 of 147; 71%) would never recommend Se, whereas only 12 respondents would recommend Se always (2 of 147; 1%) or frequently (10 of 147; 7%).

Patients with HT Not Receiving LT4

For this HT subgroup, a minority of respondents (45 of 147; 31%) would never recommend Se, whereas 102 respondents would occasionally (65 of 147; 44%), frequently (29 of 147; 20%), or always (8 of 147; 5%) do so (Fig. 3b) (for homogeneity across response categories: $p < 0.001$). Among those who recommended Se frequently or always, most (33 of 37; 89%) recommended Se to reduce thyroid autoantibody concentrations. The second most frequent cause for recommending Se was to slow down the increase in serum TSH (13/37; 35%). If the same patient, i.e., a euthyroid patient with thyroid autoantibodies, was pregnant, the majority (98 of 147; 67%) would never recommend Se, and only 13 would recommend Se always (4 of 147; 3%) or frequently (9 of 147; 6%).

Discussion

Has the increasing focus on Se in thyroid diseases led to increased use in the routine management of HT? The main finding from the responses of 212 clinically active European ETA members is somewhat paradoxical, in that only a minority of 20% of responding members find that the available evidence warrants the use of Se in HT, while a majority (66%) recommend it occasionally or frequently. The overall finding is very similar to the practice pattern among Italian AME members [14], but the current survey illustrates at least some geographical variation, as nearly all (92%) Danish respondents would not use Se outside clinical trials.

When analyzing patient subpopulations, Se is foremost recommended to incident patients with HT not yet receiving LT4, with the predominant motivation being to reduce thyroid autoantibody levels. Whether or not the documented decreases in TPO-Ab levels in both incident and prevalent HT patients [11] warrant the use of Se is debatable. TPO-Ab levels may merely be a diagnostic biomarker [15] but have been inversely associated with disease-related quality of life in HT [16]. In the GRADE guidelines, it is discussed that an effect on a disease biomarker should probably not lead to recommendations in clinical guidelines for treatment, while quality of life can generally be considered important for clinical decision making [17]. It follows that future trials should be designed to primarily assess effects on direct clinical outcomes, such as validated quality-of-life measurement. In an ongoing prospective, randomized, long-term trial enrolling LT4-treated patients with HT, following 12 months of supplementation with 200 µg/day Se-enriched

yeast, the primary outcome is thyroid-related quality of life as evaluated with the ThyPRO questionnaire [18].

Less than 10% of respondents would recommend Se to pregnant patients with HT. A randomized controlled trial from 2007 among 151 pregnant women with TPO-Ab reported that 200 µg/day Se as selenomethionine significantly reduced the incidence of postpartum thyroid dysfunction and permanent thyroid dysfunction [19]. Meanwhile, in another randomized placebo-controlled trial among 230 pregnant UK women, published in 2014, Mao et al. [20] found no effect of 60 µg/day Se-enriched yeast on thyroid autoantibody concentrations, but a tendency towards TSH decrease in TPO-Ab-positive participants. These data are of great interest because there are no recognized therapies or trace mineral supplementations with a favorable influence on the inflammatory activity and the subsequent deterioration of thyroid function in pregnant individuals with autoimmune thyroiditis. Indeed, neither iodine [21] nor levothyroxine [22] administration prevented – not even in iodine deficient areas – the occurrence of postpartum thyroiditis and permanent hypothyroidism in TPO-Ab-positive pregnant women. Notably, Se supplementation is not mentioned in the current ETA guidelines for subclinical hypothyroidism in pregnancy [23]. Thus, the minority of respondents recommending Se to pregnant patients with HT are not acting according to current guidelines, but the level of the evidence, i.e., a single robust trial, is similar in mild Graves' orbitopathy (GO) [24], where Se supplementation is recommended [25, 26]. Concerns have been raised about impaired neurocognitive development with selenium deficiency during pregnancy [27], and the research area of selenium, thyroid, and pregnancy needs more attention in the future.

Nearly half of the respondents in this survey did not state any preference as to the formulation of Se. In a systematic review by Wichman et al. [11], a comparison of 5 studies using 200 µg/day selenomethionine with 2 studies using 200 µg/day of sodium selenite showed a significant drop in TPO-Ab at 3 months in the subgroup receiving selenomethionine but not in that receiving sodium selenite. This difference cannot readily be explained by previous mechanistic studies, where both organic and inorganic supplements have led to increased selenoprotein activity [28], but it will need to be investigated further if indications for treatment are to be established.

Knowledge about background Se level was limited among survey respondents, as 63% were unaware of the Se status in their own country. Se was rarely measured prior to any recommendation, and the decision to recom-

mend Se supplementation was typically not based on Se or iodine status of the general population. The importance of knowing the Se status relates to the potential risks of excessive supplementation. Except under conditions of marked iodine deficiency [6], Se supplementation has not been reported to have adverse effects on thyroid hormone metabolism or worsened the clinical course of any thyroid disease. In contrast, recent reports have raised concern about an increased risk of type 2 diabetes and insulin resistance with high selenium exposure. Two very recent meta-analyses of observational studies reported a significant association between selenium concentrations in plasma/serum and type 2 diabetes [29, 30]. However, the association cannot prove causality, and, interestingly, in one of the studies, a separate meta-analysis of randomized controlled trials found no increased risk of type 2 diabetes following selenium supplementation compared to placebo [29].

Several previous trials conducting follow-up analyses after long-term Se supplementation have not identified serious adverse effects, but in a trial in Denmark, where there is moderately low Se status, 300 µg/day of Se-enriched yeast taken for 5 years increased all-cause mortality 10 years later compared to placebo, 100, or 200 µg/day [31]. More than 90% of survey respondents recommended Se doses ≤200 µg/day, and while this appears safe, much work remains to identify safe and effective doses, if Se does have a rightful place in the treatment of HT.

The strengths of our survey include the high number of respondents among clinically active European thyroidologists. In a previous survey on practice patterns in Graves' disease among ETA members, it was reported that 145 respondents corresponded to 38% of clinically active ETA members [32]. In analogy to those numbers, our 212 European respondents correspond to 54% of ETA clinicians. However, the spread across 34 countries did not allow for in-depth comparisons between countries, and many countries were represented by very few respondents. Other limitations include the lack of questionnaire validation and selection bias of the respondents, which may skew the results towards both over- and underestimation of any recommendation. The median age of the respondents was 51–60 years, and the relatively high respondent age might not be truly representative of European treatment practice. Finally, because Se is an over-the-counter product in most countries, many patients are totally independent of the advice of their physicians before Se supplementation.

Our survey covered the spectrum of benign thyroid disorders, and we have published the results on the use of

Se in Graves' hyperthyroidism and GO in a separate report [33]. A striking 94% of respondents recommended Se in GO sometimes (39%), frequently (30%), or always (25%), and thus the use of Se in GO is more in line with current recommendations [25, 26] than it is in HT.

In conclusion, the majority of responding ETA members stated that the available evidence does not warrant Se supplementation in HT. However, the majority recommended this to HT patients not receiving LT4 in order to decrease thyroid autoantibodies or slow TSH level increase. These effects were only partly observed in recent systematic reviews, and the available evidence has not led to recommendations in current ETA clinical guidelines. Ongoing large-scale trials [18, 34] may further clarify whether Se, an environmental factor in interplay with genetic susceptibility to autoimmune thyroid diseases [9, 35–37], translates into a role of Se supplementation in the treatment of those diseases.

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Statement of Ethics

Participation in survey studies is viewed as informed consent, and this survey complies with the regulations of the regional ethical committee of Southern Denmark.

Disclosure Statement

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

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