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Corneal epithelial permeability: Ethnic differences between Asians and non-Asians

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ABSTRACT

Purpose: To ascertain whether a difference in the permeability of the corneal epithelium to fluorescein (P_{dc}) exists between Asians and non-Asians.
Methods: From a multi-study database we extracted 632 records of baseline, open-eye P_{dc} measurements taken on both eyes of 176 subjects. Subjects were awake for a minimum of 4 h before measurement, and were free of ocular disease and central corneal staining. P_{dc} was transformed by natural logarithm to better approximate normality for statistical tests.
Results: The mean ln(P_{dc}) in the Asian group was significantly greater than in the non-Asian group [−2.34 ln(nm/s) vs. −2.58 ln(nm/s); $p < 0.001$].
Conclusions: Compared with non-Asians, Asians exhibited a less negative ln(P_{dc}), which translates to a higher P_{dc} and a more permeable corneal epithelium. We speculate that this may be related to anatomic differences responsible for greater eyelid tension in Asians.

1. Introduction

Information about ethnic differences in ocular physiology is scarce in the literature despite significant anatomical differences between Asian and Caucasian eyes. Compared with Caucasians, Asians have a distinctly different eyelid anatomy including a more oblique palpebral fissure, a smaller vertical palpebral aperture and greater herniation of the orbital fat in the lids [1–4]. Given these differences in ocular anatomy, one may presume that the ocular response to contact lens wear could also differ. Recent reports indicate that the Asian eye does respond differently to external stimuli (e.g., contact lens wear, hypoxia) than does the non-Asian eye, with a less stable pre-lens tear film [5], a thinner post-lens tear film [6], and more significant endothelial bleb formation [7]. Additionally, Asians are more susceptible to sub-clinical disruption of the corneal epithelium, causing greater corneal permeability, during contact lens wear [8,9].

Although it is documented that Asians and non-Asians differ in ocular anatomy and in response to contact lens wear, it is not known whether an underlying physiologic difference at the ocular surface exists as well. The corneal epithelium is the primary deterrent to foreign organisms entering the eye and plays a key role in modulating the innate defense system of the ocular surface [10,11]. Therefore, determining whether there are ethnic differences in the permeability of this crucial tissue layer could have implications for the pharmacokinetics of topical ocular agents, for our understanding of ocular surface health and integrity, and for the diagnosis and treatment of ocular surface disease in different patient populations.

Corneal epithelial barrier function has been quantified by measuring the rate of penetration of sodium fluorescein dye into the cornea by fluorometry [12–14]. Corneal epithelial permeability (P_{dc}) is determined by instilling the dye on the ocular surface and measuring the decay in fluorescence over time as the dye penetrates the epithelium. A higher P_{dc} (typically expressed in nm/s) indicates a more permeable corneal epithelium and thus a reduction in epithelial barrier function.

In this retrospective study, we examined baseline, open-eye P_{dc} from a large database of Asian and non-Asian non-contact lens-wearers to determine whether there are underlying ethnic differences in corneal epithelial barrier function.

2. Methods

2.1. Subjects

A total of 639 records were extracted from a database of five P_{dc} studies conducted at the University of California, Berkeley Clinical Research Center between 2004 and 2011. These studies recruited only potential subjects who had never worn contact lenses, or who had worn contact lenses in the past but discontinued more than one

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year prior to the study. Subjects were recruited from the campus of the University of California, Berkeley and surrounding community. Subjects taking systemic medications, having a prior history of seasonal allergies, or having a history of ocular surgery or disease were excluded from the studies. A subject's systemic disease status was inferred from his or her reported systemic medications. The baseline measurement protocol was identical for the five studies, with all subjects being measured after a minimum of 4 h awake. A total of 183 subjects contributed to these records, each subject having a series of fluorescence readings to determine P_{dc} taken on both eyes at one or more visits, depending on the study. A few subjects participated in more than one study. Seven outliers were removed due to poor scans, most likely from insufficient fluorescein loading caused by reflex tearing, which gave P_{dc} values of essentially zero. Therefore, in this analysis, we included 632 records from both eyes of 176 subjects. Ethnicity was self-reported by subjects; an inherent weakness is present with self-reporting but practical considerations prevented a more rigorous approach (e.g., genetic testing). In our study the Asian group included Chinese, Korean, Vietnamese and Taiwanese subjects, and the non-Asian group included Caucasians and Latinos.

Informed consent was obtained from all participants after a complete description of the goals, risks, benefits and procedures of the studies. These studies observed the tenets of the Declaration of Helsinki and were approved by the University of California, Berkeley Committee for Protection of Human Subjects.

2.2. Instrumentation and procedures

The experimental protocol common to all 5 studies required one afternoon visit by each subject to determine baseline, open-eye P_{dc}. Subjects reported to the laboratory at least 4 h after awakening for the afternoon visit. An anterior segment examination with a slit-lamp biomicroscope in white light was performed to ensure that the ocular surface was free of any disease or defect.

An automated scanning fluorometer (Fluorotron Master®, Ocumetrics, Mountain View, CA, USA) was used to measure P_{dc}. After measuring the background stromal autofluorescence, a micropipette was used to instill 2 μl of 0.35% sodium fluorescein dye onto the superior bulbar conjunctiva of a randomly selected eye. The subject was instructed to close the eye and roll it to evenly distribute the dye, then a fluorometer scan was performed on that eye. The procedure was repeated for the fellow eye, after which scans were repeated every 2 min, alternating between-eyes, for 20 min, giving a total of 10 scans per eye. At the end of this period, the eyes were thoroughly rinsed with a sterile saline solution (Unisol 4®, Alcon Laboratories, Inc., Fort Worth, TX, USA), and the stromal fluorescence of both eyes was measured again. The processing of the fluorescence decay readings and estimation of P_{dc} have been discussed in detail previously [14].

An exit slit-lamp examination, first using white light, then with sodium fluorescein under cobalt blue illumination viewed using a 530 nm yellow barrier filter, was performed after P_{dc} measurements to screen for central corneal staining and to ensure good corneal health. Central corneal staining with fluorescein was graded on a 1–4 scale, with punctate staining of fewer than five points defined as grade 1; 5–10 points, grade 2; 11–25 points, grade 3; and 26 or more points, grade 4. We have observed that fluorescein can pool and become trapped in irregularities on the ocular surface in the presence of punctate staining; although it has not been established conclusively, it is possible that with central punctate staining, such localized sources of prolonged fluorescence could bias estimates of P_{dc}. We therefore elected to exclude subjects exhibiting more than five punctate stains in the central cornea (3–4 mm) from the analysis [15].

Table 1
Descriptive statistics for raw and natural log-transformed P_{dc} in the Asian and non-Asian study groups. Both eyes and all visits for each subject are included in this summary.

	Number of records	P_{dc}		$\ln(P_{dc})$	
		Mean	SD	Mean	SD
Asian	288	0.1130	0.0731	−2.3400	0.5649
Non-Asian	344	0.0985	0.0950	−2.5846	0.7266

2.3. Statistical methods

The primary outcome variable in this analysis is P_{dc}, which was taken on both eyes of subjects participating in one or more studies, each of which may have had a single or multiple visits. Measurements on fellow eyes are often correlated as are repeated measurements on the same eye. In addition, after approximately three years a second fluorometer, identical to the first instrument, was added to the laboratory. In order to account for the repeated measures structure of the data, additional random within-subject (between-eyes) variability, the addition of a second fluorometer, and the possibility of instrument drift or shifts in observer criteria over the long time period spanned by our database, we employed a mixed effects modeling approach to analyzing the data. Because P_{dc} is a highly skewed variable, we modeled the natural log of the P_{dc} ($\ln(P_{dc})$) in order to better approximate normality. In addition to a random effect for eyes-within-subjects, potential explanatory variables included ethnicity, gender, age, and time awake before measurement. Days from first measurement and instrument were adjusted for in the models. Final models were selected based on F-test p-values, examination of effect sizes, residual and other plots, and comparison by log-Likelihood for nested models and by Akaike's Information Criterion for non-nested models.

3. Results

One hundred seventy six subjects contributed 632 records to the analysis. Subjects were 56% female and 44% male, and 47% Asian and 53% non-Asian. Subjects' ages ranged from 18 to 38 years, with a mean (SD) age of 22.04 (±3.99) years. Awake time before measurement ranged from 4 h to approximately 16 h, with a mean (SD) awake time of 9.68 h (±3.56).

The grand mean (SD) $\ln(P_{dc})$ was −2.47 (±0.67) ln(nm/s) across all measurements. Stratifying on ethnic group (Table 1), the mean (SD) $\ln(P_{dc})$ for Asians was −2.34 (±0.56) ln(nm/s), and for non-Asians was −2.58 (±0.73) ln(nm/s), with Asians having an approximately 27.7% greater P_{dc} (Fig. 1). Note that on the natural

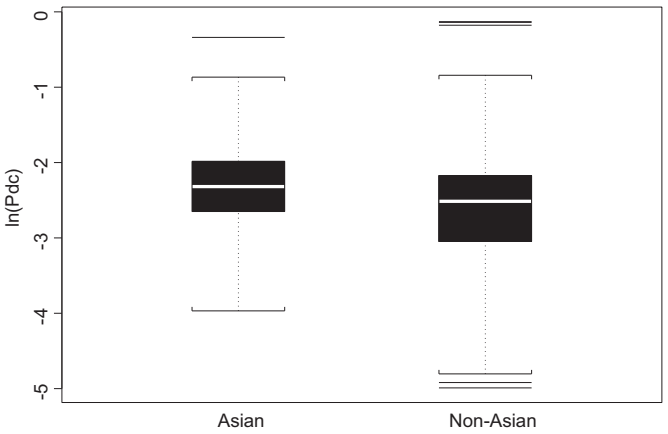

Fig. 1. Asians have a higher baseline epithelial permeability compared with non-Asians. The difference is relatively small, but significant.

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Table 2
Parameter estimates and p-values for two models of $\ln(P_{dc})$. The interaction parameter "Days: Machine" adjusts for days from first measurement on each instrument.

	Model 1		Model 2	
	Estimate	p-value	Estimate	p-value
Intercept	−2.1218	<0.001	−1.9321	<0.001
Race	−0.2269	<0.001	−0.2730	<0.001
Days: machine A	−0.0002	<0.001	−0.0002	<0.001
Days: machine B	−0.0004		−0.0003	
Time awake (min)			−0.0005	0.033

log scale, a less negative value corresponds to a higher P_{dc} and a greater corneal epithelial permeability. In our multivariate models, after adjusting for instrument and days from first measurement, Asians had significantly less negative $\ln(P_{dc})$ than did non-Asians, indicating that Asians had significantly higher baseline epithelial permeability ($p < 0.001$). There were no significant effects on $\ln(P_{dc})$ of either age or gender.

In a previous study we found that awake time before measurement could act as a confounding factor for P_{dc}. After adjusting for awake time in our models, the higher baseline epithelial permeability in Asians remained significant ($p < 0.001$). Table 2 shows the parameter estimates and p-values for the two final models.

4. Discussion

To our knowledge, this study is the first to show a ethnic difference in corneal epithelial permeability, with Asians having a significantly higher baseline P_{dc} than non-Asians by approximately 27% on relatively pristine corneas (i.e., minimal or no central epithelial disruption). After adjusting for a number of factors in multivariate models – the different fluorometers, possible changes in observer criteria over time, and the length of time subjects were awake prior to measurement – the difference between ethnicities remained statistically significant.

We propose that the difference between Asians and non-Asians in corneal epithelial permeability is due to differences in eyelid anatomy. It has been suggested that Asian eyelids exert greater shear stress on the ocular surface than do non-Asian eyelids [9]. Shear stress is created by the interaction of the eyelid and the cornea during a blink, with the magnitude of the shear stress determined by the pressure that the eyelid applies to the cornea [16]. Although few studies on eyelid pressure have been published due to the technical difficulty of making this measurement in vivo, several studies have suggested that there is a relationship between eyelid pressure and changes in corneal topography, particularly induced astigmatism [17–22]. Demographic data on refractive error show higher average levels of astigmatism in Asians compared with non-Asians, which could be due to the Asian eyelid having a narrower palpebral aperture, greater eyelid volume and thus higher eyelid tension. Eyelid morphology, including a narrower palpebral aperture, as well as conditions like ptosis, chalazion, or hemangioma, which increase the pressure of the eyelid exerted on the ocular surface, are known to be associated with astigmatic changes to the cornea [20,21,23–32]. Although it has not to date been measured directly, it is plausible that anatomical features of the Asian eyelid result in greater eyelid pressure and therefore increased shear stress at the corneal surface.

The effects of shear stress can be seen in other parts of the body, increased levels have been associated with nephron damage in renal failure [33] and endothelium damage of blood vessels in cardiovascular disease [34]; greater shear stress on the ocular surface would likely lead to increased trauma to the corneal epithelium. There may be evidence to support the proposition that corneal epithelial barrier function could be compromised by higher levels of shear stress in the Asian eye. For example, mechanical insult to the cornea induced by shear stress may be responsible for epithelial cell apoptosis, desquamation, and disruption of tight junctions [35–39] and has been implicated as a contributing factor to the inflammatory response associated with dry eye [40,41], these factors are likely responsible for increased corneal epithelial permeability. Shear stress-induced epithelial surface disruption and inflammation could explain recent studies reporting greater prevalence of dry eye in Asians compared with non-Asians [42–44]. Asians have also been found to be six times more likely than non-Asians to develop chronic dry eye six months after LASIK [45]. It is possible that these ethnic disparities may be due to up-regulation of pro-inflammatory mediators, which would also presumably disrupt epithelial tight junctions and increase epithelial permeability. Further investigation is warranted to understand the underlying causes of these ethnic differences.

The results of this study also have implications for the effectiveness and risks associated with delivery of topical pharmaceutical agents to the eye. Our data show that sodium fluorescein penetrates the Asian cornea more quickly than it does the non-Asian cornea. Although the molecular characteristics of sodium fluorescein are distinct from other topical ocular agents, it does raise the possibility that the pharmacokinetics of topical medications could vary depending on a patient's ethnicity. This will become increasingly important as residence times of topical pharmaceutical agents in the eye increase with controlled delivery through silicone hydrogel contact lenses [46–50]. Prolonged exposure of the ocular surface to some medications, allowing for greater corneal penetration, could increase the risk of side effects or overdosage. Such risk may be greater for Asians, not only because of a higher baseline P_{dc}, but also because extended-wear soft contact lenses have been shown to result in a greater increase in P_{dc} in Asians than in non-Asians [9].

In summary, we found that there is an underlying ethnic difference between Asians and non-Asians in the permeability of the corneal epithelium. It is likely that greater eyelid tension in Asians due to features of ocular anatomy increases the shear stress at the ocular surface, leading to disruption of epithelial tight junctions and a more permeable epithelium. These results underscore the potential importance for researchers to carefully consider the demographics of subject populations recruited for clinical testing, and for clinicians to critically evaluate the generalizability of clinical trial outcomes to different patient populations served in clinical practice.

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Conflict of interest statement

None.

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