

## Prevalence of Dry Eye Disease in Glaucoma

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### Abstract

Data from over 20,000 German patients with glaucoma have provided valuable information regarding the prevalence of dry eye disease (DED) in these patients. Overall, more women develop DED with glaucoma than men (56.9 versus 45.7%), and the prevalence increases with age, with more than half of patients 60 years of age having symptoms. Hypertension co-exists with glaucoma in 48.1% of patients, and the highest level of DED is found in patients with dry mouth, nose and skin (75.5%). DED occurs more often when three or more antiglaucoma eyedrops are used, and with longer disease duration. This suggests that it is related to the presence of the preservative benzalkonium chloride, and that using preservative-free eyedrops to break the vicious circle of DED is likely to enhance patient compliance and improve the care of glaucoma patients.

### Keywords

Dry eye, glaucoma, preservative-free, compliance

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Glaucoma is a chronic progredient neuropathy with typical structural changes at the optic nerve head and functional defects in the visual fields leading to blindness at the end stage. It is estimated that 60.5 million people worldwide will have this disease by 2010 and this number will increase to about 80 million by 2020. Glaucoma is the second leading cause of blindness in the world.<sup>1</sup> Furthermore, dry eye disease (DED) is a leading cause of patient visits to ophthalmologists.<sup>2</sup> Both glaucoma and DED are multifactorial disorders.<sup>3,4</sup> In a review of the prevalence of DED it was shown that the variation of prevalence of DED across studies is very high, differing from <0.1 to 33%,<sup>5</sup> depending on how DED was defined. However, in large studies the age-adjusted prevalences at >50 years of age in the US and Spain were from 3.9 to 11.9%,<sup>6-8</sup> and at ≥65 years between 15 to 34%.<sup>9</sup> At this age, the prevalence of DED increased with age and with female gender.

Since glaucoma and DED are very common in the elderly, we were interested in the prevalence of DED in different glaucoma types and in a very large sample size. The German Glaucoma and Dry Eye Register includes analysable data from a total of 20,506 individuals with diagnosed glaucoma taken from 900 ophthalmological centres across Germany. This information has allowed the relationship between the occurrence of dry eye and potential causative factors to be dissected in detail.<sup>10</sup> Overall, 52.6% of glaucoma patients have a concomitant diagnosis of dry eye versus 47.4% who do not.

### Incidence of Concomitant Diseases

Patients were asked directly about any concomitant illnesses and vascular risk factors they were aware of being affected by, and 16 such health concerns are found to co-exist with glaucoma. Irrespective of glaucoma type, hypertension is the most frequent of these, being reported by 48.1% of patients, followed by diabetes (22.5%), dry mouth,

nose and skin (11.3%) and obesity (11.2%). Overall, the presence of any concomitant disease increases the percentage of dry eye reported by glaucoma patients. Of those glaucoma patients with dry mouth, nose and skin, 75.5% also suffer from dry eye, and it is found in 68.2% of those with depressive episodes, 66.1% of those with arthritis and 65.6% of those with skin diseases.

### Gender and Age Differences

The gender distribution of the registry population is 60.9% female (n=12,493) and 39.1% male (n=8,013).<sup>10</sup> The German registry data found that women with glaucoma were significantly more likely to develop dry eye than men with glaucoma (56.9% versus 45.7%; p<0.0001). This is in agreement with other studies that found a predominance of DED in women,<sup>5,6,8,11</sup> but it seems to be an ethnic phenomenon because in Turkish normal volunteers<sup>12</sup> no significant differences in tear function between the genders have been observed, and in an Asian population the prevalence of DED was significantly higher in men compared with women.<sup>13</sup> The data from the German study indicate a steady rise in the prevalence of dry eye with increasing age, ranging from 31.3% at <40 years of age to 61.6% at 90 years of age or older. Splitting out the age-frequency data by gender shows that this factor appears to influence the occurrence of dry eye from about 50 years of age. Roughly 10% more female than male glaucoma patients 50–60 years of age report the development of dry eye, and this differential is maintained with age.

### Effect of Antiglaucoma Drug Treatment and Duration of Disease on the Incidence of Dry Eye and Other Local Symptoms

The German Glaucoma and Dry Eye Register reports a positive correlation between the number of different antiglaucoma eyedrops used and the frequency of dry eye: 50.9% of patients (n=13,474) using

one type of medication report dry eye compared with 65.3% of patients (n=118) using four medications, with the association becoming apparent when at least three drugs were used. The register also indicates a positive relationship between duration of glaucoma and the frequency of dry eye. Among those patients with glaucoma duration of under one year, 45.3% report dry eye, rising to 58.9% of patients with disease duration of >15 years.

In addition, those glaucoma patients with dry eye experience a significantly higher rate of all local symptoms, especially pain and foreign body sensation. These occur 11 and 12 times more frequently, respectively, among glaucoma patients with dry eye compared with those without dry eye; other typical symptoms include red eye, pruritus, photosensitivity and blurred vision. These local symptoms have a significant impact on the quality of life of patients, especially when severe, restricting their daily activities, mobility and self-confidence over and above the impact from glaucoma itself, which is largely asymptomatic in the early stages.

Taken together, these data suggest that the greater a patient's exposure to antiglaucoma treatment (in terms of both the number of eyedrop treatments used and the duration of their use), the greater the likelihood of dry eye and other ocular symptoms occurring. Similar findings were found in the study by Leung<sup>2</sup> in which, after adjustment for age and sex, each additional benzalkonium chloride-containing eyedrop was associated with an approximately two times higher odds of showing abnormal results on the lissamine green staining test. An explanation that is consistent with these findings is provided by the presence of preservatives in eyedrops to prevent or reduce microbial contamination.

## Benzalkonium Chloride in Glaucoma Medication Appears to Lead to Dry Eye

Apart from specific preservative-free preparations, all eyedrops available in Germany contain the preservative benzalkonium chloride in various concentrations. The deleterious effects of this substance on the conjunctiva and cornea have been extensively documented and can lead to dry eye.<sup>14-18</sup> Large-scale inflammatory changes lead to a local build-up of macrophages, lymphocytes, mast cells and fibroblasts, and to subsequent alterations in tissue structure, e.g. condensed connective tissue and conjunctival metaplasia.<sup>19-22</sup> Benzalkonium chloride has been associated with corneal cytotoxicity, decreasing cell proliferation and viability,<sup>23</sup> raised epithelial permeability<sup>24</sup> and a decrease in the tear-film break-up time due to disturbances in the lipid layer.<sup>25</sup> In addition, the active ingredients in antiglaucoma eyedrops, e.g. topical beta-blockers, carbonic anhydrase inhibitors and prostaglandin F (2 alpha) analogues, have been shown to lead to corneal damage and lymphocytic infiltration of the conjunctiva, which may also result in cases of dry eye among glaucoma patients.<sup>26</sup> In an effort to ameliorate ocular discomfort, patients often resort to the use of artificial tears. However, as these

drops also contain benzalkonium chloride, this leads to a vicious circle in which the artificial tears potentiate epithelial damage and the resulting pain and dry eye symptoms from antiglaucoma eyedrops.

## Side Effects from Preservative-containing Glaucoma Medication Reduce Compliance

The ocular discomfort that glaucoma patients experience is not only caused by the preservatives in glaucoma medication and in the drops to bathe dry eyes, but also by the disease process of glaucoma itself. As a result of dry eye and other ocular symptoms, there is a marked decrease in patient compliance and a reduction in the quality of patient care and control of glaucoma.<sup>27</sup> A recent review considering ways to improve compliance to glaucoma treatment referred to a study that systematically classified barriers to compliance in glaucoma. These latter authors found that medication- or regimen-related factors (primarily adverse effects) were responsible for 32% of reported obstacles to compliance.<sup>28</sup>

## Ways to Improve the Care of Glaucoma Patients

Glaucoma patients should be explicitly informed about their glaucoma and should be taken seriously in their daily handicap in handling all of their drop applications.

The data from the German study has provided the first large-scale opportunity to study factors affecting the care of patients with glaucoma. It is clear that lessening the effects of dry eye and local symptoms in these individuals would improve their quality of life and longer-term prognostic factors. One way to do this is through the use of preservative-free antiglaucoma medication. This would lead not only to an enhancement of the quality of life of patients, but also to improvements in glaucoma control, as the resulting lower levels of dry eye would allow a greater proportion of patients to adhere to their medication schedule. In addition, avoiding chronic therapy with preservative-containing eyedrops is likely to have beneficial effects on the health of the cornea and conjunctiva and increase the chance of glaucoma filtration surgery being successful.<sup>18,29</sup> Greater education of patients and family members about the availability of preservative-free eye drops, and that their use can reverse most of the preservative-induced ocular changes, would make an important contribution to reducing the prevalence of dry eye in glaucoma patients. ■

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