The Risk of Hip Fractures in Older Individuals With Diabetes

A population-based study

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OBJECTIVE — Compared with men and women without diabetes, individuals with type 2 diabetes have higher bone mineral density (BMD). However, they may still be at increased risk for hip fractures. Using population-based Ontario health care data, we compared the risk of hip fractures among men and women with and without diabetes.

RESEARCH DESIGN AND METHODS — Using a retrospective cohort design, we identified Ontario residents aged ≥66 years with diabetes from a validated registry from 1994 to 1995 (n = 197,412) and followed them for their first hip fracture until 31 March 2003 (mean 6.1-year follow-up). Hip fracture rates were compared with those of age-matched Ontario residents without diabetes (n = 401,400), and results were stratified by sex and adjusted for age and other covariates.

RESULTS — Compared with individuals without diabetes, individuals with diabetes had greater comorbidity, were less likely to have had a BMD test, and were more likely to be taking medications that increase risk of falling and decrease BMD. After adjusting for these differences and age, we found that diabetes increased fracture risk in both men (hazard ratio 1.18 [95% CI 1.12–1.24], $P < 0.0001$) and women (1.11 [1.08–1.15], $P < 0.0001$).

CONCLUSIONS — Men and women with diabetes have a higher risk of hip fractures compared with individuals without diabetes. Further research to elucidate the mechanisms underlying this increased risk of fracture is needed, as well as increased attention to fracture prevention strategies in patients with diabetes.

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Osteoporotic fractures, such as hip and vertebral fractures, are a major source of morbidity and mortality for both men and women. In the 1st year after a hip fracture, there is a 20% increase in mortality, and an estimated 50% of women who sustain a hip fracture do not return to their previous level of function (1).

An association between diabetes and hip fractures is becoming increasingly recognized. Both cross-sectional and prospective studies have shown that type 1 diabetes is associated with a decrease in bone mineral density (BMD) (2,3) and an increased risk of osteoporotic hip and other fractures (2,4–7). In contrast, studies in patients with type 2 diabetes have demonstrated that these patients have higher BMD, probably due to increased body weight (8–10), but have found inconsistent associations between type 2 diabetes and fractures. Some studies have shown no association (11), whereas other cross-sectional studies have demonstrated a decreased risk of fractures in this population (9,12). However, prospective studies have demonstrated that individuals with type 2 diabetes have an increased risk of osteoporotic fractures, particularly of the hip, despite having higher BMD (4–6,13–16).

Most of these findings have been documented in women (5,6,15). With respect to type 2 diabetes and fracture in men, studies either did not find an association (4,5) or did not specifically examine fracture risk by sex (14,16). Prior studies are also limited by modest sample sizes and the reliance on survey data for diabetes status, which increases the potential for misclassification because of underreporting (17). No study to date has examined the impact of diabetes on fractures in both men and women at a population level. In this study, we used a validated diabetes database and other population-based data from Ontario, Canada, to compare the risk of hip fractures in older men and women with diabetes and without diabetes.

RESEARCH DESIGN AND METHODS

— This retrospective cohort study examined hip fracture rates among individuals aged ≥66 years living in the province of Ontario, Canada. Data were obtained from anonymized, administrative health care databases that include records for all individuals eligible for the provincial health plan. Databases included were *1*) the Canadian Institute for Health Information database, which provides hospital discharge abstracts containing up to 16 diagnoses as coded by the ICD-9-CM or, after 2002, ICD-10; *2*) the Registered Persons Database, which contains demographic and residential information; *3*) the physician service claims database, which includes billing claims from physicians for consultations, visits, and procedures; *4*) the Ontario Diabetes Database, which is a validated database of diabetic patients created from hospital and physicians' claims data (described in detail below); and *5*) the drug prescription database, which lists prescriptions provided under the provincial formulary

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Abbreviations: BMD, bone mineral density; ODD, Ontario Diabetes Database.

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

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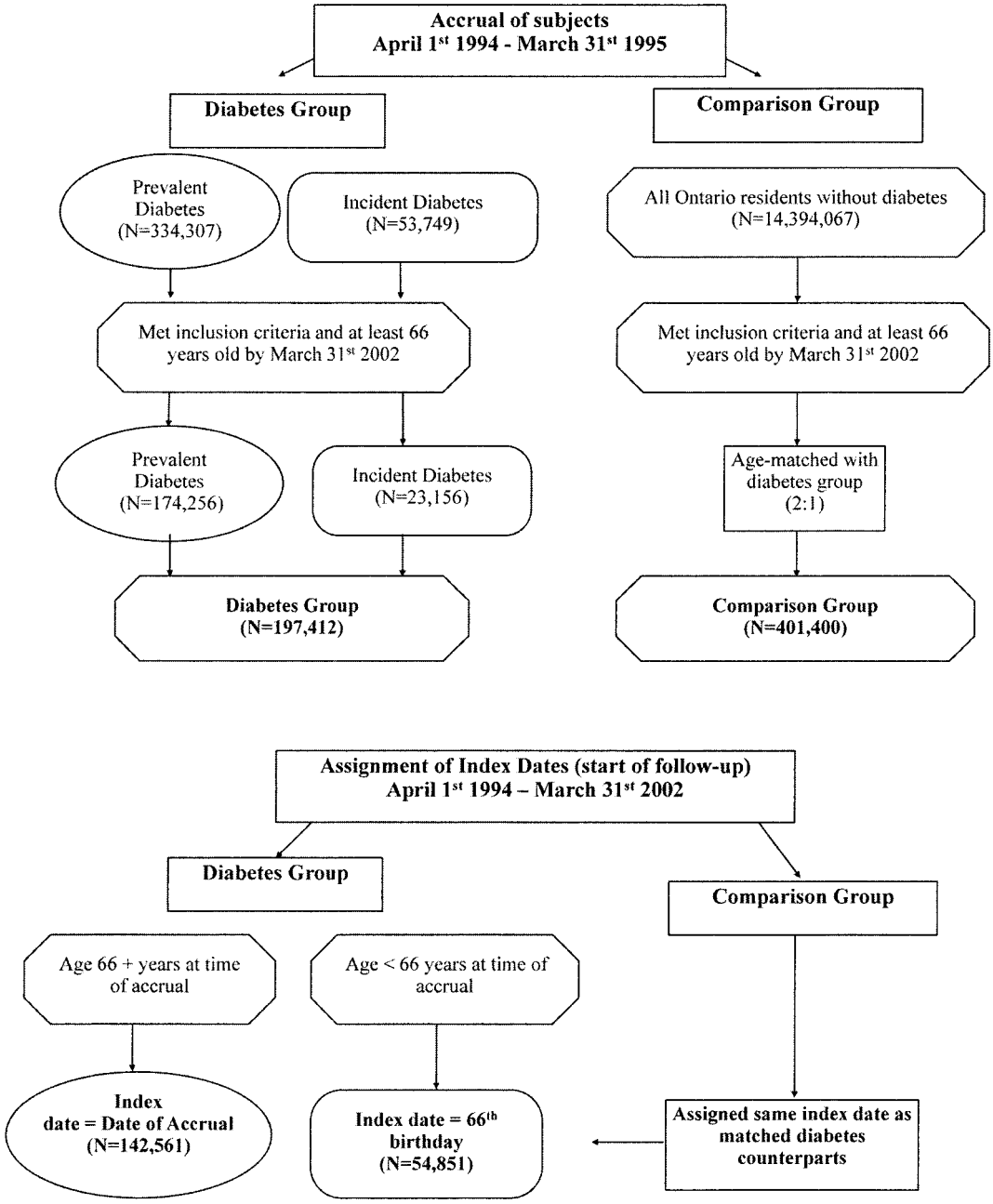

Figure 1—*Creation of diabetes and comparison groups and assignment of index dates.*

for all residents aged ≥65 years. Individuals were linked among these databases using their encrypted health card number. Subjects were accrued in fiscal year 1994 (between 1 April 1994 and 31 March 1995) and followed until 31 March 2003.

Diabetes group

The diabetes group included all individuals who appeared in the Ontario Diabetes Database (ODD) during the accrual period and who were aged ≥66 years on 31 March 2002 (Fig. 1). For the ODD, hospital discharge abstracts were used to identify patients admitted with a diagnosis of diabetes, and physicians' service claims records were used to identify outpatient visits for diabetes (code 250) (18). Any individuals having at least one hospitalization or two physicians' service claims for diabetes within a 2-year period were included in the ODD. The onset of the ODD was 1 April 1991; therefore, our accrual period (fiscal year 1994) provided a minimum look-back window of 3 years to confidently capture new patients entering the database. Therefore, we considered new entries in the ODD as "incident" diabetes, whereas those with a claim for diabetes before 1994 were considered to have "prevalent" diabetes. The ODD has been validated and shown to have a high sensitivity (86%) and specificity (97%) for identifying individuals in whom diabetes was recorded in primary care charts (18). It is not possible to distinguish between type 1 and type 2 diabetes with this database; however, it is estimated that the vast majority (>90%) of patients in this age-group have type 2 diabetes.

Comparison group

We created a matched "nondiabetic" comparison group from all Ontario residents listed in the Registered Persons Database who were at least 66 years old by 31 March 2002 and lacked records in the ODD. We used two-to-one matching with the diabetes group on the basis of age tertile (aged 66–75, 76–90, and ≥91 years) and sex (Fig. 1).

Selection criteria

We excluded individuals who had a prior hip fracture or a bilateral hip replacement, those using oral corticosteroids at any time from 1 January 1991 to study entry, and those lacking contact with the health care system during the follow-up period. We also excluded residents of a long-term care facility after the groups were matched.

Primary outcome and follow-up

The primary outcome was the first hospital admission for a hip fracture in the Canadian Institute for Health Information database (ICD-9 820-0 to 820-9 or ICD-10 S72). Each patient was assigned an index date at which time follow-up began (Fig. 1). For individuals with diabetes who were at least 66 years old at the time of accrual, their index date was their accrual date (1 April 1994–31 March 1995). If they were aged <66 years at accrual, their index date was their 66th birthday. Follow-up only began after 66 years of age to allow for a minimum of 1-year data on prescription drug use at baseline, which is available for individuals aged >65 years. Comparison subjects were assigned the same index date as their matched diabetic counterparts. Individuals were followed from their index date until they experienced an outcome or were censored or until 31 March 2003. Individuals were censored if they died, moved from the province, or had a hip fracture that was pathological (ICD-9 198.5 or 733.1; ICD-10 M84.4 or M90.7), traumatic (hip fracture plus ICD-9 E800–E848; ICD-10 T00–T07), or associated with epilepsy (hip fracture plus ICD-9 345 or 780.3; ICD-10 G40–G41).

Covariates

A number of covariates that have been shown to influence BMD, fracture, or fall risk were examined (19–25). Demographic variables included age at study entry, sex, and neighborhood income quintile based on census data for their postal code (26). Medications (any prescription within 1 year of index date) included estrogen (in women), nitrates, hydroxymethylglutaryl-CoA reductase inhibitors (statins), thiazide diuretics, inhaled corticosteroids, anticonvulsants, bisphosphonates, and a composite category of drugs that may promote falls such as β-blockers, sedatives, tranquilizers, antidepressants, antiparkinsonian drugs, and opiates (at least one prescription from this category versus none) (23).

We also assessed variables associated with diabetes that may influence falls and fractures. Comorbidity at baseline was estimated using the Johns Hopkins Adjusted Clinical Group Case-Mix assignment software (Sun Sparc/Solaris version 4.52) (27). This software assigns diagnostic categories based on ICD-9 codes from administrative outpatient records, and the collapsed ambulatory diagnostic group category of "unstable chronic disease" was used as a marker of comorbidity. This category includes conditions such as diabetes, heart disease, vascular disease, renal failure, malignancy, and other major chronic illnesses; however, the diagnostic code for diabetes was excluded. Other conditions examined were prior myocardial infarction, stroke (28,29), visual impairment (retinopathy, laser treatment, vitrectomy, cataracts, or visual loss) (2,5), peripheral neuropathy (30,31), and major or minor amputations (32). Health care utilization may also influence fracture prevention measures, and patterns may differ between those with and without diabetes (33). We therefore assessed the number of primary care or internal medicine physician visits per year and the number of BMD tests over the follow-up period. Because diabetes duration and insulin treatment have been associated with fracture risk (5,6,14,15), we examined the effect of prevalent versus incident diabetes and insulin treatment on fractures within the diabetes group.

Statistical analyses

Baseline characteristics among individuals with and without diabetes were examined using means and *t* tests for continuous variables and proportions and χ^2 tests for categorical variables. We examined the distribution of the continuous variables, and those not normally distributed were converted into categorical variables based on the distribution. Cox proportional hazards regression was used to estimate the hazard ratio (HR) of a hip fracture by diabetes. A multivariable model was used to adjust for covariates that were significantly associated ($P < 0.05$) with hip fractures on univariate analyses. We assessed for correlations between collinear and potentially collinear variables, and only the most relevant variables on the basis of clinical plausibility and prior literature were kept in the model. We examined for interactions between diabetes and the other covariates and sex and the other covariates. Multivariable subgroup analyses were done within diabetes groups to assess for the effect of incident versus prevalent diabetes and insulin treatment. All analyses were done using SAS statistical software (version 8).

Ethics

Ethics approval was obtained from the institutional review board at Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada.

RESULTS — We identified 388,056 individuals with diabetes between 1 April 1994 and 31 March 1995 (97,090 women and 100,322 men), and 207,252 individuals with diabetes met the inclusion criteria. The matched nondiabetes comparison group consisted of 414,504 individuals. After excluding 9,840 residents of long-term care facilities with diabetes, there were 197,412 individuals with diabetes (174,256 with prevalent diabetes and 23,156 incident diabetes cases). The index date was in fiscal year 1994 in 142,561 individuals with diabetes (72.2%) who were at least 66 years old at that time, and the index date was their 66th birthday for 54,851 individuals (27.8%) who were <66 years old at accrual (Fig. 1). The final comparison group consisted of 401,400 individuals (198,525 women and 202,875 men) after 13,104 long-term care residents were excluded.

There were minor differences in age-group breakdown between individuals with and without diabetes. Those with diabetes were more likely to reside in the lowest and less likely to reside in the highest income neighborhoods (with 2.6% incomplete income data) and were more likely to be taking at least one drug that increases falls or decreases BMD, with the exception of estrogen treatment in women. Individuals with diabetes also had greater comorbidity and more physician visits but were less likely to have had a BMD test compared with those without diabetes (Table 1).

Table 1—*Baseline variables by diabetes status stratified by sex*

Variable	Women			Men		
	Diabetes	No diabetes	*P*	Diabetes	No diabetes	*P*
n	97,090	198,525		100,322	202,875	
Age-group						
66–75 years	73.6	72.7	<0.001	80.0	79.6	0.037
76–90 years	25.5	26.2		19.6	19.9	
91+ years	0.9	1.0		0.4	0.4	
Income quintile						
Lowest	26.2	20.5	<0.001	21.2	18.3	<0.001
Highest	13.7	19.3	<0.001	17.3	20.9	<0.001
Comorbidity						
Chronic unstable disease	44.9	32.6	<0.001	51.4	39.8	<0.001
Previous myocardial infarction	3.3	1.0	<0.001	4.5	2.1	<0.001
Previous stroke	1.5	0.6	<0.001	2.3	1.0	<0.001
Visual impairment	29.5	20.4	<0.001	22.8	14.6	<0.001
Neuropathy	3.7	1.7	<0.001	4.5	1.9	<0.001
Amputation	0.3	0.0	<0.001	0.6	0.0	<0.001
Medications affecting BMD						
Nitrates	18.7	8.5	<0.001	20.1	11.3	<0.001
Statins	13.6	7.7	<0.001	13.6	8.1	<0.001
Thiazides	20.7	17.1	<0.001	13.3	9.7	<0.001
Inhaled corticosteroids	7.3	5.8	<0.001	6.6	6.1	<0.001
Anticonvulsants	1.0	0.7	<0.001	1.0	0.6	<0.001
Estrogen	10.2	15.2	<0.001			<0.001
Medications affecting risk of falling*	59.5	47.1	<0.001	52.3	40.1	<0.001
Health care utilization						
Number physician visits/year						
≤3	8.5	25.2	<0.001	8.7	28.2	<0.001
4–6	18.0	28.4		18.5	28.1	
7–10	30.0	25.7		29.7	23.7	
≥11	43.6	20.7		43.1	20.0	
At least 1 BMD test	22.3	33.1	<0.001	3.6	4.7	<0.001

Data are %. *Medications include β-blockers, sedatives (benzodiazepines, barbiturates, and chloral hydrate), antidepressants (tricyclic and selective serotonin reuptake inhibitors), antiparkinsonian drugs (levodopa, bromocriptine, pergolide, ropinirole, and pramipexole), and opiates (codeine and morphine).

Hip fractures

Over a mean follow-up period of 6.1 years (range 1 day–9 years), there were 22,267 hip fractures: 15,547 (69.8%) in women (8.87 per 1,000 person-years) and 6,720 (30.2%) in men (3.94 per 1,000 person-years). Of those without fractures, 66.8% were followed until 31 March 2003, 26.2% died before the end of the follow-up, 6.9% moved from the province, and 0.12% were censored because of a pathological or trauma-related hip fracture.

Women had significantly more fractures than men (unadjusted HR 2.22 [95% CI 2.16–2.28]), and diabetes was also associated with a significant increase in fractures (1.20 [1.16–1.23]). However, an interaction ($P < 0.0001$) was found between sex and diabetes, as well as between sex and income, comorbidity, statin treatment, BMD tests, and insulin treatment. Therefore, all analyses presented are stratified by sex. Diabetes increased fracture risk by ~20% in both women and men, and multivariable adjustment attenuated the association in both groups (Table 2). Variables found to increase fracture risk were age, chronic unstable disease (comorbidity), prior stroke, prior myocardial infarction, visual impairment, neuropathy, amputation, physician visits, and at least one prescription for medications that increase falls (such as β-blockers, sedatives, antidepressants, antiparkinsonian drugs, and opiates), inhaled corticosteroids, and anticonvulsants. Bisphosphonate prescriptions were also found to increase fracture risk; however, because this probably represented a marker of osteoporosis rather than a treatment effect, we excluded it from our final analysis. Variables that were associated with lowered fracture risk included a prior BMD test; at least one prescription for nitrates, statins, thiazides, and estrogen in women; and income quintile in men. Significant correlations were found between prior myocardial infarction and stroke, prior myocardial infarction and comorbidity, and physician visits and comorbidity. Because stroke and comorbidity were felt to be more important risk factors for falls and fractures (28,29,34), previous myocardial infarction and physician visits were removed from the final models.

CONCLUSIONS — In this study, diabetes was associated with a 20% increased risk of hip fractures in both women and men, and, although attenuated, the risk remained significantly increased (11 and 18%, respectively) after adjustment for a number of risk factors for fractures. These findings are surprising in light of previous studies indicating that individuals with type 2 diabetes have, on average, higher BMD than their nondiabetic counterparts (9,10).

Table 2—*Hip fracture rates by diabetes status stratified by sex and results from univariate and multivariable Cox regression models*

	Hip fractures		HR (95% CI)	
	n	Incidence/ 1,000 PY	Univariate	Multivariable
Women				
No diabetes	10,276	7.77	1.00	1.00
Diabetes	5,271	9.09	1.20 (1.16–1.24)	1.11 (1.08–1.15)*
Diabetes only				
Incident	454	6.92	1.00	1.00
Prevalent	4,817	9.36	1.34 (1.22–1.48)	1.24 (1.13–1.37)†
No insulin	4,217	8.68	1.00	1.00
Insulin	1,054	11.19	1.34 (1.25–1.43)	1.34 (1.26–1.44)‡
Men				
No diabetes	4,408	3.49	1.00	1.00
Diabetes	2,312	4.13	1.22 (1.16–1.28)	1.18 (1.12–1.24)§
Diabetes only				
Incident	193	2.92	1.00	1.00
Prevalent	2,119	4.29	1.44 (1.25–1.67)	1.37 (1.18–1.59)‖
No insulin	1,826	3.81	1.00	1.00
Insulin	486	5.98	1.64 (1.48–1.81)	1.65 (1.49–1.83)¶

Medications that increase risk of falling include β-blockers, sedatives (benzodiazepines, barbiturates, and chloral hydrate), antidepressants (tricyclic and selective serotonin reuptake inhibitors), antiparkinsonian drugs (levodopa, bromocriptine, pergolide, ropinirole, and pramipexole), and opiates (codeine and morphine). *Adjusted for age-group; chronic unstable disease; prior stroke; visual impairment; neuropathy; amputation; treatment with nitrates, statins, anticonvulsants, inhaled corticosteroids, thiazides, estrogen, and medications that increase risk of falling; and history of BMD test. †Adjusted for age-group; insulin treatment; chronic unstable disease; prior stroke; visual impairment; neuropathy; treatment with statins, thiazides, estrogen, and medications that increase risk of falling; and history of BMD test. ‡Adjusted for age-group; prevalent diabetes; chronic unstable disease; prior stroke; visual impairment; neuropathy; treatment with statins, thiazides, estrogen, and medications that increase risk of falling; and history of BMD test. §Adjusted for age-group; chronic unstable disease; prior stroke; visual impairment; neuropathy; amputation; treatment with nitrates, statins, anticonvulsants, inhaled corticosteroids, and medications that increase risk of fall; history of BMD test; and income quintile. ‖Adjusted for age-group; insulin treatment; chronic unstable disease; prior stroke; visual impairment; neuropathy; treatment with statins, thiazides, anticonvulsants, and medications that increase risk of falling; history of BMD test; and income quintile. ¶Adjusted for age-group; prevalent diabetes; chronic unstable disease; prior stroke; visual impairment; neuropathy; treatment with statins, thiazides, anticonvulsants, and medications that increase risk of falling; history of BMD test; and income quintile. $P < 0.0001$ for diabetes vs. no diabetes, insulin vs. no insulin; $P < 0.001$ for prevalent vs. incident diabetes. PY, person-years.

Our results confirm those of other studies that have demonstrated an increased risk of hip fractures, predominantly among older women with diabetes (4–6,14–16). We also found that the risk of hip fractures is increased in older men with diabetes, a particularly important finding as men tend to be underdiagnosed and undertreated for osteoporosis (35).

Why might patients with type 2 diabetes have an increased risk of fracture despite, on average, higher BMD compared with that of the general population (8–10)? One explanation may be that BMD does not account for all of fracture risk in this population (36). For example, patients with diabetes may be more likely to fall because of higher rates of visual impairment, neuropathy, or cerebrovascular disease, which may increase the risk of fractures (2,15,28–31). Our findings support this concept: we found that diabetic subjects were more likely to have risk factors for falls such as visual impairment, neuropathy, stroke, and chronic unstable disease and were more likely to have prescriptions for fall-promoting medications. In addition, the pattern and mechanism of falls may be different in diabetes. Diabetic neuropathy and neuromuscular impairment may increase the likelihood of fracture by predisposing individuals to more severe falls or falls toward the side, both of which have been associated with higher hip fracture rates (37–39).

In addition to an increased risk of falls, type 2 diabetes may be associated with factors that influence bone strength and quality. For example, individuals with diabetes may have impaired vitamin D and calcium metabolism (40,41), which may increase bone fragility independent of BMD. Dysglycemia may also lead to increased accumulation of advanced glycation end products in bone collagen, which may increase bone stiffness and fracture susceptibility (42,43). Finally, elevated blood glucose may impair calcium deposition and subsequent mineralization, which could impair bone quality and increase fracture risk (44).

We also found that patients with diabetes for at least 2 years had a higher risk of fractures compared with those with newly diagnosed diabetes. This finding suggests that a longer diabetes duration increases fracture risk, consistent with other studies (5,6,15). A longer duration of diabetes may be associated with increased risk of falls or impaired bone quality, possibly due to more prolonged exposure to dysglycemia. Insulin treatment was also associated with higher fracture rates among individuals with diabetes. Some (6,14), but not all (5,16), prior studies reported an increased risk of fractures with insulin treatment. Insulin treatment may be a marker of disease duration or severity, which may explain the association between insulin treatment and fractures. However, we found that the association persisted after adjustment for prevalent diabetes, a marker of diabetes duration. An alternative explanation may be that insulin induces hypoglycemia and increases numbers of falls; we could not test this hypothesis in our study. The positive association between insulin treatment and increased fractures is somewhat surprising given in vitro data suggesting that insulin, via insulin-like growth factor–I, has anabolic effects on bone (45,46), and one would expect this effect to translate to an increase in BMD in vivo. However, our study and others highlight that, at least among individuals with type 2 diabetes, there are factors other than BMD that contribute to fracture risk.

Our study has several strengths. We used population-based data across a large geographically and ethnically diverse jurisdiction. In addition, comprehensive health care administrative data were deterministically linked using a unique numeric identifier, and individuals with diabetes were identified using a validated administrative data algorithm. With almost 600,000 individuals, this was the largest study to examine this association. There are, however, limitations to our findings. First, the use of administrative data confers a potential for misclassification. Based on validation of our diabetes

database (18), up to 14% of diabetes cases may have been missed. However, at most this would have underestimated our findings because of misclassification of diabetes cases in the comparison group. Second, although it is likely that the vast majority of our diabetic group had type 2 diabetes, we could not differentiate between type 1 and type 2 diabetes. It is possible that the inclusion of some type 1 diabetic patients contributed to the higher fracture risk associated with prevalent diabetes and insulin treatment. Third, we were not able to adjust for a number of important variables that may have an impact on fracture risk, including falls, BMD, calcium and vitamin D status, and glycemic control. Fourth, most covariates were ascertained at baseline, which may not fully reflect their impact at the time of fracture. Finally, we did not examine other fractures, such as vertebral or wrist fractures or those of the ankle and foot, which may be more common in patients with diabetes (15).

In summary, this population-based study showed a significant increase in hip fractures among both men and women with diabetes. The prevalence of diabetes has increased dramatically over the past 20 years; global estimates approached 170 million in 2000 (47). Moreover, with the current obesity epidemic, this number is expected to double by 2030 (47). Therefore, even a small increase in hip fracture risk among individuals with diabetes, regardless of the reason, will have a substantial public health impact. In addition, the morbidity and mortality after hip fractures may be even greater with individuals with diabetes because of their higher rates of comorbidity and disability. Until there is further understanding of the mechanisms of diabetes and fractures, broad fracture risk assessment of all diabetic patients and enhanced prevention strategies in this population are warranted.

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