Review Article

A Systematic Review on the Role of Antioxidants in Thyroid Eye Disease

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Abstract

Purpose: To systematically review the role of antioxidants in management of patients with thyroid eye disease (TED).

Methods: A literature search of the electronic databases was performed without restrictions on the date of publication till the end of March 2021, using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Clinical trials, case–control studies, cohorts, case series, case reports, and experimental (including in vitro) studies in the English language were included. The primary outcome in human studies was improvement in severity, activity scores, and/or quality of life scores. There was a decrease in the level of H₂O₂-dependent oxidative stress, Hyaluronic acid release, reactive oxygen species, cell proliferation, or antifibrotic/antiproliferative actions in the in vitro studies.

Results: Out of 374 initially screened articles, 157 studies were selected, the full texts of 82 were reviewed, and 14 papers were finally included. There were 4 clinical and 10 in vitro studies from 1993 to 2018. While β-carotene, retinol, Vitamin E, melatonin, resveratrol, N-acetyl-l-cysteine, and quercetin showed some efficacy in in vitro studies; allopurinol, nicotinamide, pentoxifylline, and selenium (Se) were effective in both clinical and experimental reports. Se was the only recommended antioxidant based on one high-level randomized controlled trial.

Conclusion: While different antioxidants could potentially be effective in the management of TED, no strong recommendation for any or combination of antioxidants could be made to be implemented in the daily practice.

Keywords: Antioxidants, Selenium, Systematic review, Thyroid eye disease

INTRODUCTION

Thyroid eye disease (TED) is an autoimmune inflammatory disease known as the most common cause of orbital disease worldwide. Although it is mostly associated with hyperthyroidism (Graves’ disease [GD]), hypothyroidism and euthyroidism are present in some patients. TED is clinically present in one-third of the patients with different underlying thyroid diseases. Clinical presentation of the TED is the same for different underlying thyroid diseases and between patients with unilateral versus bilateral orbital involvement. While the quality of life (QoL) is impaired in patients with TED, medical and surgical treatments lead to improvement of both visual and psychosocial QoL. To prevent the progression of TED to sight threatening stages with detrimental effect on QoL of patients, early diagnosis and treatment of TED among patients with thyroid dysfunction has received added emphasis.

Oxidative stress is a process which is normally controlled under physiological conditions. It is believed that any alteration of cell oxidative stability leads to cell damage. A rise in several parameters of oxidative stress seems to be involved in the development of some autoimmune and endocrine diseases namely hyperthyroidism and TED. Therefore, antioxidants...
have been studied to find out how they might change the effect of oxidative stress in different diseases. Consequently, a few studies have attempted to investigate the role of antioxidants in autoimmune hyperthyroidism/thyroiditis and TED treatment with inconsistent conclusions on the effect and type of antioxidants in this regard. This study was designed to investigate the efficacy and safety of reported antioxidants in patients with TED.

**METHODS**

A comprehensive literature search of the EMBASE, PubMed, MEDLINE, Google Scholar, and Scopus electronic databases was performed without restrictions on the date of publication till the end of March 2021, using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The research keywords were “Thyroid eye disease OR Thyroid-associated ophthalmopathy OR Thyroid-associated orbitopathy OR Graves’ ophthalmopathy OR Graves’orbitopathy,” AND “Antioxidants OR Selenium OR Pentoxifylline OR Vitamin C OR Vitamin E OR Carotenoids OR Glutathione OR Uric acid.”

Included articles were the clinical trials, case–control studies, cohorts, case series, case reports, and experimental (including in vitro) studies published in the English language. Review articles, patents, book chapters, commentaries, editorials, animal studies, and articles with irrelevant content or insufficient information were excluded. Two authors (S.C. and S.A.) independently followed the search strategy, screened the abstracts, then the full-text, and also the quality of evidence of the selected articles, and finally included the articles for the systematic review. Disagreement was resolved by the involved senior author (M.B.K.). The reference list of included papers was checked for further reports and citations of published or unpublished researches, and simultaneously registered trials were screened on three different websites including https://clinicaltrials.gov, https://who.int and https://www.cochranelibrary.com.

Extracted and documented data were the authors’ name and year of publication, the design of the study, average age, stage of TED, thyroid function status, type of antioxidants, results, follow-up duration, and side effects.

The primary outcome in human studies was improvement in severity, activity scores, and/or QoL scores. Reduced lid retraction, proptosis, and/or diplopia were the outcome measures in the studies where the primary outcomes had not been reported.

The primary outcome of in vitro studies was a decrease in the level of H$_2$O$_2$-dependent oxidative stress, hyaluronic acid (HA) release, reactive oxygen species (ROS), cell proliferation or antifibrotic/antiproliferative actions.

The risk of bias was evaluated using a rating scheme [Table 1]. Briefly, the level of evidence was assessed using “hierarchy of evidence pyramid.”

**RESULTS**

Out of 386 initially screened articles, 177 studies were selected for more assessment. Reviewing the abstracts led to exclusion of 81 articles. Full-text review was performed on the remaining 96 articles, from which 76 did not have a defined outcome. Finally, 20 papers met the inclusion criteria and were considered in this review [Figure 1]. There were four human studies and sixteen in vitro studies from 1993 to 2021 [Table 2]. Fifteen studies were from Taiwan (2), Canada (1), Greece (1), Brazil (2), Poland (1), the USA (1), Japan (1), Italy (5), South Korea (3), Germany (1), China (1), and one was supervised by the international multicentral European Group on Graves’ Orbitopathy (EUGOGO) association.

Chang et al. investigated the role of PTX (0.1–1,000 mg/L) on cultured fibroblasts in 1993. The cultures were collected from biopsies of extraocular muscles (EOM) from two severe TED patients during orbital decompression surgery and two normal EOM tissues of individuals with strabismus during resection surgery and from the skin of two patients affected with pretibial myxedema. Dose-dependent inhibition of orbital fibroblast proliferation and glycosaminoglycan (GAG) release was reported.

In 1997, the human orbital fibroblast was obtained from two severe TED patients and two normal controls to investigate the effect of allopurinol (1.0 mM) and nicotinamide (10 µM) on cell proliferation induced by xanthine oxidase/hypoxanthine system. The proliferation inhibition was significant after preincubation with allopurinol, nicotinamide, and methimazole (0–25 µM), but not with propylthiouracil (10 µM).

The role of nicotinamide was exclusively evaluated on orbital fibroblast to explore cell surface expression of human leukocyte antigen (HLA)-A, B, C antigen, HLA-DR antigen, intercellular adhesion molecule 1 (ICAM-1), CD44, and Fas expression induced by cytokines (interferon-γ [IFNγ] and tumor necrosis factor-α [TNFα]). Tissue harvest was from four TED and three glaucomatous patients. It was observed that nicotinamide did not interfere with induction of HLA-A, B, C, or CD44 expression but demonstrated an inhibitory effect on ICAM-1 and HLA-DR expression as well as the proliferation of orbital fibroblasts.

To investigate the effect of quercetin on orbital fibroblasts, tissue samples from 5 TED patients and 5 control subjects were exposed to quercetin or its glycosides rutin and quercitrin, and subsequently, apoptosis, necrosis, cell proliferation, HA production, and cell cycle were measured. Quercetin inhibited cell proliferation and HA production in both TED patients and control subjects.

Another study assessed the effect of quercetin on fibrotic markers and matrix metalloproteinases (MMP) of cultures from 13 TED patients and 3 normal females aged between 51 and 63. Quercetin decreased the secretion of MMP-2 and MMP-9...
proteins and inhibited fibrotic markers in the TED group. Its antifibrotic effects occurred through a noncytotoxic process. In 2013, Tsai et al. 33 examined the biphasic effect of H$_2$O$_2$ on cellular proliferation of Graves’ orbitopathy (GO) orbital fibroblasts and also protective effect of N-acetyl-l-cysteine (NAC) and Vitamin C against it. Cultures from seven GO patients and five age-matched normal subjects were exposed to various concentrations of H$_2$O$_2$. The peak cellular proliferation was observed at 6.25 µM of H$_2$O$_2$ in GO fibroblasts. Protective effects were reported when GO cells pretreated with NAC (200 µM) and Vitamin C (500 µM) for 1 h and followed by the addition of 6.25 µM H$_2$O$_2$ for 24 h, by reversing enhanced proliferation and increased levels of transforming growth factor, beta 1 (TGF-β1), interleukin-1 β (IL1 β), and superoxide anion.

Kim et al. 34 exposed orbital connective tissue of 6 TED patients and 4 controls to assess the effect of resveratrol (30–50 µM) treatment on intracellular ROS levels and the expression of heme oxygenase-1 (HO-1), superoxide dismutase (SOD), catalase, and thioredoxin. It decreased ROS production, adipogenesis, and HO-1 level induced by oxidative stress. Treatment with 50 µM resveratrol also reduced ROS levels during adipogenesis.

Selenium (Se), in the form of selenium-(Methyl) selenocysteine (SeMCys), was examined on primary cultures of orbital fibroblasts from 6 TED patients and 6 control subjects in 2017. 35 While SeMCys inhibited proliferation and HA secretion just in TED patients, its effect on various concentrations of H$_2$O$_2$-induced oxidative stress (glutathione disulfide [GSSG]) and cytokines were similar in both groups. SeMCys was also investigated in another experiment. 36 Tissue samples from six GO patients and six normal ones were collected and preincubated for 2 days at 37°C with a medium containing a 10 µM concentration of SeMCys hydrochloride, then treated with a concentration of 50 µM H$_2$O$_2$. Increased GSSG, apoptosis, and lactate dehydrogenase as a measure of necrosis were counteracted by SeMCys with no differences between GO and control fibroblasts.

Tissue samples from 6 TED patients and 6 patients with other conditions lacking fibroadipose tissue were treated with retinol, β-carotene, and Vitamin E at various concentrations. β-carotene significantly decreased the raised H$_2$O$_2$-induced proliferation in TED but not the control fibroblasts. Retinol and Vitamin E had no effect. None had a significant effect on HA. Among TNFα, IL1 β, IFNγ, and endogenous cytokines which are involved in the pathogenesis of TED, IL1 β was the only responder to all the three antioxidant substances. Its H$_2$O$_2$-dependent rise significantly reduced in both TED and control fibroblasts.

Antioxidant effects of Vitamin C, NAC, and melatonin on primary cultures of 6 TED patients and 6 normal individuals were evaluated. 38 Vitamin C and NAC reduced H$_2$O$_2$-induced proliferation in TED fibroblasts. Melatonin and NAC decreased IFNγ in the TED fibroblasts.

Obtained orbital adipose/connective tissue samples from seven GO patients and five individuals with noninflammatory problems were studied to determine the effect of Se in the form of sodium selenite at various concentrations. 39 Hyaluronan, ROS production, and inflammatory cytokines including IL1α, IL1 β, IL6, IL8, and TNFα concentrations were measured and showed that serum Se suppressed hyaluronan production, IL1α, and TNFα in cultured orbital fibroblasts of patients with GO in a dose-dependent manner while suppression intracellular ROS generation and IL8 were not dose-dependent. IL1 β and IL6 were not suppressed by sodium selenite in cultured GO orbital fibroblasts.

Se and selenoprotein P (SePP) concentrations were assessed against clinical activity score (CAS) and severity status (based
on NOSPECS [No sign or symptoms, only signs, soft tissue involvement with symptoms and signs, proptosis, extraocular muscle involvement, corneal involvement, sight loss]) as well as concentrations of thyroid stimulating hormone (TSH) receptor autoantibody (TRAB) or IGF1 receptor (IGF1R-αAB) autoantibodies in 31 mild and 53 moderately severe TED patients. Se level did not significantly correlate with thyroid hormone concentrations, activity, and the severity of TED. Se or SePP concentrations were significantly different among the patients with mild versus moderately severe and active versus inactive TED. A significant inverse correlation was reported between serum Se and TRAB. This was not significant for the SePP. There were also no connections between IGF1R-αAB levels and serum SePP/serum Se concentrations.

In 2017, Federige et al. studied and compared Se and SePP values in patients with GD with and without GO, Hashimoto’s thyroiditis (HT) patients and in control individuals. Although serum Se levels were similar among all groups, SePP serum was lower in GO and HT patients compared to the control group.

Serum trace elements were assessed in four groups of newly diagnosed GD patients, GD and GO patients in euthyroid status or subclinical thyroidism after treatment, and normal controls in a population in northeast China. Among evaluated elements, serum Se levels in three first groups were significantly lower than those in normal individuals and serum copper levels were significantly low only in the GO group than those in normal ones.

The effect of thyroid hormone abnormalities on selected antioxidant parameters were investigated in GD patients with thyroid-associated orbitopathy (TAO) from both hyperthyroid and euthyroid patient categories. The blood was collected, and the sera were obtained after centrifugation.
| Writer/year          | Study design                  | Population                        | Mean age (year) | TED grade                      | Thyroid status    | Type of antioxidant treatment | Follow-up | Result                                                                 | Side effects               |
|---------------------|-------------------------------|-----------------------------------|-----------------|--------------------------------|-------------------|------------------------------|-----------|------------------------------------------------------------------------|----------------------------|
| 1. Akbarian, et al., 1993<sup>27</sup> | Experimental, orbital fibroblast cell culture | Case: 2 Normal: 2 (2 PMT) | 32              | Moderately severe, activity not specified with OD | Not mentioned | PTX                          | NA        | Inhibition of GAG release and fibroblast proliferation                 | NA                         |
| 2. Balazs et al., 1997<sup>20</sup> | Quasi-experimental, pilot study | Case: 10                     | 45.2            | Moderately severe, activity not specified with OD | Euthyroid       | PTX                          | 12 weeks | ↓Serum GAG and ↑MMP-2 and ↑PTX | Moderate and persistent nausea at the begging |
| 3. Burch et al., 1997<sup>20</sup> | Experimental, orbital fibroblast cell culture | Case: 2 Normal: 2          | Not available  | Moderately severe, activity not specified with OD | Not mentioned | Allopurinol nicotinamide | NA        | ↑Patient satisfaction and ↓ICAM-1 and HLA-DR expression and ↑Cell proliferation | None                      |
| 4. Hiromatsu et al., 1998<sup>20</sup> | Experimental, orbital fibroblast cell culture | Case: 4 Normal: 3           | Not available  | Activity and severity are not specified with OD | Not mentioned | Nicotinamide                 | NA        | ↑QoL and ↓CAS and Se (none) gastrointestinal with PTX               | NA                         |
| 5. Bouzas et al., 2000<sup>23</sup> | Prospective nonrandomized comparative study | Case: 11 Normal: 11          | 36.7            | Mild and moderately severe, active | Euthyroid       | Allopurinol nicotinamide | 3 months | ↑Total eye score (NOSPECS) and ↓MMP-2 and MMP-9, fibrotic markers and suppressive effects | Nausea, abdominal pain |
| 6. Finamor et al., 2004<sup>20</sup> | Prospective randomized trial | Case: 9 Normal: 9            | 41.5            | All 3 severity stages but inactive | Euthyroid       | PTX                          | 6 months | ↑Propensity and questionnaire scores                                  | NA                         |
| 7. Marcocci et al., 2011<sup>20</sup> | Prospective randomized double-blind, placebo-controlled trial | Total: 159 Normal: 9 Se: 43 PTX: 43.7 Placebo: 44.6 | 52              | Mild GO, active and inactive | Not mentioned | Se, PTX                      | 12 months | ↑QoL and ↓CAS and ↑Hyp/Se and ↓Se/SePP | Se (none) gastrointestinal with PTX |
| 8. Lisi et al., 2011<sup>20</sup> | Experimental, orbital fibroblast cell culture | Case: 5 Normal: 5            | 47.4            | Moderately severe, inactive with OD | Euthyroid       | Quercetin                    | NA        | ↑Cell proliferation and ↓HA release and ↓MMP-2 and MMP-9, fibrotic markers and suppressive effects | NA                         |
| 9. Yoon et al., 2012<sup>22</sup> | Experimental, orbital fibroblast cell culture | Case: 13 Normal: 3           | 46              | Moderately severe, inactive with OD | Euthyroid       | Quercetin                    | NA        | ↑Oxidative stress and ROS                                              | NA                         |
| 10. Tsai et al., 2013<sup>23</sup> | Experimental, orbital fibroblast cell culture | Case: 7 Normal: 5           | 37.6            | Severity is not specified inactive with OD | Euthyroid       | Nicotinamide, N-acetyl-l-cysteine | NA        | ↑Oxidative stress and cell proliferation and superoxide anion          | NA                         |
| 11. Kim et al., 2015<sup>23</sup> | Experimental, orbital fibroblast cell culture | Case: 6 Normal: 4           | Not available  | Moderately severe, (CAS <4)/with OD | Euthyroid       | Resveratrol                  | NA        | ↑Oxidative stress and ROS                                              | NA                         |
| 12. Dottore et al., 2017<sup>25</sup> | Case-control, serum elements study | Total: 84 Mild: 31 Severe: 53 Active: 62 Inactive: 22 | Not available (median: 46) | Used NOSPECS (mild, moderately severe, and sight threatening), active and inactive | Hyper: 51 Hypo: 10 Eu: 23 | Serum Se, SePP | NA | ↑Oxidative stress and cell proliferation                              | NA                         |

Contd...
| Writer/year | Study design | Population | Mean age (year) | TED grade | Thyroid status | Type of antioxidant treatment | Follow-up | Result | Side effects |
|-------------|--------------|------------|----------------|-----------|----------------|-------------------------------|-----------|--------|--------------|
| 14 Dottore et al., 2017 | Experimental, orbital fibroblast cell culture | Case: 6 Normal: 6 | Case: 60.1 Control: 66.1 | Severity is not specified inactive/ with OD | Not mentioned | Se | NA | ↓Apoptosis, LDH (necrosis), inhibition of oxidative stress (↓GSSG) | NA |
| 15 Federige et al., 2017 | Case-control, serum elements study | GD without GO: 19 GD with GO: 21 HT: 14 HT+LT4: 19 Control: 21 | Case: 52.5 Control: 51 | GO defined as having proptosis and CAS >1, severity is not specified | Euthyroid | Serum Se, SePP | NA | ↓SePP serum level in GO and HT patients | NA |
| 16 Dottore et al., 2018 | Experimental, orbital fibroblast cell culture | Case: 6 Normal: 6 | Case: 49.1 Control: 62.6 | Moderately severe, inactive/with OD | Not mentioned | Retinol, β-carotene, Vitamin E | NA | ↓H₂O₂-dependent oxidative stress, antiproliferative action | NA |
| 17 Dottore et al., 2018 | Experimental, orbital fibroblast cell culture | Case: 6 Normal: 6 | Case: 49.1 Control: 62.6 | Moderately severe, inactive/with OD | Not mentioned | Vitamin C N-acetyl-L-cysteine, Melatonin | NA | ↓H₂O₂-dependent oxidative stress | NA |
| 18 Liu et al., 2018 | Case-control, serum elements study | Newly diagnosed GD: 66 Euthyroid GD: 55 Euthyroid GO: 57 Control: 66 | Case: 38.06 Control: 42.3 | Mild-to-moderate GO according to EUGOGO classification, severity is not specified | Euthyroid/ subclinical hyper | Serum Vitamin C, Uric acid | NA | ↓Se serum level in all cases than control group | NA |
| 19 Olesik et al., 2020 | Case-control, serum elements study | TAO: 56 Control: 20 | Case: Hyper: 53 Eu: 48 Control: Not available | Active (CAS >3), moderate-to-severe according to EUGOGO classification | Hyper: 34 Eu: 22 | Serum Vitamin C, Uric acid | NA | Lower Vitamin C, higher uric acid levels in active TAOs than controls | NA |
| 20 Kim et al., 2021 | Experimental, orbital fibroblast cell culture | Case: 7 Normal: 5 | Case: Not available Control: Not available | Inactive (CAS <3), severity is not specified | Euthyroid | Se | NA | Suppression of hyaluronic production, IL1α, and TNFα (all in dose-dependent manner) Inhibition of ROS generation and IL8 | NA |

TED: Thyroid eye disease, PTX: Pentoxifylline, GD: Graves’ disease, GO: Graves’ orbitopathy, HT: Hashimoto’s thyroiditis, TAO: Thyroid-associated orbitopathy, Se: Selenium, NOSPECS: No sign or symptoms, only signs, soft tissue involvement with symptoms and signs, proptosis, extraocular muscle involvement, corneal involvement, sight loss, CAS: Clinical activity score, EUGOGO: European Group on Graves’ Orbitopathy, SePP: Selenoprotein P, GAG: Glycosaminoglycan, TNFα: Tumor necrosis factor-α, ICAM-1: Intercellular adhesion molecule 1, HLA: Human leukocyte antigen, QoL: Quality of life, MMP-2: Matrix metalloproteinase-2, ROS: Reactive oxygen species, LDH: Lactate dehydrogenase, GSSG: Glutathione disulfide, IL: Interleukin, NA: Not applicable, H₂O₂: Hydrogen peroxide, PTM: Pretibial myxedema, LT4: Levothyroxine, OD: Orbital decompression, HA: Hyaluronic acid, HLA-DR: Human leukocyte antigen-DR isotype, Eu: Euthyroid, ↓: Decreased, ↑: Increased
Enzymatic and nonenzymatic components of the antioxidant system were assessed, including the activity of glutathione peroxidase (GPx), SOD, and paraoxonase 1, as well as the total oxidant status expressed as the ferric reducing ability of plasma. The levels of Vitamin C, uric acid, and lipid peroxidation products (conjugated dienes [CD] and malondialdehyde [MDA]) were examined as well. While in hyperthyroid patients all values were significantly different from those in control ones, in euthyroid patients, only the activity of GPx was significantly higher than in controls, and other values nonsignificantly changed compared with the control group.

A pilot study of 10 patients described the beneficial effects of PTX therapy in euthyroid moderately-severe TED in 1997. PTX (200 mg/day) was administered intravenously for 10 days and continued at 1800 mg/day orally for the first 4 weeks and then 1200 mg/day for the rest of treatment. Any improvement in total eye score of NOSPECS was defined as response. Serum GAG, TNFα, anti-TSH-receptor, anti-eye-muscle, anti-thyroglobulin, and anti-thyroid peroxidase antibodies were also documented sequentially. Soft tissue inflammation significantly improved in 80% of cases (8/10) with less significant improvement in proptosis and extraocular myopathy. Although moderate and persistent nausea was reported by two cases at the beginning of therapy, it did not interrupt treatment and responders continued oral PTX 1200 mg/day to maintain initial clinical benefit after 12 weeks.

Allopurinol and nicotinamide (300 mg/day, oral, 3 months) were compared with a placebo in a prospective nonrandomized study in 2000. Treatment improved NOSPECS total eye score from 4.3 ± 1.9 to 2.0 ± 1.0 (P = 0.0001) and self-reported satisfaction in 22 newly diagnosed mild or moderately-severe TED patients.

Finamore et al. compared an oral PTX (1200 mg/day) in 9 TED patients with placebo (9 TED patients) in a crossover (6-month) study. Exophthalmometry and health-related QoL questionnaire were the outcomes which were measured at baseline, 3, and 6 months after the treatment. Both showed significant improvement in the treatment group compared with placebo group. Gastrointestinal symptoms were, however, notable. The questionnaire scores were 5.5 and 5 (P = 0.01) at baseline and 6th months in the treatment group, respectively. A significant (P < 0.05) improvement of proptosis was also reported in the treatment group. Neither of the criteria changed significantly in the placebo group within two-time intervals of the crossover study.

In a randomized clinical trial, Se, PTX, and placebo were compared in 159 patients with mild TED. They were assigned to three groups receiving sodium selenite (100 µg twice daily), PTX (600 mg twice daily), or placebo (twice daily) orally for 6 months and were followed for the next 6 months without treatment. Significant (P < 0.001) improvements in QoL (GO-QoL), CAS, soft tissue involvement and eyelid retraction with a less progression in TED severity (P = 0.01) were observed in the Se as compared with the placebo group. PTX group, however, did not show significant improvement as compared with the placebo group. While skin and gastrointestinal side effects were observed in the PTX group, no adverse effect was in the Se and placebo groups.

The result of hierarchical evaluation for included studies has been detailed in Table 1. Among all, the experiments of Finamor et al. and Marcocci et al. are in level 2, while the ones for Balazs et al. and Bouzas et al. are in level 3. According to defined criteria, the studies by Dehina et al., Federige et al., Liu et al., and Olesik et al. stand at level 4, and the rest lie at the lowest part of the pyramid.

**Discussion**

Impaired balance between production of oxidative stress and consumption of antioxidant defenses (inactivation or excessive usage) leads to oxidative damage of biological membranes and molecules, which can be measured by either direct estimation of the ROS or indirect methods including detection of the resulting damage to biomolecules (DNA/RNA damage, lipid peroxidation, and protein oxidation/nitration) and antioxidant levels. Increased oxidative stress and decreased scavenging ability of the cells have been recognized to be involved in the pathogenesis of autoimmune disorders particularly GD and TED. Using a variety of techniques to induce oxidative stress while applying diverse measuring systems (ROS production, MDA, SOD activity, LPO, 8-OhdG, GSH, and GSH/GSSG ratio), certain studies have found a significant imbalance of prooxidant/antioxidants status in TED versus normal orbital fibroblasts. This imbalance accounts for proliferation of orbital fibroblasts, synthesis of autoantibodies, breakdown of preadipocytes into adipocytes, secretion of endogenous cytokines (TNFα, IL1β and IFNγ), and increased production and secretion of GAGs in TED patients which consequently lead to fibroadipose tissue expansion and infiltration of EOM.

The aim of this systematic review was to provide the clinicians with essential information about potential role of antioxidant agents in the management of TED. Some of the studies have compared the efficacy of more than one type of antioxidant, and secretome studies were found to discuss their clinical results. While quercetin, Vitamin C, and nicotinamide have shown both proliferation inhibition and improved patient satisfaction and total eye

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**Academic Performance**

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score in clinical studies. Exposed orbital fibroblast cultures to PTX demonstrated inhibition of GAG release and fibroblast proliferation. PTX treatment also led to a marked improvement in total eye score of 80% of TED patients (after 12 weeks), and progressive improvement of proptosis and QoL questionnaire response. However, no significant difference in overall ophthalmic outcome at 6-month was observed between PTX and placebo in another study.

Decreased serum Se level was reported in all groups of patients regardless of TED presentation, and SePP status was lower in GO and HT patients than in normal controls. Serum Se and SePP concentrations were not different between mild versus moderately severe as well as active versus inactive TED patients. However, this study was unable to draw a strong conclusion about Se supplementation as it was not a longitudinal study and did not include a control group of healthy subjects or GD patients without TED.

SeMCys suppressed fibroblast proliferation, HA secretion, apoptosis, and necrosis in TED orbital fibroblasts in the Dottore et al.’s in vitro studies. While sodium selenite form of Se inhibited ROS production and inflammatory cytokines (except IL1 β and IL6) in a laboratory experiment, it decreased eye involvement, improved QoL, and slowed TED progression in comparison to PTX and placebo in a randomized controlled trial (RCT). Consequently, European Thyroid Association/EUGOGO released a guideline in 2016, in which they recommended a 6-month use of antioxidants, mainly Se for mild TED in order to prevent its progression to advance stages and improve ocular manifestations and QoL.

Although there are some published reviews on the role of antioxidants in patients with TED, to the best of our knowledge, this is the first systematic review on this topic. While it is clear that antioxidants play an important role in the management of TED, no strong recommendation for any or combination of antioxidants could be made to be implemented in the daily practice on the grounds that all the reviewed studies had used different methods, stage of disease, patient selection, and randomization in this regard. Therefore, further well-designed RCTs are required to especially compare single or combined antioxidants in different severity grades of TED.

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**Conflicts of interest**
There are no conflicts of interest.

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