

Diabetes and Risk of Hip Fracture in the Singapore Chinese Health Study

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OBJECTIVE — Asian populations are documenting rapid increases in the rates of diabetes and hip fracture, but there are no prospective data linking both diseases in Asian studies. We investigated this association among a cohort of Chinese in Singapore.

RESEARCH DESIGN AND METHODS — A prospective cohort of 63,257 Chinese in the Singapore Chinese Health Study, established between 1993 and 1998, was followed up for a mean duration of 12 years. Diabetes status was ascertained by baseline interviews, and incidence of hip fracture post-enrollment was identified through a nationwide hospital discharge database.

RESULTS — The risk of hip fracture, after adjustment for other risk factors, was almost double among people with diabetes compared with people without diabetes (relative risk 1.98, 95% CI 1.71–2.29). When stratified by BMI, the increase in risk of hip fracture among people with diabetes relative to people without diabetes was similar in all four strata. There was a very strong dose-dependent relationship between duration of diabetes and risk of hip fracture (P for trend <0.0001). Compared with people without diabetes, the relative risk (95% CI) among subjects with diabetes for <5 years at recruitment was 1.40 (1.08–1.82), and this risk increased to 2.66 (2.04–3.47) among individuals with diabetes for ≥ 15 years.

CONCLUSIONS — Asians with diabetes, like their Western counterparts, experience an increased risk of hip fracture. Early assessment for osteoporosis and increased fracture risk, as well as prevention of falls, should be part of the management of diabetes.

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The incidence of diabetes and osteoporotic hip fractures, two major causes of morbidity and mortality, is increasing rapidly among Asian populations. It has been predicted that in 2030, the prevalence of diabetes in Asian countries will be more than double the rates in 2000 (1). Similarly, it has been forecasted that while the current rates of osteoporotic hip fractures in Asian populations are lower than the rates seen among the Western populations, 50% of all hip fractures in the world will be occurring in Asia by the year 2050 (2). A meta-analysis using prospective data from 11 cohort studies done in Western populations has

shown that a baseline history of diabetes is associated with a relative risk (RR) of 1.8 (95% CI 1.3–2.4) for hip fracture (3). However, none of these studies included Asian populations, which are known to have distinct anthropometric measurements and differ in dietary and other habits relative to their Western counterparts (4). Therefore, it is important to investigate the association between diabetes and hip fracture risk in Asian populations, which are documenting a rapid and parallel increase in the rates of both diseases. Furthermore, it is also not clear if the association between diabetes and hip fracture risk may differ between men and

women, or between lean and obese individuals.

In the present study, we examined the association between baseline history and duration of diabetes, and risk of hip fracture within a prospective cohort of 63,257 Chinese men and women (the Singapore Chinese Health Study). Furthermore, we examined whether BMI has a modifying effect on diabetes–hip fracture association.

RESEARCH DESIGN AND METHODS

The Singapore Chinese Health Study is a population-based cohort of 63,257 Chinese women and men, aged 45–74 years and enrolled between April 1993 and December 1998 from government housing estates, where 86% of the entire Singapore population resided (4). Our cohort subjects were drawn from the two major dialect groups of Chinese in Singapore, the Hokkiens and the Cantonese, who originated from two contiguous prefectures in southern China. The Institutional Review Boards at the National University of Singapore and the University of Minnesota approved this study.

At recruitment, subjects were interviewed in person using a structured questionnaire that asked for information including demographics, use of tobacco, menstrual (including menopausal status) and reproductive (including use of hormone replacement therapy) histories (women only), medical history, as well as a dietary component assessing current intake patterns (4). The subjects were asked if they had a history of physician-diagnosed diabetes, and positive subjects were also asked for their ages at the time of diagnosis to compute duration of disease as the difference between age of diagnosis and age at recruitment.

Identification of hip fracture cases among cohort members was accomplished through record linkage of cohort files with databases of the MediClaim System, which has captured inpatient discharge information from all private and public hospitals in Singapore since 1990 (5). All cases identified via linkage were verified by records of the appropriate surgical procedures or manual review of medical records. Records of death were

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Table 1—Baseline characteristics of cohort members by history of diabetes and incident hip fracture status: the Singapore Chinese Health Study (1993–2008)

	Diabetes			Hip fracture		
	No	Yes	P	No	Yes	P
n	57,486	5,668	—	61,941	1,213	—
Age at recruitment (years)	56.1 ± 8.0	60.0 ± 7.7	<0.001	56.3 ± 8.0	64.5 ± 6.6	<0.001
BMI (kg/m ²)	23.0 ± 3.3	24.0 ± 3.3	<0.001	23.1 ± 3.3	22.9 ± 3.2	0.034
Sex (%)						
Male	44.4	42.6	0.012	44.5	28.2	<0.001
Female	55.6	57.4		55.5	71.8	
Dialect (%)						
Cantonese	46.3	45.9	0.572	46.3	45.5	0.576
Hokkien	53.7	54.1		53.7	54.5	
Level of education (%)						
No formal education	26.6	35.2	<0.001	27.0	46.3	<0.001
Primary school (1–6 years)	44.4	44.0		44.4	42.2	
Secondary and above	29.0	20.8		28.6	11.5	
History of stroke (%)						
No	98.8	95.3	<0.001	98.6	96.1	<0.001
Yes	1.2	4.7		1.4	3.9	
Cigarette smoking (%)						
Never-smokers	69.6	68.0	<0.001	69.4	69.9	0.705
Former smoker	10.6	16.0		11.1	11.5	
Current smokers	19.8	16.0		19.5	18.6	
Cigarettes/day*	17.2 ± 11.3	18.2 ± 12.6	<0.001	17.3 ± 11.5	15.5 ± 10.8	0.003
Years of smoking*	33.1 ± 11.7	33.3 ± 12.0	0.386	33 ± 11.7	36.9 ± 10.8	<0.001
Weekly moderate activity (%)						
No	78.0	76.5	0.017	77.9	78.1	0.116
0.5–3 h/week	13.9	14.5		13.9	12.4	
≥4 h/week	8.1	9.0		8.2	9.5	
Soy isoflavones (mg/1,000 kcal/day)	11.9 (9.1)	11.7 (9.7)	0.229	11.9 (9.2)	11.1 (9.3)	0.006
Calcium (mg/1,000 kcal/day)	267.0 ± 122.5	292.4 ± 138.1	<0.001	269.1 ± 123.8	280.2 ± 141.9	0.002

Data are means ± SD or percent. *Among ever-smokers only.

captured through linkage with the Singapore Registry of Births and Deaths. As of 31 December 2008, 1,316 hip fracture cases were identified through record linkage. We excluded from statistical analysis 103 prevalent cases of hip fracture that occurred before subjects' recruitment to the cohort. Thus, 1,213 subjects with hip fractures and 61,941 subjects without hip fractures were included in the final analysis.

For each study subject, person-years were counted from the date of baseline interview to the date of hip fracture diagnosis, date of death, or 31 December 2008—whichever occurred first. We used the χ^2 test (for categorical variables) or the Student's *t* test (for continuous variables) to examine the difference in distributions of baseline characteristics between case subjects and non-case subjects. Proportional hazards regression methods were used to examine the diabetes–hip fracture associations in men and women separately and both sexes com-

bined, with adjustment for sex. To adjust for the potential confounding effects of other demographic and exposure characteristics on the diabetes–hip fracture association, the following variables were included in all regression models: age at recruitment (years), year of recruitment, dialect group (Hokkien, Cantonese), level of education (no formal education, primary, secondary or higher), weekly vigorous work or strenuous sports (yes, no), BMI (kg/m²), number of cigarettes smoked per day (never smoker, 1–12, 13–22, or ≥23), number of years of smoking (never-smoker, 1–19, 20–39, or ≥40), number of years since quitting smoking (continuous smoker, <1, 1–4, 5–19, ≥20, or never smoker), total calcium intake from food and supplement (mg/1,000 kcal/day), total soy isoflavone intake (mg/1,000 kcal/day), and history of physician-diagnosed stroke. Linear trend tests for exposure-disease associations were based on the ordinal values of the quartiles. Statistical computing was

conducted using SAS version 9.1 (SAS Institute, Cary, NC). All cited *P* values were two-sided. *P* values <0.05 were considered statistically significant.

RESULTS— After excluding the 103 subjects with hip fractures before recruitment, among the 63,154 subjects included in this analysis, 5,668 (9.0%) reported a history of physician-diagnosed diabetes. The age at diagnosis of diabetes was 51.8 ± 9.5 years (mean ± SD), with a range of 30–74 years. People with diabetes were older, were less educated, had higher BMI, were more likely to have smoked cigarettes over their lifetime, were more likely to have a history of stroke, and consumed greater amount of dietary calcium (Table 1). As of 31 December 2008, after a mean duration of 12.2 ± 3.3 years in follow-up, 1,213 incident cases (342 men and 871 women) of hip fracture had occurred in this cohort. The mean age at fracture was 72.8 ± 7.2 years. There were significantly more

Table 2—Risk of hip fracture and history of diabetes in the Singapore Chinese Health Study (1993–2008)

Stratifying variables	Subjects without a history of diabetes			Patients with diabetes			
	Person-years	Case subjects	RR (95% CI)	Person-years	Case subjects	RR (95% CI)*	RR (95% CI)†
All	710,226	981	1.00	59,341	232	2.00 (1.73–2.31)	1.98 (1.71–2.29)
Sex							
Male	306,246	296	1.00	24,211	46	1.67 (1.22–2.29)	1.77 (1.29–2.43)
Female	403,980	685	1.00	35,130	186	2.11 (1.79–2.48)	2.06 (1.75–2.43)
						<i>P</i> _{interaction} = 0.129	<i>P</i> _{interaction} = 0.199
BMI (kg/m ²)							
<20	111,130	173	1.00	4,467	24	2.25 (1.46–3.46)	2.22 (1.44–3.44)
20 to <24	386,545	563	1.00	29,984	135	2.03 (1.68–2.45)	1.97 (1.62–2.38)
24 to <28	164,208	193	1.00	17,912	58	2.11 (1.57–2.84)	2.03 (1.51–2.74)
≥28	48,343	52	1.00	6,978	15	1.77 (0.99–3.16)	1.82 (1.02–3.26)
						<i>P</i> _{interaction} = 0.608	<i>P</i> _{interaction} = 0.593

*Adjusted for age at recruitment, sex (for all), year of recruitment, dialect group (Hokkien, Cantonese), level of education (no formal education, primary, secondary or higher). †Further adjusted for weekly vigorous work or strenuous sports (yes, no), BMI (kg/m²), number of cigarettes smoked per day (never-smoker, 1–12, 13–22, or ≥23), number of years of smoking (never-smoker, 1–19, 20–39, or ≥40), number of years since quitting smoking (continuous smoker, <1, 1–4, 5–19, ≥20, or never smoker), total calcium intake from food and supplement (mg/1,000 kcal/day), total soy isoflavone intake (mg/1,000 kcal/day), and self-reported stroke.

women among hip fracture cases. Compared with nonfracture subjects, case subjects were less educated, more likely to have a history of stroke, and possessed a lower BMI. Patients with hip fracture smoked for a greater number of years, if they ever smoked, than subjects without hip fracture. Hip fracture patients had lower intake of soy isoflavones but higher intake of calcium than individuals without hip fracture (Table 1).

The risk of hip fracture among people with diabetes was twice that among individuals without diabetes (RR 1.98, 95% CI 1.71–2.29) after adjustment for other risk factors, including BMI, physical activity, smoking, calcium and soy consumption, and self-reported history of stroke. The risk estimate in the model that did not include BMI as a covariate was essentially unchanged (RR 1.94, 95% CI 1.68–2.25). This risk elevation was present in both sexes regardless of levels of BMI (Table 2). After excluding 10% of subjects with diabetes whose age at diagnosis was ≤40 years, the results remained essentially the same (RR 1.83, 95% CI 1.57–2.13).

Table 3 shows the diabetes–hip fracture association according to the duration of physician-diagnosed diabetes at the time of the baseline interview. Because most subjects with longer duration of disease might be older than subjects with shorter disease duration, we adjusted for age at recruitment in these analyses. Risk of hip fracture increased with increasing duration of diabetes. While the relative risk (95% CI) for hip fracture among pa-

tients with diabetes diagnosed <5 years before baseline interview was 1.40 (1.08–1.82) compared with subjects without a history of diabetes, the risk increased to 2.66 (2.04–3.47) for patients with diabetes whose initial diagnosis was ≥15 years before the recruitment (Table 3).

CONCLUSIONS— Our results are consistent with the body of epidemiologic evidence from Western populations that links a history of diabetes with risk of osteoporotic hip fractures. To our knowledge, this is the first prospective cohort study that examines such an association

in a nonwhite population living in Asia. Our results show that the risk of hip fracture is higher among people with diabetes than among individuals without diabetes; this risk increases with duration of diabetes, and the risk estimates are similar between men and women, as well as between lean and obese individuals.

The results in this study are compatible with the results of a meta-analysis involving 11 cohort studies from Western populations that documented a risk elevation of 1.8 (95% CI–1.3–2.4) among people with diabetes relative to individuals without a history of diabetes. Although

Table 3—Risk of hip fracture and duration of diabetes in the Singapore Chinese Health Study (1993–2008)

Duration of diabetes at baseline	Person-years	Case subjects	RR (95% CI)*	RR (95% CI)†
No diabetes	710,226	981	1.00	1.00
With diabetes for 0 to <5 years	24,754	61	1.40 (1.08–1.81)	1.40 (1.08–1.82)
With diabetes for 5 to <10 years	14,891	62	2.22 (1.72–2.88)	2.21 (1.71–2.86)
With diabetes for 10 to <15 years	10,451	50	2.18 (1.64–2.90)	2.15 (1.62–2.87)
With diabetes for ≥15 years	9,245	59	2.74 (2.10–3.57)	2.66 (2.04–3.47)
<i>P</i> for trend			<0.0001	<0.0001

*Adjusted for age at recruitment, sex, year of recruitment, dialect group (Hokkien, Cantonese), level of education (no formal education, primary, secondary or higher). †Further adjusted for weekly vigorous work or strenuous sports (yes, no), BMI (kg/m²), number of cigarettes smoked per day (never-smoker, 1–12, 13–22, or ≥23), number of years of smoking (never-smoker, 1–19, 20–39, or ≥40), number of years since quitting smoking (continuous smoker, <1, 1–4, 5–19, ≥20, or never-smoker), total calcium intake from food and supplement (mg/1,000 kcal/day), total soy isoflavone intake (mg/1,000 kcal/day), and self-reported stroke.

we did not differentiate between the two types of diabetes in this study, it can be assumed from the age of onset that the majority in this middle-aged and elderly cohort had type 2 diabetes. Consequently, our results are similar to the risk documented for type 2 diabetes in this meta-analysis, which was lower than that for type 1 diabetes (3). While the earlier World Health Organization hip fracture risk prediction tool (FRAX) did not include diabetes as a clinical risk factor (6), a more recently developed hip fracture assessment algorithm derived from a cohort in the U.K., The QFractureScore, included type 2 diabetes as a significant clinical factor and documented that men with diabetes had a 38% increased risk, whereas women with diabetes had a 67% increased risk compared with their counterparts without diabetes, respectively, in a multivariate model. This elevation in risk was comparable to other well-established risk factors such as moderate smoking and current use of corticosteroids (7).

Several mechanisms have been proposed to explain the increased fracture risk associated with diabetes (8). Although bone mineral density is decreased in type 1 diabetes but increased in type 2 diabetes (9), both types of diabetes may be linked to inhibited bone formation from hyperglycemia (10,11). Human studies also concur with experimental animal models that suggested that bone samples from animals with diabetes were weaker than those from animals without diabetes, possibly due to mechanical deterioration and decrease in bone strength (12,13). While osteoporosis is often defined in terms of bone mineral density according to World Health Organization guidelines, in light of recent advances on the structural basis of skeletal fragility, it became clear that bone density represents only one of the contributors to bone strength. Even if bone mineral density is within the acceptable range, disruption of bone microarchitecture or alteration in the amount and variety of proteins in bone can still increase the risk of fractures (14). Patients with diabetes also experience accelerated bone loss from hypercalciuria, impaired renal function, endogenous insulin deficiency, and microvascular complications. Other complications of diabetes, including retinopathy, peripheral neuropathy, and vasculopathy, can also potentially increase the risk of falls in elderly patients with diabetes (8).

High BMI or obesity, which is common among people with diabetes, is a known protective factor for hip fracture (15). Consistent with published literature, we have earlier reported results from this cohort that showed an inverse dose-dependent relation between BMI and hip fracture risk (16). In the present study, we show that higher BMI does not provide any significant protection for individuals with diabetes, since the risk estimates with and without adjustment for BMI were essentially the same. These results are consistent with published data from cohort studies that adjusted for BMI (17–19). A study of U.S. women in the Nurses' Health Study divided the women into two groups using a cutoff of 30 kg/m² and showed that the association between diabetes and hip fracture risk was similar in obese and nonobese women (20). Our results support this earlier finding in showing that the impact of diabetes on hip fracture risk is consistent across four strata of BMI. Thus, our results do not support the notion that increased BMI in people with diabetes may ameliorate the increased hip fracture risk associated with diabetes (9).

Although a meta-regression analysis did not show any significant association between duration of diabetes and bone mineral density (9), the meta-analysis of 10 cohort studies in Western populations showed that the risk of hip fracture among patients with diabetes was higher in studies with >10 years of follow-up compared with patients with shorter durations of follow-up (3). A study among elderly Australians from the Blue Mountains Eye study showed significant association between duration of diabetes and risk of fracture of proximal humerus but not the hip (21), while another prospective study on elderly women from the Iowa Women's Health Study failed to show significant associations with duration of diabetes <12 years at baseline (22). We hypothesized that if diabetes played an etiologic role in hip fracture, the impact of diabetes on the risk of developing hip fracture would be stronger in patients with diabetes who had longer duration than patients who had shorter duration of the disease. In this study, we had a sufficient number of patients with diabetes to allow us to conduct analysis across four different time intervals between the diagnosis of diabetes and the interview at baseline. These results showed a compelling dose-dependent association with diabetes duration as well as

a significant 40% increase in risk, even in patients with diabetes <5 years from baseline, which concurred with findings from the Nurses' Health Study (20).

Study strengths and limitations

Because the information about the diagnosis and duration of diabetes, as well as other lifestyle and dietary factors, was obtained before the occurrence of hip fracture, the exposure data can be considered free of recall bias and allow us to establish the temporal sequence in this diabetes–hip fracture risk association. Hip fractures have the most devastating consequence in morbidity and mortality among all osteoporotic fractures, and the incidence of hip fracture is commonly used to indicate the prevalence of osteoporosis (23). Hence, the examination of hip fracture risk has direct and important public health implication on prevention of osteoporosis in any population. Singapore is a small city-state with a system for easy access to specialized medical care. Because practically all hip fracture case subjects will seek medical attention immediately and the majority of case subjects are hospitalized for surgical intervention, our capture of hip fracture incidence in this cohort can be considered complete by using linkage with this comprehensive nationwide hospital database that was established 3 years before the initiation of the cohort study. Unlike other Western studies with few subjects in the low BMI categories, this Singapore Chinese cohort had enough subjects in the low range of BMI to examine if BMI had a modifying effect on diabetes–hip fracture association.

Although the diagnosis of diabetes was obtained through self-report, in another study conducted on a subset of 1,651 subjects who had a self-reported history of physician-diagnosed diabetes in this cohort, 98.8% had their diabetes status verified either by their hospital records of diabetes in the MediClaim System or through a second interview specific to the diagnosis, treatment, or complications of diabetes (24). On the other hand, undiagnosed diabetes among the 57,486 subjects who did not report a history of diabetes is a real possibility. However, since diabetes status was ascertained before the hip fracture outcome, any misclassification of diabetes would probably not differ by fracture status, and such nondifferential misclassification of exposure would only lead to an attenuation of the real risk estimate.

A limitation of the current study is its

lack of information on potential confounders such as previous history of falls, use of corticosteroids, and serum vitamin D status. We also did not have information on treatment or control of diabetes, or information on other complications related to diabetes that may increase the risk of falls, such as hypoglycemia, retinopathy, and neuropathy. When this cohort was established between 1993 and 1998, only individuals between 45 and 74 years of age (a mean age of 58 years) were eligible for the cohort study. Hence, the average age of hip fracture among our cohort was younger (72.8 years) than that observed in a general population. A previous report showed that the incidence of hip fracture increased markedly with age after the age of 64 years in Singapore, which is similar to the trend in Western populations such as the U.S. (25).

Implications

Our results fill the existing void in population-based prospective data derived from nonwhite populations. This study strengthens the epidemiologic evidence of an association between diabetes and hip fracture risk. The exact mechanism linking diabetes and osteoporosis remains to be elucidated. However, because of the dire consequences of hip fracture, we propose that active management of osteoporosis through early and regular assessment of bone mineral density, regular exercise to improve muscle strength and balance, and specific measures for preventing falls should be included in the management of elderly individuals with longstanding diabetes.

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W.-P.K. researched data and wrote the manuscript, R.W. analyzed data, L.-W.A. and D.H. researched data and reviewed the manuscript, and J.-M.Y. and M.C.Y. reviewed and edited the manuscript.

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