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Effects of metformin exposure on neurodegenerative diseases in elderly patients with type 2 diabetes mellitus

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ABSTRACT

Epidemiological evidence reveals that patients with type 2 diabetes mellitus (T2DM) have an increased risk of neurodegenerative diseases (NDs), including dementia and Parkinson's disease (PD). The effects of metformin exposure on dementia and PD risk in patients with T2DM are unknown. We evaluated the effects of metformin exposure on the risk of dementia and PD in patients with T2DM. We performed a cohort study by using Taiwan's National Health Insurance Research Database. We recruited 4651 patients in the metformin cohort and a comparable number of nonmetformin controls by using propensity score matching. Multivariate Cox proportional hazards regression was used to estimate the effects of metformin on the risk of dementia and PD after adjustment for several confounding factors. During the 12-year follow-up, the metformin cohort exhibited a higher risk of PD than the nonmetformin cohort (hazard ratio [HR]: 2.27, 95% confidence interval [CI] = 1.68–3.07). The metformin cohort had an increased risk of all-cause dementia (HR: 1.66, 95% CI = 1.35–2.04). Moreover, metformin exposure increased the risk of Alzheimer's disease (HR: 2.13, 95% CI = 1.20–3.79) and vascular dementia (HR: 2.30, 95% CI = 1.25–4.22). The effects of exposure duration and dosage on dementia and PD occurrence were also observed. Long-term metformin exposure in patients with T2DM may lead to the development of NDs, including dementia and PD. Additional large-scale, prospective controlled trials are required to confirm the observed association in patients with T2DM.

1. Introduction

Dementia and Parkinson's disease (PD) are two major neurodegenerative diseases (NDs). Dementia is characterized by a progressive deterioration of cognitive function, and PD is a progressive disorder of the central nervous system that mainly affects motor function. Both are major public health problems, with a substantial economic impact (Wimo et al., 2013; Findley, 2007); they are severely disabling for patients and are often distressing for their caregivers and families. With the considerable global increase in life expectancy over the past century, the prevalence and incidence of these two diseases have been exhibiting increasing trends (Liu et al., 2016; World Health Organization and Alzheimer's Disease International, 2012). The rising prevalence of type 2 diabetes mellitus (T2DM) is another major public health concern. Growing epidemiologic evidence suggests that patients with T2DM are at an increased risk of dementia (Ninomiya, 2014), Alzheimer's disease (AD) (Sridhar et al., 2015), and PD (Cereda et al., 2011). Some pathogenic mechanisms, including chronic hyperglycemia, acute hypoglycemic episodes, microvascular disease, inflammation, obesity, and dyslipidemia, have been reported (Ninomiya, 2014; Cereda et al., 2011; Sridhar et al., 2015). Because most patients with T2DM ultimately receive oral antidiabetic drugs (OADs) (Yurgin et al., 2007; Sharma et al., 2016; Oishi et al., 2014), investigating the effects of antidiabetic medications on the development of dementia and PD is necessary. Metformin, an orally active biguanide, is inexpensive and well tolerated. Because of its favorable risk-benefit profile and the

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capacity to be combined with other antidiabetic agents, metformin has become increasingly popular for treating T2DM and is recommended as the first-line oral therapy either as mono- or combination therapy (Yurgin et al., 2007; Sharma et al., 2016; Oishi et al., 2014).

In the literature, human studies investigating the effects of metformin on the development of dementia are limited and have variable study design and results (Hsu et al., 2011; Imfeld et al., 2012; Moore et al., 2013; Schernhammer et al., 2011; Wahlqvist et al., 2012). Hsu et al. reported that metformin use can reduce the risk of dementia by 24% (HR = 0.76 [95% CI = 0.58–0.98]) (Hsu et al., 2011) compared with patients with T2DM who do not take any antidiabetic medication. A study by Moore et al. revealed that poor cognitive performance was associated with metformin use in patients with T2DM (Moore et al., 2013). Another population-based case–control study by Patrick et al. demonstrated that long-term users of metformin prescriptions were at an increased risk of AD (Imfeld et al., 2012). Regarding the association between OADs and PD, Wahlqvist et al. reported that a sulfonylurea further increased the risk of PD by 57%, which was avoided by combining it with metformin (Wahlqvist et al., 2012); however, the comparison group in their study comprised patients with T2DM who did not use oral antihyperglycemic agents. Another population-based case–-control study in Denmark revealed that patients with diabetes who used OADs were positively associated with PD (odds ratio = 1.37 [95% CI = 1.10–1.71]) (Schernhammer et al., 2011). Nevertheless, because a large proportion of patients with T2DM receive multidrug combination therapies in the real world (Yurgin et al., 2007; Sharma et al., 2016; Oishi et al., 2014), evaluating the effect of a single drug on ND risk is more complicated. The aforementioned studies had some limitations, including lack of sufficient information on the severity of diabetes, the potential combination with other medications, and other comorbidities that could act as major confounding factors, which may bias the interpretation of the results. Therefore, our large population-based cohort study examined the effects of metformin exposure on the risk of NDs, including dementia and PD in patients with T2DM compared with those who did not use metformin under similar baseline characteristics, including the same frequency of exposure to other antidiabetic drugs or other confounding factors.

2. Materials and methods

2.1. Database

In 1995, Taiwan implemented the National Health Insurance (NHI) program, which covers > 99% of Taiwan's 23 million residents. The National Health Insurance Research Database (NHIRD), established by the cooperation of the Bureau of NHI and the National Health Research Institutes (NHRI), is one of the largest administrative health care databases in the world, and it is open to scientists for research.

This study was established using the Longitudinal Health Insurance Database (LHID2000), a claims database of 1 million Taiwanese NHI insurants. The details of the LHID2000 have been adequately described previously (Kuan et al., 2016; Hu et al., 2016). The Taiwan NHI records disease history on the basis of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

2.2. Data availability statement

The dataset used in this study is held by the Taiwan Ministry of Health and Welfare (MOHW). The MOHW must approve our application to access this data. Any researcher interested in accessing this dataset can submit an application form to the MOHW requesting access. Please contact the staff of MOHW (e-mail: stcarolwu@mohw.gov.tw) for further assistance. Taiwan MOHW Address: No. 488, Sec. 6, Zhongxiao E. Rd., Nangang Dist., Taipei City 115, Taiwan (R.O.C.). Phone: + 886-2-8590-6848. All relevant data are presented in the paper.

2.3. Ethics statement

The NHIRD encrypts patients' personal information to protect privacy and provides researchers with anonymous identification numbers associated with relevant claims information, including sex, date of birth, medical services received, and prescriptions. Therefore, patient consent is not required to access the NHIRD. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH104-REC2-115-CR1). The IRB also specifically waived the consent requirement.

2.4. Study population

This retrospective cohort study included patients who were aged > 50 years, had received a new diagnosis of T2DM (ICD-9-CM code 250), had complete information with regard to age and sex between January 1, 2000, and December 31, 2010. The patients were divided into two cohorts on the basis of their metformin use: the metformin cohort, comprising patients with T2DM who had received metformin therapy for at least 90 days; and the nonmetformin cohort, comprising patients with T2DM who had not received metformin therapy. The index date in the metformin cohort was the 90th day of metformin use, and the index date in the nonmetformin cohort was the same as that in the metformin cohort. Patients with a history of PD (ICD-9-CM code 332) or dementia (ICD-9-CM codes 290.0–290.4, 294.1, 294.2, 331.0–331.1) before the index date were excluded.

Patients in the metformin and nonmetformin cohorts were matched at a ratio of 1:1 on the basis of a propensity score (Rosenbaum and Rubin, 1985). The propensity score was calculated using the probability of the treatment assignment by using a logistic regression model and included the following baseline variables: year of receiving metformin treatment; age; sex; Charlson Comorbidity Index (CCI) score; Adapted Diabetes Complications Severity Index (aDCSI) (Young et al., 2008); comorbidities of hypertension (ICD-9-CM codes 401–405), chronic kidney disease (ICD-9-CM codes 580–589), hyperlipidemia (ICD-9-CM code 272), heart failure (ICD-9-CM code 428), arrhythmia (ICD-9-CM codes 427), stroke (ICD-9-CM codes 430–438), head injury (ICD-9-CM codes 310.2, 800, 801, 803, 804, 850–854, and 959.01), and coronary artery disease (ICD-9-CM codes 410–414); and antidiabetic medications, including alpha-glucosidase inhibitors, sulfonylurea, thiazolidinediones, insulin, antihypertensive medications, and statins.

2.5. Main outcome measure

The study outcome was a diagnosis of PD and dementia during the 12-year follow-up. The PD event was defined by the ICD-9-CM diagnostic code 332. The dementia event was defined by ICD-9-CM codes of 290.0–290.4, 294.1, 294.2, and 331.0–331.1. Subtypes of dementia, including AD and vascular dementia (VD), were also investigated. The AD event was defined by the aforementioned ICD-9-CM codes of dementia in addition to the use of a combination of acetylcholinesterase inhibitors (AChEIs) or memantine. In Taiwan, only patients with AD and without any comorbidities that affect cognitive function are reimbursed for AChEIs or memantine. Claims for AChEI or memantine prescriptions by patients with AD must undergo a special review process that assesses the medical records, biochemistry data, and neuroimages of the patients. An individual was defined as having VD according to the ICD-9-CM code 290.4. We further analyzed the dose–response effect among patients using metformin. We calculated the average dose of metformin per year by dividing the total prescribed dose by the follow-up period and recorded the total number of days of metformin use as cumulative exposure day. We classified the patients into four subgroups by quartile.