# Racial Differences in Ocular Oxidative Metabolism:

## Implications for Ocular Disease

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## Abstract

**Objective**—To compare the $PO_2$ distribution in different regions in the eyes of patients undergoing intraocular surgery.

**Methods**—Before initiation of intraocular cataract and/or glaucoma surgery, an optical oxygen sensor was introduced into the anterior chamber via a peripheral corneal paracentesis. The tip of the flexible fiberoptic probe was positioned by the surgeon for 3 measurements in all patients: (1) near the central corneal endothelium, (2) in the mid–anterior chamber, and (3) in the anterior chamber angle. In patients scheduled to undergo cataract extraction, $PO_2$ was also measured (4) at the anterior lens surface and (5) in the posterior chamber just behind the iris. Oxygen measurements at the 5 locations were compared using a 2-tailed unpaired *t* test and multivariate regression.

**Results**—The $PO_2$ value was significantly higher in African American patients at all 5 locations compared with Caucasian patients. Adjusting for age increased the significance of this association. Adjusting for race revealed that age was associated with increased $PO_2$ beneath the central cornea.

**Conclusions**—Racial differences in oxygen levels in the human eye reflect an important difference in oxidative metabolism in the cornea and lens and may reflect differences in systemic physiologic function. Increased oxygen or oxygen metabolites may increase oxidative stress, cell damage, intraocular pressure, and the risk of developing glaucoma. Oxygen use by the cornea decreases with age.

Glaucoma is one of the leading causes of blindness and visual disability worldwide, affecting more than 60 million individuals.[1] The prevalence of glaucoma is disproportionately higher in African populations.[2] In the United States, the Baltimore Eye

Survey[3] found that the prevalence of glaucoma in individuals of African descent was 6 times more than the levels in the Caucasian population in some age groups. Primary open-angle glaucoma is the leading cause of blindness in the African American population, where it is 16 times more likely to result in blindness than in Caucasian Americans.[4,5] Glaucoma is also diagnosed approximately 10 years earlier and shows more rapid progression in the African American compared with the Caucasian population.[6] Ocular hypertension, the most important risk factor for the development of primary open-angle glaucoma, occurs 12 years earlier in this population, with a higher percentage of African Americans compared with Caucasians progressing to the development of glaucoma.[6] Population-based studies outside the United States found similar results. The Barbados Eye Study showed that 1 in 11 Afro-Caribbeans older than 50 years and 1 in 6 older than 70 had open-angle glaucoma.[7] On the West Indian island of St Lucia, the homogeneous Afro-Caribbean population has a prevalence of glaucoma significantly greater than that of the Caucasian populations in other studies.[8] Investigations in Tanzania and South Africa confirmed the high prevalence of glaucoma in individuals of African descent.[9,10]

Several studies[11–13] have suggested that oxidative damage contributes to the development of glaucoma. Oxidative damage may contribute to primary open-angle glaucoma by increasing intraocular pressure and by directly damaging retinal ganglion cells or their axons. Sources of oxidative damage include by-products of normal cellular metabolism, such as superoxide anion and hydrogen peroxide, which increase when cells are exposed to oxygen at higher than normal levels.

Studies[14,15] have shown that removal of the vitreous body, the gel between the lens and the retina, during retinal surgery exposed the posterior surface of the lens to increased oxygen, and oxidative damage was associated with the rapid progression of nuclear cataracts. Chang[16] found that vitrectomy also increased the risk of primary open-angle glaucoma, especially after cataract surgery. He hypothesized that oxygen or an oxygen metabolite, such as hydrogen peroxide, damaged cells in the outflow pathway, the main site of damage, leading to increased intraocular pressure. To test the predictions of the Chang hypothesis, we[17] measured the $PO_2$ in the eyes of patients undergoing surgical intervention for cataract and/or glaucoma. During this study, we noted significant differences in $PO_2$ in the eyes of African American and Caucasian patients in a reference group of eyes that had not had previous cataract or vitrectomy operations. These differences in oxygen distribution reflect underlying differences in oxygen use that may be important contributors to the risk of ocular and, perhaps, systemic disease.

## METHODS

### STUDY DESIGN

The Human Resource Protection Office and the Institutional Review Board of the Washington University School of Medicine, in adherence with the tenets of the Declaration of Helsinki, approved this study, which is compliant with Health Insurance Portability and Accountability Act guidelines. Informed consent was obtained from the individuals after explanation of the nature and possible consequences of the study interventions. The study was designed to compare oxygen distribution in different regions of the eye in a reference

group (no previous cataract or vitrectomy surgery) with oxygen distribution in patients with previous vitrectomy, cataract surgery, or both. Patients for the present analysis composed the reference group.

## PATIENTS AND $PO_2$ MEASUREMENTS

Patients undergoing cataract and/or open-angle glaucoma surgical procedures in the subspecialty practice of one of the authors (C.J.S.) were eligible for this study. Patients were excluded from the study if they had evidence of corneal endothelial dysfunction, ischemic ocular disease, anterior chamber angle closure, inflammatory disease, ocular neoplasia, or monocular status. Those who had undergone ocular surgical procedures, except for laser therapy and incisional glaucoma procedures, were also excluded from participation.

A complete general medical and ophthalmic history was obtained and a complete ophthalmic examination was performed. Central corneal thickness was measured by ultrasonography (Pachmate DGH 55; DGH Technology, Inc, Exton, Pennsylvania). Axial length measurements were recorded on patients undergoing cataract extraction (Zeiss IOLMaster; Carl Zeiss Meditec, Jena, Germany). Race was self-reported, using a standardized questionnaire. The pupils of patients undergoing cataract surgery were dilated, and pupil size was measured in all patients. As per usual surgical protocol, the patient was placed in the supine position and intravenous sedation was administered. Supplemental oxygen was provided by nasal cannula. The surgical field was separated from the cannula by an adhesive surgical drape to avoid any additional oxygen exposure to the eye. Arterial oxygen saturation monitoring was performed by continuous pulse oximetry. The surgical eye was prepped and draped and a lid speculum was placed. A sub-Tenon injection of 3 mL of lidocaine, 2%, and bupivacaine, 0.375% (50:50 ratio), was administered to provide local anesthesia. A 30-gauge needle was used for entry into the anterior chamber to fashion a peripheral corneal paracentesis, and the optical oxygen sensor (Oxylab $pO_2$ optode; Oxford Optronix, Oxford, England) was carefully introduced into the anterior chamber without leakage of aqueous humor (Figure 1A). Instrument calibration was checked before and after each set of measurements. The tip of the flexible fiberoptic probe was positioned for 3 measurements in all patients by the surgeon (C.J.S.; Figure 1B): (1) near the central corneal endothelium, (2) in the mid–anterior chamber, and (3) in the anterior chamber angle. In patients scheduled to undergo cataract extraction, additional measurements were taken (4) at the anterior lens surface and (5) in the posterior chamber just behind the iris. This avoided the risk of damage to the lens in patients whose eyes were to remain phakic after the operative procedure. Patients were monitored postoperatively for any complications.

## STATISTICAL ANALYSIS

Results are expressed as mean (SE). Outliers were defined as 1.5 times the interquartile range above or below the 75th or 25th percentile, respectively. Only 1 outlier was detected; removing it had no effect on the statistical significance of any of the results. Statistical analyses were performed using commercial software (SPSS, version 17.0; SPSS, Inc, Chicago, Illinois). Multivariate regression analyses were performed, with adjustment for all potential confounding variables measured. A 2-tailed unpaired $t$ test was used to compare $PO_2$ in the eyes of both groups. $P < .05$ was considered statistically significant.

## RESULTS

Characteristics of the 72 patients who participated in the study are noted in Table 1. There were no significant differences in sex, and similar numbers of patients underwent surgical intervention for glaucoma, cataract, or the combined procedure. The $PO_2$ in different regions of the eye was not related to surgical diagnosis, whether the 3 groups were compared (glaucoma only, cataract only, and cataract and glaucoma) or divided into all glaucoma vs no glaucoma or all cataract vs no cataract. The study included patients with no previous ocular surgery (48 eyes) and those with glaucoma (24 eyes) who had previously undergone a glaucoma surgical procedure (laser trabeculoplasty, iridotomy, or trabeculectomy). Excluding eyes that had undergone previous glaucoma operations had no significant effect on comparison of eyes of African Americans and Caucasians. The African American patients were significantly younger, but central corneal thickness, axial length, and arterial oxygen saturation during surgery were not significantly different between racial groups ($P$ > .10 for all comparisons). The classes and combinations of antiglaucoma medications were similar in the 2 racial groups. Some participants had diabetes mellitus (6 Caucasian [13%] and 6 African American [32%]), but none had ischemic diabetic retinopathy. Diabetes was not significantly related to oxygen levels in the anterior segment of the eye. None of the patients regularly wore contact lenses.

Steep oxygen gradients were identified in all eyes (Figure 2). Subsequent measurements in the same patient were within 1 mm Hg, illustrating the stability of the oxygen gradients when the probe was manipulated in the eye. Measurements in rabbits also demonstrated that intraocular oxygen gradients were stable and showed that they were not affected by convective mixing due to the position of the head (supine vs upright; unpublished data, July 2009). The approximate $PO_2$ of air is 160 mm Hg (21 kPa). There was a 5-fold to 7-fold $PO_2$ steady-state gradient across the cornea. A steep oxygen gradient was also present in the anterior chamber between the inner corneal surface and the anterior lens surface in both groups, with intermediate $PO_2$ in the mid–anterior chamber. The mean $PO_2$ measured in the anterior chamber angle was significantly lower than the measurement at the central cornea. The posterior chamber measurement of $PO_2$ behind the iris was similar to the $PO_2$ anterior to the lens.

Statistical comparison revealed significantly increased $PO_2$ in each of the 5 locations in the eyes of African American compared with Caucasian patients (Figure 2 and Figure 3). After adjusting for age, the differences in $PO_2$ between the racial groups became more significant at all 5 locations (Table 2 and the eTable [http://www.archophthalmol.com]). Adjusting for race revealed a significant age-dependent increase in $PO_2$ beneath the central cornea and in the central anterior chamber. No age-related change in oxygen level was detected near the lens, in the anterior chamber angle, or in the posterior chamber.

## COMMENT

### RACIAL DIFFERENCES IN OCULAR OXIDATIVE METABOLISM

The significantly higher intraocular $PO_2$ detected in African American patients is likely to reflect an important, underlying physiologic difference. The amount and distribution of

oxygen in the eye are an indication of the metabolic activity of the ocular tissues. For example, oxygen diffuses from the air across the avascular cornea. The steady-state $PO_2$ in the aqueous humor at the inner surface of the cornea depends on the diffusion constant of oxygen, diffusion distance, and the consumption of oxygen by the cornea. The diffusion constant of oxygen in corneal tissue would be expected to vary little among individuals with a normal corneal stroma and, in the study group, the $PO_2$ beneath the central cornea was not related to corneal thickness. Therefore, the $PO_2$ at this location is determined primarily by the consumption of oxygen by corneal cells. If oxygen consumption were lower, the $PO_2$ at the inner surface of the cornea would be higher. Therefore, the greater mean $PO_2$ at the inner surface of the cornea in African Americans reflects decreased oxygen consumption by the corneal cells. The corneas of the patients enrolled in this study were clear and without obvious corneal disease. Therefore, the African Americans in this study maintained normal corneal function while consuming less oxygen. Similarly, the higher $PO_2$ measured anterior to the lens and at the other locations in the eyes of African Americans is likely to be the consequence of decreased oxygen consumption by the lens epithelium and other metabolically active tissues. Decreased oxygen consumption could be the result of increased efficiency of oxidative metabolism (less oxygen consumed per mole of adenosine triphosphate produced) or an altered balance between oxidative and glycolytic metabolism (more glucose and less oxygen consumed per mole of adenosine triphosphate produced). It is currently unclear which of these explanations accounts for the observed differences. Altered mitochondrial oxidative metabolism may be associated with diabetes,[18] but we did not find any significant differences in oxygen levels between patients with and those without diabetes in this study.

Oxidative stress has been implicated as an important contributor to age-related cataract and open-angle glaucoma.[15,19–21] Because all patients in this study had cataract, glaucoma, or both, the results would not reveal whether the elevated $PO_2$ in the eyes of African Americans predisposed them to either disease. However, persons of African descent have a significantly greater risk of developing glaucoma compared with Caucasian individuals.[4,5,7,8] Those of African descent also have increased risk for age-related cortical cataracts.[22] The risk of these diseases could be affected by exposure to increased intraocular oxygen. Oxygen reacts with the high ascorbate in the ocular fluids,[23] leading to the production of hydrogen peroxide.[24,25] Peroxide in the aqueous can be degraded by catalase, but excess production could overwhelm this protective mechanism. Excess oxygen could also directly increase production of reactive oxygen species in the cells of the lens and the aqueous outflow system, the trabecular meshwork. The trabecular meshwork cells regulate intraocular pressure and are damaged and depleted in patients with open-angle glaucoma.[11,26] If the differences in oxygen metabolism detected in the anterior segment of the eye reflect similar differences in the retina or optic nerve, increased oxidative stress in these tissues could also contribute to racial differences in glaucoma susceptibility and progression.

The racial differences in oxygen metabolism detected in this study may reflect genetic variation or arise from other factors. However, there is significant genetic contribution to the risk of developing glaucoma.[27,28] Several studies[29–33] have mapped chromosomal regions associated with dominantly inherited increased risk of open-angle glaucoma, including a recent study of individuals of African descent from Barbados.[29] However, the causative

genetic modifications at these loci have not been identified, and the functions of all the genes lying within the mapped intervals are not known. It would be particularly interesting if one or more genes residing at these loci were involved in oxidative metabolism or susceptibility to oxidative damage.

Results of studies that examined racial differences in oxidative metabolism are consistent with the possibility that the differences in oxygen use detected in the present study reflect differences in systemic physiology. Several studies identified lower maximal oxygen consumption ($\dot{V}O_2$max) in African American than in Caucasian individuals. This racial difference was present in prepubertal children[34]; adolescent girls[35]; sedentary, premenopausal women[36]; and similarly trained male distance runners.[37] In one study,[36] physiologic analysis revealed that mitochondrial oxidative capacity and oxygen delivery capability accounted for most of the measured differences in maximum oxygen consumption. It is unclear whether similar biochemical differences account for the racial variation in oxygen metabolism in the eye. However, the anterior segment of the eye provides an excellent location to study the biochemical factors influencing oxygen use since the avascular nature of the lens and cornea permits measurements that are not influenced by changes in local or systemic blood flow.

Although the racial differences in $PO_2$ were highly significant at all 5 locations measured, the study was not designed to measure racial differences. The number of African Americans enrolled was, therefore, relatively small. In addition, self-reported race does not accurately reflect the extent of admixture in the African American population.[38] In future studies, genetic classification would provide a more objective and accurate definition of racial background to evaluate disease association. Confirmatory studies are warranted. Further analysis of corneal oxygen consumption by noninvasive methods is planned.[39] If such noninvasive tests correctly predict intraocular $PO_2$ in patients, they could be useful for larger-scale clinical, epidemiologic, and genetic analyses.

Topical antiglaucoma medications, many of which inhibit the secretion of aqueous humor, were used by most of the patients in both racial groups before the glaucoma operation. Common glaucoma medications, such as carbonic anhydrase inhibitors, adrenergic agonists, and β-blockers, could alter oxygen consumption in the ciliary epithelium. Carbonic anhydrase inhibitors could also affect metabolism in the corneal endothelium. However, there were no differences between races in the classes of medications or the combinations used.

Central corneal thickness is a highly hereditable trait that has been linked[40,41] to increased risk of glaucoma and progression of glaucomatous damage. Individuals of African descent have been reported[42] to have thinner corneas. However, for the relatively small number of African Americans in the present study, central corneal thickness was not significantly associated with race or $PO_2$ beneath the central cornea.

## INFLUENCE OF AGE ON $PO_2$ AND CORNEAL FUNCTION

As a group, the African Americans in this study were significantly younger than the Caucasian patients. Adjustment for age substantially increased the statistical significance of

the racial differences in intraocular $PO_2$, revealing an effect of age on ocular oxygen metabolism. After adjusting for race, increasing age was associated with a significant increase in $PO_2$ beneath the central cornea and in the mid-anterior chamber. This observation may be consistent with reports[43] of age-related decline in the number of corneal endothelial cells. It raises the possibility of a similar decline in the oxidative metabolism of the cornea, which may be linked to or separate from the decline in corneal endothelial cell density. We believe that this is the first report of an age-related change in corneal oxidative metabolism.

### PHYSIOLOGIC DIFFERENCES AND RACIAL VARIATION IN DISEASE SUSCEPTIBILITY

Although we do not yet know the biochemical basis for the physiologic variations revealed by measuring intra-ocular $PO_2$, the differences identified in this study may be significant in areas other than the eye. Racial differences in oxidative metabolism at the cellular level or in isolated mitochondria would appear to be worthy of further study. Understanding the biochemical and genetic basis of differences in oxygen metabolism could be relevant to racial variation in the prevalence of systemic diseases or drug metabolism and function.

## Acknowledgments

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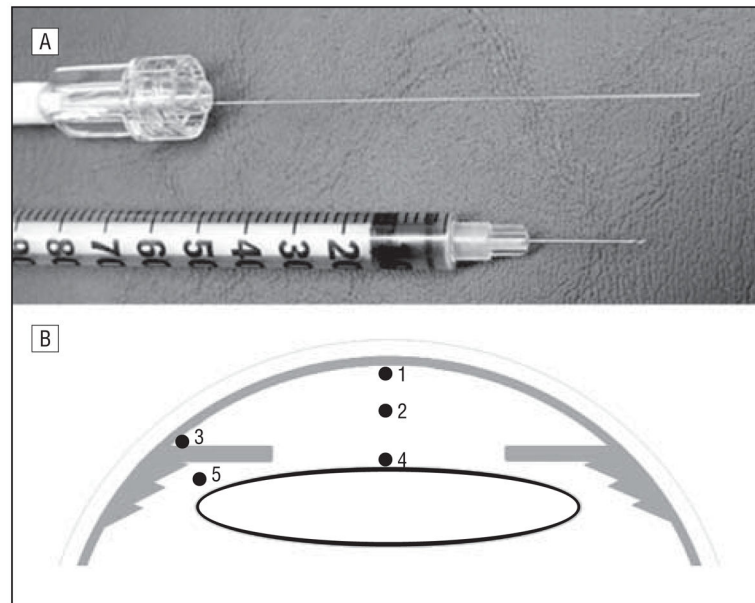
**Figure 1.**
Instrument and technique of $PO_2$ measurement in the human eye in vivo. A, Optical oxygen sensor shown next to a standard 30-gauge tuberculin syringe needle. B, The locations in the eye where $PO_2$ was measured: (1) beneath the central corneal endothelium, (2) mid–anterior chamber, (3) anterior chamber angle, (4) anterior lens surface, and (5) posterior chamber.
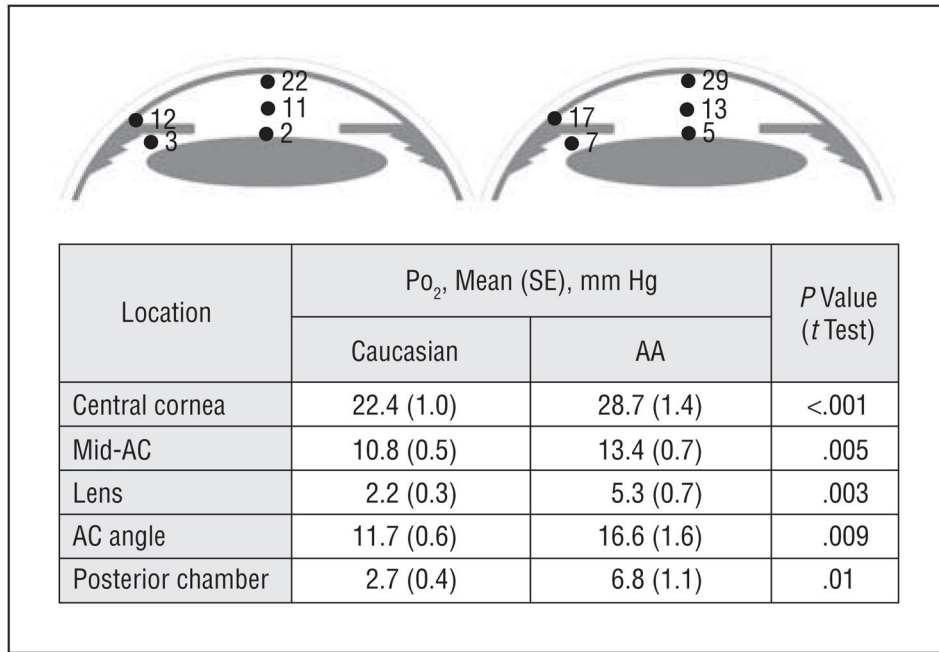
| Location | Po$_2$, Mean (SE), mm Hg | | P Value (t Test) |
|---|---|---|---|
| | Caucasian | AA | |
| Central cornea | 22.4 (1.0) | 28.7 (1.4) | <.001 |
| Mid-AC | 10.8 (0.5) | 13.4 (0.7) | .005 |
| Lens | 2.2 (0.3) | 5.3 (0.7) | .003 |
| AC angle | 11.7 (0.6) | 16.6 (1.6) | .009 |
| Posterior chamber | 2.7 (0.4) | 6.8 (1.1) | .01 |

**Figure 2.**
Diagram of PO$_2$ at 5 location in the eye (see Figure 1). Measured values are shown next to those locations in the illustration. The table provides the mean (SE) and statistical significance of the differences in PO$_2$ between Caucasian and African American (AA) participants, unadjusted for race or age. All differences were statistically significant. AC indicates anterior chamber.
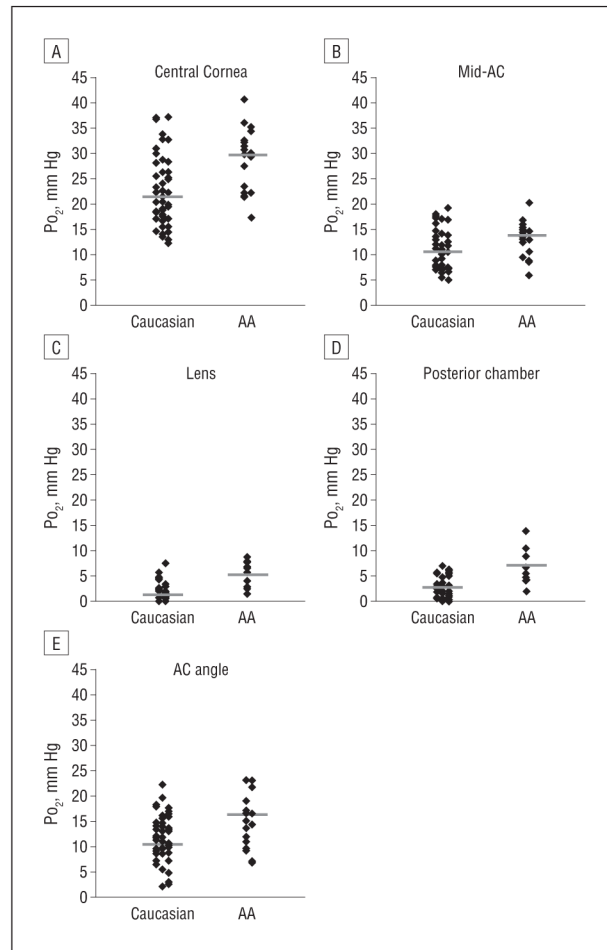
**Figure 3.**
Scatterplots of $PO_2$ in Caucasian and African American (AA) patients at each of 5 intraocular locations. Solid black bars identify the mean value of the distribution. AC indicates anterior chamber.

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**Table 1**

Patient Characteristics

| Characteristic | Group | | | P Value |
|---|---|---|---|---|
| | African American (n = 19) | Caucasian (n = 53) | All Patients (N = 72) | |
| Age, mean (SD), y | 64.1 (12.5) | 72.0 (10.1) | 69.9 (11.2) | .02[a] |
| Sex, No. | | | | |
| Male | 10 | 26 | 36 | .79[b] |
| Female | 9 | 27 | 36 | |
| Surgical diagnosis, No. | | | | |
| Cataract | 7 | 17 | 24 | |
| Glaucoma | 9 | 10 | 19 | .02[b] |
| Cataract and glaucoma | 3 | 26 | 29 | |

[a]By $t$ test.

[b]By $\chi^2$ test.

**Table 2**

Differences in PO$_2$ at Each Location in the Eye After Adjusting for Race or Age

| | Adjusted for Race[a] | | | |
| | Effect of Age | | Effect of Race | |
| Location | Regression Coefficient | P Value | Regression Coefficient | P Value |
|---|---|---|---|---|
| Central cornea | 0.19 | **.01** | 7.80 | <**.001** |
| Mid-AC | 0.09 | **.03** | 3.32 | **.001** |
| Lens | 0.01 | .85 | 3.06 | <**.001** |
| AC angle | 0.03 | .63 | 5.05 | **.001** |
| Posterior chamber | 0.02 | .61 | 4.17 | <**.001** |

Abbreviation: AC, anterior chamber.

[a]Statistically significant P values are shown in bold.