JOURNAL OF BONE AND MINERAL RESEARCH
Volume 23, Number 8, 2008
Published online on March 17, 2008; doi: 10.1359/JBMR.080323

Fracture Risk in Type 2 Diabetes: Update of a Population-Based Study

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ABSTRACT: We found no significant excess of fractures among Rochester, MN, residents with diabetes mellitus initially recognized in 1950–1969, but more recent studies elsewhere have documented an apparent increase in hip fracture risk. To explore potential explanations for any increase in fractures, we performed an historical cohort study among 1964 Rochester residents who first met glycemic criteria for diabetes in 1970–1994 (mean age, 61.7 ± 14.0 yr; 51% men). Fracture risk was estimated by standardized incidence ratios (SIRs), and risk factors were evaluated in Andersen-Gill time-to-fracture regression models. In 23,236 person-years of follow-up, 700 diabetic residents experienced 1369 fractures documented by medical record review. Overall fracture risk was elevated (SIR, 1.3; 95% CI, 1.2–1.4), but hip fractures were increased only in follow-up beyond 10 yr (SIR, 1.5; 95% CI, 1.1–1.9). As expected, fracture risk factors included age, prior fracture, secondary osteoporosis, and corticosteroid use, whereas higher physical activity and body mass index were protective. Additionally, fractures were increased among patients with neuropathy (hazard ratio [HR], 1.3; 95% CI, 1.1–1.6) and those on insulin (HR, 1.3; 95% CI, 1.1–1.5); risk was reduced among users of biquanides (HR, 0.7; 95% CI, 0.6–0.96), and no significant influence on fracture risk was seen with sulfonylurea or thiazolidinedione use. Thus, contrary to our earlier study, the risk of fractures overall (and hip fractures specifically) was increased among Rochester residents with diabetes, but there was no evidence that the rise was caused by greater levels of obesity or newer treatments for diabetes.
J Bone Miner Res 2008;23:1334–1342. Published online on March 17, 2008; doi: 10.1359/JBMR.080323

Key words: cohort study, diabetes, epidemiology, fractures, hip fracture

INTRODUCTION

We thought we had conducted a definitive study when we assessed fracture risk among all 986 Rochester, MN, residents initially diagnosed with diabetes mellitus in 1950–1969: these laboratory-confirmed cases were matched by age and sex to randomly selected community controls without diabetes, and both diabetic and control cohorts were followed for >10,000 person-years with comparable ascertainment of all clinically diagnosed fractures through review of each subject's complete community medical records.[1] Compared with controls, there was no increase in fractures other than the known association of diabetes with lower limb fractures.[2–4] Indeed, there seemed to be an overall reduction in osteoporotic fractures, with a relative risk of subsequent proximal femur (hip) fractures of only 0.8.[1] This is consistent with the fact that 82% of the study subjects had non–insulin-dependent (type 2) diabetes, and most studies have found unchanged or increased BMD in such individuals.[5] Given the quantitative relation between fracture risk and BMD of the femoral neck,[6] a 0.27 SD increase in hip BMD in patients with type 2 diabetes[7] would be expected to result in a 10% reduction in fracture risk generally and an 18% reduction in hip fractures.

However, a systematic review of more recent reports suggests that hip fracture risk is now elevated among diabetic women and men.[8] For example, in the Study of Osteoporotic Fractures, 48 of 657 elderly women with self-reported diabetes had a self-reported (but radiographically confirmed) hip fracture compared with 501 of 8997 nondiabetic women; the relative risk of hip fracture was 1.8 and was little altered by adjustments for age, body mass index (BMI), calcaneal BMD, or a host of other osteoporosis risk factors.[9] Similarly, the Iowa Women's Health Study found a 1.7-fold increase based on 38 self-reported hip fractures among 1682 postmenopausal women with self-reported diabetes.[10] Other than insulin use and longer duration of diabetes, consistent determinants of fracture risk in these patients have not been apparent.[8–14]

Presuming that these epidemiologic data are all correct, the possibility arises that fracture risk has changed substantially over time. Whereas secular trends in fracture incidence have been modest,[15,16] diabetes has increased dramatically: in Rochester, the age-adjusted incidence rose 67% in men and 42% in women between 1970 and 1994.[17] This change was accompanied by a marked increase in obesity, including a doubling of diabetic patients who were morbidly obese (BMI ≥ 40 kg/m^2) when their diabetes was

The authors state that they have no conflicts of interest.

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recognized.[18] However, fat mass protects against hip fractures by limiting impact forces during falls,[19] maintaining hip strength through skeletal loading[20] and preserving bone mass through enhanced endogenous estrogen production.[21] Therefore, one might have expected a further reduction in fracture risk over time, not an increase. Moreover, a recent meta-analysis concluded that there is no association of diabetes with distal forearm or vertebral fractures,[8] the other traditional osteoporotic fracture sites. Instead, a stronger link is usually seen with lower limb fractures, which is variously ascribed to diabetic neuropathy, peripheral vascular disease or impaired lower limb function generally rather than to osteoporosis.[1–4,9,22–24]

Regardless of the exact pathophysiology responsible for these fractures, the number of diabetic individuals in this country is rising rapidly in association with the ongoing obesity epidemic.[25] An estimated 10% of the U.S. population ≥45 years of age will have diabetes in 2010,[26] and it is imperative to know, as a practical matter, whether their risk of fractures is really increased. Thus, we followed a new population-based cohort of patients to determine whether adult-onset diabetes is associated with an increase in fractures of all types, whether this represents a change from the past, and whether fracture risk is related to morbid obesity, diabetes treatment, or the comorbid conditions linked with diabetes.

MATERIALS AND METHODS

Rochester is well suited for disease association studies such as this because comprehensive medical records for the residents are available for review and are accessible through a centralized index to diagnoses made by essentially all medical care providers serving the local population.[27] After approval by Mayo's Institutional Review Board, this unique database (the Rochester Epidemiology Project) was used to identify 1992 Rochester residents who first met glycemic criteria for diabetes mellitus from January 1, 1970 through December 31, 1994. As described in detail elsewhere,[17] all Rochester residents who met research criteria for type 2 diabetes (i.e., onset at age ≥30 yr) were identified using a two-stage ascertainment protocol: first, residents ever assigned any diagnosis suggestive of diabetes were selected from the database, assuming that the chronic nature of the condition would ultimately lead to a clinical diagnosis for most individuals. Community medical records (including all glucose values) for each candidate case were reviewed by trained data abstractors, beginning with the date of first contact with a local health care provider until emigration, death, or December 31, 1994. Standardized criteria that approximated National Diabetes Data Group (NDDG) recommendations[28] were applied to confirm case status (i.e., two consecutive fasting plasma glucose levels ≥ 7.8 mmol/dl [140 mg/dl] or both 1- and 2-h levels ≥ 11.1 mmol/dl [200 mg/dl] during a standard oral glucose tolerance test as recorded in contemporary medical records). Individuals who failed to meet glycemic criteria, but who used oral agents or insulin for at least 2 wk or until death, were also included.

After additional approval by the Institutional Review Board, these confirmed cases were followed forward in time through their linked medical records in the community (retrospective, or historical, cohort study) until death or the most recent clinical contact. However, 19 subjects were excluded because they declined to authorize the use of their medical records for research[29]; 2 additional subjects were deleted who only had gestational diabetes, and a further 7 were removed who proved not to be Rochester residents at the time they first met glycemic criteria. Thus, 1964 diabetic Rochester residents were included in this analysis. Their complete inpatient and outpatient community medical records were reviewed by trained nurse abstractors to collect information about lifestyle factors (e.g., tobacco and alcohol use, reproductive history), as well as a diverse array of conditions predisposing to secondary osteoporosis (e.g., rheumatoid arthritis, hyperparathyroidism, malabsorption syndrome) or to falls (e.g., stroke, epilepsy, parkinsonism).[30] BMI was recorded at the time diabetes criteria were met, and obesity was defined as BMI ≥30 kg/m^2 and morbid obesity as BMI ≥40 kg/m^2.[25] Physical activity was assessed on a six-point scale, with subjects in the highest two categories classified as physically active. In addition, detailed data were collected from contemporary clinical notes regarding the use of various classes of drugs associated with bone loss or osteoporosis treatment, as well as diabetes treatments and clinically diagnosed diabetic comorbidities (i.e., neuropathy, nephropathy, and retinopathy).

All inpatient and outpatient records at any local provider of medical care were searched for the occurrence of any fracture. Mayo Clinic records, for example, contain the details of every inpatient hospitalization, every outpatient office or clinic visit, all emergency room and nursing home care, as well as all laboratory results, all radiographic and pathology reports, including autopsies, and all correspondence with each patient.[27] The records contained the clinical history and the radiologist's report of each fracture, but the original radiographs were not available for review. Thus, the diagnosis of vertebral fracture was accepted on the basis of a radiologist's report of compression or collapse of one or more vertebrae.[31] Ascertainment of clinically evident fractures is believed to be complete.[16] Fractures were classified according to the circumstances of the injury: by convention, daily activities and falls from standing height or less were considered moderate trauma, whereas motor vehicle accidents and falls from a greater height were deemed severe trauma.

The influence of diabetes on fracture risk was evaluated using three basic methods of analysis, all carried out in SAS (SAS Institute, Cary, NC, USA). The primary analysis compared the number of fractures observed at each skeletal site (based on the first fracture of a given type per person) to the number expected in this cohort during their follow-up in the community (i.e., standardized incidence ratios [SIRs]). Expected numbers were derived by applying calendar year–, age-, and sex-specific incidence rates from the local population for these fractures[15,16,31–36] to the calendar year–, age-, and sex-specific person-years of follow-up in the diabetes cohort and summing over the strata. 95% CIs

for the SIRs were calculated assuming the expected rates are fixed and the observed fractures follow a Poisson distribution.[37]

In the second method of analysis, the cumulative incidence of a new fracture (1 minus the probability of survival-free-of-fracture) was projected for up to 30 yr after the recognition of diabetes using product-limit methods.[38] In the customary approach, patients who die are censored; when the death rate is high, however, this overestimates cumulative fracture incidence as observed by attending physicians. Therefore, we treated death as a competing event in this analysis.[39] Kaplan-Meier methods were also used to assess survival, with expected death rates from the Minnesota white population. Observed and expected cumulative incidence estimates, as well as survival curves, were compared using the log-rank test.[40]

In the final approach, Andersen-Gill time-to-fracture regression models[41] were used to assess the impact of various covariates (e.g., age when glycemic criteria were met, prior fracture history, BMI, insulin use) on the subsequent risk of fracture among the diabetic patients. These models allow for the use of multiple fractures per subject while appropriately accounting for the correlation. Univariate relationships between the risk of specific fractures and each clinical characteristic under consideration were first assessed. Stepwise methods with forward selection and backward elimination were used to choose independent variables for the final models. The dependent variable was time until fracture, and the independent variables were age, sex, and the clinical characteristics at baseline; the various drug exposures were handled as time-dependent variables. For both univariate and multivariate models, the assumption of proportional hazards was examined and was not violated for the variables considered.

RESULTS

The mean ± SD age of the Rochester residents when glycemic criteria for diabetes were met was 61.7 ± 14.0 yr (median, 62 yr; range, 30–97 yr), and 992 (51%) were men. Ninety-six percent were white, reflecting the racial composition of the community (98% white in 1980). On average, these patients had been attended in the community for 32.6 yr (median, 33 yr) before recognition of their diabetes and for 11.8 yr afterward (median, 12 yr). As anticipated, survival was impaired in this cohort: By 30 yr after diabetes criteria were met, only 10% were still alive compared with an expected 24%. Ninety-five percent of the subjects were followed for fractures until the time of death or at least 2000 if they were still alive.

During 23,236 person-years of follow-up in this cohort (range, 1 day to 37 yr per subject), 700 diabetic individuals experienced 1369 different fractures. After 30 yr of follow-up, an estimated 52% of these patients had experienced at least one new fracture (Fig. 1). Almost one fifth of the fractures were caused by severe trauma (e.g., motor vehicle accidents), but the majority (71%) were attributed to moderate trauma (Table 1). Of these, 560 fractures were caused by a fall from standing height or less, whereas 414 (mostly vertebral and rib fractures) apparently occurred "spontaneously" in the course of everyday activities. The latter included 132 vertebral fractures found incidentally on radiographs taken for some other purpose. Altogether, 45 fractures (3%) resulted from a specific pathological lesion, and the etiology of the remaining 87 fractures was uncertain.

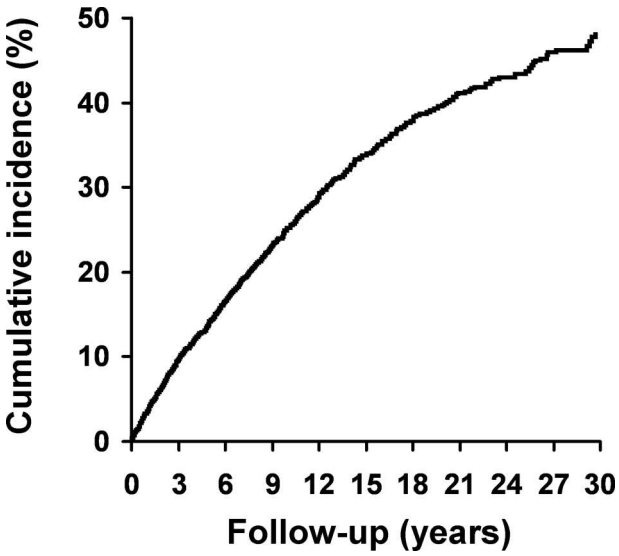

FIG. 1. Observed cumulative incidence of any fracture among 1964 Rochester, MN, residents after first recognition of diabetes mellitus in 1970–1994, with death considered a competing risk.

Compared with expected rates, there was a 1.3-fold (95% CI, 1.2–1.4) increase in overall fracture risk after the recognition of diabetes. Given the large number of fractures observed, the increase was statistically significant among men (SIR, 1.4; 95% CI, 1.3–1.6) and women (SIR, 1.3; 95% CI, 1.2–1.4). The relative risk of fractures at specific skeletal sites for men and women, separately, is delineated in Table 2. For both sexes combined, statistically significant increases were seen for a number of skeletal sites, particularly the vertebrae (SIR, 3.7; 95% CI, 3.3–4.1). Overall, the relative risk of any fracture of the axial skeleton was 1.8 (95% CI, 1.6–1.9) compared with only 1.1 (95% CI, 0.99–1.2) for all limb fractures combined.

The overall increase in fracture risk was confined to the subset of fractures attributed to moderate trauma (SIR, 1.5; 95% CI, 1.4–1.6). There was no increase in fractures from severe trauma (SIR, 1.0; 95% CI, 0.8–1.1) or pathologic causes (SIR, 0.8; 95% CI, 0.5–1.2). As previously noted, however, 132 vertebral fractures were found incidentally, along with 24 fractures at other sites. When nonpathological, nonincidental fractures caused by moderate trauma (two thirds of all fractures observed) were considered alone, the overall relative risk of an axial skeleton fracture was 1.4 (95% CI, 1.2–1.6) and was 2.8 (95% CI, 2.4–3.2) for that subset of vertebral fractures (Table 2). The relative risk of any osteoporotic fracture (hip, spine, or wrist fracture caused by moderate trauma but not pathologic nor incidental) was 1.0 (95% CI, 0.9–1.2) for women, 1.9 (95% CI, 1.6–2.3) for men, and 1.3 (95% CI, 1.1–1.4) for both sexes combined.

TABLE 1. DISTRIBUTION OF FRACTURES AMONG 1964 ROCHESTER, MN, RESIDENTS AFTER RECOGNITION OF DIABETES MELLITUS IN 1970–1994 BY FRACTURE SITE AND CAUSE

	Fracture cause					
	Severe trauma	*Fall from standing*	*Spontaneous*	*Pathological*	*Uncertain*	*All causes*
Fracture site	*n* (%*)	*n* (%*)	*n* (%*)	*n* (%*)	*n* (%*)	*n* (%†)
Skull/face	8 (28.6)	20 (71.4)	0 (0)	0 (0)	0 (0)	28 (2.1)
Hands/fingers	38 (57.6)	25 (37.9)	1 (1.5)	0 (0)	2 (3.0)	66 (4.8)
Distal forearm	11 (13.9)	66 (83.5)	0 (0)	0 (0)	2 (2.5)	79 (5.8)
Proximal humerus	7 (9.2)	63 (82.9)	2 (2.6)	2 (2.6)	2 (2.6)	76 (5.6)
Other arm	13 (34.2)	25 (65.8)	0 (0)	0 (0)	0 (0)	38 (2.8)
Clavicle/scapula/sternum	6 (20.0)	15 (50.0)	3 (10.0)	4 (13.3)	2 (6.7)	30 (2.2)
Ribs	40 (21.7)	63 (34.2)	38 (20.7)	12 (6.5)	31 (16.8)	184 (13.4)
Vertebrae	27 (6.0)	53 (11.8)	339 (75.2)	20 (4.4)	12 (2.7)	451 (32.9)
Pelvis	5 (8.8)	35 (61.4)	8 (14.0)	2 (3.5)	7 (12.3)	57 (4.2)
Proximal femur	13 (11.1)	95 (81.2)	1 (0.9)	3 (2.6)	5 (4.3)	117 (8.5)
Other leg	37 (29.4)	81 (64.3)	2 (1.6)	2 (1.6)	4 (3.2)	126 (9.2)
Feet/toes	58 (49.6)	19 (16.2)	20 (17.1)	0 (0)	20 (17.1)	117 (8.5)
All sites	263 (19.2)	560 (40.9)	414 (30.2)	45 (3.3)	87 (6.4)	1369 (100)

* Percentage (%) of each type of fracture.
† Percentage (%) of total.

The potential impact of duration of follow-up after the date that glycemic criteria for diabetes were met is explored in Table 3. For both sexes and at most skeletal sites, the risk of moderate trauma fractures (excluding pathological and incidental fractures) was slightly greater during follow-up beyond 10 yr compared with the first 10 yr of follow-up. For hip fractures, specifically, the relative risks were 1.5 (95% CI, 1.1–2.0) for late follow-up and 0.8 (95% CI, 0.6–1.1) for early follow-up, respectively. The estimated relative hip fracture risk for women in follow-up beyond 10 yr was 1.5 (95% CI, 1.04–2.1), whereas it was not increased in the first decade after the recognition of diabetes (SIR, 0.7; 95% CI, 0.5–1.03). Among men, the estimated relative risk of a hip fracture in follow-up beyond 10 yr was 1.5 (95% CI, 0.8–2.5) compared with 1.2 (95% CI, 0.7–1.9) in the first 10 yr.

The predictors of these fractures were assessed in multivariate models. As shown in Table 4, the independent predictors of any subsequent fracture ($n = 1369$) included the age when glycemic criteria were met (per 10 yr: hazard ratio [HR], 1.3; 95% CI, 1.2–1.4) and female sex (HR, 1.6; 95% CI, 1.3–1.9). History of a prior osteoporotic fracture was also an independent predictor of any new fracture (HR 1.6; 95% CI, 1.03–2.4), albeit only 48 subjects had experienced one. Greater physical activity (activity score 5 or 6: HR, 0.6; 95% CI, 0.5–0.8) and BMI (per unit increase: HR, 0.98; 95% CI, 0.97–0.99) were protective. Indeed, fracture risk was reduced even among those with BMI ≥30 or ≥40 kg/m^2 in the univariate analysis (data not shown). Fracture risk was elevated in patients with other conditions associated with secondary osteoporosis (HR, 1.2; 95% CI, 1.1–1.5) and users of systemic corticosteroids (HR, 1.6; 95% CI, 1.3–2.0) or specific osteoporosis treatments (e.g., oral bisphosphonates; HR 2.0; 95% CI, 1.4–2.9). Use of estrogen or selective estrogen receptor modulators (SERMs) did not influence fracture risk after adjusting for other factors (e.g., sex). There was no increase in fracture risk associated with a more recent year of meeting glycemic criteria for diabetes (HR, 1.0; 95% CI, 0.99–1.01).

Among the diabetes-specific factors, fracture risk was increased among persons with neuropathy (HR, 1.3; 95% CI, 1.1–1.6) but not those with clinically diagnosed nephropathy (HR, 1.1; 95% CI, 0.8–1.3) or retinopathy (HR, 1.0; 95% CI, 0.8–1.2) after adjustment for age. The risk was also enhanced among the 1075 who required insulin therapy to manage their diabetes (HR, 1.3; 95% CI, 1.1–1.5), although greater duration of insulin therapy had no additional effect. No increase in fractures was seen among the 1243 users of various sulfonylureas (HR, 0.9; 95% CI, 0.8–1.1) or the 159 treated with thiazolidinediones (TZD; HR, 0.7; 95% CI, 0.5–1.1) in age-adjusted analyses. Of the latter group, 46 patients took troglitazone, 21 of whom were later switched to rosiglitazone or pioglitazone, and 113 used only the latter agents. Use of biquanides was protective even after adjusting for other risk factors (HR, 0.7; 95% CI, 0.6–0.96). There was no association of fracture risk with baseline fasting plasma glucose level (per 10 mg/dl increase: HR, 1.0; 95% CI, 0.99–1.02). The same risk and protective factors were generally seen when the outcomes were restricted to the 1061 fractures attributed to moderate trauma, the 562 osteoporotic fractures that were observed, or the 101 hip fractures alone (Table 5).

DISCUSSION

In contrast to our earlier report that Rochester residents whose diabetes was initially diagnosed in 1945–1969 had no increase in fractures generally or hip fractures specifically,[1] this update among the residents who first met glycemic criteria for diabetes in 1970–1994 found significant increases in both of these categories. This could relate partly to use in the earlier study of criteria[42] analogous to recent American Diabetes Association criteria for diabetes,[43] whereas we used the more stringent NDDG glycemic criteria[28] applicable at the time our study cohort was identified; this defined a more severe clinical spectrum of disease.[42] In addition, the update may reflect greater use of imaging modalities. Thus, the greatest disparity in results

TABLE 2. FRACTURES OBSERVED AMONG 1964 ROCHESTER, MN, RESIDENTS AFTER RECOGNITION OF DIABETES MELLITUS IN 1970–1994 COMPARED WITH THE NUMBERS EXPECTED AND SIRS, WITH 95% CIS

	Women: all fractures			*Men: all fractures*			*Both sexes: all fractures*			*Both sexes: nonpathologic, nonincidental moderate trauma fractures*		
Fracture site	*Observed*	*Expected*	*SIR (95% CI)*	*Observed*	*Expected*	*SIR (95% CI)*	*Observed*	*Expected*	*SIR (95% CI)*	*Observed*	*Expected*	*SIR (95% CI)*
Skull/face	16	8.0	2.0 (1.2–3.3)*	12	14.5	0.8 (0.4–1.4)	28	22.5	1.2 (0.8–1.8)	20	9.8	2.0 (1.2–3.2)*
Hands/fingers	31	27.8	1.1 (0.8–1.6)	34	30.8	1.1 (0.8–1.5)	65	58.6	1.1 (0.9–1.4)	27	25.9	1.0 (0.7–1.5)
Distal forearm	61	56.6	1.1 (0.8–1.4)	13	13.1	1.0 (0.5–1.7)	74	69.7	1.1 (0.8–1.3)	63	53.5	1.2 (0.9–1.5)
Proximal humerus	53	25.5	2.1 (1.6–2.7)*	18	14.2	1.3 (0.8–2.0)	71	39.7	1.8 (1.4–2.3)*	62	31.8	2.0 (1.5–2.5)*
Other arm	23	19.8	1.2 (0.7–1.8)	14	10.7	1.3 (0.7–2.2)	37	30.4	1.2 (0.9–1.7)	24	21.9	1.1 (0.7–1.6)
Clavicle/scapula/sternum	15	13.0	1.2 (0.6–1.9)	15	14.7	1.0 (0.6–1.7)	30	27.7	1.1 (0.7–1.5)	18	13.8	1.3 (0.8–2.1)
Ribs	72	50.2	1.4 (1.1–1.8)*	78	54.3	1.4 (1.1–1.8)*	150	104	1.4 (1.2–1.7)*	101	72.5	1.4 (1.1–1.7)*
Vertebrae	198	63.4	3.1 (2.7–3.6)*	131	26.2	5.0 (4.2–5.9)*	329	89.6	3.7 (3.3–4.1)*	198	71.0	2.8 (2.4–3.2)*
Pelvis	40	31.3	1.3 (0.9–1.7)	11	9.1	1.2 (0.6–2.2)	51	40.4	1.3 (0.9–1.7)	44	31.9	1.4 (1.0–1.8)
Proximal femur	66	67.0	1.0 (0.8–1.2)	40	28.4	1.4 (1.01–1.9)*	106	95.4	1.1 (0.9–1.3)	92	83.8	1.1 (0.9–1.4)
Other leg	68	66.1	1.0 (0.8–1.3)	40	34.5	1.2 (0.8–1.6)	108	101	1.1 (0.9–1.3)	78	63.8	1.2 (0.97–1.5)
Feet/toes	72	46.8	1.5 (1.2–1.9)*	26	22.1	1.2 (0.8–1.7)	98	68.9	1.4 (1.2–1.7)*	53	20.8	2.5 (1.9–3.3)*
Any fracture	402	317	1.3 (1.2–1.4)*	298	205	1.4 (1.3–1.6)*	700	523	1.3 (1.2–1.4)*	497	386	1.3 (1.2–1.4)*

Note that the number of fractures observed at specific skeletal sites may differ from those reported in Table 1 because only the first fracture of each type per patient was counted in this analysis.
* $p < 0.05$.

was evident for vertebral fractures. Although the previous study directly compared diabetic subjects with equally followed age- and sex-matched controls, attention to vertebral fractures likely increased over time. Indeed, the crude incidence of vertebral fractures among those with diabetes was 3 per 1000 person-years in the earlier study compared with 15 per 1000 in this analysis. Because we estimated relative risk with standardized incidence ratios, there is a potential for bias: expected numbers were determined from clinically diagnosed fracture rates in this community, but such rates do not include fractures found incidentally on radiographs and never formally diagnosed (e.g., healed rib fractures and some vertebral body deformities), which may have been overascertained among the diabetic subjects. When the analysis was limited to moderate trauma fractures, but excluding pathologic fractures and those found incidentally, the relative risk of vertebral fracture fell from 3.7 to 2.8.

The overall increase was confined to the fractures caused by moderate trauma; fractures attributed to other causes were not increased compared with expected. Moderate trauma (or fragility) fractures are the ones linked most closely with osteoporosis. Although osteoporosis is increasingly identified clinically,[44] the increased fracture risk associated with diabetes did not seem to reflect a secular trend: each calendar year increase in the date that diabetes criteria were met (index year) was associated with an HR of 1.0. As expected, greater BMI was protective of fractures,[45] and fracture risk was lower even among the diabetic patients whose BMI at diagnosis was ≥30 or ≥40 kg/m^2. Fracture risk was slightly increased among the insulin users, as seen in a number of other studies,[10–13,46] but not among the users of sulfonylureas.[47] The earlier cohort of diabetic Rochester residents could have been exposed to these same agents, although insulin use was less frequent at that time.[48] Regarding the newer diabetic drugs, the biquanides were associated with a reduced risk of fractures, whereas TZDs were not associated with fracture risk after adjustment for age. The latter result conflicts with recent reports of greater bone loss among diabetic women treated with these agents[49] and an increase in appendicular fractures.[50,51] Among the 75 women in our study so treated (85% with exposure to rosiglitazone or pioglitazone) for durations up to 9 yr, the 6 appendicular fractures observed were slightly more than the 4.5 fractures expected.

There was, however, an important effect of diabetes duration. Compared with the first decade of follow-up after the recognition of diabetes, relative risk estimates for most specific fracture types, as well as overall fracture risk, were greater in follow-up beyond 10 yr. Our result is consistent with a recent Canadian study that documented an increase in osteoporotic fractures (including hip fractures) >5 yr after the diagnosis of diabetes but not before; indeed, newly diagnosed patients had reduced fracture risk.[14] This could help explain conflicting reports regarding hip fractures. Thus, elevated hip fracture risk is typically seen in studies of diabetic prevalence cohorts and patients with long follow-up[8] compared with diabetes inception cohorts with shorter follow-up where no excess hip fracture risk has been observed in some studies.[1,14,52] Greater duration of insulin

TABLE 3. SIRs, WITH 95% CIs, FOR MODERATE TRAUMA FRACTURES (EXCLUDING PATHOLOGIC FRACTURES AND THOSE FOUND INCIDENTALLY) AMONG 1964 ROCHESTER, MN, RESIDENTS AFTER RECOGNITION OF DIABETES MELLITUS IN 1970–1994, BY FOLLOW-UP INTERVAL

	Women		*Men*	
Fracture site	*<10 yr [SIR (95% CI)]*	*≥10 yr [SIR (95% CI)]*	*<10 yr [SIR (95% CI)]*	*≥10 yr [SIR (95% CI)]*
Skull/face	3.5 (1.7–6.4)*	3.4 (1.2–7.3)*	0.0 (0.0–1.2)	2.0 (0.5–5.1)
Hands/fingers	1.0 (0.5–1.8)	1.0 (0.4–2.1)	1.2 (0.5–2.4)	1.1 (0.3–2.9)
Distal forearm	1.1 (0.7–1.5)	1.2 (0.7–1.9)	1.5 (0.6–3.0)	1.6 (0.4–4.0)
Proximal humerus	1.9 (1.2–2.8)*	3.0 (1.9–4.4)*	1.0 (0.4–2.2)	1.7 (0.7–3.4)
Other arm	1.1 (0.5–2.0)	0.8 (0.3–1.9)	1.4 (0.5–3.3)	1.5 (0.3–4.4)
Clavicle/scapula/sternum	1.1 (0.4–2.6)	1.8 (0.6–4.1)	1.0 (0.3–2.5)	1.7 (0.5–4.3)
Ribs	1.2 (0.8–1.8)	1.4 (0.9–2.1)	1.6 (1.1–2.2)*	1.4 (0.8–2.2)
Vertebra	2.2 (1.7–2.7)*	2.3 (1.7–3.1)*	5.6 (4.1–7.3)*	3.8 (2.4–5.7)*
Pelvis	1.0 (0.6–1.6)	1.8 (1.1–2.8)*	0.9 (0.2–2.7)	2.6 (0.96–5.7)
Proximal femur	0.7 (0.5–1.03)	1.5 (1.04–2.1)*	1.2 (0.7–1.9)	1.5 (0.8–2.5)
Other leg	1.0 (0.6–1.4)	1.6 (1.0–2.3)	1.4 (0.8–2.2)	1.2 (0.5–2.4)
Feet/toes	2.1 (1.3–3.1)*	3.8 (2.4–5.7)*	2.2 (0.7–5.2)	1.4 (0.2–5.1)
Any fracture	1.1 (0.97–1.3)	1.3 (1.05–1.5)*	1.5 (1.2–1.8)*	1.5 (1.2–1.9)*

* $p < 0.05$.

TABLE 4. UNIVARIATE AND MULTIVARIATE HRs* FOR THE DEVELOPMENT OF ANY NEW FRACTURE (N = 1369) AMONG 1964 ROCHESTER, MN, RESIDENTS AFTER RECOGNITION OF DIABETES MELLITUS IN 1970–1994

Risk factor†	*Univariate [HR (95% CI)]*	*Age-adjusted [HR (95%CI)]*	*Multivariate [HR (95% CI)]*
Age at recognition (per 10 yr)	1.5 (1.4–1.6)	—	1.3 (1.2–1.4)
Female sex	1.7 (1.5–2.0)	1.6 (1.3–1.9)	1.6 (1.3–1.9)
Prior osteoporotic fracture	2.5 (1.6–3.8)	1.8 (1.2–2.7)	1.6 (1.03–2.4)
Physically active	0.4 (0.3–0.5)	0.5 (0.4–0.7)	0.6 (0.5–0.8)
BMI (per unit increase)	0.97 (0.95–0.98)		0.98 (0.97–0.99)
Secondary osteoporosis	1.5 (1.3–1.8)	1.4 (1.2–1.6)	1.2 (1.1–1.5)
Renal failure	1.8 (1.4–2.5)	1.6 (1.2–2.2)	
Falling factors	1.5 (1.2–1.7)		
Neuropathy	1.4 (1.2–1.7)	1.4 (1.2–1.7)	1.3 (1.1–1.6)
Use of insulin	1.3 (1.1–1.5)	1.5 (1.3–1.7)	1.3 (1.1–1.5)
Use of biquanides	0.6 (0.5–0.8)	0.7 (0.6–0.95)	0.7 (0.6–0.96)
Use of thiazolidinediones	0.6 (0.4–0.9)		
Use of corticosteroids	2.0 (1.6–2.4)	1.9 (1.6–2.3)	1.6 (1.3–2.0)
Use of osteoporosis drugs	3.1 (2.1–4.6)	2.5 (1.7–3.7)	2.0 (1.4–2.9)
Use of estrogens	1.4 (1.1–1.7)	1.5 (1.2–1.8)	
Use of progestins		2.2 (1.4–3.5)	
Use of SERMS	3.1 (1.6–6.2)	2.6 (1.3–5.3)	
Use of diuretics	1.3 (1.1–1.6)		
Use of anticoagulants	1.5 (1.3–1.8)	1.3 (1.1–1.5)	
Use of thyroid replacement	1.4 (1.2–1.7)	1.4 (1.2–1.7)	

* Proportional hazards models where the event is a fracture and the dependent variable is survival time (days) free of fracture.
† Only risk factors that were significant in the univariate and/or multivariate analysis are included in the table.

therapy did not account for the influence of diabetes duration on fracture risk.

Our results are also consistent with other work showing no association of diabetes with distal forearm fractures.[8] In contrast to many previous reports,[1–4,9,22–24] however, we found no overall increase in lower limb fractures, exclusive of the hip, although there was a 1.2-fold increase in ankle fractures that was not significant. The apparent increase in vertebral fractures is also at odds with most reports,[8] but this result was inflated by ascertainment bias. We observed 329 subjects with at least one vertebral fracture compared with only 90 expected on the basis of clinically evident vertebral fracture rates in the community.[31] Because the majority of vertebral fractures do not come to clinical attention,[53] it might be preferable to base the expected number on incidence rates derived from vertebral fracture prevalence data that take into account asymptomatic vertebral deformities.[54] Using the latter data, the expected number of subjects with a vertebral fracture rises to 304 and the resulting SIR falls to 1.0 (95% CI, 0.9–1.1). This agrees with detailed morphometric studies, which have found no association of diabetes with vertebral deformities.[9,55–58]

The other risk factors for fracture among the diabetic

TABLE 5. MULTIVARIATE HRs* FOR THE DEVELOPMENT OF A NEW MODERATE TRAUMA FRACTURE (N = 1061), OSTEOPOROTIC FRACTURE (N = 562), OR HIP FRACTURE (N = 101) AMONG 1964 ROCHESTER, MN, RESIDENTS AFTER RECOGNITION OF DIABETES MELLITUS IN 1970–1994

Risk factor†	*Moderate trauma [HR (95% CI)]*	*Osteoporotic fracture [HR (95%CI)]*	*Hip fracture [HR (95% CI)]*
Age at recognition (per 10 yr)	1.5 (1.4–1.7)	1.6 (1.5–1.8)	2.0 (1.7–2.5)
Female sex	1.8 (1.5–2.1)	1.6 (1.3–2.0)	
Prior osteoporotic fracture	1.7 (1.1–2.6)		
Physically active	0.6 (0.5–0.9)	0.7 (0.5–0.98)	0.5 (0.3–0.96)
BMI (per unit increase)	0.8 (0.7–0.99)	0.8 (0.6–0.98)	0.95 (0.91-0.99)
BMI (≥30)			
Secondary osteoporosis	1.4 (1.1–1.7)	1.4 (1.1–1.8)	
Falling factors	1.2 (1.01–1.5)	1.3 (1.1–1.7)	5.2 (2.7–10)
Neuropathy	1.4 (1.1–1.7)		
Use of insulin	1.3 (1.1–1.6)	1.3 (1.04–1.7)	
Use of biquanides	0.7 (0.5–0.97)		
Use of corticosteroids	1.5 (1.2–1.8)	1.6 (1.3–2.0)	
Use of osteoporosis drugs	2.0 (1.4–3.0)	2.2 (1.3–3.8)	3.9 (1.5–9.9)
Use of anticoagulants		1.4 (1.1–1.7)	

* Proportional hazards models where the event is a fracture and the dependent variable is survival time (days) free of fracture.
† Only risk factors that were significant in the multivariate analysis are included in the table.

subjects are not unexpected because they resemble those for the population generally as derived from an extensive analysis of the world's epidemiology data[59,60] and used by the World Health Organization (WHO) to create a new fracture risk prediction algorithm.[61] As expected from those analyses, fracture incidence was greater among the women and rose with age in both sexes. After adjusting for age, there was a 1.8-fold increase in fractures among the subjects who had already experienced an osteoporotic fracture. Indeed, such fractures are one of the strongest predictors of future fracture risk.[62] The new WHO fracture prediction algorithm also includes cigarette smoking and excessive alcohol intake as risk factors and higher BMI as a protective factor.[59] In this analysis, cigarette and alcohol use did not have a significant influence on future fracture risk, although the protective effect of higher BMI accords with previous work.[45]

The adverse effect of systemic corticosteroid use on fracture risk is well known,[63,64] but the WHO algorithm also considers secondary osteoporosis independently of corticosteroid use,[59] and we found an adverse effect of such conditions in aggregate. The term "secondary osteoporosis" includes many diverse disorders,[30] and we observed a particular association with renal failure in the univariate analysis (HR, 1.8; 95% CI, 1.4–2.5), although not with nephropathy generally. Renal failure has been linked to fracture risk in other studies,[65,66] in part on the basis of an increased likelihood of falling.[67] Falling contributes to fractures in diabetic patients generally,[5] and we saw a 1.5-fold increase in overall fracture risk among the subjects with one or more risk factors for falling, but this variable was not an independent predictor of fractures in the multivariate analysis after adjusting for peripheral neuropathy. The positive association of fractures with various osteoporosis drugs is because of the fact that elevated fracture risk is an indication for treatment: whereas these therapies can reduce fractures compared with untreated patients,[68] they do not eliminate the increased risk entirely.

This study has a number of strengths. The study subjects represented a large, population-based inception cohort registered at the time their diabetes was first confirmed. Because of the unique records linkage system in Rochester, which provides access to the medical records of the entire community,[27] there should be nearly complete ascertainment of diabetes by NDDG criteria to the extent that the condition came to clinical attention: one third of the population has at least one plasma glucose test annually,[17] and patients who were ever diagnosed with diabetes or a related condition were screened for the study.[69] The clinical characteristics were recorded before any knowledge of resulting fractures, which were documented in the detailed inpatient and outpatient medical records that spanned each subject's entire period of residency in the community. Fracture ascertainment should also be nearly complete because the vast majority come to medical attention.[16]

There are also corresponding limitations of a study based on medical records. One may be the generalizability of these data from a small Midwestern community that is predominantly white and better educated than the white population of the United States as a whole,[27] although the incidence of hip fractures in this community is quite comparable to national figures for U.S. whites generally.[15] More importantly, measurements of BMD or biochemical markers of bone turnover were not routinely performed, so the role of bone loss in fracture risk could not be assessed directly. However, fracture etiologies beyond osteoporosis are implied by the modest increases in overall fracture risk, especially among women, plus the failure of most other studies to find a strong association with vertebral fractures[8] along with the observation that bone density is generally increased in type 2 diabetes.[7] Unfortunately, observational studies do not represent a strong design for evaluating causality. Nonetheless, the data indicate that overall fracture risk may be modestly elevated, which is consistent with the 1.2-fold increase documented in a recent

meta-analysis.[8] The increase relative to our earlier study in the community did not seem to be related to morbid obesity or use of new diabetic treatments. Instead, the risk factors for fracture were generally those proposed to identify high-risk individuals for osteoporosis treatment in the nondiabetic population.[61] This suggests that standard osteoporosis assessment strategies can be used for most patients with type 2 diabetes.

ACKNOWLEDGMENTS

The authors thank Leona Bellrichard, RN, Marcia Erickson, RN, Wendy Gay, RN, Joan LaPlante, RN, and Barbara Nolte, RN, for assistance with data collection and Mary Roberts for help in preparing the manuscript. This project was supported in part by Grants AG-04875 and AR-30582 from the National Institutes of Health, U.S. Public Health Service.

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Received in original form September 25, 2007; revised form March 13, 2008; accepted March 13, 2008.