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Long-term effects of pioglitazone on first attack of ischemic cerebrovascular disease in older people with type 2 diabetes

A case-control study in Taiwan

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Abstract

Long-term studies demonstrating the effect of pioglitazone use on primary prevention of ischemic cerebrovascular disease in older people with type 2 diabetes mellitus are lacking. This study investigated the relationship between pioglitazone use and first attack of ischemic cerebrovascular disease in Taiwan.

We conducted a case-control study using the database of the Taiwan National Health Insurance Program. There were 2359 type 2 diabetic subjects aged ≥65 years with newly diagnosed ischemic cerebrovascular disease from 2005 to 2011 as the case group and 4592 sex- and age-matched, randomly selected type 2 diabetic subjects aged ≥65 years without ischemic cerebrovascular disease as the control group. The odds ratio (OR) with 95% confidence interval (CI) of ischemic cerebrovascular disease associated with pioglitazone use was measured by the multivariable unconditional logistic regression model.

After adjustment for confounding factors, the multivariable logistic regression analysis disclosed that the adjusted ORs of first attack of ischemic cerebrovascular disease associated with cumulative duration of using pioglitazone were 3.34 for <1 year (95% CI 2.59–4.31), 2.53 for 1 to 2 years (95% CI 1.56–4.10), 2.20 for 2 to 3 years (95% CI 1.05–4.64), and 1.09 for ≥3 years (95% CI 0.55–2.15), respectively.

Our findings suggest that pioglitazone use does not have a protective effect on primary prevention for ischemic cerebrovascular disease among older people with type 2 diabetes mellitus during the first 3 years of use. Whether using pioglitazone for >3 years would have primary prevention for ischemic cerebrovascular disease needs a long-term research to prove.

Abbreviations: ICD-9 code = International Classification of Diseases, 9th Revision, Clinical Modification.

Keywords: diabetes mellitus, ischemic cerebrovascular disease, National Health Insurance Program, pioglitazone

1. Introduction

Thiazolidinedione, as an insulin-sensitizing drug, is classified as a novel oral antidiabetic drug and is commonly prescribed to treat patients with type 2 diabetes mellitus.[1] Pioglitazone is one of thiazolidinedione class. Overall, pioglitazone use is well tolerated and effective in clinical practice. In addition to its antidiabetic effect, some studies have shown that pioglitazone use has secondary prevention for ischemic cerebrovascular disease in patients with or without diabetes mellitus.[2–4] However, the research on its primary prevention for ischemic cerebrovascular disease remains little in older people with type 2 diabetes mellitus.

The population aged ≥65 years accounted for 12.5% of the total population in Taiwan in 2015.[5] In addition, cerebrovascular disease and diabetes mellitus were the 3rd and 5th leading causes of death in Taiwan in 2014.[6] Because diabetes mellitus is a well-known risk factor for cerebrovascular disease, whether pioglitazone use has a benefit effect on primary prevention of cerebrovascular disease in older people with type 2 diabetes mellitus remains unknown. If more information can be available, more preventive interventions for ischemic cerebrovascular disease can be performed in older people. Therefore, we conducted a case-control study to investigate the relationship between pioglitazone use and first attack of ischemic cerebrovascular disease in older people with type 2 diabetes mellitus.

2. Methods

2.1. Study population

This was a case-control study using the claims data of the National Health Insurance Program in Taiwan. In brief, this

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S-WL and H-FL equally contributed to this study.

Authorship: S-WL planned and conducted this study. He substantially contributed to the conception of the article, initiated the draft of the article, and critically revised the article. H-FL and C-LL conducted the data analysis and critically revised the article. K-FL planned and conducted this study. He participated in the data interpretation and critically revised the article.

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national insurance program has a coverage rate of >99% of residents living in Taiwan.[7] The database included information on insured demographic status, outpatient care, inpatient care, and record of medication use. International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9 code, 2001 edition) was used to identify disease diagnosis. Data files can be linked with scrambled identification to secure patient privacy. The details of this program have been written in previous studies.[8–17] This study was approved by the Institutional Review Board of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115).

2.2. Inclusion and exclusion criteria

We selected type 2 diabetic subjects aged ≥65 years with newly diagnosed ischemic cerebrovascular disease as the case group during the period of 2005 to 2011 (based on ICD-9 codes 433, 434, and 435). We randomly selected type 2 diabetic subjects aged ≥65 years without diagnosis of ischemic cerebrovascular disease as the control group from the same database. The date of diagnosing ischemic cerebrovascular disease was defined as the index date. The case and control groups were matched with sex, age (per 5 years), comorbidities, and index year of diagnosing ischemic cerebrovascular disease. Subjects with other types of cerebrovascular disease (ICD-9 codes 430–432 and 436–438) before the index date were excluded. To diminish the biased results, subjects with any prescription of rosiglitazone before the index date were also excluded.

2.3. Exposure definition of pioglitazone and other antidiabetic drugs

To investigate the effect of medications on risk of ischemic cerebrovascular disease, pioglitazone and other antidiabetic drugs were included. Other antidiabetic drugs available in Taiwan were included as follows: sulfonylurea, metformin, alpha-glucosidase inhibitor, dipeptidyl peptidase 4 inhibitor, and insulin. The definition of medication use was adapted from previous studies.[18,19] Ever use of medication was defined as subjects who ever had a prescription of medication studied. Never use was defined as those who never had a prescription of medication studied.

2.4. Comorbidities potentially related to ischemic cerebrovascular disease

Comorbidities potentially related to ischemic cerebrovascular disease before the index date were included as follows: alcohol-related disease, atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, hyperlipidemia, and hypertension. All comorbidities were diagnosed with ICD-9 codes. On the basis of ICD-9 codes, the diagnosis accuracy of comorbidities has been well examined in previous studies.[20–24]

2.5. Statistical analysis

We first compared the case and control groups for distributions of demographic status, medications, and comorbidities. The χ^2 test for categorical variables and the t test for continuous variables were used to examine the differences. In the beginning, all variables were included in the univariable unconditional logistic regression model. Only those found to be significant in the univariable analysis were further included in the multivariable unconditional logistic regression model to estimate the odds ratio (OR) and 95% confidence interval (CI) of ischemic cerebrovascular disease associated with pioglitazone use, other antidiabetic drugs use, and comorbidities. We conducted a further analysis on the dose-dependent effect among those with ever use of pioglitazone. The average daily dose of pioglitazone use was calculated by using the total quantity of pioglitazone divided by total number of days supplied. The average daily dose was divided into 2 levels according to the median dose for dose-dependent relationship analysis, <30 mg and ≥30 mg. The probability value <0.05 was considered statistically significant (SAS software version 9.2; SAS Institute Inc, Cary, NC).

3. Results

3.1. Characteristics of the study population

Table 1 discloses that there were 2359 subjects with ischemic cerebrovascular disease as the cases and 4592 subjects without ischemic cerebrovascular disease as the controls, with similar distribution of sex. The mean ages (standard deviation) were 69.4 (11.7) years in cases and 67.8 (12.6) years in controls (t test, $P<0.001$). The cases were more likely to have a higher proportion of ever use of pioglitazone than the controls (9.6% vs 3.7%, χ^2 test, $P<0.001$). The cases were more likely to have a higher proportion of atrial fibrillation than the controls (8.5% vs 6.7%, χ^2 test, $P=0.01$).

3.2. Association between ischemic cerebrovascular disease, medications, and comorbidities

After adjustment for confounding factors, the multivariable logistic regression analysis disclosed that the adjusted OR of first attack of ischemic cerebrovascular disease was 2.78 for subjects with ever use of pioglitazone (95% CI 2.26–3.41), when compared with those with never use of pioglitazone. In addition, age (every 1 year, adjusted OR 1.01, 95% CI 1.01–1.02) and atrial fibrillation (adjusted OR 1.21, 95% CI 1.00–1.46) were factors significantly associated with first attack of ischemic cerebrovascular disease (Table 2).

3.3. Risk of ischemic cerebrovascular disease associated with cumulative duration of pioglitazone use

In subanalysis, after adjustment for age and atrial fibrillation, the multivariable logistic regression analysis disclosed that the adjusted ORs of first attack of ischemic cerebrovascular disease associated with cumulative duration of using pioglitazone were 3.34 for <1 year (95% CI 2.59–4.31), 2.53 for 1 to 2 years (95% CI 1.56–4.10), 2.20 for 2 to 3 years (95% CI 1.05–4.64), and 1.09 for ≥3 years (95% CI 0.55–2.15), respectively (Table 3).

3.4. Risk of ischemic cerebrovascular disease associated with average daily dose of pioglitazone use

We further conducted an analysis on the dose-dependent effect among those with ever use of pioglitazone. After adjustment for age and atrial fibrillation, the adjusted ORs of first attack of ischemic cerebrovascular disease were 2.57 for subjects with average daily dose of pioglitazone <30 mg (95% CI 2.07–3.18), and 6.62 for subjects with average daily dose of pioglitazone ≥30 mg (95% CI 3.12–14.1), when compared with subjects with never use of pioglitazone (Table 4).

Table 1

Characteristics between ischemic cerebrovascular disease group and nonischemic cerebrovascular disease group.

Characteristic	Nonischemic cerebrovascular disease, N = 4592		Ischemic cerebrovascular disease, N = 2359		P*
	n	(%)	n	(%)	
Sex					0.98
Female	2070	45.1	1064	45.1	
Male	2522	54.9	1295	54.9	
Age group, y					0.97
65–74	1571	34.2	800	33.9	
75–84	1397	30.4	719	30.5	
≥85	1624	35.4	840	35.6	
Age, y, mean (standard deviation)†	67.8	12.6	69.4	11.7	<0.001
Use of pioglitazone					<0.001
Never use	4422	96.3	2132	90.4	
Ever use	170	3.7	227	9.6	
Use of other antidiabetic drugs					0.74
Never use	946	20.4	489	20.7	
Ever use	3656	79.6	1870	79.3	
Comorbidities before index date‡					
Alcohol-related disease	324	7.1	181	7.7	0.35
Atrial fibrillation	306	6.7	200	8.5	0.01
Chronic kidney disease	475	10.3	269	11.4	0.18
Chronic obstructive pulmonary disease	1482	32.3	770	32.6	0.76
Coronary artery disease	2230	48.6	1150	48.8	0.88
Hyperlipidemia	2637	57.4	1353	57.4	0.95
Hypertension	4171	90.8	2136	90.6	0.70

Data are presented as the number of subjects in each group with percentages given in parentheses, or mean with standard deviation given in parentheses.

* χ^2 test.

† *t* test comparing subjects with and without ischemic cerebrovascular disease.

‡ The index date was defined as the date of newly diagnosed ischemic cerebrovascular disease.

3.5. Interaction effect between pioglitazone use and other hypoglycemic agents use on risk of ischemic cerebrovascular disease

We conducted a further analysis about interaction effect between pioglitazone use and other hypoglycemic agents use on risk of ischemic cerebrovascular disease (Table 5). As a reference of subjects with never use of pioglitazone and never use of other hypoglycemic agents, the adjusted OR of first attack of ischemic cerebrovascular disease were 4.04 for subjects with ever use of pioglitazone and ever use of other hypoglycemic agents (95% CI 3.16–5.17). We could not find subjects with ever use of pioglitazone and never use of other hypoglycemic agents.

Table 2

Crude and adjusted OR and 95% CI of ischemic cerebrovascular disease associated with pioglitazone use and other comorbidities.

Variable	Crude OR (95% CI)	Adjusted* OR (95% CI)
Sex (male vs female)	1.00 (0.90–1.10)	
Age (per 1 y)	1.01 (1.01–1.02)	1.01 (1.01–1.02)
Use of pioglitazone (never use as a reference)		
Ever use	2.77 (2.25–3.40)	2.78 (2.26–3.41)
Use of other antidiabetic drugs (never use as a reference)		
Ever use	0.98 (0.87–1.11)	
Comorbidities before index date (yes vs no)		
Alcohol-related disease	1.10 (0.91–1.32)	
Atrial fibrillation	1.30 (1.08–1.56)	1.21 (1.00–1.46)
Chronic kidney disease	1.12 (0.95–1.31)	
Chronic obstructive pulmonary disease	1.02 (0.92–1.13)	
Coronary artery disease	1.01 (0.91–1.11)	
Hyperlipidemia	1.00 (0.90–1.10)	
Hypertension	0.97 (0.82–1.15)	

CI = confidence interval, OR = odds ratio.

* Variables found to be significant in the univariable unconditional logistic regression model were further examined by the multivariable unconditional logistic regression model. Additionally adjusted for age and atrial fibrillation.

4. Discussion

In this case-control study, we noticed that pioglitazone use was associated with increased odds of first attack of ischemic cerebrovascular disease in older people with type 2 diabetes mellitus, particularly in the first 3 years of use. We noticed that the ORs were decreased with using period. Using >3 years, no significant association can be detected (Table 3). Pioglitazone is usually recommended as the 2nd or 3rd line therapy for type 2

Table 3

Risk of ischemic cerebrovascular disease associated with cumulative duration of pioglitazone use.

Never use of pioglitazone as a reference	Case/N	Crude OR	(95% CI)	Adjusted OR*	(95% CI)
	2132/4422	1.00	(Reference)	1.00	(Reference)
Pioglitazone use					
<1 y	162/102	3.29	(2.56–4.24)	3.34	(2.59–4.31)
1–2 y	38/30	2.63	(1.62–4.25)	2.53	(1.56–4.10)
2–3 y	14/14	2.07	(0.99–4.36)	2.20	(1.05–4.64)
≥3 y	13/24	1.12	(0.57–2.21)	1.09	(0.55–2.15)

CI = confidence interval, OR = odds ratio.

* Adjusted for age and atrial fibrillation.

Table 4

Risk of ischemic cerebrovascular disease associated with average daily dose of pioglitazone use.

Variable	Case number/ control number	Crude OR	(95% CI)	Adjusted OR*	(95% CI)
Never use of pioglitazone as a reference		1.00	(Reference)	1.00	(Reference)
Average daily dose of pioglitazone use					
<30 mg	199/161	2.56	(2.07–3.18)	2.57	(2.07–3.18)
≥30 mg	28/9	6.45	(3.04–13.7)	6.62	(3.12–14.1)

CI = confidence interval, OR = odds ratio.
* Adjusted for age and atrial fibrillation.

diabetes mellitus. That is why we cannot find patients who had ever used pioglitazone and never used other hypoglycemic agents (Table 5). That is, pioglitazone cannot serve as a monotherapy in this study. To our mind, the pioglitazone users are often patients whose glycemic status is more difficult to be controlled and therefore potentially have a more significant disease. Similarly, those receiving higher dose of pioglitazone or receiving combined therapy with pioglitazone and other antidiabetic drugs could be those whose glycemic status is more difficult to be controlled and therefore potentially have a more significant disease. That is why patients with average daily dose of pioglitazone ≥30 mg or patients with ever use of pioglitazone and ever use of other hypoglycemic agents remain to be significantly associated with risk of ischemic cerebrovascular disease (Tables 4 and 5). Therefore, the risk of ischemic cerebrovascular disease would be higher initially among those adding pioglitazone as dual therapy or triple therapy. Only when glycemic control is well improved can the risk be decreased. Therefore, pioglitazone use is not the direct reason for increased odds of ischemic cerebrovascular disease, but the reflection of the control status of diabetes.

A prospective, double-blind, randomized controlled trial by Dormandy et al has shown that the number needed to treat is 48. That is, at least 48 patients should be treated with pioglitazone for ≥3 years to avoid one episode of major cardiovascular events including myocardial infarction and stroke.[2] This finding is partially compatible with our study that using pioglitazone <3 years could not have a protective effect on primary prevention for ischemic cerebrovascular disease. In our opinion, with currently available evidence, it would take ≥3 years to provide beneficial effects on primary prevention for ischemic cerebrovascular disease among those treated with pioglitazone.

On the basis of the above discussion, we summarize a rational explanation that those initially using pioglitazone could have poor glycemic control, which places these patients at higher risk of ischemic cerebrovascular disease. As time goes by, glucose-lowering effect of pioglitazone gradually becomes pronounced. Thus, as glycemic control is improved, the risk of ischemic cerebrovascular disease is gradually decreased. The decreasing ORs in our study can partially explain this hypothesis (Table 3). Moreover, these findings indicate that clinicians still should be cautious of the risk of ischemic cerebrovascular disease during the first 3 years of pioglitazone use.

Table 5

Interaction effect between pioglitazone use and other hypoglycemic agents use on risk of ischemic cerebrovascular disease.

Variable				
Pioglitazone	Other hypoglycemic agents	Case number/ control number	Adjusted OR*	(95% CI)
Never use	Never use	262/766	1.00	(Reference)
Ever use	Never use	—	—	—
Ever use	Ever use	227/170	4.04	(3.16–5.17)

CI = confidence interval, OR = odds ratio.
* Adjusted for age and atrial fibrillation.

In fact, the biological mechanism underlying pioglitazone use associated with increased odds of first attack of ischemic cerebrovascular disease cannot be completely clarified by our observational study. We reviewed the relevant literature to explain it. In a rat-model study, pioglitazone use could improve the recovery from ischemic cerebrovascular disease.[25] A case-matched controlled study by Lee and Reding has shown that thiazolidinedione use, no matter pioglitazone or rosiglitazone, is associated with good functional recovery from cerebrovascular disease in patients with type 2 diabetes mellitus.[26] These neuroprotective benefits of pioglitazone might be mediated by anti-inflammatory effect against ischemic injury and by promotion of neuronal regeneration, and by insulin-sensitizing effect.[25,26] A cohort study by Wilcox et al has shown that pioglitazone use is associated with a 47% risk reduction of recurrent fatal or nonfatal cerebrovascular disease in patients with type 2 diabetes mellitus.[3] However, the authors did not find that pioglitazone use has primary prevention for cerebrovascular disease. Similarly, another prospective, double-blind cohort study by Kernan et al has also shown that pioglitazone use is associated with a 24% risk reduction of recurrent fatal or nonfatal cerebrovascular disease in patients without type 2 diabetes mellitus.[4] Both studies highlight that pioglitazone use has a protective effect on secondary prevention for recurrence of ischemic cerebrovascular disease, no matter patients with or without diabetes mellitus, but primary prevention has not yet been proved.

Some limitations should be discussed in this study. First, due to the natural limitation of this database used, a few of key risk factors associated with ischemic cerebrovascular disease, such as alcohol consumption, cigarette smoking, and obesity, were not documented in this database. Therefore, alcohol-related disease was included instead of alcohol consumption. Chronic obstructive pulmonary disease was included instead of cigarette smoking. Coronary artery disease, hyperlipidemia, and hypertension were included instead of obesity. These similar limitations have been mentioned in previous studies.[27–31] Second, due to the same limitation, there is no measure of hemoglobin A1c. We cannot differentiate that the risk of ischemic cerebrovascular disease related to pioglitazone use is associated with good glycemic control or poor control. It indicates a future direction of research. Third, the major limitation of this study is the lack of patient outcome data. Therefore, we cannot prove the long-term effect of pioglitazone use on primary prevention for ischemic cerebrovascular disease.

Our study has several strengths. To diminish the biased results, patients with any prescription of rosiglitazone, another type of thiazolidinedione, before the index date were excluded. Therefore, this study is to focus on pioglitazone use alone. We used a well-organized database with a large sample size to increase its statistic power.

We conclude that pioglitazone use does not have a protective effect on primary prevention for ischemic cerebrovascular disease among older people with type 2 diabetes mellitus during the first 3 years of use. Whether using pioglitazone for >3 years would

have primary prevention for ischemic cerebrovascular disease needs a long-term research to prove.

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