Age and Sex May Significantly Interact With Diabetes on the Risks of Lower-Extremity Amputation and Peripheral Revascularization Procedures

Evidence from a cohort of a half-million diabetic patients

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OBJECTIVE — Using the National Health Insurance claim data, we prospectively investigated the age- and sex-specific incidence density and relative hazards of nontraumatic lower-extremity amputation (LEA) and peripheral revascularization procedure (PRP) of the diabetic population in Taiwan.

RESEARCH DESIGN AND METHODS — A total of 500,868 diabetic patients and 500,248 age- and sex-matched control subjects, selected from the ambulatory care claim (1997) and the registry for beneficiaries, respectively, were linked to inpatient claims (1997–2002) to identify hospitalizations due to nontraumatic LEA and PRP. Incidence density was calculated under the Poisson assumption, and the Kaplan-Meier analysis was used to assess the cumulative event rates over a 6-year follow-up period. We also evaluated the age- and sex-specific relative hazards of nontraumatic LEA and PRP in relation to diabetes with Cox proportional hazard regression model adjusted for demographics and regional areas.

RESULTS — The estimated incidence density of nontraumatic LEA and PRP for diabetic men was 410.3 and 317.0 per 100,000 patient-years, respectively. The corresponding data for diabetic women were relatively low at 115.2 and 86.0 per 100,000 patient-years. Compared with control subjects with the same age and sex, diabetic patients consistently suffered from significantly elevated relative hazards of nontraumatic LEA. Young and female patients were especially vulnerable to experience increased risks of nontraumatic LEA, but such effect modification by age and sex was less apparent for PRP.

CONCLUSIONS — Multidisciplinary diabetes foot care systems, including the provision of revascularization procedures, should be further enforced to reduce subsequent risks of nontraumatic LEA, especially in young and female diabetic patients.

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Chronic hyperglycemia is a risk factor for peripheral vascular disease (1), and the severe form of diabetic foot disease usually leads to lower-extremity amputation (LEA). Diabetes increased the risk of LEA by a magnitude of 10–28 times (2–6), but Holstein et al. (7) reported that lower-extremity revascularization procedure was observed to be a successful therapy for limb salvage in diabetic patients with critical limb ischemia. Nevertheless, the relative hazard of peripheral revascularization procedure (PRP) associated with diabetes has rarely been investigated in previous studies. In Taiwan, most of the reports on diabetes-related amputation were either hospital- (8) or community- (9) based rather than population-based studies. The objective of this study was to use a nationally representative diabetic cohort selected from the National Health Insurance (NHI) database to estimate the incidence density and relative hazards of nontraumatic LEA and PRP according to various age and sex stratifications.

RESEARCH DESIGN AND METHODS

— We used a registry-based prospective design to estimate the incidence density and relative risk of nontraumatic LEA and PRP among the diabetic population in Taiwan. A universal NHI program has been implemented in Taiwan since March 1995. Some 96% of the total Taiwanese population has enrolled in the NHI program (10), and, by the end of 1996, the Bureau of NHI (BNHI) had contracted with 97% of hospitals and clinics throughout the nation (11). The BNHI accumulates all administrative and claims data for Taiwan. The National Health Research Institute (NHRI) cooperates with the BNHI to establish an NHI research database. The NHRI safeguards the privacy and confidentiality of all beneficiaries and transfers the health insurance data to health researchers after ethical approval has been obtained. To ensure the accuracy of the claim files, the BNHI performs expert review on a random sample of every 50–100 ambulatory and inpatient claims quarterly (12), and false report of diagnosis results in severe penalty from the BNHI (12,13). For the current analysis, we used diabetic ambulatory care claims

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Abbreviations: BNHI, Bureau of National Health Insurance; LEA, lower-extremity amputation; NHI, National Health Insurance; NHRI, National Health Research Institute; PIN, personal identification number; PRP, peripheral revascularization procedure.

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

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(1997–2002), inpatient claims (1997–2002), and the updated registry for beneficiaries (1995–2002). All datasets can be interlinked with each individual personal identification number (PIN).

Diabetic ambulatory care claim records those patients coded with diabetes-related diagnoses by either ICD-9 250 or A-code 181. An individual was classified as a diabetic patient if he or she had an initial diabetes-related diagnosis in 1997 and then experienced another one or more diagnosis within the subsequent 12 months. Additionally, the first and last outpatient visits during the 12-month period had to be separated by at least 30 days to avoid accidental inclusion of miscoded patients. The final diabetic cohort therefore consisted of 500,868 patents. The index date for patients in the diabetic group was the date of their first outpatient visit in 1997.

Using a frequency-matching technique, the age- and sex-matched control group was identified from the registry of beneficiaries, which accumulated information of all beneficiaries including PIN, date of birth, sex, geographic area of each member's NHI unit, and date of enrollment and withdrawal from NHI each time between March 1995 and December 2002. Due to missing information on age or sex for 620 diabetic patients, we could select only 500,248 control subjects in this analysis. The index date for subjects in the control group was the first date of enrollment to NHI. If their first date of enrollment was before 1 January 1997, the index date was set as 1 January 1997, which was the starting point for the study.

The age of each study subject was estimated by the difference in time between the index date and the date of birth. We grouped the area of each member's NHI unit, either the beneficiaries' residential area or location of their employment, into four geographic areas or three urbanization statuses according to the National Statistics of Regional Standard Classification (14).

Study end points

The inpatient claims include the records of all hospitalization events and provide various pieces of information, including PIN, date of birth, sex, and date of admission and discharge (maximum of five leading discharge diagnoses and four operation procedure codes). With the unique PIN, we linked subjects in both the diabetic and control groups to inpatient claims (1997–2002) to identify the first instance, if any, of primary and secondary procedure codes of nontraumatic LEA (ICD-9: 84.1 and 84.10–84.18) and nontraumatic PRP (ICD-9: 39.25, 39.29, and 39.59) as the end points of this study. Both outcomes were analyzed separately. We regarded all diagnoses without E-codes as nontraumatic cases. The date of encountering each clinical end point was the 1st day of hospitalization. The 6-year follow-up period began on 1 January 1997 and ended on 31 December 2002.

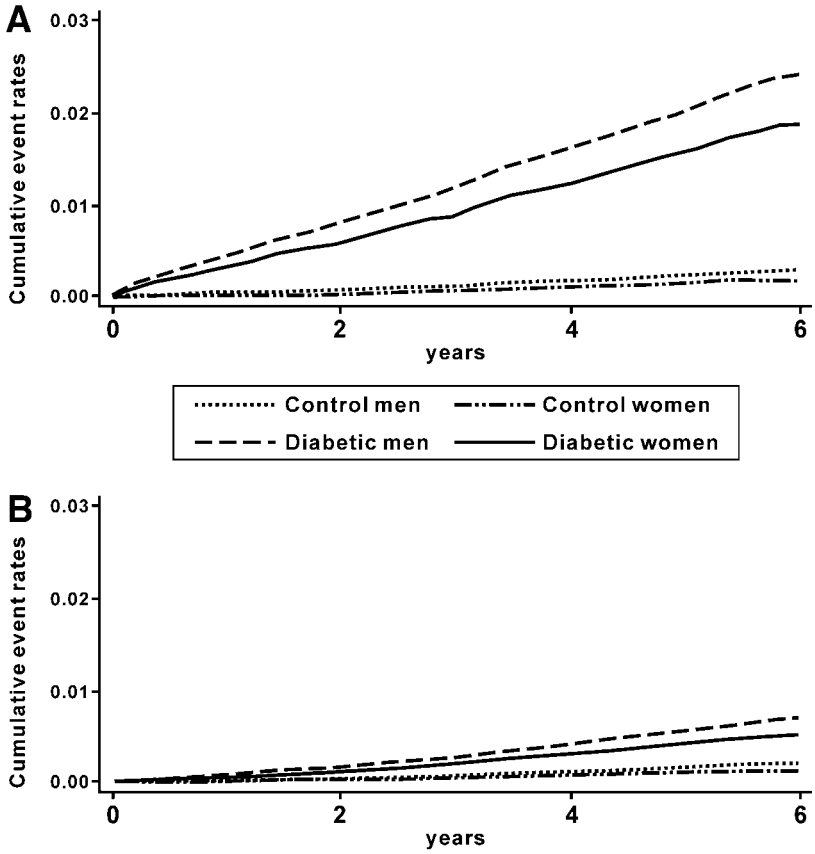

Figure 1—*Kaplan-Meier survival curves for LEA* (A) *and PRP* (B).

Statistical analysis

Two major statistical analyses were performed in the study. First, the age- and sex-specific incidence density estimate was calculated with person-years as the denominator under the Poisson assumption. Second, the Kaplan-Meier analysis was used to calculate the cumulative event rates of LEA and PRP according to different sexes over a 6-year (1997–2002) 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 on which they died. If the subject 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 on the risks of LEA and PRP, we conducted Cox proportional hazard regression models with age, sex, geographic area, and urbanization status adjusted simultaneously in the model. Adjustment for the latter two geographic variables was made to account for possible geographic variations in medical care resources, which were considered to pose considerable influences on a clinical decision regarding performing LEA and PRP (15,16). All statistical analyses were performed with SAS (version 8.2; SAS Institute, Cary, NC). A P value <0.05 was considered statistically significant. Survival curves were depicted by Stata Statistical Software (release 8.0; Stata, College Station, TX).

RESULTS — The mean (±SD) age of the diabetic group was 59.71 ± 12.52 years, while that for the control group was 59.61 ± 12.64 years. Age and sex were equally distributed in both groups. The

Table 1—*Overall and age- and sex-specific incidence densities and relative hazards of nontraumatic LEA (ICD-9: 84.1 and 84.10–84.18) in the diabetic and control groups*

Variables*	Control group			Diabetic group			Adjusted HR (95% CI)‡ in association with diabetic group
	Patients (*n*)	No. of events	ID (per 100,000 patient-years) (95% CI)†	Patients (*n*)	No. of events	ID (per 100,000 patient-years) (95% CI)†	
Men (years of age)							
<35	7,333	0	0	7,332	35	86.8 (58.1–115.6)	NA§
35–44	25,017	13	11.2 (5.1–17.3)	25,010	232	169.6 (147.8–191.4)	14.12 (8.07–24.70)
45–54	47,114	35	15.6 (10.4–20.8)	47,078	724	283.1 (262.5–303.7)	17.40 (12.39–24.43)
55–64	63,512	105	36.6 (29.6–43.7)	63,463	1,538	460.5 (437.4–483.5)	12.44 (10.21–15.17)
65–74	69,768	220	64.3 (55.8–72.8)	69,701	1,840	526.9 (502.9–551.0)	8.30 (7.21–9.55)
75–84	20,541	109	121.8 (98.9–144.6)	20,511	574	635.7 (583.7–687.7)	5.40 (4.39–6.64)
>84	1,369	3	62.3 (−8.2 to 132.8)	1,368	29	585.2 (372.2–798.2)	10.56 (3.20–34.89)
Total	234,654	485	44.4 (40.5–48.4)	234,463	4,972	410.3 (398.9–421.7)	9.22 (8.39–10.12)
Women (years of age)							
<35	7,830	1	3.2 (−3.1 to 9.4)	7,830	31	71.0 (46.0–96.0)	22.17 (3.02–162.85)
35–44	19,315	6	6.5 (1.3–11.8)	19,310	148	137.0 (115.0–159.1)	19.82 (8.76–44.86)
45–54	49,469	15	6.4 (3.2–9.6)	49,450	512	185.5 (169.4–201.6)	27.92 (16.71–46.66)
55–64	83,549	73	18.5 (14.3–22.7)	83,525	1,288	282.3 (266.9–297.7)	15.10 (11.91–19.15)
65–74	77,409	133	35.0 (29.0–40.9)	77,364	1,747	436.6 (416.1–457.1)	12.44 (10.42–14.85)
75–84	25,992	99	85.7 (68.8–102.6)	25,965	697	587.9 (544.2–631.5)	6.93 (5.60–8.58)
>84	2,024	11	149.6 (61.2–238.0)	2,016	48	644.5 (462.2–826.9)	4.25 (2.20–8.24)
Total	265,588	338	26.9 (24.0–29.8)	265,460	4,471	317.0 (307.0–326.3)	11.67 (10.44–13.05)

*Inconsistency between total population and population summed for individual variables was due to missing information. †Based on Poisson assumption. ‡Based on Cox proportional hazard regression with adjustment for age, sex, geographic area, and urbanization status. §Not applicable (NA) due to no event of clinical end points for the control group <35 years of age. ID, incidence density.

percentage of study subjects aged <35, 35–44, 45–54, 55–64, and >64 years was 3.03, 8.86, 19.31, 29.40, and 39.40%, respectively. Female patients were slightly predominant in both groups.

Figure 1 presents the Kaplan-Meier survival curves for LEA and PRP in the diabetic and control groups over a 6-year period. Diabetic men were observed to be more susceptible to both procedures of interest than diabetic women. The 6-year cumulative event rates of LEA for diabetic men and women were 2.40 and 1.87%, respectively, while those of control men and women were 0.28 and 0.17%, respectively (*P* for log-rank test <0.0001). Similarly, the cumulative event rates of PRP for the diabetic group (0.7% in diabetic men and 0.52% in diabetic women) were significantly higher than the corresponding data observed in the control group (0.20% in control men and 0.15% in control women) (*P* for log-rank test <0.0001).

Table 1 shows the overall and age- and sex-specific incident densities and relative hazards of LEA. The overall incidence density of LEA was estimated at 410.3 and 317.0 per 100,000 person-years for diabetic men and women, respectively. The corresponding data for control male and female populations were much lower at 44.4 and 26.9 per 100,000 person-years. In both diabetic and control groups, the incidence density of LEA increased with age up to 75–84 years in men, but it peaked up to >84 years in women. Except for those aged >84 years, men in all age-groups had consistently higher incidence densities than women, irrespective of diabetes status. Compared with the control subjects with the same age and sex, the relative hazards of LEA significantly increased for all age-groups in both sexes, and the highest hazard ratios (HRs) were observed in the diabetic patients between 45 and 54 years of age (17.40 [95% CI 12.39–24.43] in men and 27.92 [16.71–46.66] in women). In addition, there was a tendency for the age-specific HR to decrease with age in both diabetic men and women.

For the nontraumatic revascularization procedures, the overall incidence density estimated for diabetic men and women was 115.2 and 86.0 per 100,000 person-years. The corresponding data for control men and women were 31.3 and 21.4 per 100,000 person-years. Again the incidence density also increased with age up to 65–74 years and decreased thereafter in both groups irrespective of sex. The incidence density of PRP was observed to be higher in men than women in the middle age-groups (45–84 years), but women in the lower (<45 years) and higher (>84 years) age-groups experienced higher incidence densities than men of the same ages. Such sex-specific pattern of incidence density was similarly observed irrespective of diabetes status. Generally, nearly all age- and sex-specific HRs of PRP are significantly elevated at ~4, except for some particularly high risk estimates that were noted in diabetic men 35–44 years of age (HR 15.68 [95% CI 3.80–65.24]) and diabetic women 35–44 (6.00 [2.34–15.22]) and 45–54 (8.72 [4.93–15.41]) years of age (Table 2). Although younger diabetic men and women tended to experience higher HRs of PRP than older patients, the decline trend of age-specific HR was less apparent for PRP than LEA. Moreover, the age-specific HR of PRP was also less heterogeneous between men and women.

CONCLUSIONS — Direct comparisons of the incidence densities of LEA between our diabetic population and those investigated in previous studies are difficult, even nearly impossible, mainly be-

Table 2—*Overall and age- and sex-specific incidence density and relative hazards of nontraumatic PRP (ICD-9: 39.25, 39.29, and 39.59) in the diabetic and control groups*

	Control group			Diabetic group			Adjusted HR (95% CI)‡ in association with diabetic group
Variables*	Patients (*n*)	No. of events	ID (per 100,000 patient-years) (95% CI)†	Patients (*n*)	No. of events	ID (per 100,000 patient-years) (95% CI)†	
Men (years of age)							
<35	7,333	2	7.0 (−2.7 to 16.7)	7,333	8	19.8 (6.1–33.5)	2.71 (0.57–12.88)
35–44	25,017	2	1.7 (−0.677 to 4.1)	25,018	41	29.9 (20.7–39.0)	15.68 (3.80–65.24)
45–54	47,114	23	10.3 (6.1–14.4)	47,112	146	56.7 (47.5–65.9)	3.99 (3.11–5.11)
55–64	63,511	70	24.4 (18.7–30.2)	63,502	429	127.4 (115.4–139.5)	5.05 (3.91–6.52)
65–74	69,769	196	57.3 (49.3–65.3)	69,749	629	178.8 (164.9–192.8)	3.06 (2.60–3.60)
75–84	20,542	48	53.6 (38.4–68.7)	20,538	146	160.1 (134.2–186.1)	3.03 (2.18–4.22)
>84	1,369	1	20.8 (−19.97 to 61.5)	1,369	5	99.9 (12.3–187.5)	5.51 (0.63–47.89)
Total	234,655	342	31.3 (28.0–34.6)	234,722	1,405	115.2 (109.1–121.2)	3.56 (3.18–4.03)
Women (years of age)							
<35	7,830	0	0	7,830	11	25.2 (10.3–40.1)	NA§
35–44	19,315	5	5.5 (0.7–10.2)	19,312	36	33.2 (22.4–44.1)	6.00 (2.34–15.22)
45–54	49,469	13	5.5 (2.5–8.5)	49,466	138	49.8 (41.5–58.2)	8.72 (4.93–15.41)
55–64	83,549	75	19.0 (14.7–23.3)	83,545	367	80.1 (71.9–88.2)	3.99 (3.11–5.11)
65–74	77,411	129	33.9 (28.1–39.8)	77,406	528	131.0 (119.9–142.2)	3.82 (3.14–4.64)
75–84	25,993	45	39.0 (27.6–50.3)	25,990	130	108.5 (89.9–127.2)	2.81 (1.99–3.96)
>84	2,024	2	27.1 (−10.57 to 64.7)	2,024	10	132.5 (50.4–214.7)	4.61 (0.99–21.50)
Total	265,591	269	21.4 (18.9–24.0)	265,629	1,220	86.0 (81.2–90.9)	3.92 (3.43–4.47)

*Inconsistency between total population and population summed for individual variables was due to missing information. †Based on Poisson assumption. ‡Based on Cox proportional hazard regression with adjustment for age, sex, geographic area, and urbanization status. §Not applicable (NA) due to no event of clinical end points for the control group <35 years of age. ID, incidence density.

cause of different study designs including dissimilarity in baseline demographic characteristics, dissimilarity in methods of outcome ascertainment, and variation in length of follow-up. Generally, the incidence density of LEA of the diabetic cohort noted in our study was lower than that of previous studies (17–22). A relatively low incidence (23,24) and prevalence (25) rate of LEA among diabetic patients was also previously reported in Eastern-Asian ethnic groups. It has been postulated that a lower incidence rate of LEA associated with Asian people may be due to a lower prevalence of peripheral vascular disease (26). Old age and male sex, risk factors for peripheral vascular disease (27), were also found to be associated with increased hazards of amputation in our study.

We found high relative HRs (9.22 in men and 11.67 in women) of LEA in the diabetic population in Taiwan, but such HRs were still lower than those of previous studies (2–6,28). Age showed an apparent effect modification in our data; younger patients tended to have higher HRs, and the highest HRs were observed in subjects between 45 and 54 years of age for both sexes. O'Connor et al. (29) argued that younger diabetic patients tended to have poor glycemic control, poor health-related behaviors, less frequent clinic visits, and irregular assessment of diabetes-related complications, which could worsen the prognosis of young diabetic patients. The risks of amputation in diabetic women were also higher, and their unfavorable lipid profile (30–32) and impaired endothelial function (33) might have eliminated the female advantage in those diabetic patients.

Increasing evidence has shown that it is cost-effective to establish a multidisciplinary foot care team with screening, patient and staff education, and multifactorial treatment of foot ulcers (34) for the prevention of diabetes-related amputation. Employing podiatrists and increasing the number of foot clinics in Dutch hospitals (35) and providing a comprehensive medical, surgical, and orthopedic program for diabetic foot ulcers in Sweden (36) were reported to decrease the amputation rate. In Texas, implementation of a population-based screening and treatment program for diabetic foot dramatically reduced hospitalizations and improved clinical outcomes (37). From the clinical and public health perspectives, it is necessary to implement such an integrated and well-structured diabetes foot care system in Taiwan to prevent loss of limb in high-risk diabetic patients.

The incidence density of nontraumatic PRP in Taiwan was found to be lower than that of the U.S. veterans with diabetes (38). This was probably due to a low prevalence of foot ulceration among diabetic patients in Taiwan (9) or differences in surgical practice between nations. As for the effects of diabetes on the risks of PRP, we observed that the overall HRs were ~9.22 (95% CI 8.39–10.12) in diabetic men and ~11.67 (10.44–13.05) in diabetic women. Nonetheless, unlike the observation for LEA, the overall and age-specific HRs of PRP between men and women were less obvious. Moreover, age did not seem to pose considerable effect modification on the HR of PRP in both sexes. Whether these findings are indicative of inadequate provision of PRP to the high-risk groups, such as young and female diabetic patients, deserves further investigation.

Our study had several methodological strengths. First, we used the NHI claim, which is representative and allows little room for selection or recall bias, and there is small likelihood of nonresponse and loss to follow-up of cohort members. Second, one of the potential advantages of

using insurance claim datasets is that the longitudinal records for a large sample of geographically dispersed patients can be easily obtained (39). Third, such a large number of study subjects also made it possible for us to make age- and sex-stratified analyses without compromising the required sample size. Fourth, since the decisions regarding whether to perform procedures can be dependent on the medical resources and physicians' behavior, adjustment for geographic location and urbanization of living or employment areas of the study subjects was likely to reduce such geographic-related confounding.

There were also several limitations in our study. First, exclusive reliance on claim data might result in potential disease misclassification bias in our study, as the type of reimbursement system could influence the assignment of hospital discharge codes to increase payment to hospitals (40). However, we used at least two diabetes-related diagnoses, with the first and the last visits >30 days apart, which would largely reduce the likelihood of disease misclassification. Second, we could not differentiate between type 1 and type 2 diabetes among the diabetic population included in our study. In Taiwan, type 1 diabetes constitutes only 1.8% of all types of diabetes (41) and the ratio of newly diagnosed type 2 to type 1 diabetes among school children aged 6–18 years is approximately six to one (42). Therefore, the majority of our young diabetic patients tends to be comprised of type 2 diabetic patients.

In conclusion, our study showed very high relative risks of LEA in a diabetic cohort, especially in young and female patients. As LEA is a significant economic burden for our society, it is necessary to implement a multidisciplinary diabetes foot care system that includes the provision of revascularization procedures for high-risk diabetic patients.

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