

# The relationship between Graves' ophthalmopathy and dry eye syndrome

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**Background:** A complex relationship between Graves' ophthalmopathy (GO) and dry eye syndrome exists. New research brings more insight into the association between these two diseases.

**Methods:** A review of the literature was conducted using the query terms "Graves' Ophthalmopathy", "Thyroid Eye Disease", and "Dry Eye" in MedLine (PubMed) and Scopus. A total of 55 papers were reviewed. Case reports were excluded.

**Conclusion:** This review paper shows the close relationship between dry eye syndrome and GO. The underlying mechanisms behind their association suggest mechanical impairment of orbital muscles and immune-mediated lacrimal gland dysfunction as the causes of dry eye in GO patients. However, there are a variety of treatment options available for patients with GO with signs of dry eye, which help combat this issue.

**Keywords:** Graves' ophthalmopathy, dry eye, thyroid eye disease, ocular inflammation

## Introduction

Dry eye syndrome (DES) is defined by an abnormal tear film that results in changes to the ocular surface, which can lead to ocular discomfort.<sup>1,2</sup> Its symptoms may include blurred vision, burning, itchiness, redness, or grittiness in the eye, and sensitivity to light.<sup>1-3</sup> DES is a common disease and is increasingly prevalent among people with autoimmune disease and thyroid disorders, in postmenopausal women, and in the elderly.<sup>1-3</sup>

Graves' ophthalmopathy (GO) is a disease often associated with DES that is the most frequent cause of ocular discomfort in GO patients.<sup>4</sup> GO, also known as thyroid-associated orbitopathy, thyroid eye disease, or Graves' orbitopathy, is an autoimmune disease in which autoantibodies to the thyroid-stimulating hormone receptor lead to the excess production of thyroid hormone and induce an inflammatory response in the orbital tissues.<sup>5</sup> GO occurs in about half of Graves' disease (GD) cases;<sup>6,7</sup> onset is usually within 12–18 months of the systemic GD symptoms with an active phase that is followed by spontaneous remission. Unfortunately, in some patients, the active phase can later return.<sup>8</sup> The estimated occurrence of GO in women is 16 cases per 100,000 people per year, and in men, 3 cases per 100,000 people per year.<sup>9,10</sup> GO is most often seen with concomitant hyperthyroidism (80%); however, it can also be seen in hypothyroid and euthyroid states.<sup>11</sup>

In GO, it is hypothesized that there is a cross-reactivity against an antigen that is in both thyroid and orbital tissues, which leads to an autoimmune orbital reaction.<sup>7,12</sup> T lymphocytes invade into orbital tissue and musculature in response to a similar antigen found in thyroid tissue.<sup>5</sup> This inflammatory process often leads to glycosaminoglycan deposition, fibrosis of extraocular muscles, and adipogenesis in the area around the

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orbit.<sup>13,14</sup> Clinically, this autoimmune response can result in the classic presentation of eyelid retraction in 80%–90% of patients, lagophthalmos, exophthalmos, restrictive myopathy, and diplopia.<sup>9</sup> These clinical manifestations can lead to problems with vision, ocular motility, and physical disfigurement. Due to these problems, particularly dry eye symptoms, the quality of life of people with GO is often diminished.<sup>15</sup>

Although the association between DES and GO has long been known, recent research has increased our understanding of the mechanism behind this relationship with potential treatments for these concurrent diseases. This paper reviews current knowledge about the relationship between GO and DES.

## Discussion

### Epidemiology

DES is one of the most common ophthalmologic complaints, affecting millions of people around the world and is a significant health care concern.<sup>16</sup> Severe DES can have as large an impact on quality of life as end-stage renal disease.<sup>17</sup> Large-scale population-based studies suggest that the prevalence of DES is approximately 14%–15% of the population aged 50 and older.<sup>3,16,18</sup> DES patients are often elderly and have

some other type of systemic disease or comorbid medical condition.<sup>19</sup>

Nonetheless, DES is especially common in patients who have concurrent thyroid disease. Many studies around the world demonstrate that there is an increased risk of having DES in patients who have thyroid disease.<sup>18,20,21</sup> Studies that specifically examine GO show that an estimated 65%–85% of GO patients also have dry eye symptoms.<sup>10,22–24</sup>

### Ocular surface changes

Clinical researchers have recognized the importance of accurate assessment of ocular surface health in GO, and the major GO classification schemes include either qualitative or quantitative ocular surface assessments.<sup>25–27</sup> These classification systems include the NOSPECS, Clinical Activity Score, and the VISA system, which all utilize some aspect of ocular surface damage in GO to help determine disease severity in patients (Table 1).<sup>25–27</sup> Patients with GO and DES often have significant ocular surface damage compared to healthy eyes.<sup>28</sup> Patients with GO and dry eye have significantly lower Schirmer tests (14.4±8.34 mm) compared with normal controls (24.9±3.57 mm), suggesting inadequate

**Table 1** Classification systems used for Graves' ophthalmopathy

#### NOSPECS

Class 0: No signs or symptoms

Class 1: Only signs (limited to upper lid retraction and stare, with or without lid lag)

Class 2: Soft tissue involvement (edema of conjunctivae and lids, conjunctival injection, etc)

Class 3: Proptosis

Class 4: Extraocular muscle involvement (usually with diplopia)

Class 5: Corneal involvement (primarily due to lagophthalmos)

Class 6: Sight loss (due to optic nerve involvement)

#### VISA

Vision loss (optic neuropathy)

Inflammation/congestion and activity in TED

Strabismus/motility

Appearance/exposure

#### CAS

Pain

1: Painful, oppressive feeling on or behind the globe during the last 4 weeks

2: Pain on attempted up, side, or down gaze during the last 4 weeks

Redness

3: Redness of the eyelid(s)

4: Diffuse redness of the conjunctiva, covering at least one quadrant

Swelling

5: Swelling of the eyelid(s)

6: Chemosis

7: Swollen caruncle

8: Increase of proptosis of >2 mm or more during a period between 1 month and 3 months

Impaired function

9: Decrease in eye movements in any direction greater than or equal to 5° during a period of 1–3 months

10: Decrease in visual acuity of greater than or equal to one line on the Snellen chart (using a pinhole) during a period of 1–3 months

**Notes:** For each of the signs present, one point is given. The sum of these points defines the activity score.

**Abbreviations:** TED, thyroid eye disease; CAS, Clinical Activity Score.

tear production.<sup>4</sup> The tear breakup time in GO patients with dry eye ( $5.84\pm 3.31$  s) is significantly lower than controls ( $11.4\pm 3.75$  s), suggesting an unstable tear film.<sup>22,29,30</sup> Multiple studies demonstrate that the tear film osmolarity in GO patients is significantly higher than controls, as determined by auto-osmometry ( $290.80\pm 13.58$  mOsm in control and  $340.38\pm 18.74$  mOsm in the patients).<sup>28,31</sup> The ocular surface disease index (OSDI) is an assessment tool used by ophthalmologists to determine the symptoms of dry eye in their patients; GO patients are noted to have an increased OSDI compared with controls.<sup>29</sup>

Rose Bengal and fluorescein staining show significantly more ocular damage in patients with GO and dry eye compared with controls. In one study, impression cytology in GO and dry eye patients showed a reduced goblet cell density, a decreased nuclear/cytoplasmic ratio, and excessive desquamation in conjunctival cells compared with normal controls.<sup>29</sup> Another study using impression cytology finds epithelial dystrophy with cell polymorphism and epithelial keratinization with local leukocyte infiltration in GO patients' eyes.<sup>24</sup> When examining patients' eyes with confocal microscopy, there is a significant reduction in surface epithelial cells in the cornea of patients with GO and dry eye compared with controls ( $1,011.36\pm 199.36$  cell/mm<sup>2</sup> in patients and  $1,517.15\pm 130.65$  cells/mm<sup>2</sup> in controls). There is also an increased stromal cell density ( $1,215.81\pm 88.71$  cells/mm<sup>2</sup> in patients and  $971.15\pm 103.56$  cells/mm<sup>2</sup> in controls) with increased hyperreactive activated keratocytes ( $6.04\pm 2.93$  cells/frame in patients and  $0.42\pm 0.73$  cells/frame in controls), suggesting corneal inflammation in these patients.<sup>8</sup> Patients with early signs of GO also have reduced corneal sensitivity.<sup>23</sup> GO patients, when examined using confocal microscopy, have a lower number of nerve fibers in the cornea than controls.<sup>8</sup>

## Mechanism behind the association between DES and GO

Although the association is well established, the mechanism to explain the relationship between GO and DES is not completely known. Increased ocular surface exposure due to proptosis and eyelid retraction as well as aqueous tear deficiency appear to be primarily responsible; however, in GO, it is thought that both mechanisms can contribute to dry eye symptoms in patients.

There is evidence to implicate the mechanical impairment of the lids, which is associated with GO as the reason for the symptoms of "evaporative dry eye". In GO, the mechanical impairment is caused by the hypertrophy of extra-orbital

muscles, fibrosis of the levator muscle complex, and the increase in orbital fat and connective tissue.<sup>28</sup> Combined, these factors can lead to increases in the intra-orbital contents, and therefore, an increase in intra-orbital pressure, eye lid retraction, palpebral fissure widening, proptosis, and eventually, the inability to close the lid.<sup>28</sup> Incomplete blinking results in inadequate tear distribution over the ocular surface, and a widened palpebral fissure permits excess tear evaporation.<sup>28</sup> One study finds that GO patients' palpebral fissure height correlates with their tear film breakup time. Those with a wider fissure are more likely to have a shorter tear film breakup time, which leads to tear film instability.<sup>32</sup>

Patients with GO have an abnormally high tear film osmolarity,<sup>31</sup> and this may result from excess evaporation. In mice, tear hyperosmolarity stimulates pro-inflammatory cytokines including interleukin 1B, tumor necrosis factor  $\alpha$ , and matrix metalloproteinase 9.<sup>33</sup> These cytokines activate MAPK cascades, which stimulate further inflammatory cytokines.<sup>34</sup> This cycle can lead to a high amount of ocular inflammation. Evidence suggests that ocular inflammation mediated by T lymphocytes is important in the pathogenesis of DES.<sup>35</sup> Hyperosmolarity may also cause pathological changes to the corneal epithelium cells, where MMP-9 can lyse substrates such as the corneal epithelial basement membrane and tight junction proteins that normally have a corneal epithelial barrier function.<sup>36</sup> Other changes can include increased desquamation, blunting and loss of microvillae, and cellular swelling.<sup>37</sup> This epithelial damage then induces more inflammation and apoptosis. These inflammatory cytokines in the tear film lend further evidence to increased exposure and resultant inflammation as a potential cause of DES.<sup>38</sup>

Reduced aqueous tear production also results from the inflammatory process of GO.<sup>39</sup> Studies indicate that the lacrimal gland might be directly involved in the pathogenesis of dry eye disease.<sup>40,41</sup> The lacrimal gland also expresses thyroid-stimulating hormone receptors, which makes it a potential target for the autoantibodies in GO.<sup>29</sup> Therefore, the autoantibodies that bind to lacrimal thyroid-stimulating hormone receptors in GO patients can cause aberrant signal transduction and potentially contribute to lacrimal gland impairment and resulting aqueous-deficient dry eye.<sup>29</sup>

GO patients also have an abnormal proteinaceous composition of their tear fluid, which is consistent with dysfunction in the lacrimal gland.<sup>29</sup> One study shows that the IgA/lysosome ratio is increased in 33% of GO patients but in only 3% of controls.<sup>42</sup> Also, in a study of the tear fluid in patients with GO, 28% of them have an abnormal tear film protein

profile.<sup>43</sup> Therefore, the autoantibodies present in GO result in lacrimal gland impairment and abnormal tear fluid, which can lead to aqueous-deficient dry eye.

Although the complete explanation for the mechanism through which GO leads to DES is not entirely known, it is most likely that multiple mechanisms are involved and have a synergistic effect. Known mechanisms include tear film dysfunction due to increased evaporation and/or ocular inflammation, aberrant stimulation of lacrimal glands leading to hyposecretion, and other currently unknown mechanisms currently combining to cause the symptoms and signs of DES.

## Treatments of GO associated with DES

GO has many different treatment options including orbital radiotherapy and surgical interventions.<sup>9,39</sup> Due to a lack of clinical trials, it is difficult to determine if these treatments contribute to the development or progression of DES.

Nevertheless, there is some evidence to suggest that treatment can exacerbate the symptoms of DES. In a study examining the impact of orbital radiotherapy in patients with GO, although stabilization of the disease was achieved in 12/17 patients, chronic DES developed in 6/17 patients.<sup>44</sup> In two other studies examining orbital radiotherapy, over 90% of patients had stabilization of their GO, but 10%–12% of patients had resulting chronic dry eye concerns.<sup>45,46</sup>

Surgery to correct GO, such as lid retraction repair, will reduce evaporative tear loss. However, there is a risk that surgery could damage the lacrimal gland, and lead to lacrimal gland dysfunction and the potential for aqueous deficiency.<sup>47</sup> Although the patient populations are small in many of these retrospective studies, they nevertheless point to a potential issue in that the treatments of GO might be related to the symptoms of dry eye. Further study is necessary to better determine the dry eye consequences of these treatments.

## Treatments of GO improving DES

Both symptomatic and anti-inflammatory treatments should be used to manage dry eye in GO patients. Electrolyte and polymeric solutions are used for tear replacement.<sup>48</sup> Lubricant therapy, especially overnight for patients with lagophthalmos, is also helpful.<sup>48</sup> Decreasing the elevated tear osmolarity in these patients is another potential option. A hypotonic solution can be used, but it causes only a brief decrease in osmolarity.<sup>49</sup> Alternatively, there are solutions that enter epithelial cells and decrease their osmotic difference. This protects these cells from hyperosmotic damage.<sup>50</sup> Surgical management to repair the dysfunctional eyelid position can also help protect the ocular surface and tear film.<sup>48</sup>

Because inflammation is involved in the pathogenesis of dry eye, anti-inflammatory treatments can bring dry eye relief to patients with GO. Cyclosporine A can inhibit T-cell proliferation and stop apoptosis of ocular surface cells.<sup>51,52</sup> However, there is conflicting evidence as to the impact of cyclosporine A treatment for DES in GO patients. In one study, after 2 months of topical cyclosporine A treatment, GO patients showed increased Schirmer tests and tear film breakup time, decreased OSDI score, and decreased apoptosis and MMP-9 expression in conjunctiva epithelial cells.<sup>36</sup> However, conversely, another study did not find cyclosporine A to be advantageous compared to artificial tears in dry eye treatment for GO patients.<sup>53</sup> Other topical steroids and tetracyclines are other anti-inflammatory agents sometimes used to treat DES in GO patients.<sup>54</sup>

## Conclusion

The association between GO and DES has long been established in the literature. This paper sought to review the mechanisms through which DES manifests in GO patients. The evidence points to mechanical impairment of the muscles in the orbit and immune-mediated lacrimal gland dysfunction as the causes of the altered tear film that leads to dry eye in GO patients. Ocular inflammation from these problems also contributes to ocular surface damage. Treatment for DES should be carefully considered in the context of GO, as some treatments for GO may contribute to dry eye symptoms. However, there are multiple treatment considerations that can be used to help with DES in these GO patients.

## Disclosure

Dr Sikder is a consultant for Allergan. The other authors have no proprietary or commercial interests in any concept or product discussed in this article.

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