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Original Article

Selenium: Could It Be the Game-Changer for Ocular Surface and Anterior Chamber in Graves' Disease?

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Abstract

Objectives: To evaluate the effects of selenium supplementation on ocular surface parameters and anterior segment architecture in euthyroid Graves' disease (GD) patients without ophthalmopathy.

Methods: This cross-sectional study included 218 consecutive euthyroid GD patients without clinical manifestations of Graves' ophthalmopathy (GO). Patients underwent comprehensive ophthalmological examination, including the Ocular Surface Disease Index (OSDI) questionnaire, tear film break-up time (T-BUT), Oxford scale scoring, and Pentacam Scheimpflug imaging for anterior segment parameters assessment. Selenium intake was questioned, and based on selenium intake, participants were divided into two groups: the selenium intake group (n=106), receiving selenium supplementation (100 µg twice daily for 6 months) with standard anti-thyroid therapy, and the control group (n=112), receiving only standard anti-thyroid therapy.

Results: The mean age was 45.7±7.8 years (range: 30–61) in the selenium intake group (n=106; 48 females, 58 males) and 46.1±7.5 years (range: 30–60) in the control group (n=112; 52 females, 60 males), with no significant difference between groups (p=0.821 for age, p=0.904 for gender distribution). The mean duration of selenium supplementation was 11.4±4.2 months. The selenium group showed significantly better ocular surface parameters, with lower OSDI scores and higher T-BUT values compared to the control group (p<0.001 for both). Oxford staining scores were lower in the selenium group, though not statistically significant (p=0.244). Pentacam analysis revealed significantly higher anterior chamber volume (p=0.024) and central corneal thickness (p<0.001) in the selenium group, while anterior chamber depth and angle width were higher but not statistically significant (p=0.322 and p=0.276, respectively).

Conclusion: Selenium supplementation is associated with better ocular surface parameters and different anterior segment architecture in euthyroid GD patients without ophthalmopathy. Clinical associations observed in these cases may be related to selenium's antioxidant and anti-inflammatory properties through glutathione peroxidase and thioredoxin reductase activity, suggesting selenium as a potentially beneficial therapeutic approach for ocular surface integrity in GD.

Keywords: Graves' disease, ocular surface, selenium supplementation

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Introduction

Graves' disease (GD) is an autoimmune condition in which antibodies bind to the thyrotropin receptor and stimulate thyroid hormone production, representing the majority of hyperthyroidism cases (1). The most frequent extrathyroidal manifestation of GD is Graves' ophthalmopathy (GO), which is an immune-mediated inflammatory disorder affecting orbital tissues, where autoantibodies target thyroid-stimulating hormone receptors expressed on orbital fibroblasts (2). This leads to various clinical manifestations, including proptosis, eyelid retraction, corneal exposure, periorbital edema, and potentially optic neuropathy.

Selenium, an essential trace element highly concentrated in the thyroid gland, plays a pivotal role in maintaining endocrine function through its integration as selenocysteine into various proteins. It is crucial for the function of antioxidant enzymes like glutathione peroxidases and thioredoxin reductases, which protect the thyroid gland by neutralizing reactive oxygen species (ROS) produced during hormone synthesis (3). While these selenoprotein-dependent antioxidant systems effectively manage ROS levels in healthy individuals, patients with autoimmune thyroid disorders, including GD, often have increased oxidative stress, creating enhanced selenium requirements (4). In the pathophysiology of GD, where oxidative stress contributes to the pathogenesis, selenium's antioxidant and immunomodulating properties have emerged as therapeutically significant. This understanding has led to important clinical applications, with the European Thyroid Association/European Group on Graves' Orbitopathy now recommending 6 months of selenium supplementation for mild GO cases (5), as it reduces disease progression and improves quality of life (6,7).

Dry eye is a common complication in GO, where proptosis and upper eyelid retraction cause increased evaporation from the ocular surface, exacerbating tear film instability, resulting in reduced tear break-up time and elevated ocular surface disease scores (8). Studies suggest that ocular surface problems and dry eye can occur in GD patients even without active ophthalmopathy, indicating other possible underlying mechanisms affecting ocular health before ophthalmopathy develops (9,10).

Considering the inflammatory pathogenesis and soft tissue involvement in GD, subtle changes in corneal architecture and anterior segment parameters may be present even in patients without clinical ophthalmopathy. Pentacam (Oculus Inc., Wetzlar, Germany), a rotatory Scheimpflug imaging system, provides non-invasive, rapid, and reproducible measurements of multiple anterior segment parameters, including anterior chamber depth, volume, angle width, central corneal thickness, and corneal volume, offering potential for detecting these subtle alterations in anterior segment architecture (11).

Despite the well-known relationship between GO and ocular surface alterations, and the potential for anterior segment changes secondary to inflammatory processes, the effects of selenium supplementation on ocular surface parameters and anterior segment architecture have not been evaluated in euthyroid GD patients without ophthalmopathy. This study aims to assess these parameters, thereby expanding our understanding of selenium's effects in this specific patient population.

Methods

This study was approved by the institutional review board of Buca Seyfi Demirsoy Training and Research Hospital (approval number: 2025/416) and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants.

The study included 218 consecutive euthyroid GD patients under regular follow-up at the Department of Endocrinology and Metabolism, İzmir Buca Seyfi Demirsoy Training and Research Hospital. Only patients without clinical manifestations of GO were enrolled in the study. Euthyroid status was confirmed through thyroid function tests. Demographic data were collected from all participants.

Patients with any signs of GO or a history of compressive optic neuropathy were excluded from the study. Additional exclusion criteria comprised any systemic disease other than GD that could affect measurements, use of systemic medications except antithyroid agents, history of ocular surgery, and ophthalmological conditions requiring medical treatment (e.g., glaucoma). Patients with refractive errors beyond ±3 diopters, media opacities affecting image quality (e.g., cataract), non-euthyroid thyroid hormone levels, or a history of steroid treatment or orbital radiotherapy were also excluded from the study.

All participants underwent comprehensive ophthalmological examination by the same ophthalmologist (P.K.), including best-corrected visual acuity measurement using a Snellen chart, intraocular pressure measurement with applanation tonometry, and anterior-posterior segment evaluation with slit-lamp biomicroscopy.

Evaluation of dry eye included assessment with the Ocular Surface Disease Index (OSDI) questionnaire, tear film break-up time (T-BUT) measurement, and Oxford scale scoring. The OSDI score was calculated using the formula: OSDI = (sum of scores) × 25 / (number of questions answered). T-BUT was assessed by instilling fluorescein into the inferior fornix and measuring the time until the first break in the tear film under cobalt blue illumination, with the mean of three consecutive measurements recorded. Corneal and conjunc-

tival staining was evaluated using fluorescein under a cobalt blue filter and graded according to the Oxford scale (grades A to >E, corresponding to scores 0 to 5).

Anterior segment parameters were evaluated using Pentacam Scheimpflug imaging (Oculus Inc., Wetzlar, Germany) under standardized dark conditions without pupil dilation. Parameters analyzed included anterior chamber depth, volume, and angle width, along with central corneal thickness, corneal volume, and pupil diameter. To ensure measurement consistency, all examinations were performed by a single ophthalmologist (P.K.).

After the measurements, patients were questioned regarding selenium supplementation status and, based on selenium intake, participants were divided into two groups: the selenium intake group (n=106) received selenium supplementation (100 µg twice daily for 6 months) in addition to standard anti-thyroid medical therapy, while the control group (n=112) received standard anti-thyroid medical therapy alone. The duration of selenium supplementation was also recorded for all patients in the selenium intake group. The selenium supplementation protocol (100 µg twice daily) was chosen based on the European Thyroid Association/ European Group on Graves' Orbitopathy (EUGOGO) guidelines, which recommend this specific dosing regimen for mild Graves' ophthalmopathy management (5,6).

Statistical Analysis

IBM Statistical Package for the Social Sciences version 25 (SPSS Inc., Chicago, IL, USA) was used for statistical purposes. Categorical variables were expressed as frequencies and percentages, and numerical variables were expressed as means and standard deviations. Kolmogorov-Smirnov tests were used to determine whether the data were normally distributed. Independent t-test was used to evaluate differences in normally distributed data. Mann-Whitney U test was used to determine differences in non-normally distributed data. A p-value less than 0.05 was considered statistically significant. For statistical purposes, values from the left eyes were analyzed in both the study and control groups.

Results

The mean age was 45.7±7.8 years (range: 30–61) in the selenium intake group (n=106; 48 females, 58 males) and 46.1±7.5 years (range: 30–60) in the control group (n=112; 52 females, 60 males), with no significant difference between groups (p=0.821 for age, p=0.904 for gender distribution). The mean duration of selenium supplementation was 11.4±4.2 months (range: 6–18 months) in the selenium supplementation group.

The selenium supplementation group demonstrated significantly better ocular surface parameters compared to the non-selenium group. Mean OSDI scores were significantly lower, and T-BUT values were significantly higher in the selenium group compared to the non-selenium group (p<0.001 for both parameters). Oxford staining scores were lower in the selenium group, though this difference was not statistically significant (p=0.244).

Pentacam analysis revealed differences in anterior segment parameters between groups. The selenium group demonstrated significantly higher anterior chamber volume (p=0.024) and central corneal thickness (p<0.001). Although anterior chamber depth and angle width were higher in the selenium group, these differences did not reach statistical significance (p=0.322 and p=0.276, respectively). No significant differences were observed in corneal volume or pupil diameter between groups (p=0.534 and p=0.266, respectively) (Table 1).

Table 1. Comparison of ocular surface parameters and anterior segment measurements between groups

	Selenium Group (Mean±SD)	Non-selenium Group (Mean±SD)	p
OSDI Score	18.67±19.91	54.60±31.56	<0.001
T-BUT (seconds)	14.20±5.51	9.88±5.07	<0.001
Oxford Staining Score	0.44±0.70	0.55±0.79	0.244
Anterior Chamber Depth (mm)	2.80±0.22	2.59±0.52	0.322
Anterior Chamber Volume (mm³)	155.47±23.43	139.97±38.05	0.024
Anterior Chamber Angle Width (°)	37.89±5.89	33.19±7.44	0.276
Pupil Diameter (mm)	2.94±0.58	2.92±0.79	0.266
Central Corneal Thickness (µm)	558.90±23.34	530.16±28.63	<0.001
Cornea Volume (mm³)	60.89±2.85	59.17±3.01	0.534

OSDI, Ocular Surface Disease Index; T-BUT, tear film break-up time; SD, standard deviation.

Discussion

Selenium's critical role in thyroid function is well established through its high thyroid tissue concentration and essentiality in antioxidant enzyme systems (3,4). *In vitro* studies have shown that selenium helps to reduce orbital fibroblast proliferation while protecting them from oxidative stress-induced damage and decreasing inflammatory cytokine production (12,13). Selenium also demonstrates anti-inflammatory effects through reduction of tumor necrosis factor-α and inhibition of nuclear factor-κB activation. These antioxidant and anti-inflammatory properties are especially important in GD patients, who require increased selenium levels to compensate for elevated oxidative stress (3).

Selenium supplementation has shown benefits in patients with GO in several studies. Marcocci et al. (6) reported improvements in quality of life and reduced ocular involvement and disease progression. Wang et al.'s study (14) confirmed these results. Additionally, Khong et al. (15) found lower selenium levels in GO patients compared to those with GD without ophthalmopathy in the Australian population. Potita et al. (16) found selenium supplementation improved eyelid and soft tissue symptoms in mild GO. In an Egyptian study, serum selenium levels were found to be lower in patients with GO compared to those with GD without ophthalmopathy, with levels progressively decreasing as disease severity increased (17).

However, it is important to acknowledge that not all studies have demonstrated consistent benefits of selenium supplementation in thyroid-related ocular conditions. The recent SeGOSS trial by Ahn et al. (18), a randomized controlled study of 84 patients with mild to moderate Graves' ophthalmopathy in selenium-sufficient regions, found no improvement in quality of life scores or clinical parameters at 6 months with selenium supplementation, despite some transient benefits observed at 3 months. This finding suggests that selenium's effectiveness may vary depending on baseline selenium status and geographic selenium sufficiency. Additionally, Halawa et al. (19) observed that while selenium status showed a significant negative correlation with Graves' disease, this correlation did not extend to Graves' ophthalmopathy specifically, implying that selenium's role may be more complex than initially thought. These conflicting results highlight the importance of considering baseline selenium status and patient selection criteria when evaluating selenium supplementation outcomes.

In this study of euthyroid GD patients without ophthalmopathy, significant differences were detected in ocular surface parameters between those receiving selenium supplementation and those who were not. The selenium supplementation group demonstrated significantly better OSDI scores and tear break-up time (T-BUT) values.

Although dry eye is a well-known condition in GO, studies by Kocabeyoglu et al. (20), Gürdal et al. (21), and Carreira et al. (22) have demonstrated significant ocular surface impairment in GD patients even without ophthalmopathy, with findings of higher OSDI scores and reduced T-BUT values. Additionally, Carreira et al. (22) found decreased corneal epithelial thickness regardless of ophthalmopathy status, suggesting subclinical chronic inflammation affects tear film stability and ocular surface integrity before obvious ophthalmopathy develops.

The pathogenesis of ocular surface disease in GD involves multiple inflammatory mechanisms. Lacrimal glands containing thyroid-stimulating hormone receptors become autoimmune targets, leading to increased tear film osmolarity, which triggers pro-inflammatory cytokines that damage the corneal surface (23,24). This process, combined with meibomian gland dysfunction and blinking abnormalities, creates an inflammatory cycle that compromises tear film stability before clinical ophthalmopathy develops (8,25).

The observed associations between selenium supplementation and improved ocular surface parameters may be related to its potential anti-inflammatory and antioxidant properties, though the exact mechanisms remain unclear. Oxidative stress plays a key role in GD pathogenesis, with studies showing elevated reactive oxygen species (ROS) in affected tissues, and selenium may help neutralize these through its antioxidant properties (4). The tear film stability improvements observed in our selenium group might be associated with selenium's anti-inflammatory effects, potentially reducing inflammatory mediators that disrupt ocular surface homeostasis. However, our cross-sectional design limits definitive conclusions about these mechanistic relationships. Supporting our findings, a recent study reported that selenium treatment in mild GO led to significant improvements in symptoms, including tearing, grittiness, and conjunctival congestion, compared to placebo during the first 6 months (26).

Regarding anterior segment measurements, Pentacam analysis revealed that the selenium group had significantly higher anterior chamber volume and central corneal thickness. Although anterior chamber depth and angle width were also higher in the selenium group, these differences did not reach statistical significance.

While there are no studies evaluating corneal thickness in GD patients without ophthalmopathy, previous studies have shown conflicting results regarding corneal thickness in GO. In our study, the non-selenium supplement group had thinner corneas, aligning with Bahceci et al. (27) and Bassiouny et al.'s (28) findings that showed corneal thickness

negatively correlating with thyroid hormone levels, despite Babić Leko et al. (29) reporting thicker corneas in GO. The higher corneal thickness observed in the selenium group may reflect potential anti-inflammatory properties, though causal relationships cannot be established from our study design. This hypothesis is supported by Zhang's (30) study, showing that inflammatory processes in GO lead to corneal thinning through soft tissue inflammation and fibrosis, with more pronounced thinning in moderate-severe cases. However, without baseline measurements, we cannot determine whether this represents a protective effect of selenium or pre-existing differences between groups.

Additionally, Chang et al. (31) reported that GO patients were found to have keratoconus-like changes, which aligns with our findings and suggests that selenium's anti-inflammatory properties may help prevent inflammation-induced corneal changes in our patient population.

The observed differences in anterior chamber parameters between groups are of uncertain clinical significance and require cautious interpretation. Our study found higher anterior chamber volume in the selenium-supplemented group, with non-significant trends toward increased anterior chamber depth and angle width. These findings partially align with Babić Leko et al.'s (29) observations of decreased anterior chamber parameters in patients with higher thyroid hormone levels. Selenium's anti-inflammatory and antioxidant properties may be associated with maintained anterior segment architecture, potentially through reduced inflammation and tissue remodeling (32), though prospective studies are needed to confirm these relationships.

This study has several significant limitations that must be acknowledged. First and most importantly, the cross-sectional design prevents establishment of causal relationships, and our findings should be interpreted as associations only. The lack of randomization introduces selection bias, as patients choosing selenium supplementation may differ systematically from those who do not in terms of health consciousness, dietary habits, and other protective behaviors that could independently affect ocular health. The absence of serum selenium level measurements represents a critical limitation, as selenium supplementation status was based solely on patient reporting without objective biochemical confirmation. This prevents assessment of actual selenium bioavailability, compliance, and baseline selenium status, which could significantly influence treatment response.

Additionally, baseline ocular surface and anterior segment parameters prior to selenium supplementation were not available, preventing assessment of whether groups had similar characteristics before treatment initiation. Although clinical assessments were performed prior to obtaining selenium supplementation history, the lack of complete blinding represents a potential source of observer bias. Other important confounding factors were not systematically assessed, including dietary selenium intake, systemic inflammatory markers, and potential subclinical ophthalmopathy that might not be detected by standard clinical examination.

It should be noted that our clinical recommendation follows the established 6-month selenium supplementation protocol as per EUGOGO guidelines (5,6), which has demonstrated an optimal benefit-to-risk ratio while minimizing potential adverse effects associated with prolonged high-dose selenium use, such as insulin resistance and hematological complications. The extended mean duration of selenium supplementation in our study occurred due to systemic factors affecting patients' follow-up schedules rather than by clinical design, as our protocol specifically recommends 6 months of treatment.

These limitations emphasize the need for well-designed randomized controlled trials with baseline measurements to establish the true therapeutic efficacy of selenium supplementation.

Conclusion

While studies have investigated the relationship between GD and ocular surface/anterior segment changes, and others have investigated selenium's effects in GD separately, this study uniquely combines these aspects by evaluating selenium's effects on both ocular surface and anterior segment parameters in GD without ophthalmopathy, demonstrating significant improvements in selenium-supplemented patients.

In conclusion, this study demonstrated associations between selenium supplementation and improved ocular surface parameters, as well as anterior segment differences, in euthyroid GD patients without ophthalmopathy. These findings suggest potential benefits that warrant further investigation. Prospective longitudinal studies with larger patient populations, longer follow-up periods, advanced imaging technologies, and detailed ocular surface assessments are needed to establish causal relationships and validate these preliminary findings.

Disclosures

Ethics Committee Approval: This study was approved by the Buca Seyfi Demirsoy Training and Research Hospital Ethics Committee (Date: 26.02.2025, Number: 2025/416) and conducted in accordance with the tenets of the Declaration of Helsinki.

Informed Consent: Written informed consents were obtained from all patients.

Conflict of Interest: None declared.

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