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THE EFFECT OF CORNEAL LIGHT SCATTER ON VISION AFTER PENETRATING KERATOPLASTY

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Abstract

Purpose—To determine the effect of corneal light scatter on vision after penetrating keratoplasty (PK).

Design—Cross-sectional study.

Methods—Setting: Cornea service at Mayo Clinic, Rochester, Minnesota.

Study population: 61 eyes with clear grafts at 14.6 ± 10.5 years after PK; 12 eyes with late endothelial failure at 19.7 ± 6.4 years after PK; 41 normal eyes.

Main outcome measures: Backscatter from different depths of the cornea was measured by a custom scatterometer; intraocular forward light scatter was measured with a stray light meter; high-contrast visual acuity (HCVA) was measured by ETDRS or Snellen chart; mesopic and photopic low-contrast visual acuity (LCVA) were measured with a 10% contrast chart.

Results—Backscatter from the anterior, middle (stroma) and posterior thirds of the corneas was higher in clear grafts compared to normal ($P < 0.001$), and higher in grafts with LEF compared to clear grafts ($P < 0.001$). Corneal stromal backscatter from clear grafts correlated with time after keratoplasty ($r = 0.21$, $P = 0.006$, $n = 61$). Forward light scatter was higher in eyes with clear grafts compared to normal ($P \leq 0.006$), and higher in eyes with LEF compared to clear grafts ($P \leq 0.01$). Corneal stromal backscatter from clear grafts correlated with HCVA ($r = 0.34$, $P = 0.02$, $n = 52$), mesopic LCVA ($r = 0.36$, $P = 0.01$, $n = 28$), and photopic LCVA ($r = 0.57$, $P < 0.001$, $n = 28$). Forward scatter in eyes with clear grafts correlated with photopic LCVA ($r = 0.38$, $P = 0.04$, $n = 26$).

Conclusions—Light scattered from the cornea increases with time after PK and is associated with decreased high- and low-contrast vision.

INTRODUCTION

Penetrating keratoplasty (PK) is a successful procedure for restoring vision in eyes with abnormal corneal clarity or curvature, with 70% of grafts surviving for 15 years after surgery.

¹ In an otherwise healthy eye after PK, visual acuity is typically limited by high or irregular astigmatism,^{2–4} whereas subtle changes in corneal clarity after PK are not typically considered

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to be visually significant. Gross decreases in graft clarity, such as scarring or other opacity, result in poor vision and such grafts are considered to have failed.¹

Late endothelial failure (LEF) is a leading cause of graft failure^{1,5} and is characterized by chronic graft endothelial dysfunction with stromal translucency in the absence of an immune or inflammatory process, and unresponsive to corticosteroid therapy.^{6,7} In clinical practice, we have observed that subtle stromal translucency can be an early sign of LEF, and in the present study, we objectively quantified corneal backscatter (haze) in penetrating grafts that were either considered healthy or had LEF. We also explored the relationships between scattered light and vision in these eyes and compared the findings to eyes with normal corneas.

METHODS

Subjects

Patients with penetrating grafts were recruited from the cornea service at Mayo Clinic. Sixty-one grafts in 46 patients at 14.6 ± 10.5 years after PK (mean $\pm$ standard deviation; range, 1 to 30 years; median, 20 years) were deemed clear by slit-lamp examination, and 12 grafts in 11 patients at 19.7 ± 6.4 years after PK (range, 6 to 28 years; median, 20 years) had LEF. Eyes with graft opacities other than LEF were excluded. Forty-one eyes of 41 subjects with normal corneas recruited to another study⁸ served as controls. This study adhered to the tenets of the Declaration of Helsinki and was approved by the Mayo Clinic Institutional Review Board. Informed consent was obtained from all subjects after explanation of the nature and possible consequences of the study.

Scattered Light and Vision

Central corneal backscatter (haze) was measured by using a custom scatterometer.⁸ Briefly, a modified slit-lamp was used to acquire high-magnification images of a narrow slit-beam through the cornea. Backscattered light from the anterior, middle and posterior thirds of the cornea was measured from the intensity across the digitized image of the cornea. All measurements were standardized to a reference and expressed in scatter units (SU).⁸ Although we use the term “backscatter” to mean corneal haze, this term includes light that is reflected, in addition to scattered back, from the cornea.⁹ Central graft thickness of the clear grafts was measured by using the scatterometer, which is a modified video pachometer,^{8,10} and by using an ultrasonic pachometer (DGH-1000, DGH Technologies, Inc., Frazer, PA).

Intraocular forward light scatter was measured with a stray light meter,¹¹ which used the direct compensation method to measure retinal stray light.¹² This instrument measured the effect on central vision of light scattered within the eye from incident light sources at angles of 3.5°, 10°, and 28° from the visual axis. A “stray light parameter” was defined as $\log(\phi^2 L/E)$, where ϕ was the angle between the optical axis and the ring of modulated lights, L was the luminance of the compensating light at the center of the field, and E was the illuminance on the subject’s eye from the ring of lights.¹² Forward light scatter was proportional to the stray light parameter. Forward light scatter was measured in 43 of the 61 eyes with clear grafts that had corneal backscatter measurements; after excluding 5 eyes with visually-significant cataracts and 1 eye with macular disease (which might contribute to poor fixation), forward light scatter data were available for 37 of the 61 eyes (61%) with clear grafts that had backscatter measurements. In the LEF group, forward light scatter was measured in 4 of the 12 eyes that had corneal backscatter measurements; after excluding 1 eye with a visually-significant cataract, forward light scatter data were available for 3 of the 12 eyes (25%) with LEF. Forward light scatter measurements were available in all 41 control eyes, which had normal corneas and no other ocular abnormality.

Best spectacle-corrected high-contrast visual acuity (HCVA) was measured by the electronic Early Treatment of Diabetic Retinopathy Study (eETDRS) protocol¹³ in 19 eyes with clear grafts, and by Snellen chart in 33 eyes with clear grafts and all 12 eyes with LEF. Visual acuity was converted to logarithm of the minimum angle of resolution (logMAR). After excluding 5 eyes with visually-significant cataracts and 4 eyes with macular disease, HCVA data were available for 52 of the 61 eyes (85%) with clear grafts that had corneal backscatter measurements. In the LEF group, we excluded 1 eye with a visually-significant cataract, leaving HCVA data available for 11 of the 12 eyes (92%) that had corneal backscatter measurements. HCVA was measured by eETDRS in all 41 eyes of controls.

Best spectacle-corrected low-contrast visual acuity (LCVA) was measured by using a backlit 10% Sloan Translucent Low Contrast Chart (Precision Vision, La Salle, IL) with a testing distance of 4 meters. LCVA was measured in a darkened room and recorded as letter scores under photopic (screen brightness, 139 cd/m²) and mesopic (screen brightness, 1.1 cd/m²) conditions; mesopic conditions were achieved by placing a neutral density (2 ND) filter in front of the low-contrast chart. The backlight for the translucent chart acted as a source of glare. Letter scores were converted to logarithm of the minimum angle of resolution (logMAR). At our testing distance, the largest letters on the low contrast chart represented a visual acuity of 1.1 logMAR (Snellen equivalent, 20/317), and eyes that could not read any letters were assumed to have LCVA of 1.1 logMAR, even though their LCVA might have been worse. LCVA was measured in 32 of the 61 eyes with clear grafts that had corneal backscatter measurements; after excluding 3 eyes with visually-significant cataracts, and 1 eye with macular disease, LCVA data were available for 28 of the 61 eyes (46%) with clear grafts that had corneal backscatter measurements. In the LEF group, LCVA was measured in 5 of the 12 eyes that had corneal backscatter measurements; after excluding 1 eye with a visually-significant cataract, forward light scatter data were available for 4 of the 12 eyes (33%) with LEF. LCVA was only recorded in 20 of the 41 (49 %) control eyes.

For clear grafts, endothelial cell density (ECD) and keratocyte density were measured by using confocal microscopy *in vivo*. Confocal images of the endothelium were acquired with the ConfoScan 3 or ConfoScan 4 confocal microscopes (Nidek Technologies, Greensboro, NC) and images were analyzed by using the HAI Cell Analysis System Corners Method (HAI Labs, Lexington, MA).¹⁴ After excluding 1 eye because the endothelial images were uncountable, ECD was measured from 60 of the 61 grafts (98%) that had corneal backscatter measurements. Full-thickness mean keratocyte density and keratocyte density in the middle third of the stroma were measured from images acquired by using a Tandem Scanning confocal microscope (Tandem Scanning Corporation, Reston, VA) and analyzed by using a custom automated program, as described in detail previously.^{15,16} Keratocyte density measurements were available for 57 of the 61 grafts (93%) that had backscatter measurements, and were a subset of keratocyte density data from a larger group of eyes after PK.¹⁷

Data Analysis

Corneal backscatter, intraocular forward light scatter, HCVA and LCVA were compared between clear grafts, grafts with LEF, and normal corneas. Because subjects with PKs and subjects with normal corneas were not matched for HCVA, we calculated the low-contrast loss of acuity by subtracting HCVA (logMAR) from LCVA (logMAR),^{18,19} and compared low-contrast loss between groups. All comparisons were completed by using generalized estimating equation models to account for potential correlation between fellow eyes of the same patient.²⁰ $P \leq 0.05$ was considered statistically significant. Minimum detectable differences were calculated for non-significant differences ($\alpha=0.05$, $\beta=0.20$). For clear grafts, correlations (Pearson correlation coefficients) were assessed between corneal backscatter, intraocular

forward light scatter, HCVA, LCVA, ECD, keratocyte density, and central corneal thickness, and significances were determined by using generalized estimating equation models.

RESULTS

Corneal backscatter was increased by 80% ($P < 0.001$), 49% ($P < 0.001$) and 34% ($P = 0.01$) in grafts with LEF ($n=12$) compared to clear grafts ($n=61$) in the anterior, middle and posterior thirds of the cornea, respectively (Table 1, Figure 1). Backscatter was increased by 16% ($P < 0.001$), 18% ($P < 0.001$) and 29% ($P < 0.001$) in clear grafts ($n=61$) compared to normal corneas ($n=41$) in the anterior, middle and posterior thirds of the cornea, respectively (Table 1, Figure 1). Backscatter from clear grafts correlated with time after keratoplasty in the anterior ($r=0.23$, $P=0.005$), middle ($r=0.21$, $P=0.006$) and posterior ($r=0.32$, $P=0.003$) thirds of the cornea (Figure 2).

Intraocular forward light scatter was higher in eyes with clear grafts at all incident angles compared to eyes with normal corneas ($P \leq 0.006$), and was higher in eyes with LEF at all incident angles compared to eyes with clear grafts ($P \leq 0.01$, Table 2). HCVA was 0.19 ± 0.19 logMAR in clear grafts ($n=52$), and was almost 4 lines of vision better than in grafts with LEF ($n=11$, $P < 0.001$, Table 3). Mesopic and photopic LCVA were lower by 4 and 5 lines of vision, respectively, in eyes with clear grafts compared to eyes with normal corneas ($P < 0.001$). Mesopic and photopic LCVA did not differ between eyes with LEF and eyes with clear grafts ($P=0.18$ and 0.25 respectively, Table 3); the minimum detectable differences were 0.12 logMAR and 0.39 logMAR respectively. Mesopic and photopic low-contrast loss were higher in eyes with clear grafts compared to eyes with normal corneas ($P < 0.001$), and higher in eyes with clear grafts compared to eyes with LEF ($P < 0.001$, Table 3). In 8 eyes with clear grafts that had HCVA of ≤ 0 logMAR (Snellen equivalent, 20/20 or better), mesopic low-contrast loss (0.84 ± 0.16 logMAR) and photopic low-contrast loss (0.38 ± 0.13 logMAR) were higher than in eyes with normal corneas ($P < 0.001$).

Central corneal thickness in the clear grafts was 561 ± 49 μm when measured with the scatterometer, and 584 ± 53 μm when measured with the ultrasonic pachometer ($P < 0.001$, $n=61$, paired test). Corneal thickness measurements from the scatterometer and the ultrasonic pachometer were highly correlated ($r=0.89$, $P < 0.001$, $n=61$).

For clear grafts, backscatter from the middle third of the cornea (i.e. corneal stroma) correlated with HCVA ($r=0.34$, $P=0.02$, $n=52$), mesopic LCVA ($r=0.36$, $P=0.01$, $n=28$; Figure 3), photopic LCVA ($r=0.57$, $P < 0.001$, $n=28$; Figure 3) and with forward light scatter at an incident angle of 10° ($r=0.41$, $P < 0.001$, $n=35$; Figure 4). For eyes with clear grafts, intraocular forward scatter at an incident angle of 10° was correlated with photopic LCVA ($r=0.38$, $P=0.04$, $n=26$; Figure 5). ECD did not correlate with backscatter from the anterior third of the cornea ($r=-0.21$, $P=0.06$, $n=60$), but did correlate with backscatter from the middle ($r=-0.21$, $P=0.04$, $n=60$) and posterior ($r=-0.29$, $P=0.004$, $n=60$) thirds of the cornea. Backscatter from the middle third of the cornea was correlated with full-thickness keratocyte density ($r=-0.17$, $P=0.004$, $n=57$) and with keratocyte density in the middle third of the stroma ($r=-0.25$, $P=0.002$, $n=57$). Backscatter from the middle third of the cornea did not correlate with central corneal thickness ($r=0.08$, $P=0.32$, $n=61$).

DISCUSSION

Corneal backscatter in penetrating grafts with LEF was higher than in grafts that were deemed clear by slit-lamp examination. Clear penetrating grafts scattered more light than normal corneas, and the increase in backscatter with age of the graft was associated with a decrease in visual acuity.

Immediately after PK, corneal backscatter is higher than normal and can be partially attributed to corneal edema, but even after the edema resolves, increased backscatter persists for much of the first year after PK.²¹ The results of our present study indicate that beyond the first year after PK, backscatter does not return to normal, but gradually increases over three decades. Although central corneal thickness increases in grafts with time after PK,¹ we detected increased backscatter with time after PK independently of the effect of corneal thickness. Absolute light scatter increases as corneal thickness increases because light traverses a longer distance through the cornea; our backscatter parameter does not report absolute backscatter but instead reports backscatter per a defined percentage of corneal thickness.⁸ Therefore, our backscatter parameter is independent of corneal thickness, as demonstrated by the lack of correlation between backscatter and corneal thickness in this study. Because backscatter after PK increases independently of the increase in corneal thickness, increased backscatter could be the result of ultrastructural changes in the graft stroma, which might be related to decreases in endothelial cell density,¹ endothelial permeability,²² keratocyte density,¹⁷ or a combination of these processes. Our study suggested weakly predictive associations between corneal backscatter and keratocyte density, and between corneal backscatter and ECD. Whether the increase in backscatter with time in otherwise healthy penetrating grafts forms a continuum with the onset of stromal translucency noted in early LEF could not be determined from our study, which was cross-sectional, and will only be determined in a large prospective long-term study.

Corneal backscatter *per se* does not affect vision because backscattered light does not affect retinal image quality. Forward light scatter does degrade the retinal image and can affect contrast perception, but the relationship between forward light scatter and backscatter is complex under low scattering conditions.^{23–25} Indeed, we did not establish a relationship between vision and a minimal increase in corneal backscatter after LASIK,²⁶ although after photorefractive keratectomy, in which backscatter (haze) is more evident than after LASIK,²⁷ decreased low-contrast vision has been associated with increased corneal backscatter.²⁸ In the present study, we were able to demonstrate correlations between corneal backscatter, forward light scatter for the whole eye, and vision, possibly because of the higher scattering conditions compared to normal. Because we excluded other sources of light scatter, such as eyes with cataracts, the penetrating graft was the source of increased forward light scatter in our study.

Visual degradation after PK is predominantly caused by postoperative astigmatism,^{2–4} and uncorrected high-order aberrations after PK have been associated with loss of low-contrast vision despite good high-contrast vision.²⁹ Our data indicate that scattered light is also associated with visual degradation after PK, but the weak correlation between forward light scatter and vision in our study might result from the dominant effect of uncorrected astigmatism,¹⁹ because vision was not assessed with contact lens correction. Nevertheless, the relationship between scattered light and vision after keratoplasty will be important when considering the long-term visual outcomes of posterior lamellar keratoplasty. Astigmatism does not change after posterior lamellar keratoplasty,^{21,30,31} whereas corneal backscatter is significantly higher compared to normal and compared to after PK.²¹ Scatter from the lamellar interface and host cornea after posterior lamellar keratoplasty combined with increased scatter from the donor tissue with time after keratoplasty might contribute to decreased vision over the long-term after lamellar keratoplasty. The effect of scattered light on vision will be more prominent when posterior lamellar keratoplasty is performed for hazy penetrating grafts with endothelial failure.³²

Low-contrast loss of vision is the difference between high-contrast and low-contrast logMAR acuities and the measurement has been used when groups of patients are not matched for HCVA.^{18,19,29} When eyes could not perceive the largest letters on the low-contrast chart,

they were considered to have LCVA of 1.1 logMAR (the lowest acuity measurable with our chart). Low-contrast loss data must therefore be interpreted with caution, because LCVA was probably worse than 1.1 logMAR in many instances, and as a result, photopic low-contrast loss was more representative of vision loss than mesopic low-contrast loss because only 4 of 32 eyes with clear grafts could not perceive the largest letters under photopic conditions, whereas 13 of 32 eyes with clear grafts could not perceive the largest letters under mesopic conditions. Similarly, low-contrast loss appeared falsely lower in eyes with LEF than in eyes with clear grafts because 2 of 4 eyes could not perceive the largest letters under photopic conditions and 3 of 4 eyes could not perceive the largest letters under mesopic conditions. Low-contrast loss was significantly higher in eyes after PK that had HCVA ≤ 0 logMAR (Snellen equivalent, 20/20 or better) compared to normal eyes with mean HCVA ≤ 0 logMAR, indicating that contrast testing is better at discriminating vision loss than simply testing HCVA. Based on our results, low-contrast loss after PK might be partially attributed to scattered light in addition to high-order aberrations.

Our study was limited because visual acuity was measured with spectacle correction and not with rigid contact lens correction, which would have minimized the effect of astigmatism on vision. If rigid contact lenses had been placed, vision might still have been affected by increased scatter caused by inducing corneal edema, especially in older grafts with poor endothelial function. Although another study has suggested that vision after PK is limited by high-order aberrations and not from scattered light, because that study also failed to measure vision with rigid contact lens correction, scattered light could not be ruled out as a source of loss of vision.²⁹ Total high-order aberrations were increased by almost a factor of three within the first year after PK (Baratz et al., IOVS 2007;48:ARVO E-Abstract 3527). The mean RMS of coma increased by more than 4 times while the mean RMS of spherical aberration and trefoil increased by more than 2.5. These changes would have certainly degraded the point-spread-function on the retina and may have been as significant as the image degradation by forward scatter. The other limitation is that vision in most patients with LEF was affected by other ocular diseases, preventing an analysis between scatter and vision in this group.

In summary, corneal backscatter in penetrating grafts was higher than in normal corneas and increased with time after PK. Increased backscatter from the cornea after PK was associated with increased intraocular forward light scatter and with decreased visual acuity. Although astigmatism might be the major limiting factor of visual recovery after PK, corneal scatter after PK does have an effect on vision and might be a more important factor that limits visual recovery after endothelial keratoplasty for failed penetrating grafts.

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d. *Conformity with Author Information:* The study was approved by the Mayo Clinic Institutional Review Board, was in compliance with the Health Information Portability and Accountability Acts (HIPAA), and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all study participants.

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Figure 1. Corneal backscatter after penetrating keratoplasty (PK)

Backscatter was measured by using a custom scatterometer in clear grafts 14.6 ± 10.5 years after PK ($n=61$), in grafts with late endothelial failure 19.7 ± 6.4 years after PK ($n=12$), and in normal (unoperated) corneas ($n=41$). Backscatter from the anterior, middle and posterior thirds of the cornea was higher in clear grafts compared to normal ($P<0.001$), and was higher in grafts with LEF than in clear grafts ($P<0.001$). Backscatter was expressed in scatter units (SU).⁸

Figure 2.

The relationship between corneal backscatter and time after penetrating keratoplasty. Backscatter from the middle third (i.e. corneal stroma) of the cornea of clear penetrating grafts increased with time after keratoplasty ($r=0.21$, $P=0.006$, $n=61$). Backscatter was expressed in scatter units (SU).⁸

Figure 3. The relationship between visual acuity and corneal backscatter after penetrating keratoplasty

Backscatter from the middle third (i.e. corneal stroma) of the cornea of clear penetrating grafts correlated with low-contrast visual acuity (LCVA) measured under mesopic ($r=0.35$, $P=0.01$, $n=28$) and photopic conditions ($r=0.57$, $P<0.001$, $n=28$). Backscatter was expressed in scatter units (SU),⁸ and LCVA was expressed as the logarithm of the minimum angle of resolution (logMAR).

Figure 4. The relationship between corneal backscatter and intraocular forward light scatter after penetrating keratoplasty

Backscatter from the middle third (i.e. corneal stroma) of the cornea of clear penetrating grafts correlated with intraocular forward light scatter ($r=0.41$, $P<0.001$, $n=35$). Backscatter was expressed scatter units (SU).⁸

Figure 5. The relationship between visual acuity and intraocular forward light scatter after penetrating keratoplasty
Photopic low-contrast visual acuity (LCVA) correlated with intraocular forward light scatter ($r=0.38$, $P=0.04$, $n=26$). LCVA was expressed as the logarithm of the minimum angle of resolution (logMAR).

Table 1

Corneal backscatter in clear and failed grafts after penetrating keratoplasty

Depth of cornea	Normal Corneas (n=41)	Clear Penetrating Grafts (n=61)	Grafts with Late Endothelial Failure (n=12)
Anterior third	458 ± 38	533 ± 73 [*]	961 ± 579 [†]
Middle third	278 ± 27	327 ± 56 [*]	488 ± 206 [†]
Posterior third	243 ± 27	314 ± 60 [*]	420 ± 152 [†]

Mean ± standard deviation (Scatter Units⁸).^{*} P < 0.001 vs. normal corneas[†] P ≤ 0.01 vs. clear grafts

Table 2

Intraocular forward light scatter in eyes with clear and failed grafts after penetrating keratoplasty.

Stray Light Incident Angle	Stray Light Parameter		
	Normal Corneas (n=40)	Clear Penetrating Grafts (n=37)	Grafts with Late Endothelial Failure (n=3)
3.5°	1.04 ± 0.35	1.40 ± 0.32 [*]	1.67 ± 0.11 [‡]
10°	1.17 ± 0.22	1.47 ± 0.25 [*]	1.64 ± 0.11 [#]
28°	1.13 ± 0.27	1.31 ± 0.32 [‡]	1.56 ± 0.21 [#]

Mean ± standard deviation

^{*} P< 0.001,[‡] P=0.006, vs. normal corneas[‡] P< 0.001,[#] P= 0.01 vs. clear grafts

Table 3

Visual acuity in eyes with clear and failed grafts after penetrating keratoplasty.

	Visual Acuity, logMAR [Snellen Equivalent] (n)		
	Normal Corneas	Clear Penetrating Grafts	Grafts with Late Endothelial Failure
HCVA	-0.09 ± 0.07 [20/16] (41)	0.19 ± 0.19 [*] [20/31] (52)	0.56 ± 0.30 [#] [20/73] (11)
LCVA (Photopic)	0.17 ± 0.18 [20/30] (20)	0.70 ± 0.30 [*] [20/100] (28)	0.85 ± 0.29 [‡] [20/142] (4)
LCVA (Mesopic)	0.54 ± 0.13 [20/69] (20)	0.98 ± 0.16 [*] [20/191] (28)	1.07 ± 0.07 [†] [20/235] (4)
Low-contrast loss (Photopic)	0.28 ± 0.15 (20)	0.51 ± 0.18 [*] (28)	0.32 ± 0.10 [#] (4)
Low-contrast loss (Mesopic)	0.64 ± 0.11 (20)	0.79 ± 0.15 [*] (28)	0.54 ± 0.19 [#] (4)

Mean ± standard deviation; logMAR, logarithm of the minimum angle of resolution; HCVA, high-contrast visual acuity; LCVA, low-contrast visual acuity; low-contrast loss of acuity was defined as the difference between HCVA and LCVA.¹⁸

^{*} P < 0.001 vs. normal corneas

[#] P < 0.001 vs. clear grafts

[†] P = 0.18,

[‡] P = 0.25 vs. clear grafts; the minimum detectable differences were 0.39 logMAR and 0.12 logMAR for photopic and mesopic respectively.