Efficacy of Selenium Supplementation on Autoantibody Titers in Graves' Ophthalmopathy

Marc Gregory Yu, M.D.*; Antonio Faltado, Jr., M.D.* and Laura Rosario Acampado, M.D.*

Abstract

Background: Selenium (Se) shows potential benefit in Graves' disease (GD) especially those with active Graves' ophthalmopathy (GO).

Objectives: To evaluate the efficacy of Se supplementation among patients with GD and GO.

Methodology: We performed a meta-analysis of trials evaluating the efficacy of Se supplementation among adult patients with GD and active GO, versus either placebo or an alternative drug, and on top of standard therapy. Results were presented as mean differences, standard errors, and 95% confidence intervals, and graphically presented as forest plots. Estimates were calculated using the inverse variance method for continuous variables and pooled using the fixed effects model. I^2 and Chi^2 tests were used to assess heterogeneity.

Results: Only two trials were ultimately included in the analysis. Both studies totaled 197 participants with GD and non-severe GO on standard therapy, and compared Se supplementation to placebo. The only common outcomes of interest were changes in TSH receptor antibody (TRAB) and thyroid peroxidase antibody (TPOAB) titers. We found no statistically significant difference in either TRAB (95% CI, -1.38 (-3.19, 0.44), p=0.14) or TPOAB (95% CI, 36.66 (-32.56, 105.88), p=0.30) titers between Se and placebo groups on follow up. However, our analysis was limited by the small number of included studies, a small sample size, and lack of other synthesizable outcomes.

Conclusion: This is the first meta-analysis summarizing the available data on Se supplementation in patients with GD and non-severe GO. We found no statistically significant differences in both TRAB and TPOAB titers between Se and placebo groups. We recommend larger studies to validate these findings.

Keywords: selenium, Graves' disease, Graves' ophthalmopathy, autoantibodies, thyroid gland

Introduction

Graves' disease (GD) is characterized by the presence of activating autoantibodies (TRAB) against the thyroid-stimulating hormone (TSH) receptor.[1] These lead to signs and symptoms of excessive thyroid hormone production and in approximately half of patients, Graves' ophthalmopathy (GO).[2] Standard treatment for GD involves medications blocking thyroid hormone synthesis, radioiodine (RAI) therapy, and thyroidectomy, which all render the patient euthyroid.[3] However, despite effectively addressing the glandular component, these therapies have proven suboptimal for patients with GO, adversely affecting daily activities and health-related quality of life (HRQoL).[4]

Selenium (Se) is a trace element incorporated in several key human enzymes.[5] Levels in food and in humans reflect soil content, which vary worldwide due to factors such as flora and agriculture.[6,7,8] The thyroid has the highest Se concentration per weight among all body tissues.[9] As a component of selenoproteins such as glutathione peroxidase (GPx) and thioreduxin reductase (TRx), Se helps combat the highly oxidative milieu in GD and GO and further appears to influence the immune system by decreasing levels of TRAB and thyroid peroxidase antibodies (TPOAB), which are found in 80% of patients with GD.[10,11] Conversely, Se deficiency has been associated with increased thyrocyte damage and greater production of reactive oxygen species (ROS), an important aspect of the inflammatory process in GD and GO.[12] Decreased levels of Se were found in GD patients compared to controls, with significantly lower levels found in GD patients with GO as compared to those without GO.[13,14] Yet another study showed that GD patients in remission had the highest Se levels and the lowest TRAB levels compared to those with active disease and relapse.[15]

*Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, Philippine General Hospital, Manila, Philippines

This paper was presented at the following scientific meetings:
1. *ESE Meeting Grant Award and selected as part of guided poster tours, 2016 European Congress of Endocrinology, Munich, Germany, May 28-31, 2016*
2. *Poster Presentation, 46th Annual Convention of the Philippine College of Physicians, Manila, Philippines, April 30-May 3, 2016*
3. *Poster Presentation, Philippine Society of Endocrinology, Diabetes, and Metabolism Annual Convention, Manila, Philippines, March 16-18, 2016.*
4. *Finalist, Research Poster Competition (Thyroid Category), 18th ASEAN Federation of Endocrine Societies Congress, Kuala Lumpur, Malaysia, December 10-13, 2015*

Corresponding Author: Marc Gregory Yu, M.D.ORCID # 0000-0002-0376-9574
Email: marcgreggy@yahoo.com

Given the crucial role of Se in the pathogenesis of GD and GO, this study aims to consolidate current available information and evaluate the possible efficacy of Se supplementation in patients with GD and GO.

Methods

The study was performed in accordance with the PRISMA guidelines for reporting systematic reviews and meta-analyses.

Search Strategy

Electronic databases including MEDLINE, Scopus, Embase, Hinari, ClinicalTrials.gov, Google Scholar, and the Cochrane Central Register of Controlled Trials were systematically searched by two independent investigators for inclusion of articles in the study. The following terms were used individually and in combination: "selenium", "selenite", "selenoprotein", "thyroid", "Graves' disease", "Basedow disease", "thyrotoxicosis", "hyperthyroidism", "ophthalmopathy", "orbitopathy", and "thyroid-related eye disease." These key terms were utilized as text words, Medical Subject Headings (MeSH), and Clinical Queries. Cross-references of original publications, books of abstracts, and conference proceedings from the WHO Network of Collaborating Clinical Trial Registers, US FDA registry, and International Committee of Medical Journal Editors (ICMJE) were searched as well. Manufacturers of selenium brands were also contacted via email for possible inclusion of any unpublished studies. The search was not restricted to any study design, language, or time frame, and any discrepancy was resolved by discussion and consensus through a third author.

Study Selection

Randomized controlled trials (RCTs) or meta-analyses involving Se supplementation in adult GD patients with active GO, as compared to placebo or alternative interventions, and on top of standard therapy, were included in this study. There were no restrictions on ethnicity or gender. Exclusion criteria included pregnancy, comorbid systemic or ocular disease, severe GO requiring steroid use at outset, and previous or ongoing use of Se-containing supplements. Outcome measures must include any or a combination of the following: clinical activity of GO as measured through objective examination or symptom scores; levels of selenium or selenoproteins, TSH, thyroid hormones, TRAB and TPOAB; and overall HRQoL.

Data Extraction and Management

Three authors independently screened potential studies using a data eligibility form. Studies agreed upon for exclusion were excluded at this stage, with the reason for exclusion documented. Eligible studies then underwent methodological quality assessment based on the Cochrane Collaboration's tool for assessing risk of bias. The validity criteria included randomization, allocation concealment, baseline characteristics, blinding, and adequacy of follow-up. Any disagreements were resolved by consensus. Studies that passed all screenings underwent independent data extraction by all authors, with the following data extracted from each trial: author, year of publication, duration of therapy, intervention, type of comparator, sample size and type of population, and study outcomes.

Statistical Analysis

The study was analyzed using Review Manager, version 5. Results were presented as mean differences and standard errors with 95% confidence intervals, and graphically presented as forest plots. Estimates were calculated using the inverse variance method for continuous variables and pooled using the fixed effects model. Heterogeneity was defined as $I^2>50\%$ and $p<0.1$ utilizing the I^2 and Chi^2 tests, respectively. Unit of analysis issues were resolved by looking for uniformity among the analyses of the individual studies. In cases of multiple observations for the same outcome, it was agreed upon that the last measure will be included in the study. Missing data was dealt with by contacting the trial authors.

Results

Search Results

Fourteen potentially relevant articles were retrieved. On initial deliberation, only nine were deemed eligible for inclusion; the other five articles were excluded because they were animal studies, editorials, or review articles. Of the nine initially screened-in articles, seven were further excluded because they either had no or different interventions, different disease populations, different outcome measures, or were still ongoing trials. Two studies ultimately satisfied the selection criteria and were included in the analysis. Figure 1 shows the general flowchart for study selection, while the list of the two included studies, together with their corresponding characteristics, is outlined in Table I. Table II, on the other hand, summarizes the methodological quality assessment results for each of the included studies, while Table III summarizes the excluded studies and the reasons for exclusion.

Study Characteristics

Both selected studies were conducted in Europe and were published within the last four years. Duration of therapy

was six months in one study (with additional exploratory evaluations at twelve months) and nine months in the other. A total of 197 participants aged 18-70 years old were enrolled in the two studies, and all had GD with non-severe GO. Both studies compared Se with placebo; with one study

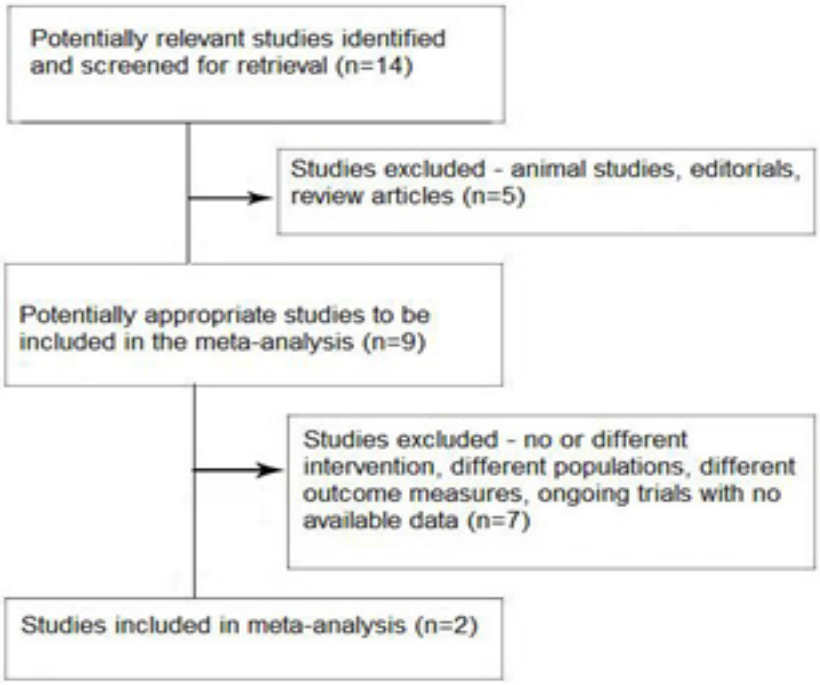

Figure 1. Flowchart of the process of retrieval and selection of studies for the review.

Table I. Characteristics of the studies included in the review.

Study	Marcocci 2011[18]	Calissendorff 2015[19]
Title	Selenium and the course of mild Graves' ophthalmopathy	A prospective investigation of Graves' disease and selenium: thyroid hormones, auto-antibodies, and self-rated symptoms
Design	RCT	RCT
Therapy Duration	6 months	9 months
Sample Size	159	38
Population	Adult GD patients aged 18-70 with mild GO <18 mo duration	Adult GD patients aged 18-55 without severe GO
Outcomes	Eye evaluation, GO-QoL score, clinical activity score, diplopia score, TRAB, TPOAB	Selenoprotein concentration, self-rated symptom score, anxiety and depression score, TSH, ft4, fT3, TRAB, TPOAB
Intervention	Se 200 ug/day	Se 200 ug/day
Comparator	Placebo, pentoxifylline	Placebo

Table II. Methodological quality assessments for studies included in the review.

Study	Marcocci 2011[18]	Calissendorff 2015[19]
Randomization	Adequate	Adequate
Allocation Concealment	Yes	Yes
Baseline Characteristics	No significant difference	No significant difference
Blinding	Double blind	Double blind
Follow-up Rates	Adequate	Adequate

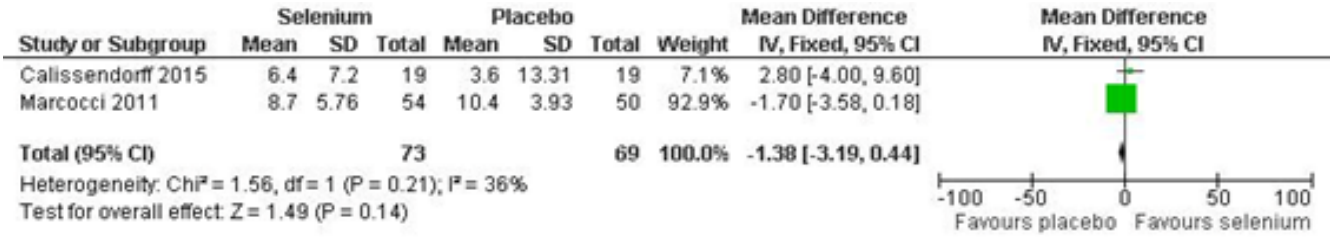

Figure 2. Mean difference in TRAB titers between the selenium and placebo groups.

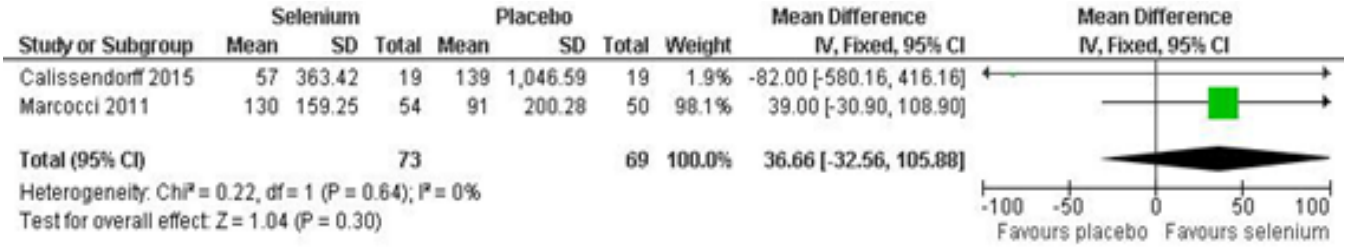

Figure 3. Mean difference in TPOAB titers between the selenium and placebo groups.

further comparing Se with pentoxifylline, another drug with putative anti-oxidative properties. The outcomes of interest were objective eye evaluations, HRQoL scores (as measured via the GO-QoL Questionnaire), clinical activity scores, and diplopia scores in the first study; and self-rated symptom scores (as assessed via a modified version of the Rivermead Post-Concussion Questionnaire), anxiety and depression scores (as measured via the Hospital Anxiety and Depression Questionnaire), and levels of TSH, thyroid hormones, TRAB, and TPOAB in the second. With regards to methodological quality, both studies were randomized, double-blind RCTs with adequate follow-up rates. The baseline characteristics of the groups being compared yielded no significant differences in either study.

For this meta-analysis, the placebo arm was used as the control group in all outcome measures. Moreover, since TRAB and TPOAB measurements were common to both studies, we focused on autoantibody titers as the outcomes of interest in this meta-analysis.

Data Synthesis

Effects of Se Supplementation on TRAB Titers

Both studies reported TRAB titers at baseline and on follow up. No statistically significant difference (95% CI, -1.38 (-3.19, 0.44), p=0.14) was found in TRAB titers among patients given Se supplementation as compared to the placebo group (Figure 2.) Significant heterogeneity (I^2=36%) was not observed in this analysis.

Effects of Se Supplementation on TPOAB Titers

Both studies also reported TPOAB titers at baseline and on follow up. No statistically significant difference (95% CI,

Table III. List of excluded studies and reasons for exclusion.

Study	Reason for Exclusion
Watt 2013[17]	Ongoing trial, no data yet available
Wertenbruch 2007[15]	Case control design, no intervention
Kwong 2014[14]	Case control design, no intervention
Pedersen 2013[13]	Cross-sectional design, no intervention
Vrca 2003[20]	Different intervention and outcome measures
Smith 2011[4]	Review article
Duntas 2011[21]	Review article
Dharmasena 2014[22]	Review article
Sturniolo 2013[23]	Editorial
Toulis 2010[24]	Different disease population
Fan 2014[16]	Different disease population
Xu 2011[25]	Animal study

36.66 (-32.56, 105.88), p=0.30) in TPOAB values was similarly detected among patients given Se supplementation as compared to the placebo group (Figure 3). Significant heterogeneity (I^2=0%) was also not observed in this analysis

Discussion

This is the first meta-analysis summarizing the current available data on the effect of Se supplementation on autoantibody titers in patients with GD and non-severe GO. We found no statistically significant difference in both TRAB and TPOAB levels among patients given Se supplementation as compared to the placebo group. In contrast, a meta-analysis performed in patients with autoimmune thyroiditis showed a significant decrease in TPOAB titers among the Se-administered population as compared to controls at a similar time frame of six months.[16]

Several limitations may have accounted for the differences in the key findings of our study in contrast to the theorized mechanisms of Se cited in literature. First, our meta-analysis only included two trials both with relatively small sample sizes, thus affecting the power of the study to gauge overall treatment effect. In terms of outcomes, the study was also limited to the evaluation of autoantibody titers as these were the only measures common to both studies. We were unable to pool results from other clinical endpoints – objective eye evaluations and diplopia, clinical activity, and GO-QoL scores in one study; and symptom scores, anxiety and depression scores, and selenoprotein, TSH and thyroid hormone levels in the other. Specifically, we were unable to pool results from self-rated outcomes as different questionnaires and scoring systems were used, with no known longitudinal correlations of change and similarities of responsiveness between them. An alternative recourse would have been to pool data in a dichotomous fashion, however dichotomous data was not presented in the trials included (one study did not report the number of patients who improved in the placebo arm while the other presented the data entirely as mean scores for the whole study population).

More importantly, neither study evaluated other important outcomes such as rates of mortality, hospitalization, remission, relapse, and treatment failure. Serum Se levels were also not measured in one study (given the premise that patients with GD and GO have lower serum Se levels.) It must be noted that both trials were conducted in one geographical area (Europe) alone, with different diets, genetics, and Se soil content as compared to other regions, and hence any conclusions made may not always apply to populations living in other parts of the world.

Nevertheless, both studies included in this review were generally of good quality, with adequate randomization, blinding, and rates of follow-up. Despite the fact that no significant heterogeneity was found during the analysis of both TRAB and TPOAB titers, it must be remembered that the utility of the I^2 and Chi^2 tests in this regard is limited, since these possess low power in the situation of a meta-analysis involving only a few studies or small sample sizes. For this study, a relative lack of data on the role of Se in GD and GO was encountered, largely due to the novelty of its use in the disease. A funnel plot to assess publication bias was rendered unfeasible by the presence of only two studies. Minimization of selection bias was done via pre-specified inclusion and exclusion criteria, performance of a systematic search, and independent evaluation of trial quality by the reviewers.

The results of this study reinforce the fact that our present knowledge on the efficacy of Se supplementation in GD remains much to be desired. An ongoing study, the selenium supplementation for patients with Graves' hyperthyroidism (GRASS) trial, possesses a larger sample size and focuses on other still unevaluated outcomes such as proportion of participants with treatment failure.[17] This plus other trials registered at ClinicalTrials.gov may help enhance our understanding on the true benefit of Se supplementation in GD and GO.

Conclusion

Se supplementation in patients with GD and non-severe GO was not associated with statistically significant differences in both TRAB and TPOAB titers. We recommend studies with larger populations and more clinical outcomes to validate these findings. Such investigations will help improve current guidelines on the optimal management of patients with GD and GO.

Conflicts of Interest

The authors declare no competing interests. No external funding source was involved in the conduct of this study.

References

1. **Weetman, A.P.** Graves' disease. New Engl J Med, 343 (17): 1236-48, 2000.
2. **Bartalena, L., Pinchera, A and Marcocci, C.** Management of Graves' ophthalmopathy: reality and perspectives. Endocr Rev, 21: 168-99, 2000.
3. **Cooper, DS.** Antithyroid drugs. New Engl J Med, 352: 905-917, 2005.
4. **Smith, TJ and Douglas, RS.** Does selenium supplementation improve Graves' ophthalmopathy? Nat Rev Endocrinol, 7: 505-6, 2011.
5. **Weeks, BS, Hanna, MS and Cooperstein, D.** Dietary selenium and selenoprotein function. Med Sci Monit, 18 (8): 127-132, 2012.
6. **Xia, Y; Hill, KE; Byrne, DW; Xu, J; and Burke, RF.** Effectiveness of selenium supplements in a low-selenium area in China. Am J Clin Nutr, 81 (4): 829-834, 1998.
7. **Hira, CK, Partal , K and Dhillon, KS.** Dietary selenium intake by men and women in high and low selenium areas of Punjab. Public Health Nutr, 7 (1): 39-43, 2004.
8. **Rayman, MP.** The argument for increasing selenium intake. Proc Nutr Soc, 61: 203-15, 2002.
9. **Drutel, A, Archambeaud, F and Caron, P.** Selenium and the thyroid gland: more good news for clinicians. Clin Endocrinol, 78 (2): 155-64, 2013.
10. **Abalovich, M; Llesuy, S; Gutierrez, S; and Repetto, M.** Peripheral parameters of oxidative stress in Graves' disease: the effects of methimazole and 131 iodine treatments. Clin Endocrinol, 59 (3): 321-7, 2003.
11. **Eskes, SA; Endert, E; Fliers, E; Birnie, E; Hollenbach, B; Schomburg, L et al.** Selenite supplementation in euthyroid subjects with thyroid peroxidase antibodies. Clin Endocrinol, 80: 444-451, 2014.
12. **Rayman, MP.** The importance of selenium to human health. The Lancet, 356 (9225): 233-41, 2000.
13. **Pedersen, IB; Knudsen, N; Carle, A; Schomburg, L; Kohrle, J; Jorgensen, T et al.** Serum selenium is low in newly-diagnosed Graves' disease: a population-based study. Clin Endocrinol, 79 (4): 584-90, 2013.
14. **Kwong, 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, 80: 905-10, 2014.
15. **Wertenbruch, T, Willenburg, HS and Sagert, C.** Serum selenium levels in patients with remission and relapse of Graves' disease. Med Chem, 3 (3): 281-4, 2007.
16. **Fan, YF; Xu, SH; Zhang, HF; Cao, W; Wang, K; Chen, GF et al.** Selenium supplementation for autoimmune thyroiditis: a systematic review and meta-analysis. Int J Endocrinol, 1-8, 2014.
17. **Watt, T; Cramon, P; Bjorner, JB; Bonnema, SJ; Feldt-Rasmussen, U; Gluud, C et al.** Selenium supplementation for patients with Graves' hyperthyroidism. Trials, 119: 14, 2013.
18. **Marcocci, C; Kahaly, GJ; Krassas, GE; Bartalena, G; Prummel, M; Stahl, M et al.** Selenium and the course of mild Graves' orbitopathy. New Engl J Med, 364 (20): 1920-31, 2011.
19. **Calissendorff, J; Mikulski, E; Larsen, EH; and Moller, MA.** A prospective investigation of Graves' disease and selenium: thyroid hormones, autoantibodies, and self-rated symptoms. Eur Thyroid J, 4 (2): 93-8, 2015.
20. **Vrca, VB; Skreb, F; Cepelak, I; Romic, Z; and Mayer, L.** Supplementation with antioxidants in the treatment of Graves' disease; the effect on glutathione peroxidase and concentration of selenium. Clinica Chimica Acta, 341 (1-2): 55-63, 2004.
21. **Duntas, L.** The evolving role of selenium in the treatment of Graves' disease and ophthalmopathy. J Thyroid Res, 736161, 2012.
22. **Dharmasena, A.** Selenium supplementation in thyroid associated ophthalmopathy: an update. Int J Ophthal, 7 (2): 365-75, 2014.
23. **Sturniolo, G and Mesa, J.** Selenium supplementation and autoimmune thyroid diseases. Endocrinol Nutr, 60 (8): 423-6, 2013.
24. **Toulis, KA; Anastasilakis, AD; Tzellos, TG; Goulis, DG; and Kouvelas, D.** Selenium supplementation in the treatment of Hashimoto's thyroiditis: a systematic review and a meta-analysis. Thyroid, 10: 1163-73, 2010.
25. **Xu, J; Liu, XL; Yang, XF; Guo, HL; Zhao, LN; Sun, XF et al.** Supplemental selenium alleviates the toxic effects of excessive iodine on thyroid. Biol Trace Elem Res, 141 (1-3): 110-118, 2011.