Primary Open-angle Glaucoma, Intraocular Pressure, and Diabetes Mellitus in the General Elderly Population

The Rotterdam Study

Ida Dielemans, MD, PhD,1,2 Paulus T. V. M. de Jong, MD, PhD, FRCOphth,2,3,4 Ronald Stolk, MD, PhD,2 Johannes R. Vingerling, MD, PhD,1,2 Diederick E. Grobbee, MD, PhD,2 Albert Hofman, MD, PhD2

Purpose: To investigate the association of primary open-angle glaucoma and intraocular pressure (IOP) with newly diagnosed diabetes mellitus.

Methods: Subjects participating in the Rotterdam Study (n = 4178; ages, 55 years and older) were examined according to standard protocols, including a medical history interview, perimeter, applanation tonometry, funduscopy, and a nonfasting glucose tolerance test. Glaucoma was defined by the presence of a glaucomatous visual field defect. A distinction was made between high-tension glaucoma and normal-tension glaucoma. The relation of glaucoma and IOP with newly diagnosed diabetes mellitus and blood glucose was analyzed using regression analysis.

Results: The presence of diabetes mellitus was associated with an overall rise in mean IOP of both eyes of 0.31 mmHg (95% confidence interval, 0.12–0.50), and with a threefold increased prevalence of high-tension glaucoma (odds ratio, 3.11; 95% confidence interval, 1.12–8.66). A 10-mmol/l higher random serum glucose level was borderline significantly associated with a mean IOP that was, on average, 0.41 mmHg (95% confidence interval, −0.02–0.84) higher and with an odds ratio of 2.82 (95% confidence interval, 0.92–8.58) for high-tension glaucoma. A 10-mmol/l rise in serum glucose on a glucose tolerance test was associated with an overall rise of mean IOP of 0.59 mmHg (95% confidence interval, 0.26–0.92) and with an odds ratio of 1.88 (95% confidence interval, 0.81–4.32) for high-tension glaucoma.

Conclusion: Newly diagnosed diabetes mellitus and high levels of blood glucose are associated with elevated IOP and high-tension glaucoma.

Ophthalmology 1996;103:1271–1275

Originaly received: May 12, 1995.
Revision accepted: May 1, 1996.

1 Institute of Ophthalmology, Erasmus University Medical School, Rotterdam.
2 Department of Epidemiology & Biostatistics, Erasmus University Medical School, Rotterdam.
3 The Netherlands Ophthalmic Research Institute, Amsterdam.
4 Department of Ophthalmology, Academie Medical Center, Amsterdam.

Supported by the Nestor program for geriatric research in The Netherlands (Ministry of Health and Ministry of Education, Rijswijk); Topcon Europe BV, Rotterdam; Haagsch Oogheelkundig Fonds, The Hague; Stichting Blindenhulp, The Hague; Rotterdamse Vereniging voor Blindenbelangen, Rotterdam; Stichting Bevordering van Volkskracht, Rotterdam; The Netherlands Society for the Prevention of Blindness, Utrecht; Verhagen Stichting, Rotterdam; Stichting Fondsenvordering Volksgezondheid, The Hague; Stichting voor Ooglĳders, Rotterdam; Diabetes Fonds Nederland, Amersfoort; Landelijke Stichting voor Blinden en Slechtzienden, Utrecht; Physiotherapeutisch Instituut, Rotterdam, and Stichting ROOS, Rotterdam, The Netherlands.

The authors have no proprietary interest in any instrument mentioned in this study.

Correspondence to Paulus T. V. M. de Jong, MD, PhD, FRCOphth, The Netherlands Ophthalmic Research Institute, PO Box 12141, 1100 AC Amsterdam, The Netherlands.
One of the putative risk factors of primary open-angle glaucoma is diabetes mellitus. Various epidemiologic studies have suggested that diabetes mellitus is associated with both primary open-angle glaucoma\(^3\) and intraocular pressure (IOP).\(^4\,5\,7\,9\) No relation\(^1\) or a negative relation\(^2\) between diabetes and IOP have been observed. In the Beaver Dam Eye Study and the Framingham Eye Study, these relations have been investigated in the community.\(^5\,10\,11\) In the Beaver Dam Eye Study, persons with diabetes mellitus had a risk of 1.84 for having primary open-angle glaucoma (95% confidence interval, 1.09–3.11). The Framingham Eye Study and the Baltimore Eye Study did not find significant associations between diabetes and glaucoma.\(^5\,11\) The current study focuses on the relationship between primary open-angle glaucoma and IOP, and diabetes mellitus and serum glucose levels in a population-based study in Rotterdam, The Netherlands.\(^1\)

Materials and Methods

Population

The current study was performed as part of the Rotterdam Study. The Rotterdam Study is a single-center prospective follow-up study of a cohort of 10,275 people, 55 years of age or older, living in a suburb of Rotterdam, The Netherlands. The design of the study has been described previously.\(^1\) The study has been approved by the Medical Ethics Committee of the Erasmus University. Written informed consent was obtained from all participants. The objective of the study is to clarify the determinants of the occurrence of chronic, disabling ophthalmologic, cardiovascular, neurogeriatric, and locomotor diseases. The study comprises an extensive home interview, followed by two visits at the examination center for a clinical examination.

The initial cohort was defined before the start of the study. From June 1990 until January 1993, 7120 residents had been invited to participate in the study, and 5673 subjects had actually participated. The overall participation rate was 80%. Because visual field examination often was impossible in the institutionalized persons, we confined the analyses presented here to the noninstitutionalized individuals 55 to 95 years of age (4266 subjects). In 4095 persons, data on IOP, diabetes mellitus, and blood glucose levels were available.\(^15\) All respondents except those with anti-diabetes mellitus medication received a glucose tolerance test. To study the relation between IOP and diabetes mellitus, it was necessary that the persons in the study group were as comparable as possible with each other in relation to the effect of glucose load on IOP. Therefore, persons using anti-diabetic medication, who did not receive a glucose tolerance test, were excluded, leaving 4012 persons eligible for the analysis.

Measurements

The glaucoma screening was performed in three phases.\(^15\) In the first phase, the IOP was measured three times on each eye with the Goldmann applanation tonometer (Haag-Streit, Bernt, Switzerland),\(^16\) and the median value of each eye was noted.

In the same phase, the 24-2 test points of the Humphrey perimeter (Humphrey Visual Field Analyzer, Zeiss, Oberkochen, Germany) were tested as a suprathreshold screening test in all persons, to detect visual field defects in the central 30°. Three or more contiguous points on the screening test were taken as indication for a visual field defect. The reliability of a test result was stated by the perimeter and ultimately determined by the technician. In mydriasis direct ophthalmoscopy was performed to assess the vertical cup/disc ratio. In the second phase of the study, which was performed 2 weeks after the first phase by a perimetrist masked to the location of the defects in phase 1, visual fields were retested with the same screening test in subjects with an abnormal or unreliable visual field test in the first phase. In the third phase, carried out within a few weeks after the second phase, subjects with an abnormal or unreliable visual field test result in the second phase of the study, were recalled for perimetry with the Goldmann perimeter. Perimetry was performed according to a standard protocol\(^1\); the perimetrist knew that the subjects had shown visual field defects twice but was unaware of their location or depth. When a glaucomatous visual field defect was present, which could not be explained by other ocular abnormalities, remeasurement of the IOP and gonioscopy were performed by one of us (PTVMdeJ) before looking at the data.

The definition of primary open-angle glaucoma was based on the presence of a glaucomatous visual field defect on Goldmann perimetry\(^1\) in combination with either a vertical cup/disc ratio of 0.5 or greater or a difference in cup/disc ratio of 0.2 or more between the right and left eye, or an IOP greater than 21 mmHg, with a normal and open anterior chamber angle, without any other abnormality that could have caused the visual field defect. High-tension glaucoma was defined as primary open-angle glaucoma with an IOP of more than 21 mmHg in at least one of the two measurement sessions in phases 1 and 3 in the same eye as the visual field defect, or any treatment for glaucoma. Normal-tension glaucoma was defined as primary open-angle glaucoma with an IOP of 21 mmHg or less and no treatment for glaucoma.

Newly diagnosed diabetes mellitus was considered to be present if the random serum glucose level or the serum glucose level 2 hours after a nonfasting glucose load (75 g) was higher than 11.0 mmol/L. Subjects using antidiabetic medication (tablets or insulin) were excluded from the analyses because it was inappropriate to submit them to a glucose tolerance test.

Height and weight were measured in indoor clothing and without shoes. Body mass index was calculated as weight divided by the square of height (kg/m²).

Analysis

For the analysis, the mean of the IOP of each eye was used. The relation between the mean IOP of the right and
the left eye versus diabetes mellitus was studied by multiple linear regression analysis. Intraocular pressure, the dependent variable, was taken as a continuous outcome and diabetes, the independent variable, as a dichotomous variable (present, absent) in the model. The association with diabetes was expressed in terms of regression coefficients with 95% confidence limits.

The relation between mean IOP of both eyes and random serum glucose level also was studied with linear regression analysis after verification of the linear relation. Intraocular pressure and serum glucose level were entered as continuous variables in the linear model. Regression coefficients were expressed per 10 mmol/l glucose.

The relation between glaucoma and random serum glucose also was studied using regression analysis. Serum glucose values, as independent variable, were entered as continuous variables, and primary open-angle glaucoma, the dependent variable, was entered as a dichotomous variable (present, absent) in the multiple logistic regression model. The associations between random serum glucose and primary open-angle glaucoma were expressed as odds ratios per 10 mmol/l glucose, which is an approximation of the relative risk. The association of diabetes mellitus with high-tension glaucoma was studied in the same way. All analyses were adjusted for age, sex, and body mass index, and when appropriate for systolic blood pressure.

**Results**

Mean values of IOP are shown for 4012 subjects without diabetes and with untreated diabetes, for men and women separately, in age groups of patients younger than 70 years of age and 70 years of age or older (Table 1). Newly diagnosed diabetes was associated with a slightly, but consistently, higher mean IOP than absence of diabetes. No significant effect for age or sex was observed. With linear regression, the presence of newly diagnosed diabetes was associated with a significant overall rise in mean IOP of 0.31 mmHg (95% confidence interval, 0.12–0.50).

A change of 10 mmol/l of random serum glucose level was associated with a borderline significant overall rise in mean IOP of 0.41 mmHg (95% confidence interval, −0.02–0.84). For the post-load glucose levels, this association was 0.59 mmHg (95% confidence interval, 0.26–0.92). No significant difference existed between women and men. Additional adjustment for systolic blood pressure did not significantly change the association between mean IOP and blood glucose level. Exclusion of subjects treated for glaucoma (n = 8) did not change the results.

In the current study, 37 subjects had glaucoma. Average IOP was 18.3 mmHg in 23 subjects with high-tension glaucoma and 12.6 mmHg in 14 subjects with normal-tension glaucoma.

A 10-mmol/l higher random serum glucose level was associated with a 2.82 (95% confidence interval, 0.92–8.58) higher risk of having high-tension glaucoma. For the post-load glucose levels, this association was 1.88 (95% confidence interval, 0.81–4.32). Additional adjustment for systolic blood pressure did not significantly change the association between serum glucose and high-tension glaucoma.

The relation between newly diagnosed diabetes mellitus and high-tension glaucoma is presented in Table 2. Newly diagnosed diabetes mellitus was related to an odds ratio of 3.11 (95% confidence interval, 1.12–8.66) for high-tension glaucoma, after adjusting for age, sex, and body mass index. In persons with normal-tension glaucoma, no case of newly diagnosed diabetes mellitus was present.

**Discussion**

Our findings in this cross-sectional study in a population 55 years of age and older suggest that newly diagnosed diabetes mellitus and elevated serum glucose levels are associated with a higher mean IOP and high-tension glaucoma.

The relation between diabetes and IOP found in this study was similar to that found in case–control studies1-5,7-9 and in population-based studies9,10 on a smaller sample than the current study. The same relation was found between serum glucose levels and IOP, which also was found in case–control studies7,8,10 and in a smaller population-based study.11 It is not likely that the glucose load had much impact on the analyses because it was given to all subjects in this study.

In the current study, the associations between diabetes, blood glucose level, and IOP were the same in women and men. These associations also were found in other studies8,12. In two studies8,13 of persons with diabetes, a slightly higher IOP was found in women. Some studies11,18 did not analyze the difference in associations between women and men.

Few epidemiologic studies have suggested that diabetes mellitus is associated with primary open-angle glaucoma3,5 or, as in our study, with high-tension glaucoma.4 Most of these studies2-5 have considered persons with diabetes as those receiving medication for their disease. In the Beaver Dam Eye Study, the presence of diabetes mellitus was defined as either a history of treatment of diabetes or a glycated hemoglobin level greater than two standard deviations above the mean and a casual blood sugar level of greater than 11.1 mmol/l. The authors6 found that diabetes mellitus was related, with an odds ratio of 1.84 (95% confidence interval, 1.09–3.11), to primary open-angle glaucoma, which was lower than that found in the current study for high-tension glaucoma. A possible explanation is that persons with normal-tension glaucoma were included in the analysis of the Beaver Dam Eye Study, which could have led to a lower odds ratio. In the Framingham Eye Study,10,11 in which the presence of diabetes mellitus was based on the presence of diabetic retinopathy, regardless of whether the patients were known to have diabetes, no association could be observed between diabetes and primary open-angle glaucoma. Because the glucose tolerance test could have influenced the level of IOP, and people who were treated for their diabetes mellitus were, in the current study, excluded from having a glucose load, only untreated persons at baseline not known
Table 1. Intraocular Pressure of Subjects without Diabetes Mellitus and with Newly Diagnosed Diabetes Mellitus

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th>Men</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>55–69 Yrs</td>
<td>70–94 Yrs</td>
<td>Total</td>
<td>55–69 Yrs</td>
<td>70–94 Yrs</td>
<td>Total</td>
</tr>
<tr>
<td>No. without diabetes mellitus*</td>
<td>1303</td>
<td>965</td>
<td>2268</td>
<td>912</td>
<td>576</td>
<td>1488</td>
</tr>
<tr>
<td>IOP (mean ± SD)</td>
<td>14.46 ± 2.95</td>
<td>14.37 ± 3.08</td>
<td>14.42 ± 3.01</td>
<td>14.72 ± 3.06</td>
<td>14.65 ± 3.30</td>
<td>14.69 ± 3.16</td>
</tr>
<tr>
<td>No. with newly diagnosed diabetes†</td>
<td>65</td>
<td>85</td>
<td>150</td>
<td>52</td>
<td>54</td>
<td>106</td>
</tr>
<tr>
<td>IOP (mean ± SD)</td>
<td>14.95 ± 2.47</td>
<td>14.65 ± 2.85</td>
<td>14.78 ± 2.69</td>
<td>15.29 ± 3.38</td>
<td>14.69 ± 3.04</td>
<td>14.98 ± 3.21</td>
</tr>
</tbody>
</table>

IOP = intraocular pressure; SD = standard deviation.
* Glucose levels ≤ 11.0 mmol/l.
† Glucose levels > 11.0 mmol/l.

To have diabetes mellitus were considered. This exclusion could have led to an underestimation of the association that was found between diabetes mellitus and primary open-angle glaucoma, because the diabetes mellitus could have had longer and more serious pathologic influence in persons who already were treated for their diabetes mellitus.

Associations between diabetes and normal-tension glaucoma could not be assessed, because of the small number of persons with normal-tension glaucoma.

The average IOP (18.3 mmHg) of the 23 subjects with high-tension glaucoma can be explained by the effect of glaucoma treatment in one third of them.

An association between blood glucose and both IOP as well as high-tension glaucoma was observed in this study. In additional analyses, it appeared that these associations were not significantly influenced by systolic blood pressure; therefore, the relations between blood glucose levels, IOP, and high-tension glaucoma are not confounded by systolic blood pressure.

The mechanism of the association between hyperglycemia and elevated IOP is not clear. Possibly, the elevated blood glucose level in diabetes mellitus may induce an osmotic gradient and attract fluid into the intraocular space, which may result in an elevated IOP. In another study, a slight decrease in the coefficient of outflow with increasing severity of diabetic retinopathy has been found, apart from the advanced proliferative form. Armaly et al suggested that more than one effect may exist and effects may act in opposite directions. In addition, it is possible that diabetes mellitus increases the susceptibility of the optic nerve fibers, leading to visual field defects because of common genetic factors, the effect of diabetes mellitus on the small vessels of the eye, or diabetic neuropathy.

In conclusion, the current population-based cross-sectional study confirms that diabetes mellitus and blood glucose levels are associated with a higher IOP and with high-tension glaucoma, as found in earlier mainly case-controlled studies.

Table 2. Newly Diagnosed Diabetes Mellitus and High-tension Glaucoma*

<table>
<thead>
<tr>
<th>Newly diagnosed diabetes mellitus</th>
<th>Absent</th>
<th>Present</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>3818</td>
<td>18</td>
<td>3836</td>
</tr>
<tr>
<td>Present</td>
<td>254</td>
<td>5</td>
<td>259</td>
</tr>
<tr>
<td>Total</td>
<td>4072</td>
<td>23</td>
<td>4095</td>
</tr>
</tbody>
</table>

* The crude odds ratio was 4.18 (95% confidence interval, 1.54–11.34) and the odds ratio adjusted for age, sex, and body mass index was 3.11 (95% confidence interval, 1.12–8.66), see text.

References


---

**Centennial Advertisement**


**No. 1134.** Morton's Improved Ophthalmoscope, complete, with plane, concave and short focus mirrors, silver pupil meter and condensing lens, in case..............$25 00

* Centennial advertisement provided courtesy of the Museum of Ophthalmology, Foundation of the American Academy of Ophthalmology, San Francisco, California