Real-World Database Examining the Association Between Avascular Necrosis of the Femoral Head and Diabetes in Taiwan

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OBJECTIVE

No study has been conducted to evaluate the association between avascular necrosis of the femoral head and diabetes. This study's aim was to assess this issue in Taiwan.

RESEARCH DESIGN AND METHODS

A population-based cohort study was performed to analyze the database of Taiwan's National Health Insurance Program. There were 27,869 subjects aged 20–84 years with newly diagnosed diabetes from 2000 to 2012 as the group with diabetes. The group without diabetes included 111,476 sex- and age-matched subjects without diabetes. The incidence of avascular necrosis of the femoral head at the end of 2013 was measured. A multivariable Cox proportional hazards regression model was used to measure the hazard ratio (HR) and 95% CI for avascular necrosis of the femoral head associated with diabetes.

RESULTS

The overall incidence of avascular necrosis of the femoral head was 1.37-fold higher in the group with diabetes than in the group without diabetes (6.53 vs. 4.76 per 1,000 person-years [95% CI 1.31–1.43]). After adjusting for confounders, the HR of avascular necrosis of the femoral head was 1.16 (95% CI 1.11–1.21) for the subjects with diabetes compared with the subjects without diabetes.

CONCLUSIONS

Patients with diabetes have a 1.16-fold increased risk for developing avascular necrosis of the femoral head.

Avascular necrosis of the femoral head is an important clinical issue. It is a debilitating complication resulting from the vascular compromise of the femoral head, which leads to the death of bone cells, femoral head collapse, irreversible destruction of the hip joint, and eventually total hip arthroplasty (1,2). Microvascular and macrovascular complications of diabetes have been well established (3,4), but an association between avascular necrosis of the femoral head and diabetes has not been previously described. To address this issue, a population-based retrospective cohort study was performed to analyze the database of Taiwan's National Health Insurance Program.

RESEARCH DESIGN AND METHODS

Study Design and Data Source

A population-based retrospective cohort study was performed to analyze the database of Taiwan's National Health Insurance Program. The program was launched

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on 1 March 1995, and it covers ~99.6% of the 23 million people living in the independent country of Taiwan (5,6). The program details have been documented in previous studies (7,8).

Ethics Statement

Insurance reimbursement claims data used in this study are available for public access. Patient identification numbers have been scrambled to ensure confidentiality. Patient informed consent is not required. This study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115).

Study Subjects

Subjects aged 20–84 years with newly diagnosed diabetes from 2000 to 2012 were selected as the group with diabetes (ICD-9, Clinical Modification, code 250). The date for diagnosing diabetes was defined as the index date. For every subject with diabetes, four sex-matched and age-matched subjects without diabetes were selected as the group without diabetes. The groups with and without diabetes were matched for sex, age (every 5-year interval), and the year of the index date.

Major Outcome

The groups with and without diabetes were followed until a new diagnosis of avascular necrosis of the femoral head was made or until the end of 2013, whichever came first.

Comorbidities Studied

Comorbidities before the index date were selected as follows: alcohol-related disease, cardiovascular disease (including coronary artery disease, heart failure, cerebrovascular disease, and peripheral atherosclerosis), chronic kidney disease, chronic obstructive pulmonary disease, hyperlipidemia, hypertension, hip fracture, thalassemia, and oral corticosteroid use. All comorbidities were diagnosed based on ICD-9 codes, which have been well assessed in previous studies (9–11).

Statistical Analysis

Demographic characteristics and the prevalence of comorbidities were compared between the groups with and without diabetes. The categorical variables were analyzed by using a χ^2 test, and the continuous variables of the baseline characteristics of the groups with and without diabetes were analyzed by using a Student *t* test. We assessed the overall, sex-specific, and age-specific incidences of avascular necrosis of the femoral head for the groups with and without diabetes. Univariable Poisson regression models were performed to estimate the incidence rate ratios (IRRs) and 95% CI of developing avascular necrosis of the femoral head associated with diabetes, as compared with the group without diabetes. Univariable and multivariable Cox proportional hazards regression models were used to assess the risk of avascular necrosis of the femoral head associated with diabetes, and the hazard ratio (HR) and the 95% CI were estimated. A multivariable model was performed by controlling for sex, age, alcohol-related disease, cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, hyperlipidemia, hypertension, hip fracture, thalassemia, and oral corticosteroid use. We executed all data analyses by using SAS, version 9.4 (SAS Institute, Inc., Cary, NC). The level of significance was set to $P < 0.05$, and the tests were two tailed.

RESULTS

Baseline Characteristics of the Study Population

Table 1 demonstrates the distributions of sex, age, and comorbidities between the two groups. There were 27,869 subjects in the group with diabetes and 111,476 subjects in the group without diabetes. Males constituted a higher proportion in both the group with diabetes and the group without diabetes (55%). The mean ages (SD) of the study subjects were 58.7 years (12.7) in the group with diabetes and 57.8 years (13.1) in the group without diabetes (Student *t* test, $P < 0.001$). The proportions of alcohol-related disease, cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, hyperlipidemia, hypertension, hip fracture, and oral corticosteroid use were significantly higher in the group with diabetes than the group without diabetes (χ^2 test, $P < 0.05$ for all).

Incidences of Avascular Necrosis of the Femoral Head

Table 2 demonstrates that the overall incidence of avascular necrosis of the femoral head was 1.37-fold higher in the group with diabetes than in the group without diabetes at the end of the follow-up (6.53 vs. 4.76 per 1,000 person-years [95% CI 1.31–1.43]). The incidences of avascular necrosis of the femoral head, when stratified by sex and age, were significantly higher in the group with diabetes than in the group without diabetes, except in the age-group 65–84 years old. The male group with diabetes had the highest incidence (7.89 per 1,000 person-years).

Figure 1 demonstrates that the group with diabetes had a higher cumulative incidence of avascular necrosis of the femoral head than the group without diabetes at the end of follow-up ($P < 0.001$).

The HR of Avascular Necrosis of the Femoral Head Associated With Diabetes and Comorbidities

After adjusting for confounding factors, the HR of avascular necrosis of the femoral head was 1.16 for the subjects with diabetes (95% CI 1.11–1.21), compared with the subjects without diabetes (Table 3). In addition, sex, age, alcohol-related disease, cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, hyperlipidemia, hypertension, hip fracture, thalassemia, and oral corticosteroid use were other factors significantly associated with avascular necrosis of the femoral head.

CONCLUSIONS

To date, there are numerous risk factors that have been identified to be associated with avascular necrosis of the femoral head, including trauma, alcohol consumption, and corticosteroid therapy (12,13). Association between avascular necrosis of the femoral head and diabetes has not yet been described, as not enough studies have been conducted that could be compared with each other on the association of avascular necrosis of the femoral head with diabetes. In our study, subjects with diabetes had a 1.16-fold increased hazard of avascular necrosis of the femoral head compared with subjects without diabetes (Table 3). We observed that the risk of avascular necrosis of the femoral head substantially persisted over time after a diagnosis of diabetes (Fig. 1). Since avascular necrosis of the femoral head is predominantly a result of a compromised blood supply to the femoral head, these findings add to

Table 1—Baseline information between groups with and without diabetes

	Without diabetes (n = 111,476)		With diabetes (n = 27,869)		
Variable	n	%	n	%	P value*
Sex					0.99
Female	50,052	44.9	12,513	44.9	
Male	61,424	55.1	15,356	55.1	
Age-group (years)					0.99
20–39	28,508	25.5	7,127	25.5	
40–64	45,092	40.5	11,273	40.5	
65–84	37,876	34.0	9,469	34.0	
Age (years), mean ± SD†	57.8 ± 13.1		58.7 ± 12.7		<0.001
Baseline comorbidities					
Alcohol-related disease	3,056	2.74	1,568	5.63	<0.001
Cardiovascular disease	25,598	23.0	10,500	37.8	<0.001
Chronic kidney disease	4,140	3.71	1,551	5.57	<0.001
Chronic obstructive pulmonary disease	18,174	16.3	5,641	20.2	<0.001
Hyperlipidemia	21,099	18.9	11,964	42.9	<0.001
Hypertension	38,388	34.4	17,215	61.8	<0.001
Hip fracture	855	0.77	259	0.93	0.01
Thalassemia	312	0.28	80	0.29	0.84
Oral corticosteroid use	73,046	65.5	19,829	71.2	<0.001

*χ^2 test comparing subjects with and without diabetes. †Student t test comparing subjects with and without diabetes.

the list of vascular pathology resulting from the diabetic disease process.

Although the pathogenesis on the increased risk of avascular necrosis of the femoral head associated with diabetes was not our focus, we can make a rational hypothesis that the vascular compromise of the femoral head associated with vascular complications of diabetes is involved, which subsequently leads to avascular necrosis of the femoral head (14).

Some limitations should be mentioned. First, due to the natural limitation of the database used, information on alcohol consumption, cigarette smoking, and BMI was not recorded in the database. To address the first two, alcohol-related disease was included instead of alcohol consumption, and chronic obstructive pulmonary disease was included instead of cigarette smoking. These points have been documented in previous studies (10,15). However, the impact of the third, BMI, on our data could not be addressed. Next, due to the same limitation, information regarding trauma history was not recorded in the database. We cannot know what percentage of trauma history was detected before the diagnosis of avascular necrosis of the femoral head. A subanalysis demonstrated that among 146 events of avascular necrosis of the femoral head in the group with diabetes, five cases (3.4%) involved hip fractures before the diagnosis of avascular necrosis of the femoral head. We cannot be sure whether there is a direct link between hip fracture and avascular necrosis of the femoral head in these subjects. Third, due to the same limitation, the information on hemoglobin A_{1c} was not recorded in the database. We cannot know whether there is an association between avascular necrosis of the femoral head and hemoglobin A_{1c} levels. A subanalysis demonstrated that among the group with diabetes, subjects receiving antidiabetic medications were associated with a decreased hazard of avascular necrosis of the femoral head compared with those subjects not receiving antidiabetic medications (adjusted HR 0.25 [95% CI 0.13–0.48]). Additional data are required for confirmation that good glycemic control could be beneficial for the prevention of avascular necrosis of the femoral head. Fourth, sickle cell disease is not commonly found in Taiwan. We did not include it for adjustment, but we included thalassemia for adjustment. Fifth, a subanalysis demonstrated that among the age-group 65–84 years old, 50.5% of subjects with diabetes had ever taken aspirin, compared with 38.8% of subjects without diabetes. We speculate that the antiplatelet effect of aspirin at least partially contributes to the lower incidence of avascular necrosis of the femoral head for subjects with diabetes aged 65–84 years (4.36 vs. 6.13 per 1,000 person-years) (Table 2). Because no other studies could be compared with each other, further real-world data are needed to clarify this issue.

Despite the above limitations, some special strengths should be mentioned. To the best of our knowledge, this is

Table 2—Incidences of avascular necrosis of the femoral head stratified by sex and age between groups with and without diabetes

	Without diabetes				With diabetes					
Variable	n	Event	Person-years	Incidence†	n	Event	Person-years	Incidence†	IRR#	95% CI
All	111,476	451	947,209	4.76	27,869	146	223,573	6.53	1.37	1.31–1.43
Sex										
Female	50,052	188	446,238	4.21	12,513	53	105,641	5.02	1.19	1.11–1.27
Male	61,424	263	500,971	5.25	15,356	93	117,932	7.89	1.50	1.42–1.59
Age-group (years)										
20–39	28,508	80	252,304	3.17	7,127	44	59,803	7.36	2.32	2.15–2.51
40–64	45,092	190	399,584	4.75	11,273	72	94,939	7.58	1.59	1.49–1.70
65–84	37,876	181	295,321	6.13	9,469	30	68,831	4.36	0.71	0.65–0.78

†Per 1,000 person-years. #With diabetes vs. without diabetes.

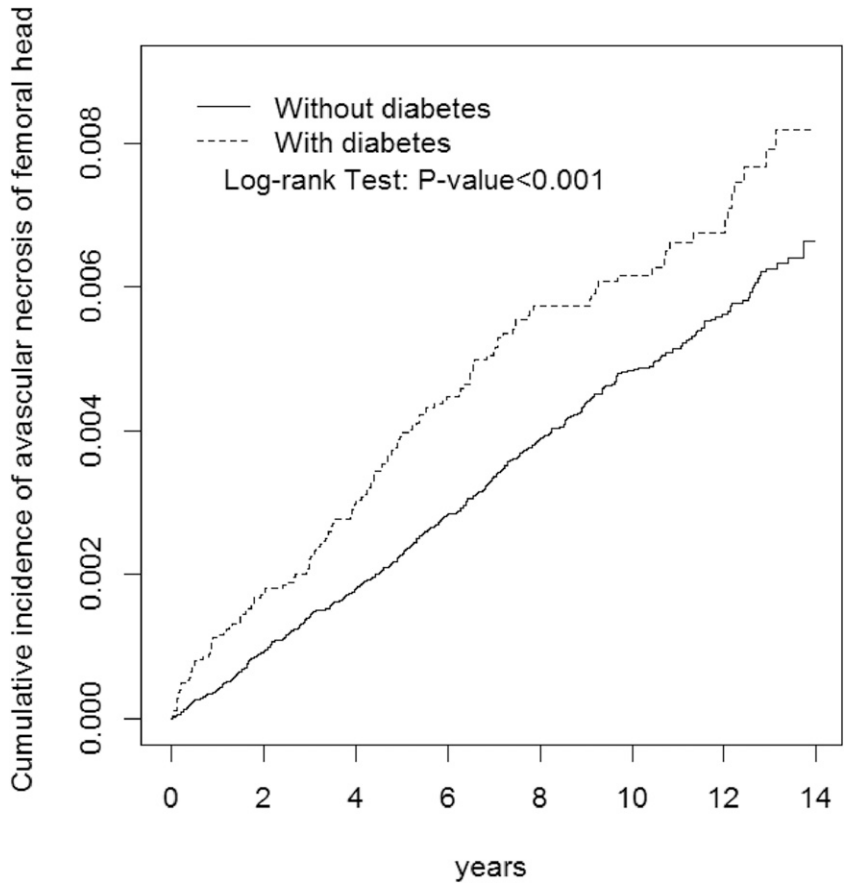

Figure 1—Kaplan-Meier model demonstrates that the group with diabetes had a higher cumulative incidence of avascular necrosis of the femoral head than the group without diabetes at the end of follow-up ($P < 0.001$).

the first population-based cohort study to investigate the association between avascular necrosis of the femoral head and diabetes in Taiwan. It is an interesting study based on a national health insurance database with a large number of subjects with diabetes and a good statistical power. This study adds updated evidence to the literature on the complications of diabetes.

Table 3—HR and 95% CI of avascular necrosis of the femoral head associated with diabetes and comorbidities

	Crude		Adjusted†	
Variable	HR	95% CI	HR	95% CI
Sex (male vs. female)	1.31	1.12–1.55	1.30	1.25–1.35
Age (every 1 year)	1.01	1.004–1.02	1.01	1.003–1.01
Diabetes (yes vs. no)	1.37	1.14–1.65	1.16	1.11–1.21
Baseline comorbidities (yes vs. no)				
Alcohol-related disease	4.54	3.46–5.94	3.80	3.56–4.05
Cardiovascular disease	1.53	1.28–1.81	1.11	1.06–1.17
Chronic kidney disease	1.67	1.18–2.37	1.24	1.14–1.35
Chronic obstructive pulmonary disease	1.58	1.30–1.92	1.18	1.13–1.24
Hyperlipidemia	1.39	1.17–1.66	1.11	1.06–1.16
Hypertension	1.49	1.27–1.75	1.17	1.12–1.22
Hip fracture	4.96	3.02–8.15	4.21	3.75–4.73
Thalassemia	2.35	0.76–7.29	2.08	1.60–2.70
Oral corticosteroid use	1.50	1.25–1.80	1.34	1.28–1.39

†Adjusting for sex, age, alcohol-related disease, cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, hyperlipidemia, hypertension, hip fracture, thalassemia, and oral corticosteroid use.

We conclude that patients with diabetes have a 1.16-fold increased risk for developing avascular necrosis of the femoral head. We suggest that other real-world studies are needed to clarify whether avascular necrosis of the femoral head is a microvascular or macrovascular complication of diabetes, as well as the effects of glycemic control on this risk.

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