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Metalloproteinase-9 on the Ocular Surface of Patients With Implanted Boston Type 1 Keratoprosthesis

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Purpose: The aim of this study was to characterize the presence of ocular surface inflammation, using matrix metalloproteinase-9 (MMP-9) as a marker, on the ocular surface of eyes with implanted Boston keratoprosthesis type 1 (KPro).

Methods: Patients with implanted KPro at a single tertiary center were recruited to assess ocular inflammation. MMP-9 was measured using the InflammaDry test in both eyes of each patient. The non-KPro eye served as the control. Rate of positivity of MMP-9 was compared between groups. Possible associations between ocular surface inflammation and the development of postoperative complications were evaluated using univariate statistical analysis.

Results: Fifty eyes from 25 patients were included. The mean age was 50 years. Noninflammatory indications for KPro were predominant among patients. Eighty-eight percent of KPro eyes had a positive test for MMP-9 while only 25% of control eyes were positive ($P < 001$). The most common complications were retroprosthetic membrane, epithelial defects, and sterile corneal melt. The presence of a strong positive result was associated with a higher frequency of complications (80% of eyes) compared with a faint positive test (54%) and a negative test (33%).

Conclusions: The KPro device seems to increase MMP-9 levels on the ocular surface. High MMP-9 levels may be associated with higher risk of complications. MMP-9 testing can be useful to assess subclinical ocular surface inflammation with a potential role in the postoperative care of patients with KPro.

Key Words: keratoprosthesis, inflammation, MMP-9, metalloproteinase

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Boston keratoprosthesis type 1 (KPro) (Massachusetts Eye and Ear Infirmary, Boston, MA) is the most common implanted keratoprosthesis in the world[1,2] and has shown to be a good option for visual rehabilitation in patients with poor prognosis for keratoplasty. Over time, improvements to the prosthesis design and postoperative treatment have led to improved outcomes and lessened complications.[3–5] However, despite these improvements, several postoperative complications are still highly prevalent and can limit visual outcomes and prosthesis retention. Studies have demonstrated that patients with ocular surface disease have lower retention rates and are at higher risk of postoperative complications[4,6,7] including sterile corneal melt and infections that can limit the long-term success of KPro.[2,3,8]

Matrix metalloproteinases (MMPs) are enzymes responsible for collagen and extracellular matrix degradation and are associated with sterile corneal ulceration.[7] Specifically, gelatinase-B (MMP-9), a subtype of these enzymes, has been shown to play a pathogenic role in different inflammatory conditions including dry eye and other systemic diseases such as arthritis, cardiovascular disease, and cancer.[7,9–12] MMP-9 is released during the respiratory burst of neutrophils and then activated by other tear film and ocular surface inflammatory factors including interleukin 1 (IL-1) and tumor necrosis factor alpha (TNFα). These events trigger the release of substance P and subsequent release of more MMP-9, creating a continuous cycle of inflammation, secretory dysfunction, and corneal surface disease.[13]

Immunoassay testing for MMP-9 is commercially available (InflammaDry test, Quidel, San Diego, CA) and can be used in office as a point-of-care testing (POCT) to measure the presence of MMP-9 in both active and inactive forms on the ocular surface.[12,13] MMP-9 was shown to be useful not only for diagnosis but also to follow treatment response in patients with dry eye.[12]

To the best of our knowledge, there are no studies characterizing the presence of MMP-9 using POCT on the ocular surface of patients with KPro. This current study aimed to explore the potential utility of MMP-9 as a marker for ocular surface inflammation in patients with KPro and its association with risk of postoperative complications.

MATERIALS AND METHODS

Study Design and Population

This is a single center cross-sectional cohort study. Approval from the Institutional Review Board of the

University of Illinois at Chicago and individual participant informed consent were obtained. Study participants with previous KPro implantation who were followed in the Cornea service at the University of Illinois at Chicago, Department of Ophthalmology and Visual Sciences, were recruited during their regularly scheduled visits. Subjects aged 18 years or older with >1 month since KPro implantation were considered eligible for the study. Subjects with a history of any ocular surgery or other procedures during the preceding month were excluded.

A complete ocular history, medication review, and slit-lamp evaluation were performed on the day of enrollment. Medical records were reviewed to identify participants' demographics, previous ocular diagnosis, previous surgeries, and postoperative complications. Preoperative diagnoses were grouped by diagnostic category (autoimmune disease, chemical burns, and noninflammatory disease) based on the classic prognostic hierarchy after Boston KPro.[14]

Assessment of Exposure

Metalloproteinase-9 immunoassay (InflammaDry test, Quidel) was performed according to manufacturer's instructions. Before administration of dye or topical drops, tear samples were collected from the palpebral conjunctiva with the sample collector fleece until it glistened, indicating that it was saturated. The sampling fleece is then placed on the test cassette with the addition of the buffer solution. If there is any MMP-9 antibody–antigen interaction on the immunoassay test strip, 2 lines (1 red and 1 blue) will be present on the result window. According to the manufacturer, the intensity of the red line is directly related to the amount of MMP-9 present on the ocular surface. The minimum level of detection of the test is 40 ng/mL; however, a faint line can be appreciated with levels between 30 and 40 ng/mL.[13] As the test is qualitative in nature, the test strip was photographed and then results were scored visually by a trained ophthalmologist as negative, faint positive, or strong positive. The same test strip was read by 2 masked investigators for quality control. MMP-9 was tested in the KPro eye and the contralateral eye (control) of each patient. For all patients, samples were taken in 1 visit.

Assessment of Outcomes

Presence or absence of MMP-9 on the ocular surface was measured using MMP-9 immunoassay. Test results were classified as negative, weak positive, or strong positive as previously described. All tests were independently interpreted by the same investigators (M.S.C. and A.C.A.) at 10 minutes of the collection of the sample to maintain consistency in the results. After the MMP-9 test was performed, each patient underwent a full slit-lamp examination and ancillary testing as indicated. Postoperative complications developed by each patient were noted based on clinical evaluation on the day of study visit and on chart review.

Statistical Analysis

All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc, Cary, NC). Chi-squared test was used to assess for differences in the presence of MMP-9 between KPro and control groups. Univariate analysis was used to assess potential associations between inflammatory status measured by the presence of MMP-9 with our complications of interest. Because of the small sample size, the inflammatory status was dichotomized as a binary variable between negative and positive results for part of the analysis. The odds ratio and 95% confidence interval were calculated. The mean difference and 95% confidence interval are reported.

RESULTS

Fifty eyes of 25 patients were tested. There was 1 failed test; therefore, 49 eyes from 25 patients were included in the described analyses. One of 25 patients had bilateral KPro implantation; therefore, 26 eyes were included in the KPro group and 23 eyes in the control group. Demographic characteristics for our study participants are shown in Table 1. Fifty-two percent of patients were male and the mean age was 50 years (SD ± 20.25). The mean total follow-up time for this cohort was 6 years (range 7 months–14 years). The most common preoperative diagnoses were within the non-inflammatory category which represented 88% of eyes, followed by chemical injuries (8%), and autoimmune disease (4%). At the time of the tear collection, all KPro eyes were on antibiotic prophylaxis (fluoroquinolone and/or vancomycin) and 81% of eyes (n = 22) were on topical steroids (1% prednisolone acetate).

Eighty-one percent of eyes in the KPro group (n = 21) and only 5% (n = 1) in the control group wore contact lenses routinely. Ninety percent of patients with KPro on contact lenses (n = 19) wore soft contact lenses, specifically Kontur (Kontur Kontact Lens Co Inc, CA) with excellent retention and average exchange time of 3 months.

In the KPro group, 23 of 26 eyes (88%) had a positive MMP-9 test compared with 6 of 23 eyes (26%) in the control group (Table 2). This difference was statistically significant ($P < 0.001$). Eyes with KPro were 21 times more likely to have a positive MMP-9 test (odds ratio 21.7; 95% CI 4.75–99.4). Of all KPro eyes with a positive MMP-9 test, 47% were not using any form of topical steroids while 53% of eyes were on low-dose (once a day) topical steroids (1% prednisolone acetate). Eyes with a positive MMP-9 test were almost equally distributed between the strong positive

TABLE 1. Demographic Characteristics of Study Participants (N = 25)

Characteristic	Mean (SD) or N (%)
Age	50.7 (20.0)
Sex	
Male	13 (52)
Female	12 (48)
Preoperative diagnosis	
Noninflammatory	22 (88)
Chemical	2 (8)
Inflammatory	1 (4)

TABLE 2. Presence of MMP-9 by Immunoassay in KPro and Control Eyes

		KPro, n = eyes (%)	Control, n = eyes (%)
MMP-9 immunoassay	Positive	23 (88)	6 (26)
	Negative	3 (12)	17 (74)
Odds ratio (95% CI)		21.7 (4.75, 99.4)	
P value*		<0.001	

*Chi-square test.

(n = 10) and faint positive groups (n = 13). All KPro eyes with a negative MMP-9 test (n = 3) were on high-dose topical steroids (4 times a day). In the control group, only 26% of eyes (6/23) had a positive result and only 1 of the 6 MMP-9-positive eyes was on once-a-day steroid dosing. In this group, 1 of 6 (17%) had an underlying autoimmune pathology (Stevens–Johnson), 1 of 6 (17%) wore an ocular prosthesis explaining for both cases a probable cause of increased surface inflammation, and 1 of 6 (17%) had a history of multiple graft failure. We failed to find a difference in MMP-9 positivity rates among the different preoperative diagnostic categories.

In our cohort, there were 6 patients (12 eyes) with bilateral disease. In more detail, Stevens–Johnson disease (1/6), chemical injuries (2/6), and history of multiple graft failures (3/6). When analyzing this group, 6 of 6 eyes with KPro (100%) had a positive MMP-9 result compared with 1 of 6 eyes (17%) without KPro.

Sixty-five percent of eyes (17/26) in the KPro group and 33% (8/24) in the control group were taking at least 1 glaucoma medication (average of 2.4, range 1–5) daily. In the control group, 100% of the patients on glaucoma medication had a negative MMP-9 test. By contrast, 88% of eyes (15/17) in the KPro group using glaucoma medications had a positive MMP-9 result. None of the patients were on preservative-free formulations.

The most common postoperative complications in this cohort included retroprosthetic membrane (RPM) (50% of eyes; n = 13), epithelial defects (19%; n = 5), and corneal melt (15%; n = 4). Table 3 summarizes the distribution of ocular complications in KPro eyes by the presence or absence of MMP-9 on the ocular surface. Ninety-two percent of eyes with RPM had a positive MMP-9 result. Specifically, 38% of eyes (n = 5) had a strong positive (SP) result and 54% (n = 7) had faint positive (FP) results. Only 1 eye with RPM had a negative result. The presence of MMP-9 on the ocular surface was associated with an odds ratio of 5.88 (95% CI: 1.44, 23.63) for the presence of RPM. All patients with epithelial defects and corneal melts showed a positive MMP-9 immunoassay result (n = 5). Eighty-three percent of KPro eyes with an epithelial defect had a faint positive and 17% had a strong positive MMP-9 immunoassay result.

In the KPro eyes with a positive MMP-9 result, 15 of 23 eyes had at least 1 complication versus only 1 eye developing complications in the negative MMP-9 group. The presence of a strong positive result was related to a higher frequency of complications (80% of eyes) compared with a faint positive test (54%) and a negative test (33%).

DISCUSSION

Boston type 1 KPro is a good option for visual rehabilitation in patients with corneal blindness who are not good candidates for other forms of transplantation; however, postoperative complications continue to limit outcomes.[4,5,15] It is postulated that the presence of inflammatory disease increases the risk of complications and worsens the prognosis for patients with KPro. Yaghouti et al first described the prognostic categories and found that inflammatory conditions fared worse than other noninflammatory diseases.[6,14] Since then, several other studies have confirmed that the presence of ocular surface disease specifically increases the risk of complications including infections, corneal melt, and extrusion.[16–18] Multiple studies have shown that severe and ongoing ocular surface inflammation is associated with increased expression of different mediators including MMPs, IL-1, and TNFα.[12,13] Ocular surface breakdown causes dysregulation of the MMPs and excessive release of inflammatory cells which in turn create a hostile environment for the corneal epithelium interfering with the restoration of stable epithelial/stromal adhesion.[7,9]

In our study, we found higher levels of MMP-9 in KPro eyes compared with controls (88% of eyes with KPro had a positive MMP-9 result compared with 24% in the contralateral eye) even in the presence of bilateral underlying disease (100% eyes with KPro had positive results compared with 17% of the control eye). This suggests that the presence of the KPro device generates a heightened inflammatory state on the ocular surface independently of the underlying indication for surgery. Our study results agree with a previous study by Robert et al that analyzed the presence of MMP and myeloperoxidase in tears of 40 patients with Boston KPro 1 with different underlying pathologies (mostly noninflammatory etiology). This study found an increased level of these mediators, especially in those with a history of chemical

TABLE 3. Postoperative Complications in KPro Eyes With Positive and Negative MMP-9 Immunoassay on the Ocular Surface

	MMP-9				
Complications	**Complete Cohort n = 26**	**Negative Group n = 3**	**Positive Group n = 23**	**Odds Ratio (95% CI)**	***P***
Retroprosthetic membrane					
Yes	13 (50)	1 (33)	12 (52)	2.2 (0.17, 24.6)	0.55
No	13 (50)	2 (67)	11 (48)		
Epithelial defect					
Yes	5 (19)	0 (0)	5 (22)	*	*
No	21 (81)	3 (100)	18 (78)		
Corneal melt					
Yes	4 (15)	0 (0)	4 (17)	*	*
No	22 (185)	3 (100)	19 (83)		

*Undefined because of cells with no observations.

injuries.[7] In contrast to Robert et al, we failed to find a difference across diagnostic categories.

The Boston KPro is made from polymethyl methacrylate (PMMA) and titanium, both highly biocompatible materials. In fact, PMMA has been used in intraocular lenses without significant reports of inflammation when well positioned for many decades. However, direct contact between the PMMA and titanium of the KPro device and corneal stroma may incite an inflammatory response. In addition, friction between the device and the corneal tissue caused by blinking may also lead to wear out and inflammation.[19] Furthermore, increased expression of MMP-9 has been shown in biofilms.[20,21] The KPro device itself and continuous contact lens wear increase the risk of biofilm development.[22] The biofilm structure facilitates the survival of microorganisms as they are protected from immunologic and antibiotic penetrance and leads to low-grade inflammation.[20,23] Together, these factors may explain the higher levels of MMP-9 in KPro eyes found in our study.

The use of topical medications, particularly glaucoma drops, can also lead to ocular inflammation.[24–26] Zaleska-Zmijewska et al[26] measured ocular surface inflammation using the InflammaDry test and found that there was an increase in MMP-9 levels in patients on benzalkonium chloride (BAK)-containing medications versus patient on preservative-free formulations. In our cohort, we failed to find an association between the use of glaucoma drops and increased levels of MMP-9, although we recognize that a proinflammatory effect from glaucoma medications cannot be ruled out in this study.

Postoperative complications after KPro implantation are relatively common and cause attrition of visual acuity over time limiting long-term outcomes.[4,15,27,28] Retroprosthetic membrane is the most common complication ranging from 30% to 52%, followed by persistent corneal epithelial defects (10%–43%) and sterile keratolysis in 16% to 26% of KPro eyes among other complications.[3–6,27–30] Aligned with previous studies, the most common complications in our cohort included RPM, epithelial defect, and corneal melt. Unsurprisingly, our results also suggest that eyes with KPro and a positive MMP-9 test have an increased risk of postoperative complications. In fact, our study found that 100% of eyes developing epithelial defects and corneal melts had a positive MMP-9 test. Mohan et al[9] suggested that the presence of MMP-9 can alter corneal reepithelization and lead to continuous epithelial breakdown. MMP-9 destabilizes the tear film and directly contributes to dysfunction of the corneal barrier by breaking down epithelial tight junctions. This process facilitates inflammatory cell migration and leads to tear film abnormalities and a hostile ocular surface environment.[7,11–13]

To the best of our knowledge, the use of MMP-9 immunoassay in patients with KPro has not been described previously. This point-of-care test is easy to use and can be performed at a regular office visit. Patients with KPro are usually in a prophylactic regimen that includes topical antibiotics ± steroid drops. Usually, topical steroids are used in high frequency during the early postoperative care, and they are typically tapered or even discontinued in some cases several months after surgery. The risk of long-term steroid use is weighed against the higher risk of complications particularly related to ocular surface inflammation for each patient. MMP-9 results may aid the clinician in assessing the presence of subclinical inflammation in KPro eyes and may be used along with other clinical findings to inform frequency of steroid dosing and speed of taper and whether steroid therapy should be maintained or discontinuation may be considered. Because so many complications in patients with KPro are mediated by inflammation, a more specific and tailored immunomodulatory regimen can potentially decrease the risk and improve outcomes.

Our study has several important limitations. First, we have a small sample size that limits the statistical analysis. As a result, our statistical power is greatly diminished, and our null associations should not be interpreted directly. In addition, inflammatory status of the cornea is a dynamic process that is constantly changing; therefore, a single survey of MMP-9 on the ocular surface may not be representative of the true inflammatory state. Furthermore, the InflammaDry test is a qualitative test that is assessed visually. Despite our quality control by having multiple investigators read the same test strip independently, there is still a risk of exposure misclassification. Furthermore, we are limited in the design of the study as it is cross-sectional where the MMP-9 test was not necessarily measured at the same point in time as when the postoperative complications were reported and there is a lack of baseline (preoperative) MMP-9 levels. As a result of these, we are limited in causal inference as we cannot infer temporality.

In conclusion, our results suggest that the KPro device induces a heightened inflammatory state on the ocular surface as evidenced by the increased levels of MMP-9 in KPro compared with control eyes. It also suggests that a positive MMP-9 test may be associated with a higher risk of complications. Further studies are needed to confirm these findings and to better understand the role that POCT of MMP-9 can have in the postoperative care of patients with KPro.

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