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Goblet cells suffer from glaucoma treatment

Glaucoma is the most common cause of blindness worldwide. The disease is a result of increased intraocular pressure (IOP), which is caused by an impaired balance between the production and drainage of aqueous liquid produced by nonpigmented epithelial cells of the ciliary body.[1]

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With time, the increased IOP will lead to loss of the inner retinal nerve cells, the retinal ganglion cells,[2–4] and therefore the aim of glaucoma treatment is reduction of the IOP.

The most common glaucoma treatment comprises pressure-lowering eye drops.[5] The commercially available eye drops consist of prostaglandin analogues, beta-blockers, alpha-2-receptor-agonists, and muscarinic agonists.[4] However, a common complication of the chronic use of anti-glaucomatous eye drops is ocular surface disease, which often leads to decreased quality of life and impaired compliance in patients with glaucoma.[6]

Ocular surface disease is caused by increased tear osmolarity, the accumulation of inflammatory cells, disruption of the ocular surface, and alterations in the tear film.[7–9]

The pathogenesis of ocular surface disease has increasingly been ascribed to damage of the conjunctival goblet cells.[10] The conjunctival goblet cells contribute to the immune system of the ocular surface and produce mucins, MUC5AC in particular, which is an important component of the tear film.[11]

The tear film is composed of three layers (Figure 1): A superficial lipid layer originating from the meibomian gland; a middle aqueous layer containing water, electrolytes, proteins, peptides, and glycopeptides; and the innermost

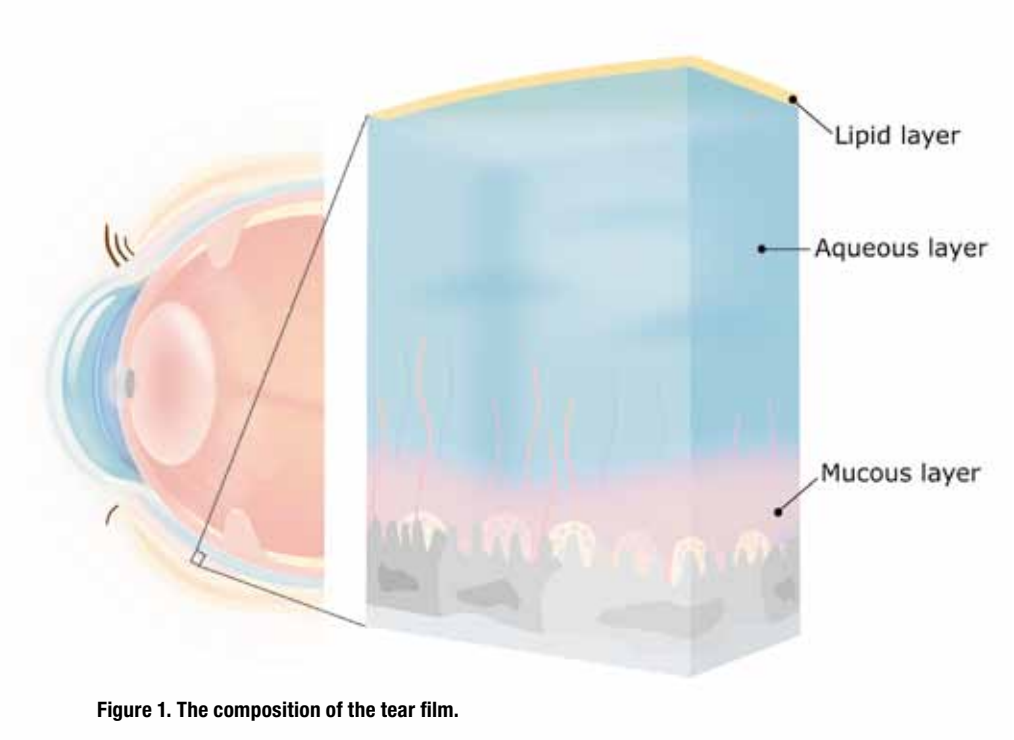

Figure 1. The composition of the tear film.

layer of mucins.[11] The mucin layer is crucial for the tear film stability as well as for providing a smooth refractive surface and lubrication of the cornea.[11–14]

The emerging literature highlights the adverse effects of anti-glaucomatous eye drops on the conjunctival goblet cells.[15–17] In addition to the impact of the active compound on the goblet cells, focus has increasingly shifted to the preservatives contained in the eye drops as well as the vehicles.[16–18] In particular, preservatives are damaging to the ocular surface.[15,18] The most commonly used preservative is benzalkonium chloride (BAK), which is present in more than 70% of preservative-containing eye drops.[19]

Based on significant evidence of the negative impact of preservatives on the conjunctival goblet cells,[15,20–22] formulations containing the active compound only, known as preservative-free anti-glaucomatous eye drops, have been introduced.[17,18,23]

Studies investigating the efficacy of preservative-free solutions have shown promising results in terms of sparing the goblet cells and preventing the development of ocular surface disease;[17,18,24] however, the majority of anti-glaucoma drops still contain preservatives.[15] In addition to preservatives, the impact of vehicle components and bottle designs on efficacy, adverse effects, and adherence are yet to be discovered.[17,23,25]

The majority of patients achieve reduction of the IOP by anti-glaucomatous eye drops, but a significant number of patients, even with maximal IOP-lowering eyedrops and/or laser treatment, continue to lose visual field.[26] In this context, filtration surgery is indicated,[4] with trabeculectomy being the most successful procedure.[27,28] Despite the fact that trabeculectomy is an effective treatment, it is also an invasive procedure, and the amount of surgical failure is significant.[29] In this context, goblet cell density has been proposed as a predictor of surgical outcome.[30,31] Hence, maintenance of goblet cells may

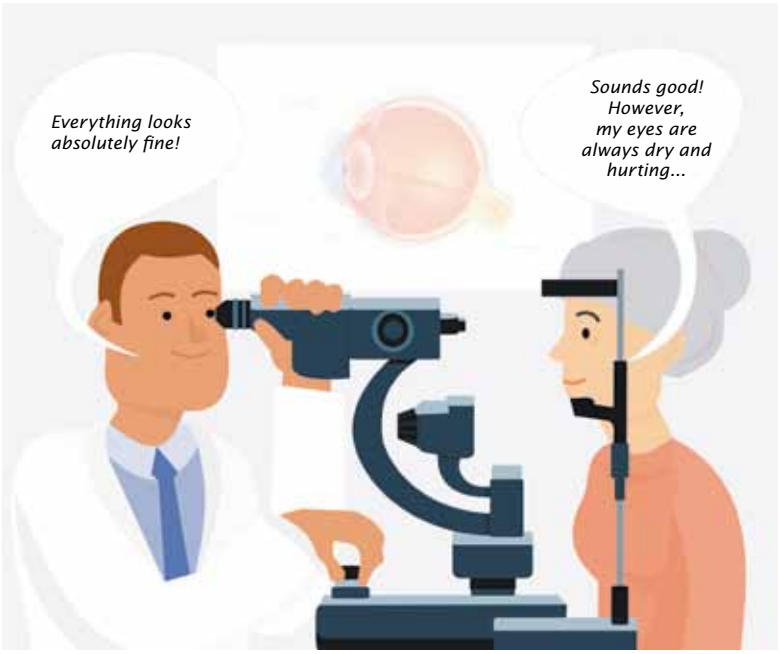

Figure 2. Decreased quality of life among glaucoma patients with ocular surface disease.

not only increase patient quality of life but also increase surgery outcome in patients in need of a filtering operation.

Anti-glaucomatous eye drops

The impact of anti-glaucomatous eye drops on goblet cells depends on multiple factors, including the active component, vehicle, and preservatives.

Of the available active components, there is robust evidence that prostaglandin analogues spare the goblet cells the most,[16,17,23,32,33] and it has even been argued that applying prostaglandin analogues will initially increase the goblet cell density.[17]

On the other hand, the existing literature suggests that other anti-glaucomatous eye drops cause more damage to the goblet cells. Among these, beta-blockers with and without preservatives[16,33] cause damage to the goblet cells. Moreover, a comparison study between a preservative-free beta-blocker and preservative-containing prostaglandin analogues found a significantly greater loss of goblet cell density in the former compared to the different types of preservative-containing prostaglandin analogues.[16] It is worth mentioning that one study has opposing results and concluded that 12-month treatment with a preservative-free beta-blocker does not cause decreased goblet cell density.[24] In line with this, we wish to emphasize that despite the fact that the negative effects of beta-blockers on the conjunctival goblet cells have been demonstrated, the literature is sparse and results are not unanimous.

Studies involving patients treated with alpha-2-adrenergic agonists have also reported a decrease in goblet cell density.[32,33] In line with this, alpha-2-adrenergic agonists have furthermore been shown to damage goblet cells more compared to prostaglandin analogues.[32,33]

The effect of the muscarinic agonist, pilocarpine, on goblet cells has also been investigated.[33] In this context, one study has suggested that pilocarpine is less damaging compared to beta-blockers but is more harmful towards goblet cells compared to both prostaglandin analogues and alpha-2-adrenergic agonists.[33]

In addition to the active ingredients, vehicle factors such as pH, viscosity, drop size, and buffer capacity are obvious factors that may impact the ocular surface. In this context, the literature has shown that these vehicle factors differ according to the specific eye drops, in particular, between original and generic ophthalmic solutions.[34]

Emerging concerns have been raised regarding preservatives in anti-glaucomatous eye drops. Preservatives are added to prevent contamination after the container has been opened, and their presence is thought to enhance penetration of the active ingredient.[15] Even so, the negative impact of preservatives in eye drops is evident. [15,35–38] To our knowledge, the preservatives added to ophthalmic solutions include BAK, polyquaternium, purite, and benzododecinium bromide.[16,33,39] Despite of the different possibilities in preservative selection, BAK is by far the most common in ophthalmic solutions.[19] This may be because of its excellent antimicrobial preservation, which, allegedly as the only preservative, includes inhibition of the microorganism Staphylococcus aureus, a common skin bacteria that is easily transferred from the skin to the eye drops container and finally to the conjunctival surface.[40] Even so, the toxicity of BAK to the eye structures has been reported since the 1940s.[41] The literature has found that symptoms of ocular surface disease are proportionally related to the difficulty of glaucoma and to the BAK exposure.[42] Additionally, BAK causes decreased vitality of the corneal epithelia, enhanced the inflammatory response, and increaseds epithelial apoptosis[43] as well as decreased mucin production.[44]

Comparing BAK to other existing preservatives, the odds ratio of the ocular surface disease score index is three times higher for patients

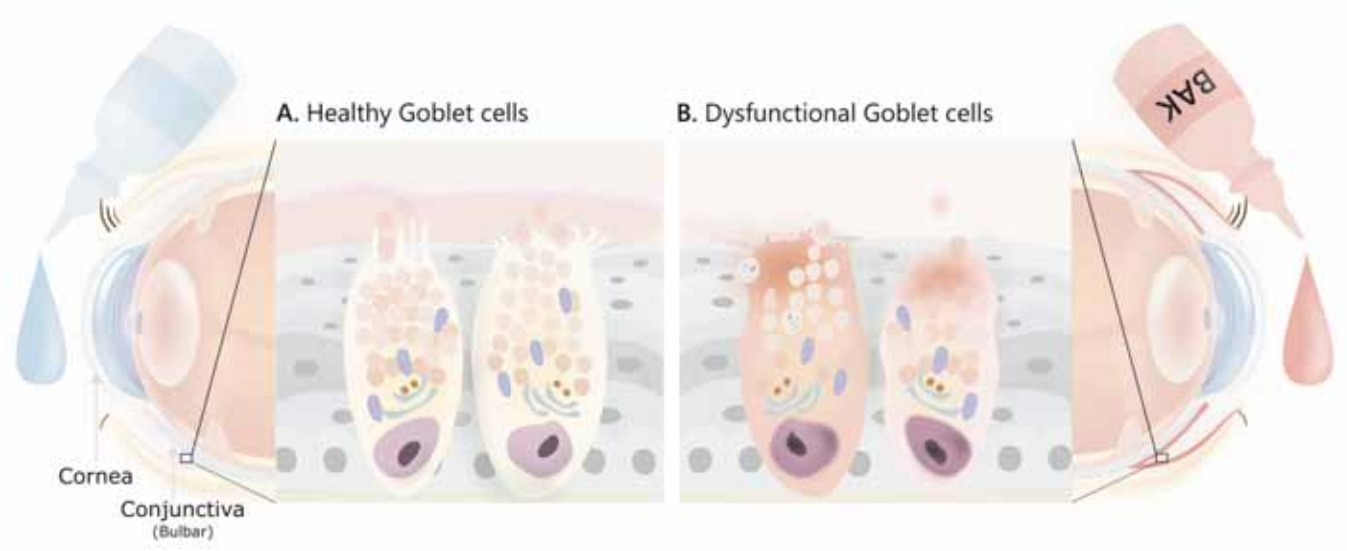

Figure 3. A) Healthy conjunctival goblet cells following the application of non-preserved eye drops. B) Toxic effect of benzalkonium chloride with impaired conjunctival goblet cells.

treated with BAK-containing anti-glaucomatous eye drops compared to purite-containing eye drops.[45] The purite-containing alpha-2-adrenergic agonist, brimonidine, is better tolerated following 12 months of treatment compared to treatment with BAK-containing brimonidine.[46] Furthermore, polyquaternium has been suggested to cause less damage to the goblet cells compared to BAK.[22,39,47]

Even though the literature on the available preservatives and their impact on conjunctival goblet cells is sparse, it is clear that BAK exhibits significant toxic effects on the ocular surface, which should be considered when treating patients with glaucoma. The damaging effects of BAK is illustrated in Figure 3.

Goblet cells and trabeculectomy

It is well-known that the efficacy of anti-glaucomatous eye drops lessens over time, and a great number of patients require more than one type of eye drops to control the IOP following 2 years of treatment.[48] Despite the overall benefits of pressure-lowering anti-glaucomatous eye drops, a significant number of patients will eventually need surgical intervention, most often a trabeculectomy. The trabeculectomy results in a reservoir of aqueous liquid underneath the conjunctiva, denoted as a filtering bleb.[49]

As filtration surgeries are invasive procedures, which imply significant complications, a predictor of the result would be of significant importance. In this context, the emerging literature has found that goblet cell density prior to surgical intervention correlates with successful outcome, defined as significantly lower IOP 12 months following surgery.[49–51]

Additionally, it has been proposed that the goblet cell density of filtering blebs following trabeculectomy differs between functioning and non-functioning filtering blebs.[52] Functioning filtering blebs display a specific type of cell with similar characteristics to goblet cells. The goblet-like cells are described as atypical goblet cells with no or limited staining of the gel-forming mucin, MUC5AC. The cells are thought to facilitate the transportation of the aqueous liquid and thereby lower the IOP.[52] Meanwhile, the atypical goblet cells are not found in non-functioning blebs, which may partly explain surgical failure.

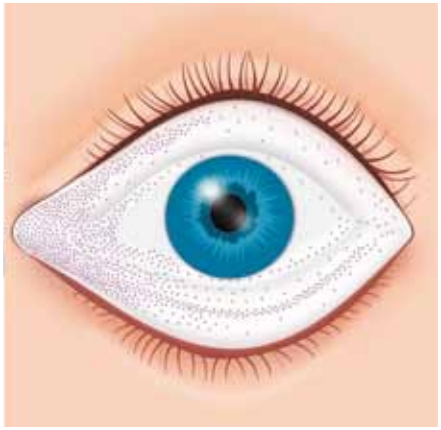

Figure 4. Goblet cells.

While goblet cells have been proposed as a predictor of successful surgical outcome, inflammation of the conjunctiva has additionally been correlated to surgical failure.[51] Thus, dendritic cells, which are antigen-presenting cells that populate the ocular surface and modulate the immune response toward local stimuli, display a significant correlation to surgical outcome.[51] As conjunctival inflammation possibly results in high dendritic cell density and low goblet cell density, there may be a connection between conjunctival inflammation, the presence of dendritic cells, low goblet cell density, and failure of trabeculectomy.[51]

Thoughts on the future

The existing literature imply that prostaglandin analogues are the better choice of treatment in terms of sparing the goblet cells and preventing the adverse effects of anti-glaucomatous eye drops. However, we wish to underline that the number of studies is sparse and that further evidence is needed to clarify the impact of anti-glaucomatous eye drops on conjunctival goblet cells.[16,17,23,32,33]

BAK was previously considered the best choice of preservative because of its potent antimicrobial and weakly allergenic properties.[15] However, the harmful effect of BAK has become evident.[15,18,45] Meanwhile, other preservatives, such as purite and polyquaternium, have been compared to BAK and found superior in terms of preventing ocular surface disease. For this reason, we suggest a paradigm shift with much less or no involvement of BAK in anti-glaucomatous eye drops by either applying other preservatives to the ophthalmic solutions or even better, leaving preservatives out of anti-glaucomatous eye drops.

Multiple studies agree that high goblet cell density prior to surgical intervention is important for the surgical outcome of trabeculectomy.[50,51,53] Trabeculectomy is usually the last treatment option, and the majority of patients have been in long-term treatment with anti-glaucomatous eye drops before this. Thus, these patients are at high risk of surgical failure, as their conjunctival goblet cell density may have been harmed by the anti-glaucomatous eye drops. Meanwhile, treatments including eye drops containing sodium hyaluronate or diquafosol that increase goblet cell density exist, and patients about to undergo trabeculectomy may benefit from preoperative treatment with such agents.[54,55]

Finally, it has been suggested that atypical goblet cells facilitate the transportation of aqueous liquid through the functioning filtering bleb.[52] As goblet cell density is most often higher in the nasal conjunctiva (Figure 4)[56] we suggest that locating the filtering bleb towards the nasal part of the superior conjunctiva may increase surgical success.

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