Endothelial Morphometric Measures to Predict Endothelial Graft Failure After Penetrating Keratoplasty

Beth Ann Benetz, MA; Jonathan H. Lass, MD; Robin L. Gal, MSPH; Alan Sugar, MD; Harry Menegay, PhD; Mariya Dontchev, MPH; Craig Kollman, PhD; Roy W. Beck, MD, PhD; Mark J. Mannis, MD; Edward J. Holland, MD; Mark Gorovoy, MD; Sadeer B. Hannush, MD; John E. Bokosky, MD; James W. Caudill, MD; for the Cornea Donor Study Investigator Group

**Importance:** Endothelial morphometric measures have potential value in predicting graft failure after penetrating keratoplasty.

**Objective:** To determine whether preoperative and/or postoperative central morphometric measures (endothelial cell density [ECD], coefficient of variation [CV], and percentage of hexagonality [HEX]) and their postoperative changes are predictive of graft failure caused by endothelial decompensation after penetrating keratoplasty to treat a moderate-risk condition, principally Fuchs dystrophy or pseudophakic corneal edema.

**Design:** In a subset of Cornea Donor Study participants with graft failure, a central reading center determined preoperative and postoperative ECD, CV, and HEX from available central endothelial specular images.

**Setting:** Cornea Image Analysis Reading Center of the Specular Microscopy Ancillary Study.

**Participants:** Eighteen patients with graft failure due to endothelial decompensation and 54 individuals matched for most donor and recipient measures at baseline whose grafts did not fail.

**Main Outcome Measure:** Change in ECD, CV, and HEX values.

**Results:** Preoperative ECD was not associated with graft failure ($P = .43$); however, a lower ECD at 6 months was predictive of subsequent failure ($P = .004$). Coefficient of variation at 6 months was not associated with graft failure in univariate ($P = .91$) or multivariate ($P = .79$) analyses. We found a suggestive trend of higher graft failure with lower HEX values at 6 months ($P = .02$) but not at the established statistical significance ($P < .01$). The most recent CV or HEX values, as time-dependent variables, were not associated with graft failure ($P = .26$ and $P = .81$, respectively). Endothelial cell density values decreased during follow-up, whereas CV and HEX appear to fluctuate without an apparent trend.

**Conclusions and Relevance:** Endothelial cell density at 6 months after penetrating keratoplasty is predictive of graft failure, whereas CV and HEX appear to fluctuate postoperatively, possibly indicating an unstable endothelial population in clear and failing grafts.

**Trial Registration:** clinicaltrials.gov Identifier: NCT00006411


©2013 American Medical Association. All rights reserved.

---

The Cornea Donor Study (CDS)\(^1\) has enhanced our understanding of many factors surrounding the success of penetrating keratoplasty (PKP) for conditions with endothelial dysfunction, notably Fuchs dystrophy and pseudophakic/aphakic corneal edema. The CDS has shown that corneas from donors up to 75 years,\(^1\) other donor factors (method of retrieval, processing factors, and timing of donor cornea use),\(^2\) and ABO incompatibility\(^3\) had no effect on graft survival 5 years postoperatively. On the other hand, the risk for graft failure was approximately 4-fold higher in eyes with pseudophakic/aphakic corneal edema than in eyes with Fuchs dystrophy, whether pseudophakic or not; prior glaucoma surgery and/or preoperative glaucoma medication use also substantially increased the graft failure rate.\(^4\)

Endothelial cell density (ECD) also was assessed in a subset of participants in an ancillary study of the CDS, the Specular Microscopy Ancillary Study (SMAS),\(^5,6\) to examine its relationship with these same donor and recipient factors. A slight association between increasing donor age and greater post-PKP corneal endothelial cell loss by 5 years was found among eyes...
whose grafts were successful at 5 years. Female donors and larger grafts were associated with less cell loss, whereas baseline ECD and other donor and recipient factors had no influence on ECD by 5 years. Although baseline ECD was not predictive of graft failure, the 6-month ECD was.

The literature has suggested that changes in morphometric measures including coefficient of variation (CV), reflecting variation in cell size expressed by the calculated CV of cells areas (polymegathism), and the calculated percentage of hexagonal cells or hexagonality (HEX), reflecting variation in cell shape (pleomorphism), may be more sensitive than ECD in assessing endothelial health and dysfunction. Although the original SMAS was designed to examine ECD solely determined by a variable frame analysis method accommodating all types of image quality, study design and morphometric analysis methods were developed from existing donor and postoperative images to explore whether changes in morphometric measures over time are predictive of graft failure after PKP for endothelial dysfunction conditions. If these measures are more sensitive than ECD in predicting changes in endothelial function after PKP and in identifying possible endothelial dysfunction, monitoring morphometric measures could be more important than monitoring ECD alone.

**METHODS**

**SPECULAR MICROSCOPY ANCILLARY STUDY**

Of the 1090 eligible persons participating in the CDS, the optional SMAS included 596 individuals who participated at 43 CDS clinical sites. Donor corneas were assigned to the SMAS subjects by 31 of 43 participating CDS eye banks, but not all of these eye banks participated in the SMAS, which was also optional for the eye banks. In the SMAS, ECD was determined using the HAI Laboratories variable frame method.

**STUDY COHORT**

This morphometric study was designed as a case-comparison group study and included the baseline donor and the follow-up endothelial images collected after PKP from 72 of these 596 SMAS participants. The primary criterion for inclusion as a case in the study was (1) graft failure due to endothelial decompensation without prior intraocular surgery, trauma, or graft rejection that could have adversely affected the endothelial cells and (2) availability of a specular image within 1.5 years before the date of failure. In addition to the 18 participants with failed grafts who met these criteria, a comparison group was selected that included individuals without graft failure. This comparison group included 3 individuals matched by certain baseline characteristics to each of the 18 cases with graft failure (n=54). The matching variables included diagnosis of Fuchs dystrophy or pseudophakic/aphakic corneal edema, donor age, and reading center–determined ECD. In addition, each person in the comparison group was required to have at least as many months of follow-up as the corresponding case’s time to graft failure and an image that corresponded to the last image before graft failure of the corresponding case.

Sixty-nine baseline images (3 of the graft failure cases did not have an eye bank baseline image) and 270 follow-up images underwent morphometric analysis to obtain assessments of ECD, CV (standard deviation of the mean cell area divided by mean cell area), and HEX. Of the 339 images available for image analysis, 326 gradable images were included in the statistical analysis (68 baseline and 258 follow-up images).

**MORPHOMETRIC IMAGE ANALYSIS**

The Case Western Reserve University Cornea Image Analysis Reading Center used the corners method and the center method for analyses. The corners method is the standard method for determining CV and HEX. For a cell to be gradable, the reader must be able to determine the location of each of the cell’s corners. For our study, at least 5 gradable cells per image were required for the image to be graded. This minimal number was chosen to accommodate postoperative images at high magnification with ECD of less than 800 cells/mm². Readers were required to grade every cell visible, meaning all cell corners could be distinguished accurately. Individual cells did not have to be contiguous to other cells. Mean cell area, CV, and HEX were then calculated using the corners program software (CAS/CL 1.10 Cell Analysis System; HAI Laboratories).

The center method was developed by Konan Medical, Inc, in the 1990s and has become a standard technique for clinical morphometric analysis. For a cell to be gradable, the reader must be able to determine the location of the center of the cell. Therefore, cells for which the center could not be determined owing to indeterminable cell borders or only a portion of the cell being visible in the frame were not graded. The largest area of contiguous cells in the image where the centers could be distinguished accurately was selected by the reader. Any cell that extended outside the frame was not analyzable and thus not marked. The center of all contiguous, analyzable cells was marked. We used the manufacturer’s image analysis software system (KSS-400; Konan Medical, Inc) to calculate mean cell area, ECD, CV, and HEX.

All images were graded by 2 readers and adjudicated by an experienced third reader (B.A.B.) based on defined limits for interobserver variability for the number of cells analyzed per image and ECD, CV, and HEX. The adjudicator initially reviewed all image sets that exceeded the allowable difference in number of cells graded (≥20% difference in total number of cells per time point for images in which the maximum number of cells per image counted by either reader was >50; ≥30% difference for images in which the maximum number of cells per image counted by either reader was ≤50) to determine whether 1 reader or both readers should regrade the image set for that time point. The adjudicator flagged the image set for regrading if a sampling error or an improper corner placement was detected. A second adjudication step compared the ECD, CV, and HEX values and flagged for adjudication all image sets in which the ECD analyses varied by at least 5.0% between readers, the CV varied by more than 15%, and/or the HEX varied by more than 15%. The adjudicator then completed an independent assessment for all images that were flagged for adjudication. A final review of all image assessments was performed if the interobserver variability between the readers and the adjudicator was still above those limits.

**MORPHOMETRIC ANALYSIS OF PREOPERATIVE DONOR IMAGES**

The SMAS required only 1 donor image to be provided to the reading center for analysis. Because of the quality limitations of the donor images, most could not be analyzed using the corners method; thus, the center method was chosen for analysis of the entire donor image set for this study.
MORPHOMETRIC ANALYSIS
OF POSTOPERATIVE IMAGES

As many as 3 images of the central endothelium were collected at 6, 12, 24, 36, 48, and 60 months postoperatively from participants in the SMAS. Because pilot studies (data not shown) determined the clinical images were of sufficient quality to undergo corners analysis, the corners method was used for most of the images.

Images deemed unanalyzable using the corners method were analyzed using the center method. Adjudication for postoperative images analyzed using the center method used the same approach described for the donor images. Images that could not be analyzed with the center method were rejected and excluded from analyses.

STATISTICAL ANALYSIS

The data of the 72 participants in this study were censored at the first occurrence of a confounding event (eg, intraocular surgical procedure, ocular trauma, graft rejection) or the last visit date. The proportional hazards model was used to assess the association of graft failure and morphometric measures (ECD, CV, and HEX) preoperatively at baseline and at 6 months postoperatively. Models also were fit with the most recent morphometric value as a time-dependent variable. No significant deviation from the proportional hazards assumption was detected for these models.

We compared the 5-year morphometric measures (CV and HEX values at 5 years and the percentage of change from baseline to 5 years) between the 2 donor age groups (<66 and ≥66 years) using analysis of covariance models. All models were fit with the rank-normalized transformation (van der Waerden scores) of the morphometric variable (CV or HEX) and adjusted with the baseline values.

The relationship between the ECD obtained in the morphometric study using the corners and center methods and the ECD obtained in the SMAS study using the variable frame method was assessed by means of the Spearman rank correlation coefficient. The ECD values obtained by the 2 different methods of image analysis were comparable for all clinical images (cor-
participants was 71 (8) years; 46 (64%) were women, and 66 (92%) were non-Hispanic white. Forty-eight participants (67%) underwent PKP because of a diagnosis of pseudophakic/aphakic corneal edema; 68 (94%) were pseudophakic after the surgery (Table 1). The variables used for matching (baseline diagnosis, donor age, and preoperative ECD) were distributed similarly between the 18 participants with graft failure and the 54 without failure (Table 1).

**MORPHOMETRIC MEASURES AND GRAFT FAILURE**

Preoperative morphometric measures were not associated with graft failure due to endothelial decompensation (for ECD, \( P = .43 \); for CV, \( P = .91 \); and for HEX, \( P = .86 \)). Among 14 graft failure cases with baseline data available, the median ECD at baseline was 2526 (interquartile range [IQR], 2385-2969) cells/mm\(^2\); median CV, 0.33 (0.29-0.36); and median HEX, 61% (54%-65%). The corresponding values in the comparison group were 2664 (IQR, 2418-2905) cells/mm\(^2\), 0.33 (0.31-0.36), and 59% (55%-64%) (Table 2).

**Figures 1, 2, and 3** illustrate the changes in the morphometric measures over time in the graft failure and comparison groups. Unlike the ECD values, which tended to decrease steadily during the study follow-up, the CV and HEX values appeared to fluctuate without an apparent upward or downward trend. Six months after surgery, the median ECD fell to 1752 (IQR, 1234-2558) cells/mm\(^2\), the median CV decreased to 0.25 (0.23-0.28), and the median HEX decreased to 57% (50%-63%) in the graft failure group; the corresponding values in the comparison group were 2394 (IQR, 2005-2649) cells/mm\(^2\), 0.25 (0.23-0.28), and 63% (57%-70%). In univariate analyses, the 6-month ECD values were associated with subsequent failure (\( P = .04 \)), whereas the 6-month CV values were not (\( P = .91 \)). We found a suggestive trend of higher graft failure with lower HEX values at 6 months (\( P = .02 \)); however, this association did not meet our criteria for statistical significance (\( P < .01 \)). When analyzed as time-dependent variables, the most recent CV or HEX values were not associated with subsequent graft failure (\( P = .26 \) and \( P = .81 \), respectively).

### Table 2. Morphometric Measures According to Graft Failure Status

<table>
<thead>
<tr>
<th>Graft Failure Status</th>
<th>No. of Patients</th>
<th>ECD, Cells/mm(^2)</th>
<th>CV</th>
<th>HEX, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td>Median (IQR)</td>
<td>( P ) Value</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Graft failure</td>
<td>14</td>
<td>2526 (2385 to 2969)</td>
<td>.43</td>
<td>0.33 (0.29 to 0.36)</td>
</tr>
<tr>
<td>Nonfailure</td>
<td>54</td>
<td>2664 (2418 to 2905)</td>
<td>.36</td>
<td>0.33 (0.31 to 0.36)</td>
</tr>
<tr>
<td>6 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subsequent graft failure</td>
<td>11</td>
<td>1752 (1234 to 2558)</td>
<td>.004</td>
<td>0.25 (0.23 to 0.28)</td>
</tr>
<tr>
<td>Nonfailure</td>
<td>35</td>
<td>2394 (2005 to 2649)</td>
<td></td>
<td>0.25 (0.23 to 0.28)</td>
</tr>
</tbody>
</table>

Abbreviations: CV, coefficient of variation; ECD, endothelial cell density; HEX, hexagonality; IQR, interquartile range.

\( a \)Generated from univariate Cox models fitted with the continuous morphometric measures at baseline and 6 months. The models with the 6-month measures and the 6-month relative change are conditional on graft survival by 6 months.

\( b \)One of the 69 baseline images available for morphometric analysis was nongradable.

\( c \)Calculated as the difference between the morphometric values at 6 months and baseline divided by the baseline value. The relative change is expressed as a percentage, with a negative sign indicating loss of ECD or decreased HEX or CV.

### RESULTS

**PARTICIPANTS**

The mean (SD) age at the time of PKP for the 72 study participants was 71 (8) years; 46 (64%) were women, and...
All 3 morphometric measures were included as model covariates in a multivariate analysis assessing factors associated with graft failure (Table 3). Similar results were generated from the multivariate models with morphometric measures at baseline and at 6 months. The multivariate model with time-dependent covariates illustrated that CV (P = .85) and HEX (P = .98) did not contribute any additional predictive value for graft failure besides that of ECD alone (P < .001).

We found no association between donor age and CV and HEX values at baseline (Figure 4) or at 5 years. Among the 27 patients with 5-year morphometric measures available (16 patients received corneas from donors aged <66 years and 11 received corneas from donors aged ≥66 years), the baseline median CV was 0.32 (IQR, 0.30-0.34) in the younger donor group and 0.36 (0.31-0.37) in the older donor group (P = .25), which decreased to 0.25 (0.19-0.29) and 0.27 (0.21-0.37), respectively, at 5 years (P = .78). The median HEX at 5 years increased to 64% (IQR, 53%-70%) in the younger donor group and to 63% (49%-69%) in the older donor group (P = .76) from 61% (56%-66%) at baseline in both groups (P = .67).

This study showed that preoperative ECD determined from a morphometric approach was not predictive of graft failure, whereas the 6-month ECD was. Results were similar to those from the overall SMAS analysis. The 6-month HEX results were suggestive of a weak association with subsequent graft failure, whereas CV was not predictive of graft failure despite theoretical and thermodynamic hypotheses that a more stressed endothelium that could be at risk for progression to graft failure would demon-

**Table 3. Morphometric Measures and Graft Failure Due to Endothelial Decompensation: Proportional Hazards Regression Multivariate Analyses**

<table>
<thead>
<tr>
<th>Covariate</th>
<th>No. of Patients</th>
<th>Hazard Ratio (95% CI)²</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative (baseline) VF-ECD</td>
<td>68</td>
<td>1.06 (0.87-1.28)</td>
<td>.56</td>
</tr>
<tr>
<td>Preoperative (baseline) CV</td>
<td></td>
<td>1.10 (0.96-1.34)</td>
<td>.92</td>
</tr>
<tr>
<td>Preoperative (baseline) HEX</td>
<td></td>
<td>0.94 (0.33-2.70)</td>
<td>.91</td>
</tr>
<tr>
<td>Model 2c</td>
<td>46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VF-ECD at 6 mo</td>
<td></td>
<td>1.20 (1.04-1.38)</td>
<td>.01</td>
</tr>
<tr>
<td>CV at 6 mo</td>
<td></td>
<td>0.79 (0.60-1.10)</td>
<td>.79</td>
</tr>
<tr>
<td>HEX at 6 mo</td>
<td></td>
<td>2.57 (1.20-5.50)</td>
<td>.02</td>
</tr>
<tr>
<td>Model 3c</td>
<td>72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most recent VF-ECD (time dependent)</td>
<td>1.28 (1.13-1.46)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Most recent CV (time dependent)</td>
<td>1.08 (0.51-2.28)</td>
<td>.85</td>
<td></td>
</tr>
<tr>
<td>Most recent HEX (time dependent)</td>
<td>0.99 (0.62-1.59)</td>
<td>.98</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CV, coefficient of variation; ECD, endothelial cell density; HEX, hexagonality; VF, variable frame.

¹A hazard ratio value greater than 1.00 denotes increased graft failure with lower VF-ECD values, higher CV values, and lower HEX values. The hazard ratio is calculated per 100-cells/mm² change in ECD, 0.10 change in CV, and 10% change in HEX. Morphometric values are treated as continuous variables in all models. Results were similar when the morphometric ECD was used instead of VF-ECD in all models.

²The Cox model is conditional on graft survival at 6 months. Excluded patients include those with graft failure before 6 months (n = 1) or missing 6-month morphometric values (n = 25).

³The Cox model is fitted with all 3 morphometric measures as time-dependent covariates. The most recent covariate is the last morphometric value before graft failure or the last examination date.

This study showed that preoperative ECD determined from a morphometric approach was not predictive of graft failure, whereas the 6-month ECD was. Results were similar to those from the overall SMAS analysis. The 6-month HEX results were suggestive of a weak association with subsequent graft failure, whereas CV was not predictive of graft failure despite theoretical and thermodynamic hypotheses that a more stressed endothelium that could be at risk for progression to graft failure would demon-

![Figure 2. Box plot of the coefficient of variation of cell area over time in study participants with graft failures due to endothelial decompensation (n = 18) and in those whose grafts did not fail (n = 54). Numbers above the whiskers indicate the number of failed grafts available for analysis; numbers below, grafts that did not fail that were available for analysis. Black dots indicate mean values; horizontal lines in the boxes, medians; the bottom and top of the boxes, the 25th and 75th percentiles, respectively; and whiskers, minimum and maximum values.](image1)

![Figure 3. Box plot of the percentage of hexagonal cells (HEX) over time in study participants with graft failures due to endothelial decompensation (n = 18) and in those whose grafts did not fail (n = 54). Numbers above the whiskers indicate the number of failed grafts available for analysis; numbers below, grafts that did not fail that were available for analysis. Black dots indicate mean values; horizontal lines in the boxes, medians; the bottom and top of the boxes, the 25th and 75th percentiles, respectively; and whiskers, minimum and maximum values.](image2)
months with regard to graft failure. To our knowledge, this study is the first examination of the use of these morphometric measures at baseline or at 6 months to predict graft failure with PKP. The simpler use of ECD at 6 months determined by variable frame analysis or morphometrically remains the best measure to predict endothelial failure after PKP.

In a previous series of reports analyzing the performance of corneal preservation media, no major changes were found in CV or HEX as long as 1 year after PKP for endothelial dysfunction and keratoconus. In a series of studies examining a cohort at 5, 10, 15, and 20 years with a declining number of clear grafts after PKP for endothelial dysfunction conditions and keratoconus, the authors noted (1) no significant change in CV for as long as 3 years postoperatively at 0.26 and then a progressive increase to 0.33 by year 10, with stable values thereafter; (2) fluctuation of HEX, starting at 68% and moving down and up during the first 5 years postoperatively and then a progressive decline to 52% by year 20; and (3) a progressive increase in central corneal thickness, from 0.54 μm at 2 months to 0.59 μm in the 20th year. The authors attributed these changes to the increasing number of late endothelial failures during this entire period. Notably, however, by 20 years, only 22% of the 41 clear grafts (of 388 grafts total) were available for analysis, and no imputation was made to relate the missing data from deaths, loss to follow-up, and graft failures to the changes in CV and HEX.

Although our study and others have not shown CV and HEX to be predictors of endothelial and graft failure, these measures have been somewhat more successful in predicting endothelial recovery after intraocular procedures. Schultz et al showed the dynamic changes in CV and HEX after cataract surgery with recovery and restoration of normal corneal thickness 3 months postoperatively. Several long-term studies (a 4- to 5-year period) on phakic intraocular lenses have documented significant changes in CV and HEX that are associated with cell loss, but changes were not correlated with ultimate corneal decompensation. In one study, HEX showed a greater change in individuals with severe diabetes mellitus 6 months after phacoemulsification compared with individuals without diabetes mellitus who underwent similar surgery, suggesting that these diabetic patients had more compromised endothelium. In a separate study, the same group correlated an increase in corneal thickness and CV in patients with diabetes mellitus for more than 10 years compared with patients with diabetes mellitus for less than 10 years and similarly found a lower HEX with an increase in thickness. The greater dynamic changes in cell morphology and loss of endothelial cells after PKP in the grafts that survive and those that fail, unlike cataract surgery, appear to preclude the use of these measures to predict graft failure.

A factor that reduces the utility of CV and HEX to predict graft failure after PKP and may have contributed to the fluctuation we observed in these measures over time.
is the difficulty in achieving a highly reproducible measurement of both variables given the compromised endothelial image quality and heterogeneous population of a relatively small sample of cells to analyze. This lack of reproducibility may not have been apparent in prior morphometric studies with PKP because all these studies used a single trained reader. Nevertheless, in this study, the use of a dual-grading method with trained readers—highly successful for ECD determination—demonstrated greater interobserver variability for CV and HEX than was reported in the prior study. To reduce this variability, we implemented a 2-step adjudication process. Much of this variability was due to differences in cell selection by the 2 readers, which accentuated differences in the CV and HEX with 50 cells or less of varying size and shape to analyze. This variability is not surprising and has been observed previously in polymegathous corneas, including those undergoing PKP, but not in normal corneas. We believe that using the corners method with dual grading and adjudication remains the best approach to measure CV and HEX, particularly in this population of polymegathous corneas, but only when image quality is good to excellent, as in normal corneas.

Interest remains in determining whether morphometric measures (CV and HEX) could be more sensitive than ECD in detecting endothelial dysfunction after PKP. Although we believe that the apparent fluctuation in these measures represented an unstable endothelial population in clear and failing grafts, the fluctuation could also be attributed to measurement error. The cases (failures) included only those grafts that failed solely because of endothelial decompensation without prior intraocular surgery, ocular trauma, or graft rejection that could have adversely affected the endothelial cells. Perhaps with a larger sample size, different study design, and greater inclusion of cases with graft failure due to other causes, different results may have been found. Endothelial imaging at intervals more frequent than every year, given the continued dynamic changes in the endothelial population after PKP, also may reveal greater predictive value of changes in these morphometric measures. Finally, studies also would be improved with increased emphasis on photographer training to yield better-quality donor and postoperative images.

In summary, the study results show that ECD at 6 months was predictive of subsequent graft failure. The CV and HEX fluctuated down and up during the 5-year follow-up period and did not add to the predictive value of ECD.

Submitted for Publication: July 6, 2012; final revision received September 26, 2012; accepted October 3, 2012.
Published Online: March 14, 2013. doi:10.1001/jamaophthalmol.2013.1693

Author Affiliations: Department of Ophthalmology and Visual Sciences, Case Western Reserve University and University Hospitals Eye Institute, Cleveland, Ohio (Ms Benetz and Drs Lass and Menegay); Jaeb Center for Health Research, Tampa, Florida (Ms Gal and Dontchev and Drs Kollman and Beck); W. K. Kellogg Eye Center, University of Michigan, Ann Arbor (Dr Sugar); Eye Center, University of California Davis Health System, Sacramento (Dr Mannis); Cincinnati Eye Institute, Cincinnati, Ohio (Dr Holland); Gorovoy Eye Specialists, Ft Meyers, Florida (Dr Gorovoy); Wills Eye Institute, Jefferson Medical College, Philadelphia, Pennsylvania (Dr Hannush); Eye Care of San Diego, San Diego, California (Dr Bokosky); and Charleston Eye Care, Charleston, West Virginia (Dr Caudill).

Correspondence: Jonathan H. Lass, MD, c/o Cornea Donor Study Coordinating Center, Jaeb Center for Health Research, 15310 Amberly Dr, Ste 350, Tampa, FL 33647 (jonathan.lass@uhhospitals.org).

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported by cooperative agreements EY12728 and EY12358 with the National Eye Institute, National Institutes of Health, Department of Health and Human Services; Eye Bank Association of America; Bausch & Lomb, Inc; Tissue Banks International; Vision Share, Inc; San Diego Eye Bank; The Cornea Society; Katena Products, Inc; ViroMed Laboratories, Inc; Midwest Eye-Banks (Michigan Eye-Bank, Illinois Eye-Bank); Konan Medical Corp; Eye Bank for Scleral Restoration; SightLife; Sight Society of Northeastern New York (Lions Eye Bank of Albany); and Lions Eye Bank of Oregon.

Additional Contributions: Christopher R. Croasdale, MD, Mark J. Milfin, MD, and Joel Sugar, MD, members of the CDS Publications Committee, independently reviewed and approved the manuscript for submission.

REFERENCES


Minocycline-Induced Scleral and Dermal Pigmentation
Jaclyn L. Kovach, MD
Bradley T. Kovach, MD

Photographs showing bluish pigmentation of bilateral sclera within the palpebral fissure in both the right eye (A) and the left eye (B) of a 65-year-old white man who developed scleral and skin pigmentation after 30 years of using minocycline hydrochloride for the treatment of ocular rosacea. Dermal pigmentation can also be seen on the left medial malleolus (C).