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ORIGINAL RESEARCH

Diabetes, glycemic control and risk of medical glaucoma treatment: A population-based case-control study

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Purpose: To examine the association between diabetes and risk of medical glaucoma treatment and to assess the role of long-term glycemic control in the putative association.

Design: Population-based case-control study.

Methods: Cases of treated glaucoma were all persons filling at least three prescriptions for glaucoma medication for the first time within one year between 2001 and 2006 in Northern Jutland, Denmark. We used risk set sampling to select 10 gender- and age-matched general population controls per case using the Danish Civil Registration System. Data on diabetes, comorbidities, and laboratory tests, including glycosylated hemoglobin (as a measure of glycemic control) were obtained from population-based medical registries. We calculated odds ratio (OR) as an estimate of relative risk for treated glaucoma comparing patients with and without diabetes, adjusted for comorbid conditions and medication use.

Results: We included 5,991 persons with incident medical glaucoma treatment and 59,910 population controls. The adjusted OR for treated glaucoma for patients with diabetes was 1.81 (95% confidence interval: 1.65–1.98). The strength of the association between diabetes and glaucoma risk did not vary by diabetes duration or by the level of glycemic control.

Conclusions: Regardless of glycemic control, diabetes is associated with a substantially increased risk for medical glaucoma treatment.

Keywords: diabetes, glaucoma, glycemic control, prescriptions, population-based case-control study

Introduction

The morbidity, mortality and costs related to diabetes are escalating epidemically. A US citizen born in 2000 will have a 33% lifetime risk of developing diabetes.[1–3] Eye complications are important adverse effects of diabetes. Reduced intraocular blood flow in diabetic patients causes secondary nerve cell damage and leads to diabetic retinopathy.[4] Diabetes may also cause a thicker central corneal thickness[5] and a rise in intraocular pressure (IOP)[6,7] made worse by poor long-term control of diabetes.[6] Long-term control of diabetes can be assessed with measurements of glycosylated hemoglobin (HbA_{1c}).[8,9]

Glaucoma is the most common cause of irreversible blindness worldwide.[10] The visual field loss in glaucoma caused by loss of retinal nerve cells can be worsened by nerve cell apoptosis, which is increased in diabetic patients. The previous epidemiologic studies that examined diabetes as a potential risk factor for glaucoma had conflicting conclusions.[7,11–16] Moreover, while hyperglycemia is known to play a role in the development of diabetic retinopathy, to our knowledge no study has examined

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the association between the level of glycemic control and risk of glaucoma.

We hypothesized that diabetes is a risk factor for glaucoma, and that poor long-term glycemic control and longer duration of diabetes may increase the risk of glaucoma. We conducted a large case-control study using population-based Danish medical databases.

Methods

We conducted the study in the former Danish counties of Northern Jutland and Aarhus, with a total population of 1.14 million mixed rural and urban inhabitants, representing 20% of the Danish population.[17] The population is 93% Caucasian, and less than 2% migrate annually from or into the counties.[17] The Danish National Health Service provides tax-financed primary medical care and free access to hospitals to all citizens. Furthermore, the National Health Service partially reimburses the costs of prescription medications, including those for glaucoma and diabetes. We linked data from several Danish population-based databases and medical registries. The unambiguous individual-level linkage is possible thanks to the Danish Civil Registration System, whereby a unique 10-digit civil registration number (CRN) encoding date of birth and sex is assigned to every Danish citizen at birth. The Civil Registration System[18] was established in 1968. It is updated daily and tracks vital status, residence, and migrations. The CRN is used in all public databases to uniquely identify individuals.[18]

Cases of medically treated glaucoma

Glaucoma treatment cases were identified and categorized using the Danish National Registry of Patients (DNRP)[19] and prescription databases of the two former counties merged into a research database at Aarhus University. Established in 1977, the DNRP tracks all hospitalizations and, from 1994 onwards, all outpatient visits. Recorded data include dates of admission and discharge, surgical procedures performed, and up to 20 diagnoses per visit or hospitalization. The diagnoses are coded by medical doctors using the 8th revision of the International Classification of Diseases (ICD-8) through the end of 1993 and the 10th revision (ICD-10) thereafter. The prescription databases hold information on every sale of prescription medication in the counties, including date of dispensing and type of drug coded according to the Anatomical Therapeutic Chemical (ATC) classification system.

We defined an incident case of glaucoma treatment as a person filling three or more prescriptions for a glaucoma medication (ATC code group S01E) over 365 days or less during the study period, from January 1st, 2001 to December 31st, 2006. We required a minimum of three filled prescriptions on separate dates in order to exclude cases of possible short-term secondary glaucoma associated with prior ocular surgery or uveitis. Glaucoma medication is sold only by prescription in Denmark and is prescribed for primary or secondary glaucoma or for ocular hypertension (OHT), but not for any other condition. We did not consider as cases patients with prescription for Acetazolamide tablets (ATC code S01 EC01), since these are used for other indications, including high-altitude sickness; moreover, they are rarely used for long-term glaucoma treatment. The date on which the patient filled his or her third prescription for a glaucoma medication was considered the glaucoma case index date. In order to be eligible for inclusion in the study, persons had to reside in one of the counties for at least five years before the index date. In order to only include patients with incident glaucoma, we excluded persons with prescriptions for a glaucoma medication filled within five years prior to the beginning of the study period and patients with a previous hospital contact with angle-closure glaucoma in the DNRP (ICD-10 diagnosis H40.2). We also excluded patients with glaucoma surgery or laser treatment prior to index date (procedure codes KCHD all, or KCHF 05-10-15-20-30 or 99, obtained from the DNRP). We identified incident glaucoma cases based on glaucoma medications rather than ICD-10 codes in our study because the majority of glaucoma patients in Denmark are treated in private practices that do not report diagnosis codes to the DNRP.

Population controls

Using data from the Civil Registration System to ascertain vital status and residence at the time of sampling, we randomly selected 10 population controls for each glaucoma case, matching birth-year, sex, and residence in one of the two counties for at least five years prior to the case's index date. Control selection was done by risk set sampling,[20,21] whereby controls had to be alive and at risk of filling their third prescription for a glaucoma medication on the index date of their corresponding case. Odds ratios (OR) calculated from samples drawn using risk-set sampling provide estimates of the incidence rate ratio that would be observed in the underlying cohort.[22] In this study OR was used as a measure of relative risk. The same eligibility and exclusion criteria were applied to cases and controls.

Identification of diabetes

Presence of diabetes for all subjects was ascertained by a validated method using prescription and hospital data.[23]

We used the DNRP to identify all persons with a hospitalization or outpatient diagnosis of diabetes mellitus recorded since 1977 (ICD-8 codes 249–250 and ICD-10 codes E10–14). From the counties' prescription databases we identified all persons with at least one prescription for insulin or an oral antidiabetic drug.

Diabetes was classified as type 1 diabetes mellitus (T1DM) for patients first diagnosed before the age of 30 years, treated with insulin monotherapy, and without history of taking an oral antidiabetic medication; the remaining diabetes patients were considered to have type 2 diabetes mellitus (T2DM). The use of insulin and oral antidiabetic medication was ascertained by selecting prescriptions with ATC codes A10A and A10B recorded in the prescription databases.[23,24] Duration of diabetes was computed as the time elapsed from the first record of diabetes treatment or hospital diagnosis until the index date. Information on HbA_{1c} levels was obtained by linkage of the regional laboratory databases.[25] These databases contain information on all specimens submitted for analysis by hospitals and practitioners, including the exact time of blood sample collection. The most recent measurement was used for analysis. We only could identify 27 T1DM patients in the case group; of these, 25 (93%) had vitreoretinal surgery recorded before the index date, indicating secondary glaucoma. We refrained from making individual analysis on T1DM patients as this subgroup was too small and analyzed all diabetes patients together.

Covariates

We retrieved data on variables that are putative risk factors for glaucoma and also may be associated with diabetes. A recent review article identified cardiovascular events, hypertension, thyroid disease and migraine as risk factors for glaucoma.[26] We considered as potential confounders the following conditions, which were considered present if they were identified by a diagnosis in DNRP or by a relevant medication in the prescription database within five years prior to the index date for cases and matched controls: cardiovascular disease (ICD-10: E78; I20–26, 35.0–35.2, 60–61, 63–67, 69, 70, 74, 82), hypertension (ICD-10: I10–15), thyroid disease (ICD-10: E01–07, O90.5 and ATC: H03), migraine (ICD-10: G43 and ATC: N02C), autoimmune disorders (ICD-10: M05–9, M30–35, D86, K50–51, MO2.3, M45.9, M02.9, M03.2, M03.6, I73), alcoholism-related diagnoses (ICD-10: F10, K86.0, Z72.1, R78.0, T51, K 29.2, G62.1, G72.1, G31.2, I42.6), cataract (ICD-10: H25–26, 28.0 and procedure codes KCJA,C,D,E), retinal detachment (ICD-10: H33.0 and procedure codes KCKC60,70, KCKD25,30) and uveitis (ICD-10: H20, 22, 30, 32.0 and ATC-codes S01BA). Furthermore, we ascertained use of potential IOP-lowering systemic drugs: oral beta-adrenoceptor blockers (ATC: C07), statins (ATC: C10AA), and angiotensin-converting enzyme (ACE) inhibitors (ATC: C02E, C02L, C09A, C09B, C08DA51).[27–30]

Statistical analysis

We used conditional logistic regression to compute the crude and adjusted OR with 95% confidence intervals (CI) for glaucoma according to presence of diabetes. Diabetes exposure was categorized by duration of diabetes (<5 years, ≥5–<10 years, ≥10 years) and HbA_{1c} levels (<7%, ≥7%–<8%, ≥8%–<9%, ≥9%, unknown).[8,31] We conducted analysis stratified by sex and age group: 0–50 years, 51–60 years, 61–70 years, 71–80 years, 81–90 years, >90 years. We adjusted for cardiovascular disease, hypertension, thyroid disease, other autoimmune disorders, migraine, alcoholism-related disorders, and use of ACE inhibitors, beta-blockers, and statins. Analyses were conducted both with and without adjustment for retinal detachment, cataracts, and uveitis, as these conditions could represent intermediate steps between diabetes and development of glaucoma. All analyses were performed using Stata software (version 9.2; StataCorp, College Station, TX, USA).

Results

From January 1st, 2001 to December 31st, 2006, 9,295 patients filled at least one prescription for glaucoma medication in the counties' pharmacies; of these, 6,737 filled at least three prescriptions on different dates. Of these, 268 patients had more than 365 days between the first and the third glaucoma medication prescription, 384 patients moved away from the counties, and 94 patients had a history of angle-closure glaucoma or other glaucoma, laser treatment or surgery, and were therefore excluded, leaving 5,991 patients with medically treated incident glaucoma for analysis. Table 1 has descriptive data of the 5,991 cases with treated incident glaucoma and the 59,910 age- and sex-matched control subjects. Seven hundred and four patients using glaucoma medication had diabetes (11.8%) compared with 3,975 (6.6%) of the 59,910 controls. Patients using glaucoma medication were substantially more likely than controls to have a history of uveitis, cataract, and retinal detachment. Most other comorbidities and use of medications were slightly more prevalent among glaucoma cases than among matched controls (Table 1).

Table 1 Adjusted and crude ORs for glaucoma according to presence of diabetes mellitus

Risk factor	Cases	Controls	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Sex				
Male	2,492 (41.6)	24,920 (41.6)		
Female	3,499 (58.4)	34,990 (58.4)		
Age, years, median (IQR)	70.4 (60.8–78.4)	70.3 (60.8–78.4)		
Diabetes				
Absent	5,287 (88.25)	55,935 (93.37)	1.0 (ref)	1.0 (ref)
Present	704 (11.75)	3,975 (6.63)	1.95 (1.79–2.12)	1.81 (1.65–1.98)
Thyroid disease	439 (7.3)	3,603 (6.0)	1.24 (1.12–1.38)	1.20 (1.08–1.34)
Migraine	203 (3.4)	1,568 (2.6)	1.31 (1.13–1.53)	1.32 (1.13–1.54)
Auto immune disorders	244 (4.1)	1,915 (3.2)	1.29 (1.12–1.47)	1.25 (1.09–1.43)
Cardiovascular risk factors	765 (12.8)	7,919 (13.2)	0.96 (0.88–1.04)	0.76 (0.70–0.84)
Hypertension	593 (9.9)	4,772 (8.0)	1.28 (1.17–1.40)	1.19 (1.07–1.31)
Alcohol related diagnoses	47 (0.8)	494 (0.8)	0.95 (0.70–1.29)	0.91 (0.68–1.24)
ACE inhibitors	1,042 (17.4)	8,616 (14.4)	1.26 (1.18–1.36)	1.08 (1.00–1.17)
Oral beta adrenoceptor blockers	1217 (20.3)	11,695 (19.5)	1.05 (0.98–1.13)	0.96 (0.89–1.03)
Statins	828 (13.8)	6,307 (10.5)	1.05 (0.98–1.13)	1.29 (1.18–1.41)
Cataract	686 (11.5)	3,995 (6.7)	1.90 (1.74–2.08)	1.42 (1.29–1.56)
Retinal detachment	135 (2.3)	159 (0.3)	8.65 (6.86–10.90)	6.15 (4.82–7.85)
Uveitis	523 (8.7)	1,349 (2.3)	4.21 (3.79–4.68)	3.60 (3.22–4.02)
Duration of diabetes				
Diabetes absent	5,287 (88.25)	55,935 (93.37)	1.0 (ref)	1.0 (ref)
<5 years	320 (5.34)	1,689 (2.82)	1.88 (1.66–2.14)	2.03 (1.79–2.29)
≥5–<10 years	200 (3.34)	1,210 (2.02)	1.64 (1.41–1.92)	1.77 (1.52–2.06)
≥10 years	211 (3.52)	1,111 (1.85)	1.87 (1.60–2.18)	2.02 (1.74–2.35)
HbA_{1c}				
Diabetes absent	5,287 (87.3)	55,935 (93.37)	1.0 (ref)	1.0 (ref)
HbA_{1c} < 7%	213 (3.6)	1,074 (1.79)	1.97 (1.69–2.30)	2.12 (1.83–2.47)
HbA_{1c} ≥ 7%–<8%	150 (2.5)	660 (1.10)	2.24 (1.86–2.69)	2.44 (2.04–2.92)
HbA_{1c} ≥ 8%–<9%	88 (1.5)	421 (0.70)	2.05 (1.62–2.60)	2.24 (1.77–2.82)
HbA_{1c} ≥ 9%	84 (1.4)	380 (0.63)	2.20 (1.73–2.80)	2.36 (1.86–3.00)
HbA_{1c} unknown	196 (3.3)	1,475 (2.46)	1.34 (1.15–1.57)	1.41 (1.21–1.65)

Notes: Data on cases and controls are n (%). [a]OR adjusted by conditional logistic regression for thyroid disease, migraine, autoimmune disorders, cardiovascular events, hypertension, alcohol-related disorders, angiotensin-converting enzyme inhibitors, oral beta adrenoceptor blockers and statins.
Abbreviations: ACE, angiotensin-converting enzyme; CI, confidence interval; HbA_{1c}, glycosylated hemoglobin; IQ, interquartile range; OR, odds ratio.

The crude OR for using glaucoma medication in patients with diabetes was 1.95 (95% CI: 1.79–2.12) (Table 1). After adjusting for confounding factors, the OR decreased slightly to 1.81 (95% CI: 1.65–1.98). When the eye disorders of retinal detachment, cataracts, and uveitis were added to the model, the OR further decreased slightly, to 1.75 (95% CI: 1.60–1.92).

One or more measurement of HbA_{1c} within the year prior to index date was available for 535 patients treated with glaucoma medication (73.3%) with diabetes and for 2,535 of the controls (63.0%) with diabetes. Diabetes was associated with about twofold increased risk for glaucoma at all levels of HbA_{1c}: adjusted ORs among diabetic subjects with an HbA_{1c} level of <7%, ≥7%–<8%, ≥8%–<9%, and ≥9% were 1.97 (95% CI: 1.69–2.30), 2.24 (95% CI: 1.86–2.69), 2.05 (95% CI: 1.62–2.60), and 2.20 (95% CI: 1.73–2.80), respectively (Table 1). Fifty-six percent of the diabetes patients who used glaucoma medication had had diabetes for more than five years. The duration of diabetes did not modify relative risk estimates considerably: OR = 1.88 (95% CI: 1.66–2.14) for diabetes duration under five years, OR = 1.64 (95% CI: 1.41–1.92) for duration between five

and 10 years, and OR = 1.87 (95% CI: 1.60–2.18, n = 200) for duration of more than 10 years.

The strength of association between diabetes and risk of using glaucoma medication decreased with age, with OR decreasing from 3.35 (95% CI: 3.50–5.08) for patients aged 60 years or younger to 1.12 (95% CI: 0.91–1.31) for patients older than 80 years. The effect of diabetes was greater among men with OR = 2.04 (95% CI: 1.79–2.31) than among women with OR = 1.61 (95% CI: 1.42–1.83) (Table 2).

Discussion

We found that diabetes mellitus was associated with a 1.8-fold increased risk of medically treated glaucoma. The increased risk was independent of diabetes duration or of level of glycemic control. The relative effect associated with diabetes was greatest among persons aged under 60 years, possibly due to the lower baseline glaucoma risk in younger individuals. The effect was greater in men than in women.

The effect of diabetes on the risk of using glaucoma medication estimated in our study was similar to that estimated in the only other study of comparable size and design. In the Scottish Tayside study (2000), a cohort of all T2DM patients (n = 6,631) in the Tayside region was followed for two years between 1993 and 1995.[32] The investigators used prescription data and operation codes as surrogate measures for glaucoma, while estimating, based on a case notes review, the extent of misclassification thus introduced. Based on 65 incident glaucoma cases in the T2DM cohort and 963 incident cases in the general Tayside population, relative risk was estimated at 1.57 (95% CI: 0.99–2.48) for the association between T2DM and glaucoma. Four large cross-sectional studies found positive associations between diabetes and glaucoma including the Beaver Dam study (1994; OR = 1.84; n = 4,926, glaucoma cases = 105);[11] the Rotterdam study (1995; OR = 3.11; n = 4,178, glaucoma cases = 37);[7] the Blue Mountain Eye study (1997; OR = 2.12; n = 3,654, glaucoma cases = 108);[12] and the Los Angeles Latino Eye Study (LALES, 2008; OR = 1.4; n = 5,894, glaucoma cases = 288).[13] Other cross-sectional studies, including the Baltimore Eye Survey (n = 5,308, glaucoma cases = 161)[15] and the Ocular Hypertension Treatment Study (n = 1,636, glaucoma cases = 119)[14] showed no or even a negative association between diabetes and glaucoma. A meta-analysis that included most of the case-control and cross-sectional studies concluded that diabetes patients are at a significantly increased risk of glaucoma (OR = 1.5, 95% CI: 1.16–1.93).[33] Two recent prospective population-based cohort studies found no association between diabetes and incident glaucoma: the Barbados Eye Study cohort (n = 3,222, glaucoma cases = 125, OR diabetes = 1.2) was followed for nine years[16] and the Rotterdam cohort (n = 3,387, glaucoma cases = 87, OR diabetes = 0.82,) was followed for seven years.[34] In two subsequent letters, Ellis and Quigley propose that a potential surveillance bias in diabetic patients in previous studies may fully explain the apparent increased risk of glaucoma in diabetes patients.[35,36] Our study is the first to demonstrate the equal risk of glaucoma associated with diabetes at all levels of glycemic control and duration of diabetes.

Table 2 Odds ratio (OR) for glaucoma according to presence of diabetes stratified by age and sex

	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Age		
0–60 years	4.22 (3.50–5.08)	3.35 (2.72–4.14)
61–70 years	2.55 (2.17–2.99)	2.26 (1.90–2.69)
71–80 years	1.54 (1.32–1.79)	1.47 (1.25–1.73)
>80 years	1.08 (0.89–1.33)	1.12 (0.91–1.37)
Sex		
Female	1.74 (1.54–1.96)	1.61 (1.42–1.83)
Male	2.20 (1.95–2.49)	2.04 (1.79–2.31)

Notes: [a]Odds ratio adjusted by conditional logistic regression for thyroid disease, migraine, autoimmune disorders, cardiovascular events, hypertension, alcohol related disorders, ace-inhibitors, oral beta adrenoceptor blockers and statins.
Abbreviation: CI, confidence interval.

Our findings must be interpreted in the context of the study's methodological strengths and weaknesses. The universal health coverage of Denmark's national health care system enabled us to conduct a large, truly population-based study, while using population-based data sources with independently and routinely recorded data. These features tend to reduce the risks of selection and information bias. As in previous studies of this issue, it is difficult to rule out surveillance bias stemming from greater likelihood of diabetic patients to undergo ophthalmological investigations compared with general population.[11,32,34–36] As shown in the Beaver Dam study, diabetes patients with glaucoma were significantly more likely than glaucoma patients without diabetes to have consulted an ophthalmologist over a two-year period (49.2 vs 39.6%).[11] Some evidence for such bias in our data comes from the observation that glaucoma patients with diabetes tended to be slightly younger than other glaucoma patients (median age of 68.8 years vs. 71.1 years). Moreover, our case group is likely to include patients treated for OHT as in the Tayside Study.[32] Our data did not allow us to differentiate primary from secondary glaucoma, neither

could we differentiate between different types of glaucoma (pseudoexfoliation, angle closure, pigment dispersion, etc). Also, glaucoma diagnoses in this population-based study were made by approximately 60 different ophthalmologists who may have had different thresholds for commencement of medical treatment for glaucoma. Quigley and colleagues suggested that it is not safe to conclude that most physicians prescribe glaucoma medication according to preferred practice patterns, and that many patients fill their prescriptions so irregularly that they keep "reappearing" as incident glaucoma cases.[37] We aimed to solve this potential problem with our defined medication algorithm.

Ascertainment of medication use and of data on covariates through independent administrative registries reduced potential patient-related (differential recall) or investigator-related information bias, which might affect studies with primary data collection. In order to become a glaucoma case in this study, patients had to buy glaucoma medication at least three different times within one year. These cases are very likely to actually use the medication and to have glaucoma rather than a temporary increase in IOP. Prescriptions can only be filled at a pharmacy, and all Danish pharmacies report complete data to the prescription database. Glaucoma medications purchased in pharmacies are partially refunded by the national health insurance, and the share of Internet-based or foreign purchases is negligibly small.

We were able to adjust our analysis for several potential confounders measured by data from the medical databases that aim to track complete prescription and medical history, including all surgical procedures performed. Known strong risk factors for glaucoma are older age, family history, and race. Hispanics[13] and blacks[16,38] are known to have a higher risk than Caucasians for both diabetes and glaucoma, but are hardly represented in this study performed in a very homogenous population of Caucasians. Most of the recently reviewed risk factors for glaucoma[26] were more prevalent among cases than among controls in our study, but adjustment for their effects explained only 15%–20% of the observed diabetes effect. Of note, cardiovascular disease did not confound our analysis. While cardiovascular diseases and hypertension were associated with diabetes, they were equally prevalent among glaucoma cases and controls, which suggests that only a small part of the risk increase conferred by diabetes was mediated by these disorders.

In conclusion, our findings, representing the everyday practice pattern of Danish ophthalmologists, and based on a large population-based sample, corroborate and extend the existing evidence of diabetes mellitus as a risk factor for medical glaucoma treatment.

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Disclosures

The authors report no conflicts of interest in this work.

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