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Ocular Surface Homeostasis After Scleral Lens Usage

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Short Title: Tear film inflammatory changes after scleral contact lens wear

Article contents: 1 figure and 2 tables

Date of submission: Monday 13 March 2023

Date of revision: Thursday 8 June 2023

Key words: Scleral contact lens; inflammation; cytokine; tear film

Acknowledgements and Financial Disclosure: This study was realized by a Fund for Research in Ophthalmology (FRO) grant. The authors would like to thank Microlens Contactlens Technology b.v. (Arnhem, The Netherlands) and Maarten Van Hoey for providing and fitting the contact lenses used in this study.

No author has a financial or proprietary interest in any material or method mentioned.

ABSTRACT

Objectives: The aim of this prospective study is to examine the effects of five hours of well fitted mini-scleral contact lens (mini-SL) wear on the tear film cytokine expression in healthy eyes.

Methods: Twenty-three healthy participants were included in the study. One eye of each participant was selected at random and a mini-SL measuring 16.5 mm in diameter was fitted by an experienced contact lens specialist. The contact lens remained in place for five hours. Pre-corneal tear fluid was collected using capillary tubes at three different time-points: baseline before SL insertion (T0), after five hours of SL wear (T1), and three hours after SL removal (T2). The concentration of 40 inflammatory cytokines at the three different time points was determined by using multiplex bead assay.

Results: Mini-scleral lens wear did not result in significant changes in the cytokine-to-protein ratio after five hours of wear on a healthy eye.

Conclusions: While a well-fitted mini-SL reduces the rate at which the pre-corneal tear film is refreshed, five hours of lens wear did not appear to significantly affect the tears cytokine to protein ratio, suggesting that scleral lenses have minimal impact on corneal cytokine expression.

INTRODUCTION

Scleral contact lenses (SLs) are large-diameter contact lenses designed to vault the cornea and limbus, with the haptic landing zone bearing entirely on the sclera and overlying conjunctiva.[1] While the concept of scleral contact lenses is not new, with some examples dating back to the 19th century, it is only in the past two decades that technological improvements have made these large lenses a viable option for patients. The initial attempts using originally glass lenses were disappointing as they tended to induce visually significant corneal oedema due to relative hypoxia. This hypoxic reaction was not immediate but developed over a number of hours of lens wear and was referred to by names such as Müller's Mist and Fick's phenomenon [2].

Adaptations to improve scleral lens oxygenation by allowing turnover of the tear film under the lens were attempted by use of flatter haptics or fenestrations, though these changes were often made at the expense of patient comfort [3]. Improvements in highly oxygen permeable materials have meant that modern scleral contact lenses can be affixed to the eye, form a seal, and avoid the development of oedema for the most part. While overt signs of corneal edema are not seen, it is possible that preventing the refreshment of the pre-corneal tear film can have more subtle, deleterious effects. In older eyes, or those with reduced endothelial cell counts, the development of corneal edema can still be seen, suggesting that there is still a degree of hypoxia induced by modern contact lenses [4].

Mini-scleral contact lenses (mini-SLs) are a sub-group of scleral contact lenses, smaller than their predecessors, with a total lens diameter between 15 and 18mm.[5] They are primarily used for the correction of corneal surface irregularities that are difficult to correct with standard spectacle or contact lens correction (e.g. keratoconus [6], post-penetrating keratoplasty [7]), or as a therapeutic option for ocular surface diseases including Sjögren syndrome[8], exposure keratopathy[9], and Stevens-Johnson Syndrome[10]. In terms of physiological interaction, mini-SLs still differ considerably from other types of contact lenses as they limit the tear exchange underneath the lens, like the original scleral lenses [11].

To date, only limited studies have been conducted examining the corneal response to mini-SL wear, showing minimal central corneal swelling [4,12]. While some recent studies have investigated the impact of scleral lenses on corneal thickness and topography [13,14], little is known about the biochemical effect of these lenses on the ocular surface. Lens thickness, the partially static post-lens reservoir and the minimal tear exchange are potential hypoxic drives inherent in the lens design, and therefore can potentially compromise ocular health. A reduced oxygenation may

affect cell metabolism, cause tissue swelling, loss of corneal transparency, and/or promote corneal neovascularization [15].

In this study, we aimed to examine the cytokine response (i.e., the concentration of pro-inflammatory cytokines) of the ocular surface during and after mini-SL wear, to determine whether a potentially reduced refreshment of the pre-corneal tear film and concentration of oxygen can have a knock-on effect on ocular inflammation. Determining the potential for scleral lenses to induce elements of the inflammatory cascade might provide additional insight into the safety and efficacy of these devices.

PATIENTS AND METHODS

This prospective study was approved by the Antwerp University Hospital research ethics committee and adhered to the tenets of the Declaration of Helsinki (Belgian Federal Agency for Medicines and Health Products registry number B300201732868). Written informed consent was obtained from all 23 participants after explanation of the nature and possible consequences of the study.

Inclusion and Exclusion Criteria

The inclusion criteria included a lack of ocular abnormalities (other than refractive errors), a corrected distance visual acuity (CDVA) of 20/20 or better, and no regular contact lens wearing history. The exclusion criteria included eyes with trauma, active allergies, ectasia, conjunctival lesions (for example pterygium), iatrogenic diseases, use of any topical medications other than artificial tears, or any surgery history, including refractive surgery, keratoplasty, and intrastromal ring segments. Presence or absence of these criteria was assessed by slit lamp examination. Patients were screened for dry eye disease using the validated Ocular Surface Disease Index (OSDI) questionnaire [16].

Scleral Contact Lens Fitting

All mini-SL fittings were performed by the same experienced optometrist (MVH). The SL design applied for all participants was miniMISA SL (Microlens, Arnhem, Netherlands) with spherical haptic landing zone. The SLs were all made of highly gas-permeable materials with an oxygen permeability (Dk) of 125, central thickness of 300 µm, a diameter of 16.5 mm, base curve radius of 7.8 mm and scleral curve of 13.5 mm.

The SL filled with preservative-free saline (Braun Mini Plasco physiologic NaCl 0.9%) was placed on a randomly determined eye for each participant. The position and vault were evaluated by slit-lamp examination and optical coherence tomography (OCT, figure 1). If regions of corneal bearing were observed, the sagittal depth of the lens was increased by 125 µm increments and the fit reassessed until proper placement was achieved. In cases where the contact lens caused discomfort despite optimal fitting, the lens was removed, and the participant was excluded from the study.

Tear Sample Collection

The tear sample collection was conducted on the same day SLs were properly fitted. The tear fluid samples were collected by the same experienced clinician at three time points: 1) The baseline samples (T0), which were obtained before SLs fitting by using a 30 µL glass capillary tube (Drummond Microcaps disposable pipets) applied to the tear meniscus at the lateral inferior fornix; 2) The samples after five hours of continuous well-fitted SLs wearing (T1), which were collected by capillary tube from the post-wear lens reservoir; 3) The samples three hours after SL removal (T2), with identical collection method as T0. Once obtained, the samples were transferred into cryovials (Sarstedt screw cap micro tubes 0.5 mL) and promptly stored at -80 °C. Transport with temperature monitoring was organized via a biopharmaceutical courier service (World Courier, Zaventem, Belgium) and took place one month after final specimen collection.

Tear Fluid Analyses

The Cytokine profiling of the collected tear fluid was performed at the Department of Medical Biochemistry of the Oslo University Hospital.

Prior to analyses, the samples were diluted with phosphate-buffered saline (PBS) and the protein concentration was measured according to recommendations from the manufacturer (Thermo Scientific, Rockford, IL, US). Second, the samples were transferred into fresh tubes and diluted with PBS containing bovine serum albumin (final BSA concentration 0.5%). Then, all samples were centrifuged at 10 000 g for 10 minutes at 4°C, and 25 µL of the supernatants were loaded onto 96 well plates.

Finally, the multiplex analysis was performed according to a previously published protocol [17]. The broad screening kit was used for the analysis (Bio-Plex Pro Human Cytokine 40-plex Assay, Cat. No. 171AK99MR2, Bio-Rad Laboratories, Inc.) and included targets against: IL (interleukin)-1B, IL-2, IL-4, IL-6, IL-8, IL-10, IL-16l; (C-C Motif Chemokine Ligand) CCL1, CCL2 (also referred

to as MCP-1), CCL3, CCL7, CCL8, CCL11, CCL13, CCL15 (also called MIP-1d), CCL17, CCL19, CCL20, CCL21, CCL22, CCL23, CCL24, CCL25, CCL26, CCL27; CXCL (C-X-C Motif Chemokine Ligand)1, CXCL2, CXCL5, CXCL6, CXCL9, CXCL10, CXCL11, CXCL12, CXCL13, CXCL16, CX3CL1 (also known as fractalkine), tumor necrosis factor (TNF-α), interferon gamma (IFN-γ), granulocyte-macrophage colony-stimulating factor (GM-CSF), and macrophage migration inhibitory factor (MIF) . All values obtained from the assay were in an acceptable range according to recommendations from the manufacturer (intra-percent coefficient of variation <11 and inter-percent coefficient of variation >21).

Since some samples did not contain any fluid (due to the evaporation during transportation), the cytokine concentration could not be determined, and instead the cytokine-to-protein ratio was calculated. The mean value ± standard deviation (SD) of all adjusted cytokine levels (pg cytokine/ug protein) was calculated for the three timepoints under analysis.

Statistical analysis

Statistical analysis was performed using SPSS software (Version 24.0; SPSS Inc., Chicago, Illinois, United States). One-way repeated measurements (ANOVA) with Bonferroni correction to control type-one error was used to assess differences within sessions. A significance level α of 0.05 was considered for all tests.

RESULTS

Demographics

A total of 23 healthy volunteers (15 females and 8 males) aged between 18 and 45 years were included in this study. One male subject was excluded due to an insufficient tear volume sample. 40% of study subjects had a history of occasional soft contact lens use; none reported previous scleral lens wear (table 1).

Dry eye symptoms

None of the subjects had significant dry eye disease, as substantiated by an OSDI of 1,3 ± 1,2 (mean ± SD).

Contact lens discomfort

When comparing the data pool of subjects that reported contact lens discomfort during scleral wear (N = 5) against the data pool that did not report any symptoms, no statistically significant differences in cytokine concentration was found between sessions (t0 vs t0, t1 vs t1 and t2 vs t2).

Cytokine levels

Interleukins

No statistically significant difference in cytokine level was found between the three timepoints (t0, t1 and t2) for the interleukins IL-1B, IL-2, IL-4, IL-6, IL-8, IL-10, and IL-16.

Chemokines

No statistically significant difference in cytokine level was found between the three timepoints (t0, t1 and t2) for the CC-chemokines CCL1, CCL2, CCL3, CCL7, CCL8, CCL11, CCL13, CCL15, CCL17, CCL19, CCL20, CCL21, CCL22, CCL23, CCL24, CCL25, CCL26, CCL27, nor for the CXC-chemokines CXCL1, CXCL2, CXCL5, CXCL6, CXCL9, CXCL10, CXCL11, CXCL12, CXCL13, CXCL16, and CX3CL1 (fractalkine).

Other cytokines

No statistically significant difference in cytokine level was found between the three timepoints (t0, t1 and t2) for TNF-α, IFN-γ, GM-CSF and MIF.

(table 2)

DISCUSSION

While indications for scleral lens use have been expanding over the years, little is known about the relationship between these contact lenses and the inflammatory state of the eye. In our study, no significant alteration in cytokine concentration could be detected after five hours of lens wear, suggesting that scleral lenses have little to no impact on short term ocular surface cytokine expression.

Irrespective of contact lens wear, the use of tear biomarkers to monitor pathological ocular conditions has been extensively studied over the last few years. For instance, there is mounting evidence that inflammation plays a key role in the pathogenesis of dry eye and ocular surface disease (OSD), with tear film analysis showing increased levels of IL-1, IL-6, IL-8, CX3CL1 and TNF-a [18 19 20 21]. These findings were substantiated by the most recent reports of the Dry Eye Workshop Study (DEWS II) which included ocular surface inflammation into the definition of this multifactorial pathology [22]. The same inflammatory cytokines were shown to be elevated in patients with Sjögren syndrome [23]. In addition, studies analyzing tear film composition in keratoconus have found increased levels of interleukin-6 (IL-6), tumor necrosis factor-α(TNF-α), and matrix metalloproteinase (MMP)-9. Along the same lines, eye rubbing, a proven risk factor for keratoconus, has also been shown recently to increase tear levels of MMP-13, IL-6, and TNF-α. These findings suggest that keratoconus could be, at least in part, an inflammatory condition [24]. Moreover, several pro-inflammatory cytokines including IL-1b, IL-9 and IL-17A were found to be significantly elevated in tear fluid from aniridia patients. Increased inflammation of the ocular surface may be a factor in the development of MGD in these patients [17].

In our review of the literature, we discovered only one study, recently published by Walker and colleagues, addressing the tear film cytokine composition with SL use in a group of healthy, soft contact lens wearers [25]. The researchers determined the concentration of several inflammatory biomarkers (IL-4, IL-8, MMP-9, and MMP-10) present in the scleral lens fluid reservoir and basal tear samples. Results showed greater concentrations of MMP-9 and -10 in the fluid reservoir in comparison to the basal tear samples, while no significant difference in IL-4 and IL-8 could be noted. However, since that study compared the tears beneath and outside of the scleral lens (at the same time point), rather than pre- and post-wear as in our study design, caution should be exercised juxtaposing these results. Additionally, while our array contained a wider range of inflammatory cytokines, it did not include MMP's.

Another study by Carracedo et al assessed short-term scleral lens wear in keratoconus patients, showing these lenses could improve signs and symptoms of dry eye. The authors also discovered an increase of MMP-9 concentration in the precorneal fluid reservoir, attributing this finding to tear film stagnation [26].

Considering the findings in both studies, we hypothesize the relative increase in MMP levels to be explained by tear accumulation between contact lens and ocular surface, rather than a de

facto increased synthesis of inflammatory enzymes. This would be consistent with the fact that there is a minimum tear exchange in most participants fitted with SLs [27].

We found no correlation between contact lens discomfort and inflammatory mediators in the tear film. In fact, comfort was highly variable, with approximately one out of five subjects reporting some discomfort after five hours of lens wear. This is likely explained by our subjects being either contact lens novices or being only accustomed to soft contact lenses, which are typically more comfortable. It also clarifies why some studies report improved comfort using scleral lenses in ocular surface disease [28], as these diseased eyes have a different baseline (already being in discomfort) and also a higher likelihood of having been exposed to less comfortable alternatives such as RGP lenses.

We acknowledge some limitations to this study. First, since all participants were young and healthy with a normal cornea and no history of ocular disease, these results must be interpreted with caution, as they may not be applicable to older patients or those with ocular surface abnormalities. However, performing these tests on diseased eyes, known to already have cytokine changes, would have induced far greater variability. In addition, inflammatory mediators could hypothetically have become trapped in the lens reservoir, further disrupting our findings, and compromising ocular surface integrity. Our data, derived from normal individuals, allows for controlled normative data to be plotted, which in turn can be used in future studies with similar design on diseased eyes.

Furthermore, it is possible that inflammatory changes only occur after a longer period of lens wear, so a longer study period might be needed to detect any changes. Finally, an additional limitation of the study is that only one lens design was used (mini-scleral). Therefore, longer term studies, examining both healthy eyes and eyes with compromised corneas, are required to understand the influence of extended miniscleral contact lens wear on corneal physiology, and to elucidate the involved inflammatory pathways.

CONCLUSION

To our knowledge, this is the first study to examine the biochemical changes to the ocular surface in response to scleral lens wear over time. Our results show that five hours of mini-SL wear is not associated with a change in corneal tear film cytokine levels, suggesting that these lenses have little to no impact on short term ocular surface cytokine expression in healthy eyes. Subsequent studies should continue to evaluate inflammation during scleral lens wear, particularly in diseased eyes.

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Figure 1

Optical coherence tomography (OCT) of a well-fitted mini-scleral lens, as demonstrated by a complete vault of the central cornea and a haptic landing zone on the sclera.

Table 1

Demographic data of the subject population.

Table 2

Mean value ± standard deviation and statistical significance of all adjusted cytokine levels (pg cytokine/ug protein) for the three stages under analysis.

Table 1

Demographics of the subject population.

Subjects included	N = 22
Mean Age ± SD	30 ± 7,7
Gender (% female)	68
Race	White (20), Asian (2)
History of soft contact lens use	9 subjects

Table (1 per file. Do Not Embed in TEXT)

Table 2

Mean value ± standard deviation and statistical significance of all adjusted cytokine levels (pg cytokine/μg protein) for the three stages under analysis.

Cytokine name	Baseline (t0)	Just before SCL removal (t1)	3 hours after SCL removal (t2)	P-value (one way ANOVA)
IL-1B	0.008 ± 0.005	0.009 ± 0.005	0.007 ± 0.007	0.800
IL-2	0.025 ± 0.019	0.032 ± 0.019	0.024 ± 0.023	0.581
IL-4	0.034 ± 0.023	0.043 ± 0.028	0.030 ± 0.021	0.308
IL-6	0.033 ± 0.024	0.033 ± 0.026	0.032 ± 0.028	0.988
IL-8/CXCL8	0.122 ± 0.241	0.036 ± 0.035	0.022 ± 0.015	0.056
IL-10	0.014 ± 0.007	0.014 ± 0.008	0.012 ± 0.010	0.730
IL-16	0.185 ± 0.112	0.217 ± 0.162	0.184 ± 0.174	0.786
TNF-α	0.037 ± 0.019	0.036 ± 0.019	0.036 ± 0.029	0.978
IFN-γ	0.076 ± 0.050	0.089 ± 0.072	0.078 ± 0.075	0.841
GM-CSF	0.177 ± 0.096	0.207 ± 0.148	0.166 ± 0.162	0.757
MIF	0.727 ± 0.395	1.396 ± 1.836	0.800 ± 0.974	0.174
CCL1	0.071 ± 0.031	0.118 ± 0.130	0.077 ± 0.082	0.257
CCL2	0.023 ± 0.016	0.042 ± 0.041	0.034 ± 0.029	0.162
CCL3	0.011 ± 0.010	0.011 ± 0.010	0.010 ± 0.010	0.881
CCL7	0.171 ± 0.127	0.190 ± 0.150	0.171 ± 0.168	0.908
CCL8	0.006 ± 0.004	0.007 ± 0.006	0.007 ± 0.008	0.866
CCL11	0.039 ± 0.023	0.043 ± 0.036	0.040 ± 0.036	0.935
CCL13	0.010 ± 0.005	0.009 ± 0.006	0.009 ± 0.008	0.968

CCL15	0.232 ± 0.183	0.179 ± 0.127	0.210 ± 0.166	0.589
CCL17	0.071 ± 0.053	0.093 ± 0.061	0.076 ± 0.073	0.627
CCL19	0.219 ± 0.117	0.241 ± 0.143	0.205 ± 0.157	0.734
CCL20	0.088 ± 0.039	0.086 ± 0.050	0.076 ± 0.037	0.652
CCL21	1.530 ± 2.135	2.139 ± 2.139	1.264 ± 0.693	0.343
CCL22	0.072 ± 0.032	0.079 ± 0.086	0.071 ± 0.062	0.927
CCL23	0.038 ± 0.026	0.052 ± 0.044	0.043 ± 0.040	0.563
CCL24	0.165 ± 0.118	0.182 ± 0.155	0.171 ± 0.168	0.924
CCL25	0.637 ± 0.515	0.563 ± 0.477	0.634 ± 0.669	0.900
CCL26	0.068 ± 0.053	0.090 ± 0.080	0.062 ± 0.068	0.488
CCL27	0.086 ± 0.066	0.101 ± 0.056	0.101 ± 0.115	0.852
CXCL1	0.316 ± 0.208	0.470 ± 0.576	0.290 ± 0.343	0.336
CXCL2	0.111 ± 0.047	0.168 ± 0.213	0.120 ± 0.128	0.474
CXCL5	1.406 ± 0.880	1.749 ± 1.602	1.525 ± 1.470	0.762
CXCL6	0.090 ± 0.050	0.112 ± 0.110	0.074 ± 0.064	0.337
CXCL9	0.532 ± 0.551	0.510 ± 0.485	0.407 ± 0.368	0.665
CXCL10	2.977 ± 2.886	3.161 ± 2.528	2.698 ± 4.385	0.909
CXCL11	0.207 ± 0.185	0.172 ± 0.135	0.180 ± 0.201	0.804
CXCL12	0.444 ± 0.272	0.549 ± 0.442	0.471 ± 0.450	0.733
CXCL13	0.006 ± 0.003	0.010 ± 0.013	0.007 ± 0.007	0.296
CXCL16	0.021 ± 0.012	0.018 ± 0.013	0.020 ± 0.018	0.802
CX3CL1	0.321 ± 0.123	0.396 ± 0.223	0.319 ± 0.207	0.355

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