Antidiabetic medication and risk of dementia in patients with type 2 diabetes: a nested case-control study

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Abstract

Objective: Diabetes is a risk factor for dementia, but whether antidiabetic medication decreases the risk is unclear. We examined the association between antidiabetic medication and dementia.

Design: We performed a nested case-control study within a cohort of all 176 250 patients registered with type 2 diabetes in the Danish National Diabetes Register between 1995 and 2012. This population was followed for dementia diagnosis or anti-dementia medication use until May 2018. Using risk-set sampling, each dementia case ($n = 11\,619$) was matched on follow-up time and calendar year of dementia with four controls randomly selected among cohort members without dementia ($n = 46\,476$). Ever use and mean daily defined dose of antidiabetic medication was categorized in types (insulin, metformin, sulfonylurea and glinides combined, glitazone, dipeptidyl peptidase 4 (DPP4) inhibitors, glucagon-like peptide 1 (GLP1) analogs, sodium-glucose transport protein 2 (SGLT2) inhibitors and acarbose).

Methods: Conditional logistic regression models were fitted to calculate odds ratios (ORs) for dementia associated with antidiabetic medication use, adjusting for potential confounders.

Results: Use of metformin, DPP4 inhibitors, GLP1 analogs, and SGLT2 inhibitors were associated with lower odds of dementia after multiple adjustments (ORs of 0.94 (95% confidence interval (CI): 0.89–0.99), 0.80 (95% CI 0.74–0.88), 0.58 (95% CI: 0.50–0.67), and 0.58 (95% CI: 0.42–0.81), respectively), with a gradual decrease in odds of dementia for each increase in daily defined dose. Analyses of the most frequent treatment regimes did not show any synergistic effects of combined treatment.

Conclusion: Use of metformin, DPP4 inhibitors, GLP1 analogs and SGLT2 inhibitors was associated with lower risk of dementia in patients with diabetes.

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Introduction

Dementia is a disease characterized by progressive irreversible cognitive damage. In 2015, 47 million people were living with dementia, and numbers are predicted to triple by 2050 (1). Diabetes mellitus is a well-established risk factor for dementia, and particularly patients with type 2 diabetes seem to have increased risk of dementia

(2). This risk may be caused by a shared pathophysiology of diabetes and dementia involving hyperglycemia and hyperinsulinemia (3), which raises the question of whether use of antidiabetic medications can reduce risk of dementia in patients with diabetes. Only few studies have examined this with equivocal results and, although

combination of treatment is common, none have studied combination therapy or included the newest antidiabetic medications such as dipeptidyl peptidase 4 (DPP4) inhibitors, glucagon-like peptide 1 (GLP1) analogs, and sodium-glucose transport protein 2 (SGLT2) inhibitors. Of those, especially GLP1 analogs are of interest as they have been shown to improve cognition in rodents (4, 5, 6) and to improve cerebral metabolism in Alzheimer's disease (7).

As one in eleven (425 millions) adults worldwide suffer from diabetes (8), it is important to know whether the higher risk of developing dementia in patients with diabetes could be reversed by antidiabetic medication. Moreover, it is important to establish if any effect is related to specific types of antidiabetic medication or combinations of treatment.

Against this background, we investigated whether different types of antidiabetic medication and treatment regimens (combinations of antidiabetic drugs) were associated with risk of developing dementia in Danish patients with type 2 diabetes.

Patients and methods

Study population and follow-up

The study was based on patients in Denmark registered with type 2 diabetes in the National Diabetes Register (NDR) between January 1, 1995 and December 31, 2012 ($n=178\,403$). Inclusion in this register is based on a validated algorithm combining information on diabetes ascertained by physician's diagnosis (International Classification of Disease 10 (ICD10) codes DE10–14, DH36.0, DO24) in the Danish National Patients Registry (NPR) after 1990, prescriptions of antidiabetic medication in the Danish Prescription Register, and measures of

blood glucose or referrals to feet therapists from the National Health Insurance Service Register (9). The data from the NDR were compared with historical data from the NPR and Danish Adult Diabetes Registry to improve validity (10). Patients with diabetes due to gestational diabetes (DO24.4-9; $n=1806$), starvation (DE12; $n=347$), patients with a diagnosis of type 2 diabetes under the age of 35 ($n=3695$), or a diagnosis of dementia or use of anti-dementia medication before registration in the NDR ($n=2138$) were excluded (Fig. 1). Dementia diagnoses and dementia medication were tracked back to the establishment of the NPR and Danish National Prescription Registry (DPR) in 1977 and 1995, respectively. That left a study population of 170 417 patients followed until first dementia diagnosis or prescription of dementia medication, emigration or death in the NPR and the Danish Civil Registration System or until May 2018. During a median follow-up of 7.2 years (range: 0.0–22.8 years, IQR: 3.5–11.5 years), we identified 11 619 cases of incident dementia (only diagnosis: $n=7473$; diagnosis and medication: $n=3259$; only medication: $n=887$). A case-control study was nested within the cohort of patients with type 2 diabetes using risk-set sampling generated by the procedure *stto*cc in Stata. Thus, we randomly selected controls among members in the cohort who remained dementia free and matched them on follow-up time and calendar year to case patients in a 1:4 ratio ($n=46\,476$). The matching on calendar year was to ensure that both cases and controls were followed in the same calendar time ensuring equal access to for example the newer antidiabetic drugs. The rationale for choosing a nested case-control study instead of a prospective cohort design was that this design allowed us to calculate the amount of antidiabetic medication used in the study period while avoiding immortal time bias.

Figure 1

Flowchart of the study design.

Outcome: dementia

Dementia was defined as an International Classification of Diseases 10th revision (ICD10) diagnosis of F00-F04 and G30, registered in the NPR which holds data on diagnosis and dates from all somatic and psychiatric hospital contacts for both in- and outpatients in Denmark (11). From the DPR, information on prescriptions of anti-dementia medication was obtained using the anatomic therapeutic codes (ATCs) N06D.

Exposure: antidiabetic medication

We obtained all prescriptions of antidiabetic medication from January 1995 to the index date for both cases and controls from the DPR using ATC codes A10. For each prescription, the DPR records date and a full description of the dispensed product, including ACT and the total number of daily defined doses (DDD). The DDD was defined by the World Health Organization as 'the assumed average maintenance dose per day for a drug used for its main indication in adults' (12) and is thus in our study used as a measurement of dosage per time. We categorized antidiabetic medication into the following types: insulin, metformin, sulfonylureas and glinides combined, glitazones, DPP4 inhibitors, GLP1 analogs, SGLT2 inhibitors and acarbose (Supplementary Table 1, see section on [supplementary data](#) given at the end of this article). Mean DDD was calculated for each type of antidiabetic medication and classified into sufficiently sized groups and consequently cut points differed across types of medication. As many patients used more than one type of antidiabetic medication, we also evaluated any added effect of combined treatment. We first generated all treatment regimens (a total of 128 different combinations of the antidiabetic medication types mentioned above) used in our diabetes population and extracted the 12 most commonly used (which included >1000 patients) while all other combinations used formed one single category termed 'other combinations' (Supplementary Table 2). However, as none of the most common combinations included SGLT2 inhibitors, we further categorized 'other combinations' into 'other combinations including SGLT2' and 'other combinations not including SGLT2'.

Covariables

Age was included as a continuous variable. Education was categorized as basic (7–9 grade of obligatory schooling), medium (high school degree/vocational), higher education (more than high school degree), or unknown

based on data from the Integrated Database for Labor Market Research. Information on marital status was obtained from the Danish Civil Registration System and categorized as married, unmarried, divorced or widowed. From the NPR and the DPR, we included information on hospitalization and medication for somatic or psychiatric diseases five years preceding study entry (i.e. diabetes diagnosis). Comorbidity and co-medication for ischemic heart disease, cerebrovascular disease, hypertension, obesity, hypercholesterolemia, infections, chronic obstructive pulmonary disease, inflammatory disorder, depression and alcohol use disorder was included. Finally, we included information on acute and chronic diabetes complications and the number of hospitalizations with complications after diabetes diagnosis. Acute complications included occasions with ketoacidosis or hypoglycemia, while chronic complications included diabetic nephropathy, eye complications, neurological complications, or diabetic angiopathy (Supplementary Table 1). The International Classification of Diseases 10th revision (ICD10) codes and the ATCs are shown in Supplementary Table 1. Finally, in a subgroup of patients from the Danish Adult Diabetes Registry (DADR), we included information on self-reported smoke status (never, previous or current smoking), BMI, hemoglobin A1c (mmol/mol), low-density lipoprotein cholesterol (mmol/L), and systolic blood pressure. The DADR is a database initiated in 1999, which includes clinical information on diabetes patients, and since 2004 it has been mandatory to report data to the register from outpatients clinics and hospitals (13).

Data approval

The study was approved by the Danish Data Inspection. All data were retrieved from administrative registers, and informed consent was not required of participants. Data in this study are anonymized data located at Statistics Denmark and at the Danish Clinical Registries.

Statistical analysis

Stata version 15 (StataCorp, College Station, TX, USA) was used for statistical analyses. Conditional logistic regression was used to calculate ORs using four levels of adjustment: (1) unadjusted, (2) adjusted for age groups, sex, education, (3) adding marital status, comorbidity, co-medication and number of acute and chronic diabetes complications, and finally (4) adding mutually adjustment for other types of antidiabetic medications.

We repeated all analyses with adjustment for diabetes complication type (e.g. hypoglycemia, ketoacidosis, retinopathy, nephropathy etc.) instead of number of complications, but results were similar (data not shown).

In a supplementary analysis, we identified cases and controls with data in the DADR ($n=24\,182$). Patients with a registered date for examination and blood tests in the DADR after the dementia date or corresponding date for controls ($n=11\,236$) were excluded. After these exclusions any patient lacking a corresponding control was also excluded and vice versa. Left with 5449 patients in this subgroup, we repeated analyses with further inclusion of the clinical variables from the DADR.

Results

Our study population consisted of 11 619 dementia cases and 46 476 controls. Cases were more often women, had higher mean age, were less educated and showed higher prevalence of most comorbidities and used all antidiabetic medication types less often except sulfonylureas and acarbose (Table 1). Overall, 9122 (79%) of cases and 38 572 (83%) of controls had used antidiabetic medication (unadjusted OR: 0.75 (95% confidence interval (CI): 0.71–0.78), multiple adjusted OR: 0.93 (95% CI: 0.87–0.99)). Characteristics of users of antidiabetic drugs versus non-users are shown in Supplementary Tables 3, 4, 5, 6, 7, 8, 9, 10 and 11.

Use of any type of antidiabetic medication except for sulfonylureas and acarbose were associated with lower odds of dementia in the unadjusted models (Fig. 2). After multiple adjustments, including use of other antidiabetic medications, use of insulin, metformin, DPP4 inhibitors, GLP1 analogs, and SGLT2 inhibitors remained associated with lower odds of dementia with the strongest estimates for GLP1 analogs and SGLT2 inhibitors (ORs of 0.58 (95% CI: 0.50–0.67) and 0.58 (95% CI: 0.42–0.81) respectively). Sulfonylureas were associated with slightly higher odds of dementia (OR: 1.07 (95% CI: 1.02–1.13)).

Further, increasing DDD of different types of antidiabetic medications, metformin, DPP4 inhibitors, and GLP1 analogs showed a gradual decrease in odds of dementia (Fig. 3). Insulin and sulfonylureas were not associated with dementia in a dose-dependent manner.

In the analyses of the most frequent treatment regimes, combinations with DPP4 inhibitors, GLP1 analogs, and SGLT2 inhibitors were associated with lower odds of dementia after adjustments with the lowest odds of the combinations including SGLT2 inhibitors

Table 1 Main demographic and clinical characteristics of the included patients with type 2 diabetes from the National Diabetes Register.

	Dementia cases	Controls
Number	11 619	46 476
Age (years), mean (IQR)	70.8 (51–67)	59.0 (64–78)
Men, n (%)	5566 (48)	25 900 (56)
Education, n (%)		
Short education	5522 (48)	20 112 (43)
Medium education	3187 (27)	17 566 (38)
Long education	918 (8)	5105 (11)
Unknown	1992 (17)	3693 (8)
Marital status, n (%)		
Married	6027 (52)	28 720 (62)
Unmarried	820 (7)	5696 (12)
Divorced	1538 (13)	6682 (14)
Widow/widower	3176 (27)	5106 (11)
Unknown	58 (0.5)	272 (1)
Ischemic heart disease, n (%)	1502 (13)	4589 (10)
Cerebrovascular disease, n (%)	1011 (9)	1881 (4)
Clopidogrel, warfarin, aspirin use, n (%)	4232 (36)	10 655 (23)
Hypertension, n (%)	7229 (62)	24 325 (52)
Obesity, n (%)	1054 (9)	7231 (16)
Hypercholesterolemia, n (%)	2190 (19)	9044 (19)
Infections, n (%)	2363 (20)	7322 (16)
Chronic obstructive pulmonary disease, n (%)	1718 (15)	6060 (13)
Inflammatory disorder, n (%)	543 (5)	1880 (4)
Depression, n (%)	2458 (21)	6980 (15)
Alcohol dependence, n (%)	536 (5)	1655 (4)
Chronic diabetes complications, n (%)		
0 complications	6579 (57)	26 793 (58)
1 complication	2880 (25)	11 195 (24)
2 complications	1236 (11)	4894 (11)
3 complications	562 (5)	2082 (4)
≥ 4 complications	362 (3)	1512 (3)
Acute diabetes complications, n (%)		
0 complications	11 243 (97)	45 268 (97)
≥ 1 complications	376 (3)	1208 (3)
Antidiabetic medication use, no. of ever-users (%)	9122 (79)	35 078 (82)
Any type		
Insulin	2425 (21)	12 267 (26)
Metformin	6279 (54)	30 894 (66)
Sulfonylureas	6704 (58)	26 276 (57)
Glitazones	271 (2)	2015 (4)
DPP4 inhibitors	902 (8)	6121 (13)
GLP1 analogs	246 (2)	3922 (8)
SGLT2 inhibitors	44 (0.4)	868 (2)
Acarbose	197 (2)	833 (2)

Based on 11 619 cases and 46 476 controls.

DDD, daily defined dose; DPP4, dipeptidyl peptidase 4; GLP1, glucagon-like peptide 1; SGLT2, sodium-glucose transport protein 2.

(OR of 0.39 (95% CI: 0.29–0.55)) (Fig. 4). However, the observed odds due to more than one type of treatment were nearly identical to the expected odds from the multiplicative models for the respective types of medications provided in Fig. 2.

In the supplementary analysis of the subgroup of patients included in the DADR, a total of 1446 cases and 4003 controls had clinical data available. Demographic and clinical characteristics of this subgroup are shown in Supplementary Table 12. After multiple adjustments including other antidiabetic medications, only GLP1 analogs and SGLT2 inhibitors were associated with significantly lower ORs of 0.59 (95% CI: 0.45–0.77) and 0.43 (95% CI: 0.22–0.83) (Supplementary Fig. 1). Further adjustment for clinical variables including HbA1c did not change the ORs. In analyses of DDD, both groups of GLP1 analogs stayed significant after adjustment for clinical variables (Supplementary Fig. 2).

Discussion

In this nationwide nested case-control study, we demonstrated that patients with diabetes who used

metformin, DPP4 inhibitors, GLP1 analogs, or SGLT2 inhibitors had lower odds of developing dementia even after adjustment for potential confounders and for use of other types of antidiabetic medication. The association seemed dependent on dose and duration of treatment. In the combined analysis, combinations with GLP1 analogs, DPP4 inhibitors, and SGLT2 inhibitors were associated with the lowest odds of dementia. The odds were nearly identical to the expected odds from a multiplicative model for the respective types of medications suggesting that the effect of combined use depends only on the individual drugs in the combination with no synergistic effect. Insulin seemed associated with lower risk of diabetes in the analysis of ever use of insulin (Fig. 2); however, this could not be replicated in the later analyses.

The results of our study, suggesting that use of specific types of antidiabetic medication are associated with lower risk of dementia, are supported by other studies, but direct comparison is difficult since previous studies included older antidiabetic medications only. Two studies based on National Health Insurance Research Database from Taiwan showed that in patients with diabetes, use of sulfonylureas and metformin were associated with a decreased risk of dementia compared to patients not using antidiabetic

Figure 2

Use of antidiabetic medication in type 2 diabetic patients with (cases) or without (controls) dementia during follow-up in the National Diabetes Register, based on 11,619 cases and 46,476 controls. Multiple adjustments include age, sex, education, marital status, year of dementia diagnosis, ischemic heart disease, cerebrovascular disease, clopidogrel/warfarin/aspirin use, hypertension, obesity, hypercholesterolemia, infections, chronic obstructive pulmonary disease, inflammatory disorder, depression, alcohol use disorder, and number of acute and chronic diabetes complications.

Figure 3

Previous use of antidiabetic medication in type 2 diabetic patients with (cases) or without (controls) dementia during follow-up in the National Diabetes Register based on 11,619 cases and 46,476 controls. Multifactorial is adjusted for age, sex, education, marital status, year of dementia diagnosis, ischemic heart disease, cerebrovascular disease, clopidogrel/warfarin/aspirin use, hypertension, obesity, hypercholesterolemia, infections, chronic obstructive pulmonary disease, inflammatory disorder, depression, alcohol use disorder, and number of acute and chronic diabetes complications.

medications (14), while metformin users seemed to have lower rates of dementia compared to sulfonylurea and glitazone users (15). Similarly, Orkaby *et al.* recently found that metformin decreased the risk of dementia when compared to sulfonylureas in US veterans younger than 75 years (16). This is in line with our finding that metformin use was associated with lower odds of dementia. Metformin may reduce dementia risk by reducing oxidative stress, inflammation, and apoptosis and by suppressing the damaging effects of advanced glycosylation end products which are produced during hyperglycemia and have potential toxic effects on neurons (17, 18).

By contrast, a case-control study including 7086 cases with Alzheimer's dementia (AD) recruited among patients from general practice in the United Kingdom found that long-term use of metformin was associated with increased odds of AD, while insulin, sulfonylureas, and glitazones were not as compared to non-users without diabetes (19). In our study, we did not find any consistent associations of insulin, sulfonylureas, or glitazones with dementia even though previous randomized controlled studies have suggested that especially insulin and glitazones have pro-cognitive effects (20). It may be that the antidiabetic

medications which benefit dementia patients without diabetes are not the same drugs that may prevent dementia in diabetes patients.

No population-based study so far has examined the influence of newer antidiabetic medications on dementia risk. However, many studies have described GLP1's possible protective role on cognitive symptoms (7, 21) and risk of dementia and several rodent studies have suggested that GLP-1 analogs improve cognition (5, 6). Mechanistically, GLP1 may cross the blood-brain barrier and exhibit pro-cognitive effects by improving neurogenesis, protect against apoptosis, inflammation and oxidative stress and prevent amyloid plaque formation in the brain (22) and improve cerebral glucose metabolism (7, 23).

DPP4 inhibitors inhibit the enzyme responsible for degradation of GLP1 hereby doubling the concentration of active GLP1 (24). Compared to GLP1 analogs, DPP4 inhibitors increase active GLP1 levels considerably less resulting in lower impact on both glycemic and extra-glycemic effects (e.g. body weight and blood pressure) (25). This is in accordance with the results seen in our study, where the associations for DPP4 inhibitor use were weaker than for GLP1 analog use but with the same tendency.

Figure 4

Combinations of antidiabetic medication in type 2 diabetic patients with (cases) or without (controls) dementia during follow-up in the National Diabetes Register. Based on 11,619 cases and 46,476 controls. Adjustment for age, sex, education, marital status, year of dementia diagnosis, ischemic heart disease, cerebrovascular disease, clopidogrel/warfarin/aspirin use, hypertension, obesity, hypercholesterolemia, infections, chronic obstructive pulmonary disease, inflammatory disorder, depression, alcohol use disorder, and number of acute and chronic diabetes complications. *The expected point estimates for combined use was calculated using the risk estimates in Figure 1.

SGLT2 inhibitors are a new drug class which reduces plasma glucose by increased renal excretion (26). Two rodent studies have indicated that SGLT2 inhibitors may prevent cognitive decline due to reduced oxidative stress and inflammation, improved brain mitochondrial function and plasticity in the hippocampus which is particularly affected by type 2 diabetes (27, 28). Furthermore, it has been suggested that SGLT2 inhibitors may inhibit the enzyme acetylcholinesterase, the primary target for current Alzheimer's therapy (29, 30).

The role of the glucose-lowering effect of the antidiabetic medications is unclear. We do not see a reduced risk for all medication groups but only for some and we have no evidence that patients treated with for example the newer antidiabetic drugs were more well treated. In a subanalysis, we found no impact of glycaemic control (HbA1c). Also, hypoglycemia may mediate the relationship, but severe hypoglycemia remains rare in type 2 diabetes. In our analyses, we adjusted for number of hypoglycemic episodes registered at a hospital, and this did not change the results.

Our study has several strengths. We assessed use of antidiabetic medication from a nationwide Prescription Registry, which provided detailed long-term drug use

histories and eliminated recall bias. The use of nationwide registries with nearly complete coverage and continuous updates on demographics, hospital contacts and dementia outcomes minimized selection bias and provided us with data to perform a nested case-control study including all diabetes patients diagnosed with dementia in Denmark. This design allowed us to handle the time-varying exposure without risk of immortal time bias (31). In our nested case-control study, we could calculate the exact amount of purchases of each drug for each patient which meant that we could also test whether a higher exposure was associated with dementia. Another strength of our study was that we were able to include register-based information on a number of relevant covariables including diabetes complications. The different antidiabetic medications were also mutually adjusted for limiting confounding by prescription choice. In a subgroup we could further adjust for clinical variables like HbA1c, low-density lipoprotein cholesterol, systolic blood pressure and so forth even though, unfortunately, they were not measured at the time of the diabetes diagnosis. However, we had no information on lifestyle such as physical activity, alcohol use and tobacco smoking or on social relations and, consequently, we cannot exclude that the odds could be

explained by residual confounding from other factors. The validity of the dementia diagnoses in the Danish registers has previously been evaluated in two independent studies (32, 33). These studies found that for patients admitted in 2003, 83% of the diagnosis were confirmed by an external assessor (32). The corresponding number was 70% for patients admitted in 2008. The lowest validity was seen in the youngest population (33). Our study also has several potential limitations. First, our results could be biased if users of antidiabetic medication were more likely to get a dementia diagnosis, but this would implicate that our estimates would be even stronger. Further, the association could be explained by reverse causation: patients with an early stage of cognitive decline might less often be prescribed antidiabetic medications, especially the newer drugs (SGLT2, GLP1) might less often be prescribed to patients with early cognitive decline who have not yet received a diagnosis of dementia. However, such potential channeling bias does not seem to be present for glucose-lowering drugs (34) and we found that patients with newer antidiabetic medications were relatively similar to those treated with older drugs. We also adjusted for a large number of comorbidities and clinical variables in order to eliminate any confounding by indication. Secondly, since the Prescription Registry was established in 1995 and does not include drugs received during hospitalization, antidiabetic medication use prior to 1995 or during hospital stay would be misclassified as non-use. Such assumed non-differential misclassification may have led to attenuation of risk estimates. Third, it is conceivable that, prior to diagnosis, dementia could influence adherence to medication use, for example, by affecting cognitive skills. However, any such bias would again lead to an underestimation of risks. Fourth, GLP1 analogs, DPP4 inhibitors, and SGLT2 inhibitors are all relatively new drugs and consequently follow-up time in these groups was shorter which could question causality but may indicate that these drugs postpone cognitive decline and dementia diagnosis.

In conclusion, we found that use of metformin, GLP1 analogs, DPP4 inhibitors, and SGLT2 inhibitors were associated with significantly lower odds of dementia in patients with type 2 diabetes. We propose to test the hypothesis that some especially newer antidiabetic medications may influence the risk of dementia related to diabetes in other populations and clinical trials.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-19-0259>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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Author contribution statement

I W A made the first draft of the article. M W A was responsible for analyzing the data with help from I W A and M O. I W A is responsible for the funding and data collection of the study with help from M W A, M O, and M B J. All authors took part in design, interpretation of the results, and have read and approved the final version of the article. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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