Peripheral Artery Disease and Glaucoma

The Singapore Malay Eye Study

V. Swetha Jeganathan, MD; Tien Yin Wong, FRCS, PhD; Paul J. Foster, FRCS, PhD; Jonathan G. Crowston, PhD, FRCOpht; Wan Ting Tay, BSc; Su Chi Lim, MD; Seang-Mei Saw, PhD; E. Shyong Tai, MCRP; Tin Aung, MBBS, PhD, FRCS(Edin)

Objective: To examine the relationship between peripheral artery disease (PAD) and glaucoma.

Methods: As part of a population-based study of 3280 persons of Malay descent (78.7% response) aged 40 to 80 years examined between November 2004 and June 2006, the ankle-brachial index (ABI) was assessed in all persons with known diabetes mellitus and every fifth systematically sampled participant without diabetes. Peripheral artery disease was deemed present if the ABI was 0.9 or less. Glaucoma was diagnosed using International Society of Geographical and Epidemiological Ophthalmology criteria.

Results: Of the 922 participants who had ABI measured, 79 (8.6%) had PAD and 42 (4.6%) had glaucoma. Persons with PAD were more likely to have glaucoma (11.4% vs 3.9%; age- and sex-adjusted OR, 2.80; 95% CI, 1.26-6.24), higher intraocular pressure (age- and sex-adjusted mean, 16.4 vs 15.5; \( P = .05 \)), and a larger vertical cup-disc ratio (age- and sex-adjusted mean, 0.45 vs 0.40; \( P = .02 \)). The association of PAD with glaucoma persisted while controlling for hypertension, diabetes, body mass index, serum triglyceride levels, and \( \beta \)-blocker use (multivariable-adjusted OR, 2.55; 95% CI, 1.09-5.98) and was stronger in people with diabetes (multivariable-adjusted OR, 2.91; 95% CI, 1.14-7.44).

Conclusions: Peripheral artery disease was related to glaucoma, supporting an association between large-vessel atherosclerotic disease and glaucoma. However, because the study sample included a high proportion of persons with diabetes, further research is needed to determine the relevance of these results to the general population.

Arch Ophthalmol. 2009;127(7):888-893

Author Affiliations: Centre for Eye Research Australia, University of Melbourne, Victoria (Drs Jeganathan, Wong, and Crowston); UCL Institute of Ophthalmology, University College London (Dr Foster), and National Institute for Health Research Biomedical Research Centre, Moorfields Eye Hospital (Dr Foster), London, England; and Singapore Eye Research Institute (Drs Jeganathan, Wong, Saw, and Aung and Ms Tai) and Department of Community, Occupational & Family Medicine (Dr Saw), Yong Loo Lin School of Medicine, National University of Singapore, Department of Medicine, Alexandra Hospital (Dr Lim), and Department of Endocrinology, Singapore General Hospital (Dr Tai), Singapore.

Glaucoma is a leading cause of blindness worldwide. There is increasing evidence supporting the vascular theory of glaucoma, with studies showing associations of glaucoma with cardiovascular risk factors, migraine,\(^1\) vasospastic syndrome,\(^2\) optic disc hemorrhage,\(^3\) silent myocardial ischemia,\(^2,4\) carotid artery stenosis,\(^3\) and altered ocular hemodynamics.\(^5,6\) In glaucoma patients, documentation of vascular dysregulation of the cardiovascular system has been reported.\(^8,9\) More recently, the Early Manifest Glaucoma Trial\(^10\) and the Barbados Eye Studies\(^11\) showed that lower systolic blood pressure and a history of cardiovascular disease are independent predictors of glaucoma progression.

Few studies, however, have examined direct measures of atherosclerosis and glaucoma. The Rotterdam study\(^12\) did not find any association between carotid artery atherosclerosis and glaucoma. Peripheral artery disease (PAD), another direct measure of atherosclerosis,\(^13\) is an important predictor of cardiovascular disease and mortality\(^14,15\) and is associated with cardiovascular risk factors, such as cigarette smoking.\(^16\) To the best of our knowledge, no studies have investigated the association of PAD with glaucoma. The purpose of this current analysis is to examine relationships between PAD and glaucoma in the population-based Singapore Malay Eye Study.

STUDY POPULATION

The Singapore Malay Eye Study was a population-based, cross-sectional study of urban Malay adults aged 40 to 80 years residing in Singapore. Study design and population details are described elsewhere.\(^17,18\) In brief, Malay adults were selected from a national database using an age-stratified random sampling process. Of those eligible, 3280 (78.7% response rate) were examined between August 1, 2004, and June 30, 2006.
30, 2006. The study followed the principles of the Declaration of Helsinki, with ethics approval obtained from the Singapore Eye Research Institute Review Board. Written informed consent was obtained from each participant.

MEASUREMENT OF GLAUCOMA

All participants had a standardized examination. Intraocular pressure (IOP) was measured before pupil dilation by Goldmann applanation tonometry using a standardized protocol. After pupil dilation, the optic disc was examined through a 78-diopter lens at ×10 magnification, and vertical dimensions of the disc and cup were evaluated using an eyepiece graticule, etched in 0.1 units. The vertical cup-disc ratio (CDR) was determined. Automated perimetry (SITA 24-2, Humphrey Visual Field Analyzer II; Carl Zeiss Meditec, Dublin, California) was performed with near-refractive correction for all patients suspected of having glaucoma. Participants were diagnosed as having glaucoma according to the criteria of the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) scheme, according to 3 levels of evidence. The highest level of certainty (category 1) requires an optic disc abnormality (vertical CDR >97.5th percentile in the visually normal population) and visual field defect consistent with glaucoma. In the next level of certainty (category 2), if the visual field test could not be performed adequately, a severely damaged optic disc (vertical CDR >99.5th percentile) would suffice to make the diagnosis. Finally, in category 3, if the optic disc could not be examined because of media opacity or entirely blind participants with corrected visual acuity less than 3/60 (and hence, no visual field test was possible), an IOP greater than the 99.5th percentile, or evidence of prior glaucoma surgery, may be sufficient for diagnosing glaucoma.

Primary open-angle glaucoma (POAG) was defined as an eye with an open anterior chamber angle and with evidence of glaucoma as defined by ISGEO. Primary angle closure glaucoma (PACG) was defined as an eye with occludable anterior chamber angle (diagnosed if the posterior trabecular meshwork was seen for 180° or less of the angle circumference during static gonioscopy), features of trabecular obstruction by peripheral iris (peripheral anterior synchiae, elevated IOP, iris whirling, glaukomilekken lens opacities, or excessive pigment deposition on the trabecular surface), and evidence of glaucoma as defined by the ISGEO. Pseudophakic glaucoma was found in participants with open-angle glaucoma and pseudophakia. We included patients with pseudophakic glaucoma because they may have had POAG and undergone cataract surgery, although it is possible that glaucoma was a result of the cataract surgery. Pseudoxefoliation glaucoma was defined as the presence of pseudoxefoliation material on the lens capsule, transillumination defects near the pupil, increased pigmentation and/or pseudoxefoliative material at the angle, elevated IOP, glaucomatous optic nerve changes, and visual field defect. All final glaucoma cases were reviewed by a senior glaucoma specialist (T.A.).

ANKLE-BRACHIAL INDEX ASSESSMENT AND DEFINITION OF PAD

In our study, the ankle-brachial index (ABI) was assessed in all patients known to have diabetes mellitus and in every fifth systematically and randomly sampled participant without diabetes. Ankle pressures were evaluated using a standardized Doppler ultrasonic device (8 MHz; Smartdop 20EX, bidirectional blood flow detector; Hadeco, Kawasaki, Japan), after a 5-minute rest in the supine position. The ABI was calculated as the ratio of the higher of the 2 systolic pressures (from the posterior tibial and dorsalis pedis) at the ankle to the average of the right and left brachial artery pressures, except if there was an inconsistency of 10 mm Hg or higher in blood pressures between the 2 arms. In such circumstances, the higher reading was used for ABI. Pressures in each leg then were evaluated and ABI computed individually for each leg. In the case of an unaccounted-for ABI value in one leg, the value from the other was used; the same procedure was performed for missing brachial artery pressure values in 1 arm. The ABI measurement was performed by 2 operators who were trained in the proper handling technique of the Doppler device and measurement of brachial and ankle blood pressure. The Pearson correlation between brachial systolic blood pressure measured by Doppler and by digital automated blood pressure monitor for the 922 study participants was 0.83 (P < .001).

Peripheral artery disease was defined as an ABI of 0.9 or less in at least 1 leg. The lower ABI between the 2 legs was used to define PAD. The ABI correlated well with PAD disease severity and functional symptoms and could also be used to assess disease progression and to predict cardiovascular and cerebrovascular mortality. An ABI less than 0.9 was considered diagnostic of PAD. Evaluating the diagnostic accuracy of the ABI have demonstrated that ABI can differentiate between normal and angiographically diseased limbs with a sensitivity of 97% and a specificity of 100%. Other criteria for PAD diagnosis include clinical findings of claudication, ulceration, rest pain, and gangrene. However, these findings are not present in our participants.

ASSESSMENT OF COVARIATES

Study participants underwent a standardized interview, examination, and collection of nonfasting venous blood samples. Height was quantified in centimeters, using a wall-mounted measuring tape; weight was assessed in kilograms, using a digital scale; and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Systolic and diastolic blood pressures were evaluated with a digital automatic blood pressure monitor (Dinamap model Pro Series DP110X-RW, 100V2; GE Medical Systems Information Technologies Inc, Milwaukee, Wisconsin), and hypertension was defined as a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or physician diagnosis. Nonfasting venous blood samples were analyzed for serum total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, creatinine, and glucose levels on the same day. Diabetes mellitus was identified from a plasma glucose level of 200 mg/dl or higher (to convert to millimoles per liter, multiply by 0.0555), self-reported use of diabetic medication, or physician-diagnosed diabetes mellitus. A detailed interviewer-administered questionnaire was used to gather self-reported information about medical history, cigarette smoking, alcohol consumption, and current medication use, including β-blocker use.

STATISTICAL ANALYSIS

Statistical analysis was performed using a commercially available software program (SPSS, version 15.0; SPSS Inc, Chicago, Illinois). We used analysis of covariance to estimate the mean IOP and CDR and logistic regression models to estimate the odds ratio (OR) and its 95% confidence interval (CI) of glaucoma, POAG, and category 1 glaucoma by the presence of PAD. We adjusted initially for age and sex and then further for BMI, hypertension, serum triglyceride levels, and β-blocker use. We tested the interaction between PAD and diabetes in relation to glaucoma, IOP, and CDR by adding appropriate cross-product terms into the model.
RESULTS

Among the 3280 individuals who participated in the study, 922 underwent measurement of ABI. Of the 922 who had an ABI measurement, 79 (8.6%) had PAD. Participants with PAD were older, more likely to be women, more likely to have diabetes mellitus and hypertension, and more likely to have higher systolic blood pressure and serum triglyceride as well as serum creatinine levels (Table 1).

Among the 922 study participants, 42 (4.6%) had glaucoma: 30 with POAG, 2 with PACG, 8 with pseudophakic glaucoma, 1 with pseudoxfoliation glaucoma, and 1 with glaucoma of an unspecified type. Of the 79 study participants who had PAD, 9 had glaucoma, including 5 with POAG, 1 with pseudoxfoliation glaucoma, 3 with pseudophakic glaucoma, and none with PACG. Among 288 persons without diabetes, 12 (4.2%) had glaucoma but only 1 had PAD and glaucoma (Table 2). Persons with PAD were more likely to have glaucoma (11.4% vs 3.9%; age- and sex-adjusted OR, 2.80; 95% CI, 1.26-6.24). The association of PAD with glaucoma persisted while controlling for hypertension, BMI, serum triglyceride levels, and β-blocker use (multivariable-adjusted OR, 2.55; 95% CI, 1.09-5.95; P = .03). For POAG, after similar adjustment, the pattern of association between PAD and POAG was similar, although not statistically significant (OR, 2.10; 95% CI, 0.75-5.89; P = .16) (data not shown). The direction and pattern of association between PAD and category 1 glaucoma (multivariable-adjusted OR, 2.29; 95% CI, 0.89-6.00; P = .09) and category 1 POAG (multivariable-adjusted OR, 1.86; 95% CI,

### Table 1. Participant Characteristics by the Presence of PAD

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PAD (n = 79)</th>
<th>No PAD (n = 843)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>66.4 (7.43)</td>
<td>61.0 (10.09)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>23 (29.1)</td>
<td>398 (47.2)</td>
<td>.002</td>
</tr>
<tr>
<td>BMI</td>
<td>26.4 (5.12)</td>
<td>27.0 (4.52)</td>
<td>.30</td>
</tr>
<tr>
<td>Hypertension, yes vs no, No. (%)</td>
<td>74 (93.7)</td>
<td>656 (77.8)</td>
<td>.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>166.4 (25.76)</td>
<td>149.3 (23.26)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>80.8 (12.91)</td>
<td>78.5 (10.58)</td>
<td>.07</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>216 (56)</td>
<td>208 (44)</td>
<td>.14</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>50 (14)</td>
<td>50 (12)</td>
<td>.56</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>131 (44)</td>
<td>131 (37)</td>
<td>.93</td>
</tr>
<tr>
<td>Serum triglycerides, mg/dL</td>
<td>186 (181)</td>
<td>142 (119)</td>
<td>.004</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.4 (1.4)</td>
<td>1.1 (0.9)</td>
<td>.04</td>
</tr>
<tr>
<td>Diabetes mellitus, yes vs no, No. (%)</td>
<td>63 (79.7)</td>
<td>548 (65.3)</td>
<td>.01</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>189 (98)</td>
<td>159 (89)</td>
<td>.006</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>8.2 (2.44)</td>
<td>7.5 (1.96)</td>
<td>.002</td>
</tr>
<tr>
<td>Alcohol Intake, yes vs no, No. (%)</td>
<td>1 (1.3)</td>
<td>8 (1.0)</td>
<td>.79</td>
</tr>
<tr>
<td>Current smoker, No. (%)</td>
<td>8 (10.3)</td>
<td>126 (15.0)</td>
<td>.26</td>
</tr>
</tbody>
</table>

**Abbreviations:** BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PAD, peripheral artery disease.

**SI conversion factors:** To convert cholesterol to millimoles per liter, multiply by 0.0259; serum triglycerides to millimoles per liter, multiply by 0.0113; and serum creatinine to micromoles per liter, multiply by 88.4.

**a** Data are presented as mean (SD) unless otherwise indicated.

**b** P value for the difference in characteristics by sex, adjusted for age and sex.

### Table 2. Association of PAD With Glaucoma Overall and POAG

<table>
<thead>
<tr>
<th>PAD</th>
<th>Glaucoma Overall</th>
<th>POAG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age- and Sex-Adjusted OR (95% CI)</td>
<td>Multivariable OR (95% CI)</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>79 (9 (11.4))</td>
<td>2.80 (1.26-6.24)</td>
</tr>
<tr>
<td>No</td>
<td>843 (33 (3.9))</td>
<td>1.0</td>
</tr>
<tr>
<td>P value</td>
<td>.01</td>
<td>.03</td>
</tr>
<tr>
<td>Patients with diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>66 (8 (12.1))</td>
<td>3.25 (1.36-7.79)</td>
</tr>
<tr>
<td>No</td>
<td>568 (22 (3.9))</td>
<td>1.0</td>
</tr>
<tr>
<td>P value</td>
<td>.01</td>
<td>.03</td>
</tr>
</tbody>
</table>

**Abbreviations:** OR, odds ratio; PAD, peripheral artery disease; POAG, primary open-angle glaucoma.

**a** Adjusted for age, sex, body mass index, diabetes, hypertension, serum triglyceride levels, and use of β-blocker medication.

**b** Adjusted for age, sex, body mass index, hypertension, serum triglyceride levels, and use of β-blocker medication.

©2009 American Medical Association. All rights reserved.
have further linked lower diastolic flow velocity and a higher resistivity index in the ophthalmic artery to a greater risk of future progression of glaucoma in these patients.

Common pathophysiologic processes of PAD and glaucomatous optic neuropathy, such as inflammation, may also underlie this association. Persons with immune-related conditions, such as multiple sclerosis, have optic nerve atrophy, and the immune system is also postulated to regulate the fate of glial and ganglion cells, leading to glaucomatous optic nerve degeneration. Inflammation plays a key role in the initiation and progression of atherosclerosis and atheromatous plaque development. In addition, PAD is associated with elevated levels of the proinflammatory markers C-reactive protein, fibrinogen, cytokines, adhesion molecules, and matrix.

In our study, the association between PAD and glaucoma was slightly stronger and statistically significant in persons with diabetes (P = .003) but was slightly weaker and not statistically significant in persons without diabetes (P = .06), although this interaction was not statistically significant (P = .05). In this regard, several large epidemiologic studies have reported positive associations between diabetes with POAG; however, not all population-based studies have identified such an association. There are clear biologically plausible mechanisms that support an association between diabetes and glaucoma. First, microvascular damage from diabetes could impair blood flow to the anterior optic nerve, resulting in optic nerve damage. Diabetes also impairs the autoregulation of posterior ciliary circulation, which may exacerbate glaucomatous optic neuropathy. Second, patients with diabetes often have concomitant cardiovascular risk factors (eg, hypertension) that may affect vascular perfusion of the optic nerve head. Finally, relative to those without diabetes, persons with diabetes may be more vulnerable to elevated IOP with more severe visual field loss at the same IOP level.

The strengths of our study include the population-based community sample, standardized assessments of glaucoma, objective assessment of PAD via ABI, and information regarding a range of cardiovascular risk fac-

### Table 3. Association of PAD With IOP and CDR

<table>
<thead>
<tr>
<th>PAD</th>
<th>No. at Risk</th>
<th>IOP</th>
<th>CDR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Age- and Sex-Adjusted Mean (SE)</td>
<td>Adjusted Mean (SE)</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>79</td>
<td>16.4 (0.41)</td>
<td>15.7 (0.44)</td>
</tr>
<tr>
<td>No</td>
<td>843</td>
<td>15.5 (0.12)</td>
<td>15.1 (0.20)</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>.05</td>
<td>.12</td>
</tr>
<tr>
<td>Patients with diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>66</td>
<td>16.4 (0.45)</td>
<td>15.9 (0.51)</td>
</tr>
<tr>
<td>No</td>
<td>568</td>
<td>15.8 (0.15)</td>
<td>15.4 (0.25)</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>.17</td>
<td>.25</td>
</tr>
</tbody>
</table>

**Abbreviations:** CDR, cup-disc ratio; IOP, intraocular pressure; PAD, peripheral artery disease.

a Adjusted for age, sex, body mass index, diabetes, hypertension, serum triglyceride levels, and use of β-blocker medication.

b Adjusted for age, sex, body mass index, serum triglyceride levels, and use of β-blocker medication.

0.60-5.79; P = .28) was similar, although not statistically significant. The numbers of participants with category 2 and 3 glaucoma were too small for us to appropriately comment specifically on the association of PAD on patients with category 2 or 3 glaucoma (data not shown). Persons with PAD were more likely to have higher IOP (age- and sex-adjusted mean, 16.4 vs 15.5; P = .05) and larger vertical CDR (age- and sex-adjusted mean, 0.45 vs 0.40; P = .02) (Table 3).

In analysis stratified by diabetes status, the association between PAD and glaucoma was stronger in persons with diabetes (multivariable-adjusted OR, 2.91; Table 2). Among persons without diabetes, only 13 had PAD, including only 1 with glaucoma; the association of PAD with glaucoma among persons without diabetes was not statistically significant (OR, 1.45; 95% CI, 0.15-5.79; P = .28) was similar, although not statistically significant. The numbers of participants with category 2 and 3 glaucoma were too small for us to appropriately comment specifically on the association of PAD on patients with category 2 or 3 glaucoma (data not shown). Persons with PAD were more likely to have higher IOP (age- and sex-adjusted mean, 16.4 vs 15.5; P = .05) and larger vertical CDR (age- and sex-adjusted mean, 0.45 vs 0.40; P = .02) (Table 3).

In analysis stratified by diabetes status, the association between PAD and glaucoma was stronger in persons with diabetes (multivariable-adjusted OR, 2.91; Table 2). Among persons without diabetes, only 13 had PAD, including only 1 with glaucoma; the association of PAD with glaucoma among persons without diabetes was not statistically significant (OR, 1.45; 95% CI, 0.15-5.79; P = .28). Formal testing of interaction, however, showed no statistically significant interaction between diabetes and the association of PAD with glaucoma (P value for interaction = .65), IOP (P = .30), or vertical CDR (P = .56).

We report an association between PAD and glaucoma, independent of hypertension and other vascular risk factors. The direction and pattern of association between PAD and category 1 glaucoma and category 1 POAG were similar, although not statistically significant. We are not aware of other similar studies, but the few studies that have examined the association of carotid atherosclerosis with glaucoma have not found conclusive evidence of an association.

The finding of an association of PAD with glaucoma in our Malay population supports a vascular cause of glaucoma. Studies in other Asian populations, such as in Japanese people, who have been reported to have primary vascular dysregulation, suggest a higher prevalence of normal tension glaucoma. A vascular cause of glaucoma is supported by other studies showing upregulation of hypoxia inducible factor 1α and serotonin, which may result in decreased blood flow in small optic nerve vessels and vasospasm. Color Doppler studies have linked lower diastolic flow velocity and a higher resistivity index in the ophthalmic artery to a greater risk of future progression of glaucoma in these patients.

Common pathophysiologic processes of PAD and glaucomatous optic neuropathy, such as inflammation, may also underlie this association. Persons with immune-related conditions, such as multiple sclerosis, have optic nerve atrophy, and the immune system is also postulated to regulate the fate of glial and ganglion cells, leading to glaucomatous optic nerve degeneration. Inflammation plays a key role in the initiation and progression of atherosclerosis and atheromatous plaque development. In addition, PAD is associated with elevated levels of the proinflammatory markers C-reactive protein, fibrinogen, cytokines, adhesion molecules, and matrix.

In our study, the association between PAD and glaucoma was slightly stronger and statistically significant in persons with diabetes (P = .003) but was slightly weaker and not statistically significant in persons without diabetes (P = .06), although this interaction was not statistically significant (P = .05). In this regard, several large epidemiologic studies have reported positive associations between diabetes with POAG; however, not all population-based studies have identified such an association. There are clear biologically plausible mechanisms that support an association between diabetes and glaucoma. First, microvascular damage from diabetes could impair blood flow to the anterior optic nerve, resulting in optic nerve damage. Diabetes also impairs the autoregulation of posterior ciliary circulation, which may exacerbate glaucomatous optic neuropathy. Second, patients with diabetes often have concomitant cardiovascular risk factors (eg, hypertension) that may affect vascular perfusion of the optic nerve head. Finally, relative to those without diabetes, persons with diabetes may be more vulnerable to elevated IOP with more severe visual field loss at the same IOP level.

The strengths of our study include the population-based community sample, standardized assessments of glaucoma, objective assessment of PAD via ABI, and information regarding a range of cardiovascular risk fac-
tors. The limitations of our study should be stated. First, ABI measurements were not performed for all study participants. Thus, our study was limited by a smaller sample size of persons with PAD and glaucoma. Although we found a statistically significant association between PAD and glaucoma, the number of POAG cases was small, the association between PAD and POAG was not statistically significant, although the pattern of associations was in the same direction and strength. Moreover, selection bias toward having more diabetic patients in our sample was a potential limitation in our study, and patients with glaucoma are more likely to have diabetes. Consequently, our results may not be representative of the general population. The number of participants without diabetes was too small to allow a meaningful stratification in the analysis. Thus, further larger studies are needed to clarify whether the associations between PAD and glaucoma are stronger in persons with POAG (which has both a vascular and pressure mechanism) compared with PACG (more pressure dependent) and are present in the general population in persons without diabetes. Second, although the ISGEO classification is a widely used standardized classification for glaucoma in epidemiologic studies to enable comparison among studies, comparison with the other studies that used different classification (eg, the Rotterdam study or the Blue Mountains Eye Study) may not be appropriate. Finally, selective visual field testing on patients suspected of having glaucoma may have led to underascertainment of glaucoma cases as a result of this protocol.

In summary, we demonstrate a novel association of PAD with glaucoma in an Asian population, independent of cardiovascular risk factors. These findings provide further support to the concept that vascular processes and mechanisms that are pressure independent are associated with glaucomatous optic neuropathy. Nevertheless, the results of our study should be interpreted with caution because the study sample included a high proportion of persons with diabetes and was limited by small numbers of glaucoma cases. Thus, further research is needed to determine the relevance of these results to the general population, to clarify the temporal nature of the association, and to determine the relationship of PAD with different glaucoma subtypes (POAG, PACG, and secondary glaucoma).

Submitted for Publication: March 16, 2008; final revision received November 07, 2008; accepted November 23, 2008.

Correspondence: Tin Aung, MBBS, PhD, FRCS(Edin), Glaucoma Department, Singapore National Eye Centre, 11 Third Hospital Ave, Singapore 168751 (tin11@pacific.net.sg).

Author Contributions: Drs Aung and Wong had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors meet the full criteria and requirements for authorship.

Financial Disclosure: None reported.

Funding/Support: This study was supported by National Medical Research Council grants 0796/2003, 0863/2004, and C00/002/2005 and Biomedical Research Council grant 501/1/25-5.

REFERENCES


