0021-972X/01/$03.00/0
The Journal of Clinical Endocrinology & Metabolism

Vol. 86, No. 1
Printed in U.S.A.

Older Women with Diabetes Have an Increased Risk of Fracture: A Prospective Study

ANN V. SCHWARTZ, DEBORAH E. SELLMEYER, KRISTINE E. ENSRUD, JANE A. CAULEY, HOLLY K. TABOR, PAMELA J. SCHREINER, SOPHIE A. JAMAL, DENNIS M. BLACK, AND STEVEN R. CUMMINGS, FOR THE STUDY OF OSTEOPOROTIC FRACTURES RESEARCH GROUP

Departments of Epidemiology and Biostatistics (A.V.S., D.M.B.) and Medicine (S.R.C.) and Division of Endocrinology (D.E.S.), University of California–San Francisco, San Francisco, California 94105; Section of General Internal Medicine, Minneapolis Veterans Affairs Medical Center (K.E.E.), Minneapolis, Minnesota 55417; Division of Epidemiology, University of Minnesota (K.E.E.), Minneapolis, Minnesota 55454; Department of Epidemiology (J.A.C.), University of Pittsburgh, Pittsburgh, Pennsylvania 15261; Department of Genetics and Division of Epidemiology, Department of Health Research and Policy (H.K.T.), Stanford University School of Medicine, Stanford, California 54305; and Women's College Hospital (S.A.J.), University of Toronto, Canada M5S 1B6

ABSTRACT

To determine whether type 2 diabetes is associated with fracture in older women, we analyzed data from 9654 women, age 65 yr or older, in the Study of Osteoporotic Fractures. Diabetes with age at onset 40 yr or older was reported by 657 women, of whom 106 used insulin. A total of 2624 women experienced at least one nonvertebral fracture during an average follow-up of 9.4 yr, and 388 had at least one vertebral fracture during an average interval of 3.7 yr.

Although diabetes was associated with higher bone mineral density, it was also associated with a higher risk of specific fractures. Compared with nondiabetics, women with diabetes who were not using insulin had an increased risk of hip [relative risk (RR), 1.82; 95% confidence interval (CI), 1.24–2.69] and proximal humerus (RR, 1.94; 95% CI, 1.24–3.02) fractures in multivariate models controlling for age, body mass index, bone density, and other factors associated with fractures and diabetes. Insulin-treated diabetics had more than double the risk of foot (multivariate adjusted RR, 2.66; 95% CI, 1.18–6.02) fractures compared with nondiabetics.

This study indicates that diabetes is a risk factor for hip, proximal humerus, and foot fractures among older women, suggesting that fracture prevention efforts should be a consideration in the treatment of diabetes. (*J Clin Endocrinol Metab* **86:** 32–38, 2001)

DIABETES MELLITUS IS generally not considered a risk factor for fracture among older women (1, 2). Previous studies evaluating the association between diabetes and fracture have produced conflicting results, but they have been relatively small or had limited ability to adjust for potential confounders (3–7). To test the hypothesis that type 2 diabetes is associated with risk of fractures among older women and to consider factors that might account for any association, we analyzed prospective data from the Study of Osteoporotic Fractures (SOF).

Materials and Methods

The SOF is a prospective cohort study of osteoporosis and fractures in older women. The study has been described in detail previously (8, 9). Briefly, 9704 non-black community-dwelling women aged 65 yr and older were recruited for the study from 1986–1988 from population-based listings in four areas: Portland, Oregon; Minneapolis, Minnesota; Baltimore, Maryland; and the Monongahela Valley near Pittsburgh, Pennsylvania. The Coordinating Center was located at the University of California–San Francisco. Black women were excluded because of their low rate of hip fracture (10). Women who could not walk independently and those with bilateral hip replacement were also excluded.

Received April 21, 2000. Revision received August 8, 2000. Accepted September 11, 2000.

Address correspondence and requests for reprints to: Ann V. Schwartz, Ph.D., University of California San Francisco, 74 New Montgomery Street, Suite 600, San Francisco, California 94105. E-mail: aschwartz@psg.ucsf.edu.

Participants attended a baseline clinic visit and returned for subsequent clinic visits approximately every 2 yr. The baseline visit was attended by 9704 women. At the second clinic visit, 8098 women attended and an additional 1021 provided questionnaire data by mail and telephone without attending the clinic. The visits included a self-administered questionnaire, questions administered by an interviewer, physical performance measures, and bone mineral density (BMD) measurement. All of the participants provided informed consent, and the protocol was approved by the institutional review boards of the participating institutions.

History of diabetes

At the baseline interview (1986–1988) participants were asked whether a doctor had ever told them that they had diabetes or "sugar" diabetes. Women who answered "yes" were also asked for their age at diagnosis, and whether they were currently using insulin. The interviewers did not obtain information on other antidiabetic medications. To limit the analyses to type 2 diabetes, those who were diagnosed before age 40 yr were excluded. This analysis included 9654 women. Fifty women were excluded: 25 women did not respond to the question regarding history of diabetes; 22 women with self-reported diabetes were younger than 40 yr old at diagnosis; and 3 women with diabetes did not report age at diagnosis.

Fracture ascertainment

Every 4 months participants were contacted by postcard or telephone to ask whether they had experienced any fractures. Women who reported a fracture were interviewed to determine its circumstances. Fractures due to major trauma such as a motor vehicle accident were excluded from these analyses. The average follow-up for nonvertebral fractures was 9.4 (±2.4) yr. In these analyses, we analyzed nonvertebral

fractures as a group and also analyzed hip, proximal humerus, distal forearm, ankle, and foot fractures separately.

Reported fractures were confirmed by review of radiology reports. In some cases, the presence or absence of a fracture could not be determined. These cases were identified as "uncertain" fractures and were excluded from these analyses. The percentage of fractures that were "uncertain" varied depending on the fracture location: hip (0.0%), proximal humerus (1.9%), distal forearm (3.3%), ankle (9.9%), foot (11.4%), and all nonvertebral (13.2%) fractures. The proportion of "uncertain" cases for each fracture location considered did not differ according to history of diabetes.

Incident vertebral fractures were determined morphometrically, comparing films from baseline and the third clinic visit (1993). The criteria for an incident vertebral fracture was a change of 20% and at least 4 mm in any of the three measured heights in each vertebrae (11, 12). The average time between the vertebral x-rays was 3.7 ($\pm$ 0.4) yr.

Covariates

Measurement of these variables has been described previously (8, 13–16). Briefly, at baseline, a self-administered questionnaire assessed self-reported health status, physical activity (walking for exercise and average time spent on feet each day), alcohol consumption in the past year (average number of drinks per week), current cigarette smoking, medical history (history of stroke, thyroid disease, or arthritis), falls in the previous year, and family fracture history. These questions were repeated at the fourth and fifth clinic visits. The questions concerning history of stroke and falls in the previous year were repeated at all follow-up visits.

During an in-clinic interview, participants were asked about their functional status (ability to perform six instrumental activities of daily living without assistance or the use of special equipment) and their current or past use of medications (oral estrogen, thyroid hormones, seizure medications, calcium supplements, benzodiazepines, or thiazide diuretics). Dietary calcium was estimated with a validated food frequency questionnaire, developed from the Second National Health and Nutrition Examination Survey (17). Total calcium was the sum of calcium supplements and dietary calcium. A modified version of the Mini-Mental State Examination was administered to measure cognitive function (18, 19). Participants were queried at all follow-up visits regarding functional status and current use of oral estrogen and thiazide diuretics.

Height was measured using a Harpenden stadiometer (Holtain Ltd., Dyved, UK), and weight was measured with a standard balance beam scale. Grip strength was assessed using a grip dynamometer (Preston Grip dynamometer; Takei Kiki Kogyo, Tokyo, Japan.), and the results for the right and left hands were averaged. Hip abductor and triceps extensor strength were measured on the right side using a hand-held dynamometer (Sparks Instruments and Academics, Coralville, IA) (20, 21). Static balance was measured by the length of time a participant could stand (up to 10 sec) with feet in the tandem position with the eyes closed. Gait speed (m/sec) was measured as the average time to complete two trials on a standard 6-m course. The chair stand test measured how long (sec) it took a participant to stand up from a chair five times, without using her arms. Vision measures included corrected visual acuity [letter charts of Bailey and Lovie (22)], near depth perception [random dot method (23) in sec of arc], far depth perception scored as the SD of four trials [Howard-Dolman device (24)], and contrast sensitivity (25) (Vistech contrast sensitivity test system, model 6500). Measurements of height, weight, grip strength, walking speed, tandem stand, and chair stand were repeated at subsequent clinic visits.

Peripheral neuropathy

At the second clinic visit (1998–1990), lower extremity vibration sensitivity was measured using the Vibratron II (Sensortek Inc., Clifton, NJ), and pressure sensitivity was measured using the Von-Frey type esthesiometer probes. The Vibratron II measure was administered using a two-alternative forced choice procedure (16, 26). Each participant was asked to determine which of two rods was vibrating after touching each rod to a warmed great toe. The vibration intensity was decreased until the participant made five errors in a row. Vibration threshold was calculated by averaging the five lowest intensities on which the participant scored correctly and the five errors, after excluding the highest and lowest values of these ten scores (reliability, r = 0.81). A lower vibration threshold indicates better sensitivity.

Esthesiometer testing was conducted on a warmed great toe (or adjacent toe if the great toe was missing) using six filaments of increasing size (3.22–6.10, logarithm of force applied, in 0.1 g). With the eyes closed, participants were asked to identify when the examiner was touching the toe with the filament. Participants were given two chances at each level, starting with the thinnest (least stiff and hardest to feel) of the six filaments. If an incorrect response was given, then the examiner moved to the next thicker filament. The test was terminated after two correct responses at a given level; a participant's score was equal to the size of the filament at that level (reliability, r = 0.70). The maximum (worse) score of the right and left sides was used in these analyses.

Bone densitometry

During the baseline visit, BMD was measured at the distal radius and the calcaneus (9), using single photon absorptiometry (OsteoAnalyzer; Siemens-Osteon, Wahiawa, HI). At the second clinic visit, BMD of the proximal femur (14) was measured using dual-energy x-ray absorptiometry (QDR 1000; Hologic, Inc., Waltham, MA). Measurement of bone density at the calcaneus was repeated at the fourth clinic visit.

Statistical analysis

Characteristics of the cohort are presented separately for women who reported no history of diabetes, women with diabetes who were not using insulin, and women with diabetes who were using insulin. χ^2 tests were calculated for categorical variables, and t tests were used for continuous variables to assess the statistical significance of differences between groups.

For nonvertebral fractures, the Cox proportional hazards model (27) was used to assess the association between diabetes and the time to first fracture after baseline. The risk of incident vertebral fracture was estimated using logistic regression models because the dates of occurrence for vertebral fractures were unknown. The SAS software (SAS Institute, Inc., Cary, NC) was used (28, 29).

Because risk factors for fracture differ depending on the fracture location, a separate multivariate model was developed for each skeletal site. A multivariate model for fracture site, using baseline characteristics, was constructed with backward elimination, retaining variables associated with fracture at P less than 0.05. The last five variables eliminated from the backward regression model were then each entered back into the model separately and retained if the association with fracture was statistically significant ($P < 0.05$). Variables were selected for initial entry into the multivariate models if they had previously been found to be associated with risk of hip (8, 30), proximal humerus (31), distal forearm (31), ankle (32), or foot (32) fractures in the SOF cohort or other studies and if they were significantly associated with diabetes ($P < 0.05$). The initial variables, in addition to history of diabetes, were: age, education beyond high school, maternal hip fracture, alcohol consumption in the past year, calcium intake, current caffeine intake, current estrogen use, current use of long-acting benzodiazepines, current use of thiazide diuretics, history of stroke, self-rated health compared with others, impairments in self-reported physical function, fell in the past year, resting pulse, body mass index (BMI), height, height loss since age 25, less than 4 h per day on feet, walking for exercise, grip strength, gait speed, tandem stand eyes closed, uses arms to stand up from chair, visual acuity, distant depth perception, near depth perception, contrast sensitivity, and calcaneal BMD. We modeled an interaction term for a possible interaction between diabetes and BMI but the term was not statistically significant ($P \geq 0.10$) for any of the fracture sites.

To evaluate peripheral neuropathy, models including only those women who had vibration sensitivity and light touch discrimination measured (at visit 2) and excluding fractures before visit 2 were constructed. The association between diabetes and fracture risk in a model adjusted for peripheral neuropathy, age, BMI, and BMD was compared with the association in a model adjusted for age, BMI, and BMD.

To account for changes in performance measures and health status during the course of follow-up, proportional hazards models using time-dependent covariates were constructed with backward regression. (A model with time-dependent covariates was not developed for vertebral fractures because the date of fracture was unknown.) The vari-

ables listed above for multivariate models were also initially entered into these models. Of these, the time-dependent variables were BMI, calcaneal BMD, on feet less than 4 h per day, alcohol consumption, height, height loss since age 25, falls in previous year, oral estrogen, thiazide diuretics, history of stroke, walking for exercise, self-rated health compared with others, any difficulty with daily tasks, tandem stand, walking speed, grip strength, and ability to stand from a chair without using arms.

Results

A history of diabetes with age at diagnosis of 40 yr or older was reported by 657 (6.8%) women. The average duration of diabetes was 9.2 (±7.9) yr. Of the 657 participants with diabetes, 106 (16.1%) reported using insulin at baseline. Participant characteristics, stratified by history of diabetes and insulin treatment, are reported in Table 1. As expected, women with diabetes had poorer performance on measures of balance and gait, peripheral neuropathy, and vision, and were more likely to report being in fair or poor health.

Diabetics had higher BMD at all three measured sites (Table 1). Even after adjustment for BMI and age, BMD among women with diabetes was 5.2% higher at the distal radius ($P < 0.001$), 5.1% higher at the calcaneus ($P < 0.001$), and 2.9% higher at the femoral neck ($P < 0.001$) compared with nondiabetics.

Of women without diabetes, 2426 (27.0%) had at least one nonvertebral fracture during the average follow-up of 9.4 yr; 198 (30.1%) women with diabetes experienced a fracture. For specific fracture sites, the number of women who had at least one fracture during follow-up is provided in Table 2.

Despite the finding of elevated BMD, the risk of all nonspine fractures was higher in women with diabetes in age-adjusted models [relative risk (RR), 1.22; 1.06–1.41]. When women with diabetes were stratified based on insulin use, both women who were and those who were not using insulin had an increased risk of all nonvertebral fractures compared with nondiabetics (Table 3). Among women with diabetes who were not using insulin, this increased risk seemed to be due to an elevated risk of hip and proximal humerus frac-

TABLE 1. Characteristics of older women in the SOF by history of diabetes and insulin treatment

Characteristic	Women without diabetes (n = 8997)	Noninsulin-treated type 2 diabetes (n = 551)	Insulin-treated type 2 diabetes (n = 106)
	Mean (SD)/%	Mean (SD)/%	Mean (SD)/%
Age at baseline (yr)	71.7 (5.4)	72.0 (5.1)	71.2 (5.0)
Height (cm)	159.3 (6.0)	158.7 (6.1)[a]	159.1 (6.1)
Height loss since age 25 (cm)	3.33 (3.03)	3.04 (2.90)[a]	3.06 (2.81)
BMI (kg/m^2)	26.3 (4.5)	28.8 (5.5)[a]	29.7 (5.1)[a]
Chronic conditions, lifestyle, and medications			
Duration of diabetes (yr)		8.3 (7.4)	14.2 (8.2)[b]
Resting pulse (beats/min)	68.9 (10.1)	70.9 (10.8)[a]	73.9 (12.0)[a,b]
Calcium intake (mg/day)	1062 (733)	992 (666)[a]	1019 (653)
Falls in year before baseline (visit 1)			
No falls	70.2%	68.2%	58.1%[a]
1 fall	19.3%	20.4%	24.8%
More than 1 fall	10.5%	11.5%	17.1%[a]
Falls in year before visit 5			
No falls	68.7%	62.6%[a]	57.4%
1 fall	19.0%	20.5%	14.8%
More than 1 fall	12.3%	16.9%[a]	27.9%[a]
Mother fractured hip	13.8%	8.8%[a]	6.2%
≤4 h on feet per day	9.3%	16.2%[a]	17.0%[a]
Drank alcohol past 12 months	71.7%	49.1%[a]	38.7%[a,b]
History of stroke	2.8%	6.0%[a]	10.6%[a]
Long-acting benzodiazepines (ever/never)	8.9%	12.8%[a]	11.3%
Current estrogen use	14.4%	6.7%[a]	8.6%
Vision			
Contrast sensitivity	56.7 (29.3)	50.0 (27.0)[a]	36.5 (24.5)[a,b]
Distant depth perception (cm)	2.24 (2.64)	2.36 (2.86)	3.20 (3.24)[a,b]
Strength and gait			
Grip strength (kg)	20.9 (4.3)	20.4 (4.5)[a]	19.8 (4.7)[a]
Grip strength at visit 5 (kg)	18.0 (6.6)	17.1 (7.2)	17.8 (9.5)
Walking speed (m/sec)	1.02 (0.22)	0.93 (0.21)[a]	0.90 (0.26)[a]
Walking speed at visit 5 (m/sec)	0.94 (0.24)	0.82 (0.28)	0.75 (0.31)
Peripheral neuropathy			
Vibration sensitivity[c] (vibration units)	5.75 (2.59)	6.54 (2.73)[a]	8.28 (4.02)[a,b]
Light touch discrimination[c] (log force, 0.1 gm)	4.32 (0.53)	4.41 (0.56)[a]	4.59 (0.58)[a,b]
BMD			
Calcaneal BMD (g/cm^2)	0.401 (0.094)	0.440 (0.103)[a]	0.449 (0.103)[a]
Calcaneal BMD at visit 4 (g/cm^2)	0.374 (0.093)	0.401 (0.106)[a]	0.407 (0.096)[a]
Distal radius BMD (g/cm^2)	0.360 (0.084)	0.387 (0.086)[a]	0.395 (0.088)[a]
Femoral neck BMD[c] (g/cm^2)	0.646 (0.109)	0.685 (0.124)[a]	0.681 (0.120)[a]

[a] $P < 0.05$ for comparison with nondiabetic women.
[b] $P < 0.05$ for comparison with noninsulin-treated diabetic women.
[c] Measured at second clinic visit. All others measured at baseline (visit 1) unless indicated otherwise.

TABLE 2. Incidence rates per 1000 person-years of fractures at specified skeletal sites by history of diabetes and insulin treatment

Fracture site	Total (n = 9654)	Women without diabetes (n = 8997)		Noninsulin-treated type 2 diabetes (n = 551)		Insulin-treated type 2 diabetes (n = 106)	
	n	n	Incidence rate/percent	n	Incidence rate/percent	n	Incidence rate/percent
All nonvertebral[a]	2624	2426	36.5	162	43.4	36	58.7
Hip	549	501	6.0	42	8.9	6	7.3
Proximal humerus	355	319	3.8	30	6.3	6	7.4
Distal forearm	595	560	6.8	27	5.7	8	10.0
Ankle	282	258	3.1	18	3.8	6	7.4
Foot	287	264	3.2	16	3.4	7	8.7
Vertebral[b]	388	365	4.1%	20	3.6%	3	2.8%

[a] Average follow-up for nonvertebral fractures was 9.4 (±2.4) yr.
[b] Women who experienced at least one incident vertebral fracture between the baseline and second clinic visits, on average 3.7 (±0.4) yr apart.

TABLE 3. Adjusted RRs[a] and 95% CIs for fracture among older women with diabetes, stratified by insulin use, compared with nondiabetic women

Fracture site	Model	Women with diabetes not using insulin compared with nondiabetics		Women with diabetes using insulin compared with nondiabetics	
		RR	95% CI	RR	95% CI
Hip	Age-adjusted	1.49	(1.09–2.05)	1.26	(0.56–2.81)
	Adjusted for age, BMI, BMD[b]	1.78	(1.30–2.46)	1.70	(0.76–3.81)
	Multivariate adjusted[c]	1.82	(1.24–2.69)	1.14	(0.42–3.08)
Proximal humerus	Age-adjusted	1.65	(1.13–2.40)	1.95	(0.87–4.38)
	Adjusted for age, BMI, BMD[b]	1.76	(1.21–2.58)	1.82	(0.75–4.41)
	Multivariate adjusted[d]	1.94	(1.24–3.02)	2.38	(0.97–5.81)
Distal forearm	Age-adjusted	0.83	(0.56–1.22)	1.43	(0.71–2.88)
	Adjusted for age, BMI, BMD[b]	0.93	(0.63–1.38)	1.72	(0.85–3.47)
	Multivariate adjusted[e]	0.93	(0.62–1.39)	1.52	(0.72–3.20)
Ankle	Age-adjusted	1.22	(0.76–1.97)	2.35	(1.04–5.28)
	Adjusted for age, BMI, BMD[b]	1.10	(0.68–1.79)	2.07	(0.91–4.67)
	Multivariate adjusted[f]	1.06	(0.65–1.72)	1.92	(0.85–4.34)
Foot	Age-adjusted	1.05	(0.64–1.74)	2.67	(1.26–5.66)
	Adjusted for age, BMI, BMD[b]	1.14	(0.69–1.91)	2.89	(1.36–6.16)
	Multivariate adjusted[g]	1.09	(0.64–1.84)	2.68	(1.18–6.06)
All nonvertebral	Age-adjusted	1.16	(0.99–1.37)	1.58	(1.14–2.20)
	Adjusted for age, BMI, BMD[b]	1.30	(1.10–1.52)	1.68	(1.19–2.35)
	Multivariate adjusted[h]	1.30	(1.10–1.53)	1.39	(0.97–1.98)
Vertebral	Age-adjusted	0.96	(0.60–1.53)	0.87	(0.27–2.82)
	Adjusted for age, BMI, BMD[b]	1.06	(0.66–1.73)	1.09	(0.33–3.55)
	Multivariate adjusted[i]	1.12	(0.69–1.83)	0.98	(0.30–3.20)

[a] RR of fracture estimated with Cox proportional hazards models for nonvertebral fractures and with logistic regression models for vertebral fractures.
[b] Calcaneal BMD.
[c] Adjusted for age, BMI, calcaneal BMD, height, height loss since age 25, contrast sensitivity, walking speed, consumed alcohol in past year, resting pulse, mother fractured hip, on feet ≤4 h a day, use of long-acting benzodiazepines, and calcium intake.
[d] Adjusted for BMI, calcaneal BMD, height loss since age 25, mother fractured hip, and grip strength.
[e] Adjusted for calcaneal BMD, height, fell in past year, and current estrogen use.
[f] Adjusted for BMI, fell in past year, and height loss since age 25.
[g] Adjusted for calcaneal BMD, height, distant depth perception, contrast sensitivity, use of long-acting benzodiazepines, and clinic.
[h] Adjusted for age, BMI, calcaneal BMD, height, height loss since age 25, contrast sensitivity, resting pulse, history of stroke, use of long-acting benzodiazepines, grip strength, and fell in past year.
[i] Adjusted for age, calcaneal BMD, height loss since age 25, contrast sensitivity, calcium intake, and clinic.

tures. Among women using insulin compared with nondiabetics, elevated risks were found for proximal humerus, ankle, and foot fractures. In both groups of women with diabetes distal forearm and incident vertebral fractures were not elevated compared with nondiabetics. Among women with diabetes, comparing those using insulin to those not using insulin, the risk of foot fracture was elevated in the insulin-treated group [age-adjusted RR, 2.54; 95% confidence interval (CI), 1.04, 6.17], but the RRs for the other skeletal sites were not statistically significant.

Controlling for age, BMI, and calcaneal BMD did not appreciably alter the relationship between diabetes and fracture risk compared with age-adjusted models (Table 3). Substituting distal radius or femoral neck BMD for calcaneal BMD in these models also did not substantially alter the associations between diabetes and fracture risk.

In models that were additionally adjusted for covariates associated with falls, frailty, and/or bone strength, the effect estimates for the association between diabetes and fracture risk were not substantially altered compared with the models adjusted for age, BMI, and BMD alone (Table 3). Results for multivariate models using time-dependent covariates for BMI, BMD, falls, and performance measures were similar to the multivariate models using baseline variables (results not shown).

The associations between vibration threshold and the risk of fracture in age-adjusted models were not statistically significant. Light touch discrimination was weakly associated with nonvertebral fractures (age-adjusted RR, 1.08; 95% CI, 1.03–1.13, for 1 SD increase) but was not significantly associated with fractures at specific sites. The addition of these measures of peripheral neuropathy to models adjusted for age, BMI, and BMD did not substantially attenuate the association between diabetes and fracture risk for any of the fracture sites (results not shown).

For all fracture sites, except the proximal humerus, women with diabetes who reported a longer time since diagnosis (14 or more years) tended to have a higher risk of fracture, compared with nondiabetics, than diabetics with a shorter time since diagnosis. However, this difference was only statistically significant ($P < 0.05$) for hip fracture (RR, 2.40; 95% CI, 1.55–3.71, for diabetes of >14 yr duration compared with no diabetes; RR, 1.46; 95% CI, 0.98–2.17 for diabetes of 14 or fewer years duration compared with no diabetes). Insulin treatment is associated with a longer duration of diabetes (Table 1), but this did not account for the association between insulin-treated diabetes and foot fracture. In models that adjusted for duration of diabetes as well as age, BMI, and BMD, foot fracture risk remained elevated among insulin-treated diabetics compared with other diabetics (RR, 2.54; 95% CI, 1.01–6.34).

The diabetics being treated with insulin may have included women with late onset type 1 diabetes (33, 34). Because women with type 1 diabetes tend to have a lower BMI (1), we excluded the 59 (56% of 106) insulin-treated diabetics who had a BMI less than 30 kg/m^2 (definition of obesity (35)). Women with insulin-treated diabetes who were obese (and, therefore, more likely to have type 2 diabetes) continued to have a higher risk of foot fracture compared with nondiabetic women in a model adjusted for age, BMI, and BMD (RR, 5.16; 2.07–12.9).

Discussion

We found that older women with type 2 diabetes had increased risks of specific fractures, even when the higher body mass and bone density associated with diabetes were taken into account. Women with diabetes who were not treated with insulin had higher risks of hip and proximal humerus fractures. Those treated with insulin had a higher risk of foot fracture, compared with nondiabetics.

Diabetes is not generally considered a risk factor for fracture, but some previous studies have found an association. Studies in Norway identified diabetes as a risk factor for hip fracture in middle-aged (35–49 yr old; Ref. 7) and older (≥50 yr old) women (6). Previous reports from the SOF cohort, based on a smaller set of fractures, found an increased risk of foot fracture (32) and proximal humerus fracture (31) among insulin-treated diabetics and an increased, but not statistically significant, risk of hip fracture among noninsulin-treated diabetics (8). Heath *et al.* (3), evaluating records from the Mayo Clinic, reported that the risk of ankle fractures was elevated among women with diabetes but did not find a higher risk for other fracture sites. These results, however, were not adjusted for body size or BMD.

Other studies have found no increase in the risk of fracture among women with diabetes. Melchior *et al.* (4) found no differences in hip and Colles' fracture rates for women with diabetes who were being treated with insulin compared with nondiabetic women. The Rotterdam Study found a lower risk of nonspine fracture among women with diabetes (5). The disparity between these results and our findings may be due to differences in the ages of the women in the two studies and the lower proportion of distal forearm fractures in the SOF cohort. The women in the Rotterdam Study were 50 yr or older at the time of fracture and had a preponderance of wrist and forearm fractures (60% of nonspine fractures), whereas in the SOF only 23% of all nonspine fractures were of the distal forearm. In the SOF we found no association between diabetes and risk of distal forearm fracture.

In this study, women with diabetes had a greater risk of fracture despite having higher BMD than women without diabetes. One possible explanation is that the comorbidities associated with diabetes increase the risk of fracture. Another possibility is that diabetes is associated with a decrease in bone strength that is not reflected in the measurement of BMD.

We considered a range of risk factors for fracture that are also associated with diabetes, including falls, poor vision, less exercise, limitations in functional ability, and use of long-acting benzodiazepines, in an effort to identify baseline variables contributing to the higher risk of fracture among women with diabetes. Such factors accounted for only a small portion of the association between diabetes and fracture risk in our models.

For foot fracture, in particular, we had hypothesized that peripheral neuropathy might account for the association with diabetes. Previous studies among patients with diabetes have found that peripheral neuropathy is associated with metatarsal fractures (36) and calcaneal fractures (37). However, the two measures of neuropathy available to us, vibration sensitivity and light touch discrimination, did not substantially alter the association between diabetes and foot fracture in our models. A more sensitive measure of peripheral neuropathy, such as nerve conduction velocity, was not available (38).

One possible reason that the available measures accounted for only a small portion of the association between diabetes and fracture is that these models included only measurements at baseline (or, in the case of peripheral neuropathy, at the second visit). The mean follow-up for nonspine fractures was over 9 yr. Because women with diabetes experienced a more rapid decline in several measures of health, we hypothesized that measurements obtained closer to the date of fracture might account for a larger portion of the association between diabetes and fracture. However, using time-

dependent covariates for falls, balance, strength, functional ability, bone density, and other risk factors for fracture in the multivariate models did not substantially alter the associations between diabetes and fracture compared with models with baseline variables only. It is also possible that there are risk factors that were not measured in the SOF, such as decreased renal function or retinopathy, or that were not adequately captured in the measures available in the SOF. For example, vision was only measured at baseline and may have changed more rapidly for women with diabetes.

We considered insulin treatment as one marker of severity of diabetes. There was a tendency for the fracture risk among insulin-treated diabetics to be higher for all of the fracture sites considered, except the hip, but the difference was only statistically significant for foot fracture.

Duration of diabetes also seemed to be associated with a higher risk of fracture although results were only statistically significant for hip fracture. Insulin treatment was associated with a longer duration of diabetes in our data, but duration of diabetes did not account for the association between insulin treatment and foot fracture among diabetics. A measure of glycemic control was not available on the full cohort of participants in the SOF, so we could not explore the effect of glycemic control on fracture risk.

Other limitations of this study should be noted. Because diabetes was determined by self-report, those participants identified as not having diabetes probably included some women with undiagnosed diabetes. However, this misclassification would tend to weaken any association between diabetes and fracture. In addition, some women with late onset type 1 diabetes may have been included in our group of women with diabetes. Another limitation was the relatively small number of women with diabetes who were using insulin. Study participants were volunteers, community-dwelling, ambulatory, and mainly white. Results may not apply to the broader population of older women, especially those in institutions.

These results indicate that diabetes should be considered as a risk factor for particular types of fractures. Despite having a higher bone density, on average, the women with diabetes in our study had a higher risk of hip and proximal humerus fractures. Treatment with insulin was associated with an increased risk of foot fracture. Other factors associated with frailty or fracture, including falls, did not account for the association between diabetes and fracture.

This study underscores the need for a more aggressive focus on identifying and addressing risk factors for fracture in women with diabetes. Research is needed into the efficacy of current treatments to improve bone strength among women with diabetes. Further study of the extent to which the association between diabetes and fracture risk is mediated by complications of diabetes or by an increase in falls would be useful in guiding fracture prevention efforts.

Acknowledgments

Investigators in the Study of Osteoporotic Fractures Research Group—University of California–San Francisco (Coordinating Center): S. R. Cummings (principal investigator), M. C. Nevitt (co-investigator), K. Stone (project director), D. M. Black (study statistician), H. K. Genant (director, central radiology laboratory), D. C. Bauer, T. Blackwell, W. S. Browner, M. Dockrell, T. Duong, E. Edwards, C. Fox, T. Fuerst, S. Harvey, M. Jaime-Chavez, L. Laidlaw, L. Y. Lui, G. Milani, L. Palermo, H. Tabor, E. Williams, D. Tanaka, and C. Yeung.

University of Maryland: M. Hochberg (principal investigator), R. Sherwin (co-investigator), J. Lewis (project director), D. Wright (clinic coordinator), A. Bauer, C. Boehm, G. Cullum, L. Finazzo, M. E. Flaks, T. Ford, D. Harris, B. Hohman, T. Page, J. Schlossberg, C. Shaffer, A. Trimble, and S. Trusty.

University of Minnesota: K. Ensrud (principal investigator), P. Schreiner (co-investigator), K. Margolis (co-investigator), C. Bell (project director), E. Mitson (clinic coordinator), C. Bird, D. Blanks, J. Griffith, F. Imker-Witte, K. Jacobson, K. Kiel, K. Knauth, M. Neely, N. Nelson, E. Penland-Miller, M. Riley-Alves, and G. Saecker.

University of Pittsburgh: J. A. Cauley (principal investigator), L. H. Kuller (co-principal investigator), M. Vogt (co-investigator), L. Harper (project director), L. Buck (clinic coordinator), C. Bashada, D. Cusick, G. Engleka, A. Flaugh, A. Githens, M. Gorecki, K. McCune, D. Medve, M. Nasim, C. Newman, S. Rudovsky, and N. Watson.

The Kaiser Permanente Center for Health Research (Portland, OR): E. Harris (principal investigator, project director), W. M. Vollmer (co-investigator), E. Orwoll (co-investigator), H. Nelson (co-investigator), Marge Erwin (project administrator, clinic coordinator), J. Cogswell, A. Doherty, D. Franco, R. Garza, J. Kann, M. Klein, L. Loter, K. Redden, C. Romero, K. Snider, and J. Wallace.

References

1. **Karam JH.** 1997 Pancreatic hormones and diabetes mellitus. In: Greenspan FS, Strewler GJ, eds. Basic and clinical endocrinology. Stamford, CT: Appleton & Lange; 595–663.
2. **Piepkorn B, Kann P, Forst T, Andreas J, Pfutzner A, Beyer J.** 1997 Bone mineral density and bone metabolism in diabetes mellitus. Horm Metab Res. 29:584–591.
3. **Heath H, Melton LJ, Chu CP.** 1980 Diabetes mellitus and risk of skeletal fracture. N Engl J Med. 303:567–570.
4. **Melchior TM, Sorensen H, Torp-Pedersen C.** 1994 Hip and distal arm fracture rates in peri- and postmenopausal insulin-treated diabetic females. J Intern Med. 203–208.
5. **van Daele PL, Stolk RP, Burger H, et al.** 1995 Bone density in non-insulin-dependent diabetes mellitus. The Rotterdam Study. Ann Intern Med. 122:409–414.
6. **Forsen L, Meyer HE, Midthjell K, Edna TH.** 1999 Diabetes mellitus and the incidence of hip fracture: results from the Nord-Trondelag Health Survey. Diabetologia. 42:920–925.
7. **Meyer HE, Tverdal A, Falch JA.** 1993 Risk factors for hip fracture in middle-aged norwegian women and men. Am J Epidemiol. 137:1203–1211.
8. **Cummings SR, Nevitt MC, Browner WS, et al.** 1995 Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med. 332:767–773.
9. **Cummings SR, Black DM, Nevitt MC, et al.** 1990 Appendicular bone density and age predict hip fracture in women. The Study of Osteoporotic Fractures Research Group. J Am Med Assoc. 263:665–668.
10. **Farmer ME, White LR, Brody JA, Bailey KR.** 1984 Race and sex differences in hip fracture incidence. Am J Public Health. 74:1374–1380.
11. **Black DM, Palermo L, Nevitt MC, et al.** 1995 Comparison of methods for defining prevalent vertebral deformities: the Study of Osteoporotic Fractures. J Bone Miner Res. 10:890–902.
12. **Kiel D.** 1995 Assessing vertebral fractures. National Osteoporosis Foundation Working Group on Vertebral Fractures [published erratum appears in J Bone Miner Res. 10:1605, 1995]. J Bone Miner Res. 10:518–523.
13. **Nelson HD, Nevitt MC, Scott JC, Stone KL, Cummings SR.** 1994 Smoking, alcohol, and neuromuscular and physical function of older women. Study of Osteoporotic Fractures Research Group. J Am Med Assoc. 272:1825–1831.
14. **Steiger P, Cummings SR, Black DM, Spencer NE, Genant HK.** 1992 Age-related decrements in bone mineral density in women over 65. J Bone Miner Res. 7:625–632.
15. **Bauer DC, Browner WS, Cauley JA, et al.** 1993 Factors associated with appendicular bone mass in older women. The Study of Osteoporotic Fractures Research Group. Ann Intern Med. 118:657–665.
16. **Sands ML, Schwartz AV, Brown BW, Nevitt MC, Seeley DG, Kelsey JL.** 1998 Relationship of neurological function and age in older women. The study of osteoporotic fractures. Neuroepidemiology. 17:318–329.
17. **Cumming RG, Cummings SR, Nevitt MC, et al.** 1997 Calcium intake and fracture risk: results from the study of osteoporotic fractures. Am J Epidemiol. 145:926–934.
18. **Magaziner J, Bassett SS, Hebel JR.** 1987 Predicting performance on the Mini-Mental State Examination. Use of age- and education-specific equations. J Am Geriatr Soc. 35:996–1000.

19. **Teng EL, Chui HC.** 1987 The Modified Mini-Mental State (3MS) examination. J Clin Psychiatry. 48:314–318.
20. **Bohannon RW.** 1986 Test-retest reliability of hand-held dynamometry during a single session of strength assessment. Phys Ther. 66:206–209.
21. **Seeley DG, Cauley JA, Grady D, Browner WS, Nevitt MC, Cummings SR.** 1995 Is postmenopausal estrogen therapy associated with neuromuscular function or falling in elderly women? Study of Osteoporotic Fractures Research Group. Arch Intern Med. 155:293–299.
22. **Bailey IL, Lovie JE.** 1976 New design principles for visual acuity letter charts. Am J Optom Physiol Opt. 53:740–745.
23. **Simons K.** 1981 A comparison of the Frisby, Random-Dot E, TNO, and Randot circles stereotests in screening and office use. Arch Ophthalmol. 99:446–452.
24. **Gibson JJ.** 1950 The perception of the visual world. Boston: Houghton Mifflin.
25. **Ginsburg AP.** 1984 A new contrast sensitivity vision test chart. Am J Optom Physiol Opt. 61:403–407.
26. **Maser RE, Nielsen VK, Bass EB, et al.** 1989 Measuring diabetic neuropathy. Assessment and comparison of clinical examination and quantitative sensory testing. Diabetes Care. 12:270–275.
27. **Cox DR, Oakes D.** 1984 Analysis of survival data. London: Chapman and Hall.
28. **SAS Institute Inc.** 1996 The PHREG procedure. In: SAS/STAT software: changes and enhancements through release 6.11. Cary, NC: SAS Institute Inc.; 807–884.
29. **SAS Institute Inc.** 1996 The LOGISTIC procedure. In: SAS/STAT software: changes and enhancements through release 6.11. Cary, NC: SAS Institute Inc.; 381–492.
30. **Cumming RG, Nevitt MC, Cummings SR.** 1997 Epidemiology of hip fractures. Epidemiol Rev. 19:244–257.
31. **Kelsey JL, Browner WS, Seeley DG, Nevitt MC, Cummings SR.** 1992 Risk factors for fractures of the distal forearm and proximal humerus. The Study of Osteoporotic Fractures Research Group [published erratum appears in Am J Epidemiol. 135:1183, 1992]. Am J Epidemiol. 135:477–489.
32. **Seeley DG, Kelsey J, Jergas M, Nevitt MC.** 1996 Predictors of ankle and foot fractures in older women. The Study of Osteoporotic Fractures Research Group. J Bone Miner Res. 11:1347–1355.
33. **Tuominen JT, Impivaara O, Puukka P, Ronnemaa T.** 1999 Bone mineral density in patients with type 1 and type 2 diabetes. Diabetes Care. 22:1196–1200.
34. **Zimmet P, Turner R, McCarty D, Rowley M, Mackay I.** 1999 Crucial points at diagnosis. Type 2 diabetes or slow type 1 diabetes. Diabetes Care 22(Suppl 2):B59–B64.
35. **World Health Organization.** 1998 Obesity: preventing and managing the global epidemic: report of a WHO Consultation on Obesity, Geneva, June 3–5, 1997. Geneva: World Health Organization.
36. **Cundy TF, Edmonds ME, Watkins PJ.** 1985 Osteopenia and metatarsal fractures in diabetic neuropathy. Diabetes Med. 2:461–464.
37. **Kathol MH, el-Khoury GY, Moore TE, Marsh JL.** 1991 Calcaneal insufficiency avulsion fractures in patients with diabetes mellitus. Radiology. 180:725–729.
38. **Richardson JK, Hurvitz EA.** 1995 Peripheral neuropathy: a true risk factor for falls. J Gerontol A Biol Sci Med Sci. 50:M211–M215.

5th International Workshop on Resistance to Thyroid Hormone
June 6–8, 2001
Verbania, Italy

For further details: Prof. Paolo Beck-Peccoz, Institute of Endocrine Sciences, Ospedale Maggiore IRCCS, Via F. Sforza 35, 20122 Milan, Italy. Fax: 39-02-55195438; E-mail: endosci@mailserver.unimi.it; www.infinito.it/utenti/endocrinology.