Relationship of Ocular Biometry and Retinal Vascular Caliber in Preschoolers

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PURPOSE. To systematically examine the association between ocular biometry and retinal vascular caliber in Singapore Chinese preschoolers aged 48 to 72 months.

METHODS. A total of 469 Singapore Chinese children aged 48 to 72 months were recruited through the Strabismus, Amblyopia and Refractive Error Study in Singaporean Chinese Preschoolers (STARS) from 2006 to 2008. According to standardized protocols, cycloplegic autorefraction, ocular biometry measurements, and retinal photography were performed. Retinal vascular caliber was measured quantitatively and was summarized as the central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE), respectively. Ocular magnification was corrected by using the Bengtsson formula.

RESULTS. The mean retinal arteriolar and venular calibers were 156.08 μm and 219.55 μm in boys, and 161.96 μm and 224.25 μm in girls, respectively. In multiple linear regression adjusted for age, sex, father’s education, parental myopia history, mean arterial blood pressure, body mass index, and spherical equivalent, each 1.0 mm increase in axial length was associated with a 3.52 μm decrease in retinal arteriolar caliber (P = 0.023) and a 5.55 μm decrease in retinal venular caliber (P = 0.008). Each 1.00 mm increase in corneal curvature was associated with a 13.79 μm decrease (P = 0.004) in retinal venular caliber.

CONCLUSIONS. In very young children aged 48 to 72 months, narrower retinal arteriolar and venular caliber was associated with elongated axial length. Narrower retinal venular caliber was associated with larger corneal curvature. This suggests that the major structural correlate of myopia might have an effect on retinal microvasculature from early childhood. (Invest Ophthalmol Vis Sci. 2011;52:9561–9566) DOI:10.1167/iovs.11-7969
Retinal Photography and Measurement of Retinal Vascular Caliber

After pupillary dilation using three sets of 1% cyclopentolate and 2.5% phenylephrine drops given five minutes apart, digital retinal photographs were taken using a 45° digital retinal camera (Model CR6-NM45, Canon Inc., Tokyo, Japan). Two images were obtained, one centered on the optic disc and the other centered on the macula, within which the optic disc-centered image was used for grading and analysis. Methods used to measure retinal vascular caliber from retinal photographs followed a standardized protocol as described in previous reports in adults and children.15–17 A computer imaging analysis program (IVAN; University of Wisconsin, Madison, WI) was used to measure the caliber of all retinal arterioles and venules located in zone one half to one-disc diameter from the optic disc margin in the retinal photograph (zone B). Using the revised Knudtson-Parr-Hubbard formula to compute retinal vascular caliber, the largest six arterioles and venules were used in calculating average vascular caliber, and estimates of the average diameters of arterioles and venules were summarized as the central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE).

A single grader, masked to blood pressure measurements and participant characteristics, performed all retinal vascular caliber measurements for this cohort. Intr grader reliability was assessed in 50 randomly selected retinal photographs, and the intra-class correlation coefficient was 0.95 for CRAE and 0.96 for CRVE.

To correct for ocular magnification on retinal vascular caliber measurements which was caused by telecentric camera and ocular refractive media, we used a correction factor (1−0.0017 × spherical equivalent [SE]) described by Bengtsson and Krakau20 for our fundus camera (Canon).

Autorefraction and Ocular Biometric Measurement

Cycloplegic autorefraction was performed using an autorefraction camera (Canon Autorefraction RK-F1; Canon Inc., Tokyo, Japan), where the average from five consecutive readings of spherical and cylindrical refractive error was obtained. The autorefractor readings were considered acceptable if the difference between the lowest and highest reading was 0.25 D or less. Spherical equivalent (SE) was calculated as the sphere plus half of the cylinder (SE = sphere + [cylinder]/2). Axial length, corneal curvature and anterior chamber depth of the right eye were obtained using a noncontact partial coherence interferometer (IOLMaster, Carl Zeiss, Oberkochen, Germany). A total of five consecutive readings with a signal-to-noise ratio of > 2.0 and with a difference between the lowest and highest reading being 0.05 mm or less were used to determine axial length. Then a total of 5 consecutive readings of corneal curvature and anterior chamber depth were obtained subsequently. The mean of five readings of each ocular biometric parameter was used in the analysis.

Other Measurements

Blood pressure was measured at clinics following a standard protocol.18 by using an automatic sphygmomanometer (Omron HEM-705 LP, Oron Health Care Inc.; Bannockburn, IL) with an appropriate pediatric cuff size after 5 minutes of rest. Two separate measurements were taken and their average was calculated. If the difference between the first two readings was greater than 10 mm Hg in systolic blood pressure (SBP) and/or 5 mm Hg in diastolic blood pressure (DBP), a third reading was be taken. The average of the two closest readings was used for analysis. Mean arterial blood pressure (MABP) was equal to DBP plus one third of the difference between the systolic and diastolic pressures (MABP = DBP + 1/3[SBP − DBP]).

Height and weight were both measured in the standing position according to a standard protocol by using a height and weight measuring scale (Seca model 220, Hamburg, Germany).19 Height was recorded to the nearest 1.0 mm while weight was recorded to the nearest 0.1 kg. Body mass index (BMI) was calculated as weight (kg) divided by the height squared (m²).

Interview

Parental sociodemographic information was obtained through either English or Chinese questionnaires. The father’s education was classified into four categories as follows: (1) below or equal to secondary school; (2) O/N level (O level, 4 years secondary school; N level, 5 years of secondary school); (3) A levels/diploma; and (4) University education or higher. Parental myopia history was collected through clinic interview. It was classified into two groups as follows: none of the parents had myopic condition, or at least one parent had myopic condition. Subjects’ birth parameters information such as birth weight, birth length, head circumference, and gestation week was obtained from the subjects’ health booklets which were brought along by their parents/guardians to the clinic.

Statistical Analysis

Multiple linear regression was constructed to estimate the relationship between retinal vascular caliber and three ocular parameters (axial length, corneal curvature, and anterior chamber depth) by using 2 multivariate models. Model 1 was controlled for age, sex, and SE. Model 2 was controlled for all variables in model 1, and then was further adjusted for father’s education, parental myopia history, MABP, BMI, and birth weight.

Ocular parameters were categorized into quartiles and analyzed as continuous variables. Test of trend was determined by treating quartiles of ocular parameters in their association with uncorrected and corrected retinal vascular caliber.

Potential modifiers were examined in stratified analyses. All probabilities quoted are two-sided, and a significant P value was defined as <0.05. All statistical analyses were performed using statistical software (PAWS 18.0; SPSS Inc.; Chicago, IL).

Results

All the variables were approximately normally distributed. The mean age of our study population was 60.88 ± 7.52 months in boys and 60.48 ± 7.19 months in girls. Table 1 shows the demographics of the study population stratified by sex. Among 469 Singapore Chinese children aged 48 to 72 months, except ocular biometric parameters and retinal vascular caliber, there is no significant difference between boys and girls in age, sex, father’s education, SE, MABP, BMI, and gestation week. The boys in our study had relatively greater axial length (22.62 ± 0.75 mm vs. 22.08 ± 0.71 mm; P < 0.001), greater cornea curvature (7.76 ± 0.24 mm vs. 7.65 ± 0.21 mm; P < 0.001), and greater anterior chamber depth (3.41 ± 0.25 mm vs. 3.32 ± 0.22 mm; P < 0.001) than girls, while boys had narrower CRAE (156.08 ± 15.27 μm vs. 161.96 ± 15.65 μm; P < 0.001) and narrower CRVE (219.55 ± 19.13 μm vs. 224.25 ± 21.84 μm; P = 0.013) than girls.

Table 2 describes the association between retinal vascular caliber and ocular biometric parameters. In multiple linear regression models adjusting for age, sex, right eye spherical equivalent, father’s education, parental myopia history, MABP, BMI, and birth weight, each 1.0 mm increase in axial length was associated with a 3.52 μm reduction (P = 0.008) in retinal arteriolar caliber and a 5.55 μm reduction (P = 0.007) in retinal venular caliber. Each 1.0 mm increase in corneal curvature was only associated with 13.79 μm reduction (P = 0.023) in retinal arteriolar caliber and 21.59 μm reduction (P = 0.013) in retinal venular caliber while not with retinal arteriolar caliber (P = 0.093). There was no association found between retinal vascular caliber and anterior chamber depth in both linear regression models.

Figure 1 shows the association of quartiles of axial length and quartiles of corneal curvature with retinal venular cali-
ber after controlling for age, sex, SE, father’s education, parental myopia history, MABP, BMI, and birth weight. Error plots demonstrated that highest quartile of axial length was significantly associated with narrower retinal venular caliber than the lowest quartile of axial length ($P_{\text{trend}}/H11005 = 0.023$; adjusted $R^2/adj/H11005 = 0.168$) (Fig. 1A). Highest quartile of corneal curvature was associated with narrower retinal venular caliber than the lowest quartile of corneal curvature ($P_{\text{trend}}/H11005 = 0.022$; adjusted $R^2/adj/H11005 = 0.153$) (Fig. 1B).

**DISCUSSION**

Among all ocular biometric parameters in our study, longer axial length was associated with narrowing in both retinal arteriolar and venular caliber. Larger corneal curvature was only associated with narrowing in retinal venular caliber. Anterior chamber depth was not associated with either retinal arteriolar or venular caliber.

There have been only a few studies that have reported the relationship either between axial length and retinal vascular caliber or between refractive error and retinal vascular caliber, mainly in adults.13–16 Patton et al.13 reported the negative association between axial length and retinal venular caliber by using Pearson’s coefficient correlation ($R/adj/H11005 = 0.28$; $P_{\text{trend}}/H11005 = 0.04$). In the Singapore Malay Eye Study (SiMES), conducted in adults aged 40 to 80 years, Lim et al.14 reported that per 1.0 mm increase in axial length, there was an associated 3.25 $\mu m$ and a 3.20 $\mu m$ narrowing in retinal arteriolar and venular caliber, respectively. Similar to axial length, SE was suggested to be positively related to wider retinal arteriolar and venular caliber in the Beaver Dam Eye Study (BDES)15 and SiMES.14 BDES found that each 1.0 D decrease in SE was significantly associ-
ated with a 2.8 \( \mu \)m decrease and 3.3 \( \mu \)m decrease in retinal arteriolar and venular caliber, respectively.\(^\text{15}\) SiMES found a much smaller decrease in both retinal arteriolar caliber and venular caliber as 0.46 \( \mu \)m and 0.42 \( \mu \)m, respectively.\(^\text{14}\) If refraction category was taken into account with the trend changed from hyperopia to myopia, the Blue Mountain Study reported a decreasing trend both in retinal arteriolar caliber (204.7 \( \mu \)m vs. 162.5 \( \mu \)m; \( P < 0.001 \)) and retinal venular caliber (238.9 \( \mu \)m vs. 195.9 \( \mu \)m; \( P < 0.001 \)).\(^\text{16}\) While the SiMES study only reported an decreasing trend in retinal venular caliber from hyperopia to myopia (204.35 \( \mu \)m vs. 202.08 \( \mu \)m; \( P = 0.02 \)).\(^\text{14}\) For children, there has been only one study on axial length with retinal vascular caliber among children aged 7 to 9 years, and the findings were similar to the adult study mentioned above.\(^\text{14}\) The SCORM reported per SD (1.02 mm) increase in axial length to be statistically associated with a 3.18 \( \mu \)m and a 4.62 \( \mu \)m decrease in retinal arteriolar and venular caliber, respectively.\(^\text{17}\)

It has been widely suggested to model both retinal arteriolar and venular caliber simultaneously in research relating retinal vascular caliber to systemic outcomes such as hypertension and diabetes.\(^\text{21–24}\) Up until now it has not been applied to ocular outcome.\(^\text{13,14,16,17}\) However, the application of retinal fellow vessel model in ocular outcomes should be explored more for practical statistical analysis. To be able to relate our findings with those reported in previous studies on similar topics,\(^\text{13,14,16,17}\) we prefer to take the adjustment without retinal fellow vessel as our ultimate analysis.

Increased axial elongation in myopic individuals may lead to mechanical stretching and thinning of the choroid and retinal pigment epithelium with concomitant vascular and degenerative changes.\(^\text{21}\) Regarding the possible concomitant vascular changes on retinal microcirculation, especially speculated less ocular blood flow, studies have shown some direct and indirect evidence.\(^\text{9,10,12,14,22,23}\) Using Doppler

**Figure 1.** (A) Relationship between quartiles of axial length and retinal venular caliber, after controlling for age, sex, SE, father’s education, parental myopia history, MABP, BMI, and birth weight. (B) Relationship between quartiles of corneal curvature and retinal venular caliber, after controlling for age, sex, SE, father’s education, parental myopia history, MABP, BMI, and birth weight. CI, confidence interval.
ultrasonography or Doppler velocimetry, reduction of retinal blood flow velocity or reduced retinal blood flow was reported in highly myopic eyes (≥−8.0 D),\textsuperscript{9,10} myopic eyes with open-angle glaucoma,\textsuperscript{11} and myopic eyes with choroidal neovascularization.\textsuperscript{12} Using retinal photography, retinal vascular caliber and retinal vessel geometry were all decreased in myopic eyes, which implied a decreased retinal microcirculation in myopic subjects.\textsuperscript{14} By using three-dimensional magnetic resonance imaging (MRI), axial globe enlargement to achieve a prolact shape in young children’s myopic eyes was seen, which implied that a stretched eye ball and increased axial elongation in myopic individuals probably led to mechanical stretching and thinning of the choroid and retinal pigment epithelium with concomitant vascular and degenerative changes.\textsuperscript{25,26} If a given eye begins development with a set complement of retinal vasculature, it is likely that a pathologic increase in ocular dimensions could cause stretching and elongation of the retinal vessels, leading to reduce the retinal vessel width.

The clinical implications of our study might lie in two parts. Firstly, Saw et al.\textsuperscript{24} suggested that patients with myopia, especially high myopia, may have higher risks of cataract, glaucoma, and chorioretinal abnormalities such as retinal detachment and optic disc abnormalities. Therefore, the relationship between axial length and retinal vascular caliber can shed light on the underlying pathophysiological mechanisms on how myopic subjects progress to develop pathologic complications, like retinal detachment. Secondly, in a recent study by Lim et al.,\textsuperscript{25} myopic refraction and longer axial length were associated with a lower risk of diabetic retinopathy, particularly vision-threatening retinopathy. It was hypothesized that chorioretinal thinning among highly myopic individuals may be protective both by reducing the metabolic demands of the retina and by facilitating diffusion of oxygen through the retina. Therefore, the reduced metabolic demands of the retina might be directly caused by the reduced blood flow established in this study and the previous studies. Longanesi et al.\textsuperscript{26} and Shimmyo\textsuperscript{27} found a highly significant correlation between corneal curvature and central corneal thickness. Thinner central corneal thickness (CCT) was reported to be associated with retinal arterial narrowing in the SCORM study.\textsuperscript{28} Furthermore, intraocular pressure (IOP) measurements by applanation tonometry are affected by central vascular caliber and retinal vessel geometry were all decreasing to reduce the retinal vessel width.

References


