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REVIEW ARTICLE

Topical glaucoma medications – Possible implications on the meibomian glands

Fredrik Fineide[1,2,3,4] | **Morten Magnø**[1,5,6,7] | **Kristian Dahlø**[8] | **Miriam Kolko**[9,10] | **Steffen Heegaard**[10] | **Jelle Vehof**[11,12,13] | **Tor Paaske Utheim**[1,2,5,6,8,13,14,15,16,17,18,19,20,21,22,23]

Correspondence
Fredrik Fineide, Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway.
Email: fre_fin@hotmail.com

Abstract

One of the most common causes of blindness on a global scale is glaucoma. There is a strong association between glaucoma and increased intraocular pressure (IOP). Because of this, adequate IOP-lowering is the most important treatment strategy, mostly through topical eyedrops. Well-functioning meibomian glands are paramount for maintaining a stable tear film, and their dysfunction is the most common cause of dry eye disease. There is a growing concern that both topical glaucoma medications themselves and their added preservatives damage the meibomian glands, and consequently, the ocular surface. Preserved topical glaucoma medications appear to cause dysfunction and atrophy of the meibomian glands. Upon comparison, preserved formulations caused more symptoms of dry eye, tear film instability, inflammatory changes and meibomian gland dropout than the preservative-free counterpart. However, although seemingly less detrimental, unpreserved alternatives may diminish glandular efficacy, and, depending on the active ingredient, lead to glandular death. This negatively impacts quality of life, adherence to treatment regimens and prognosis. In this review, we explore the available evidence regarding the effects of IOP-lowering eye drops on the meibomian glands.

KEYWORDS

dry eye disease, glaucoma, meibography, meibomian gland dysfunction, ocular surface, topical medications

1 | INTRODUCTION

The ciliary body produces the aqueous humour of the eye, which is mainly drained through the trabecular meshwork (Weinreb et al., 2014). The intraocular pressure (IOP) has a physiological range of 10–21 mmHg and is a result of the pressure gradient between the production and elimination of aqueous humour (Negri et al., 2019). The leading cause of irreversible blindness worldwide, glaucoma, is a progressive and chronic optic neuropathy often associated with elevated IOP (Weinreb et al., 2014). The mainstay treatment of glaucoma is topical eye drops lowering the IOP (McKinnon et al., 2008; Pflugfelder & Baudouin, 2011). The main classes of topical medications are currently commercially available and their mechanisms of action are summarised in Table S1.

The ocular tear film is made up of an inner mucoaqueous layer mainly produced by the lacrimal glands and ocular surface goblet cells and an outer lipid layer mainly consisting of meibum secreted by the meibomian glands (MGs) (Willcox et al., 2017). The MGs are modified sebaceous glands distributed along the upper and lower eyelids, secreting meibum anterior to the mucocutaneous junction at the lid margin (Knop et al., 2011). The tear film lipid layer is further divided into a nonpolar outer layer and an inner amphiphilic layer (McCulley & Shine, 1997). The ocular tear film nourishes, lubricates, and protects the ocular surface from external harmful molecules, while the tear film lipid layer lowers the surface tension and facilitates the even spreading of the tear film as well as halters evaporation of the deeper mucoaqueous layer and thus prevents dehydration of the ocular surface (Willcox et al., 2017).

For affiliations refer to page 746.

Meibomian gland dysfunction (MGD) is the most common cause of dry eye disease (DED) (Lemp et al., 2012; Rabensteiner et al., 2018; Shimazaki et al., 1995). Dry eye disease affects a large proportion of the adult population and carries with it substantial humanistic and economic burdens (Craig et al., 2017; Morthen et al., 2021, 2022, 2023; Stapleton et al., 2017). We recently conducted a review study evaluating the effects of topical glaucoma medications on the ocular surface (Fineide et al., 2022). The purpose of the present review is to assess the impact of IOP-lowering medications on the MGs specifically because their proper function is necessary for maintaining a stable tear film.

2 | METHODS

PubMed and EMBASE were searched with the keywords ((*"dry eye disease" OR "meibomian gland dysfunction" OR "meibography") AND "topical medications") OR ("eye drops" AND "glaucoma"*) on May 12th of 2023. The searches yielded 5212 and 4455 results, respectively.

Inclusion criteria were (1) full-text access, (2) English language, (3) original articles assessing topical glaucoma medications, (4) quantitative results and outcome measures regarding the MGs, (5) experiments performed on either human or animal cultured MG epithelial cells in the case of in vitro studies. Exclusion criteria were abstract only, non-English language and lack of relevance. Conference abstracts, letters to the editor and review articles were not included. The process is illustrated in Figure 1.

Articles of potential interest were evaluated for relevance, first based on the title, second on the abstract, and third on the full text. In addition, a thorough review of the reference sections of the included articles was performed. Finally, 24 research articles were included.

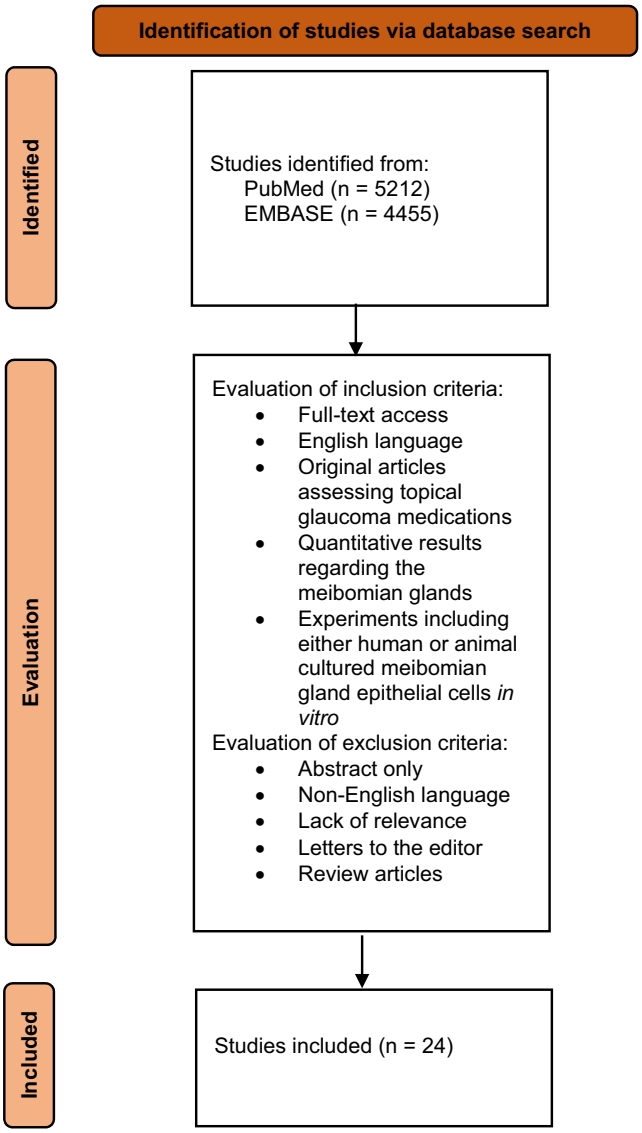

FIGURE 1 Flow diagram representing the search and inclusion process.

3 | DESIGN OF INCLUDED STUDIES

The American Academy of Ophthalmology recently adopted the Scottish Intercollegiate Guideline Network (SIGN) rating regarding the strength of evidence, presented in Table S2 (Akpek et al., 2019). The study designs of the included studies are summarised in Table 1. All included clinical studies fall within level II. There are no randomised trials included and only two prospective trials (Agnifili et al., 2019; Guo et al., 2020). However, several well-designed in vitro studies have been performed (Han et al., 2018, 2020; Jiang et al., 2022; Kam et al., 2016; Rath et al., 2019; Zhang et al., 2017).

4 | RESULTS

4.1 | Effect of preserved topical glaucoma medications on the meibomian glands

An overview of all reviewed clinical studies examining the effects of topical medications on the MGs is presented in Table 2. The impact of topical medications on ocular surface clinical parameters is summarised in Table 3.

Of the 18 clinical studies included, 12 studies used topical medications including preservatives (see Table 2). The most commonly used preservative, benzalkonium chloride (BAC), is used in concentrations from 0.004% to 0.025% in various topical ophthalmic preparations (Baudouin et al., 2010). This preservative has been demonstrated to decrease the proliferation of human MG cells in concentrations as low as 0.1 μg/mL (0.00001%) and reduce cell viability after 10 minutes of exposure to concentrations as low as 50 μg/mL (Baudouin et al., 2010; Rath et al., 2019).

Of the 12 clinical studies evaluating preservative containing (PC) medications (Agnifili et al., 2019; Arita et al., 2012a, 2012b; Cho et al., 2018; Guarnieri et al., 2020; Kim et al., 2018; Lee et al., 2018; Mocan et al., 2016; Portela et al., 2018; Samico et al., 2023; Uzunosmanoglu et al., 2016; Wong et al., 2018), two are not included in Table 3 due to applicability (Agnifili et al., 2019; Guarnieri et al., 2020). Eight studies evaluated dry eye symptoms (Arita et al., 2012a, 2012b; Cho et al., 2018; Lee et al., 2018; Mocan et al., 2016; Portela et al., 2018; Samico et al., 2023; Uzunosmanoglu et al., 2016; Wong et al., 2018), six of these report increased symptomatic

TABLE 1 Study design of included clinical studies.

Prospective, randomised trials, $n=0$	
Prospective, non-randomised trials, $n=2$	Agnifili et al. (2019), Guo et al. (2020)
Case control, $n=1$	Ha et al. (2019)
Cross-sectional, $n=15$	Agnifili et al. (2013, 2018), Arita et al. (2012a, 2012b), Cho et al. (2018), Guarnieri et al. (2020), Kim et al. (2018), Lee et al. (2018, 2019), Mocan et al. (2016), Portela et al. (2018), Samico et al. (2023), Soriano et al. (2021), Uzunosmanoglu et al. (2016), Wong et al. (2018)
In vitro studies, $n=6$	Han et al. (2018, 2020), Jiang et al. (2022), Kam et al. (2016), Rath et al. (2019), Zhang et al. (2017)

burden among patients compared to controls (Arita et al., 2012a, 2012b; Lee et al., 2018; Mocan et al., 2016; Portela et al., 2018; Samico et al., 2023; Uzunosmanoglu et al., 2016), one found no difference (Wong et al., 2018), and one study found less dry eye symptoms among the treated cohort (Cho et al., 2018). Seven studies examined tear film break-up time with fluorescein (Arita et al., 2012a, 2012b; Kim et al., 2018; Lee et al., 2018; Mocan et al., 2016; Portela et al., 2018; Uzunosmanoglu et al., 2016), six of which found decreased tear film stability (Arita et al., 2012a, 2012b; Kim et al., 2018; Lee et al., 2018; Mocan et al., 2016; Uzunosmanoglu et al., 2016), and one reported no change (Portela et al., 2018). Four studies performed non-invasive break-up time (Cho et al., 2018; Portela et al., 2018; Samico et al., 2023; Wong et al., 2018), with half reporting a reduction of tear film stability (Portela et al., 2018; Wong et al., 2018), and the other half no change (Cho et al., 2018; Samico et al., 2023). Four (Arita et al., 2012a, 2012b; Cho et al., 2018; Lee et al., 2018) out of five (Arita et al., 2012a, 2012b; Cho et al., 2018; Lee et al., 2018; Wong et al., 2018) studies found worsened meibum quality or expressibility, and five out of five increased number of lid margin abnormalities (Arita et al., 2012a, 2012b; Kim et al., 2018; Lee et al., 2018; Wong et al., 2018). Finally, among the seven studies quantifying the MG area (Arita et al., 2012a, 2012b; Cho et al., 2018; Lee et al., 2018; Portela et al., 2018; Samico et al., 2023; Wong et al., 2018), five reported a greater degree of atrophy among treated patients compared to controls (Arita et al., 2012a, 2012b; Cho et al., 2018; Lee et al., 2018; Portela et al., 2018), while one found no change (Wong et al., 2018). One study grouped patients according to administering 1–2 (group 1) or 3–4 (group 2) preserved topical glaucoma medications (Samico et al., 2023). Unexpectedly, the degree of MG dropout was higher among the patients in group 1.

4.2 | Effect of preservative-free topical glaucoma medications on the meibomian glands

The effects of preservative-free (PF) topical glaucoma medications on the MGs were evaluated in six clinical studies (Agnifili et al., 2013, 2018; Guo et al., 2020; Ha et al., 2019; Lee et al., 2019; Soriano et al., 2021) and five in vitro studies (Han et al., 2018, 2020; Jiang et al., 2022; Kam et al., 2016; Zhang et al., 2017). The impact of different classes of PF topical glaucoma medications on the MGs are summarised in Figure 2 and Table 4. Only three studies directly compared patients treated with PF medications to controls (Agnifili et al., 2013, 2018; Ha et al., 2019). One (Agnifili et al., 2018) of three (Agnifili et al., 2013, 2018; Ha et al., 2019) included studies demonstrated increased dry eye symptoms among patients treated with PF medications when compared to healthy controls. One (Agnifili et al., 2018) of two (Agnifili et al., 2018; Ha et al., 2019) studies found diminished tear film stability, and one out of one thickened meibum (Ha et al., 2019). One study compared lid margin abnormalities and found no difference (Ha et al., 2019). The same study examined MG atrophy, which was more profound in patients treated with PF medications compared to healthy controls.

An experimental study reported that pilocarpine and timolol caused a dose-dependent decrease in the survival of immortalised human MG epithelial cells cultured at various concentrations of the drugs for up to 7 days (Zhang et al., 2017). The concentrations applied clinically had detrimental effects; the concentrations reported to be present within the palpebral conjunctiva did not produce these results. However, the concentrations reaching the MGs might be higher, considering the possibility of drug penetration through the glandular orifices at the lid margin.

The adrenergic α2 agonist brimonidine proved detrimental to the survival of human MG epithelial cells in vitro when exposed to concentrations of 500 μg/mL (Han et al., 2018). Following topical administration, the concentration present at the conjunctiva is believed to be 50 μg/mL, which was not shown to damage the cultured cells. A dose-dependent decrease in Akt signalling and proliferation as well as a dose-dependent differentiation with increasing levels of the lysosome, phospholipids and neutral lipids was reported at that concentration, thus some positive effects could be seen as well.

Furthermore, a recent in vitro study conducted by the same team found that the carbonic anhydrase inhibitor dorzolamide stimulates the differentiation and inhibits the proliferation and Akt signalling pathway of immortalised human MG epithelial cells when exposed to 500 μg/mL of this inhibitor (Han et al., 2020). The authors postulated that 50 μg/mL dorzolamide in vitro is approximately equal to the in vivo concentration reaching the MGs. Neither concentrations of 50 nor 5 μg/mL had any effect on proliferation or differentiation. Interestingly, both dorzolamide and brimonidine seemed to increase the expression of light chain 3A, an autophagosome biomarker, and the amount of phospholipids (Han et al., 2018, 2020). However, only brimonidine caused an upregulation of lysosomal-associated membrane protein 1 (lysosomal biomarker) and sterol regulatory element-binding protein 1 (regulates lipogenesis) at 500 μg/mL as well as neutral lipids at 500 and 50 μg/mL.

TABLE 2 Clinical studies examining the effects of topical medications on the meibomian glands.

Study	Population	Study design	Treatment[a]	Meibographic modality/grading system	Impact on meibomian glands
Preserved formulations					
Arita et al. (2012a, 2012b)	162 glaucoma patients 75 controls	Cross-sectional, age- and sex-matched controls	Various formulations: 160 preserved with BAC, 2 preserved with SofZia. Same medication for >12 months. Mean duration of treatment for groups 1–3 were 7.2, 8.0 and 6.8 years, respectively	Non-contact meibography/ Meiboscore by Arita et al.	Greater MG dropout among glaucoma patients than controls. No difference in meiboscore with use of more eye drops. Glandular changes initiated at the orifice
Arita et al. (2012a, 2012b)	31 glaucoma patients receiving unilateral treatment	Cross-sectional, contralateral eye as control	PGA monotherapy (13); β-blocker monotherapy (8); multiple treatments (10). All preserved with BAC. Patients treated for >12 months, mean duration of treatment 7.9 years	Non-contact meibography/ Meiboscore by Arita et al.	Greater MG dropout in the treated eye for both PGA and β-blocker. The morphologic changes appeared to originate at the orifice
Mocan et al. (2016)	70 glaucoma patients 45 controls	Cross-sectional, age-matched controls	PGA monotherapy (25); PGA fixed or unfixed combination (21); non-PGA (24). Patients treated for >12 months	Meibography not performed	PGA therapy was tied to more MGD; 92% had MGD in the monotherapy and 91% in combination group, compared to 58% in non-PGA group. None of the controls had signs of MGD
Uzunosmanoglu et al. (2016)	70 glaucoma patients 45 controls. Same population as Mocan et al.	Cross-sectional, age-matched controls	PGA (46); β-blocker (40); CAI (14); α2-adrenergic agonist (5); PGA monotherapy (25); monotherapy (34); dual therapy (23); triple therapy (11); quadruple therapy (2). Mean duration of glaucoma was 12 years, duration of treatment not described	Meibography not performed	MGD was found in 80% of those with glaucoma, of which 67% had obstructive MGD and 13% had atrophic MGD. None of the controls had signs of MGD
Cho et al. (2018)	85 glaucoma patients 30 controls	Cross-sectional case–control, sex-, but not age-matched (control group significantly younger)	Topical antihypertensives, not further specified. Treatment duration not described	LipiView II/Meiboscale by Pult and Riede-Pult, manual and automatic segmentation	Greater MG dropout among glaucoma patients than controls for subjective Meiboscale and manually drawn MG loss ratio, but not for the automatically measured MG density ratio. Amount and duration of ocular antihypertensive use were correlated with the degree of MG dropout
Kim et al. (2018)	50 glaucoma patients 40 controls	Cross-sectional, age-matched controls	Various topical antihypertensives. Patients treated for >6 months, mean duration of treatment 27.4 months	Meibography not performed	MGD was more prevalent for patients with glaucoma (82% vs. 52.5%). Higher MGD staging was tied to more severe glaucoma and higher Marx line score

TABLE 2 (Continued)

Study	Population	Study design	Treatment[a]	Meibographic modality/grading system	Impact on meibomian glands
Lee et al. (2018)	45 normal-tension glaucoma patients 40 controls	Cross-sectional, age- and sex-matched controls	All PGA monotherapy, all containing BAC. Patients treated for >12 months, mean duration of treatment 42.93 months	Keratograph 5M/Meiboscore by Arita et al	MG dropout was worse in glaucoma group than for controls. Worse MG parameters were tied to lower compliance with treatment
Portela et al. (2018)	30 glaucoma patients 27 cataract patients as controls	Cross-sectional, age- and sex-matched controls	Observational study: Patients treated for >6 months	Keratograph 5M /Meiboscale by Pult and Riede-Pult	MG dropout was worse in glaucoma group than for controls.
Wong et al. (2018)	33 glaucoma patients receiving unilateral treatment	Cross-sectional, contralateral eye as control	PGA monotherapy (22); timolol (1); PGA+ β-blocker (3); bimatoprost+brimonidine+timolol (1); bimatoprost+dorzolamide+timolol (3); brimonidine+timolol (2); dorzolamide+timolol (1). Patients treated for >6 months, mean duration of treatment 5.3 years	Keratograph 5M /Meiboscale by Pult and Riede-Pult	No differences in MG dropout were found between treated and untreated eyes
Agnifili et al. (2019)	64 glaucoma patients	Prospective, age- and sex-matched participants	38 patients received trabeculectomy and 26 patients were medically treated. Preservative status unknown. Treatment was unchanged for 2 months, mean treatment duration was 68.2 and 63.7 months for surgical and medical group, respectively	IVCM/MG density and MG inhomogeneity	There were no differences at baseline. At six months, the surgical group presented with improved IVCM and impression cytology parameters as well as superior OSDI
Guarnieri et al. (2020)	168 glaucoma patients 41 controls	Cross-sectional, age-matched controls	147 patients received medical treatment; 21 patients were surgically treated. Patients treated for >12 months	Keratograph 5M /degree of MG dropout calculated for the upper eyelid using ImageJ	OSDI was correlated with MG dropout and number of drops instilled on a daily basis
Samico et al. (2023)	27 glaucoma patients	Cross-sectional	Group 1: treated with 1–2 medications; Group 2: treated with 3–4 medications. All preserved, type not described. Patients treated for >6 months	Keratograph 5M /degree of glandular atrophy graded in thirds	MG dropout was higher in group 1
Preservative free formulations					
Agnifili et al. (2013)	80 glaucoma patients 20 controls	Cross-sectional, age- and sex-matched controls	Patients grouped 1–3 according to the number of topical medications. Patients treated for >18 months. Comparing PC and PF-PGAs and β-blockers	Contact meibography and IVCM / MG dropout graded on a three-point scale ranging from no dropout, less than 50%, and more than 50% atrophy, MAD, MAA, InI, InAW	MG dropout was worse for patients with glaucoma. IVCM parameters were worse in groups 2 and 3 than for controls. PC formulations resulted in more morphological changes than PF. PC-PGA had worse IVCM parameters than PF-PGA and PC β-blockers

(Continues)

TABLE 2 (Continued)

Study	Population	Study design	Treatment[a]	Meibographic modality/grading system	Impact on meibomian glands
Agnifili et al. (2018)	75 glaucoma patients 15 controls	Cross-sectional, age- and sex-matched controls	L+T unfixed combination (15), LTFC (15), TTFC (15), BTFC (15) and PF-BTFC (15). Patients treated for >12 months	IVCM/MAD, MAA, InI, InAW	IVCM parameters were worse in L+T compared to PTFCs and PF-BTFC. PF formulations showed better IVCM parameters than PC products
Ha et al. (2019)	80 glaucoma patients 40 controls	Case control, age- and sex-matched controls	PC-PGA (42); PF-PGA(38). Treatment naïve patients, 12-month follow-up	Keratograph 5M/degree of MG dropout calculated on the upper eyelid using ImageJ	The PC group had greater MG dropout from baseline to 12-months follow up than the PF group. Both PC and PF groups showed more dropout than the control group
Lee et al. (2019)	88 glaucoma patients 64 controls	Cross-sectional, age- and sex-matched controls.	23 patients used PF tafluprost for 6 and 24 months; 21 patients used PC tafluprost for 6 and 24 months	LipiView II/Meiboscale by Pult and Riede-Pult and MG dropout rate using ImageJ	The patients with glaucoma had worse MG dropout, but not Meiboscale than controls. At 6 months, MG dropout was worse for the PC group than for the PF group, but there was no difference at 24 months. Medication duration was correlated with worsening MG dropout rate and Meiboscale. Meibomian gland dropout rate among patients who used PF-PGA for 24 months was higher than among patients who used PC-PGA for 6 months (but still lower than PC-PGA at 24 months)
Guo et al. (2020)	46 normal-tension glaucoma patients	Prospective, age- and sex-matched participants	PC latanoprost (14); PC tafluprost (14); PF latanoprost (19); PF tafluprost (20); PC latanoprost + DQS (8); PC tafluprost + DQS (9). Treatment naïve patients, 12-month follow-up	Keratograph 5M/degree of MG dropout calculated using ImageJ	MG dropout worsened from baseline to 9 and 12 months in the PC-PGA group. MG dropout was significantly worse in the PC-PGA group than in the PF-PGA and PC-PGA + DQS groups at 9 and 12 months. No changes in MG parameters were observed in the PF-PGA or PC-PGA + DQS groups
Soriano et al. (2021)	131 glaucomatous patients 92 controls	Cross-sectional, age-matched controls	99 eyes treated with BAC preserved medications and 32 eyes treated with PF medications. Patients treated for >12 months	Keratograph 5M/degree of glandular dropout graded in thirds	Eyes in the treated cohort showed higher dropout of the upper, but not lower eyelid. Preservative status influenced central and temporal Marx line displacement

Note: Keratograph 5M (Oculus, Wetzlar, Germany); LipiView II (Tear Science Inc., Morrisville, North Carolina, USA); Meiboscale by Pult and Riede-Pult (2013); meiboscore by Arita et al. (2008): dropout graded in thirds for each eyelid, summed per eye; ImageJ (Wayne Rasband, National Institute of Health, USA).

Abbreviations: BAC, benzalkonium chloride; BTFC, bimatoprost/timolol fixed combination; CAI, carbonic anhydrase inhibitor; DQS, diquafosol; InAW, inhomogeneity of acinar wall; InI, inhomogeneity of glandular interstice; IVCM, in vivo confocal microscopy; L+T, latanoprost+timolol unfixed combination; LTFC, latanoprost/timolol fixed combination; MAA, mean acinar area; MAD, mean acinar density; MG, meibomian gland; MGD, meibomian gland dysfunction; OSDI, ocular surface disease index; PC, preservative containing; PF-BTFC, preservative free bimatoprost/timolol fixed combination; PGA, prostaglandin analogue; PTFC, prostaglandin/timolol fixed combination; TTFC, travoprost/timolol fixed combination.

[a]Number of patients included in each group presented in parenthesis.

TABLE 3 Impact of topical glaucoma medications on the ocular surface and meibomian gland parameters.

Study	Symptom score	Tear film break-up time	Non-invasive break-up time	Bulbar redness/ limbal redness	Ocular surface staining	Schirmer test	Meibomian gland expressibility/meibum quality	Lid margin abnormalities	Meibomian gland area
Studies including preserved formulations only									
Arita et al. (2012a, 2012b)	↑	↓	Na	na	↑	↓	↑	↑	↓
Arita et al. (2012a, 2012b)	na	↓	na	na	↑	↓	↑	↑	↓
Mocan et al. (2016)	↑	↓	na	na	↑	↓	na	na	na
Uzunosmanoglu et al. (2016)	↑	↓	na	na	↑	↓	na	na	na
Cho et al. (2018)	↓	na	0	0	0	0	↑	na	↓
Kim et al. (2018)	na	↓	na	na	0	na	na	↑	na
Lee et al. (2018)	↑	↓	na	na	↑	↓	↑	↑	↓
Portela et al. (2018)	↑	0	↓	↑	↑	na	na	na	↓
Wong et al. (2018)	0	na	↓	↑	0	↓	0	↑	0
Samico et al., 2023)§	↑	na	0	0	0	na	na	na	↑
Studies including preservative-free formulations (all patients or PC vs. controls)									
Agnifili et al. (2013)	↑	↓	na	na	↑	↓	↑	na	↓
Agnifili et al. (2018)	↑	↓	na	na	↑	↓	na	na	na
Ha et al. (2019)	↑	↓	na	na	↑	0	↑	↑	↓
Lee et al. (2019)	↑	↓	na	na	↑	↓	↑	↑	0
Guo et al. (2020)	na	na	na	na	na	na	na	na	na
Soriano et al. (2021)	0	na	na	na	0	na	↑	0	↑
Studies including preservative-free formulations (PC vs. PF)									
Agnifili et al. (2013)	↑*	0*	na	na	0*	0*	0*	na	0*
Agnifili et al. (2018)	↑*	↓*	na	na	↑*	↓*	na	na	na
Ha et al. (2019)	↑*	↓*	na	na	↑*	0*	↑*	↑*	↓*
Lee et al. (2019)	0*	↓*	na	na	0*	0*	↑*	↑*	↓*
Guo et al. (2020)	na	na	na	na	na	na	na	na	↓*
Soriano et al. (2021)	0*	na	na	na	0*	na	0*	↑*	0*

(Continues)

TABLE 3 (Continued)

Study	Symptom score	Tear film break-up time	Non-invasive break-up time	Bulbar redness/limbal redness	Ocular surface staining	Schirmer test	Meibomian gland expressibility/meibum quality	Lid margin abnormalities	Meibomian gland area
Studies including preservative-free formulations (PF vs. controls)									
Agnifili et al. (2013)	0	?	na	na	↑	↓	?	na	?
Agnifili et al. (2018)	↑	↓	na	na	↑	↓	na	na	na
Ha et al. (2019)	0	0	na	na	↑	0	↑	0	↓
Lee et al. (2019)	na	na	na	na	na	na	na	na	na
Guo et al. (2020)	na	na	na	na	na	na	na	na	na
Soriano et al. (2021)	na	na	na	na	na	na	na	na	na

Note: na, not applicable; PC, preservative containing; PF, preservative free; ↑, significantly increased compared to controls; ↑*, significantly increased compared to preservative free; 0, unchanged compared to controls; 0*, unchanged compared to preservative free; ↓, significantly decreased compared to controls; ↓*, significantly decreased compared to preservative free;?, unclear; §, results comparing groups using different amount of medications.

Very low concentrations of BAC have been shown to impact the proliferation and cell viability of human MG cells in vitro; this effect seemed to be expedited by the addition of prostaglandin analogues (PGAs), however, PF-PGAs did not affect meibocyte viability (Rath et al., 2019). Conversely, bimatoprost has been found to reduce Akt signalling, potentially affecting the survival, growth, and proliferation of meibocytes (Kam et al., 2016).

Another in vitro study examined the effects of latanoprost on murine MG epithelial cells (Jiang et al., 2022). Increased expression of interleukin (IL)-6, IL-1β, tumour necrosis factor-α (TNF-α), matrix metalloproteinase-9 (MMP-9), chemokine (C-C-motif) ligand-5 (CCL-5) and monocyte chemoattractant protein-1 (MCP-1) were noted in a dose-dependent manner. Moreover, differentiation-related genes associated with adipogenesis were suppressed, indicating an inhibitory effect of latanoprost on lipid production in the meibocytes.

4.3 | Comparing preserved and unpreserved topical glaucoma medications

Preserved formulations were found to cause more dry eye symptoms in three (Agnifili et al., 2013, 2018; Ha et al., 2019) out of five studies (Agnifili et al., 2013, 2018; Ha et al., 2019; Lee et al., 2019; Soriano et al., 2021); to decrease tear film stability to a greater extent in three (Agnifili et al., 2018; Ha et al., 2019; Lee et al., 2019) out of four studies (Agnifili et al., 2013, 2018; Ha et al., 2019; Lee et al., 2019); to worsen meibum quality or expression in two (Ha et al., 2019; Lee et al., 2019) of four studies (Agnifili et al., 2013; Ha et al., 2019; Lee et al., 2019; Soriano et al., 2021); and to increase the amount of lid margin abnormalities in three of the three included studies (Ha et al., 2019; Lee et al., 2019; Soriano et al., 2021). When evaluating the degree of MG dropout, three (Guo et al., 2020; Ha et al., 2019; Lee et al., 2019) out of five (Agnifili et al., 2013; Guo et al., 2020; Ha et al., 2019; Lee et al., 2019; Soriano et al., 2021) studies described a greater degree of atrophy resulting from preserved medications when compared to PF alternatives. The degree of MG atrophy was found to be higher among patients who had used PF tafluprost for 24 months than for patients who had used PC tafluprost for 6 months (Lee et al., 2019). The correlation between MG dropout rate and the presence of preservatives was significant only at 6 months. Based on this, the authors speculate that tafluprost is detrimental in itself and that this is exacerbated by BAC.

5 | DISCUSSION

5.1 | Effect of preserved topical glaucoma medications on the meibomian glands

The deleterious effects of topical medications on the ocular surface have been receiving growing attention (Fineide et al., 2022; Kolko et al., 2023). The detrimental

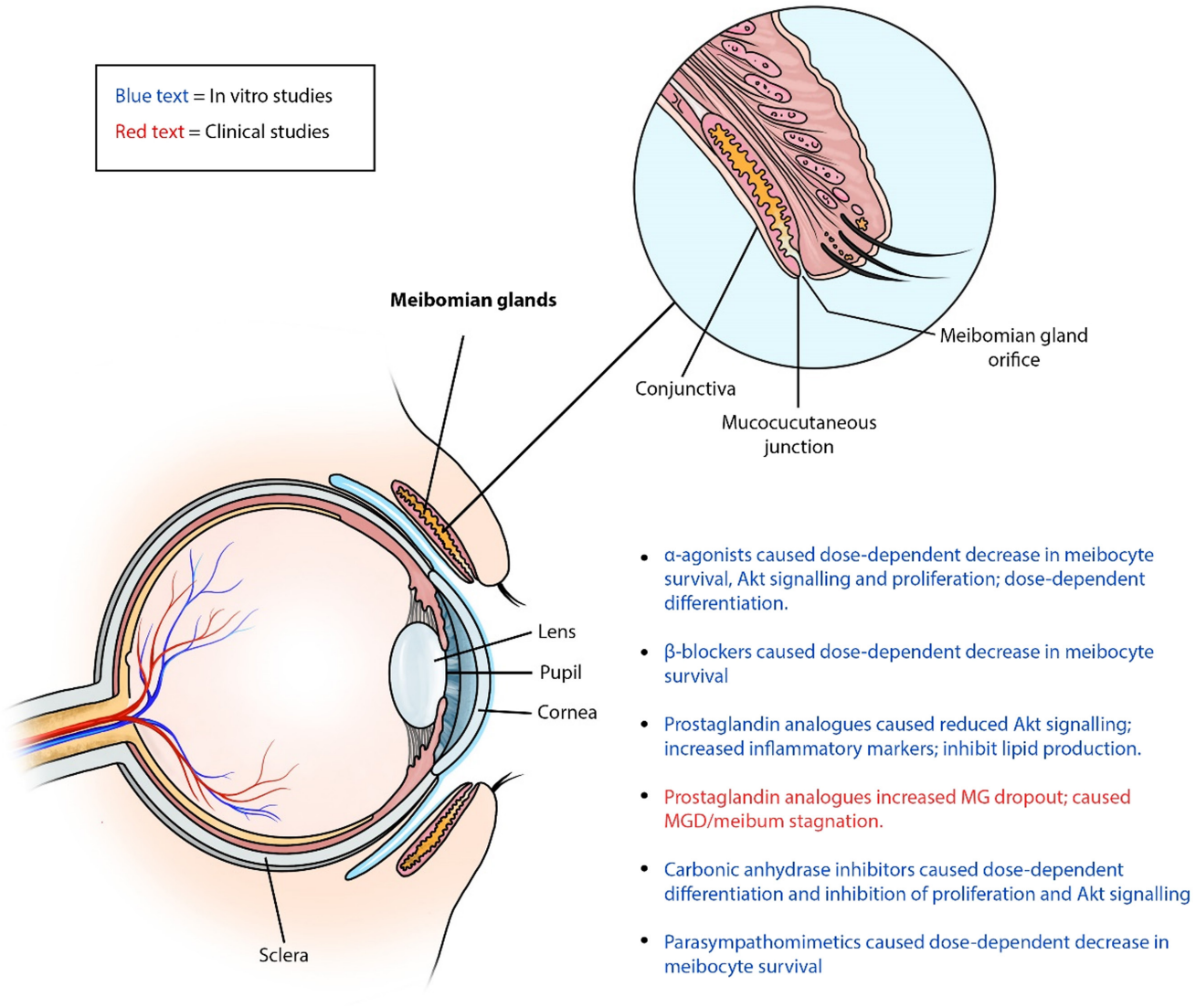

FIGURE 2 Effects of different classes of unpreserved topical glaucoma medications on the meibomian glands and meibocytes. Illustration by Kristin Skårdal.

effects of BAC previously demonstrated on different ocular cell lines in vitro include the MGs, where concentrations far below those included in ocular formulations proved cytotoxic (Rath et al., 2019).

Clinically, PC topical antihypertensives cause signs and symptoms of DED as well as MG dropout. Of the six studies examining this question included herein, five (Arita et al., 2012a, 2012b; Cho et al., 2018; Lee et al., 2018; Portela et al., 2018) found an increased degree of atrophy in treated eyes (one found no difference; Wong et al., 2018), indicating that topical glaucoma medications in combination with preservatives cause MG dropout. Arita et al. noticed that glandular changes among patients treated with topical antihypertensives tended to initiate at the orifice (Arita et al., 2012a, 2012b). Previous studies have described subclinical inflammation of the conjunctiva following preserved topical glaucoma medications (Brandt et al., 1991; Sherwood et al., 1989), as well as increased immunoglobulin E (IgE), mast cells and inflammatory cells (Baudouin et al., 1994; Broadway et al., 1994; Sherwood et al., 1989). Arita and coworkers hypothesised that these findings may represent the induction of a chronic, subclinical allergic state, arguing that the increased lid margin abnormality score is indicative of chronic inflammation, which might precede stagnation of meibum, leading to keratinisation of the glandular orifices and subsequent dropout (Arita et al., 2012a, 2012b). However, none of these studies included patients treated with PF formulations and 191 of a total of 193 included subjects within the two studies received BAC-preserved medications (Arita et al., 2012a, 2012b). Subgroup analysis revealed no differences between patients treated with PGAs or β-blockers (Arita et al., 2012a, 2012b). Compared to untreated control eyes, treatment with PC-PGAs increased ocular surface staining, mean lid margin abnormality scores and mean meibum scores, findings not found in the PC β-blocker subgroup (Arita et al., 2012a, 2012b). Of note, the sample sizes of this subgroup analysis were limited, with 13 in the PC-PGA group and only eight in the PC β-blocker group.

Whether or not the amount and duration of treatment with ocular hypotensives correlate with impact on the MGs has remained unresolved. Seven of the included studies evaluated this (Agnifili et al., 2013; Arita et al., 2012a, 2012b; Cho et al., 2018; Guarnieri et al., 2020; Guo et al., 2020; Ha et al., 2019; Lee et al., 2019). Across

TABLE 4 Impact of different classes of topical glaucoma medications on the meibomian glands or meibocytes.

Topical medication class	Active ingredient	Impact on meibomian glands or meibocytes
α-agonists	Brimonidine (Han et al., 2018)	In vitro: dose-dependent decrease in meibocyte survival, Akt signalling and proliferation; dose-dependent differentiation
β-blockers	Timolol (Zhang et al., 2017)	In vitro: dose-dependent decrease in meibocyte survival
Prostaglandin analogues	Bimatoprost (Kam et al., 2016), latanoprost (Jiang et al., 2022), tafluprost (Lee et al., 2019)	In vitro: reduced Akt signalling (Kam et al., 2016); increased inflammatory markers (Jiang et al., 2022); inhibit lipid production (Jiang et al., 2022) Clinically: increase MG dropout (Ha et al., 2019; Lee et al., 2019); cause MGD/meibum stagnation (Ha et al., 2019)
Carbonic anhydrase inhibitors	Dorzolamide (Han et al., 2020)	In vitro: dose-dependent differentiation and inhibition of proliferation and Akt signalling
Parasympathomimetic	Pilocarpine (Zhang et al., 2017)	In vitro: dose-dependent decrease in meibocyte survival
Rho-kinase inhibitors	Netarsudil	No included studies

the included studies, the effects resulting from a number of medications varied. Three studies found no difference in MG distribution regarding the number of medications (Agnifili et al., 2013;Arita et al., 2012a, 2012b; Guarnieri et al., 2020). These studies were cross-sectional and all patients were treated for a minimum of 12 (Arita et al., 2012a, 2012b; Guarnieri et al., 2020) or 18 months (Agnifili et al., 2013). If the glandular atrophy initiates prior to this, the correlation between the number of drops or duration of treatment and MG dropout might be missed. Indeed, there is evidence of MG dropout occurring as early as after 9 months of treatment with PC medications (Guo et al., 2020; Ha et al., 2019). Moreover, four studies found increased MG dropout associated with the number of daily installations and/or length of treatment (Cho et al., 2018; Guo et al., 2020; Ha et al., 2019; Lee et al., 2019). Thus, among the included studies, the majority report a correlation between the number of preserved formulations or treatment duration and the degree of glandular atrophy. This corresponds to the findings of in vivo confocal microscopy (IVCM) studies where both the number of preserved installations and preservative burden correlate with the degree of inflammation and acinar atrophy (Agnifili et al., 2013, 2018).

5.2 | Effect of preservative-free topical glaucoma medications on the meibomian glands

The underlying mechanism driving MG atrophy or changes in patients during topical glaucoma treatment remains unclear. A link between PGAs and obstructive MGD has only been presented in studies with preserved formulations (Cunniffe et al., 2011; Mocan et al., 2016). Although no studies directly examine the prevalence of obstructive MGD among patients treated with PF-PGAs or other PF ocular antihypertensives, there are reports of decreasing prevalence of anterior and posterior blepharitis upon making the switch from preserved to unpreserved medications (Jaenen et al., 2007; Milla et al., 2012). Among the included studies, only one study compared the expressibility and quality of meibum between healthy controls and patients treated with unpreserved medications (Ha et al., 2019). Patients treated with PF-PGAs demonstrated progressively worse meibum parameters. Moreover, exposure to PF-PGA caused gradual MG dropout. When compared to baseline measurements, patients treated with PF-PGAs presented with worse meibum scores as well as an increased degree of MG dropout after 12 months (Ha et al., 2019). Similar results were presented by another study reporting a greater degree of MG dropout among patients treated with PF-PGAs for 24 months compared to those treated for 6 months (Lee et al., 2019). Both studies reported that duration of treatment increased MG dropout (Ha et al., 2019; Lee et al., 2019) and one found increasing ocular surface staining (Ha et al., 2019). Another study did not find any increase in MG dropout after 12 months of treatment with PF-PGAs (Guo et al., 2020). In vivo confocal microscopy studies have revealed morphology of the MGs and surrounding tissues believed to represent inflammatory changes (Agnifili et al., 2013, 2018). This indicates that PGAs alter MG secretions and induce hypertrichosis and keratinisation causing obstructive MGD and inflammation, which ultimately may lead to glandular dropout (Cunniffe et al., 2011; Mocan et al., 2016). Collectively, these findings may indicate a multifactorial and gradual process resulting in altered MG morphology and function.

The effects on the MGs of the different active ingredients used in glaucoma treatment are varied and have complex mechanisms. For instance, some of the drugs used have direct effects on meibocytes through specific receptors. The muscarinic acetylcholine receptor 3 has been demonstrated to be present in meibocytes and is the binding site of acetylcholine analogues such as pilocarpine (Kam & Sullivan, 2011; Zhang et al., 2017). Moreover, β-adrenergic receptor mRNA, the target of medications such as timolol, has been identified in murine MGs, indicating their presence, where the receptor is thought to possibly affect lipid composition (Knop et al., 2011; Schirra et al., 2005). Whether or not neurotransmitters are released onto and act upon MG receptors remains unknown. Cytotoxic effects on human meibocytes have been found in vitro from pilocarpine, timolol and brimonidine at concentrations present in topical formulations (Han et al., 2018, 2020; Zhang

et al., 2017). This concentration is far greater than what is believed to reach the MGs in vivo. Moreover, both brimonidine and dorzolamide have been demonstrated to promote differentiation (Han et al., 2018, 2020). However, the effect of these concentrations in long-term treatment spanning several years is not known. Thus, how these medications influence the structure and function of the MGs as a whole remains undetermined.

In summary, topical glaucoma medications may cause periglandular inflammation and meibum stagnation, increase meibum viscosity, impair meibum production, reduce meibocyte survival and result in glandular atrophy. Healthy meibum plays a vital role in the outermost lipid layer of the tear film and thus in the overall tear film homeostasis and ocular surface health (Willcox et al., 2017). Meibomian gland dropout is linked to increased signs and symptoms of DED, including decreased tear film stability and increased ocular surface staining (Bron et al., 2017). Because topical glaucoma medications have a direct detrimental effect on the ocular surface inducing irritation and inflammation (Fineide et al., 2022; Kolko et al., 2023), the negative impact on the MGs will represent an additive effect inducing local eyelid symptoms as well as increased signs and symptoms from the ocular surface resulting from the iatrogenic MGD and evaporative dry eye disease.

5.3 | Comparing preserved and unpreserved topical glaucoma medications

Overall, the most important factor tied to MG damage was the presence of preservatives. When comparing PC to PF formulations, three (Guo et al., 2020; Ha et al., 2019; Lee et al., 2019) out of five (Agnifili et al., 2013; Guo et al., 2020; Ha et al., 2019; Lee et al., 2019; Soriano et al., 2021) studies found a greater degree of MG dropout among patients treated with preservatives. Although PF-PGAs cause MG dropout, this occurs earlier and is more profound in patients treated with the BAC-containing alternatives (Ha et al., 2019; Lee et al., 2019). Based on this, it was hypothesised that tafluprost is detrimental in itself and that this is exacerbated by BAC (Lee et al., 2019). Corroborating evidence of this synergy was presented by two other included studies. First, Ha et al. (2019) reported that during a 12-month follow-up study, the degree of MG dropout among patients treated with PC-PGAs increased from baseline and was higher than that observed in patients treated with PF-PGAs and controls after 1 year. Moreover, compared to the baseline, the degree of MG dropout reached significant levels in the PC-PGA group after 9 months, while it took 12 months to reach significant levels in the unpreserved cohort. Second, Agnifili et al. reported only minor IVCM changes to the MGs of patients treated with PF-PGAs and more comprehensive alterations among those receiving PC-PGAs (Agnifili et al., 2013). However, Guo et al. (2020) found that patients treated with PC-PGAs had an increased degree of MG dropout after 9 months of treatment, with no increase in MG atrophy in the group treated with PF-PGA during the 12-month follow-up.

In vivo confocal microscopy allows for evaluation of changes at a microscopic level, evaluating glandular atrophy, glandular production, secretion viscosity, meibum stagnation, duct blockage and inflammation (Agnifili et al., 2013, 2018). The results from Agnifili et al. indicate that topical glaucoma medications cause a decrease in MG area and production as well as an increase of inflammation, meibum viscosity and stagnation, all in a dose-dependent manner (Agnifili et al., 2013). Interestingly, PC-PGAs in monotherapy seemed to detrimentally affect MG number, production, meibum viscosity, and cause inflammation. These changes were not seen in PF-PGA or the β-blocker groups with the exception of increased meibum stagnation following PF-PGA compared to controls. Moreover, PC-PGA treated patients had more glandular atrophy than those treated with PC β-blockers. This differs from a study that found the same degree of MG dropout in patients exposed to PC-PGAs and PC β-blockers (Arita et al., 2012a, 2012b). Also, unpreserved bimatoprost/timolol fixed combination (two active ingredients in one bottle) caused worsening of all IVCM parameters compared to healthy controls, but to a lesser extent than that of preserved fixed combinations, which were less detrimental than unfixed (multiple medications in one container each) combinations (Agnifili et al., 2018). The authors hypothesised that these observations were due to differences in the preservative burden. These findings on the whole indicate a cascade of glandular changes initiated through inflammation and meibum stagnation, worsening in a dose-dependent manner, where both the number of active pharmaceuticals and the total dose of preservative may pose as independent risk factors.

5.4 | Shortcomings in the literature and future perspectives

Based on the included studies, one might get the impression that PC-PGAs are especially detrimental to the MGs, although this finding is not universal. Clinical comparisons of PF medications are only made between PGAs and β-blockers. Additionally, this notion might be biased, as PGAs are the most studied group. Too few studies have investigated the effect of both PC and PF formulations from other classes than PGAs on the MGs. Several authors have speculated that there might be a synergistic effect between BAC and PGAs, where the inflammation caused by BAC promotes the diffusion of PGA to the MGs (Agnifili et al., 2013; Ha et al., 2019). Indeed, this finding has been documented in vitro, where BAC combined with PGA proved more cytotoxic than BAC alone, with no effect on cell survival by PF-PGAs (Rath et al., 2019). Moreover, too few studies documented the actual active ingredient, pharmacological group, or even preservative status. No studies have explored the effects of Rho-kinase inhibitors on the MGs. Another limitation is the complete lack of prospective, randomised studies. Future studies should aim to rectify this gap in our current knowledge with prospective, randomised studies comparing the effects of different classes of PF glaucoma medications on the MGs of treatment naïve subjects. Glaucoma is currently an incurable

disease, and pharmacological treatment is oftentimes for the remainder of a patient's life. However, we identified no prospective studies with follow-up beyond 1 year. Recently a Delphi consensus statement evaluated and agreed upon outcome measures to be used in clinical studies assessing adverse effects from topical glaucoma medications (Thein et al., 2022). This will facilitate comparison of studies and enable future meta-analyses.

According to the European Glaucoma Society, laser or incisional surgery should be considered in patients with poor disease control with two daily topical medications and medical therapy should not exceed three daily drops (Glaucoma, 2021). A recent randomised controlled trial demonstrated that primary selective laser trabeculoplasty was better tolerated and more effective than medical therapy (Gazzard et al., 2023). Glaucoma filtration surgery with bleb-formation and peri-operative use of mitomycin-C or 5-fluorouracil have been demonstrated to cause MG dropout (Sagara et al., 2014). A considerable proportion of patients undergoing surgery develop post-glaucoma surgery ocular surface disease (Agnifili et al., 2023), with iatrogenic preoperative ocular surface disease and inflammation due to topical glaucoma medications being an important and modifiable risk factor for filtration bleb failure (Agnifili et al., 2022). Consequently, patients with, or in danger of developing dysfunctional and atrophied MGs and ocular surface disease, undergo surgery that might cause further MG dropout, resulting in or leading to worsening of DED. With the development of novel minimally invasive surgical techniques and an increase in surgical glaucoma treatment, there is a need for well-designed prospective trials evaluating the effect of pre- and postoperative optimisation of the ocular surface on the outcome of various surgical approaches, ocular surface disease and MG impact.

The use of preservatives has been a necessity to avoid contamination and bacterial overgrowth within the bottle. Preservative-free medications have typically been produced in impractical one-dose containers that are difficult to use, resulting in excessive plastic waste. However, advances in bottle design allow for multi-use dispensers blocking reflux into the bottle, negating the need for preservatives, and making them easier to apply.

Recent years have seen the advent of several novel preservatives, such as purite, polyquaternium-1 and SofZia. These alternatives appear to have a less deleterious effect on the lipid layer of the tear film (Georgiev et al., 2012). Some studies demonstrate a superior safety profile with these preservatives when compared to BAC, while others find no difference (Fineide et al., 2022). Their effect on the MGs, however, remains unexplored.

6 | CONCLUSION

Preserved topical glaucoma medications appear to have a direct detrimental effect on the MGs causing glandular dysfunction and atrophy. There is some evidence that the active pharmaceuticals might decrease glandular function, causing stagnation of meibum and possibly even glandular death. However, in vitro, and in vivo studies indicate that PF formulations are less harmful to both the ocular surface in general and the MGs specifically compared to their preserved counterparts. As more than 110 million people are predicted to be afflicted by glaucoma by 2040, and more than half of these may suffer from DED under topical treatment, there is a dire need for decreasing the iatrogenic burden placed on these patients. Presently, there are no randomised control studies examining the effects of topical glaucoma medications on the MGs and only two prospective trials are included herein. Consequently, there is a pressing need for further research. Of note, there is a correlation between the presence of ocular surface disease, MGD and lack of adherence to glaucoma medication. As such, it is of utmost importance that clinicians recognize the signs of ocular surface disease and MGD in this patient group and take appropriate action, switching to unpreserved alternatives and provide appropriate treatment. Through this we can achieve improved compliance, prognosis, quality of life and duration of sight for our patients.

AFFILIATIONS

[1]Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway
[2]The Norwegian Dry Eye Clinic, Oslo, Norway
[3]Department of Computer Science, Oslo Metropolitan University, Oslo, Norway
[4]SimulaMet, Oslo, Norway
[5]Department of Ophthalmology, Sørlandet Hospital Arendal, Arendal, Norway
[6]Department of Plastic and Reconstructive Surgery, Oslo University Hospital, Oslo, Norway
[7]Department of Ophthalmology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[8]Department of Ophthalmology, Oslo University Hospital, Oslo, Norway
[9]Department of Drug Design and Pharmacology, University of Copenhagen, Copenhagen, Denmark
[10]Department of Ophthalmology, Copenhagen University Hospital, Rigshospitalet, Glostrup, Denmark
[11]Department of Twin Research & Genetic Epidemiology, King's College London, St Thomas' Hospital, London, UK
[12]Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[13]Department of Ophthalmology, Vestfold Hospital Trust, Tønsberg, Norway
[14]Department of Ophthalmology, Stavanger University Hospital, Oslo, Norway
[15]Department of Ophthalmology, Vestre Viken Hospital Trust, Drammen, Norway
[16]Department of Maxillofacial Surgery, Oslo University Hospital, Oslo, Norway
[17]Department of Research and Development, Oslo Metropolitan University, Oslo, Norway
[18]Department of Clinical Medicine, Faculty of Medicine, University of Bergen, Bergen, Norway
[19]Department of Quality and Health Technology, The Faculty of Health Sciences, University of Stavanger, Stavanger, Norway
[20]Department of Oral Biology, Faculty of Dentistry, University of Oslo, Oslo, Norway
[21]Department of Optometry, Radiography and Lighting Design, National Centre for Optics, Vision and Eye Care, Faculty of Health Sciences, University of South-Eastern Norway, Kongsberg, Norway
[22]Department of Health and Nursing Science, the Faculty of Health and Sport Sciences, University of Agder, Grimstad, Norway
[23]Department of Ophthalmology, Faculty of Life Course Sciences and Medicine, King's College London, London, UK

CONFLICT OF INTEREST STATEMENT

Fredrik Fineide: co-owner of The Norwegian dry eye clinic and the Clinic of eye health, Oslo, Norway. Morten Magnø: None. Kristian Dahlø: None. Miriam Kolko: Sits on advisory boards for Thea Laboratories, Santen, and Abbvie. Is a consultant for Thea Laboratories and Abbvie. Is a speaker for Thea Laboratories, Santen,

Abbvie and Topcon. Have received research support from Thea Laboratories and Topcon. Steffen Heegaard: Alcon, Santen, Sanofi and Thea Laboratories. Jelle Vehof: Dr Vehof is a consultant for Alcon, Santen, Thea Pharma, Horus Pharma and Tramedico. Tor Paaske Utheim: co-founder and co-owner of The Norwegian dry eye clinic and the Clinic of eye health, Oslo, Norway, which delivers talks for and/or receives financial support from the following: ABIGO, Alcon, Allergan, AMWO, Bausch&Lomb, Bayer, European school for advanced studies in ophthalmology, InnZ Medical, Medilens Nordic, Medistim, Novartis, Santen, Specsavers, Shire Pharmaceuticals and Thea Laboratories. He has served on the global scientific advisory board for Novartis and Alcon as well as the European advisory board for Shire Pharmaceuticals. Utheim is the Norwegian Global Ambassador for Tear Film and Ocular Surface Society (TFOS), a Board Member of the International Ocular Surface Society, an International Member of the Japanese Lid and Meibomian gland working group (LIME), a Consultant at the Norwegian Association for the Blind and Partially Sighted, the President of the Oslo Society of ophthalmology, and the Editor-in-Chief of Oftalmolog, an eye journal distributed to all eye doctors in the Nordic region since 1980. Besides publishing articles of presumed interest to our readers, Oftalmolog publishes advertisements from pharmaceutical companies, companies selling ophthalmological equipment, and associations organising conferences and events in ophthalmology. For more information, visit: oftalmolog.com.

ORCID

Fredrik Fineide https://orcid.org/0000-0003-3835-8772
Morten Magnø https://orcid.org/0000-0002-2276-1770
Miriam Kolko https://orcid.org/0000-0001-8697-0734
Steffen Heegaard https://orcid.org/0000-0001-5906-7670
Jelle Vehof https://orcid.org/0000-0003-2804-7399

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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