Glaucoma incidence in an unselected cohort of diabetic patients: is diabetes mellitus a risk factor for glaucoma?

John D Ellis, Josie M M Evans, Danny A Ruta, Paul S Baines, Graham Leese, Thomas M MacDonald, Andrew D Morris, for the DARTS/MEMO Collaboration

Abstract

Aims—To evaluate whether diabetes mellitus is a risk factor for the development of primary open angle glaucoma or ocular hypertension (OHT).

Methods—A historical cohort study of an unselected population comprising all residents of the Tayside region of Scotland was performed using record linkage techniques followed by case note review. Ascertainment of prevalent diabetes was achieved using the Diabetes Audit and Research in Tayside Study (DARTS) validated regional diabetes register. Glaucoma and treated OHT were defined by encashment of community prescriptions and the statutory surgical procedure coding database.

Results—The study population comprised 6631 diabetic subjects and 166 144 non-diabetic subjects aged >40 years without glaucoma or OHT at study entry. 65 patients with diabetes and 958 without diabetes were identified as new cases of glaucoma or treated OHT during the 24 month study period, yielding a standardised morbidity ratio of 127 (95% CI, 96–158). Case note review demonstrated non-diagnostic misclassification of prevalent glaucoma and OHT as incident disease (diabetic cohort 20%, non-diabetic cohort 24%; p=0.56) primarily as a result of non-compliance in medically treated disease. Removing misclassified cases and adjusting for age yielded an incidence of primary open angle glaucoma in diabetes of 1.1/1000 patient years (95% CI, 0.89–1.31) compared to 0.7/1000 patient years (95% CI, 0.54–0.86) in the non-diabetic cohort; RR 1.57 (95% CI, 0.99–2.48).

Conclusions—This study failed to confirm an association between diabetes mellitus and primary open angle glaucoma and ocular hypertension. A non-significant increase in diagnosed and treated disease in the diabetic population was observed, but evidence was also found that detection bias contributes to this association.

Diabetes mellitus has been suggested as one of the risk factors for primary open angle glaucoma (POAG), along with other risk factors such as a positive family history in a first degree relative, high myopia, and black race. The inclusion of diabetes in this list is controversial. Although numerous studies have addressed this question, early studies came to differing conclusions regarding the presence of an association with some upholding and some refuting the presence of a link between the two diseases. These studies were significantly compromised by heterogeneity in the population groups studied and a lack of standardisation of the diagnostic criteria used to establish the diagnosis of POAG and the methods employed to establish the presence of diabetes. Recently, several large population based studies have demonstrated an association between the two diseases but the largest case-control study in the literature failed to find any association apart from that explained by referral bias. To the best of our knowledge, all studies to date which have addressed these issues are prevalence based; no studies of incident glaucoma or ocular hypertension (OHT) have been reported.

Our aim was to use record linkage techniques to perform a cohort study of incident cases of glaucoma and treated OHT over a 2 year period in a cohort of patients with diabetes and a similar cohort of patients without diabetes, to evaluate whether diabetes is a risk factor for the development of glaucoma or OHT.

Methods

The study was performed in the Tayside region of Scotland which is a compact geographical region with a stable 98.5% white population. The total population in 1994 (mid-study period) was 395 000 with a rural/urban split of approximately 40:60%. Migration (immigration and emigration) is around 3% per annum. The study period comprised the 24 months from 1 July 1993 to 30 June 1995.

Every patient registered with a general practitioner in Tayside is allocated a unique identifying number, the community health number
Diabetes and glaucoma

been described in detail elsewhere. In brief, community prescriptions collected at Tayside pharmacies since January 1993 are entered onto a centrally held database and mapped to the British National Formulary (BNF). The MEMO record linkage database contains the CHNo of the patient, the date the prescription was written, the individual drug code, and the amount/volume dispensed. We identified all patients prescribed glaucoma medication (BNF code 11.6 (Table 1)) between 1 January 1993 and 30 June 1995 from the MEMO database.

The secondary data source was the Tayside section of the Scottish Morbidity Record 1 (SMR1) database. The SMR1 database is a statutory record of diagnostic and surgical procedure codes (including day case surgery) for all patients admitted to any hospital in Scotland. This information is coded according to the International Classification of Diseases, ninth revision (ICD-9). The section relating to all Tayside hospitals is held in MEMO and contains all SMR1 codes since 1980.

The study was performed in two stages. For the first an electronic definition for glaucoma or treated OHT was employed in which a case was defined as any patient within the diabetic and non-diabetic cohorts who had either (1) an operation or laser procedure intended to reduce intraocular pressure (Operating and Coding Procedures Version 4, (OPSC4) codes, Table 1) in a Tayside hospital, or (2) encashed prescriptions for pressure lowering medication before or during the study period. For the second stage of the study case note review was undertaken. This was done for two reasons. The primary aim of review was to assess the validity of this electronic definition of incident glaucoma and OHT and thus to achieve an estimate of the degree of misclassification. Secondly, because the electronic definition of glaucoma and OHT could not distinguish between these and would include POAG, angle closure glaucoma, secondary glaucomas, and short term treatment for hypertensive uveitis, case note review was undertaken to assess the relative frequencies of these pathologies. It was expected that the incidence of some of the rarer forms of glaucoma would afford too few cases for meaningful analysis but the principal intention was to describe the relative incidence of POAG and OHT in the two cohorts.

In the text the term G/OHT(\(e\)) is used to refer to electronically defined glaucoma or treated OHT. The use of these diagnostic categories on their own (glaucoma or OHT) refers to the confirmed clinical diagnosis after case note review.

**Distinguishing prevalent from incident glaucoma**

All patients who encashed a prescription for glaucoma medication between 1 January 1993.
and 30 June 1993, or who had received surgical or laser treatment for glaucoma between 1980 and the start of the 2 year study period, were defined as prevalent G/OHT(\textsuperscript{e}) and excluded from analysis.

Incident G/OHT(\textsuperscript{e}) was therefore defined as all new cases of prescribing of glaucoma medication or first operation/laser procedure for glaucoma between 1 July 1993 and 30 June 1995.

**CASE NOTE REVIEW**
The case notes of all patients with diabetes and a random sample of 10\% of the non-diabetic cohort (105 notes) were reviewed. Independent review was performed by two observers (JDE/PSB). Blinding with regard to diabetic status was impossible because of frequent reference to diabetic status or retinopathy screening in the clinicians’ notes. Perimetry tests were examined. In Tayside region all perimetry performed during this period was by Humphrey 24-II full threshold testing as standard. Degree of disc cupping, rim thinning, and degree of disc asymmetry could not be independently confirmed by the reviewers since photographic records are not part of routine clinical care in Tayside.

Criteria for a diagnosis of POAG were significant disc cupping with matching field defect (at least arcuate or nasal step) in the worse eye regardless of presenting pressure. The pretreatment pressure was recorded, however, to allow distinction between POAG with elevated pressure and normal tension glaucoma. The diagnosis used in this study was that of the authors and not necessarily that recorded in the notes. Cases where there was disagreement were decided by discussion and arbitration by a third consultant ophthalmologist (CJM).

Criteria for a diagnosis of OHT were pressure greater than 21 mm Hg in the absence of a field defect or significantly asymmetric disc cupping for which treatment was deemed necessary in the judgment of the clinician(s) caring for the patient.

Further information included both the route (for example, optometrist, photographic eye screening service, general practitioner) and indication for referral. In the diabetic cohort diabetes type and duration of clinical diabetes, form and duration of treatment, and the form of routine clinic attended (hospital or primary care setting) were also recorded.

**STATISTICAL METHODS**
Randomisation of subjects from the non-diabetic cohort for case note review was undertaken using a computerised random digit generator. All analysis of relative risk and $\chi^2$ probabilities were performed using an Excel (Microsoft) based package developed in the Department of Epidemiology and Public Health, Ninewells Hospital, Dundee. $\chi^2$ Tests are Yates corrected. Significance was defined as $p<0.05$ with two tailed hypothesis testing.

**Results**

**DERIVATION OF STUDY POPULATION**
There were 175 211 residents of Tayside, Scotland, over 40 years of age who were registered with a general practitioner in January 1993 and who were either still resident in Tayside in June 1995 or who died during that period. There were 6842 people in this population with an established diagnosis of diabetes (240 type 1 diabetes, 6602 type 2 diabetes).

The median age in the non-diabetic population was 66 years compared with 58 years in the diabetic population. The sex distribution of the two populations differed significantly (diabetic population 51.9\% male, non-diabetic population 45.7\%, $p<0.001$).

The Carstairs score,\textsuperscript{17} a material deprivation measure derived from the UK decennial census, was used as a proxy for socioeconomic status. This score ranges from −8.48 (affluent) to +12.82 (deprived) and these data are available to MEMO. The average Carstairs score for the diabetic population (−0.32) and the non-diabetic population (−0.79) were very similar.

Figure 1 demonstrates the derivation of the study population. 211 of the population with diabetes and 2225 of the non-diabetic population were either using pressure lowering medication during the 6 months before 1 June 1993 or had undergone surgery during the 13 year period before the study start date. These were defined as cases of prevalent G/OHT(\textsuperscript{e}) and excluded from further analysis.

Of the remaining 6631 patients with diabetes, and 166 144 without diabetes that constituted the study population, three patients with type 1 diabetes, 62 patients with type 2 diabetes, and 958 subjects from the non-diabetic population received a first treatment (medical or surgical) for glaucoma or...
Table 2  Case note review: diagnostic categories

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Diabetic cohort (41)</th>
<th>Non-diabetic cohort (53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POAG* with elevated pressure</td>
<td>13 (31.7%)</td>
<td>20 (38.5%)</td>
</tr>
<tr>
<td>Normal tension glaucoma</td>
<td>7 (17%)</td>
<td>4 (7.7%)</td>
</tr>
<tr>
<td>Ocular hypertension</td>
<td>14 (34%)</td>
<td>14 (26.9%)</td>
</tr>
<tr>
<td>Angle closure glaucoma</td>
<td>2 (4.8%)</td>
<td>3 (5.7%)</td>
</tr>
<tr>
<td>Pseudoxfoliative glaucoma</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hypertensive uveitis</td>
<td>1</td>
<td>3 (5.7%)</td>
</tr>
<tr>
<td>Rubeosis</td>
<td>3 (7.3%)</td>
<td>3 (5.7%)</td>
</tr>
<tr>
<td>Fuchs’ heterochromic cyclitis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Post complicated cataract</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Extraction with elevated IOP</td>
<td>0</td>
<td>4 (7.7%)</td>
</tr>
</tbody>
</table>

*POAG = primary open angle glaucoma.

Table 3  Incidence rates and relative risk of POAG for diabetic patients compared with non-diabetic patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>POAG</th>
<th>All cases with elevated IOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>Diabetic</td>
<td>Non-diabetic</td>
</tr>
<tr>
<td>Incidence per 1000 patient years</td>
<td>20 (0.89–1.31)</td>
<td>24 (0.54–0.86)</td>
</tr>
<tr>
<td>Relative risk (CI)</td>
<td>1.1* (1.08–1.52)</td>
<td>1.8* (1.54–2.06)</td>
</tr>
</tbody>
</table>

*Age adjusted using Tayside non-diabetic population as reference standard.

Incidence after case note review: treated POAG and OHT incidence

The crude incidence of diagnosed and treated POAG or OHT in the cohort of patients with diabetes was 3.26 per 1000 patient years (95% CI, 2.29–4.24) and the rate in non-diabetic cohort 1.57 per 1000 patient years (95% CI, 1.16–1.97). Direct standardisation for age was performed to account for the differences in age distribution within the two cohorts. This requires age specific rates in the diabetic population and is potentially problematic because the actual numbers of cases are low and therefore the age specific rates can change significantly with the addition of only one or two extra cases. It is not possible to perform indirect standardisation, however, because the cases records of the control cohort were sampled rather than reviewed completely. The age standardised incidence for development of POAG or OHT in the diabetic cohort was 1.81 per 1000 patient years indicating that the higher average age of the diabetic cohort explains much of the observed excess in the crude rate.

Incidence after case note review: estimate of POAG incidence

Table 2 shows the diagnostic categories of the true incident cases obtained after case note review. It has been suggested that the diabetic optic disc may suffer damage at a lower given pressure than the non-diabetic disc. Intending to address this issue we recorded separately cases of POAG with presenting pressure less than 21 mm Hg in the eye with the higher pressure in the presence of disc damage and field loss (normal tension glaucoma); however, these numbers (seven with diabetes (17%) and four in the non-diabetic cohort (7.7%)) were insufficient for separate analysis. This distinction was therefore removed and the two categories combined (Table 2). POAG therefore refers to all cases of primary glaucoma with disc damage and field loss regardless of presenting IOP with an open angle.

Table 3 shows the incidence for POAG in the diabetic and non-diabetic cohorts. The relative risk and confidence intervals are shown after standardisation for age.
Table 4 Referral route

<table>
<thead>
<tr>
<th></th>
<th>Diabetic cohort (41)</th>
<th>Non-diabetic cohort (53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ophthalmic clinic attendees</td>
<td>9 (24.4%)</td>
<td>15 (29.4%)</td>
</tr>
<tr>
<td>Optometrist</td>
<td>15 (36.5%)</td>
<td>24 (46%)</td>
</tr>
<tr>
<td>General practitioner</td>
<td>11 (26.8%)</td>
<td>12 (23.5%)</td>
</tr>
<tr>
<td>Hospital diabetic clinic</td>
<td>3 (9.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Photographic screening</td>
<td>3 (7.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Private sources</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus diagnosed after commencing glaucoma medication</td>
<td>≡*†</td>
<td></td>
</tr>
</tbody>
</table>

*Diabetes diagnosed during study period. †Diabetes diagnosed 3 years after study period.

A second category of all cases with elevated pressure (POAG with presenting IOP >21 mm Hg plus OHT) is included to allow comparison with earlier studies in the literature which have used elevation of pressure as a sufficient sole diagnostic criterion for glaucoma, leading to an overestimate of the diagnosis of glaucoma.4–8

Although not statistically significant, people with diabetes had a higher risk of POAG (RR 1.57, 95% CI, 0.99–2.48) or elevated pressure (RR 1.38, 95% CI, 0.97–1.97) compared with people without.

REFERRAL ROUTE: ESTIMATE OF CONTRIBUTION OF DETECTION BIAS

Evidence that increased contact with community and hospital based ophthalmic services among diabetic patients may have contributed to detection of glaucoma was sought by recording referral routes for all cases of incident glaucoma or treated OHT (Table 4). In total, 17% of patients were referred to the ophthalmology clinic via routes wholly specific to their diabetes (attendance at the mobile photographic eye service and hospital diabetic clinic). Two of the three patients referred from the hospital diabetic clinic were referred because consultant diabetologists thought their optic disc(s) to be significantly cupped. This was also the case with one patient referred from the mobile photographic screening service. Of the 11 patients referred by their general practitioner one further case was referred with significant retinopathy. The majority of the remainder were referred with cataract. There was no excess of patients diagnosed as having glaucoma in the category of those under ongoing ophthalmic clinic review for retinopathy screening.

In two of the 41 “diabetic” patients, the diagnosis of diabetes was made by the ophthalmologist at first eye clinic attendance, illustrating that detection bias is operative in both directions. In total, detection of glaucoma in nine patients (22% of total incident cases) was attributable to detection bias. Quantification of the operation of bias resulting from increased self referral resulting from visual symptoms attributable to the increased prevalence of cataract in diabetes is not possible in this study.

Discussion

The suggestion of an association between diabetes and POAG is not new. In 1971 Becker stated: “...diabetes mellitus occurs more often in patients with primary open angle glaucoma than in non-glaucomatous populations. Similarly glaucoma is more prevalent in diabetic than in non-diabetic populations.” This statement implied clear evidence of an association. At the time considerable controversy existed in the literature and while an association between the two diseases had been described1 a number of studies had failed to observe any significant association.4–8

Most of these early studies were comparatively small, used differing definitions of glaucoma, and were clinic rather than community based, significantly limiting their generalisability.

More recently a number of population based case-control studies have been performed, with most,9–11 but not all,12–14 supporting an association.

Odds ratios (OR) of 3.11 (95% CI, 1.12–8.66) from Wisconsin,12 1.84 (95% CI, 1.09–3.11) from Wisconsin,12 and 2.12 (95% CI, 1.18–3.79) from Australia15 have been reported.

While an OR of 1.7 (95% CI, 1.03–2.86) was observed in the subgroup of patients whose glaucoma had been diagnosed before the research period in the Baltimore study, no such association was confirmed when the whole diabetic and control population was screened for glaucoma (OR 1.03 (95% CI, 0.85–1.25)).11 Using multivariate modelling in the Blue Mountains Eye Study patients with a previous diagnosis of POAG, as opposed to those in whom a diagnosis was made de novo during the study, were significantly more likely to have had some other eye disease diagnosed in the past (OR 3.4, 95% CI 1.9–6.2).20 This suggests the existence of detection bias in those patients whose glaucoma is detected by routine clinical care rather than in the context of a study.

To the best of our knowledge, there are no published cohort studies addressing the issue of a possible association between diabetes and the development of POAG. In 1975 Morgan and Drance16 attempted a prospective study of newly diagnosed glaucoma but were unable to achieve this because of significant underreporting by referring ophthalmologists.

The record linkage capabilities that exist in Tayside, allied to the relative stability of the population, afforded an unique opportunity to perform an historical cohort study in an unselected population.

We had assumed that the majority of prescribed glaucoma medication would be for POAG and were interested to find that almost one third of prescribing was for OHT (29% both groups combined 95% CI, 19.7%–38.4%). This is almost identical to the level of prescribing found in the Melbourne Visual Impairment Study where 30.2% of prescribing was for OHT.20 In contrast the Blue Mountains Eye Study found that over half of all pressure lowering agents (53%) were prescribed for OHT.20

A standardised morbidity ratio of 127 for the development of treated glaucoma (all types) or OHT in the presence of diabetes implies a small excess risk. The validity of this definition of disease derived from prescribing and surgical procedure databases was challenged by the
discovery of misclassification of prevalent disease as incident as estimated by case note review. This did not differ significantly between the diabetic and non-diabetic cohort and is unlikely to be differential. Non-differential misclassification will tend to dilute any true association between two diseases and bias the relative risk estimate towards the null value (no excess risk). When an increased relative risk is demonstrated in this context it is likely to be an underestimate of the true risk.

The possibility of differential misclassification cannot be excluded, however. Under extreme assumptions, it is possible that as few as 7% of glaucoma and OHT cases were misclassified in the diabetic cohort and as many as 34% in the non-diabetic cohort. If misclassification were operating in the reverse direction, it is possible that as many as 33% of the diabetic cohort were misclassified and as few as 14% of the non-diabetic cohort significantly reducing the relative risk. Case note review was thought more appropriate than mathematical modelling of the effect of this potential bias on the standardised schedule.

Following case note review and adjustment for age, we found a relative risk of 1.57 (95% CI, 0.99–2.48) for the diagnosis of POAG and a relative risk of 1.38 (95% CI, 0.97–1.97) for the diagnosis of elevated pressure requiring treatment (with or without disc damage).

Possible explanations for the excess of glaucoma and/or elevated pressure observed include, firstly, a lower threshold for treating OHT or diagnosing glaucoma in the presence of diabetes, secondly, increased detection of ophthalmic disease through increased contact with diabetic patients (detection bias) and, finally, a true excess risk of OHT and POAG attributable to diabetes.

A lower threshold for treatment of OHT in the presence of diabetes did not appear to explain the observed excess. The average IOP (in the higher eye) at which glaucoma medication commenced in diabetic patients was 28.8 mm Hg compared with 28.6 mm Hg in the non-diabetic cohort (t test, p=0.91). Regarding the second possible explanation for our findings, detection or unmasking bias will occur in the investigation of a possible relation between two underdiagnosed diseases if the nature or complications of the exposure (being diabetic) or disease (glaucoma) under investigation, independently leads to an increased likelihood of healthcare contact, and consequently to increased probability of detection of the second disease. This would give rise to an apparent association in the absence of a causal link and overestimate any genuine association. Both diabetes and glaucoma are exemplars of diseases with a large subclinical component, consistently estimated to be equal in size to the clinical component. While the methodology employed in this study has the advantage of describing the actual pattern of disease in the general population, it can only comment on the relation between the diagnosed or clinically apparent portion of both diseases. Increased healthcare contact with diabetic patients will often both because of routine screening and as a result of symptomatic visual deterioration attributable to the increased prevalence of cataract in the diabetic population. We found that 22% of the incident cases of glaucoma or OHT detected in diabetic patients were attributable to contact with medical services for diabetes screening. The influence of increased self referral is hard to quantify. Klein reported that significantly more diabetic than non-diabetic patients had seen an ophthalmologist in the 2 years before study evaluation (p<0.01). We estimate that this is likely to be a significant factor in the current study and in some measure to account for the clinicians’ impression of an association between the two diseases.

Finally, the excess of glaucoma or elevated pressure may be real. Most studies have observed higher mean IOPs in diabetic patients compared with non-diabetic controls or a higher percentage of patients with an IOP >21 mm Hg. A few early studies found no evidence of increased pressure in diabetes and one study found evidence of lower pressures.

In common with others we have found evidence of an excess of POAG in the diabetic population. The few early studies that found levels of prescribing of pressure lowering treatments for ocular hypertension in this population and, secondly, the demonstration of significant primary non-compliance (no medication collected for at least 6 months) in a subgroup of patients in both cohorts. This was discovered because of the use of encashed prescriptions as the data source for the Medicines Monitoring Unit and the study design’s assumption that a first prescription after a 6 month drug free period indicated incident disease.

Summary
We found a moderate excess of incident glaucoma and treated OHT in patients with diabetes detectable over a total of 345 550 patient years. These findings are compatible with those case-control studies that have demonstrated an association between the two diseases. We suspect, however, that increased healthcare contact in patients with diabetes leading to increased detection of glaucoma and OHT—asymptomatic conditions known to increase in prevalence with age—contributes significantly to this observed association. Further longitudinal studies excluding, or quantifying, the full extent of detection bias would be needed to answer this question definitively.

Presented at the Oxford Congress of Ophthalmology, July 1998. John D Ellis is a recipient of a Wellcome Trust training fellowship in clinical epidemiology (053617). Josie M M Evans is a recipient of a Wellcome Trust training fellowship in health services research (050212). Our thanks to Dr Caroline J MacEwen for clinical input in diagnosis of primary open angle glaucoma/ocular hypertension in borderline cases.