Differences in optic nerve structure between individuals of predominantly African and European ancestry: Implications for disease detection and pathogenesis

Christopher A Girkin
University of Alabama at Birmingham
School of Medicine, Birmingham, AL, USA

Abstract: Glaucoma disproportionately affects individuals of African ancestry. Additionally, racial differences in the optic nerve head have been well described that may alter the vulnerability to intraocular pressure related injury and, in addition, alter the clinical ability to detect the presence of early optic nerve injury. This paper will review the literature describing racial differences in the optic nerve head between individuals of African and European ancestry with regards to the potential effects of these differences on the ability to detect glaucoma in different racial groups and to potential differences in the pathogenesis of glaucomatous injury.

Keywords: primary open angle glaucoma, African American, optic nerve, optic disc, retinal nerve fiber layer

Introduction
The burden from glaucoma disproportionately affects individuals of African ancestry who are at much greater risk of developing glaucoma (Seddon 1991; Tielsch et al 1991; Sommer et al 1991; Sommer 1996) and blindness from glaucoma (Javitt and al 1991). Glaucoma remains the leading cause of irreversible blindness among Blacks, while it is the third leading cause among Whites. The reason for this differential burden is multifactorial and incompletely understood. While, socioeconomic disparity, differences in healthcare access, and differences in both systemic comorbidities and ocular parameters such as corneal thickness all play some role, the hypothesis central to our investigations is that variation in the structure of the optic nerve remains an important and critical factor in the more aggressive disease seen in this at-risk underserved population. This paper will review the literature concerning racial variation in the structure of the optic nerve between Blacks and Whites and the impact these differences may have on diagnosis and follow-up of glaucoma and possible implications for pathogenesis in this at-risk population.

Problems with the definition of race
Medical researchers and clinicians often categorize patients and research subjects by race in order to recognize differences in susceptibility to disease, to determine differing medical needs, and to highlight health disparities (Williams and Rucker 2000). However, several authors have raised questions as to the validity of racial classification in the strict biologic sense (Goodman 2000). Additionally, the history of the use of the term race, especially with regards to attempts to define race on a genetic basis, is full of examples of misuse in both scientific and political circles (La Veist 1996).
In response to these concerns, ethnicity has been touted as a superior, and perhaps less controversial term. However, cultural distinctions as well as racial ones define ethnicity (Hahn and Stroup 1994). Thus ethnicity may be even more ambiguous to define than race (Williams 1996).

Most of the epidemiologic literature uses self-description to define racial differences. Clearly there are limitations with using this definition and self-described race is a term that represents an amalgam of cultural, geographic, socioeconomic, and biologic characteristics and is at best an incomplete summary of human biodiversity that cannot be interpreted in the strict biologic sense (Sommer 2003). However, self-described race has demonstrated dependent and independent associations to glaucoma along with several other ocular and systemic conditions, thus it remains an important and relatively accessible factor (Tielsch et al 1991). Several researchers have used more sophisticated genetic methods to describe racial variation using multiple assays of single nucleotide polymorphism haplotypes (SNPs) to develop a profile of genetic admixture (Smith et al 2001; Rosenberg et al 2002; Gower et al 2003; Shriver et al 2003). These admixture profiles correlate highly to the biogeographic structure of human populations and can be used to summarize the genetic ancestry of mixed populations. Initial experience using these techniques with subjects participating in our studies has clearly demonstrated the imprecision of self-describe race to determine ancestral history (Figure 1). Fortunately, genetic admixture estimates of ancestral origin, generally correlate highly to self-described race, which is much easier to obtain, and thus self-described race is probably an adequate surrogate for molecular biologic testing in many situations (Rosenberg et al 2002).

While race is a tenuous biologic concept, many researchers consider that the influence of race on the delivery of medical care and clinical science is so strong that information regarding race should still be collected in clinical studies, with the acknowledgment that it is an imprecise and poorly understood measurement (Sommer 2003; Wilson 2003). We share this view and while the literature supports a significant relationship between self-described race and glaucoma, the causal factors for this association and how it is mediated remains poorly understood. However, we have continued to use self-described race in our research and are of the opinion that this can provide useful information as long as this information is obtained using standardized methodology.

Previously describe racial differences in the optic nerve
Several clinical and histological studies have characterized racial differences in optic disc structure between blacks and whites. Quantitative evaluation of conventional optic disc photography from the Baltimore Eye Survey demonstrated that mean optic disc area was 12% larger in Blacks compared to Whites (Varma et al 1994). Cup area was larger as well. While global rim area was similar in both racial groups, due to the relatively larger optic disc in Blacks, there was a decrease in rim/disc area, indicating that there may be a decrease in rim thickness and nerve fibers relative to disc size in this population. In a smaller study including 200 normal subjects, also using disc photography, Beck and colleagues also demonstrated that there was an increase in cup-to-disc ratio in Blacks relative to Whites (Beck et al 1985). Finally,
a post-mortem histological study of 30 White and 30 Black eye donors demonstrated a larger vertical diameter of the optic disc, but not in horizontal diameter in the Black group (Quigley et al 1990).

Optic disc and nerve fiber layer imaging techniques have evolved out of an attempt to acquire quantitative objective topographic information regarding optic disc structure and in-vivo measurements of retinal nerve fiber layer thickness in order to improve the ability to detect glaucoma and progressive glaucomatous damage. Current studies evaluating these instruments have previously been performed in predominantly White study populations and have not included adequate numbers of Black subjects to evaluate the role of quantitative optic disc analysis, the parameters that are most predictive of glaucoma, and optimum analysis strategies for detection of glaucoma in this at risk population.

Differences in optic disc structure between Blacks and Whites may have an effect on the ability of optic disc and nerve fiber layer imaging techniques to detect glaucoma. Broadway demonstrated that the discriminating ability of confocal scanning laser ophthalmoscopy (CSLO) varied depending on the phenotype of optic disc damage present (Broadway et al 1998). In addition, Iester et al (1997) demonstrated that optic disc area has an effect on the diagnostic precision of the CSLO. This is an important consideration in that one of the primary reported differences in optic disc structure between Blacks and Whites is disc area (Varma et al 1994).

We recently compared the CSLO results between 146 eyes from Black subjects and 97 eyes from White subjects, and found similarly that Blacks had significantly greater optic disc area, cup area and volume, and similar rim area and volume (Girkin et al 2005). Additionally, Black subjects had a deeper optic disc cup than Whites. Following adjustment for racial variation in disc area, there was no significant difference between racial groups other than cup depth, indicating that most of the normal variation in optic disc topography between Blacks and Whites seen with the CSLO is due to differences in disc area except for differences in cup depth (Table 1).

In an additional conducted study to determine the structural characteristics of the optic disc that are associated with early glaucoma in Blacks and Whites and whether these characteristics differ between these races (Girkin et al 2003), parameters of optic disc topography from 260 eyes from black participants and 193 eyes from white participants were included in the analysis. A staged multivariable logistic regression model was used to

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparison of structural parameters of the optic disc between African-American and White groups</th>
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<tbody>
<tr>
<td>CSLO Parameter</td>
<td>White n = 53 Mean (se)</td>
</tr>
<tr>
<td><strong>Ratio parameters</strong></td>
<td></td>
</tr>
<tr>
<td>Cup disc area ratio</td>
<td>0.1911 (0.014)</td>
</tr>
<tr>
<td>Vertical cup-to-disc ratio</td>
<td>0.2682 (0.023)</td>
</tr>
<tr>
<td><strong>Cup related parameters</strong></td>
<td></td>
</tr>
<tr>
<td>Cup area (mm²)</td>
<td>0.3917 (0.031)</td>
</tr>
<tr>
<td>Cup volume (mm³)</td>
<td>0.0812 (0.009)</td>
</tr>
<tr>
<td>Mean cup depth (mm)</td>
<td>0.1770 (0.009)</td>
</tr>
<tr>
<td>Maximum cup depth (mm)</td>
<td>0.4928 (0.023)</td>
</tr>
<tr>
<td>Cup shape measure</td>
<td>-0.1878 (0.007)</td>
</tr>
<tr>
<td><strong>Rim related parameters</strong></td>
<td></td>
</tr>
<tr>
<td>Rim area (mm²)</td>
<td>1.5983 (0.037)</td>
</tr>
<tr>
<td>Rim volume (mm³)</td>
<td>0.4477 (0.018)</td>
</tr>
<tr>
<td><strong>Disc margin related parameters</strong></td>
<td></td>
</tr>
<tr>
<td>Mean RNFL thickness (mm)</td>
<td>0.2488 (0.007)</td>
</tr>
<tr>
<td>CLM temporal to superior (mm)</td>
<td>0.1916 (0.008)</td>
</tr>
<tr>
<td>CLM temporal to inferior (mm)</td>
<td>0.1820 (0.009)</td>
</tr>
<tr>
<td>Maximum contour depression (mm)</td>
<td>0.2545 (0.015)</td>
</tr>
</tbody>
</table>

*Significant p-value, Bonferroni p-value <0.0042.

*Unadjusted.
†Adjusted for disc area.
‡Adjusted for disc area and reference height.

calculate the association between glaucoma and cup, rim and
disc margin parameters. To account for the effect of differences
in optic disc area, this parameter was included in the multi-
variable model at each level of interaction in constructing the
final model. To account for the intercorrelation of eyes within
persons, generalized estimating equations were used.

This study found similar racial differences between
normal control subjects with CSLO than prior studies using
photography. These differences included a larger disc
area, cup-to-disc ratio, rim area and cup area in Blacks. Additionally we found several other CSLO parameters
that were significantly different in the Black control group
including greater cup depth, and a thicker nerve fiber layer
measurement.

This study demonstrated racial differences exist in the
optic disc structural parameters that are independently predictive of early glaucoma between Blacks and Whites
even when accounting for differences in optic disc area.
While the most predictive parameter, rim area, was the same
for each racial group, the magnitude of association was higher
in Whites. Differences in disc area does account for some
of these racial differences; however, residual differences
still persist. Overall, the summary odds ratios based on the
most predictive CSLO parameters demonstrated a lower
association with glaucoma in Blacks, even when adjusted for
the effect of disc area. These differences in the relationship
between optic disc structural and visual functional measures
between Black and Whites indicate that topographic features
of the optic disc convey different information with regards to
assessing the risk of early glaucoma in differing racial groups,
which should be considered in the statistical judgment of
disease status based on these parameters.

Impact of racial variation of the
optic nerve on disease detection

Racial variation on optic nerve structure may have a sig-
nificant impact on the ability to detect glaucoma by subjec-
tive and objective techniques. Larger optic nerves have a
larger scleral canal and consequently larger optic cups for
the same rim volume and number of retinal nerve fibers.
Thus, a larger nerve is more likely to be misconstrued as
glaucomatous on casual observations, whereas a smaller
nerve with a small degree of glaucomatous cupping may
be overlooked as normal.

Differences in optic disc structure between Blacks and
Whites may have an effect on the ability of optic disc and
nerve fiber layer imaging techniques to detect glaucoma.
Broadway demonstrated that the discriminating ability of
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Our prior studies using the CSLO have also demonstrated
that racial variations in optic disc structure had little impact on
the ability of structural parameters and discriminant functions
to detect glaucomatous visual field defects. However, differ-
ces in normative values required race-specific cutoff values
to optimize specific detection strategies (Deleon-Ortega et al
2006). The widely used Moorfields regression analysis, which
takes in to account disc area, performed similarly across
racial groups, but optic disc area had a significant impact on
the diagnostic efficacy of this technique with more patients
incorrectly diagnosed as glaucomatous who had larger optic
nerves, probably reflecting the normative database used to
develop this technique (Girkin et al 2006).

Impact of racial variation of the
optic nerve on the pathogenesis
of glaucoma

Since the biomechanical behavior of any object is determined
by its morphology and its material properties, there are
potentially important biomechanical implications with the
variations in optic disc morphology our group and others
have described. While little is currently known regarding
the impact of variations in optic disc anatomy and the sus-
cceptibility of glaucoma, preliminary computational modeling
of the biomechanical behavior of the lamina cribrosa and
posterior scleral has suggested that the laminar connective
tissue may experience greater intraocular pressure-related
stress and strain in idealized eyes with larger optic disc area
(Bellezza et al 2000). Thus the larger optic nerve found more
commonly in patients of African ancestry may experience
greater strain at similar levels of pressure. Additionally, the
findings of a deeper cup in patients of African ancestry may
relate to either a thinner lamina cribrosa or a more posterior
insertion of the lamina within the scleral wall (Girkin et al
2005). The impact of these morphologic variations has yet
to be explored. The field of biomechanical modeling of the
optic nerve connective tissues is rapidly developing and will
add to our understanding of the impact of variation in the
microarchitecture of the optic nerve on the biomechanical
behavior of the critically supportive connective tissue that
are important to the development of glaucoma.
Racial differences

Conclusion

While socioeconomic differences, disparities in health care access, and differences in disease awareness, along with several differences in potential systemic risk factors all play a role in the higher prevalence of glaucoma in African-Americans, ocular characteristics (primarily in central corneal thickness and in optic disc structure) may explain the increased risk of glaucoma in this population. As our clinical ability to detect glaucomatous progression improves with the further evolution of ocular imaging and physiologic testing, these ocular differences between Blacks and Whites are important to recognize and evaluate in longitudinal trials, if this new information is to be applied for maximal benefit in this at-risk population. The exact role of these racial differences in nerve structure in the variation in susceptibility to glaucoma remains to be elucidated.

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References


La Veist TA. 1996. Why we should continue to study race. but do a better job: an essay on race, racism and health. Ethn Dis, 6:21–9.


