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REVIEW

Glaucoma and Dry Eye Disease: Opportunity to Assess and Treat

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Abstract: Dry eye disease (DED) has been found to occur at a higher prevalence in individuals with glaucoma than in individuals without glaucoma. The relationship between glaucoma and DED may be, in part, a result of glaucoma therapy. Greater number of antiglaucoma medications used and greater number of antiglaucoma eyedrops instilled per day have been associated with ocular surface disease in patients with glaucoma. Use of antiglaucoma medication has also been associated with higher levels of ocular surface inflammatory markers and ocular surface alterations. There is evidence to suggest that antiglaucoma medications with preservatives and, to some extent, antiglaucoma medication formulations without preservatives may contribute to ocular surface signs and symptoms. Trabeculectomy for glaucoma has also been associated with ocular surface signs related to DED; however, there may be benefits of trabeculectomy and other procedures for glaucoma due to reduced use of antiglaucoma medications. Patients with glaucoma with ocular surface disease have been found to have greater ocular surface symptoms, poorer vision-related quality of life, and poorer antiglaucoma medication adherence compared with patients with glaucoma without ocular surface disease. Because of the potential negative impact of DED on patients with glaucoma, patients with glaucoma may benefit from evaluation for DED. Management of DED in patients with glaucoma may include modifications to antiglaucoma medications and use of treatments for DED.

Keywords: ocular surface, quality of life, antiglaucoma medication, inflammation, preservatives

Introduction

Glaucoma is characterized by progressive deterioration of the optic nerve and vision loss.[1] It is the leading cause of irreversible blindness worldwide.[1] Deterioration of the optic nerve in glaucoma is often associated with elevated intraocular pressure (IOP), and treatments for glaucoma aim to slow the progression of the disease by lowering IOP.[1] Available treatments include topical medications, laser, or incisional surgeries.[1] Early diagnosis, ongoing treatment, and treatment adherence are critical to slowing disease progression and preventing blindness.[1–4]

Dry eye disease (DED) is an ocular surface disease, characterized by hyperosmolarity and tear film instability, that can cause discomfort and fluctuating vision and can potentially lead to ocular surface damage.[5] DED can be detected with tear-film and ocular-surface measures, including tear film breakup time, osmolarity, matrix metalloproteinase-9 (MMP-9) testing, and ocular surface staining.[6] Symptoms of DED negatively affect quality of life, and the associated visual disturbances from DED may affect activities such as reading and driving.[7] DED occurs at an increased prevalence in patients with glaucoma and has frequently been associated with the use of antiglaucoma medications.[8–13] Because of the negative impact of DED on the ocular surface and quality of life, it is important to understand the potential reasons for the association between glaucoma and DED and ways to manage DED in patients with glaucoma. This review describes the relationship between glaucoma and DED, the impact of DED on patients with glaucoma, and management strategies for DED in patients with glaucoma.

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Methods

A PubMed database search was conducted to review the literature on DED and glaucoma. Search terms included combinations of "dry eye", "ocular surface", "tear film", and "meibomian gland" with "glaucoma" and combinations of "glaucoma drainage implant", "laser", "minimally invasive glaucoma surgery", and "surgery" with "glaucoma" and "dry eye" or "ocular surface". Articles were included if the subject matter was relevant to discussing the association between DED and glaucoma, with studies in humans given priority. Review articles, editorials, articles not in English, economic analyses, and case studies were excluded.

Relationship Between Glaucoma and Dry Eye Disease

The estimated prevalence of ocular surface signs and/or symptoms in individuals with glaucoma varies across studies.[10,14–18] In a large register study, 52.6% (10,338/19,665) of those with glaucoma had a diagnosis of DED.[10] However, given the wide range of estimates of DED in the general population (5% to 50%),[7] these estimates are difficult to interpret. Studies that have included a control group have found that DED occurs at a higher rate in individuals with glaucoma than in individuals without glaucoma. In a national survey, DED was identified in 16.5% (104/629) of those with glaucoma compared with 5.6% (386/6934) of those without glaucoma.[8] Conversely, among individuals with DED, glaucoma was identified in 21.2% (104/490), compared with 7.4% (525/7073) of those without DED.[8] Although the prevalence of both DED and glaucoma increases with age, age does not fully explain the relationship between these diseases, because a higher prevalence of ocular surface signs and symptoms has been found among individuals with glaucoma when compared with age-matched controls and when age has been included as a covariate in the analysis.[19] Similar to findings in the general population,[7] DED among individuals with glaucoma has been found to be more prevalent at older ages[10,11] and more prevalent in women (56.9%) than in men (45.7%).[10]

When ocular surface symptoms and signs have been examined, individuals with glaucoma have been found to have higher rates of abnormalities compared with controls.[19–23] Among 211 patients with glaucoma, 41.7% (88/211) were found to have ocular surface symptoms, as measured by the Ocular Surface Disease Index (OSDI), compared with 25.5% (13/51) of controls without glaucoma.[19] Findings with the OSDI may need to be interpreted with caution because the vision-related component of the OSDI may be influenced by vision changes related to glaucoma as opposed to ocular surface disease.[23] Ocular surface staining has also been found to be more prevalent in individuals with glaucoma.[19,20,24–26] Ghosh et al found corneal staining (grade 2–3) in 51.3% (154/300) of those with glaucoma and 17.0% (17/100) of controls.[25] Tear breakup time has also been found to be shorter in individuals with glaucoma.[20,26,27] Furthermore, total tear breakup area has been found to be greater, and the growth rate of the dry area has been found to be steeper in those with glaucoma.[27] Tear meniscus height and Schirmer scores have also been found to be lower in eyes with glaucoma compared with controls.[24,28] Compared with fellow eyes, eyes with glaucoma have been found to have greater tear film osmolarity, greater conjunctival hyperemia, and greater eyelid margin abnormality.[28] In addition to ocular surface signs, individuals with glaucoma have been found to have greater meibomian gland loss and poorer meibum scores than controls.[29–32] The tear film lipid layer—which plays an important role in tear film stability—is made up of meibum.[33,34] Thus, meibomian gland dysfunction may lead to deficiencies in the tear film lipid layer and increased evaporation of the tear film.[34,35]

Relationship Between Glaucoma Therapy and Dry Eye Disease

Topical Antiglaucoma Medication and Dry Eye Disease

The relationship between glaucoma and DED may result from, at least in part, the use of topical antiglaucoma medications. Notably, Kuppens et al found that basal tear turnover in individuals with untreated primary open-angle glaucoma was lower than that of individuals without glaucoma, suggesting that glaucoma may in itself lead to DED;[36] however, the role of antiglaucoma medications in DED has been suggested by several studies.[9–13] Antiglaucoma medications consist of an active component and an excipient, which may include a preservative. Several types of active components exist, including prostaglandin analogues, β-blockers, α-2 adrenergic agonists, carbonic anhydrase inhibitors, pilocarpine, rho-associated kinase inhibitors, and combination medications.[9,37,38]

Several studies suggest that a greater use of antiglaucoma medications is associated with an increased risk of DED. In a large study of patients with glaucoma (N=10,325), the odds of DED were found to increase with the number of medications used (OR=1.23 with 2 medications; OR=1.63 with 3 medications; OR=2.60 with 4 medications).[9] Similarly, in a separate study, ocular surface disease prevalence was found to increase with the number of antiglaucoma medications, the number of drops instilled per day, and history of treatment changes due to ocular intolerance.[12] Several studies have found an association between specific ocular surface signs and antiglaucoma medications.[15,25,26,39,40] Greater number of antiglaucoma medications and duration of therapy were found to be predictors of abnormal ocular surface staining, Schirmer test <5 mm, and tear breakup time of ≤ 5 seconds.[25] Greater number of antiglaucoma drops instilled per day was also found to be associated with abnormal corneal staining and shorter tear breakup time.[15,26,40] Longitudinal studies of antiglaucoma medications in treatment-naïve patients with glaucoma have also shown an association between antiglaucoma medication and ocular surface signs.[41–43] In newly diagnosed individuals with glaucoma, treatment with antiglaucoma medication was associated with a decrease in tear breakup time from 11.7 seconds at baseline to 8.3 seconds at 3 months.[41] In another study, treatment with antiglaucoma medication was associated with decreased Schirmer scores, increased prevalence of tear film breakup time of <10 seconds, and increased ocular surface staining over 4 months.[42]

The Role of Preservatives and Topical Antiglaucoma Medication Formulations

Several studies have found an association between ocular surface signs and the use of preserved antiglaucoma medication (summarized in Table 1).[17,19,44–46] Preservatives such as benzalkonium chloride (BAK) are added to antiglaucoma medications for their antimicrobial actions in multidose eyedrop containers, which are susceptible to contamination.[47] Using multivariate analysis, Rossi et al found that the number of glaucoma medications, prolonged use of glaucoma medications, and exposure to at least 2000 μg of BAK were predictors of ocular surface disease (mean daily BAK was 6 μg).[45] Similarly, Lee et al found that a greater amount of BAK instilled per day was correlated with worse corneal epithelial punctate erosion and shorter tear breakup time.[48] Other studies have compared ocular surface signs in patients treated with preserved antiglaucoma medications and in patients treated with preservative-free medications. Villani et al found that individuals treated with antiglaucoma medications with BAK had shorter tear breakup times than those treated with preservative-free antiglaucoma medications, and lower Schirmer scores than those treated with preservative-free antiglaucoma medications or with antiglaucoma medications preserved with polyquad.[39] Similarly, Zaleska-Żmijewska et al found a higher prevalence of tear breakup time of <5 seconds among patients receiving antiglaucoma medication with BAK (50%) than among those receiving preservative-free antiglaucoma medications (10%).[46] In a study that examined the relationship between DED and specific antiglaucoma medications, the odds of DED were found to increase with the use of each type of medication examined (prostaglandin analogue, β-blocker, carbonic anhydrase inhibitor, pilocarpine, and combination medications) except for α-agonists.[9] It was suggested that the lack of an association between DED and α-agonists may have been related to the use of Purite® as a preservative for α-agonists as opposed to BAK or benzododecinium bromide.[9]

In addition to the preservatives in antiglaucoma medication, there is evidence to suggest that antiglaucoma medications may contribute to DED even in the absence of preservatives. One study found greater corneal epithelial punctate erosion in patients who used β-blockers compared to those who used non-β-blocker antiglaucoma medications when adjusting for amount of BAK instilled per day, suggesting that β-blockers may contribute to corneal epithelial punctate erosion independently of preservatives.[48] Furthermore, in a study that examined patients treated with preservative-free antiglaucoma monotherapy (tafluprost 0.0015% or timolol maleate 0.1%) for at least 36 months, patients treated with preservative-free timolol had shorter tear breakup times and patients treated with either preservative-free timolol or preservative-free tafluprost had higher OSDI scores than age- and sex-matched controls.[49] These findings suggest that in addition to antiglaucoma medications with preservatives, formulations without preservatives may contribute to ocular surface signs and symptoms.

Topical Antiglaucoma Medication and Meibomian Gland Dysfunction

Meibomian gland loss and meibum scores have also been associated with antiglaucoma medications, which is relevant given that meibomian gland dysfunction may contribute to DED.[33] Ha et al found that patients treated with preservative-containing antiglaucoma medications had greater meibomian gland loss and poorer meibum scores than patients treated

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Table 1 Studies Examining the Ocular Surface Effects of Preservatives in Glaucoma Medications

Study	Patient Population	Methodology	Key Findings on Preservatives
Leung et al, 2008[17]	N=101 (202 eyes; 78% of patients with OAG; 22% of patients with ocular hypertension)	Cross-sectional, multivariate evaluation of OSD in glaucoma patients	• Each additional BAK-containing eyedrop is associated with 2.03 increase in odds of abnormal lissamine green staining (OR: 2.03; 95% CI: 1.06–3.89; p=0.034)
Labbé et al, 2012[44]	N=40 patients treated for glaucoma or ocular hypertension with IOP-lowering drugs	Univariate and multivariate analysis of tear film osmolarity in patients treated with IOP-lowering drugs	• Increased tear film osmolarity was significantly correlated with the number of instillations of preservative-containing eyedrops (r = 0.629, p<0.0001) • Patients treated with more than one instillation of preservative-containing drops exhibited significantly increased osmolarity compared with patients treated without preservatives (p=0.002) and patients receiving only one instillation of preservative-containing drops (p=0.004) • Number of instillations of preservative-containing drops was significantly correlated with TBUT (r = −0.479, p=0.002) and OSDI (r = 0.372, p=0.019)
Rossi et al, 2013[45]	N=233 patients with topically treated glaucoma	Observational, cross-sectional study of OSD risk factors in glaucoma patients	• Multivariate analysis revealed that prolonged use of preservative-containing drops (OR: 5.25; p=0.005) and total BAK exposure (OR: 104.92; p<0.001) are significantly related to OSD
Lee et al, 2013[48]	N=187 glaucoma patients using topical IOP-lowering drugs in 300 eyes	Cross-sectional analysis of the effect of antiglaucoma drugs on corneal punctate epithelial erosion and TBUT	• Cumulative BAK exposure was significantly and positively correlated with corneal punctate epithelial erosion (r = 0.208, p=0.001) and significantly negatively correlated with TBUT (r = −0.131, p=0.042) • Corneal punctate epithelial erosion was significantly more severe in patients using β-blockers when adjusted for cumulative BAK exposure compared with those not using β-blockers (p=0.016)
Chen et al, 2015[9]	N=2065 glaucoma patients with newly diagnosed DED	Univariate and multivariate analysis of claims data to estimate effects of glaucoma treatments on DED risk	• Increased risk of DED was observed in all medications (prostaglandin analogues, β-blockers, carbonic anhydrase inhibitors, pilocarpine, and combinations) except for α-agonists, presumably due to the use of Purite® preservative as opposed to BAK
Villani et al, 2016[39]	N=100 patients with medically controlled POAG	Evaluation of the effect of glaucoma medication on ocular surface findings	• Patients treated with preservative-containing drugs (n=80) had reduced TBUT (p<0.05) compared with patients treated with preservative-free drugs (n=20) • Patients treated with BAK-containing drugs (n=72) had lower Schirmer test values than patients treated with Polyquad-containing drugs (n=8) and preservative-free drugs (p<0.001)

Pérez-Bartolomé et al, 2017[19]	N=211 glaucoma patients using IOP-lowering drugs and N=51 untreated healthy controls	Univariate and multivariate analysis of OSD in glaucoma patients	• Patients using preservative-free medications showed lower prevalence of corneal staining than those using BAK-containing drops, which, in turn, showed lower prevalence than BAK + polyquaternium–containing drops (p=0.000) • Presence of epitheliopathy correlated with higher daily preservative concentration and cumulative preservative concentration (p<0.005) • Abnormal fluorescein corneal staining was associated with BAK-containing drops (OR: 1.567) and drops containing BAK + polyquaternium (OR: 5.09)
Rolle et al, 2017[49]	N=51 patients with POAG (27 treated with tafluprost; 24 treated with timolol) and N=20 age-matched healthy controls	Cross-sectional evaluation of long-term safety and tolerability of tafluprost and timolol	• TBUT was significantly lower in patients treated with preservative-free timolol than in controls (p<0.05) • Patients treated with either preservative-free timolol or preservative-free tafluprost had significantly higher OSDI scores than controls (p<0.0001 for both comparisons)
Zaleska-Żmijewska et al, 2019[46]	N=60 patients with POAG; N=30 individuals with suspected POAG who were untreated	Extracellular MMP-9 assessment of ocular surface inflammation in glaucoma patients	• 46.7% of subjects treated with BAK-containing drops exhibited clinically significant levels of MMP-9 compared with 16.7% of untreated individuals or those using preservative-free medication (p=0.0125) • 50% of individuals using BAK-containing drugs and 10% of individuals using preservative-free or no treatment had TBUTs <5 s (p<0.05)

Abbreviations: BAK, benzalkonium chloride; CI, confidence interval; DED, dry eye disease; IOP, intraocular pressure; MMP-9, matrix metalloproteinase-9; OAG, open-angle glaucoma; OR, odds ratio; OSD, ocular surface disease; OSDI, Ocular Surface Disease Index; POAG, primary open-angle glaucoma; TBUT, tear breakup time.

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with a preservative-free antiglaucoma medication after 12 months.[50] However, patients treated with preservative-free drops also showed worse meibomian gland measures than normal controls, suggesting that antiglaucoma medications with or without preservatives have a negative effect on meibomian glands, but preservative use was worse for meibomian glands.[50] In a separate study, patients using prostaglandin analogues were found to have a higher prevalence of meibomian gland dysfunction compared to patients using non-prostaglandin analogue antiglaucoma medication.[51]

Topical Antiglaucoma Medications and Ocular Surface Inflammation

The association between antiglaucoma therapy and DED suggests that patients with glaucoma may benefit from evaluation of the ocular surface. Addressing DED in patients with glaucoma is important because DED can lead to ocular surface inflammation and damage.[5,33] There is evidence indicating that eyes receiving topical antiglaucoma medication have increased ocular surface expression of inflammatory markers.[22,52–56] This may be because of antiglaucoma medication, the DED, or a combination of these. Benitez-del-Castillo et al found higher expression of interleukin (IL)-6 in the tears of eyes receiving antiglaucoma medication compared with the tears of control eyes.[22] Furthermore, higher expression of IL-1β was found in eyes receiving antiglaucoma medication with preservatives compared with eyes receiving antiglaucoma medication without preservatives.[22] Increased expression of IL-6, IL-8, and IL-1β in tears of eyes receiving preserved antiglaucoma medication was also found in a study in which patients were randomized to antiglaucoma medications with preservatives or without preservatives.[53] To investigate involvement of T helper (Th) 1 and Th2 pathways in eyes receiving antiglaucoma medication, Baudouin et al examined expression of chemokine receptors CCR5 and CCR4 as markers of these pathways, respectively, in eyes treated with antiglaucoma medication for more than 1 year.[57] Increased expression of both CCR5 and CCR4 was found in the conjunctival epithelium, suggesting involvement of both allergic and Th1 mechanisms in the ocular surface of patients with glaucoma.[57] In addition to cytokines and chemokines, a higher prevalence of elevated MMP-9 levels has been found in eyes treated with antiglaucoma medications with BAK (47%) compared with untreated eyes suspected of having glaucoma (17%) and eyes treated with preservative-free antiglaucoma medication (17%), suggesting inflammation or ocular surface damage in eyes receiving antiglaucoma medications with BAK.[46] Interestingly, the tears of eyes receiving antiglaucoma medication have been found to have higher levels of IL-6, tumor necrosis factor-α, and vascular endothelial growth factor and lower levels of IL-4 than those of eyes with DED without glaucoma, suggesting activity of different inflammatory signaling pathways between the two groups.[22]

Topical Antiglaucoma Medications and Ocular Surface Alterations

In addition to inflammatory markers, studies have found anatomical differences in the ocular surface of eyes receiving antiglaucoma therapy beyond what has been observed through ocular surface staining. Kamath et al found that after 1 year of treatment with antiglaucoma medication, the prevalence of goblet cell density <50 cells/HPF increased from 2.2% at baseline to 32%, the prevalence of inflammatory cells increased from 9% to 37.5%, and the prevalence of squamous metaplasia increased from 10.2% to 45%.[54] Saini et al found that the density of basal epithelial cells in the central cornea was increased in individuals on antiglaucoma therapy compared with controls, and the number, length, and density of the central-corneal sub-basal nerve fiber layer was reduced.[58] The corneal nerve plexus is important for the health of the cornea, and damage to it can lead to a variety of ocular-surface-related issues.[58] A negative association of the central-corneal sub-basal nerve fiber layer density with corneal staining score and OSDI was found, as well as a positive association between sub-basal nerve fiber layer density and tear breakup time.[58] In addition to reduced sub-basal nerve fiber density, greater nerve tortuosity has been found with use of antiglaucoma medications. Villani et al found increased nerve length, nerve tortuosity, and dendritic cell density at the sub-basal nerve plexus in patients receiving antiglaucoma medication compared with controls, which was suggested to result from neuroinflammatory processes.[39] The effect of topical application of BAK on corneal nerves has been examined in animal models. In one study of mouse eyes, BAK-treated corneas showed significantly reduced nerve fiber density.[59] Other findings from this study included reduction in aqueous tear production, increased inflammatory cell infiltration, and corneal fluorescein staining.[59] Antiglaucoma medication formulations without preservatives may also contribute to anatomical alterations. Rolle et al found greater basal epithelial cell density, greater stromal reflectivity, a lower number of sub-basal nerves, and

greater sub-basal nerve tortuosity in patients treated with preservative-free timolol or preservative-free tafluprost compared to controls.[49] Overall, these studies indicate that there can be ocular surface alterations in patients treated with antiglaucoma medications.

Procedures for Glaucoma and Dry Eye Disease

Procedures for glaucoma, including surgery and laser procedures, may reduce the burden of antiglaucoma medications. However, similar to antiglaucoma medications, certain procedures may be associated with ocular surface signs and symptoms.[60,61] Trabeculectomy is a filtering surgery that involves the creation of a drainage path from the anterior chamber to the subconjunctival space.[62] Following trabeculectomy, Zhong et al found reductions in tear breakup time and increases in corneal staining, which did not fully recover to baseline at 3 months postsurgery.[61] Ocular surface signs following trabeculectomy may be related to the presence of the filtering bleb.[61,63] Patients with glaucoma with filtering blebs not using topical medications were found to have higher rates of DED, shorter tear breakup times, and greater corneal staining compared with individuals without glaucoma.[63,64] Shorter tear breakup times, greater corneal staining, and presence of DED were all associated with higher blebs, suggesting that the bleb may interfere with blinking and spreading of the tear film.[64] There is also evidence to suggest that trabeculectomy may contribute to loss of meibomian glands. Sagara et al found greater loss of meibomian glands in the upper-eyelid area that contacted the bleb compared with the area that did not contact the bleb in patients with glaucoma who underwent trabeculectomy with mitomycin C.[65] In contrast, other studies have found evidence of improvements in the ocular surface following trabeculectomy,[66,67] which have been postulated to be due to discontinuation of antiglaucoma medications and use of postoperative steroids.[67] In a study that compared trabeculectomy-treated eyes with fellow eyes treated with antiglaucoma medication, trabeculectomy-treated eyes were found to have longer tear breakup times and less corneal staining compared to fellow eyes.[68] Together these findings suggest that trabeculectomy may negatively affect the ocular surface, but the effects may be less than the negative effects of antiglaucoma medications.

In addition to trabeculectomy, other surgeries and procedures exist including laser trabeculoplasty, placement of tube shunts, and minimally invasive glaucoma surgery (MIGS).[69] To the authors' knowledge, a negative association between these glaucoma procedures and the ocular surface has not been demonstrated. Importantly, patients may continue to require glaucoma medications after surgical procedures.[69]

Impact of Dry Eye Disease on Patients with Glaucoma

Impact of DED on Quality of Life

The evaluation of DED in patients with glaucoma is important because of the negative impact that DED may have on quality of life. Rossi et al found that patients with glaucoma with ocular surface disease had poorer nonvisual-symptoms scores (eg, burning, tearing, dryness, itching as measured with the Glaucoma Symptom Scale [GSS]) and poorer vision-related quality of life (as measured by the National Eye Institute-Visual Function Questionnaire [NEI-VFQ 25]) compared with patients with glaucoma without ocular surface disease.[16,45] Other studies have found a relationship between antiglaucoma medications and quality of life. Camp et al found that patients on antiglaucoma medications had poorer dry eye–related emotional well-being scores (as measured with the Impact of Dry Eye on Everyday Life [IDEEL] questionnaire) compared with patients not on antiglaucoma medications.[70] Furthermore, use of a greater number of antiglaucoma medications was associated with poorer dry eye–related emotional well-being scores.[70] Similarly, Rossi et al found that a greater number of antiglaucoma drops instilled per day was associated with poorer vision-related quality of life (NEI-VFQ 25), GSS total scores, and GSS symptom scores.[71] However, this study failed to find a difference in quality of life between individuals with glaucoma and DED and individuals with glaucoma without DED.[71] Poorer quality of life has also been associated with the use of preservatives in antiglaucoma medications. Kumar et al found that patients receiving antiglaucoma medication with BAK had poorer Glaucoma Quality of Life-15 (GQL-15) scores and higher OSDI scores compared with patients receiving antiglaucoma medication without BAK and controls, suggesting poorer visual disability and ocular surface symptoms in the patients receiving antiglaucoma medication with BAK.[72] No significant difference in the GQL-15 or OSDI was found between

the patients receiving antiglaucoma medication without BAK and controls.[72] There is evidence to suggest that reducing antiglaucoma medication has a positive effect on quality of life. In a post hoc analysis examining an implanted trabecular microbypass stent (iStent *inject*® W) plus cataract surgery, the prevalence of patients who showed a response in vision-related quality of life was greater for patients who received the stent compared to patients who received cataract surgery alone.[73] Furthermore, those who showed a response in vision-related quality of life were more likely to be antiglaucoma medication–free at the end of the study, suggesting improved vision-related quality of life with reduced antiglaucoma medication use.[73]

Impact of DED on Glaucoma Management

In addition to the negative effects on quality of life, DED in patients with glaucoma may negatively affect adherence to antiglaucoma medications. Stringham et al found that the rate of topical antiglaucoma treatment compliance was lower among patients with glaucoma with dry eye symptoms (63%) than among patients with glaucoma without dry eye symptoms (89%).[74] Poorer antiglaucoma medication compliance has also been associated with greater meibomian gland loss, poorer meibum expression, and greater lid margin abnormality.[30] Since meibomian gland dysfunction is associated with DED,[33] these results further suggest a role of DED in antiglaucoma medication compliance. In another study, patients with glaucoma who experienced treatment adverse effects and those who reported being unhappy with their treatment more often experienced glaucoma disease progression.[75] These findings suggest the importance of treating DED in patients with glaucoma to facilitate treatment adherence.

There is some evidence to suggest that treatment of DED may improve management of glaucoma. In 2 case series, treatment changes aimed at addressing ocular surface disease in patients with glaucoma resulted in improvements in both ocular surface signs and in IOP.[76,77] Although these findings require further investigation, they suggest that addressing ocular surface disease in patients with glaucoma may help improve IOP in some patients.[76,77] Treatment of ocular surface disease in patients with glaucoma has also been found to result in improvement in optical coherence tomography signal quality, which is important for monitoring changes in glaucoma progression.[78] Treatment of DED may also be important for the outcome of trabeculectomy because trabeculectomy failure has been associated with higher levels of presurgical conjunctival inflammatory cells.[79]

Clinical Perspective: Managing Dry Eye Disease in Patients with Glaucoma

Assessment of DED in Patients with Glaucoma

Because of the increased risk of DED in patients with glaucoma, patients with glaucoma may benefit from evaluation for DED. An initial assessment for DED should be conducted before starting glaucoma medications to facilitate interpretations of subsequent assessments for DED. Questionnaires such as the OSDI and the Dry Eye Questionnaire – 5 item (DEQ-5) may be helpful for detecting DED.[6] The DEQ-5 may be more appropriate for patients with glaucoma than the OSDI because the DEQ-5 comprises questions on ocular surface symptoms without questions on visual function, which could be influenced by visual field loss related to glaucoma.[6,23] Ideally, ocular surface signs should also be assessed in addition to symptoms because patients with DED may have signs without symptoms, which may warrant treatment to prevent further manifestations of DED.[6] Clinical tests that can be used in the diagnosis of DED include tear breakup time, osmolarity testing, ocular surface staining, and MMP-9 testing.[6] Additional tests to consider for further characterizing the subtype of DED as primarily aqueous deficient (occurring with decreased lacrimal secretion), primarily evaporative (occurring with an increased rate of tear film evaporation and normal lacrimal secretion), or a mixed subtype include evaluation of tear volume, meibography, and meibomian expressibility.[6,33]

Treatment of DED in Patients with Glaucoma

To address DED in patients with glaucoma, antiglaucoma medications may need to be adjusted. Switching to antiglaucoma medications without preservatives has been found to result in improvements in ocular surface signs and symptoms.[80–82] Furthermore, preservative-free antiglaucoma medications have been associated with better treatment adherence than antiglaucoma medications with preservatives.[83] If preservative-free medications are not an option, combination medications may

be considered to reduce the number of drops for those patients who require more than 1 active molecule to control IOP.[84] Switching the active component may also be important in some cases because patients may have allergies or sensitivities to specific medications.[57] Furthermore, switching from a generic to a brand name for predictability of drop characteristics may also be considered.[85] A sustained-release implant for delivering bimatoprost is also available and may be considered as an alternative to topical application of antiglaucoma medication, although it is currently indicated for a single administration only and is therefore not an option for long-term treatment; moreover, it is not an option for all glaucoma patients.[86–88] In addition to switching medications or drug delivery methods, laser, MIGS, and traditional incisional procedures may also be considered to reduce the burden of antiglaucoma medications.[69] For example, MIGS has been found to result in reduced antiglaucoma medication use and improved ocular surface signs and symptoms.[89,90] Furthermore, selective laser trabeculoplasty may be considered as first-line therapy for glaucoma in place of antiglaucoma medication and has been associated with lower rates of eyelid erythema and conjunctival hyperemia compared with antiglaucoma medication.[91,92] It should be noted, however, that for some patients there are significant barriers to such interventions. For example, some patients or surgeons may not be comfortable with the risks of surgery, whereas for other patients, surgery may not be an option for their type of glaucoma.[69,91] Moreover, costs for certain procedures may be prohibitive.[69]

In addition to modifications to antiglaucoma medications, treatment for DED should be considered to restore the homeostasis of the ocular surface.[93] A variety of treatments are available for DED, the choice of which depends on the severity and subtype of DED.[93] Topical treatments for DED that may be considered for either evaporative or aqueous-deficient DED include ocular lubricants and topical anti-inflammatory treatments.[94] Ocular lubricants come in a variety of formulations, some of which have lipids to supplement the lipid layer of the tear film,[95] and some of which are preservative-free.[96] Topical anti-inflammatory treatments include corticosteroids (for short-term treatment, as long-term use is associated with numerous complications[97]), cyclosporine A, and lifitegrast.[97] For patients with evaporative DED related to meibomian gland dysfunction, topical or oral antibiotics may be considered as well as procedures such as therapeutic meibomian gland expression, thermal pulsation, intraductal probing, and intense pulsed light.[98–102] Notably, risks of dermatologic side effects with intense pulsed light may be greater for darker skin types.[103] A recently approved perfluorohexyloctane ophthalmic solution (Miebo^{TM}) has shown promise for the treatment of DED associated with meibomian gland dysfunction, and although it is not contraindicated for glaucoma patients, its safety and efficacy have yet to be evaluated in patients concomitantly administering IOP-lowering drugs.[104–107] Therapies to promote tear retention or tear production for aqueous-deficient DED include punctal plugs and varenicline solution nasal spray, respectively.[108,109] Several treatments for DED have been associated with improvements in OSDI and/or ocular surface signs for patients receiving antiglaucoma medications, including certain ocular lubricants, topical immunomodulatory treatments, and punctal plugs.[110–116] For patients who do not respond to a given treatment, additional or alternative treatments may be considered.[93] Because patients with glaucoma typically already have a medication burden, patient education on the importance of DED medications for addressing symptoms may help improve compliance with DED medications. Table 2 provides a summary of assessment and treatment considerations for addressing DED in patients with glaucoma.

Table 2 Considerations for the Assessment and Management of DED in Patients with Glaucoma

Assessment of DED in patients with glaucoma[6]	DEQ-5 Tear breakup time Osmolarity testing Ocular surface staining Tear volume Meibography Meibomian gland expressibility MMP-9 levels

(*Continued*)

Table 2 (Continued).

Management of DED in patients with glaucoma	Modifications to glaucoma therapy
	• Switch to preservative-free antiglaucoma medications
	• Consider laser, MIGS, or incisional procedures
	• Modify glaucoma drug delivery
	Treatment of DED
	• Preservative-free ocular lubricants
	• Topical anti-inflammatory therapy
	• MGD-targeted therapy
	  ○ Antibiotics
	  ○ Meibomian gland expression
	  ○ Thermal pulsation
	  ○ Intraductal probing
	  ○ Intense pulsed light
	• Tear conservation with punctal plugs
	• Nasal spray tear stimulation

Abbreviations: DED, dry eye disease; DEQ-5, Dry Eye Questionnaire – 5 item; MGD, meibomian gland dysfunction; MIGS, minimally invasive glaucoma surgery; MMP-9, matrix metalloproteinase-9.

Conclusion

DED occurs at a higher prevalence in individuals with glaucoma than in individuals without glaucoma, which may be related to therapy for glaucoma. Assessment and treatment of DED in patients with glaucoma is important to prevent ocular surface damage, improve quality of life, and facilitate treatment adherence to antiglaucoma medications. As such, patients with glaucoma may benefit from evaluation for DED. Management of DED may include modifications to antiglaucoma medications and use of treatments for DED.

Abbreviations

BAK, benzalkonium chloride; DED, dry eye disease; DEQ-5, Dry Eye Questionnaire – 5 item; GQL-15, Glaucoma Quality of Life-15; IDEEL, Impact of Dry Eye on Everyday Life; IL, interleukin; IOP, intraocular pressure; MGD, meibomian gland dysfunction; MIGS, minimally invasive glaucoma surgery; MMP-9, matrix metalloproteinase 9; NEI-VFQ 25, National Eye Institute-Visual Function Questionnaire; OR, odds ratio; OSDI, Ocular Surface Disease Index; Th, T helper.

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Author Contributions

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