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Association between comorbidities and dementia in diabetes mellitus patients: population-based retrospective cohort study

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ABSTRACT

Aims: Most diabetes mellitus (DM) patients have several comorbidities; the correlation of these comorbidities with dementia in DM requires clarification.
Methods: Using claims data from Taiwan National Health Insurance, we identified 33,709 DM adults before the year 2000 and randomly selected 67,066 non-DM patients matched by sex and age. Subjects were followed until diagnosis with dementia, excluded due to death/withdrawal from the insurance program, or followed until 2011. We compared the incidence and hazard ratio (HR) for dementia in both cohorts.
Results: Comorbidities were more prevalent in DM patients, including hypertension, hyperlipidemia, stroke, coronary artery and/or kidney disease. The HR was higher for the DM cohort with comorbidities than those without: 1.88 vs. 1.46 with hypertension; 1.56 vs. 1.39 with hyperlipidemia; 1.73 vs. 1.37 with coronary artery disease; 2.36 vs. 2.29 with stroke and 1.88 vs. 1.50 with kidney disease. The HR for dementia in diabetics rose from 1.41 in those without comorbidities to 2.49 in those with ≥4 comorbidities. In the DM cohort, HR was 1.22 for non-insulin-users and 1.41 for insulin-users, and 1.49 for type 1 DM and 1.23 for type 2 DM.
Conclusion: Diabetic patients have an elevated risk of dementia, and comorbidity increases this risk.

1. Introduction

Dementia syndrome, which is characterized by memory impairment with aphasia, apraxia, agnosia, or disturbance in executive functioning, has become a major healthcare burden worldwide in recent decades (Ferri et al., 2005; Prince et al., 2013). Patients with social and occupational dysfunction, as well as caregivers and families, may become exhausted without prompt and appropriate support, thereby leading to a vicious circle in the medical care and socioeconomic system (Hurd, Martorell, Delavande, Mullen, & Langa, 2013; Xiao et al., 2014).

Dementia is usually classified by aetiology: first, neurodegenerative (Alzheimer's, frontal–temporal and Lewy body dementia); second, cerebellar vascular-related (post-stroke and microvascular) and third, miscellaneous (Creutzfeldt-Jakob disease, alcohol- or infection-related dementia) (Apostolova, DeKosky, & Cummings, 2012). Alzheimer's disease (AD) is thought to be the most common among the dementia syndromes, but patients sometimes have two or more aetiologies upon presentation (Adelman & Daly, 2005; Feldman et al., 2008). Understanding the pathogenesis of dementia has increased gradually, but there are no curative pharmacological therapies or satisfactory non-pharmacological treatments for dementia in current clinical practice (Hogan et al., 2008; Larner, 2014). Risk factor exposure and control are highly prioritized for decreasing the burden of dementia on healthcare. Factors that are reportedly linked with dementia include age, smoking, hypertension and diabetes mellitus (DM). Recent studies have shown that the latter is a risk factor for vascular-related dementia and for AD (Fei, Yan Ping, Ru Juan, Ning Ning, & Lin, 2013; Ryan, Fine, & Rosano, 2014).

Conflicts of interest: None.

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DM patients usually manifest comorbidities, such as hypertension, hyperlipidemia, stroke, coronary artery disease and kidney disease. Similar to dementia, the prevalence of DM and comorbidities is also higher in the elderly. In the present study, we evaluated the roles of comorbidities correlated with dementia in DM patients. Medication and glucose control for DM may modify the risk of dementia, although inconclusively (Chen et al., 2009; Imfeld, Bodmer, Jick, & Meier, 2012). Insulin regimens are normally used to control DM, particularly in those with intensive control demands or where the glucose control goal cannot be achieved with oral anti-diabetes pills. We also evaluated the correlation between dementia and insulin use.

2. Methods

2.1. Data source

The National Health Insurance (NHI) of Taiwan is a governmen-t-run universal healthcare program that has covered over 99% of the total population since 1999. This study used a longitudinal dataset of 1996–2011, which comprised one million insured people randomly selected from the 23 million people covered by NHI, based on the population in the year 2000. This dataset provided information on inpatient and outpatient claims. Using a unique scrambled personal identification provided by the National Health Research Institutes, medical histories and demographic variables were used in the analysis without violating patient privacy.

2.2. Diabetes mellitus cohort and non-diabetes mellitus cohort

January 1, 2000, was set as the index date in our study, and patients were followed until 2011. In the claims data, we identified patients aged ≥40 and diagnosed with DM (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9] code 250) before the index date as DM cases, and they were enrolled in the DM cohort. After matching gender and a five-year age stratum, we identified about twice as many patients who had not been diagnosed with DM during the entire follow-up period of 11 years, until 2011, who were placed in the non-DM cohort. Those with a history of dementia (ICD-9 codes 290.0–290.4 and 331.0) before the index date were excluded from both cohorts. According to medical prescription records, DM patients were sub-grouped as insulin or non-insulin users. Each type was followed until they were diagnosed with dementia, excluded due to death or withdrawal from the insurance program, or until 2011, to determine the incidence of dementia (ICD-9 codes 290.0–290.4 and 331.0).

2.3. Age and comorbidities

The age of each study subject was calculated based on their birth and index dates. Subjects were stratified by age (cohorts: 40–49, 50–59, 60–69, 70–79 and ≥80 years). The baseline comorbidities considered as covariates comprised hypertension (ICD-9 code 401–405), hyperlipidemia (ICD-9 code 272.0–272.4), coronary artery diseases (CAD; ICD-9 code 410–413, 414.00–414.05, 414.8 and 414.9), stroke (ICD-9 code 430–438) and kidney diseases (ICD-9 code 580–589).

2.4. Statistical analysis

We assessed the intergroup age and comorbidity distributions using the chi-squared test and Student's *t*-test to compare differences. We derived the incidence density for dementia in both cohorts by gender, age and comorbidities, as well as calculating the DM cohort to non-DM cohort hazard ratio (HR) and 95% confidence interval (CI). The cumulative incidences of dementia at the end of follow-up period in both cohorts were plotted using the Kaplan–Meier model and examined using the log-rank test. Cox proportional hazards regression analysis was used to estimate the HR and 95% CI. The Cox model used to analyze the HR for dementia was linked with insulin prescription for DM and linked with type 1 and type 2 DM using SAS statistical software (Version 9.1 for Windows; SAS Institute, Inc., Cary, NC, USA). Two-tailed tests were used in the analysis, where statistically significant differences were accepted at $P < 0.05$.

3. Results

3.1. Study cohort characteristics

This study enrolled 33,709 diabetics and 67,066 non-diabetics based on NHI claims before January 1, 2000. In the age and gender matched cohorts, the proportion of male patients in the two cohorts were 48.2% and 48.4%, respectively, and the proportion of females was 51.8% and 51.6%, respectively. The mean age was 62.3 ± 11.2 years in the DM cohort and 62.1 ± 11.4 years in the non-DM cohort (Table 1). However, the comorbidities differed, where the DM patients were more prone to hypertension (67.6% vs. 32.6%), hyperlipidemia (29.4% vs. 5.23%), CAD (18.7% vs. 7.67%), stroke (8.45% vs. 2.91%) and kidney diseases (18.6% vs. 5.41%).

3.2. Incidence and hazard ratio of dementia in the diabetes mellitus and non-diabetes mellitus cohorts

By the end of the follow-up period, the average duration of a patient being diagnosed with dementia was 5.52 ± 3.04 years in the DM cohort and 5.85 ± 3.07 years in the non-DM cohort. The Kaplan–Meier model estimated that the cumulative incidence was 2.8% higher in the DM cohort than that in the non-DM cohort (6.2% vs. 9.0%, $P < 0.001$) (Fig. 1). Dementia increased with age (incidence was higher in the DM cohort than the non-DM cohort), where the DM vs. non-DM cohort overall adjusted HR was 1.26 (1.19–1.33) (Table 2). The incidence of dementia was higher in women than in men in both cohorts, while the DM cohort to non-DM cohort HRs were similar in both sexes, where the adjusted HR was 1.21 (1.10–132) in males and 1.30 (1.20–1.40) in females. The dementia incidence increased with age in both cohorts. Although the dementia HR was similar in the five age strata, the 50–59, 60–69 and 70–79 age groups differed significantly between the DM patients and non-DM patients (Table 2).

Table 3 shows the risk of dementia in patients with and without comorbidity in both DM and non-DM patients. When compared to the

Table 1
Demographics and comorbidity in DM and non-DM patients.

	DM patients N = 33709		Non-DM patients N = 67066		
	N	%	N	%	*P*-value
Sex					0.45
Men	16244	48.2	32488	48.4	
Women	17465	51.8	34578	51.6	
Age, years					0.71
40–49	5835	17.3	11670	17.4	
50–59	8417	25.0	16834	25.1	
60–69	10111	30.0	20222	30.2	
70–79	7665	22.7	14978	22.3	
≥80	1681	4.99	3362	5.01	
Mean (SD)	62.3	(11.2)	62.1	(11.4)	0.03†
Comorbidity					
Hypertension	22774	67.6	21891	32.6	<0.0001
Hyperlipidemia	9925	29.4	3506	5.23	<0.0001
CAD	6312	18.7	5141	7.67	<0.0001
Stroke	2847	8.45	1949	2.91	<0.0001
Kidney disease	6274	18.6	3630	5.41	<0.0001

Chi-squared test.
SD: standard deviation; CAD: coronary artery disease.
† *t*-test.