中文題目：第二型糖尿病的大血管病變與小血管病變關係之評估:台灣 2000-2006 全國性世代型研究分析

英文題目：Evaluation the association of macroangiopathy and microangiopathy in patients with type 2 diabetes: a national cohort study from 2000 to 2006 in Taiwan

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Aims: Hypoglycemia has been reported to be associated with the development of microvascular events. Therefore, it is important to examine the association of macroangiography risk on microangiography in type 2 diabetes.

Methods: Using complete claims data for patients with type 2 diabetes from Taiwan's National Health Insurance Research Database, we identified patients with microangiography between 2000 and 2006. Matching age, gender, index year, and medication for 1:1 to control patient. Cox regression models were used to estimate the hazard ratios (HRs) of clinical outcomes, including major adverse cardiovascular events (myocardial infarction and ischemic stroke), and all-cause death.

Results: Among 37089 cases with microanigiography and type 2 diabetes, in comparison with matched control patients, had greater risks of myocardial infarction (HR, 1.60; 95% CI, 1.50–1.70), ischemic stroke (HR, 1.19; 95% CI, 1.13–1.25), and all-cause mortality (HR, 1.11; 95% CI, 1.07–1.15). The results remained unchanged in analyses of several subgroups of patients, and were similar in analyses accounting for the competing risk of death.

Conclusion: we showed that higher risk of cardiovascular events in patients with microangiography and type 2 diabetes.

Introduction

Worldwide, the number of adults with diabetes was estimated at 382 million in 2013, a figure that is expected to increase to 592 million by 2035[1]. Chronic kidney disease (CKD) is a highly prevalent microvascular complication of diabetes mellitus, and approximately 40% of patients with diabetes develop CKD[2]. Studies have suggested strict control of blood glucose as a means to prevent complications from diabetes mellitus, particularly microvascular complications such as diabetic nephropathy [3-7]. Yet cardiovascular events remains the most common and significant causes recurrent morbidity in most people with type 1 diabetes and in many with type 2 diabetes. A systematic review of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, and the Veterans Affairs Diabetes Trial (VADT) reported that

intensive glucose therapy increased the cardiovascular risk to a control group[8]. A large community-based study of more than one million individuals showed a graded increase in cardiovascular events with decreasing glomerular filtration rate levels, establishing CKD as a strong cardiovascular risk factor[9]. However, the risk was less clear for mild and moderate CKD3 and was even questioned for older subjects[10]. Together, we believe that whether higher cardiovascular risk in patients with type 2 diabetes and microangiography or not is important. Therefore, our study provided evidence of data to assess the impact of cardiovascular events in patients with microangiography and type 2 diabetes.

Subjects and Methods

The institutional review board of Kaohsiung Municipal Ta-Tung Hospital approved this study (KMTTHIRB), and the need for a full ethical review was waived because we utilized identified claims data exclusively from Taiwan's National Health Insurance Research Database (NHIRD), which collects information for more than 99% of Taiwan's 23 million inhabitants. This information includes patient demographics, diagnoses, and procedures at outpatient, inpatient, and emergency services. Diagnostic information is based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Microangiographic cohort were those with ICD-9-CM number 25040, and the control cohort were those with ICD-9-CM 250XX but not 25040.

We collected data on the following baseline covariates: (1) demographic covariates (age, sex, year of index date, month of index date, monthly income, urbanization level); (2) concomitant use of medications associated with type 2 diabetes and hypertention (insulin, sulfonyurea, metformin, diuretics, b-blockers, calcium channel blockers, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers); and (3) relevant comorbidities, defined by ICD-9-CM codes. We matched each patient in the microangiograhy cohort to a control patient based on age, gender, index year, and medication.

Statistical analysis

We compared differences in means for the continuous variables by the Chi-square test and Independent t test were used to explore categorical variables and continuous variables respectively. Cox regression were used to estimate the hazard ratio of death ratio and the hazard ratio of Myocardial infarction and ischemic stroke event. We controlled for a vector of covariates, including patient demographics and baseline characteristics. The two-tailed significance level was set at 0.05. All analyses were conducted using SAS statistical software version 9.4.

RESULTS

In table 1, age, sex, diabetes duration, insurance range, cormobilities (hypertention, hyperlipidemia, gout, liver disease, chronic obstructive pulmonary disease(COPD)), and medication(insulin, sulfonyurea, metformin, diuretics, b-blockers, calcium channel blockers, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers) are shown to be not significantly different in the type 2 diabetic patients with microangiography and those without microangiography. Table 2 showed all cause mortality between Comparison cohort and Case cohort. We can see that people without nephropathy had lower risk for all cause mortality (Hazard ratio(HR)1.17, 95%CI 1.13-1.23) than those with microangiography. Furthermore, they also had lower risk for acute myocardial infarction (HR1.67, 95%CI 1.57-1.77) than those with microangiography in table 3. Finally, in table 4, we found that in the risk of cerebral vascular disease is lower in the cohort without microangiography (HR1.21, 95%CI 1.15-1.28).

Discussion

To our knowledge, this is the first study directly to examine the association between microangiography and macroangiography by using national health insurance research database. We found that people without nephropathy had lower risk for all cause mortality. Furthermore, they also had lower risk for acute myocardial infarction than those with microangiography. Finally, we found that in the risk of cerebral vascular disease is lower in the cohort without microangiography. Taking together, microangiography is the risk of macroangiography.

During the past decade, it became clear that inflammation is a key feature of obesity and type 2 diabetes[11]. Visceral obesity and insulin resistance increase cardiovascular risk by classical (dyslipidaemia, hypertension and glucose dysmetabolism) and less conventional mechanisms. Less conventional risk factors secreted by adipocytes and macrophages infiltrating adipose tissue, which is now considered to be an active endocrine organ, include adipokines (such as leptin and adiponectin), proinflammatory cytokines (IL-6 and CRP) and hypofibrinolytic factors (PAI-1) that, together, might lead to increased oxidative stress and endothelial dysfunction, finally promo-ting atherosclerosis [12].

A large community-based study of more than one million individuals showed a graded increase in cardiovas-cular events with decreasing glomerular filtration rate levels, establishing CKD as a strong cardiovascular risk factor. However, the risk was less clear for mild and moderate CKD and was even questioned for older subjects. Albuminuria is also a strong predictor of mortality and cardiovascular events independently of the glomerular filtration rate. Data in diabetic patients with CKD are limited and do not permit for definite conclusions.

In conclusion, our study provide that microangiography could be risk of macroangiography. This result make a point that clinicans should be pay more attention in people with type 2 diabetes and microangiography.

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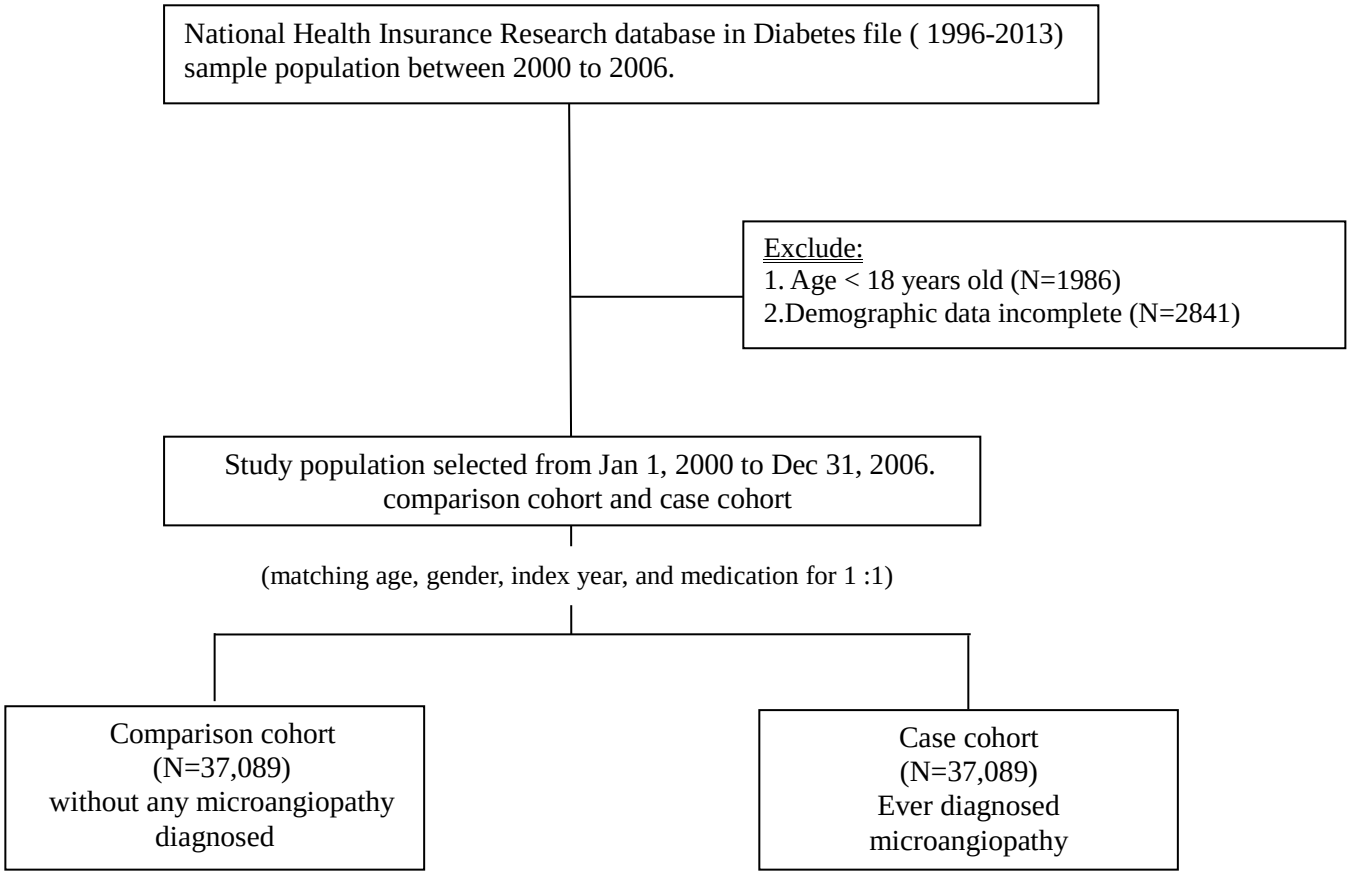

Figure 1.Flow chat of case selection

Table 1. Basic characteristics between case cohort and comparison cohort (N=74,178)

Variables	Comparison cohort (N=37,089)		Case cohort (N=37,089)		P value
	N	(%)	N	(%)	
Age					
<40	2126	(5.7)	2237	(6.0)	0.184
40-59	17350	(46.8)	17377	(46.9)	
≧60	17613	(47.5)	17475	(47.1)	
Mean (±SD)	58.84	(±12.64)	58.74	(±12.63)	
Gender					
Female	16090	(43.4)	16173	(43.6)	0.539
Male	20999	(56.6)	20916	(56.4)	
Insurance range					
< NT 15,840	22182	(59.8)	21949	(59.2)	0.184
NT 15,841-25,000	10818	(29.2)	10941	(29.5)	
>NT 25,001	4089	(11.0)	4199	(11.3)	
Comorbidities					
Hypertension	23768	(64.1)	25425	(68.6)	<0.001
Hyperlipidemia	18613	(50.2)	23416	(63.1)	<0.001
Gout	8508	(22.9)	10319	(27.8)	<0.001
Liver disease	9308	(25.1)	10736	(28.9)	<0.001
COPD	12727	(34.3)	13263	(35.8)	<0.001
Medication					
Sulfonylurea	22477	(60.6)	22612	(61.0)	0.310
Metformin	17605	(47.5)	17675	(47.7)	0.607
Insulin	830	(2.2)	719	(1.9)	0.004
ACEi	11369	(30.7)	11514	(31.0)	0.249
CCB	13935	(37.6)	13896	(37.5)	0.767
Beta-blockers	12084	(32.6)	11974	(32.3)	0.388
Diuretics	14196	(38.3)	14102	(38.0)	0.477

Table 2 All cause mortality between Comparison cohort and Case cohort (N=74,178)

	No. cases	Per 1,000 Person year	Crude HR (95%CI)	p value	Adjusted HR (95%CI)	p value
Comparison cohort	4799	27.57	Ref.		Ref.	
Case cohort	5274	30.51	1.11 (1.07-1.15)	<0.001	1.17 (1.13-1.23)	<0.001

Adjusted age, gender, insurance range , all comorbidities, and medication).

Table 3 The risk of acute myocardial infarction between Comparison cohort and Case cohort (N=70,994)

	No. cases	Per 1,000 Person year	Crude HR (95%CI)	p value	Adjusted HR (95%CI)	p value
Comparison cohort	1698	10.31	Ref.		Ref.	
Case cohort	2665	16.49	1.60 (1.50-1.70)	<0.001	1.67 (1.57-1.77)	<0.001

Adjusted age, gender, insurance range , all comorbidities, and medication).

Table 4 The risk of cerebral vascular disease between comparison cohort and case cohort (N=68,508)

	No. cases	Per 1,000 Person year	Crude HR (95%CI)	p value	Adjusted HR (95%CI)	p value
Comparison cohort	2497	16.01	Ref.		Ref.	
Case cohort	2966	19.03	1.19 (1.13-1.25)	<0.001	1.21 (1.15-1.28)	<0.001

Adjusted age, gender, insurance range , all comorbidities, and medication).

Table 5 The duration of follow-up and survival

	Follow-up duration			survival duration		
	Mean	(SD)	p value	Mean	(SD)	p value
Comparison cohort	4.69	(0.94)	<0.001	2.62	(1.39)	0.618
Case cohort	4.66	(0.98)		2.61	(1.38)	