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Diabetes, use of antidiabetic drugs, and the risk of glioma

Corinna Seliger, Cristian Ricci, Christoph R. Meier, Michael Bodmer, Susan S. Jick, Ulrich Bogdahn, Peter Hau, and Michael F. Leitzmann

Department of Neurology and Wilhelm Sander-NeuroOncology Unit, Regensburg University Hospital, Regensburg, Germany (C.S., U.B., P.H.); Department of Epidemiology and Preventive Medicine, University of Regensburg, Regensburg, Germany (C.R., M.F.L.); Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland (C.R.M., M.B.); Boston Collaborative Drug Surveillance Program, Boston University School of Public Health, Boston University, Boston, Massachusetts, (C.R.M., S.S.J.); Hospital Pharmacy, University Hospital Basel, Basel, Switzerland (C.R.M.); Department of General Internal Medicine, University of Bern, Inselspital/Universitätsspital, Bern, Switzerland (M.B.)

Corresponding Author: Dr Corinna Seliger, MD, Department of Neurology and Wilhelm Sander-NeuroOncology Unit, Regensburg University Hospital, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany (corinna.seliger@klinik.uni-regensburg.de).

See the editorial by Purow, on pages 306–307.

Background. Prior epidemiologic studies suggest inverse relations between diabetes and glioma risk, but the underlying mechanisms, including use of antidiabetic drugs, are unknown.

Methods. We therefore performed a matched case-control analysis using the Clinical Practice Research Datalink (CPRD). We identified incident glioma cases diagnosed between 1995 and 2012 and matched each case with 10 controls on age, gender, calendar time, general practice, and years of active history in the CPRD. We performed conditional logistic regression to estimate odds ratios (ORs) with 95% CIs, adjusted for body mass index and smoking.

Results. We identified 2005 cases and 20 050 controls. Diabetes was associated with decreased risk of glioma (OR = 0.74; 95% CI = 0.60–0.93), particularly glioblastoma (OR = 0.69; 95% CI = 0.51–0.94). Glioblastoma risk reduction was markedly pronounced among diabetic men (OR = 0.60; 95% CI = 0.40–0.90), most apparently for those with diabetes of long-term duration (OR for >5 vs 0 y = 0.46; 95% CI = 0.26–0.82) or poor glycemic control (OR for HbA1c ≥8 vs <6.5% = 0.20; 95% CI = 0.06–0.70). In contrast, the effect of diabetes on glioblastoma risk was absent among women (OR = 0.85; 95% CI = 0.53–1.36). No significant associations with glioma were found for use of metformin (OR for ≥30 vs 0 prescriptions = 0.72; 95% CI = 0.38–1.39), sulfonylureas (OR = 0.71; 95% CI = 0.39–1.30), or insulin (OR = 0.79; 95% CI = 0.37–1.69).

Conclusions. Antidiabetic treatment appears to be unrelated to glioma, but long-term diabetes duration and increased HbA1c both show decreased glioma risk. Stronger findings in men than women suggest low androgen levels concurrent with diabetes as a biologic mechanism.

Keywords: diabetes, epidemiology, glioma, metformin, testosterone.

Malignant gliomas account for 80% of all primary malignant tumors of the central nervous system, with a mean incidence of 5–7 cases per 100 000 person-years.[1] Gliomas can be subdivided according to their degree of malignancy into World Health Organization (WHO) grades I–IV.[2] The most common and aggressive form is glioblastoma, which has a mean overall survival of 14.6 months and a 2-year survival rate of 26.5% with standard therapy.[3] The few established risk factors for glioma include age, male gender, Caucasian ethnicity, and certain rare genetic syndromes. A high dose of ionizing radiation is the only known modifiable glioma risk factor.[4]

Diabetes mellitus is a chronic disease affecting 347 million people worldwide. Around 90% of diabetics suffer from type 2 diabetes, a condition of relative insulin deficiency and beta cell dysfunction associated with obesity and metabolic syndrome.[5] The relation of diabetes to glioma has been evaluated in numerous previous studies, many[6–11] of which reported a statistically significant inverse association between the 2, but several investigations showed statistically nonsignificant inverse,[12–14] positive,[15] null,[16–19] or mixed[20] relations. However, these studies did not examine the association between diabetes and glioma in detail.

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Furthermore, there is evidence to suggest that metformin, one of the most widely prescribed oral antidiabetic drugs, reduces cancer risk in diabetic patients,[21] and recent experimental data show distinct antiproliferative effects of metformin on glioma cells in vitro and in vivo.[22,23] However, the associations between individual antidiabetic agents and glioma have not been quantified. We therefore conducted a comprehensive examination of diabetes status, diabetes duration, glycemic control, and use of common antidiabetic agents (metformin, sulfonylureas, and insulin) in relation to glioma risk using a large, well-established primary care database.

Patients and Methods

Data Source

We used data from the UK-based Clinical Practice Research Datalink (CPRD), which encompasses data on patients from ~450 general practices representative of the UK population with respect to age, gender, and geographic distribution. General practitioners record information regarding patient demographics, clinical diagnoses, referrals, hospital admissions, and drug prescriptions using standard coding systems. Practitioners generate prescriptions using office computers, and the data are automatically recorded in the electronic patient records.[24,25] The validity of the information on drug exposures and diagnoses recorded in the CPRD database has been extensively documented.[26,27] The current study was approved by the Independent Scientific Advisory Committee for the UK Medicines and Healthcare Products Regulatory Agency.

Study Population

Case Definition

Cases were defined as all patients in the CPRD database below age 90 years with an incident glioma diagnosis between 1995 and 2012. The date of the first-time diagnosis, as defined using Read codes, will be referred to as the index date. Read codes for glioma are based on histopathology according to the WHO classification[2] (Supplementary Table 1). We excluded patients with any prior history of cancer other than glioma except nonmelanoma skin cancer, those with alcoholism or human immunodeficiency virus infection prior to the index date, and patients with less than 3 years of active history in the database prior to the index date. We considered total glioma and glioma according to WHO grade (grade IV only, grade III or IV, and grade II). We did not compare patients with grade I glioma to those with other WHO grades because these tumors have a distinct pathogenesis and affect mostly pediatric patients.[1,2]

Control Definition

We randomly selected up to 10 controls without a glioma history from the CPRD and matched them to glioma cases on calendar time (same index date), age (same year of birth), gender, general practice, and years of medical history in the database prior to the index date. The selection of controls was based on the same inclusion and exclusion criteria used for glioma cases. To minimize the risk of using control patients with misclassified glioma, we excluded control patients with a prior history of craniotomy within the past year before the index date, a time window considered sufficient given malignant glioma's highly invasive phenotype.

Exposures

Using the computerized CPRD records, we assessed diabetes status and diabetes duration. We also considered the mean hemoglobin A1c (HbA1c) level during the past 3 years prior to the index date as a proxy for long-term glycemic control. Diabetes status (yes or no) was defined using specific Read codes reflecting diagnostic criteria for diabetes in the UK in the respective time period. We defined diabetes duration as the time interval between the date of the first diabetes recording and the index date. Diabetes duration was classified into 3 categories (<2, 2–5, >5 y). HbA1c level was also classified into 3 categories (<6.5, 6.5–7.9, ≥8%). Missing values were included in a separate category.

Exposure to antidiabetic drugs was categorized based on the number of prescriptions prior to the index date. Subjects who did not receive any prescription for an antidiabetic drug prior to the index date were categorized as non-users. For subjects using more than one antidiabetic drug, we mutually adjusted for sequential or concurrent use in the multivariate model. Antidiabetic drug users were categorized according to short-term use (1–9 prescriptions prior to the index date), medium-term use (10–29 prescriptions prior to the index date), or long-term use (≥30 prescriptions prior to the index date). The number of prescriptions served as a proxy for exposure duration, since an average prescription covers 45–90 treatment days. Users of metformin, sulfonylureas, and insulin were examined separately.

Statistical Analysis

We conducted conditional logistic regression analyses to determine relative risks, estimated as odds ratios (ORs) with 95% confidence intervals (CIs) of glioma in relation to diabetes status, diabetes duration, HbA1c level, and individual antidiabetic drug use. Potential confounding variables included body mass index (BMI; <18.5, 18.5–24.9, 25–29.9, ≥30.0 kg/m^2, unknown); smoking status (never, current, past, unknown); cardiovascular conditions or diseases (dyslipidemia, stroke/transient ischemic attack, hypertension, congestive heart failure, ischemic heart disease, myocardial infarction, chronic renal failure); and use of statins (0, 1–9, ≥10 prescriptions), nonsteroidal anti-inflammatory drugs (NSAIDs; 0, 1–9, ≥10 prescriptions), aspirin (0, 1–14, ≥15 prescriptions), and estrogens (0, 1–14, ≥15 prescriptions; women only). Variables that altered the effect estimate for glioma by >10% in the multivariate analyses were retained in the model. Our final model included BMI and smoking. Tests of linear trend were conducted by modeling the median value of each category as a continuous variable in the multivariate model, the coefficient for which was evaluated using a Wald test.

To assess treatment prior to disease onset, to control for changes in antidiabetic treatment over time, and to account for potential earlier detection of preexisting diabetes in case patients caused by early symptoms of undiagnosed glioma, for all analyses we shifted the index date backward in time by one year for cases and controls.

We further assessed the role of antidiabetic drug use in relation to glioma in a subsample restricted to diabetic cases and controls. In these analyses, we newly matched diabetic glioma cases with diabetic cancer-free controls on duration of diabetes to control for duration-related biases. In a further sensitivity analysis, we additionally matched on both duration of diabetes and HbA1c level to account for the influence of glycemic control on the choice of antidiabetic treatment. The intended 1:10 matching was not fully achieved in these sensitivity analyses due to limited numbers.

To examine whether the associations of diabetes status, diabetes duration, HbA1c level, and antidiabetic drug use were modified in relation to glioma risk, we evaluated glioma risk within strata of gender (men, women) and age (<67, ≥67 y). We chose a cutpoint of 67 years because this was the median age of diabetic glioma patients. We conducted formal tests for interaction using likelihood ratio tests. For all statistical analyses, the type I error was set at 5% and tests were 2-tailed. We used SAS statistical software version 9.2.

Results

We identified 2005 incident glioma cases and 20 050 matched controls in the CPRD database. Of these, slightly over half (55.2%) were men. The mean age (±SD) for cases and controls was 55.5 (±18.7) years. The mean number of years of active history in the database for cases and controls was 10.6 (±4.7) years. Among those with available information on WHO glioma grade (1138 patients; 56.8% of total), 66 patients were diagnosed as grade I (5.8%), 152 patients as grade II (13.4%), 68 patients as grade III (6.0%), and 852 patients as grade IV glioma (74.9%).

Characteristics of glioma cases and controls are displayed in Table 1. In crude analyses, current versus never smoking (OR = 0.87; 95% CI = 0.76–0.99) and a history of congestive heart failure (OR = 0.58; 95% CI = 0.37–0.91) were associated with decreased glioma risk. Underweight (<18.5 kg/m^2) versus normal weight (18.5–24.9 kg/m^2) was also inversely related to glioma (OR = 0.53; 95% CI = 0.30–0.93). In contrast, history of dyslipidemia, stroke, hypertension, ischemic heart disease, myocardial infarction, renal failure, and use of statins, NSAIDs, aspirin, and estrogens (among women) were unrelated to glioma.

Among the 2005 glioma cases and 20 050 controls, we identified 96 (5%) and 1240 (6%) patients, respectively, with diabetes, which is consistent with diabetes prevalence in the UK population of a comparable age range.[28] The mean age of diabetic glioma patients was 66.4 (±10.4) years. There were only 2 cases (2.1% of all diabetic cases) and 33 controls (2.7% of all diabetic controls) who were classified as having type 1 diabetes (defined as patients with the combination of incident diabetes diagnosis below age 30 plus documented insulin use).

Having diabetes was associated with a decreased risk of glioma (adjusted OR = 0.74; 95% CI = 0.60–0.93) (Table 2). When analyzed by gender, the risk of total glioma was slightly more pronounced in men (OR = 0.70; 95% CI = 0.53–0.92) than women (OR = 0.84; 95% CI = 0.59–1.19), although the difference was not statistically significant (*P*-value for interaction by gender = .306). The risk of diabetes in relation to total glioma did not vary by age (*P*-value for interaction by age = .836).

When we restricted the analysis to the subset of 852 patients with glioblastoma (grade IV glioma), the OR was 0.69 (95% CI = 0.51–0.94) among those with diabetes compared with those without. Similar to total glioma, the association between diabetes and glioblastoma was stronger in men (OR = 0.60; 95% CI = 0.40–0.90) than women (OR = 0.85; 95% CI = 0.53–1.36). In addition, there was a suggestion of a more pronounced effect in older (OR = 0.54; 95% CI = 0.34–0.85) than younger subjects (OR = 0.87; 95% CI = 0.57–1.32; *P*-value for interaction by age = .138). The association between diabetes and grade III or IV glioma was similar to that for total glioma. No association was found between diabetes and grade II glioma, but the number of grade II glioma cases with diabetes was limited (Table 2).

Upon stratification by estrogen use, there was no effect of diabetes on the risk of glioma among women not exposed to estrogens (OR = 0.99; 95% CI = 0.67–1.46), whereas estrogen-exposed women had a strong but not statistically significant inverse effect on risk due to small numbers (OR = 0.34; 95% CI = 0.10–1.13, based on 5 female diabetic cases and 105 female diabetic controls exposed to estrogens).

To address whether the relation of diabetes to glioma was confounded by antidiabetic treatment, we evaluated the association between diabetes and glioma after adjusting for antidiabetic drugs. The relation of diabetes to glioma was slightly attenuated after adding sulfonylureas to the model (OR for diabetes = 0.86; 95% CI = 0.65–1.14), but it was unaffected by inclusion of metformin, insulin, or other antidiabetic drugs in the model (ORs for diabetes = 0.72, 0.78, and 0.70, respectively).

We next investigated the association between diabetes duration and glioma (Table 3). Long duration of diabetes had an inverse association with total glioma (OR = 0.67; 95% CI = 0.50–0.90; *P*-value for trend = .006). When analyzed according to WHO glioma grade, long-term diabetes duration was inversely associated with grade IV glioma (OR = 0.57; 95% CI = 0.37–0.87) and grade III or IV glioma (OR = 0.62; 95% CI = 0.41–0.94), but not with grade II glioma (OR = 1.53; 95% CI = 0.58–4.05; *P*-value for interaction by WHO grade = .019). Additional stratification of grade IV glioma analyses by gender yielded ORs for long-term diabetes duration of 0.46 (95% CI = 0.26–0.82) for men and 0.81 (95% CI = 0.41–1.58) for women (*P*-value for interaction by gender = .198).

We also examined the association between glycemic control and risk of glioma (Table 3). As compared with HbA1c <6.5%, HbA1c ≥8.0% was associated with a strong reduction in total glioma risk (OR = 0.57; 95% CI = 0.33–0.96). Risk reduction appeared to be most pronounced for grade IV glioma (OR = 0.52; 95% CI = 0.25–1.09), though also present for grade III or IV glioma (OR = 0.62; 95% CI = 0.31–1.24), but not grade II glioma (OR = 0.96; 95% CI = 0.16–5.74; *P*-value for interaction by WHO grade = .058). Similarly, when the analysis was restricted to diabetic patients, high versus low HbA1c level was inversely associated with glioma (OR = 0.34; 95% CI = 0.10–1.22), particularly grade IV glioma (OR = 0.12; 95% CI = 0.01–1.22), but those effect estimates did not reach statistical significance.

When stratified by gender, the risk associated with poor glycemic control was stronger in men (OR for total glioma = 0.40; 95% CI = 0.19–0.81) and strongest among glioblastoma cases (OR = 0.20; 95% CI = 0.06–0.70). High HbA1c was not

Table 1. Characteristics of glioma cases and controls

Variable	Number of Cases (%) ($n = 2005$)	Number of Controls (%) ($n = 20\,050$)	Crude OR (95% CI)	*P*
Age, y[a]				
0–9	63 (3.14)	630 (3.14)	–	–
10–19	74 (3.69)	740 (3.69)	–	–
20–29	87 (4.34)	870 (4.34)	–	–
30–39	137 (6.83)	1370 (6.83)	–	–
40–49	215 (10.72)	2150 (10.72)	–	–
50–59	454 (22.64)	4540 (22.64)	–	–
60–69	503 (25.09)	5030 (25.09)	–	–
70–79	368 (18.35)	3680 (18.35)	–	–
80–90	104 (5.19)	1040 (5.19)		
Sex[a]				
Men	1106 (55.16)	11 060 (55.16)	–	–
Women	899 (44.84)	8990 (44.84)	–	–
BMI (kg/m^2)				
<18.5	13 (0.65)	236 (1.18)	0.53 (0.30–0.93)	***.026***
18.5–24.9	604 (30.12)	5780 (28.83)	1.00 (referent)	–
25–29.9	611 (30.47)	5833 (29.09)	1.00 (0.89–1.13)	.968
≥30.0	307 (15.31)	3133 (15.63)	0.94 (0.81–1.08)	.382
Unknown	470 (23.44)	5068 (25.28)	0.89 (0.78–1.01)	.064
Smoking status				
Never smoker	970 (48.38)	8976 (44.77)	1.00 (referent)	–
Current smoker	322 (16.06)	3440 (17.16)	0.87 (0.76–0.99)	***.033***
Past smoker	434 (21.65)	4358 (21.74)	0.92 (0.82–1.04)	.178
Unknown	279 (13.92)	3276 (16.34)	0.79 (0.69–0.91)	***.001***
Comorbidities				
Dyslipidemia	168 (8.38)	1778 (8.87)	0.94 (0.80–1.11)	.462
Stroke/TIA	74 (3.69)	731 (3.65)	1.01 (0.79–1.29)	.918
Hypertension	469 (23.39)	4663 (23.26)	1.01 (0.90–1.12)	.892
CHF	20 (1.00)	343 (1.71)	0.58 (0.37–0.91)	***.018***
IHD	168 (8.38)	1725 (8.60)	0.97 (0.82–1.15)	.735
MI	55 (2.74)	695 (3.47)	0.79 (0.60–1.04)	.090
Renal failure	53 (2.64)	440 (2.19)	1.21 (0.91–1.62)	.195
Statins				
No prior use	1715 (85.54)	17 133 (85.45)	1.00 (referent)	–
1–9 Rx	79 (3.94)	797 (3.98)	0.99 (0.78–1.25)	.935
≥10 Rx	211 (10.52)	2120 (10.57)	0.99 (0.86–1.16)	.941
NSAIDs				
No prior use	658 (32.82)	6500 (32.42)	1.00 (referent)	–
1–9 Rx	1255 (62.59)	12 688 (63.28)	0.98 (0.89–1.08)	.646
≥10 Rx	92 (4.59)	862 (4.30)	1.05 (0.84–1.33)	.651
Aspirin				
No prior use	1950 (97.26)	19 440 (96.96)	1.00 (referent)	–
1–14 Rx	35 (1.75)	446 (2.22)	0.78 (0.55–1.11)	.166
≥15 Rx	20 (1.00)	164 (0.82)	1.22 (0.76–1.94)	.412
Estrogens[b]				
No prior use	677 (75.31)	6781 (75.43)	1.00 (referent)	–
1–14 Rx	146 (16.24)	1477 (16.43)	0.99 (0.82–1.19)	.918
≥15 Rx	76 (8.45)	732 (8.14)	1.04 (0.81–1.34)	.754

Abbreviations: TIA, transient ischemic attack; CHF, congestive heart failure; IHD, ischemic heart disease; MI, myocardial infarction; Rx, total number of prescriptions prior to index date.
[a]Matching variables: age, sex, general practice, and number of years of active history in the database.
[b]Women only.

Table 2. Risk of glioma in relation to diabetes status, overall and stratified by gender, age, and glioma grade

Variable	Number of Cases (%)	Number of Controls (%)	Adjusted OR[a] (95% CI)
Total glioma	$n = 2005$	$n = 20\,050$	
Diabetes	96 (4.79)	1240 (6.18)	0.74 (0.60–0.93)
Stratification by gender			
Men	59 (61.46)	819 (66.05)	0.70 (0.53–0.92)
Women	37 (38.54)	421 (33.95)	0.84 (0.59–1.19)
Stratification by age			
<67 y	46 (47.91)	583 (47.02)	0.75 (0.54–1.02)
≥67 y	50 (52.08)	657 (52.98)	0.75 (0.55–1.01)
Glioblastoma	$n = 852$	$n = 8520$	
Diabetes	48 (5.63)	667 (7.83)	0.69 (0.51–0.94)
Stratification by gender			
Men	27 (56.25)	428 (64.17)	0.60 (0.40–0.90)
Women	21 (43.75)	239 (35.83)	0.85 (0.53–1.36)
Stratification by age			
<67 y	27 (56.25)	306 (45.88)	0.87 (0.57–1.32)
≥67 y	21 (43.75)	361 (54.12)	0.54 (0.34–0.85)
Grade III or IV glioma	$n = 920$	$n = 9200$	
Diabetes	53 (5.76)	693 (7.53)	0.74 (0.55–0.99)
Stratification by gender			
Men	30 (56.60)	448 (64.64)	0.64 (0.44–0.95)
Women	23 (43.40)	245 (35.35)	0.91 (0.58–1.44)
Stratification by age			
<67 y	30 (56.60)	324 (46.75)	0.92 (0.62–1.37)
≥67 y	23 (43.40)	369 (53.25)	0.58 (0.37–0.91)
Grade II glioma	$n = 152$	$n = 1520$	
Diabetes	7 (4.61)	64 (4.21)	1.12 (0.49–2.56)
Stratification by gender			
Men	6 (85.70)	39 (60.94)	1.57 (0.61–4.02)
Women	1 (14.29)	25 (30.06)	0.42 (0.06–3.21)
Stratification by age			
<67 y	5 (71.43)	46 (71.88)	1.14 (0.44–2.98)
≥67 y	2 (28.57)	18 (28.13)	1.04 (0.21–5.20)

The %-values in the stratification groups refer to the diabetic subcohort.
Information on glioma grade was missing for 867 glioma patients. The median age of diabetic glioma patients was 67 years.
[a]Matched on age, sex, general practice, number of years of active history in the database, and adjusted for BMI and smoking.

associated with risk of glioma in women (total glioma OR = 0.95; 95% CI = 0.42–2.13; glioblastoma OR = 1.36; 95% CI = 0.48–3.84, *P*-value for interaction by gender = .160).

We also examined the associations between use of antidiabetic medications and glioma (Table 4). As compared with no prior use of metformin, increasing dosages of metformin yielded no clear association with glioma, although there was a suggestion of an association in the highest dose category. The ORs for 1–9, 10–29, and ≥30 prescriptions were 1.11, 1.42, and 0.72, respectively (95% CI = 0.38–1.39) (*P*-value for trend = .283). Inverse but statistically nonsignificant associations were observed with sulfonylurea use (corresponding ORs = 0.71, 0.58, and 0.71; 95% CI = 0.39–1.30; *P*-value for trend = .291) and insulin use (ORs = 0.96, 0.63, and 0.79; 95% CI = 0.37–1.69; *P*-value for trend = .498).

To control for the effects of diabetes duration and glycemic control, we restricted an analysis to diabetic glioma cases and diabetic controls and matched on diabetes duration and HbA1c level. Results for long-term use of metformin (OR = 0.58; 95% CI = 0.24–1.44) and insulin (OR = 0.68; 95% CI = 0.11–4.27) remained consistent with those from our main analysis. However, the previous inverse relation of long-term sulfonylurea use to total glioma was rendered positive in this matched analysis (OR = 1.76; 95% CI = 0.76–4.09).

Discussion

In this large, population-based case-control analysis, we observed a statistically significant inverse relation between history of diabetes and subsequent risk of glioma, particularly glioblastoma. The inverse association was most evident for long-standing or poorly controlled diabetes. We found no statistically significant associations of treatment with metformin, sulfonylureas, or insulin to glioma risk. This indicates that the observed

Table 3. Risk of glioma in relation to duration of diabetes and HbA1c level

Variable	Number of Cases (%)	Number of Controls (%)	Adjusted OR[a] (95% CI)
Total glioma	$n = 2005$	$n = 20\,050$	
Duration of diabetes, y			
Nondiabetic	1909 (95.21)	18 810 (93.82)	1.00 (referent)
<2	21 (1.05)	237 (1.18)	0.85 (0.54–1.34)
2–5	25 (1.25)	290 (1.45)	0.83 (0.55–1.26)
>5	50 (2.49)	713 (3.56)	0.67 (0.50–0.90)
P-value for trend			***.006***
HbA1c level			
Unknown	1893 (94.41)	18 749 (93.51)	0.97 (0.71–1.32)
<6.5%	48 (2.39)	451 (2.25)	1.00 (referent)
6.5%–7.9%	42 (2.09)	488 (2.43)	0.81 (0.52–1.25)
≥8.0%	22 (1.10)	362 (1.81)	0.57 (0.33–0.96)
P-value for trend			.070
Total glioma, diabetic patients only	$n = 96$	$n = 1240$	
Duration of diabetes, y			
<2	21 (21.88)	237 (19.11)	1.00 (referent)
2–5	25 (26.04)	290 (23.39)	0.65 (0.22–1.91)
>5	50 (52.08)	713 (57.50)	0.62 (0.23–1.66)
P-value for trend			.446
HbA1c level			
Unknown	11 (11.46)	177 (14.27)	1.17 (0.11–12.42)
<6.5%	22 (22.92)	243 (19.60)	1.00 (referent)
6.5%–7.9%	41 (42.71)	463 (37.34)	0.71 (0.27–1.87)
≥8.0%	22 (22.92)	357 (28.79)	0.34 (0.10–1.22)
P-value for trend			.091

[a]Matched on age, sex, general practice, and number of years of active history in the database, and adjusted for BMI and smoking. The *P*-value for trend did not include subjects with unknown HbA1c level.

decreased glioma risk among diabetics is not likely due to medications taken to treat diabetes, but rather to diabetes itself.

The first paper that found a lower frequency of intracranial neoplasms in diabetic patients was published in 1965.[29] Since then, 3 prospective studies[6–8] and 6 case-control studies[9–14] found statistically significant[6–11] or nonsignificant[12–14] inverse associations between diabetes and risk of glioma[6,9–14] or brain cancer.[7,8] In contrast, one prospective study[15] reported a statistically nonsignificant positive relation of diabetes to glioma, and another prospective study[20] noted a statistically significant positive association with brain cancer in women, whereas the relation was null in men. Three additional prospective studies[16–18] and one case-control study[19] observed no association between diabetes and brain cancer.

Our observation of a stronger apparent protective effect against glioma with increasing diabetes duration is consistent with one cohort[8] and one case-control study[9] that found significantly decreased glioma risk with longer time since diabetes diagnosis. In contrast, one case-control study observed no association with diabetes duration.[10] That study, however, was based on hospital discharge diagnoses of diabetes and may have encompassed fewer patients with early stages of diabetes. Insufficient variation at the low end of the diabetes severity spectrum may have limited the ability of that study to detect a relation with diabetes duration.

Our study is the first to suggest that poor glycemic control, as assessed by elevated HbA1c level, is associated with decreased glioma risk. One prospective study[30] found an inverse relation of blood glucose levels to brain cancer in men and a statistically nonsignificant positive association in women. Another prospective study[31] found a suggestive positive association between blood glucose levels and brain cancer in Korean men. However, both these investigations[30,31] lacked specification on the type of brain cancer. Also, blood glucose levels are a poor proxy for glycemic control because they only capture glucose levels at the time measured and are sensitive to various other factors, such as food intake and physical activity.[32]

The current study is the first to comprehensively explore individual antidiabetic agents in relation to glioma. Our results do not strongly support the proposition that the inverse relation of diabetes to glioma is explained by antidiabetic treatment.

We found, however, that the highest category of metformin duration was associated with statistically nonsignificantly reduced glioma risk (OR = 0.72; 95% CI = 0.38–1.39). The association became stronger after matching on duration of diabetes and HbA1c (OR = 0.58; 95% CI = 0.24–1.44), indicating that biases related to disease duration and glycemic control do not account for the observed relations. This is consistent with a number of laboratory investigations showing antitumorigenic effects of metformin on tumor cells and established tumors in animal models.[22,23] However, our data are not directly

Table 4. Risk of glioma in relation to number of prescriptions for antidiabetic drugs

Antidiabetic Drug and No. of Prescriptions	Glioma Cases and Controls			Diabetic Glioma Cases and Controls, Matched on Duration of Diabetes			Diabetic Glioma Cases and Controls, Matched on Duration of Diabetes and HbA1c Level		
	Cases (%) ($n = 2005$)	Controls (%) ($n = 20\,050$)	Adjusted OR[a,b] (95% CI)	Cases (%) ($n = 93$)	Controls (%) ($n = 842$)	Adjusted OR[a] (95% CI)	Cases (%) ($n = 86$)	Controls (%) ($n = 598$)	Adjusted OR[a] (95% CI)
Metformin									
0	1948 (97.16)	19 334 (96.43)	1.00 (referent)	38 (40.86)	354 (42.04)	1.00 (referent)	35 (40.70)	295 (49.33)	1.00 (referent)
1–9	14 (0.70)	170 (0.85)	1.11 (0.59–2.12)	12 (12.90)	120 (14.25)	0.97 (0.47–2.02)	11 (12.79)	78 (13.04)	1.07 (0.47–2.40)
10–29	23 (1.15)	216 (1.08)	1.42 (0.81–2.47)	23 (24.73)	146 (17.34)	1.40 (0.74–2.67)	21 (24.42)	123 (20.57)	1.06 (0.53–2.11)
≥30	20 (1.00)	330 (1.65)	0.72 (0.38–1.39)	20 (21.51)	222 (26.37)	0.63 (0.29–1.34)	19 (22.09)	102 (17.06)	0.58 (0.24–1.44)
P-value for trend			.283			.237			.229
Sulfonylureas									
0	1966 (98.05)	19 447 (96.99)	1.00 (referent)	54 (58.06)	491 (58.31)	1.00 (referent)	50 (58.14)	407 (68.06)	1.00 (referent)
1–9	9 (0.45)	131 (0.65)	0.71 (0.34–1.49)	9 (9.68)	85 (10.10)	1.07 (0.47–2.43)	9 (10.47)	53 (8.86)	1.32 (0.54–3.26)
10–29	10 (0.50)	182 (0.91)	0.58 (0.29–1.18)	10 (10.75)	122 (14.49)	0.75 (0.34–1.66)	8 (9.30)	70 (11.71)	0.87 (0.36–2.09)
≥30	20 (1.00)	290 (1.45)	0.71 (0.39–1.30)	20 (21.51)	144 (17.10)	1.35 (0.65–2.80)	19 (22.09)	68 (11.37)	1.76 (0.76–4.09)
P-value for trend			.291			.453			.271
Insulin									
0	1991 (99.30)	19 819 (98.85)	1.00 (referent)	81 (87.10)	714 (84.80)	1.00 (referent)	78 (90.70)	553 (92.47)	1.00 (referent)
1–9	3 (0.15)	41 (0.20)	0.96 (0.28–3.27)	3 (3.23)	27 (3.21)	0.76 (0.21–2.76)	3 (3.49)	14 (2.34)	0.77 (0.17–3.47)
10–29	3 (0.15)	58 (0.29)	0.63 (0.19–2.10)	3 (3.23)	43 (5.11)	0.63 (0.18–2.25)	2 (2.33)	14 (2.34)	0.90 (0.17–4.79)
≥30	8 (0.40)	132 (0.66)	0.79 (0.37–1.69)	6 (6.45)	58 (6.89)	0.62 (0.20–1.95)	3 (3.49)	17 (2.84)	0.68 (0.11–4.27)
P-value for trend			.498			.391			.659

[a]Matched on age, sex, general practice, and number of years of active history in the database, and adjusted for BMI, smoking, and all antidiabetics used by the study population.
[b]Additionally adjusted for diabetes status.

comparable to laboratory studies, which examined the effect of metformin on tumor progression and not tumor incidence and used metformin dosages that often greatly exceeded the levels achievable in humans.

Possible underlying biologic mechanisms of a protective effect of diabetes on glioma development are poorly understood. Advanced stages of diabetes mellitus are associated with lower levels of circulating insulin and insulin-like growth factor 1 (IGF-1) and higher levels of IGF binding protein 3 (IGFBP-3).[33] IGFs possess anabolic functions in astrocytes and neurons and show enhanced expression in glioma.[34] Moreover, IGF-1 has mitogenic potential in glioma cells, and antisense strategies against IGF-1 have been tested for clinical use as antitumor treatment.[34] Therefore, decreased signaling via insulin and IGFs represent a potential pathway to explain the observed apparent protective effect of diabetes on glioma. However, a previous study relating IGF-1 and IGFBP-3 to glioma risk failed to support this hypothesis.[35] We therefore discuss potential additional mechanisms in greater detail.

In our study, the inverse association between diabetes and glioblastoma was more apparent in men than women, and it was more pronounced in older than younger individuals. Age and gender-specific hormonal changes in diabetic individuals could serve as a possible explanation. For example, gliomas are more frequent in men than women, and an underlying effect of testosterone was argued as early as the 1950s.[36] Since then, the testosterone hypothesis has been largely neglected and the gender difference in glioma incidence was mainly attributed to protective female reproductive factors.[37]

We hypothesize that testosterone plays a role in mediating the inverse association between diabetes and glioma in men. Early laboratory studies reported that castrated male rats showed significantly lower incidence and delayed onset of brain tumors than uncastrated male rats.[38,39] More recently, in vitro studies have found that testosterone increases tumor cell proliferation in glioma cells[40] and modulates the phosphatidylinositol-3 kinase/Akt and mitogen-activated protein kinase signaling cascade, forming major oncogenic pathways in glioma.[41] Androgens, as steroid hormones, easily pass the blood–brain barrier, and glioma cells frequently express androgen receptors.[41]

Human studies show that metabolic syndrome and type 2 diabetes are strongly linked to lower androgen levels in men, with an increased prevalence of hypogonadism of up to 50% in men with type 2 diabetes mellitus.[42] Age-related hypogonadism in men, also referred to as andropause, is an established clinical syndrome, with serum testosterone levels <11 nmol/L and clinical symptoms including decreased libido, erectile dysfunction, depression, and fatigue, conditions that are also common among diabetic patients.[43] Diabetes and associated lower androgen levels are also related to reduced prostate cancer incidence, a malignancy on which the effects of androgens are well established.[44]

In contrast to their male counterparts, postmenopausal women with type 2 diabetes have increased levels of both bioavailable estradiol and testosterone.[45] In women, hormonal contraception, which often includes anti-androgenic substances, reduces risk of glioma.[37] In our study, diabetic women with estrogen use had a markedly stronger reduction in glioma risk than diabetic women without estrogen use. Conceivably, certain hormonal changes associated with diabetes in women could lower glioma risk (eg, increased circulating levels of estrogen), whereas others could enhance risk (eg, increased levels of testosterone). The null association we observed between diabetes and glioma in women may be explained by the possibility that the protective effects of increased estrogen were partially offset by the adverse effects of increased testosterone.

Our observation that glioma risk was more pronounced in grade IV than grade I or II gliomas may partly be accounted for by the different ages of onset of these malignancies. High-grade gliomas occur later in life than low-grade gliomas, which increases the amount of time needed for long-term diabetes to confer its protective effects. In addition, physiological hormonal changes in older men, such as waning testosterone levels, may be amplified by diabetes-induced decreases in testosterone.

Our observation that glioma risk decreased with increasing diabetes duration may be explained by the fact that in men, early stages of type 2 diabetes are accompanied by hyperinsulinemia, which is associated with reduced IGFBP-3 and sex hormone binding globulin (SHBG), and consequently enhanced IGF-1 and testosterone. However, as diabetes progresses to hypoinsulinemic stages, IGFBP-3 and SHBG levels increase, and IGF-1 and bioavailable testosterone levels decrease.[33] Also, poor glycemic control is associated with a decline in ß-cell function.[46]

Previous investigators have attempted to explain the inverse relation of diabetes to glioma with a mechanism related to allergy and autoimmune diseases,[8,9,11,14] with inflammation also contributing to the pathogenesis of type 2 diabetes.[47] A further explanation for the observed decreased glioma risk associated with diabetes is the presence of diabetes-related single nucleotide polymorphisms (SNPs) inversely related to glioma. While genetic susceptibility to diabetes may play a certain role in glioma risk, the currently sparse data available point toward null associations between known diabetes SNPs and glioma.[11]

Certain potential shortcomings of our study should be mentioned. The inverse association between diabetes and glioma may be confounded by factors associated with both glioma and diabetes, such as a sedentary lifestyle, obesity, smoking, and lower socioeconomic status. However, cases and controls were matched on general practice, which at least partially controls for socioeconomic status, and we adjusted for BMI and smoking. We were unable to control for physical activity or other lifestyle factors, but prior studies suggested no meaningful associations between adulthood lifestyle factors and glioma risk.[48] Our findings may not apply to non-Caucasian populations because 86% of individuals in our database were Caucasian.[49]

Our study has numerous strengths. We used a large, longitudinal, well-established, and validated database.[25–27] Our study is not likely prone to selection bias because both glioma cases and randomly selected controls were generated from the CPRD. Also, our study is free from recall bias because the data regarding medical conditions and medications were collected prospectively. In addition, potential diagnostic bias caused by an earlier diagnosis of diabetes among those with early symptoms of undiagnosed glioma was minimized by shifting the index date back by one year. Further, we conducted a large number of informative sensitivity analyses. Finally, only

patients with an active history of at least 3 years in the CPRD database were included in the current study, which likely improved the quality and quantity of patient information due to more frequent practice visits among those subjects.

In summary, we observed an inverse relation between diabetes and risk of glioma, an association that was most pronounced among those with long-term and poorly controlled diabetes. In addition, the apparent protective effect of diabetes on glioma development appeared to be stronger in men than women, and in older than younger individuals. Antidiabetic medications were unrelated to glioma, but a potential protective effect of heavy metformin use on glioma risk cannot be entirely excluded. Our findings raise the possibility that lower androgen levels, concurrent with type 2 diabetes, have a protective effect on risk of glioma.

Supplementary Material

Supplementary material is available at Neuro-Oncology Journal online (http://neuro-oncology.oxfordjournals.org/).

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