Increased risks of hip fracture in diabetic patients of Taiwan: A population-based study

Hua-Fen Chen, MD, MSc¹, Ching-An Ho, MD², Chung-Yi Li, PhD³

¹Department of Endocrinology, Far-Eastern Memorial Hospital, Taipei Hsien, Taiwan
²Department of Orthopedic Surgery, Catholic Mercy Hospital, Hsinchu Hsien, Taiwan
³Department of Health Care Management, National Taipei College of Nursing, Taipei, Taiwan.

Running title: Hip fracture in diabetic patients

Corresponding Author:
Dr. Chung-Yi Li,
Department of Health Care Management
National Taipei College of Nursing
89, Neichiang St., Taipei 108, Taiwan.
E-mail: cyli@ntcn.edu.tw

Received for publication 6 June 2007 and accepted in revised form 11 October 2007.
ABSTRACT

**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 the age- and sex-matched control group (n=500,248) were linked to the inpatient claims (1997-2002) to identify hospitalizations of non-transport accident hip fracture. 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 Cox proportional hazard regression model.

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

**Conclusions:** In Taiwan, diabetes increased the risk of hip fracture in both genders in all age groups except in diabetic men aged >74 and diabetic women aged >84. Higher HRs of hip fracture were disproportionately observed in younger diabetic patients and in those living in rural areas.
Incidence of hip fracture is expected to increase worldwide (1), and subsequent functional disability, morbidity and mortality contributes 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). Many of the previous research, however, focused on women (4,5,8), or older patients aged above 65 years (4,9) so that relatively few data were available for specific risks in various age 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, high incidence (12) of hip fracture in general population was previously reported, but the incidence of hip fracture among diabetic patients was yet to be investigated. Using a nationally representative diabetic cohort retrieved from the National Health Insurance (NHI) database, this study aims 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 non-selected diabetic population in Taiwan.

**RESEARCH DESIGN AND METHODS**

**Study design and data source.** This is a registry-based cohort study, between 1997 and 2002, of hip fracture among diabetic population in Taiwan. Data were obtained from the NHI Database, which has been routinely collected by the National Health Research Institutes (NHRI), and 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 has 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 50-100 ambulatory and inpatient claims in each hospital and clinics quarterly, and false reports of diagnosis will receive severe penalty from the BNHI (14). With the ethical approval from the NHRI, we used data of diabetic ambulatory care claims (1997-2002), all inpatient claims (1997-2002), and the updated registry for beneficiaries (1995-2002) for this study. All the dataset can be inter-linked through each individual’s personal identification number (PIN).

**Selection of the 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 experienced another one or more diagnosis within the subsequent 12 months. The first and last outpatient visits within a year had to be
more than 30 days apart to avoid accidental inclusion of miscalculated patients. The final diabetic cohort was 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 of those patients already included in the diabetic group. It was selected by matching to the diabetic group on the frequency distributions of both age (in every five 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 to the NHI. If their first date of enrollment was before January 1, 1997, we set the index date as January 1, 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 endpoints.** With the unique PIN, 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 endpoint of this study. We excluded diagnoses with transport accident (E800-E848) from the outcomes of interest. The date of encountering clinical endpoint of interest was the first day of hospitalization. The study period was between January 1, 1997 and December 31, 2002.

**Statistical analysis.** The age-, sex-, and urbanization level-specific incidence density of hip fracture was calculated with person-years as the denominator under the Poisson assumption. The non-parametric Kaplan-Meier analysis was used to determine the cumulative event rates of non-transport accident hip fracture according to gender 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 their last withdrawal from NHI or the date of study termination (i.e. December 31, 2002). To assess the independent effects of diabetic 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 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 percent (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, while that of the control group was 59.61 ± 12.64 years. Age and sex distributions were equal in both groups. The percentage of people in <35, 35-44, 45-54, 55-64, 65-74, 75-84, >85 years was 3.04%, 8.87%, 19.33%, 29.41%, 29.40%, 9.28%, and 0.67%, respectively. Female patients were slightly predominant in both groups.

Fig. 1 shows the sex-specific Kaplan-Meier’s survival curves for non-transport 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 diabetic status. The 6-year cumulative event rates for diabetic men and women were 1.74 % (95% confidence interval [CI] 1.68%-1.80%) and 3.87% (95% CI 3.79%-3.95%), respectively while those for control men and women were 1.50% (95% CI 1.44%-1.56%) and 2.55% (95% CI 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 less than 35 years who sustained hip fracture in the control group so that we 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 density for diabetic men and women was 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 >84 years old irrespective of sex and diabetic status. Generally, the age-sex-specific incidence density of hip fracture in diabetic patients was higher than that of control subjects except in men >74 years old and in women >84 years old.

Compared to the control subjects, diabetic men and women showed increase risks of hip fracture by a magnitude of 28% (Hazard ratio [HR]: 1.28; 95% CI 1.21-1.34) and 72% (HR: 1.72; 95% CI 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 gender. The diabetic patients with younger ages had higher HRs, but the diabetic men above 74 years and diabetic women above 84 years had similar risks as control subjects. The highest sex-age-specific HR of hip fracture was observed for the diabetic men (HR: 2.45; 95% CI 1.65-3.64) and women between 35-44 years (HR: 3.19; 95% CI 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 diabetic status, but such 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 to 6.70% for men aged 55-64, then declined thereafter. For women, there was also increase in PAR% from aged 35-44 (2.20%) to 55-64 (15.48%). The PAR% decreased to 10.03% and 2.53% for women aged 65-74 and 75-84, respectively. The overall PAR% for men and women was estimated at 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 of European countries, but was higher than those of Beijing, Hong Kong and US white men. In our population-based study, we noted that diabetes might have further increased the risk of hip fracture in Taiwanese diabetic population. Except for the elderly subjects, the overall and age-sex-specific incidence densities of non-transport 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, which were consistent with our study. Moreover, the incidence rates of hip fracture in the diabetic population observed in our study were similar to the above study (3), but were higher than those observed in the USA (5,8).

Compared to the age- and sex-matched control group, the overall risks of sustaining hip fracture were higher in both diabetic male and female populations in Taiwan. Though we could not differentiate type 1 and type 2 diabetes in our diabetic patients, type 1 diabetes constitutes only 1.8% of all types of diabetes in Taiwan (19). The majority of the diabetic patients in our study, therefore, might have been made up of type 2 diabetic patients. Consequently, the overall risk estimated from our female study subjects was comparable with the reports from other Caucasian studies of type 2 diabetic women (4,5,7-9). For type 2 diabetic men, most of the previous studies did not reveal association of diabetes mellitus 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 2- and 3-fold respectively in male and female diabetic patients aged 35-54 years, but the relative risk attenuated with increasing age. In >74 year old diabetic men and >84 year old diabetic women, the sex-specific risks of hip fracture was 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 between 50-74 years with >5 years duration (HR: 1.8; 95% CI 1.1-2.9), but there was no significantly increased risk of hip fracture in >75 years old diabetic patients (HR: 1.41; 95% CI 0.9-2.1). The studies by Meyer et al. (2) and Holmberg et al. (6), recruited only middle aged subjects, reported a significantly increased risk of hip fracture in diabetic patients. The study by Dobning et al (20) who included only individuals above 70 years, however, observed 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 HRs reported in our study for the oldest age groups. A recent Canadian study (21) also noted a similar pattern.
with high risk ratio of hip fracture in younger diabetic patients (<60 years), but with reduced risk in older patient with diabetes.

The mechanism with 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), as well as by 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, femur of the diabetic rats were found to have lower energy absorption capacity and increased bending stiffness (27), which may have predisposed to fracture with minimal trauma. Such low bone quality with increased frequency of fall in younger adult diabetic patients might have caused higher risk of non-traumatic accident hip fracture which is relatively rare in general population less than 50 years old (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, increased proportion of type 1 diabetes, who are reported to have higher risk of hip fracture (3,5,8,10), in younger diabetic population might also have contributed to increased HR of hip fracture in our younger patients.

To our best knowledge, literature regarding the geographic variation of hip fracture incidence in 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 diabetic status, but such urban-rural difference in incidence rate was less obvious in women. Interestingly, we noted that there was a significant urban-rural difference in HR of hip fracture associated with diabetes especially in male patients. The significant interaction of diabetes with urbanization level of living/working area can be of 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 those from urban areas. Such differential increased risk of macrovascular complications, which could increase risk of fall, in rural diabetic patients might have been caused by inequality of medical resources or difference in medical practice between urban and rural areas. Further investigations are required to detect the underlying reason as well as measures that can effectively solve such urban-rural difference in the diabetic patients.

Our study had several methodological strengths. First, the diabetic cohort and control group were collected from NHI database, which is population-based and is highly representative, which allows little room for recall and selection bias, and there is also less likelihood of non-response and loss to follow-up of cohort members. Second, the advantage of using insurance claim data sets in clinical research is easy access to the longitudinal records for a large sample of geographically dispersed 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 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 more than 30 days apart, which would largely reduce the likelihood of disease misclassification. The control group might have also mixed up with new onset or undiagnosed diabetes. Furthermore, potential inaccurate record of the claim data could also pose possible misclassification of hip fracture. Such misclassification bias, however, was likely to be non-differential, which would tend to underestimate rather than over-estimate the true relative hazard (31). Second, as we previously described, 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 body mass index, physical activity, duration of diabetes, bone mineral density and prevalence of co-morbidities 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 little influence on the relative risk estimates of hip fracture associated with diabetes.

In conclusion, over a six-year study period, the diabetic male and female populations in Taiwan were observed to have increased risks of non-transport accident hip fracture by a magnitude of 28% and 72%, respectively. Increased risks were observed in all age groups except older diabetic men aged >74 and women aged >84. Given 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 population.

ACKNOWLEDGEMENTS
This study was partially supported by a contract with the National Scientific Council (NSC 95-2314-B-030-002).
REFERENCES

11. Chen HF: Risks of macrovascular complications among the diabetic population in Taiwan, Master thesis of Fu-Jen Catholic University, 2005
health care improvement program in rural Taiwan. *J Rural Health* 21:372-377, 2005
Table 1 Overall and age- and sex-specific incidence densities and relative hazards of non-transport accident hip fracture (ICD-9: 820) in the diabetic and control groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control group</th>
<th>Diabetic group</th>
<th>Adjusted HR (95% CI) in association with diabetic group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of patients</td>
<td>No of events</td>
<td>ID (per 1,000 patient-years) (95% CI) ‡</td>
</tr>
<tr>
<td>Men (years of age)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-44</td>
<td>25016</td>
<td>33</td>
<td>0.29 (0.19-0.38)</td>
</tr>
<tr>
<td>45-54</td>
<td>47115</td>
<td>106</td>
<td>0.47 (0.38-0.56)</td>
</tr>
<tr>
<td>55-64</td>
<td>63510</td>
<td>298</td>
<td>1.04 (0.92-1.16)</td>
</tr>
<tr>
<td>65-74</td>
<td>69762</td>
<td>1182</td>
<td>3.47 (3.27-3.67)</td>
</tr>
<tr>
<td>75-84</td>
<td>20531</td>
<td>892</td>
<td>10.09 (9.43-10.76)</td>
</tr>
<tr>
<td>&gt;84</td>
<td>1369</td>
<td>113</td>
<td>24.23 (19.76-28.70)</td>
</tr>
<tr>
<td>Total</td>
<td>227303</td>
<td>2624</td>
<td>2.48 (2.38-2.57)</td>
</tr>
<tr>
<td>Women (years of age)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-44</td>
<td>19314</td>
<td>7</td>
<td>0.08 (0.02-0.13)</td>
</tr>
<tr>
<td>45-54</td>
<td>49468</td>
<td>73</td>
<td>0.31 (0.24-0.38)</td>
</tr>
<tr>
<td>55-64</td>
<td>83548</td>
<td>488</td>
<td>1.24 (1.13-1.35)</td>
</tr>
<tr>
<td>65-74</td>
<td>77404</td>
<td>2154</td>
<td>5.71 (5.47-5.95)</td>
</tr>
<tr>
<td>75-84</td>
<td>25974</td>
<td>2108</td>
<td>18.73 (17.93-19.53)</td>
</tr>
<tr>
<td>&gt;84</td>
<td>2023</td>
<td>287</td>
<td>41.33 (36.55-46.11)</td>
</tr>
<tr>
<td>Total</td>
<td>257731</td>
<td>5117</td>
<td>4.21 (4.09-4.32)</td>
</tr>
</tbody>
</table>

* Inconsistency between total population and population summed for individual variable was due to missing information
† Based on Poisson assumption, ID= incidence density, CI=confidence interval
‡ Based on Cox proportional hazard regression model, HR=hazard ratio
§ Adjusted for geographic area and urbanization status
‖ Adjusted for age as a continuous variable, geographic area and urbanization status
Table 2 Overall and urbanization status-specific incidence densities and relative hazards of non-transport accident hip fracture (ICD-9: 820) in the diabetic and control groups

<table>
<thead>
<tr>
<th>Variables*</th>
<th>Control group</th>
<th>Diabetic group</th>
<th>Adjusted HR (95% CI) in association with diabetic group‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of patients</td>
<td>No of events</td>
<td>ID (per 1,000 patient-years) (95% CI)†</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban areas</td>
<td>149195</td>
<td>1791</td>
<td>2.61 (2.49-2.73)</td>
</tr>
<tr>
<td>Rural areas</td>
<td>75085</td>
<td>801</td>
<td>2.24 (2.08-2.39)</td>
</tr>
<tr>
<td>Total</td>
<td>227303</td>
<td>2624</td>
<td>2.48 (2.38-2.57)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban areas</td>
<td>166457</td>
<td>3251</td>
<td>4.21 (4.07-4.36)</td>
</tr>
<tr>
<td>Rural areas</td>
<td>87844</td>
<td>1807</td>
<td>4.21 (4.02-4.40)</td>
</tr>
<tr>
<td>Total</td>
<td>255731</td>
<td>5117</td>
<td>4.20 (4.09-4.32)</td>
</tr>
</tbody>
</table>

* Inconsistency between total population and population summed for individual variable was due to missing information
† Based on Poisson assumption, ID= incidence density, CI=confidence interval
‡ Based on Cox proportional hazard regression model, HR= hazard ratio; 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
Figure 1 Kaplan-Meier survival curves for non-transport accident hip fracture in diabetic and control groups