Increased Risk of Fracture and Postfracture Adverse Events in Patients With Diabetes: Two Nationwide Population-Based Retrospective Cohort Studies

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

The relationship between diabetes and fracture is not completely understood. This study evaluated fracture risk and postfracture mortality in patients with diabetes.

RESEARCH DESIGN AND METHODS

We identified 32,471 adults newly diagnosed with diabetes in 2000–2003 using Taiwan's National Health Insurance Research Database. A comparison cohort of 64,942 adults without diabetes was randomly selected from the same dataset, with frequency matched by age and sex. Fracture events in 2000–2008 were ascertained from medical claims. Adjusted hazard ratios (HRs) and 95% CIs of fracture associated with diabetes were calculated. A nested cohort study of 17,002 patients with fracture receiving repair surgeries between 2004 and 2010 calculated adjusted odds ratios (ORs) and 95% CIs of adverse events after fracture in patients with and without diabetes.

RESULTS

During 652,530 person-years of follow-up, there were 12,772 newly diagnosed fracture cases. The incidences of fracture for people with diabetes and without were 24.2 and 17.1 per 1,000 person-years, respectively ($P < 0.0001$). Compared with people without diabetes, the adjusted HR of fracture was 1.66 (95% CI 1.60–1.72) for people with diabetes. The ORs of postfracture deep wound infection, septicemia, and mortality associated with diabetes were 1.34 (95% CI 1.06–1.71), 1.42 (95% CI 1.23–1.64), and 1.27 (95% CI 1.02–1.60), respectively.

CONCLUSIONS

Diabetes was associated with fracture. Patients with diabetes had more adverse events and subsequent mortality after fracture. Prevention of fracture and postfracture adverse events is needed in this susceptible population.

Although the epidemiology, pathogenesis, prevention, and treatment of diabetes have been well established over the past two centuries (1), diabetes remains a pandemic chronic disease that is projected to reach an estimated global prevalence of 4.4% by 2030 (2). Diabetes also presents a high economic burden, with an estimated cost of 245 billion USD in 2012 in the U.S. (3). Recognized complications

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of diabetes include cardiovascular and cerebrovascular disease, peripheral vascular disease, renal dysfunction, and microvascular disease (1).

Fracture is one of the major causes of disability and mortality (4). For example, in the U.S. in 2005, more than two million fracture incidents cost an estimated 17 billion USD (5). Osteoporosis (defined as bone mineral density 2.5 SD or more below the average value for premenopausal women) is considered an important contributor to fracture (6) and has been investigated as a comorbidity in diabetic patients (7). Many epidemiological studies document that patients with diabetes had increased risk of fracture (8–27). However, these previous reports were limited by several factors, including a focus on specific populations (8–20), small samples of diabetic patients (11–14,20–22,27), case-control study design (13,21–23), inadequate adjustment for potential confounders (13,14,16–22,24,27), and reporting only a single type of fracture (10,13,16,21,25,26). The impact of diabetes on postfracture outcomes also remains unknown.

We used Taiwan's National Health Insurance reimbursement claims to investigate the incidence and risk of fracture after adjustment for potential confounding factors for adults with diabetes in a nationwide retrospective cohort study. More importantly, we conducted a nested cohort study to investigate the impact of diabetes on postfracture outcomes.

RESEARCH DESIGN AND METHODS

Source of Data

Taiwan's National Health Insurance system has registered all medical claims since 1996, and this database is available to researchers with identification numbers of those insured scrambled to protect patient privacy. Sets of information available for this study include sex, birth dates, diagnoses, health care received, medications prescribed, admissions, discharges, medical institutions, and physicians providing services. For research and administrative purposes, Taiwan's National Health Research Institute has released a data subset of claims data for one million randomly selected insurance enrollees aged 0–113 years in 2005. This random subgroup represents ~5% of Taiwan's insured population. Information about medical care for these persons was collected between 1996 and 2008 (28–30).

Ethics Approval

Insurance reimbursement claims used in this study were from Taiwan's National Health Insurance Research Database. For protection of personal privacy, the electronic database was decoded with patient identifications scrambled for further public access for research. This study was evaluated and approved by Taiwan's National Health Research Institutes; this organization's regulations do not require informed consent because patient identification has been decoded and scrambled (28–30). This study was conducted in accordance with the Declaration of Helsinki.

Study Design

In this longitudinal cohort of one million insured individuals, we identified as the exposed cohort 32,471 patients age 20 years or older with new diagnosis of diabetes between 2000 and 2003 (without any previous record of diagnosis or treatment for diabetes from the database since 1996) and without a history of fracture before the index date. Previous studies (28,30) considered patients with diabetes as those who had made two visits for outpatient diabetes care. For identification of patients with diabetes more strictly, this study required at least three visits (attributable to diabetes or related complications) for outpatient or inpatient medical services with a principal diagnosis of diabetes within the preoperative 24-month period. During the same index period, we identified 64,942 people age 20 years or older matched by age and sex who had no diabetes diagnosis and no history of fracture before the index date as the

Table 1—Sociodemographic factors, coexisting medical conditions, and fracture in people with and without diabetes

	No diabetes (*N* = 64,942)		Diabetes (*N* = 32,471)		
	n	%	*n*	%	*P*
Sex					1.00
Female	33,112	51.0	16,556	51.0	
Male	31,830	49.0	15,915	49.0	
Age, years					1.00
20–29	1,152	1.8	576	1.8	
30–39	4,258	6.6	2,129	6.6	
40–49	13,066	20.1	6,533	20.1	
50–59	17,192	26.5	8,596	26.5	
60–69	17,414	26.8	8,707	26.8	
≥70	11,860	18.3	5,930	18.3	
Urbanization					0.0009
Low	16,701	25.7	8,570	26.4	
Moderate	15,471	23.8	7,851	24.2	
High	15,977	24.6	8,028	24.7	
Very high	16,793	25.9	8,022	24.7	
Low income	1,419	2.2	1,169	3.6	<0.0001
Coexisting medical conditions					
Hypertension	20,449	31.5	16,584	51.1	<0.0001
Mental disorders	15,914	24.5	10,561	32.5	<0.0001
COPD	12,027	18.5	7,715	23.8	<0.0001
Ischemic heart disease	6,913	10.6	7,012	21.6	<0.0001
Hyperlipidemia	4,741	7.3	5,482	16.9	<0.0001
Stroke	3,026	4.7	4,027	12.4	<0.0001
Liver cirrhosis	1,815	2.8	2,628	8.1	<0.0001
Osteoporosis	4,122	6.4	2,386	7.4	<0.0001
Renal dialysis	342	0.5	1,082	3.3	<0.0001
Use of osteoporosis medication					<0.0001
No	63,628	98.0	31,631	97.4	
Yes	1,314	2.0	840	2.6	
Fracture					<0.0001
No	57,710	88.9	26,931	82.9	
Yes	7,232	11.1	5,540	17.1	

COPD, chronic obstructive pulmonary disease.

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nonexposure cohort. Patients with any diagnosis of fracture between 1 January 1996 and 31 December 2003 were excluded to ensure that all study participants were free of fracture at the start of both cohorts. Follow-up started 1 January 2000 and lasted until censoring due to death, loss to follow-up, or other causes by 31 December 2008. We sought to determine whether individuals with diabetes faced an increased risk of fracture.

To investigate the impact of diabetes on postfracture outcomes, a nested retrospective cohort study was conducted. We identified 17,002 hospitalized patients with fracture between 2004 and 2010, including 2,971 patients with prefracture diabetes and 14,031 without diabetes. We compared postfracture septicemia, deep wound infection, pneumonia, urinary tract infection, and mortality for a 30-day period postoperatively between fracture patients with and without prefracture diabetes.

Measures and Definitions

We identified income status by defining low-income patients as those qualifying for waived medical copayment because this status is verified by the Bureau of National Health Insurance. Population density was calculated by dividing the population (persons) by the area (square kilometers) for each administrative unit of Taiwan and then sorting these areas into quartiles of low, moderate, high, and very high urbanization. These categories were used as surrogates for residential urbanization. Use of osteoporosis medications such as alendronate, pamidronate disodium, risedronate sodium, zoledronic acid, and hormone replacement therapy was also noted.

We used codes from the ICD-9-CM to define coexisting medical conditions and postfracture complications. Prefracture diabetes (ICD-9-CM 250) was defined as an exposure. Coexisting medical conditions were determined from medical claims for the follow-up period and included hypertension (ICD-9-CM 401–405), mental disorders (ICD-9-CM 290–319), chronic obstructive pulmonary disease (ICD-9-CM 490–496), ischemic heart disease (ICD-9-CM 410–414), hyperlipidemia (ICD-9-CM 272.0, 272.1, and 272.2), stroke (ICD-9-CM 430–438), liver cirrhosis (ICD-9-CM 571), and osteoporosis (ICD-9-CM 733.0). Renal dialysis was identified by administration code (D8, D9). Fracture is the main outcome of this retrospective cohort study, including skull bone fracture (ICD-9-CM 800–804) and fractures of neck and trunk (ICD-9-CM 805–809), upper limb (ICD-9-CM 810–819), and lower limb (ICD-9-CM 820–829). Complications after fracture were analyzed as secondary outcomes, including septicemia (ICD-9-CM 038 and 998.5), pneumonia (ICD-9-CM 480–486), urinary tract infection (ICD-9-CM 599.0), and deep wound infection (ICD-9-CM 958.3). Postfracture in-hospital mortality was also considered an outcome in the nested cohort study.

Statistical Analysis

Our study used χ^2 tests to compare sociodemographic characteristics and coexisting medical conditions between people with and without diabetes. We calculated the hazard ratios (HRs) with 95% CIs for risk of fracture after diabetes, adjusting for age, sex, low income, urbanization, hypertension, mental disorders, chronic obstructive pulmonary disease, ischemic heart disease, hyperlipidemia, stroke, liver cirrhosis, osteoporosis, and renal dialysis in multivariate Cox proportional hazards regression models. The risk and incidence of fracture among categories of diabetes were determined, and sex- and age-stratified analyses for the adjusted HRs of fracture associated with diabetes were calculated.

In the nested cohort study, the sociodemographics and coexisting medical conditions between fracture patients with and without diabetes were compared by using χ^2 tests. The adjusted odds ratios (ORs) and 95% CIs of postfracture septicemia, deep wound infection, pneumonia, urinary tract infection, and mortality associated with prefracture diabetes were calculated in the multivariate logistic regressions with adjustment for age, sex, low income, urbanization, hypertension, mental disorders, chronic obstructive pulmonary disease, ischemic heart disease, hyperlipidemia, stroke, liver cirrhosis, osteoporosis, and renal dialysis. SAS, version

Table 2—Risk of fracture for cohorts with and without diabetes

	n	Person-years	Fracture events	Incidence*	HR	95% CI
No diabetes	64,942	423,320	7,232	17.1	1.00	Reference
All diabetes†	32,471	229,210	5,540	24.2	1.66	1.60–1.72
Type 1	2,992	22,627	382	16.9	1.22	1.10–1.36
Type 2	29,479	206,583	5,158	25.0	1.70	1.64–1.76
Female‡						
No diabetes	33,112	213,999	4,249	19.9	1.00	Reference
Diabetes	16,556	115,328	3,498	30.3	1.76	1.68–1.85
Male‡						
No diabetes	31,830	209,321	2,983	14.3	1.00	Reference
Diabetes	15,915	113,882	2,042	17.9	1.52	1.43–1.61
20–39 years§						
No diabetes	5,410	36,717	314	8.9	1.00	Reference
Diabetes	2,705	19,240	255	13.3	1.70	1.43–2.03
40–49 years§						
No diabetes	13,066	87,620	928	10.6	1.00	Reference
Diabetes	6,533	47,046	790	16.8	1.86	1.68–2.06
50–59 years§						
No diabetes	17,192	112,343	1,695	15.1	1.00	Reference
Diabetes	8,596	60,900	1,381	22.7	1.77	1.64–1.91
60–69 years§						
No diabetes	17,414	113,549	2,086	18.4	1.00	Reference
Diabetes	8,707	62,138	1,664	26.8	1.74	1.62–1.86
≥70 years§						
No diabetes	11,860	73,090	2,209	30.2	1.00	Reference
Diabetes	5,930	39,886	1,450	36.4	1.41	1.32–1.51

*Per 1,000 person-years. †Adjusted for age, sex, urbanization, low income, coexisting medical conditions, and use of osteoporosis medication. ‡Adjusted for age, urbanization, low income, coexisting medical conditions, and use of osteoporosis medication. §Adjusted for sex, urbanization, low income, coexisting medical conditions, and use of osteoporosis medication.

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9.1 (SAS Institute, Inc., Cary, NC), statistical software was used for data analyses; two-sided $P < 0.05$ indicated significant differences between groups.

RESULTS

After the frequency matching by age and sex between cohorts with and without diabetes, there were no significant differences in age and sex (Table 1). Compared with the cohort without diabetes, patients with diabetes had higher proportions of living in the least urbanized areas ($P < 0.0001$) and of having low-income status ($P < 0.0001$), hypertension ($P < 0.0001$), mental disorders ($P < 0.0001$), osteoporosis ($P < 0.0001$), chronic obstructive pulmonary disease ($P < 0.0001$), ischemic heart disease ($P < 0.0001$), hyperlipidemia ($P < 0.0001$), stroke ($P < 0.0001$), liver cirrhosis ($P < 0.0001$), renal dialysis ($P < 0.0001$), and use of osteoporosis medication ($P < 0.0001$).

Table 2 shows that higher incidence of fracture was found in patients with diabetes than those without diabetes (24.2 vs. 17.1 per 1,000 person-years, $P < 0.0001$) during the follow-up period; the corresponding HR of fracture associated with diabetes was 1.66 (95% CI 1.60–1.72). The association between diabetes and fracture risk was more significant in females (HR 1.76 [95% CI 1.68–1.85]) than in males (HR 1.52 [95% CI 1.43–1.61]). Patients with diabetes were at greater risk of fracture in all age-groups.

Among 17,002 patients with fracture receiving related surgeries (Table 3), higher proportions of diabetic patients than patients without diabetes were noted among females, older people, those living in the least urbanized areas, and those with low income, hypertension, hyperlipidemia, liver cirrhosis, renal dialysis, mental disorders, ischemic heart disease, stroke, chronic obstructive pulmonary disease, and use of osteoporosis medication. In the nested retrospective cohort study (Table 4), patients with diabetes had higher risk of mortality (OR 1.27 [95% CI 1.02–1.60]), septicemia (OR 1.42 [95% CI 1.23–1.64]), deep wound infection (OR 1.34 [95% CI 1.06–1.71]), and urinary tract infection (OR 1.48 [95% CI 1.33–1.64]) after fracture with surgeries compared with those without diabetes. Postfracture mortality was associated with several characteristics of diabetes: diabetes-related hospitalization (OR 1.58 [95% CI 1.23–2.03]), ketoacidosis (OR 3.03 [95% CI 1.45–6.31]), renal manifestations (OR 1.87 [95% CI 1.32–2.64]), eye involvement (OR 1.79 [95% CI 1.27–2.52]), and peripheral circulatory disorder (OR 1.65 [95% CI 1.00–2.70]). Among patients with diabetes, inadequate control for diabetes (OR 1.61 [95% CI 1.11–2.34]) and type 1 diabetes (OR 1.93 [95% CI 1.14–3.26]) were independent risk factors for postfracture mortality.

Table 3—Characteristics of fracture patients at admission with and without diabetes

	No diabetes (N = 14,031)		Diabetes (N = 2,971)		
	n	%	*n*	%	*P*
Sex					<0.0001
Female	6,183	44.1	1,793	60.4	
Male	7,848	55.9	1,178	39.6	
Age, years					<0.0001
20–29	2,231	15.9	25	0.8	
30–39	2,042	14.6	70	2.4	
40–49	2,466	17.6	218	7.3	
50–59	2,372	16.9	538	18.1	
60–69	1,632	11.6	669	22.5	
≥70	3,288	23.4	1,451	48.8	
Urbanization					<0.0001
Low	3,504	25.0	982	33.1	
Moderate	3,479	24.8	693	23.3	
High	3,492	24.9	637	21.4	
Very high	3,556	25.3	659	22.2	
Low income					0.0005
No	13,502	96.2	2,818	94.9	
Yes	529	3.8	153	5.1	
Coexisting medical conditions					
Hypertension	3,348	23.9	1,668	56.1	<0.0001
Hyperlipidemia	781	5.6	434	14.6	<0.0001
Liver cirrhosis	491	3.5	233	7.8	<0.0001
Renal dialysis	92	0.7	82	2.8	<0.0001
Mental disorders	3,677	26.2	1,195	40.2	<0.0001
Ischemic heart disease	1,274	9.1	711	23.9	<0.0001
Stroke	707	5.0	454	15.3	<0.0001
COPD	2,370	16.9	835	28.1	<0.0001
Use of osteoporosis medication					<0.0001
No	13,372	95.3	2,685	90.4	
Yes	659	4.7	286	9.6	

COPD, chronic obstructive pulmonary disease.

CONCLUSIONS

This nationwide retrospective cohort study based on Taiwan National Health Insurance claims data analyzed long-term risk of all types of fracture in patients with diabetes during the follow-up period, with significant findings in women and elderly patients. Another nested cohort study in patients with diabetes showed increased rates of septicemia, deep wound infection, urinary tract infection, and postfracture mortality in patients receiving surgeries. Postfracture mortality was associated with ketoacidosis, renal manifestations, eye involvement, and peripheral circulatory disorder, which are all diabetes-related comorbidities. Large sample size, cohort study design, multivariate adjustment, including all types of fracture, and not being restricted by specific populations are strengths of this investigation.

Older age (11,19,25), female sex (19,25), low income (31), and urbanization (31) have been recognized as risk factors for fracture; these sociodemographic factors have also been associated with diabetes (29). These four factors were considered potential confounding factors in the association between diabetes and fracture. To investigate risk and outcomes of fracture in diabetic patients, we adjusted these sociodemographic characteristics in the multivariate regression models.

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Table 4—Risks of in-hospital complications and mortality during fracture admission for patients with diabetes

				Risk of outcome	
	n	Events	Incidence (%)	OR	95% CI*
Risk of postfracture septicemia					
No diabetes	14,031	837	5.97	1.00	Reference
Diabetes	2,971	376	12.66	1.42	1.23–1.64
Risk of postfracture deep wound infection					
No diabetes	14,031	389	2.77	1.00	Reference
Diabetes	2,971	101	3.40	1.34	1.06–1.71
Risk of postfracture pneumonia					
No diabetes	14,031	1,027	7.32	1.00	Reference
Diabetes	2,971	407	13.70	1.13	0.98–1.29
Risk of postfracture UTI					
No diabetes	14,031	1,776	12.66	1.00	Reference
Diabetes	2,971	813	27.36	1.48	1.33–1.64
Risk of postfracture mortality					
No diabetes	14,031	294	2.10	1.00	Reference
Diabetes	2,971	134	4.51	1.27	1.02–1.60
Diabetic patients with					
Hospitalization for diabetes	1,760	102	5.80	1.58	1.23–2.03
Inadequate control of diabetes	624	37	5.93	1.61	1.11–2.34
Diabetes-related PCD	318	19	5.97	1.65	1.00–2.70
Diabetes-related eye involvement	706	46	6.52	1.79	1.27–2.52
Diabetes-related renal manifestations	616	48	7.79	1.87	1.32–2.64
Diabetes-related ketoacidosis	101	9	8.91	3.03	1.45–6.31
Diabetes-related coma	101	10	9.90	1.88	0.93–3.81
Categories of diabetes					
Type 1 diabetes	225	18	8.00	1.93	1.14–3.26
Type 2 diabetes	2,746	116	4.22	1.21	0.96–1.53

PCD, peripheral circulatory disorder; UTI, urinary tract infection. *Adjusted for age, sex, teaching hospital, low income, urbanization, coexisting medical conditions, and use of osteoporosis medication.

That osteoporosis is a risk factor for fracture has been noted in both general populations and diabetic patients (5–7,20). Hypertension (32), mental disorders (33), COPD (34,35), ischemic heart disease (34,35), hyperlipidemia (36), stroke (34), liver cirrhosis (35), and renal failure (35) have been shown to be independently associated with higher risk of fracture. These conditions commonly coexist with diabetes (29). However, previous studies were limited by inadequate control of coexisting medical conditions when investigating the association between diabetes and fracture risk (13,14,16–22,24). The current study found that fracture risk increased in patients with diabetes after adjustment for these potential confounding factors.

A cohort study based on a small sample reported that diabetic patients had higher perioperative adverse events after fracture than people without diabetes; these events were cardiac diseases, urinary tract infection, gastrointestinal symptoms, and prolonged length of hospital stay (27). However, this previous study was limited because it did not control confounding factors. Although previous studies have reported that diabetic patients had increased fracture risk (8–27), the current study is the first investigation suggesting that patients with diabetes have increased risks of postfracture septicemia, deep wound infection, and urinary tract infection after multivariate adjustment for sociodemographics and coexisting medical conditions. Adverse outcomes after noncardiac surgeries in diabetic patients were noted in our previous study (29).

In the present nested cohort study, type 1 diabetes, prefracture inpatient care for diabetes, inadequate control of glucose, diabetes-related ketoacidosis, coma, renal manifestations, eye involvement, and peripheral circulatory disorder were severity-related clinical predictors of postfracture mortality in diabetic patients. These interesting findings have not been reported previously, though previous investigations have studied the crude association between diabetes and fracture (8–27).

Possible explanations for the association between diabetes and fracture risk include altered bone mineral density and subsequent osteoporosis in diabetic patients. The strong correlation between poor bone mineral density and fracture suggested that losing bone mineral density may be one cause of diabetic patients suffering fracture (6,7). A second possible explanation is that the rapid rise in incidence of obesity and type 2 diabetes in all age-groups might result in substantial increases in prevalence of diabetes-related cognitive dysfunction (37) or mental illness that were identified as risk factors for fracture. Third, people with diabetes-related eye involvement such as cataract, glaucoma, and retinopathy have been found to be more likely to have fracture (38). Inadequate control for glucose resulting in hypoglycemic coma is another possible explanation for increased fracture risk in patients with diabetes (39).

This study has some limitations: First, we used insurance claims data that lacked information on sociodemographics, lifestyle, hormonal status, fasting glucose, glycated hemoglobin, and other biomedical measures. A second limitation is possible underreporting from use of records from reimbursement claims for coexisting medical conditions. Such cases could include patients with prediabetes (patients with impaired fasting glucose [100–125 mg/dL] or HbA_{1c} [5.7–6.4%]) (40), those who received medical services fewer than three times within the preoperative 24-month period, and those who did not receive hypoglycemic medication. Such underreporting might also be a factor due to patients with minor fractures, such as those who neglected to seek care for or did not know that they experienced fractures. However, these data should be distributed equally between both groups without causing bias in the results. Third, though the accuracy of major diagnosis codes from the research database in studies based on these has been accepted by peer reviewers for prominent scientific journals worldwide (28–30), validity of diabetes, fracture, and other comorbidities and complications codes might still be a limitation of this study. Future research is needed

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that includes prospective design and clinical measures, lifestyle information, and detailed severity of diabetes as covariates in multivariate analyses.

In conclusion, this detailed analysis showed that diabetes is an important independent risk factor for fracture and postfracture adverse events. Poorly controlled diabetes, type 1 diabetes, and diabetes-related complications contributed to mortality after fracture with repair surgeries. This study provides comprehensive assessment of fracture risk and postfracture outcomes in patients with diabetes. Further studies are needed to develop specific strategies to decrease fracture risks and postfracture adverse outcomes for this challenging patient population.

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