Increased Risks of Hip Fracture in Diabetic Patients of Taiwan

A population-based study

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OBJECTIVE — Using Taiwan's National Health Insurance claim data, we evaluated the age-, sex-, and urbanization-specific incidence density and relative risks of hip fracture in the diabetic population.

RESEARCH DESIGN AND METHODS — Diabetic patients (n = 500,868) and an age- and sex-matched control group (n = 500,248) were linked to inpatient claims (1997–2002) to identify hospitalizations for nontransport accident hip fracture. The person-year approach with Poisson assumption and Kaplan-Meier analysis were used to estimate the incidence and the cumulative event rates. We also assessed the age-, sex-, and urbanization-specific relative risks of hip fracture in relation to diabetes with the Cox proportional hazard regression model.

RESULTS — The overall incidences of hip fracture for diabetic men and women, respectively, were 3.01 and 6.75/1,000 person-years, which were higher than those for control men and women. There were significant interactions of diabetes and age and diabetes and urbanization statuses. Hazard ratios (HRs) of diabetic patients aged 35–44 years (men 2.45 [95% CI 1.65–3.64]; women 3.19 [1.39–7.33]) were higher than those of diabetic patients aged 55–64 years (men 1.90; women 2.81), but in diabetic men aged >74 years and diabetic women aged >84 years, the HRs were compared with null statistically (HRs 0.98 and 0.91, respectively). Diabetic patients living in rural areas tended to have higher HRs of hip fracture.

CONCLUSIONS — In Taiwan, diabetes increased the risk of hip fracture in both sexes in all age-groups except in diabetic men aged >74 years and diabetic women aged >84 years. Higher HRs of hip fracture were disproportionately observed in younger diabetic patients and in those living in rural areas.

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The incidence of hip fracture is expected to increase worldwide (1), and subsequent functional disability, morbidity, and mortality contribute tremendous health problems to our society. Diabetic patients, who have already been crippled by various microvascular and macrovascular complications, were reported to have increased risks of hip fracture (2–10). Much of the previous research, however, focused on women (4,5,8) or on older patients aged >65 years (4,9) so that relatively few data were available for specific risks in various age-groups and sex groups. Nearly all published studies were conducted in whites (10), and little information is available for Asian diabetic populations. Moreover, a recent study indicated that the relative risk of macrovascular disease associated with diabetes showed a significant geographic variation in Taiwan, implying a differential quality of care delivered to the diabetic patients in certain areas (11). No study so far has been conducted to investigate whether there is an urban-rural difference in incidence and relative risk of hip fracture in diabetic patients. In Taiwan, the high incidence (12) of hip fracture in the general population was reported previously, but the incidence of hip fracture among diabetic patients has yet to be investigated. Using a nationally representative diabetic cohort retrieved from the National Health Insurance (NHI) database, in this study we aimed to investigate age-, sex-, and urban area–specific effects of diabetes on the incidence and relative risks of hip fracture between 1997 and 2002 among the nonselected diabetic population in Taiwan.

RESEARCH DESIGN AND METHODS

— This was a registry-based cohort study, conducted between 1997 and 2002, of hip fracture among the diabetic population in Taiwan. Data were obtained from the NHI database, which has been routinely collected by the National Health Research Institutes and is supervised by the state-run Bureau of NHI (BNHI). The NHI program is a universal health program in Taiwan implemented in March 1995. Some 96% of the Taiwanese population were enrolled in the NHI program, and the BNHI had contracted with 97% of hospitals and clinics throughout the nation by the end of 1996 (13). To ensure the accuracy of the claim data, the BNHI performs expert reviews on a random sample of every 50 to 100 ambulatory and inpatient claims in each hospital and clinic quarterly, and false reports of diagnosis generate a severe penalty from the BNHI (14). With ethical approval from the National Health Research Institutes, we used data for diabetic ambulatory care claims (1997–2002), all inpatient claims (1997–2002), and the updated registry for beneficiaries (1995–2002) for this study. The entire dataset can be interlinked through each individual's personal identification number.

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Abbreviations: BNHI, Bureau of National Health Insurance; NHI, National Health Insurance; PAR%, population attributable risk percentage.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

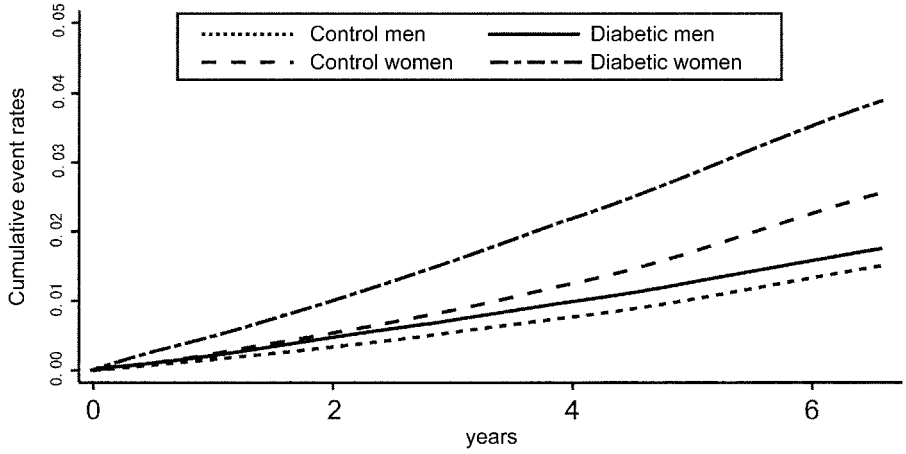

Figure 1—*Kaplan-Meier survival curves for nontransport accident hip fracture in diabetic and control groups.*

Details of the claim data and methods of selection of diabetic and control groups were described in our previous reports (15,16). Briefly, an individual was classified as a diabetic patient if he or she had an initial diabetes-related diagnosis (ICD-9 250 or A code 181) at any time in 1997 and had another one or more diagnoses within the subsequent 12 months. The first and last outpatient visits within 1 year had to be >30 days apart to avoid accidental inclusion of miscoded patients. The final diabetic cohort consisted of 500,868 patients, and the index date was set to be the date of their first outpatient visit with a diabetic code in 1997.

The 500,248 control subjects were identified from the registry of beneficiaries after deleting the data for those patients already included in the diabetic group. The control group was selected by matching to the diabetic group on the frequency distributions of both age (every 5 years from 0–105 years) and sex. The pool of control candidates was first stratified according to the predetermined age and sex classification (a total of 42 strata), and then a simple random sampling technique was applied to select control subjects from each stratum. The index date for subjects in the control group was the first date of enrollment in the NHI. If their first date of enrollment was before 1 January 1997, we set the index date as 1 January 1997.

The age of each study subject was calculated by the difference in time between the index date and the date of birth. We grouped the geographic area of each study subject's NHI unit, either the beneficiaries' residential area or the location of their employment, into four geographic areas (North, Central, South, and East) or two levels of urbanization (urban and rural) according to the National Statistics of Regional Standard Classification (17).

Study end points

With the unique personal identification number, we linked study subjects in both diabetic and control groups to inpatient claim records (1997–2002) to identify the first episodes of primary or secondary diagnoses of hip fracture (ICD-9 820) used as the end point of this study. We excluded diagnoses with transport accident (E800–E848) from the outcomes of interest. The date of encountering the clinical end point of interest was the first day of hospitalization. The study period was between 1 January 1997 and 31 December 2002.

Statistical analysis

The age-, sex-, and urbanization level–specific incidence densities of hip fracture were calculated with person-years as the denominator under the Poisson assumption. Nonparametric Kaplan-Meier analysis was used to determine the cumulative event rates of nontransport accident hip fracture according to sex and diabetes over a 6-year follow-up period, and the log-rank test was used to test the difference between the survival curves. The study subjects who died in the hospital for reasons not relevant to the clinical outcomes of interest were considered censored in the survival analysis, and the date of censoring was the date of their deaths. If the study subjects did not encounter in-hospital mortality, the date of censoring was either the date of their last withdrawal from NHI or the date of study termination (i.e., 31 December 2002). To assess the independent effects of diabetes status on the risks of hip fracture, we conducted Cox proportional hazard regression models with age, sex, geographic area, and urbanization status adjusted simultaneously in the model. We adjusted the latter two regional variables because there is a clear urban-rural difference in accessibility to medical care in Taiwan (18). To avoid unnecessary overadjustment of age, which might bias the risk estimation, we used age as a continuous variable in the model. Additionally, by using the 1997 diabetic prevalence rate, we also calculated the overall and age-specific population attributable risk percentage (PAR%) to assess the public health impact of diabetes on fracture. All statistical analyses were performed with SAS (version 9.1; SAS Institute, Cary, NC). A P value < 0.05 was considered statistically significant. Survival curves were depicted with Stata statistical software (release 8.0; Stata, College Station, TX).

RESULTS — The mean ± SD age of the diabetic population was 59.71 ± 12.52 years, and that of the control group was 59.61 ± 12.64 years. Age and sex distributions were equal in both groups. The percentages of people aged <35, 35–44, 45–54, 55–64, 65–74, 75–84, >85 years were 3.04, 8.87, 19.33, 29.41, 29.40, 9.28, and 0.67%, respectively. Female patients were slightly predominant in both groups.

Figure 1 shows the sex-specific Kaplan-Meier survival curves for nontransport accident hip fracture in the diabetic and control groups over a 6-year period. Women were more likely than men to sustain hip fracture irrespective of diabetes status. The 6-year cumulative event rates for diabetic men and women were 1.74% (95% CI 1.68–1.80%) and 3.87% (3.79–3.95%), respectively, whereas those for control men and women were 1.50% (1.44–1.56%) and 2.55% (2.48–2.62%), respectively. The four survival curves were significantly different (P for log-rank test < 0.0001).

There was only one man and two women aged <35 years who sustained hip fracture in the control group; we therefore excluded this age-group for further analyses to avoid unreliable risk estimation. The overall and age- and sex-specific incident densities and relative hazards of hip fracture are presented in Table 1. The overall incidence densities

Table 1—*Overall and age- and sex-specific incidence densities and relative hazards of nontransport accident hip fracture (ICD-9 820) in the diabetic and control groups*

Variables*	Control group			Diabetic group			Adjusted HR (95% CI) in association with diabetic group‡
	No. of patients	No. of events	ID (per 1,000 patient-years) (95% CI)†	No. of patients	No. of events	ID (per 1,000 patient-years) (95% CI)†	
Men (years of age)							
35–44	25,016	33	0.29 (0.19–0.38)	25,012	97	0.71 (0.57–0.86)	2.45 (1.65–3.64)§
45–54	47,115	106	0.47 (0.38–0.56)	47,102	251	0.99 (0.86–1.11)	2.04 (1.63–2.56)§
55–64	63,510	298	1.04 (0.92–1.16)	63,485	656	1.98 (1.83–2.13)	1.90 (1.65–2.18)§
65–74	69,762	1,182	3.47 (3.27–3.67)	69,718	1,530	4.46 (4.23–4.68)	1.28 (1.19–1.38)§
75–84	20,531	892	10.09 (9.43–10.76)	20,507	850	9.80 (9.14–10.46)	0.98 (0.89–1.08)§
>84	1,369	113	24.23 (19.76–28.70)	1,364	73	16.03 (12.35–19.71)	0.65 (0.48–0.87)§
Total	227,303	2,624	2.48 (2.38–2.57)	227,289	3,460	3.01 (2.91–3.11)	1.28 (1.21–1.34)‖
Women (years of age)							
35–44	19,314	7	0.08 (0.02–0.13)	19,313	27	0.25 (0.16–0.34)	3.19 (1.39–7.33)§
45–54	49,468	73	0.31 (0.24–0.38)	49,461	272	0.99 (0.87–1.11)	3.11 (2.39–4.03)§
55–64	83,548	488	1.24 (1.13–1.35)	83,512	1,623	3.59 (3.42–3.77)	2.81 (2.53–3.11)§
65–74	77,404	2,154	5.71 (5.47–5.95)	77,271	4,202	10.84 (10.51–11.17)	1.89 (1.79–1.99)§
75–84	25,974	2,108	18.73 (17.93–19.53)	25,879	2,650	24.16 (23.24–25.08)	1.30 (1.23–1.38)§
>84	2,023	287	41.33 (36.55–46.11)	2,006	245	37.58 (32.87–42.28)	0.91 (0.77–1.08)§
Total	257,731	5,117	4.21 (4.09–4.32)	257,498	9,019	6.75 (6.61–6.89)	1.72 (1.66–1.78)‖

*Inconsistency between total population and population summed for individual variable is due to missing information. †Based on Poisson assumption, ID, incidence density. ‡Based on Cox proportional hazard regression model. §Adjusted for geographic area and urbanization status. ‖Adjusted for age as a continuous variable, geographic area, and urbanization status.

for diabetic men and women were 3.01 and 6.75 per 1,000 person-years, respectively. The corresponding figures for control men and women were 2.48 and 4.21 per 1,000 person-years. In both diabetic and control groups, the incidence density of hip fracture increased with age, and the highest incidence density was found in the group of patients >84 years old irrespective of sex and diabetes status. Generally, the age- and sex-specific incidence density of hip fracture in diabetic patients was higher than that of control subjects except in men aged >74 years and in women aged >84 years.

Compared with the control subjects, diabetic men and women showed increased risks of hip fracture by a magnitude of 28% (hazard ratio [HR] 1.28 [95% CI 1.21–1.34]) and 72% (1.72 [1.66–1.78]), respectively. There was a significant interaction of diabetes with age ($P < 0.0001$) for both men and women so that we performed the stratified analysis to estimate the age-specific HRs for each sex. The diabetic patients with younger ages had higher HRs, but the diabetic men aged >74 years and diabetic women aged >84 years had risks similar to those of control subjects. The highest sex- and age-specific HR of hip fracture was observed for the diabetic men (2.45 [1.65–3.64]) and women between 35 and 44 years (3.19 [1.39–7.33]).

The sex- and urbanization level–specific incidence densities of hip fracture and relative hazards of hip fracture associated with diabetes are shown in Table 2. A higher incidence of hip fracture was observed in men from the urban areas than in those from the rural areas irrespective of their diabetes status, but such an urban-rural difference was not apparent in women of both groups. We noted significant interactions of diabetes with level of urbanization in both men ($P = 0.0053$) and women ($P = 0.0248$). The adjusted HR of hip fracture was higher in both men (HR 1.43 vs. 1.22) and women (HR 1.82 vs. 1.67) from rural areas than in their urban counterparts

The age-specific PAR% increased from 1.84% for men aged 35–44 years to 6.70% for men aged 55–64 years and then declined thereafter. For women, there was also an increase in PAR% from those aged 35–44 years (2.20%) to those aged 55–64 years (15.48%). The PAR% decreased to 10.03 and 2.53% for women aged 65–74 and 75–84 years, respectively. The overall PAR% for men and women was estimated to be 0.39 and 1.35%.

CONCLUSIONS — Chie et al. (12) reported that the incidence of hip fracture of the general population in Taiwan was close to those in European countries but was higher than those of Beijing, Hong Kong, and U.S. white men. In our population-based study, we noted that diabetes might have further increased the risk of hip fracture in the Taiwanese diabetic population. Except for the elderly subjects, the overall and age- and sex-specific incidence densities of nontransport accident hip fracture were consistently and significantly higher in the diabetic cohort than in the control group. A Norwegian study (3) reported that the incidence of hip fractures increased with age, and female diabetic subjects had higher incidences of hip fracture than diabetic men, results that were consistent with our study. Moreover, the incidence rates of hip fracture in the diabetic population observed in our study were similar to those in the above study (3) but were higher than those observed in the U.S. (5,8).

Compared with the age- and sex-matched control group, the overall risks of sustaining a hip fracture were higher in both diabetic male and female populations in Taiwan. Although we could not differentiate type 1 and type 2 diabetes in our diabetic patients, type 1 diabetes constitutes only 1.8% of all diabetes in Taiwan (19). The majority of the diabetic patients in our study, therefore, might have been type 2 diabetic patients. Consequently, the overall risk estimated from our female study subjects was comparable

Table 2—*Overall and urbanization status-specific incidence densities and relative hazards of nontransport accident hip fracture (ICD-9 820) in the diabetic and control groups*

	Control group			Diabetic group			
Variables*	No. of patients	No. of events	ID (per 1,000 patient-years) (95% CI)†	No. of patients	No. of events	ID (per 1,000 patient-years) (95% CI)†	Adjusted HR (95% CI) in association with diabetic group‡
Men							
Urban areas	149,195	1,791	2.61 (2.49–2.73)	152,246	2,378	3.07 (2.94–3.19)	1.22 (1.14–1.29)§
Rural areas	75,085	801	2.24 (2.08–2.39)	72,032	1,051	2.87 (2.69–3.04)	1.43 (1.30–1.56)§
Total	227,303	2,624	2.48 (2.38–2.57)	227,289	3,460	2.99 (2.89–3.09)	1.28 (1.21–1.34)‖
Women							
Urban areas	166,457	3,251	4.21 (4.07–4.36)	166,714	5,810	6.70 (6.53–6.88)	1.67 (1.60–1.74)§
Rural areas	87,844	1,807	4.21 (4.02–4.40)	87,321	3,090	6.80 (6.56–7.04)	1.82 (1.72–1.93)§
Total	255,731	5,117	4.20 (4.09–4.32)	257,498	9,019	6.74 (6.60–6.88)	1.72 (1.66–1.78)‖

*Inconsistency between total population and population summed for individual variable is due to missing information. †Based on Poisson assumption, ID, incidence density. ‡Based on Cox proportional hazard regression model; *P* value for the interaction between diabetes and urbanization status was 0.0053 and 0.0248 for men and women, respectively. §Adjusted for age as a continuous variable and geographic area. ‖Adjusted for age as a continuous variable, geographic area, and urbanization status.

with reports from other studies of Caucasian type 2 diabetic women (4,5,7–9). For type 2 diabetic men, most of the previous studies did not reveal an association of diabetes and hip fracture (3,7), but diabetic men in our study showed a 28% increase in the risk of hip fracture, a risk estimate slightly higher than findings from a recent Canadian study (9).

Age was a significant effect modifier in our data ($P < 0.0001$); the relative risk of hip fracture was increased to two- and threefold, respectively, in male and female diabetic patients aged 35–54 years, but the relative risk attenuated with increasing age. In diabetic men aged >74 years and diabetic women aged >84 years, the sex-specific risks of hip fracture were very similar to those of control subjects. In a Norwegian study (3), an increased risk of hip fracture was found in type 2 diabetic women aged between 50 and 74 years with >5 years duration of diabetes (HR 1.8 [95% CI 1.1–2.9]), but there was no significantly increased risk of hip fracture in diabetic patients aged >75 years (1.41 [0.9–2.1]). In their studies, Meyer et al. (2) and Holmberg et al. (6) recruited only middle-aged subjects and reported a significantly increased risk of hip fracture in diabetic patients. The study by Dobnig et al. (20), who included only individuals aged >70 years, however, showed a HR for hip fracture of 0.90 (95% CI 0.60–1.34), adjusted for age and weight, a result that is quite similar to the HRs reported in our study for the oldest age-groups. A recent Canadian study (21) also noted a similar pattern with a high risk ratio of hip fracture in younger diabetic patients (aged <60 years) but with reduced risk in older patient with diabetes.

The mechanism by which diabetes may have caused a higher chance of hip fracture among diabetic patients has not been clearly elucidated. Previous studies indicated that people with diabetes were much more likely to have a fall (22) aggravated by poor balance, loss of pressure sensitivity due to peripheral neuropathy (22), or visual impairment due to retinopathy and cataract (23). Stroke, which is the common complication of diabetes, is also associated with an increased risk of hip fracture (24). Additionally, bone formation in diabetic patients might be impaired by osteoblast dysfunction (25), and advanced glycation end products induced osteoblast apoptosis (26). In the animal model, femurs of diabetic rats were found to have lower energy absorption capacity and increased bending stiffness (27), which may have predisposed them to fracture with minimal trauma. Such low bone quality with increased frequency of falls in younger adult diabetic patients may have caused a higher risk of nontraumatic accident hip fracture, which is relatively rare in the general population aged <50 years (28). People with diabetes, especially younger adults, are a lot less physically active than people without diabetes, which in turn might lead to lower bone density. Moreover, an increased proportion of individuals with type 1 diabetes, who are reported to have a higher risk of hip fracture (3,5,8,10), in the younger diabetic population might also have contributed to the increased HR of hip fracture in our younger patients.

To our knowledge, the literature on geographic variations of hip fracture incidence in the diabetic population is scarce. In our study, men living or working in urban areas had a modestly higher risk of hip fracture than men from rural areas regardless of their diabetes status, but such an urban-rural difference in incidence rate was less obvious in women. Interestingly, we noted that there was a significant urban-rural difference in the HR of hip fracture associated with diabetes, especially in male patients. The significant interaction of diabetes with urbanization level of living/working area can have important implications. With the same study cohort, Chen (11) reported that the increased risk of macrovascular disease was higher in diabetic men and women from rural areas than in those from urban areas. Such differential increased risk of macrovascular complications, which could increase the risk of falls in rural diabetic patients might have been caused by inequality of medical resources or differences in medical practice between urban and rural areas. Further investigations are required to detect the underlying reason as well as measures that can effectively eliminate such urban-rural differences in diabetic patients.

Our study had several methodological strengths. First, the diabetic cohort and control group were collected from the NHI database, which is population based and is highly representative, allowing little room for recall and selection bias, and there is also less likelihood of nonresponse and loss to follow-up of cohort members. Second, the advantage of using

insurance claim datasets in clinical research is easy access to the longitudinal records for a large sample of geographically disperse patients (29). Third, such a large number of study subjects also made it possible for us to make stratified analyses according to certain variables of interest such as age, sex, and urbanization status.

Despite the above strength, several limitations were found in our study. First, exclusive reliance on the claim data might have resulted in potential misclassification bias in our study. The accuracy of a single diabetes diagnosis in the NHI claim data in 2000 was reported to be 74.6% (30), but we used at least two diabetes-related diagnoses with the first and the last visits >30 days apart, which largely reduced the likelihood of disease misclassification. The control group might have also been mixed up with new onset or undiagnosed diabetes. Furthermore, potential inaccurate records of the claim data could also pose possible misclassification of hip fracture. Such misclassification bias, however, was likely to be nondifferential, which would tend to underestimate rather than overestimate the true relative hazard (31). Second, as we described previously, we were unable to differentiate between type 1 and type 2 diabetes in our study, which also limits specific interpretation of the study results. Third, we could not determine the BMI, physical activity, duration of diabetes, bone mineral density, and prevalence of comorbidities of the study population, which might also have confounded the study results. Lastly, we had no information on study subjects' prior histories of hip fracture, which could spuriously overestimate the incidence rate of hip fracture of the study population, but it would have had little influence on the relative risk estimates of hip fracture associated with diabetes.

In summary, over a 6-year study period, the diabetic male and female populations in Taiwan were observed to have increased risks of nontransport accident hip fracture by magnitudes of 28 and 72%, respectively. Increased risks were observed in all age-groups except older diabetic men aged >74 years and women aged >84 years. Given the potentially serious health and economic consequences of hip fracture, we must look into the underlying causes for increased risk of hip fracture among young and rural diabetic patients and implement a multifaceted intervention program accordingly to ensure the effective prevention of hip fracture in these high-risk diabetic populations.

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