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Risk factors of dementia in type 2 diabetes mellitus: The Hong Kong diabetes study

Yau-Lam Alex Chau [1,a,i,j], Ji Won Yoo [1,a,i,j], Jiandong Zhou [b,i,j], Cosmos LiutaoGuo [c,i,j], Wing Tak Wong [d,i,j], Carlin Chang [e,i,j], Tong Liu [f,i,j], Kamalan Jeevaratnam [g,i,j], Qingpeng Zhang [b], Gary Tse [f,g,h,i,*], Sharen Lee [**,c,i,j]

[a] Faculty of Pharmaceutical Sciences, The University of British Columbia, British Columbia, Canada
[b] School of Data Science, City University of Hong Kong, Hong Kong, Hong Kong, China
[c] Laboratory of Cardiovascular Physiology, Shenzhen Research Institute, Faculty of Medicine, Chinese University of Hong Kong, Shenzhen, China
[d] School of Life Sciences, Chinese University of Hong Kong, Hong Kong, China
[e] Department of Medicine, Queen Mary Hospital, Hong Kong, China
[f] Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin 300211, China
[g] Faculty of Health and Medical Sciences, University of Surrey, GU2 7AL, Guildford, United Kingdom
[h] School of Nursing and Health Studies, Hong Kong Metropolitan University, Hong Kong, China
[i] Kent and Medway Medical School, Canterbury, Kent, CT2 7NZ, UK
[j] Diabetes Research Unit, Cardiovascular Analytics Group, PowerHealth Limited, Hong Kong, China

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ABSTRACT

This population-based cohort study investigated the risk factors of incident dementia and vascular dementia in type 2 diabetic patients (≥45 years old) attending the Hong Kong Hospital Authority between 1st January and 31st December 2009.Of the 273,876 patients included,9994 showed incident dementia (median follow-up: 4245 days). Multivariable Cox regression identified older age (HR: 1.09 [95% CI: 1.08–1.10]) and antiplatelet use (HR: 1.36 [1.14–1.62]) as risk factors for incident dementia, and older age (HR: 1.07 [1.06–1.08]), ischemic stroke (HR: 1.47 [1.09–1.98]), fasting blood glucose (HR: 1.10 [1.01–1.20]), antiplatelets (HR: 1.92 [1.51–2.44]), and calcium channel blocker (HR: 1.28 [1.04–1.57]) use as risk factors of incident vascular dementia.

Introduction

Diabetes mellitus (DM) has progressed into one of the premier threats against public health worldwide. Uncontrolled T2DM represents significant morbidity and mortality, resulting in preventable but crippling outcomes such as nephropathy and strokes [1].With an aging population and changing lifestyles, prevalence of T2DM has nearly doubled worldwide over the past three decades [2], leading to increased burden of T2DM-related complications, such as dementia. Dementia is characterized by decreased cognition, deteriorated memory, speech, and control, and the World Health Organization estimates that 55 million people have dementia worldwide [3,4]. Comorbidities such as atrial fibrillation (AF) and different medications can alter the risk of dementia development [5,6]. T2DM is a well-established risk factor for dementia partly attributed to its deleterious effects on vascular function. An understanding of predictors for dementia in T2DM can allow for highly targeted preventative measures[7]. For example, pharmacotherapy such as anti-diabetic and anticoagulant agents can reduce the risks of incident dementia or slow its progression [7]. Consequently, our objective was to evaluate the risk factors associated with incident dementia, particularly the vascular subtype in the T2DM population.

* Corresponding author at: Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin 300211, China, School of Nursing and Health Studies, Hong Kong Metropolitan University, Hong Kong, China.
** Corresponding author at: Diabetes Research Unit, Cardiovascular Analytics Group, China-UK Collaboration, Hong Kong, China.
E-mail addresses: gary.tse@kmms.ac.uk (G. Tse), sharen212@gmail.com (S. Lee).
[1] joint first authors

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Methods

Study design

This study received approval from The Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee and The Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. Patients meeting all the following criteria were recruited: 1) age 45 or above; 2) diagnoses of T2DM documented under the International Classification of Disease, Ninth Edition (ICD-9) coding system, or prescribed with anti-diabetic agents by any hospitals or outpatient clinics managed by the Hong Kong Hospital Authority between January 1st to December 31st of 2009; 3) no prior diagnosis of dementia. The data from the Clinical Data Analysis and Reporting System (CDARS), a territory-wide electronic healthcare database that compiles data from local public hospitals and their associated outpatient and ambulatory facilities to establish comprehensive patient health records, were extracted. The system has been utilized by both our and other local teams to conduct population-based studies [8,9], including those on diabetes mellitus [10,11] or new onset dementia [12,13].

The primary outcomes of this study were new onset dementia, including Alzheimer's disease, or vascular dementia as documented by ICD-9 coding. Patients were followed up until December 31st, 2019 or the date of mortality, whichever was earlier. The following data was extracted from CDARS:1) demographics; 2) diabetes duration (diabetes onset until December 31st, 2009); 3) pre-existing comorbidities; 4) antidiabetic agents and cardiovascular medications prescribed; 5) lipids (high-density lipoprotein-cholesterol (HDL), low-density lipoprotein-cholesterol (LDL), total cholesterol, triglyceride) and glycemic profile (fasting blood glucose and HbA1c); 6) baseline anemic status. Baseline measurements were defined as the latest measurement from 2008. Mean and variability of lipid and glycemic profiles between January 1st, 2004 and December 31st, 2008 were calculated. Glycemic and lipid variability were assessed by standard deviation (SD). Baseline anemia is defined as hemoglobin count below 12 g/dL (female) or 13 g/dL (male). Fulfillment of any of the following criteria, whichever earlier, defines onset of diabetes: 1) earliest documentation of T2DM associated ICD-9 codes; 2) earliest record of fasting blood glucose (FBG) $>$ 7 mmol/L; 3) earliest documentation of HbA1c $>$ 6.5%.

The following comorbidities were extracted: 1) renal, neurological, and ophthalmological diabetic complications; 2) heart failure (HF); 3) AF, coronary heart disease (CHD), and hypertension (HT); 4) peripheral vascular disease (PVD); 5) ischemic stroke and transient ischemic attack; 6) intracranial hemorrhage; 7) chronic obstructive pulmonary disease (COPD). Information on the following classes of antidiabetic agents was extracted: biguanides, sulphonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors (DPP4I), glucagon-like peptide-1 agonists (GLPA), meglitinides, alpha-glucosidase inhibitors and insulin. For cardiovascular medications, data on angiotensinogen-converting enzyme inhibitors (ACEI)/ angiotensin receptor blockers (ARB), beta blockers, calcium channel blockers (CCB), diuretics, lipid-lowering agents, antiplatelet agents, and warfarin were extracted.

Statistical analysis

Univariable Cox regression was used to identify significant impact factors associated with incident dementia and vascular dementia. The hazard ratio, (HR), 95% confidence interval (CI) and P-value were reported. Significant univariable factors were selected into a multivariable Cox regression model. Variables with HR between 0.67 and 1.5 were assigned a score of 1. Otherwise, a score of 2 was assigned. Continuous variables were dichotomized by maximizing sensitivity and specificity through the Liu method[14]. The Liu method is an accurate binary classification procedure, ideal for devising a cut-off to identify low and high-risk patients[14]. The receiver operator characteristic (ROC) curve and the area under the curve (AUC) for the dichotomized scores were then generated. Statistical significance was defined as P-value $<$ 0.05. RStudio (Version: 1.1.456) was used for data analysis and figure generation.

Results

The cohort included 273,876 patients with T2DM (median age = 57.8, interquartile range of age = 66.8–75.6 years, male = 47.3%). Baseline characteristics of the cohort are presented in Supplementary Table 1. The most common comorbidity was hypertension (23.6%), followed by CHD (9.88%), HF (4.12%), ischemic stroke/TIA (3.24%) and AF (2.88%).

Over the study period, 9994 patients showed new onset of dementia, of which 4876 were vascular subtype over a median follow-up of 4245 days (interquartile range: 3117–4245 days). After adjusting for significant variables, the risk factors for incident dementia were older age (HR: 1.09, 95% CI: [1.08, 1.10], $P<0.001$), and antiplatelet use (HR: 1.36 [1.14, 1.62], $P = 0.001$). Older age (HR: 1.07 [1.06–1.08], $P<0.001$), ischemic stroke (HR: 1.47 [1.09–1.98], $P = 0.011$), fasting blood glucose (HR: 1.10, 95%CI=[1.01–1.20], $P = 0.024$), antiplatelet (HR: 1.92 [1.51–2.44], $P<0.001$) and CCB (HR: 1.28 [1.04–1.57], $P = 0.021$) use were risk factors for vascular dementia in the multivariable analysis (Table 1). Using the risk scoring system in Supplementary Table 2, the AUC of the ROC for incident dementia was 0.688, whilst for incident vascular dementia a score of >4 determined an AUC of 0.687 (Supplementary Fig. 1, top left and top right panels). The Kaplan-Meier plots based on the dichotomized score for predicting dementia and vascular dementia were generated (Supplementary Fig. 1, bottom left and bottom right panels). Patient with scores lower than the cut-off determined using the Liu method had lower probabilities of incident dementia and vascular dementia ($p < 0.0001$).

Discussion

Our study found that antiplatelet medication use was associated with incident dementia and vascular dementia. This finding could be explained by the baseline characteristics of the patients who use them. Diabetic patients are at an increased risk for cardiovascular comorbidities, which may predispose them to dementia through the increased likelihood of cerebral ischemia, microbleeds, and cerebral hypoperfusion[15]. Consequently, why antiplatelet agents increase the risk of incident or vascular dementia could be rationalized by their baseline risks such as previous history of stroke, which prompts antiplatelet use [16].

By acting on vascular smooth muscles to increase arterial diameter, CCBs have been thought to improve cerebrovascular perfusion and reduce the risk of vascular dementia[17]. However, results have been controversial given the heterogeneity of these studies regarding agent used, dose, and endpoints. In contrast to what has been described in literature, our study found that CCB use was associated with increased risk of vascular dementia. It is unclear why this is observed, but one possible explanation would be that our patient population was wholly diabetic in contrast to some studies where diabetics represented less than 20% of the patient population[17]. In addition, CCB users are more likely to have hypertension, a risk factor for dementia [17]. Future studies would benefit from exploring the relationship between CCB use in the diabetic population and the risk for vascular dementia.

Limitations

Firstly, medication compliance was unknown because this was an administrative database study. Secondly, the inclusion of all patients taking anti-diabetic medications may have inadvertently included non-diabetics. Thirdly, there is the possibility of under-coding or missing data given that input was completed by physicians with no adjudications

Table 1
Multivariable Cox regression to identify the impact factors of incident dementia and vascular dementia.

	Dementia			Vascular Dementia		
	Hazard Ratio	95% Confidence Interval	P-value	Hazard Ratio	95% Confidence Interval	P-value
Age (per year)	1.09	(1.08 - 1.10)	**< 0.001**	1.07	(1.06 - 1.08)	**< 0.001**
Male	0.76	(0.64 - 0.88)	**<0.001**	0.93	(0.76 - 1.14)	0.483
Sulphonylurea	1.12	(0.94 - 1.34)	0.203	1.15	(0.91 - 1.45)	0.244
Insulin	1.08	(0.88 - 1.33)	0.452	1.16	(0.90 - 1.50)	0.251
Thiazolidinedione	0.97	(0.64 - 1.48)	0.899	N/A	N/A	N/A
ACEI/ARB	1.12	(0.95 - 1.31)	0.181	1.12	(0.91 - 1.40)	0.286
Beta blocker	1.08	(0.92 - 1.26)	0.333	1.19	(0.97 - 1.47)	0.091
Calcium channel blocker	1.17	(1.00 - 1.36)	0.051	1.28	(1.04 - 1.57)	**0.021**
Diuretic	0.73	(0.60 - 0.88)	**0.001**	0.71	(0.56 - 0.91)	**0.006**
Lipid-lowering agent	0.97	(0.82 - 1.15)	0.730	0.97	(0.77 - 1.21)	0.773
Neurological diabetic complications	1.59	(0.98 - 2.59)	0.060	N/A	N/A	N/A
Ophthalmological diabetic complications	1.12	(0.77 - 1.64)	0.540	1.14	(0.71 - 1.84)	0.582
Ischemic stroke	1.25	(0.98 - 1.60)	0.078	1.47	(1.09 - 1.98)	**0.011**
Atrial fibrillation	1.00	(0.72 - 1.39)	0.991	1.11	(0.74 - 1.68)	0.609
Heart failure	0.95	(0.72 - 1.25)	0.697	1.02	(0.72 - 1.45)	0.891
Intracranial hemorrhage	1.33	(0.82 - 2.17)	0.252	1.49	(0.83 - 2.68)	0.177
Coronary heart disease	0.84	(0.68 - 1.02)	0.085	0.76	(0.58 - 0.98)	**0.037**
Hypertension	0.95	(0.81 - 1.11)	0.527	1.10	(0.88 - 1.36)	0.405
Chronic obstructive pulmondary disease	1.16	(0.43 - 3.13)	0.774	N/A	N/A	N/A
Anemia	0.83	(0.67 - 1.04)	0.100	N/A	N/A	N/A
Baseline HbA1C(%)	1.03	(0.98 - 1.08)	0.229	1.03	(0.97 - 1.10)	0.325
Fasting blood glucose (mmol/L)	1.06	(0.99 - 1.14)	0.082	1.10	(1.01 - 1.20)	**0.024**
LDL (mmol/L)	1.07	(0.80 - 1.44)	0.637	1.17	(0.80 - 1.71)	0.409
HDL (mmol/L)	1.31	(0.50 - 3.45)	0.585	0.96	(0.28 - 3.30)	0.950
Total cholesterol (mmol/L)	0.99	(0.74 - 1.34)	0.968	0.95	(0.65 - 1.38)	0.774
Triglyceride (mmol/L)	1.04	(0.93 - 1.16)	0.496	N/A	N/A	N/A
Antiplatelet	1.36	(1.14 - 1.62)	**0.001**	1.92	(1.51 - 2.44)	**<0.001**
Warfarin	1.16	(0.75 - 1.79)	0.510	1.14	(0.64 - 2.03)	0.657

ACEI/ARB: angiotensinogen-converting enzyme inhibitor/ angiotensin receptor blocker; HDL: high density lipoprotein cholesterol; LDL: low desensity lipoprotein cholesterol;.

on these diagnoses. Therefore, the severity of dementia and diagnostic accuracy is unknown.

Conclusions

One quarter of patients with T2DM showed new onset of dementia over 12 years of follow-up. Older age and use of antiplatelet agents were risk factors for incident dementia, whilst older age, ischemic stroke, fasting blood glucose, and the use of antiplatelet agents and calcium channel blockers were risk factors for incident vascular dementia.

Declarations

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Author Contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Jiandong Zhou and Cosmos Liutao Guo. The first draft of the manuscript was written by Yau-Lam Alex Chau and Ji Won Yoo, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Code availability

Code available upon request to the corresponding author.

Ethics approval

This single-center retrospective observational study was approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee.

Consent to participate and for publication

Informed consent was waived by the Ethics Committee due to the retrospective, observational nature of the study and the use of deidentified data only.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data available upon request to the corresponding author.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahr.2023.100155.

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