Relationship of Retinal Vascular Caliber with Optic Disc Diameter in Children

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PURPOSE. To describe the relationships of retinal vascular caliber to optic disc diameter in children.

METHODS. A school-based cross-sectional study of 746 children aged 7 to 9 years who participated in the Singapore Cohort Study of the Risk Factors for Myopia. Digital retinal photographs of both eyes were taken in 2001 and graded for retinal vascular caliber, vertical optic disc diameter, and vertical cup-to-disc ratio (CDR) according to standardized protocols. All measurements in pixels were analyzed after correction of the magnification.

RESULTS. In this study population, the mean retinal arteriolar caliber (SD) was 5.95 (0.51) pixels, retinal venular caliber was 8.58 (0.69) pixels, vertical disc diameter was 73.02 (7.48) pixels, and vertical CDR was 0.34 (0.09). In multiple linear regression analysis with adjustment for age, gender, ethnicity, body mass index, and birth weight, arteriolar caliber decreased by 0.011 pixel ($P < 0.001$) and venular caliber decreased by 0.016 pixel ($P < 0.001$), for each pixel decrease in vertical optic disc diameter. The associations remained similar and statistically significant with further adjustment for blood pressure. Vertical CDR was not related to retinal vascular caliber.

CONCLUSIONS. In this population of generally healthy children, smaller vertical optic disc diameter was associated with narrower retinal arteriolar and venular calibers. The findings of this study, in conjunction with studies in adults, suggest anatomic relationships between the optic disc and retinal vasculature that may provide additional insights into the vascular etiology of glaucomatous and nonarteritic anterior ischemic optic neuropathy. However, because the detected differences in retinal vascular caliber were small, the clinical significance of the study findings remains uncertain. (*Invest Ophthalmol Vis Sci.* 2007;48:4945–4948) DOI:10.1167/iovs.07-0472

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Supported by the National Medical Research Council, Singapore; NMRC/0975/2005 (SSM); a SingHealth Foundation Grant, the Biomedical Research Council; and a Science Technology and Innovation grant, Victoria, Australia (TYW).

Submitted for publication April 20, 2007; revised May 31 and June 20, 2007; accepted August 14, 2007.

Disclosure: **N. Cheung**, None; **L. Tong**, None; **G. Tikellis**, None; **S.M. Saw**, None; **P. Mitchell**, None; **J.J. Wang**, None; **T.Y. Wong**, None

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Recent advances in image-analytical techniques have allowed reliable measurement of retinal vascular caliber from fundus photographs.[1] Using quantitative methods, studies now show that retinal vascular caliber changes are related to different systemic[2–6] and ocular[7–10] conditions. Narrower retinal arterioles, for example, are related to hypertension[6] and the risk of coronary artery disease.[3] In contrast, wider retinal venular caliber has been associated with hyperglycemia, obesity, and systemic inflammatory markers[11] and found to predict the progression of diabetic retinopathy.[10]

Few studies have been conducted to examine the relationship of retinal vascular caliber with optic disc parameters. This relationship is important because of its relevance in understanding the vascular etiology of glaucoma[12] and nonarteritic ischemic optic neuropathy in eyes with small optic discs.[13] Data from the Blue Mountains Eye Study show that glaucomatous optic neuropathy is associated with narrower retinal arteriolar caliber, but these findings have not been replicated in the Beaver Dam Eye Study and Rotterdam Study.[14,15] These inconsistencies may be related to differences in frequency of cardiovascular risk factors (e.g., diabetes, hypertension) and other characteristics (e.g., smoking, medication use) between studies of older adults, and suggest the need to gain further understanding of normal anatomic relationships between optic disc parameters and retinal vascular caliber. Children, who are generally free of potential confounding effects from systemic and ocular factors, are ideal for studying these relationships.[16]

In the present study, we examined the relationship of optic disc diameter and cup-to-disc ratio with retinal vascular caliber in a cohort of children aged 7 to 9 years.

METHODS

Study Population

The Singapore Cohort Study of Risk Factors for Myopia (SCORM) is a study of 1979 children aged 7 to 9 years at baseline. Participants were recruited from 1999 to 2001. Details of the study population are reported elsewhere.[16–20] In brief, 2913 children were initially recruited for the study, with a participation rate of 67.9% (1979 participants). Children with serious medical conditions (e.g., heart disorders, syndrome-associated myopia) or eye disorders (e.g., cataract) were excluded from the study. In 2001, 851 randomly selected children from the SCORM (half of the full cohort) were offered retinal photography. Of these, 775 (91%) children had photographs taken of at least one eye.[16] Characteristics of the children with and without gradable retinal photographs are described elsewhere[20] and are briefly summarized in Table 1. Children with incomplete ocular ($n = 25$) or anthropometric measurements ($n = 4$) were excluded, leaving 746 participants for analysis.

The Ethics Committee of the Singapore Eye Research Institute approved the study, and the protocol adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all parents.

Retinal Photography

Children were examined on the school premises by a team of ophthalmologists, optometrists, and research assistants. After pupil dilatation

Table 1. Characteristics of Children with and without Gradable Retinal Photographs

Characteristics	Nongradable			Gradable		
	N	*n* (%)	Mean (SD)	*N*	*n* (%)	Mean (SD)
Gender, male	1181	597 (49.4)		768	403 (52.5)	
Ethnicity						
Chinese		824 (67.7)			654 (85.1)	
Malay		274 (22.7)			75 (9.8)	
Indian		97 (8.1)			31 (4.0)	
Other		17 (1.5)			7 (0.9)	
Age (y)	1211		7.78 (0.83)	768		7.92 (0.85)
BMI (kg/m^2)	1097		17.18 (3.21)	768		17.07 (3.1)
Birth weight (g)	1156		3155 (482)	757		3195 (460)
Spherical equivalent refraction (D)	1211		0.36 (1.03)	768		−1.45 (1.84)
Axial length (mm)	1181		23.0 (0.78)	764		23.8 (1.02)

Data are proportions or means (SD). *N,* number at risk; *n,* number with categorical endpoint.

with cyclopentolate 1%, standard settings were used to obtain 45° digital retinal photographs of both eyes.[16]

Methods used to measure and summarize retinal vascular caliber from digitized photographs according to standardized protocols are detailed elsewhere.[21,22] Briefly, a computer-based program was used to measure the caliber of all retinal vessels located one half to one disc diameter from the optic disc margin in digitized retinal photographs. Individual retinal vascular caliber measurements from an eye were summarized as average indices according to formulas described elsewhere.[21–23] These indices, the central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE), represented the hypothesized summary measures of the arteriolar and venular calibers of that eye. One grader masked to participant identity and characteristics performed all retinal measurements for this study. Remeasurement of 50 retinal images 2 weeks apart showed high reproducibility, with intraclass correlation coefficients of 0.853 for arteriolar caliber and 0.973 for venular caliber.[16]

Assessments of optic disc characteristics have been described elsewhere.[24] Optic disc and cup dimensions were measured from monoscopic retinal photographs by using National Institutes of Health image-analysis software (ImageJ 1.37; available by ftp at zippy.nimh.nih.gov/ or at http://rsb.info.nih.gov/nih-image; developed by Wayne Rasband, National Institutes of Health, Bethesda, MD), according to a standardized protocol.[24]

All optic disc and retinal vessel measurements were analyzed in pixels, with ocular magnification corrected by using the Bennett formula: $q = 0.01306(x - 1.82)$, where q is the magnification factor and x is the axial length in millimeters.[25,26]

Collection of Other Information

Standardized methods were used to measure refraction and ocular biometric parameters for all participants.[17–19] Cycloplegic autorefraction was performed with an autokeratorefractometer (model RK5; Canon, Tochigiken, Japan) and measurements were based on the average of five consecutive measurements. Axial length was measured with ultrasound biometry (probe frequency 10 mHz; Echoscan US-800; Nidek, Tokyo, Japan).[17–19] Anthropometric factors, including body height and weight, were also obtained and used to calculate body mass index (BMI).[20] BMI was calculated as the weight in kilograms divided by the square of the height in meters. Blood pressure was measured from half of the randomly selected children in this study using standardized protocols described elsewhere.[16,27] Blood pressure was measured with the subjects in a seated position after 5 minutes of rest using an automated sphygmomanometer. The average of three separate measurements was used for analysis. Blood pressure data was available for 369 (49% of studied population) children. Information regarding birth weight was obtained from a health booklet completed by medical personnel soon after birth.[16]

Statistical Analysis

We compared characteristics of children with and without gradable photographs. Results were reported as means or proportions, with differences tested using analysis of variance or χ^2 tests, respectively. Analyses of covariance (ANCOVA) and linear regression models were used to determine the association between vertical optic disc diameter and retinal arteriolar and venular calibers. We used multiple linear regression to estimate the differences in arteriolar and venular calibers for each unit (pixel/unit) decrease in vertical optic disc diameter and cup-to-disc ratio, initially adjusted for age, gender, ethnicity, BMI, and birth weight (model 1) and further adjusted for systolic and diastolic blood pressure in children with blood pressure data (model 2, 49% of study population). All probabilities quoted are two-sided, and all statistical analyses were undertaken with commercial software (SPSS, ver. 12.0.1; SPSS, Chicago, IL).

Results

Table 1 shows that the children included in our study were more likely to be Chinese ($P < 0.001$) and to have myopia ($P < 0.001$), but were similar in other characteristics. In our study population, the mean retinal arteriolar caliber (SD) was 5.95 (0.51) pixels, the retinal venular caliber was 8.58 (0.69) pixels, the mean vertical disc diameter was 73.02 (7.48) pixels, and the vertical CDR was 0.34 (0.09).

Table 2 shows that in multiple linear regression analysis with further adjustment for birth weight and BMI (model 1), arteriolar caliber decreased by 0.011 pixel ($P < 0.001$) and venular caliber decreased by 0.016 pixel ($P < 0.001$) for each pixel decrease in vertical optic disc diameter. Vertical CDR was not related to retinal vascular caliber. In children with blood pressure data (model 2, 49% of the studied population), the associations were largely unchanged (Table 2). To ensure that our results are not due to residual confounding from magnification, we also added adjustment for spherical equivalent refraction in model 1, and the associations remained similar and statistically significant (data not shown).

Discussion

In this study of generally healthy 7- to 9-year-old children, we showed that eyes with smaller vertical optic disc diameter had smaller retinal arteriolar and venular calibers, independent of magnification, ethnicity,[16] BMI,[20] and other potential confounding factors.

Our findings are consistent with observations in older adults (mean age, 69 years) in the Beaver Dam Eye Study, which

Table 2. Relationship of Optic Disc Measures and Retinal Arteriolar (CRAE) and Venular (CRVE) Caliber

Optic Disc Parameters (per pixel/unit decrease)	CRAE Mean Difference (95% CI)	*P*	CRVE Mean Difference (95% CI)	*P*
Vertical disc diameter				
Model 1*	−0.011 (−0.016 to −0.006)	<0.001	−0.016 (−0.022 to −0.009)	<0.001
Model 2†	−0.009 (−0.016 to −0.001)	0.02	−0.014 (−0.024 to −0.004)	0.01
Vertical CDR				
Model 1*	−0.485 (−0.903 to −0.066)	0.02	0.214 (−0.35 to 0.778)	0.46
Model 2†	−0.22 (−0.809 to 0.37)	0.47	−0.214 (−1.03 to 0.602)	0.61

* Adjusted for age, gender, ethnicity, birth weight and body mass index.

† Adjusted for age, gender, ethnicity, birth weight, body mass index, and systolic and diastolic blood pressure ($n = 369$).

showed that eyes with the smallest optic discs had smaller retinal arteriolar and venular calibers, as measured with similar retinal vessel measurement software.[13] However, because many ocular and systemic disease processes are associated with retinal arteriolar narrowing in older adults, the validity of these associations in the Beaver Dam Eye Study was uncertain. Although the Beaver Dam analysis controlled for some of these factors (e.g., age and blood pressure), the possibility of residual confounding from chronic blood pressure changes and other risk factors, such as smoking, medication use and diabetes, cannot be totally excluded.[11] Our present study in young, healthy children is therefore important, as it indicates that the association between optic disc size and retinal vascular caliber is very likely a true anatomic relationship. To the best of our knowledge, there are no other comparable studies (i.e., in children) in the current literature.

As hypothesized by previous investigators,[13] an association of smaller optic disc size with narrower retinal vessels could be related to the primary biological mechanism involved in the pathogenesis of nonarteritic ischemic optic neuropathy.[28] The association between smaller optic discs and narrower retinal vessels has been attributed to the crowding at the lamina cribrosa in eyes with small optic discs, which in turn may lead to compression of retinal vessels at the disc, and thereby predispose eyes to nonarteritic ischemic optic neuropathy.[13]

Our findings may also have implications in future studies of retinal vascular caliber in ocular and systemic diseases. Most existing studies did not consider the ocular factors likely to influence retinal vascular caliber. Although we demonstrated in prior work that intraocular pressure is not associated with retinal vascular caliber,[29] the present study indicates that variation in optic disc dimensions may be relevant factors to be accounted for in studies of retinal vascular caliber with ocular outcomes.

Strengths of our study include its sample of healthy children, generally free of confounding factors arising from systemic and ocular diseases, and the masked evaluation of retinal vascular caliber by a previously validated retinal image-analysis program, shown to have high reproducibility. However, there are several potential limitations. First, our study population was drawn from only three schools and may therefore not truly represent the entire community. Second, although our study sample was randomly drawn from the SCORM cohort, selection bias cannot be totally excluded, as our participants had some characteristics that differed from those of the remaining cohort. Third, our findings could reflect proportional changes due to confounding from magnification or anthropometric factors, though we believe that this is unlikely to be the case, as the optic disc and retinal vessel measurements were both corrected for magnification, and BMI was included in our multivariate analysis. Finally, although our observed associations between optic disc diameters and retinal vascular caliber were significant, the magnitude of differences in retinal vascular caliber (in pixels) was small. Thus, the clinical significance of our findings remains unclear.

In conclusion, in our cohort of generally healthy 7- to 9-year-old children, eyes with smaller optic discs had narrower retinal arterioles and venules. This anatomic relationship provides additional insights into the retinal vascular pattern in relation to optic disc morphology, which may be relevant to understanding vascular changes in diseases such as glaucomatous and ischemic optic neuropathies.

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