

# Ocular Surface Health during 30-Day Continuous Wear: Rigid Gas-Permeable versus Silicone Hydrogel Hyper-O<sub>2</sub> Transmitted Contact Lenses

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**PURPOSE.** To determine the effects on corneal epithelial permeability and ocular response of 30 nights of continuous wear (CW) of gas permeable (GP) and silicone hydrogel (SiH) contact lenses.

**METHODS.** Ninety-one subjects successfully completed 30 days of CW of either GP ( $n = 42$ ) or SiH ( $n = 49$ ) contact lenses. Epithelial permeability ( $P_{dc}$ ) was measured by scanning fluorometer at an afternoon (PM) baseline session and again the next morning (AM). One randomly selected eye of each subject was patched overnight and the patch removed immediately before the AM visit.  $P_{dc}$  measurements and ocular examinations were conducted at baseline and after 30 days of CW.

**RESULTS.** Epithelial permeability increased significantly after 30 days of CW in the patched eyes of the GP group ( $P = 0.022$ ) and in the unpatched eyes of the SiH group ( $P = 0.004$ ). The increase was driven primarily by the Asian subjects in each group (GP,  $P = 0.015$ ; SiH,  $P = 0.001$ ). There was no significant increase in either lens group in the non-Asian subjects. Multivariate models suggest that the change in AM  $P_{dc}$  from baseline to 30 days of CW was also related to lens type ( $P = 0.035$ ), time awake before measurement ( $P = 0.001$ ), palpebral aperture size ( $P = 0.003$ ), lens deposits ( $P = 0.020$ ), and horizontal lens bearing ( $P = 0.003$ ).

**CONCLUSIONS.** Subclinical increases in epithelial permeability can be caused by contact lens CW, despite the elimination of hypoxia. GP lenses permit recovery of the epithelium more quickly than do SiH lenses. Asians appear to be more susceptible to contact lens-induced epithelial changes than do non-Asians. (*Invest Ophthalmol Vis Sci.* 2011;52:3530–3538) DOI:10.1167/iov.10-6025

It has been well established that contact lens wear poses an increased risk of ocular complications. A compromised corneal epithelium can result from hypoxia, eye closure, and the presence of a contact lens.<sup>1–3</sup> The permeability of the epithelium increases after overnight lens wear of both gas permeable (GP)<sup>4</sup> and soft lenses,<sup>2,5</sup> and the magnitude of the increase is dependent in part on the level of lens oxygen transmissibil-

ity.<sup>2,3</sup> Although hypoxia has been significantly reduced with the advent of hyper-O<sub>2</sub> transmitting lenses, contact lens-induced complications have not been completely eradicated (Levy B, et al. *IOVS* 2000;41:ARVO Abstract 387).<sup>6,7</sup> Consequently, the focus of contact lens research has shifted from studying the effects of hypoxia on corneal physiology to investigating and improving the biocompatibility between the contact lens and the ocular surface.

Many studies have shown a greater incidence of contact lens-related infections in silicone hydrogel (SiH) lens wearers than in those wearing GP contact lenses.<sup>8–10</sup> There are many differences in the physical properties of these two lens types that may explain the differences in ocular surface response. For example, a GP lens is inflexible and retains its postlens tear film (PLTF), as opposed to a soft lens, which can settle against the corneal surface and thereby thin the PLTF (Polse KA, et al. *IOVS* 2002;43:ARVO E-Abstract 970).<sup>11–13</sup> According to dispersive mixing models, a thicker PLTF enhances tear mixing,<sup>14</sup> which can renew a stagnant PLTF and flush out unwanted trapped substances. It is possible that a thicker PLTF and enhanced tear mixing, such as are found with GP lens wear, play an important role in maintaining epithelial barrier function with continuous contact lens wear (CW).

In this study, we compared the ocular response after 30 days' (P30D) CW between GP lenses and SiH lenses. We examined the differences between lens types in corneal epithelial permeability assessed by fluorometry and ocular surface response assessed by biomicroscopy and investigated other factors that might play a role in corneal epithelial permeability changes after 30 days of CW.

## METHODS

### Instrumentation and Measurements

Biomicroscopy (model SL 120; Carl Zeiss Meditec, Inc., Dublin, CA) was used to evaluate ocular surface health in conjunction with the IER (Institute for Eye Research, formerly CCLRU [Cornea and Contact Lens Research Unit]) grading scale.<sup>15</sup> Bulbar and limbal hyperemia, papillae of the upper and lower palpebral conjunctiva, conjunctival and corneal staining with sodium fluorescein (BioGlo; Hilco, Plainville, MA) examined under cobalt blue light with a filter (Wratten 12; Kodak, Rochester, NY) were graded on a 0 to 4 scale. Ocular surface signs were graded separately in the nasal, temporal, superior, and inferior quadrants. The type, depth, and extent of corneal staining were also graded centrally.

A scanning fluorometer (Fluorotron Master; Ocumetrics, Mountain View, CA) was used to perform permeability measurements. The protocol for corneal epithelial permeability ( $P_{dc}$ ) measurement is published elsewhere.<sup>16</sup>

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TABLE 1. Parameters for the SiH and GP Contact Lenses

	SiH	GP
Commercial name	Focus Night & Day	Menicon Z Alpha 1
Material Type	Lotrafilcon A	Tisilfocon A
Average CT, mm	0.08	0.18
Dk	140	163
Dk/t	175	90.6
Total diameter, mm	13.8	9.2 and 9.6

**Contact Lenses**

The two hyper-Dk contact lenses investigated in this study were Menicon Z Alpha 1 (Menicon Co. Ltd., Nagoya, Japan) and Focus Night & Day (CIBA Vision Corp., Duluth, GA). The details of the lenses and the parameters used in the study are provided in Table 1.

**Study Protocol**

According to sample size calculations, approximately 32 subjects in each lens group were needed to detect a difference of 25% in  $P_{dc}$  between lens types with 95% confidence and 80% power. We projected dropout rates of 20% and 15% with the GP and SiH lenses, respectively, as well as a 15% failure rate for  $P_{dc}$  measurements due to insufficient initial fluorescein loading or bad scans caused by a subject's eye movement or blinking and therefore sought to enroll 50 subjects in each lens group.

Prospective subjects aged 18 to 39 years were eligible to participate. No contact lens wear was permitted within 12 months before the

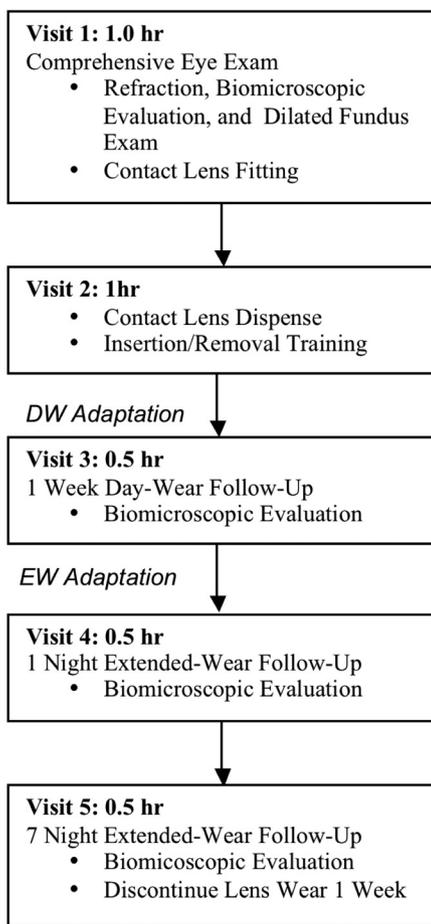
first visit. Subjects with clinically significant dry eye, ocular disease, or systemic conditions with ocular manifestations were excluded. Smokers, frequent swimmers, and those taking medications that could affect the ocular surface or tear film were also excluded. Prospective subjects having spectacle prescription sphere powers between -1.00 and -5.75 D with astigmatism of  $\leq 0.75$  D and between -6.00 and -10.00 D with astigmatism of  $\leq 1.25$  D were eligible.

Figure 1 represents the flow of patient visits. The study consisted of two stages: recruitment and contact lens adaptation (stage 1) and  $P_{dc}$  measurement and ocular health evaluation (stage 2).

Stage 1 began with a comprehensive eye examination to determine eligibility. Once enrolled, the subjects were required to adapt first to daily wear and then to extended wear, with each adaptation period lasting for a minimum of 1 week. The subjects were then asked to discontinue all contact lens wear for a minimum of 1 week, to ensure that ocular surface integrity recovered to baseline before commencing CW in stage 2. The means and standard deviations of the washout periods in the GP and SiH lens groups were well matched and not significantly different.

Stage 2 consisted of  $P_{dc}$  measurements and anterior ocular health evaluations.  $P_{dc}$  measurements were taken at baseline (BL) before CW and 30 days (P30D) after the start of CW. Morning (AM)  $P_{dc}$  was measured within 2 hours of awakening and afternoon (PM)  $P_{dc}$  was measured after at least 4 hours awake. On the evening before the AM  $P_{dc}$  measurements, the subjects were required to patch one randomly selected eye, and the patch was removed the next morning immediately before the first AM measurement. Patching one eye until immediately before measurement served to minimize potential changes in  $P_{dc}$  due to oxygen exposure and blinking associated with open-eye

**Stage 1: Contact Lens Adaptation**



**Stage 2:  $P_{dc}$  Measurements**

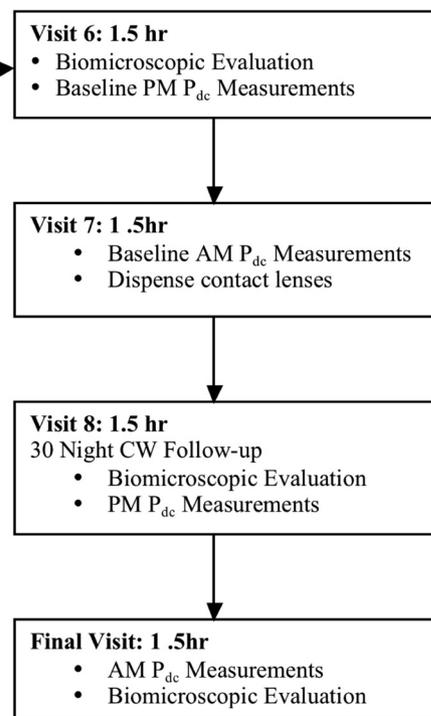


FIGURE 1. Flow of study visits through stage 1 (recruitment and contact lens wear adaptation) and stage 2 ( $P_{dc}$  measurement).

conditions and could provide a more accurate assessment of epithelial barrier function at the time of awakening. The subjects were trained by optometrists in proper patching technique to avoid putting additional pressure on the lens during overnight wear, and proper placement of the patch was verified at the AM visit.

This study adhered to the tenets of the Declaration of Helsinki and was approved by institutional review board (Committee for the Protection of Human Subjects, University of California, Berkeley).

## Statistical Methods

In allocating subjects to the GP and SiH lens groups, a block-randomization scheme was used, such that approximately equal numbers of subjects were enrolled in the two lens groups at any given time throughout the study. This scheme minimized the chance that a systematic bias would be introduced by shifts in observer criteria, change of personnel, or instrument drift during the course of the study.

After a thorough exploratory analysis, we constructed multivariate, linear, mixed-effects models of epithelial permeability, with a random effect for the pairs of eyes within subjects and fixed effects for lens type, study design factors, and both time-variant and time-invariant covariates. The types of explanatory variables examined included study design factors (baseline/P30D, PM/AM, patched/unpatched), demographic information, properties of ocular morphology and tear film, ocular response variables, and contact lens fitting and performance measures. In some cases, statistical power was gained by using a continuous variable (e.g., time awake before measurement), rather than the categorical factor (e.g., AM versus PM). Since both eyes were unpatched all day before the PM measurements, the time awake was the same for both eyes—approximately 500 minutes, on average. The patched and unpatched eyes were distinguished at the AM visit by their awake times of approximately 5 and 50 minutes on average, respectively. The means, standard deviations, and distributions of awake time were well matched in the GP and SiH groups and were not significantly different. The raw  $P_{dc}$  readings were transformed by natural logarithm where necessary, to ensure the approximate normality required by statistical tests. Additive main effects and multiplicative interactions were examined as potential explanatory variables. The fitted models were evaluated by comparing  $F$ -test  $P$  values, examining regression diagnostic plots, comparing log-likelihood values between nested models, and comparing Akaike's Information Criterion between non-nested models.

## RESULTS

A total of 152 subjects were eligible for the study, elected to participate, signed informed consent, and were enrolled in the study. Ninety-one subjects completed the study: 42 in the GP group and 49 in the SiH group. Of the 61 subjects who did not successfully complete the study, 37 belonged to the GP group and 24 to the SiH group (Table 2). In the GP group, 30 (81%) of the 37 subjects who did not complete the study withdrew because of discomfort or inability to adapt to CW. In contrast, in the SiH group, 16 (67%) of the 24 subjects who did not complete the study were disqualified due to contact lens-related ocular complications (see below).

### Adverse Events

Nineteen subjects developed adverse events during the study that contraindicated continuous contact lens wear and subsequently were disqualified from the study. These events included extensive corneal and/or conjunctival staining, contact lens-induced acute red eye, superior epithelial arcuate lesions, asymptomatic infiltrates, and recurrent corneal erosion. The majority of adverse events occurred in the SiH group (84%) compared with the GP group (16%).

TABLE 2. Disposition of Subjects at End of Study

Subjects (n)	Total	GP	SiH
Enrolled	152	79	73
Completed study	91	42	49
DO/DQ	61	37	24
Comfort or adaptation problems	32	30	2
Adverse events	19	3	16
Extensive corneal staining	14	2	12
CLARE	1	0	1
SEAL	2	0	2
AI	1	0	1
RCE	1	1	0
Other DO/DQ	10	4	6
Inadequate best VA	1	1	0
Failed Pdc	5	3	2
Noncompliance	2	0	2
CEF	1	0	1
Lost to follow-up	1	0	1

DO, Dropped Out (voluntarily); DQ, Disqualified (by clinician); CLARE, Contact Lens-induced Acute Red Eye; SEAL, Superior Epithelial Arcuate Lesion; AI, Asymptomatic Infiltrates; RCE, Recurrent Corneal Erosion; CEF, Conjunctival Epithelial Flap (voluntary withdrawal).

### Study Design Factors

Figure 2 shows an increase of 45% in epithelial permeability after 30 days of CW in the patched eyes of the GP group and an increase of 60% in the unpatched eyes of the SiH group. As shown in Table 3, these changes were statistically significant ( $P = 0.022$  and  $P = 0.004$ , respectively). The P30D changes in  $\ln(P_{dc})$  for the unpatched eyes of the GP group (9%,  $P = 0.614$ ) and for the patched eyes of the SiH group (4%,  $P = 0.833$ ) were not significant.

### Demographics

It is well known that Asians and non-Asians differ in several aspects of ocular anatomy and physiology, and several studies in our laboratory have suggested that ethnic differences exist in ocular response to contact lens wear, including changes in epithelial permeability.<sup>4,17</sup> In this study, 50% of the subjects were of Asian descent, including subjects of Chinese, Japanese, South Pacific Islander, Korean, Laotian, Vietnamese, and Taiwanese ethnicities. Caucasians constituted approximately 31% of the subject sample, with 19% other ethnicities, including Hispanics, African Americans, Native Americans, and Indians. Figure 3 shows the changes in  $\ln(P_{dc})$  stratified on ethnicity (Asian/non-Asian) in the patched eyes of the GP group and in the unpatched eyes of the SiH group. It is apparent from Figure 3 and Table 4 that the significantly increased permeability in the patched eyes for GP lenses and in the unpatched eyes for SiH lenses noted above were primarily driven by the Asian subjects in each group. Among the Asian subjects, the change in  $\ln(P_{dc})$  P30D CW with GP lenses (patched eye) was significant at the 0.015 level, and the change with SiH lenses (unpatched eye) was significant at the 0.001 level. Neither of these P30D changes in  $\ln(P_{dc})$  was significant in the non-Asian group.

Ages were similarly distributed in the GP and SiH groups, with median ages of 20 and 21 years, respectively. After adjustment for awake times, there appeared to be a significant decrease in epithelial permeability with age ( $P = 0.010$ ). However, it should be noted that our study population, drawn from the University of California at Berkeley (UCB) campus and the surrounding community, was predominantly younger than 25 years. Contact lens wearers older than 30 years were not well represented in our sample, and we did not recruit subjects older than 39 years of age. Therefore, our data did not allow for a rigorous evaluation of age-related changes in epithelial per-

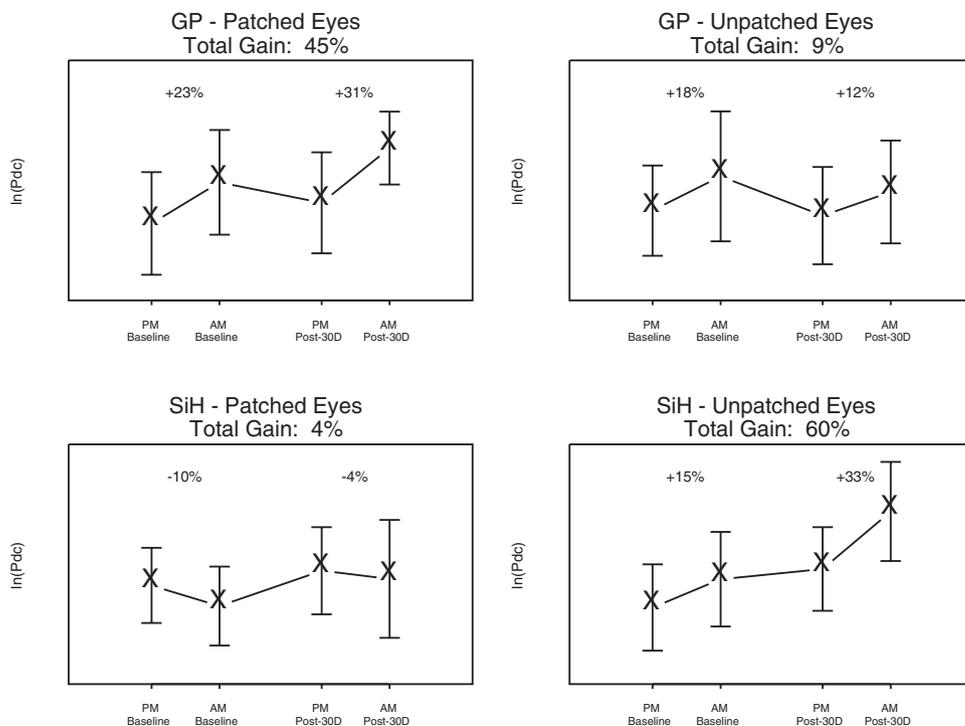


FIGURE 2. The increase in epithelial permeability was observed in the patched eyes wearing the GP lenses and in the unpatched eyes wearing the SiH lenses.

meability. Further study is required to determine whether this result will hold with a larger sample size and whether it may be generalized to the broader age range in the contact lens-wearing population at large.

After adjustment for awake times, there was no significant difference between the genders for either lens type.

**Ocular Morphology and Tear Film**

In our two study groups, palpebral aperture size (PAS) ranged from approximately 6 to 13 mm, with a median PAS in the GP group of 9.6 mm and in the SiH group of 10.0 mm. Figure 4 reveals a slight trend toward greater epithelial permeability after 30 days of CW associated with smaller PAS, which would be consistent with past studies showing higher  $P_{dc}$  among Asians.<sup>4</sup> Models taking the study design variables into account show PAS to be significantly related to  $\ln(P_{dc})$  in the GP group ( $P = 0.039$ ), but not in the SiH group ( $P = 0.682$ ).

Measured perpendicular to the PAS, the horizontal visible iris diameter (HVID) was not significantly related to  $\ln(P_{dc})$  in either lens group and was similarly distributed, with lens group medians of 11.6 and 11.7 mm, respectively.

Corneal curvatures, measured by keratometry in the horizontal (HK) and vertical (VK) meridians, were similarly distrib-

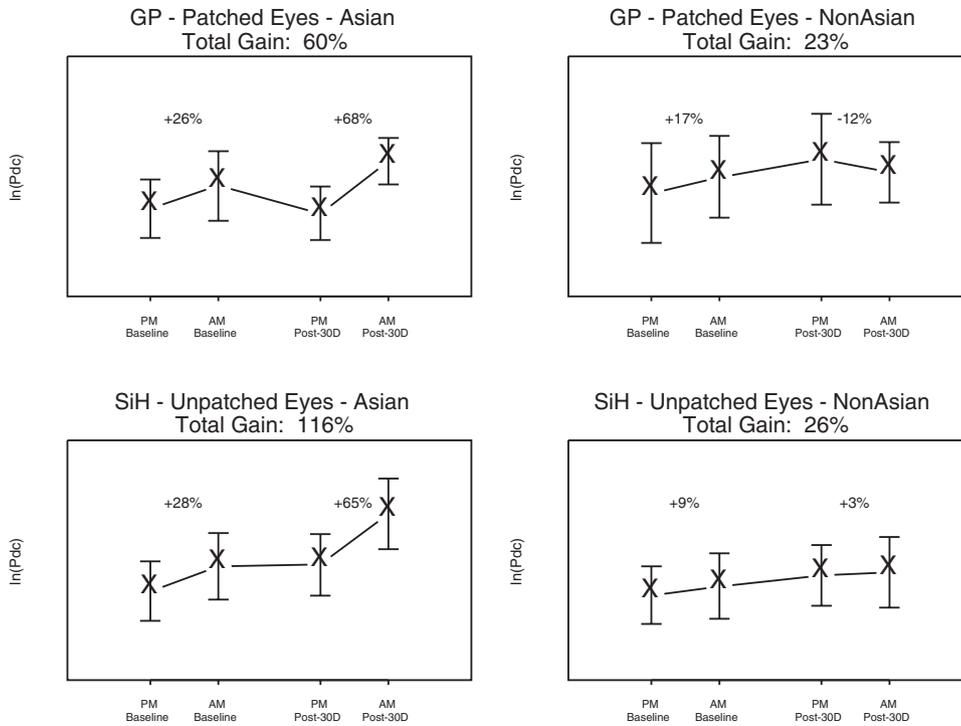
uted in the two study lens groups and highly correlated (Pearson correlation coefficients of 0.964 in the GP group and 0.944 in the SiH group). Figure 5 suggests that greater vertical corneal curvature was associated with greater epithelial permeability in the GP group, but with lower epithelial permeability in the SiH group. Models taking into account the study design factors showed a significant relationship between  $\ln(P_{dc})$  and VK in the GP ( $P = 0.027$ ) and SiH groups ( $P = 0.007$ ). Baseline VKs among Asian subjects (mean, 43.7 D) and non-Asian subjects (mean, 44.4 D) were significantly different ( $P = 0.003$ ). A nearly identical pattern held for horizontal corneal curvature.

Precorneal tear breakup time (TBUT) was taken three times at each visit, and the mean within-eye breakup time (MTBUT) was examined as a predictor of  $\ln(P_{dc})$ . MTBUT was distributed similarly in the GP and SiH groups, with median times of 10 and 11 seconds, respectively. MTBUT was not significantly related to  $\ln(P_{dc})$  in either lens group. Because most clinicians employ a TBUT criterion of  $\geq 10$  seconds to signify "normal" tear film stability, we examined  $\ln(P_{dc})$  stratifying on this criterion and found no significant difference in  $\ln(P_{dc})$  between subjects with normal and subnormal MTBUT. Tear meniscus height and clinical grade of tear debris did not show any significant relationships to  $\ln(P_{dc})$ .

TABLE 3. GP and SiH Contact Lenses at Baseline and after 30 Nights of CW

	Baseline PM	P30D AM	% $\Delta \ln(P_{dc})$	<i>P</i> (b/w visits)
<b>GP</b>				
Patched eye	-2.36 ± 0.13	-1.99 ± 0.09	45% ↑	<b>0.022</b>
Unpatched eye	-2.30 ± 0.11	-2.21 ± 0.13	9% ↑	0.614
<b>SiH</b>				
Patched eye	-2.26 ± 0.10	-2.22 ± 0.15	4% ↑	0.833
Unpatched eye	-2.36 ± 0.11	-1.89 ± 0.13	60% ↑	<b>0.004</b>

Data are the mean  $\ln(P_{dc}) \pm$  SD. Significance is shown in bold.



**FIGURE 3.** The increases in epithelial permeability in the patched eyes of the GP lens group and in the unpatched eyes of the SiH lens group, were primarily driven by the Asian subjects in each group.

**Ocular Response to Contact Lens Wear**

In the temporal quadrant, there was one case of grade 2 or greater bulbar hyperemia in the GP group compared with nine cases in the SiH group ( $P = 0.070$ ). In no quadrant was bulbar hyperemia significantly related to  $\ln(P_{dc})$  for either lens group. In all four quadrants, there were more eyes with grade 2 or greater limbal hyperemia in the SiH group than in the GP group, although none significantly so. Limbal hyperemia was found to be significantly related to  $\ln(P_{dc})$  in the temporal quadrant for the GP group ( $P = 0.049$ ) but not for the SiH group ( $P = 0.323$ ). Blepharitis and meibomian gland dysfunction at the upper and lower margins were not significantly related to  $\ln(P_{dc})$  in either lens group.

Inferior palpebral conjunctival injection was observed in 13 eyes in the GP group, compared to 35 eyes in the SiH group ( $P = 0.013$ ). There were no significant differences between

lens groups in superior palpebral conjunctival injection or in inferior or superior papillae. There were few cases of grade 2 or greater conjunctival staining in either lens group. No conjunctival signs were significantly related to  $\ln(P_{dc})$  for either lens group.

There were no significant differences between lens groups in corneal staining type, depth, or extent. There were no reliable multivariate models that showed a significant relationship between  $\ln(P_{dc})$  and corneal staining.

In total, there were 45 (34%) subjects who developed conjunctival epithelial flaps (CEFs) during the course of the study. Of the cases of CEF, 42% occurred in the GP group and 58% occurred in the SiH group ( $P = 0.003$ ). Presence or absence of CEF was not related to  $\ln(P_{dc})$  in either lens group. A more detailed report on CEF has been published previously.<sup>18</sup>

**TABLE 4.** GP and SiH Contact Lenses at Baseline and after 30 Nights of CW, Stratified on Ethnicity

	Baseline PM	P30D AM	% $\Delta$ $\ln(P_{dc})$	<b>P</b> (b/w visits)
<b>Asian</b>				
<b>GP</b>				
Patched eye	-2.42 (-2.71 to -2.13)	-1.95 (-2.18 to -1.72)	60% $\uparrow$	<b>0.015</b>
Unpatched eye	-2.25 (-2.51 to -1.98)	-2.16 (-2.48 to -1.84)	9% $\uparrow$	0.694
<b>SiH</b>				
Patched eye	-2.01 (-2.25 to -1.77)	-1.82 (-2.12 to -1.51)	21% $\uparrow$	0.297
Unpatched eye	-2.41 (-2.70 to -2.11)	-1.64 (-1.99 to -1.29)	116% $\uparrow$	<b>0.001</b>
<b>Non-Asian</b>				
<b>GP</b>				
Patched eye	-2.27 (-2.76 to -1.77)	-2.06 (-2.36 to -1.76)	23% $\uparrow$	0.503
Unpatched eye	-2.39 (-2.81 to -1.98)	-2.29 (-2.72 to -1.86)	11% $\uparrow$	0.770
<b>SiH</b>				
Patched eye	-2.36 (-2.65 to -2.08)	-2.51 (-2.93 to -2.09)	14% $\downarrow$	0.547
Unpatched eye	-2.45 (-2.73 to -2.16)	-2.22 (-2.57 to -1.87)	26% $\uparrow$	0.319

Data are the mean  $\ln(P_{dc})$  (95% confidence interval [CI]). Significance is shown in bold.

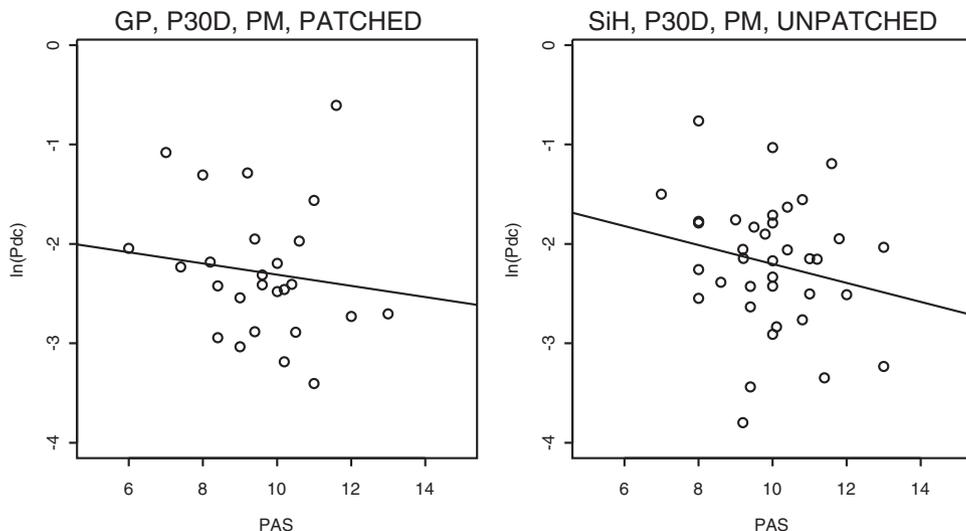


FIGURE 4. There was some suggestion of a trend of greater epithelial permeability associated with smaller PAS.

**Contact Lens Fitting and Performance**

The lens/cornea-bearing relationship was calculated in diopters from the lens base curve radius minus the horizontal or vertical corneal curvature by keratometry. In models taking into account the study design variables, lens-bearing in the two meridians showed no significant relationship to  $\ln(P_{dc})$  in either lens group. As expected, horizontal lens bearing was significantly different between lens types ( $P < 0.001$ ) and was also significantly different between ethnic groups ( $P < 0.001$ ). In the GP group, mean horizontal lens-bearing was  $-0.14$  mm in the Asian subjects and  $-0.09$  mm in the non-Asian subjects; in the SiH group, the mean horizontal lens-bearing was  $-3.19$  mm in the Asian subjects and  $-4.22$  mm in the non-Asian subjects. A similar pattern held for vertical lens-bearing.

Corneal coverage was calculated from the lens diameter and HVID and, as expected, differed significantly between lens types ( $P < 0.001$ ). Corneal coverage was not significantly

related to  $\ln(P_{dc})$  in either lens group. Contact lens wettability, clinical grading of front surface deposits, and lens movement after push-up test also were not significantly related to  $\ln(P_{dc})$ .

**Mixed-Effects Models**

In this section we are primarily interested in the change in epithelial barrier function over 30 days of CW, which can be quantified in different ways. There could be a change in permeability that would be reflected only in the AM  $P_{dc}$  measurements, if the epithelium were still able to recover during open-eye day wear. There could be a more substantial alteration of the epithelium, which would be reflected in the PM  $P_{dc}$  measurements, if after 30 days of CW, the epithelium did not completely recover to baseline levels during the day. There could also be a change in the within-eye percentage overnight change in  $P_{dc}$  at baseline versus P30D CW. We therefore examined three different outcome variables in multivariate models: (1) PMD, the difference in afternoon, open-eye  $P_{dc}$

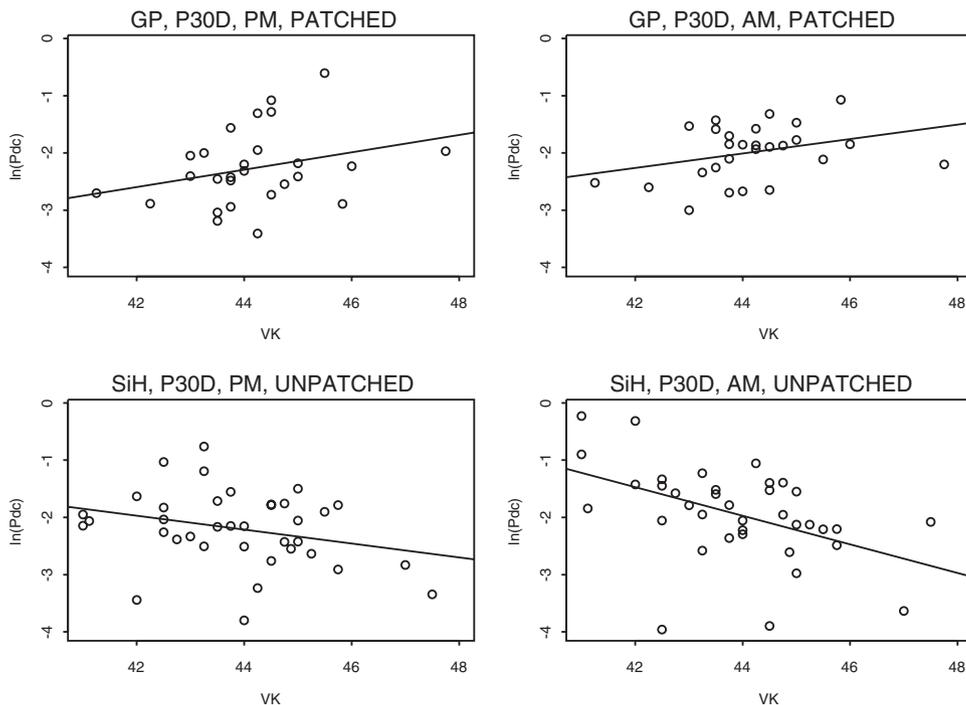


FIGURE 5. Greater epithelial permeability was associated with steeper corneas in the GP lens group, but with flatter corneas in the SiH group.

**TABLE 5.** Outcomes in the GP and SiH Contact Lens Groups after 30 Nights of CW

Outcome Measure	GP		SiH	
	Mean	95% CI	Mean	95% CI
AMD	-0.005	(-0.052 to 0.042)	0.044	(-0.005 to 0.094)
PMD	-0.003	(-0.035 to 0.030)	0.017	(-0.016 to 0.050)
OND	-3.56	(-79.46 to 72.34)	40.34	(-38.73 to 119.41)

Data are the mean  $P_{dc}$ . AMD, difference in AM  $P_{dc}$  after 30 nights of CW; PMD, difference in PM  $P_{dc}$  after 30 nights of CW; OND, difference in percentage of overnight change in  $P_{dc}$  after 30 nights of CW.

after a minimum of 4 hours awake between baseline (no lens wear) and P30D CW; (2) AMD, the difference in morning  $P_{dc}$  between baseline (no lens wear) and P30D CW; and (3) OND, the difference in the percentage of overnight change in  $P_{dc}$  between baseline (no lens wear) and P30D CW.

Table 5 shows the mean and confidence interval for each of these outcome measures, stratified by lens group. In all three cases, the change in epithelial permeability after 30 days of CW was greater for the SiH lenses than for the GP lenses, although not significantly so. Taking into account the study design factors, demographic information, ocular response, and lens performance variables, we found no model that revealed a significant difference between lens types in PMD or OND.

In contrast, there were several significant factors that are associated with AMD. As Table 6 shows, the increase in AM  $P_{dc}$  over P30D CW was significantly greater for SiH lenses than for GP lenses ( $P = 0.035$ ). Asian subjects had a significantly greater reduction in AM epithelial barrier function P30D CW than did Caucasian subjects and other ethnicities ( $P = 0.047$ ). Those with larger PAS had a somewhat greater increase in AM  $P_{dc}$  after 30 days of CW ( $P = 0.003$ ). A flatter horizontal lens-bearing relationship resulted in a lesser 30-day increase in AM  $P_{dc}$  for the GP lenses ( $P = 0.003$ ), but a greater 30-day increase for the SiH lenses ( $P = 0.061$ ). Curiously, those with more front surface deposits on the lens had a lesser increase in AM  $P_{dc}$  ( $P = 0.020$ ).

## DISCUSSION

Results in our previous studies suggest that hypoxia without contact lens wear under open- and closed-eye conditions has very little impact on the integrity of the corneal epithelium. However, the combined effect of contact lens-induced hypoxia and overnight contact lens wear increases corneal epithelial permeability, possibly leaving the eye susceptible to ocular complications. This study was conducted to explore other factors that may contribute to increased corneal epithelial permeability after overnight wear by significantly reducing contact lens-induced hypoxia through the use of hyper-Dk contact lenses. Because these lens materials have similar Dk values but substantially different tear-flushing rates (tisilfocon A, T95 = 5 minutes; lotrafilcon A, T95 = 21 minutes),<sup>19-21</sup> their possibly different effects on the corneal surface may reveal other factors that affect corneal epithelial integrity at P30D CW.

We found significantly increased epithelial permeability after 30 days of CW in the patched eyes wearing GP lenses and in the unpatched eyes wearing SiH lenses. This result may point to differences between the two lens types in how they affect the corneal surface during CW. In the unpatched eyes wearing GP lenses, which have a thicker PLTF and faster tear exchange than do SiH lenses, unwanted debris (e.g., inflammatory cells, metabolic byproducts) that has accumulated under

the lens during sleep is rapidly flushed out when the eyes are opened and blinking begins, and no significant increase in  $P_{dc}$  was observed after approximately an hour of awake time. In contrast, in the patched eyes wearing GP lenses, it appears that immediately on awakening, before blinking and tear exchange under the lens, there is a significantly increased  $P_{dc}$ . Because GP lenses maintain a relatively thick PLTF, this suggests that on awakening with GP lens CW, there is a chemical mechanism (i.e., a stagnant PLTF with altered chemistry compared to fresh tears) operating to compromise epithelial barrier function. Because of the faster tear-flushing rate with GP lenses, the PLTF can be efficiently replaced with fresh tears, preventing further deleterious effects and allowing the corneal epithelium to recover more quickly.

The results for SiH lens CW were quite different. In the unpatched eyes wearing SiH lenses, which have a much thinner PLTF, relatively poor tear exchange and may conform to the corneal surface (unlike rigid GP lenses), unwanted debris that has accumulated under the lens during sleep may be causing a mechanical insult to the ocular surface as the eyes open and blinking begins. After approximately an hour of open-eye wear, we saw a significantly increased  $P_{dc}$ , which was not seen in the patched eyes wearing SiH lenses. This finding suggests that during SiH lens CW, both mechanical and chemical mechanisms may be operating to compromise corneal epithelial integrity, with the mechanical mechanism predominating. This notion is further supported by the fact that a greater 30-day change in AM  $P_{dc}$  with SiH wear is associated with a flatter fit.

Interestingly, these effects turned out to be primarily driven by the Asian subjects in the two study groups. Asians appeared to be more susceptible to epithelial damage due to overnight contact lens wear. Increased epithelial permeability was associated with steeper corneas in the GP lens group and with flatter corneas in the SiH lens group. We found the Asians in our study to have significantly flatter corneas, on average, compared with non-Asians. This finding is in agreement with past studies in our laboratory<sup>4</sup> as well as several published reports<sup>22,23</sup>; however, other studies have found that non-Asians have steeper corneas on average,<sup>24</sup> or that there is no significant difference in corneal curvature between Asians and non-Asians.<sup>25,26</sup> We also found that the 30-day change in AM  $P_{dc}$  was associated with steeper lens fit in the GP group and with flatter fit in the SiH group. The Asians in our study did tend to be fit steeper in the GP group and flatter in the SiH group. However, it appears that this is not a simple case of confounding, because ethnicity was a significant factor in the model, even after adjustment for the lens/cornea-bearing relationships.

Although it is not completely understood why Asians and non-Asians differ with respect to the impact of overnight contact lens wear on the epithelium, one of the most obvious anatomic differences between ethnic groups is the palpebral aperture size, which is generally smaller in epicanthic eyes. There is evidence that aperture size can be related to epithelial

**TABLE 6.** Parameter Estimates and  $P$  for a Multivariate Model of AMD

Explanatory Variable	Effect Size	$P$
Intercept	-0.2670	0.106
Lens type	0.2339	0.035
Time awake	0.0002	0.001
Ethnicity	-0.0296	0.079
PAS	0.0201	0.003
Deposits	-0.0523	0.020
Horizontal bearing	-0.0431	0.003
Lens-bearing interaction	0.0878	0.061

changes in overnight contact lens wear, due to differing interactions among the corneal surface, lids, and contact lens for large versus small PAS.<sup>4</sup> In our study, PAS was significantly related to corneal epithelial permeability in the GP group but not in the SiH group. In addition, the Asian and non-Asian subjects in the study had approximately the same PAS, on average. This may be due to the misclassification bias inherent in self-reported ethnicity data from a genetically mixed study population such as the UCB campus community, or may be due to errors in performing the manual PAS measurement (e.g., apprehensive subjects tend to open their eyes more during measurement). In models of the 30-day change in AM  $P_{dc}$ , we found a significant association between increased permeability and Asian ethnicity, PAS, and the lens type-bearing interaction. Because ethnicity was still a significant factor, even after adjustment for these other covariates, the model suggests that ethnicity is not simply a proxy variable for PAS and lens fit and that there may be inherent differences between Asian and non-Asian tear biochemistry or susceptibility of the ocular surface to mechanical disruption from a contact lens or chemical insult from a stagnant PLTF. In addition to the anatomic differences between Asians and non-Asians, it has been shown in a recent study that the elasticity and viscosity of the tear lipids are significantly different between these two groups (Lin MC, et al. *IOVS* 2010;51:ARVO E-Abstract 4155). It is possible that these differences contributed to the differences observed in the effect of CW on corneal epithelial integrity between these two ethnic groups, as tear biophysical properties can play a significant role in maintaining ocular surface homeostasis.

Adverse events occurred in 3 (3.8%) of the 79 subjects in the GP group and in 16 (21.9%) of the 73 subjects in the SiH group. Morgan et al.<sup>8</sup> found the percentage of adverse events for GP and SiH lens groups to be 8% and 32%, respectively, and the U.S. Food and Drug Administration (FDA) safety and effectiveness studies<sup>27,28</sup> reported approximately 0.8% of subjects having adverse events in the GP lens study, with 13.4% of subjects having adverse events in the SiH lens study. The differences between these studies can be explained, not only by slightly different definitions of adverse events, but also by differences in eligibility criteria. Although our study recruited only neophytes, Morgan et al. recruited 50 experienced contact lens wearers and 50 neophytes, and the FDA studies recruited approximately 91% experienced contact lens wearers. There is a fundamental difference between neophytes and experienced contact lens wearers: experienced contact lens wearers can arguably be considered at lower risk for developing adverse events as a group, because many patients with an increased risk will have already been eliminated from the successful contact lens-wearing population; in contrast, the risk level for contact lens-related adverse events in a neophyte group is unknown and is likely to include a range of individual risk levels from low to high. Both our study and Morgan et al. which included neophyte subjects, showed considerably higher rates of adverse events compared with the FDA studies.

There was a greater proportion of discontinuations from the study due to unacceptable comfort or inability to adapt to CW from the GP group (79%) than from the SiH group (21%). In Morgan et al., 57% of the clinical discontinuations were GP wearers and 43% were SiH wearers. Of the total discontinuations in the two FDA studies, 51% were from the GP group, and 49% were from the SiH group. Again, these discrepancies may be attributed to the different recruitment criteria for the studies. In our study, in which only neophytes were recruited, subjects were new to lens wear, especially rigid contact lens wear, and had a more difficult time adapting. The proportions of discontinuations among GP and SiH wearers were much closer in Morgan et al. and virtually the same in the FDA studies

that enrolled approximately 91% experienced contact lens wearers.

A potential limitation of this study is that it was not possible for optometrists to be masked, because of the obvious physical differences between SiH and GP lenses. Although every effort was made to adhere to standardized clinical grading scales (e.g., for corneal staining), the grading is a potential source of bias. Epithelial permeability measurements, in contrast, were taken by technicians who were masked and who adhered to a priori criteria for accepting or rejecting fluorometer scans.

While contact lens-induced hypoxia is a contributing factor to reduced corneal epithelial integrity, this study suggests that other factors play a role, including contact lens type; ethnicity; ocular anatomy, such as lid aperture size and corneal curvature; and the fit of the contact lens on the eye. In particular, it is plausible that the higher rate of postlens aqueous tear flushing with the GP lenses was responsible for the lower  $P_{dc}$  in the unpatched eyes after approximately an hour awake, compared with the SiH lenses. Therefore, a better understanding of the tear flow dynamics during contact lens CW with different lens materials and identification of patients most likely to achieve success with certain lens materials based on ethnicity and ocular anatomy can help minimize the risk of corneal morbidity with continuous contact lens wear.

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### References

- McNamara NA, Chan JS, Han SC, Polse KA, McKenney CD. Effects of hypoxia on corneal epithelial permeability. *Am J Ophthalmol*. 1999;127:153-157.
- Lin MC, Soliman GN, Song MJ, et al. Soft contact lens extended wear affects epithelial permeability: hypoxic or mechanical mechanism? *Contact Lens Anterior Eye*. 2003;26:11-16.
- Lin MC, Polse KA. Hypoxia, overnight wear, and tear stagnation effects on the corneal epithelium: data and proposed model. *Eye Contact Lens*. 2007;33(6):378-381.
- Lin MC, Graham AD, Fusaro RE, Polse KA. Impact of rigid gas-permeable contact lens extended wear on corneal epithelial barrier function. *Invest Ophthalmol Vis Sci*. 2002;43:1019-1024.
- McNamara NA, Polse KA, Fukunaga SA, Maebori JS, Suzuki RM. Soft lens extended wear affects epithelial barrier function. *Ophthalmology*. 1998;105:2330-2335.
- Yeniad B, Adam YS, Bilgin LK, Gozum N. Effect of 30-day continuous wear of silicone hydrogel contact lenses on corneal thickness. *Eye Contact Lens*. 2004;30:6-9.
- Nilsson SE. Seven-day extended wear and 30-day continuous wear of high oxygen transmissibility soft silicone hydrogel contact lenses: a randomized 1-year study of 504 patients. *CLAO J*. 2001;27:125-136.
- Morgan PB EN, Maldonado-Codina C, Efron S. Adverse events and discontinuations with rigid and soft hyper Dk contact lenses used for continuous wear. *Optom Vis Sci*. 2005;82:528-535.
- Gleason W, Tanaka H, Albright RA, Cavanagh HD. A 1-year prospective clinical trial of Menicon Z (tisilfocon A) rigid gas-permeable contact lenses worn on a 30-day continuous wear schedule. *Eye Contact Lens*. 2003;29:2-9.
- Stapleton F, Keay L, Edwards K, et al. The incidence of contact lens-related microbial keratitis in Australia. *Ophthalmology*. 2008;115:1655-1662.
- Lin MC, Graham AD, Polse KA, Mandell RB, McNamara NA. Measurement of post contact lens tear thickness. *Invest Ophthalmol Vis Sci*. 1999;40:2833-2839.
- Wang J, Fonn D, Simpson TL, Jones L. Precorneal and pre- and postlens tear film thickness measured indirectly with optical co-

- herence tomography. *Invest Ophthalmol Vis Sci.* 2003;44:2524-2528.
13. Nichols JJ, King-Smith PE. The effect of eye closure on the post-lens tear film thickness during silicone hydrogel contact lens wear. *Cornea.* 2003;22:539-544.
  14. Creech JL, Chauhan A, Radke CJ. Dispersive mixing in the posterior tear film under a soft contact lens. *Indus Eng Chem Res.* 2001;40:3015-3026.
  15. CCLRU Grading Scales. In: Phillips AJ, Speedwell L, eds. *Contact Lenses.* Oxford, UK: Boston: Butterworth-Heinemann; 1997:xxi,889.
  16. McNamara NA, Fusaro RE, Brand RJ, Polse KA, Srinivas SP. Measurement of corneal epithelial permeability to fluorescein: a repeatability study. *Invest Ophthalmol Vis Sci.* 1997;38(9):1830-1839.
  17. Lin MC, Chen YQ, Polse KA. The effects of soft lens and ocular characteristics on the post-lens tear thickness. *Eye Contact Lens.* 2003;29(1 suppl):S33-S36; discussion S57-S59, S192-S194.
  18. Graham AD, Truong TN, Lin MC. Conjunctival epithelial flap in continuous contact lens wear. *Optom Vis Sci.* 2009;86:e324-331.
  19. Kok JH, Boets EP, van Best JA, Kijlstra A. Fluorophotometric assessment of tear turnover under rigid contact lenses. *Cornea.* 1992;11:515-517.
  20. Paugh JR, Stapleton F, Keay L, Ho A. Tear exchange under hydrogel contact lenses: methodological considerations. *Invest Ophthalmol Vis Sci.* 2001;42:2813-2820.
  21. Miller KL, Lin MC, Radke CJ, et al. Tear mixing under soft contact lenses. In: Sweeney DF, ed. *Silicone Hydrogels.* Oxford, UK: Butterworth-Heinemann; 2004:57-89.
  22. Congdon NG, Youlin Q, Quigley H, et al. Biometry and primary angle-closure glaucoma among Chinese, white, and black populations. *Ophthalmology.* 1997;104(9):1489-1495.
  23. Wong MK, Lee TT, Poon MT, Cho P. Clinical performance and factors affecting the physical fit of a soft toric frequent replacement contact lens. *Clin Exp Optom.* 2002;85:350-357.
  24. Ip JM, Huynh SC, Robaei D, et al. Ethnic differences in refraction and ocular biometry in a population-based sample of 11-15-year-old Australian children. *Eye.* 2008;22:649-656.
  25. Shimmyo M, Ross AJ, Moy A, Mostafavi R. Intraocular pressure, Goldmann applanation tension, corneal thickness and corneal curvature in Caucasians, Asians, Hispanics and African Americans. *Am J Ophthalmol.* 2003;136(4):603-613.
  26. Matsuda LM, Kame RT, Hayashida JK. Clinical comparison of corneal diameter and curvature in Asian eyes with those of Caucasian eyes. *Opt Vis Sci.* 1992;69(1):51-54.
  27. U. S. Food and Drug Administration, Center for Devices and Radiological Health. Summary of Safety and Effectiveness: MeniconZ™ (tisilfocon A) Rigid Gas Permeable (RGP) Contact Lenses. July 2000. Available at: [http://www.accessdata.fda.gov/cdrh\\_docs/pdf/P990018b.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf/P990018b.pdf). Accessed April 12, 2010.
  28. U.S. Food and Drug Administration, Center for Devices and Radiological Health. Summary of Safety and Effectiveness Data: Focus® Night & Day™ (Iotrafalcon A) Soft Contact Lenses. October 2001. Available at: [http://www.accessdata.fda.gov/cdrh\\_docs/pdf/P000030b.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf/P000030b.pdf). Accessed April 12, 2010.