0021-972X/06/$15.00/0
*Printed in U.S.A.*

The Journal of Clinical Endocrinology & Metabolism 91(9):3404–3410

doi: 10.1210/jc.2006-0614

# Risk of Fracture in Women with Type 2 Diabetes: the Women's Health Initiative Observational Study

Denise E. Bonds, Joseph C. Larson, Ann V. Schwartz, Elsa S. Strotmeyer, John Robbins, Beatriz L. Rodriguez, Karen C. Johnson, and Karen L. Margolis

*Departments of Epidemiology and Prevention and Internal Medicine (D.E.B.), Wake Forest University School of Medicine, Winston-Salem, North Carolina 27157; Fred Hutchinson Cancer Research Center (J.C.L.), Seattle, Washington 98109; Department of Epidemiology and Biostatistics (A.V.S.), University of California San Francisco, San Francisco, California 94105; Department of Epidemiology (E.S.S.), University of Pittsburgh, Pittsburgh, Pennsylvania 15213; Department of Internal Medicine (J.R.), University of California, Davis, Davis, California 95817; Department of Geriatric Medicine (B.L.R.), University of Hawaii at Manoa, Honolulu, Hawaii 96817; Department of Preventive Medicine (K.C.J.), University of Tennessee Health Science Center, Memphis Tennessee 38105; and HealthPartners Research Foundation (K.L.M.), Minneapolis, Minnesota 55440-1524*

**Context:** Some but not all studies have shown higher rates of fracture in individuals with type 2 diabetes.

**Objective:** The objective of the study was to determine the risk of fracture in postmenopausal women with type 2 diabetes and determine whether risk varies by fracture site, ethnicity, and baseline bone density.

**Design, Setting, and Participants:** Women with clinically diagnosed type 2 diabetes at baseline in the Women's Health Initiative Observational Cohort, a prospective study of postmenopausal women (n = 93,676), were compared with women without diagnosed diabetes and risk of fracture overall and at specific sites determined.

**Main Outcome Measures:** All fractures and specific sites separately (hip/pelvis/upper leg; lower leg/ankle/knee; foot; upper arm/shoulder/elbow; lower arm/wrist/hand; spine/tailbone) were measured. Bone mineral density (BMD) in a subset also was measured.

**Results:** The overall risk of fracture after 7 yr of follow-up was higher in women with diabetes at baseline after controlling for multiple risk factors including frequency of falls [adjusted relative risk (RR) 1.20, 95% confidence interval (CI) 1.11–1.30]. In a subsample of women with baseline BMD scores, women with diabetes had greater hip and spine BMD. The elevated fracture risk was found at multiple sites (hip/pelvis/upper leg; foot; spine/tailbone) among black women (RR 1.33, 95% CI 1.00–1.75) and women with increased baseline bone density (RR 1.26, 95% CI 0.96–1.66).

**Conclusion:** Women with type 2 diabetes are at increased risk for fractures. This risk is also seen among black and non-Hispanic white women after adjustment for multiple risk factors including frequent falls and increased BMD (in a subset). (***J Clin Endocrinol Metab* 91: 3404–3410, 2006**)



OSTEOPOROTIC FRACTURES ARE associated with significant morbidity, mortality, and reduction in quality of life (1–3). Known risk factors associated with the development of osteoporosis and fractures include female gender, older age, lower body mass index (BMI), and family history (4, 5). Diabetes is not well recognized as a risk factor for fractures, despite increasing evidence of association. Studies have reported lower bone mineral density (BMD) (6–8) and increased risk of fractures (6.9- to 12-fold increase) in patients with type 1 diabetes (9–11). The relationship among type 2 diabetes, osteoporosis, and fractures is less well defined. Patients with type 2 diabetes often have higher BMI and thus might be expected to be at lower risk for the development of osteoporosis and fracture. Supporting this, several studies have found increased BMD (12–15) in women with diabetes when compared with controls, although other studies have reported no difference (8, 16, 17). Despite higher BMD, patients with type 2 diabetes appear to have higher rates of foot and ankle (18, 19), hip (9–11, 19–21), and arm fractures (19, 22). This paradoxical increase in fracture rate may be a result of increased rate of falls among patients with diabetes (15) or lower bone quality (23). The Women's Health Initiative Observational Study (WHI-OS), enrolled a racially diverse group of postmenopausal women (n = 93,676), collected detailed data on risk factors for fractures, and prospectively followed up women for incident falls and fractures. We sought to further elucidate the relationship among type 2 diabetes, fractures, falls, and BMD.

**First Published Online June 27, 2006**

Abbreviations: BMD, Bone mineral density; BMI, body mass index; CI, confidence interval; NHW, non-Hispanic white; RR, relative risk; SERM, selective estrogen receptor modulator; WHI-OS, Women's Health Initiative Observational Study.

**JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.**

## Subjects and Methods

The WHI-OS is a prospective cohort study established to explore the predictors of morbidity and mortality of postmenopausal women. Full details have been previously published (24–26). Participants were enrolled at 40 centers throughout the United States between October 1, 1993, and December 31, 1998. Potential subjects were excluded if they did not plan to reside in the area for at least 3 yr; had medical conditions predictive of survival less than 3 yr; or had complicating conditions such as alcoholism, drug dependency, or dementia. All participants provided informed consent using materials approved by institutional review boards at each center. Demographic, risk exposure data, family medical history, and number of falls were obtained by self-report using standardized questionnaires. Certified staff took physical measurements

(blood pressure, height, and weight) and blood samples at the baseline clinic visit and again 3 yr later. Participants were asked to bring all medications (prescription and over the counter) and supplements to the baseline clinic visit. The product or generic name was entered into the study database and matched to the corresponding item in a pharmacy database: the Master Drug Data Base (Medi-Span, Indianapolis, IN). Participants were mailed annual forms to update selected exposures and ascertain medical outcomes. This study was approved by the institutional review boards at each clinical site and the coordinating center.

### *Diabetes ascertainment*

Our primary definition of diabetes was an affirmative answer to the question asked at baseline: did a doctor ever say that you had sugar diabetes or high blood sugar when you were not pregnant? or the reported use of a medication to treat diabetes at baseline. Participants with type 1 diabetes, defined as those diagnosed before age 20 yr or who were ever hospitalized for a diabetic coma, were excluded from the analysis (n = 185) as were those individuals with missing baseline diabetes information (n = 87). After these exclusions there were 5285 women with probable type 2 diabetes. To account for potential undiagnosed diabetics at baseline, we compared the results obtained with our primary definition to results obtained using two alternative definitions of diabetes: 1) affirmative answer to the diabetes question or the baseline medication inventory included a drug to treat diabetes or a glucose greater than 125 mg/dl (in those with an available baseline blood glucose) or 2) self-reported use of insulin or pills to treat diabetes at any time during the study. For more restrictive criteria, we defined diabetes in sensitivity analysis as an affirmative answer to the diabetes question at baseline, and the baseline medication inventory included a drug to treat diabetes.

### *Fracture ascertainment*

Questions on fractures were included in the annual questionnaire. Participants were asked whether they had had a fracture since they last completed the medical history questionnaire and to identify the location (vertebral, shoulder, upper arm, lower arm, wrist, hip, upper leg, lower leg, and foot). All hip fractures were adjudicated by centrally trained adjudicators. Nonhospitalized fractures were collected through self-report only. A validation study of self-reported fractures was conducted on the WHI-OS (27) and found good agreement between self-report and adjudicated fracture for hip (78%) and forearm/wrist (81%) but lower agreement for clinical spine fractures (51%) (27). Fracture data through August 31, 2004, were included in this analysis.

### *BMD ascertainment*

BMD was performed at three (n = 6,384) of the 40 clinical sites in the Women's Health Initiative using dual-energy x-ray absorptiometry (QDR 2000, 2000+, or 4500W; Hologic, Inc., Bedford, MA). BMDs were obtained at baseline and yr 3, 6, and 9 (with fewer performed in yr 9). One set of spine, hip, and linearity phantoms was circulated during 1995 for measurement on the five QDR2000 scanners (two at Pittsburgh, two at Tucson, one at Birmingham). The variability in scanners did not warrant correction factors across sites. Multivariate models including BMD have been adjusted for scanner used to account for the slight differences found. For longitudinal changes in each scanner, correction factors were derived from spine and hip phantoms measured throughout the study (28). In Tucson, a QDR2000 scanner was replaced with a QDR4500W in 1999; the same upgrade was made in Birmingham in 2003. Before the upgrades, measurements were obtained on the same subjects on both the QDR2000 and QDR4500 (50 subjects in Tucson and 25 in Birmingham). Linear regression was used to derive correction factors from these *in vivo* cross-scanner measurements to allow conversion of the QDR4500 to QDR2000 values.

### *Other variables*

Several possible confounding variables were obtained. Ethnicity, educational level, previous fractures, and history of osteoporosis were obtained from self-report at baseline. Participants were asked whether they were current, past, or never smokers. Alcohol use was also determined through survey, and the average number of drinks per week was determined at baseline. Physical activity was reported as the expenditure of energy from recreational physical activity reported at baseline (including walking, mild, moderate, and strenuous physical activity) and computed in metabolic equivalent task scores (29). Total calcium and vitamin D intake was obtained by combining the dietary intake as determined through the food frequency questionnaire administered at baseline and the daily intake from supplements. BMI was calculated using height and weight measured by clinic staff. To account for the increased risk of fracture in women with frequent falls, a time-dependent variable defined as three falls in the past 12 months at baseline or two or more falls in the last 6 months during follow-up was included.

### *Statistical analysis*

Descriptive statistics, including means, frequencies, and percentages, were used to both describe the study population and look at differences between those participants with type 2 diabetes at baseline and those without (Table 1). Comparisons for the continuous variables were done by running ANOVA models with a response of the continuous covariate of interest and an explanatory variable of type 2 diabetes at baseline (yes/no). Means and SD values are presented. For the categorical covariates, a $\chi^2$ test was used to evaluate differences in the distribution of the categorical levels of the covariate of interest between the diabetic and nondiabetic women. Frequencies and percentages are presented.

Incidence rates of fracture per 1000 person-years were computed for each possible fracture site by dividing the total person-years of eligible follow-up by the total number of fractures for the given site and then multiplying by 1000 (see Table 3). A participant's eligible follow-up was defined as the time from baseline to event if they had the fracture of interest and time from baseline to the date of death, loss to follow-up, or August 31, 2004 (whichever occurred first) for those without an event. Comparisons between the incidence rates of those with and without diabetes at baseline were done by running an unadjusted Cox proportional hazards model with a response of the fracture site of interest and explanatory variable of diabetes at baseline. A participant was counted once at the time of their first fracture for the any fracture outcome. Individuals could be included in several site-specific outcomes (*i.e.* wrist and hip) but only once for any particular site.

To evaluate the relationship between diabetes and incident fracture, a series of successive Cox proportional hazards models was run for each fracture end point (see Table 4). For each fracture outcome, the first model was adjusted for age. Next, a second model was run, also adjusting for baseline height, weight, and falls as a time-dependent variable. Finally, the primary outcome was run, a fully adjusted model, adjusting for the same covariates as the first two with the addition of ethnicity, alcohol use, smoking, hormone use, physical activity, calcium/vitamin D intake, moderate to severe trouble seeing, history of fracture, history of osteoporosis, bisphosphonate use at baseline, steroid use, selective estrogen receptor modulator (SERM) use at baseline, insulin use, and thyroid hormone use. The hazard ratios for baseline diabetes along with its 95% confidence limits are presented for each model run. The Cox proportional hazards assumption was checked graphically, whereas collinearity was checked by analyzing a table of correlations between the various covariates in the model. All analyses were done in the SAS System for Windows (version 9.1; SAS Institute, Cary, NC).

## Results

At baseline there were 5,285 women with type 2 diabetes and 88,120 without diabetes. The women with diabetes had mean duration of disease of 9.3 yr, and 16.7% used insulin at baseline. In comparison with women without diabetes, the women with diabetes were older at baseline (Table 1), were less likely to be white, reported lower energy expenditure, and had more trouble seeing. They were equally likely to have a history of osteoporosis and slightly less likely to have a previous fracture but were more likely to have a history of a fall and be a current smoker. They also reported less calcium, vitamin D, and bisphosphonate use but were more

**TABLE 1.** Baseline characteristics of the population

| Variable | Diabetic women (n = 5,285), mean ± SD or percentage (n) | Nondiabetic women (n = 88,120), mean ± SD or percentage (n) | *P* value |
|---|---|---|---|
| Age at screening (yr) | 64.9 ± 7.0 (5,285) | 63.5 ± 7.4 (88,120) | <0.01 |
| Duration of diabetes (yr) | 9.3 ± 10.0 (5,079) | | |
| Ethnicity/race | | | |
| NHW | 65% (3,443) | 84% (74,400) | <0.01 |
| Black | 21% (1,091) | 7% (6,495) | |
| Hispanic | 7% (358) | 4% (3,241) | |
| American Indian | 2% (86) | 0.5% (330) | |
| Asian/Pacific Islander | 4% (214) | 3% (2,452) | |
| Unknown | 2% (93) | 1% (1,202) | |
| Total METs per week | 9.9 ± 12.6 (5,207) | 13.3 ± 14.4 (87,153) | <0.01 |
| Moderate or severe trouble seeing | 11.2% (581) | 5.0% (4,338) | <0.01 |
| History of previous fracture | 37% (1,924) | 39% (33,623) | 0.02 |
| History of osteoporosis | 10% (503) | 9% (7,750) | 0.07 |
| Falls at baseline or follow-up | 44% (2,277) | 32% (28,219) | <0.001 |
| Smoking history | | | |
| Never | 52% (2,681) | 51% (44,199) | <0.01 |
| Previous | 41% (2,124) | 43% (37,289) | |
| Current | 7% (369) | 6% (5,400) | |
| Alcohol use | | | |
| Nondrinker | 20% (1,020) | 11% (9,410) | <0.01 |
| Past drinker | 39% (2,051) | 18% (15,433) | |
| Less than one drink per month | 12% (628) | 12% (10,071) | |
| Less than one drink per week | 15% (793) | 20% (17,892) | |
| One to less than seven drinks per week | 10% (534) | 27% (23,265) | |
| Seven or more drinks per week | 4% (191) | 13% (11,488) | |
| Calcium intake (mg/d) | 1043.3 ± 672.6 (4,926) | 1185.3 ± SD 758.7 (84,734) | <0.01 |
| Vitamin D intake (IU/d) | 381.8 ± 278.7 (4,926) | 414.6 ± 287.0 (84,734) | <0.01 |
| Estrogen usage | | | |
| Never used | 53.4% (2,818) | 39.9% (35,090) | <0.01 |
| Past user | 15.8% (835) | 14.8% (13,040) | |
| Current user | 30.8% (1,625) | 45.3% (39,912) | |
| Bisphosphonate usage | 1.6% (85) | 2.6% (2,286) | <0.01 |
| Steroid usage | 2.4% (126) | 1.4% (1,247) | <0.01 |
| SERM usage | 0.06% (3) | 0.04% (39) | 0.68 |
| Thiazide diuretic usage | 8.7% (460) | 4.4% (3,834) | <0.01 |
| Statin usage | 17.1% (904) | 7.7% (6,768) | <0.01 |
| Thyroid hormone usage | 16.5% (871) | 14.4% (12,723) | <0.01 |
| Insulin usage | 16.7% (881) | | |
| Height (cm) | 160.8 ± 6.8 (5,245) | 161.7 ± 6.7 (87,409) | <0.01 |
| Weight (kg) | 82.1 ± 19.8 (5,261) | 71.1 ± 16.5 (87,673) | <0.01 |

MET, Metabolic equivalent task.

likely to have used oral steroid hormones. Women with diabetes were shorter at baseline and heavier (Table 1) and, for the subset that underwent BMD measurements at baseline, had a higher hip and spine BMD (Table 2).

After an average of 7 yr of total follow-up, there was a higher rate of fracture among women with diabetes (Table 3). When fractures were broken down by location, women with diabetes had a higher rate of hip/pelvis/upper leg, lower leg/ankle/knee, foot, upper arm/shoulder/elbow, and spine/tailbone fractures. There was an equal rate of fracture of the lower arm/wrist/hand reported by both groups.

Women with diabetes were 29% more likely to have suffered a fracture during the follow-up period (Table 4). This increased risk remained after adjustment for other baseline differences in the multivariate adjusted model, our primary outcome. When fractures by region were compared, women with diabetes had a significantly increased risk of the hip/pelvis/upper leg, foot, and spine/tailbone fracture (Table 4). There was also an increased risk of lower leg/ankle/knee and upper arm/shoulder/elbow fractures that did not meet statistical significance.

In sensitivity analyses, we reran the above analyses using

**TABLE 2.** BMD measurements at spine and hip[a]

| | Spine BMD (g/cm$^2$) | | Hip BMD (g/cm$^2$) | |
|---|---|---|---|---|
| | Diabetic women (n) | Nondiabetic women (n) | Diabetic women (n) | Nondiabetic women (n) |
| Baseline[b] | 1.04 ± 0.19 (472) | 0.97 ± 0.17 (5922) | 0.90 + 0.16 (469) | 0.84 ± 0.14 (5915) |
| Year 3 | 1.06 ± 0.20 (331) | 0.99 ± 0.17 (4839) | 0.89 ± 0.16 (331) | 0.84 ± 0.13 (4831) |
| Year 6 | 1.07 ± 0.21 (253) | 1.00 ± 0.18 (4203) | 0.87 ± 0.16 (261) | 0.84 ± 0.13 (4262) |
| Year 9 | 1.12 ± 0.24 (91) | 1.02 ± 0.18 (1608) | 0.88 ± 0.17 (92) | 0.82 ± 0.13 (1606) |

[a] All comparisons of diabetic women *vs.* nondiabetic women were $P < 0.01$.
[b] Corrected for the use of multiple scanners and the longitudinal nature of the data.

**TABLE 3.** Rate of fracture per 1000 person-years for women with diabetes *vs.* nondiabetic women

| | Fractures per 1,000 person-yr (n) | | *P* value |
|---|---|---|---|
| | Diabetic women | Nondiabetic women | |
| Any fracture | 28.6 (899) | 22.0 (12,575) | <0.0001 |
| Hip/pelvis/upper leg | 3.8 (128) | 2.5 (1,531) | <0.0001 |
| Lower leg/ankle/knee | 6.2 (207) | 4.7 (2,828) | 0.0001 |
| Foot | 4.6 (153) | 3.2 (1,940) | <0.0001 |
| Upper arm/shoulder/elbow | 3.8 (129) | 2.8 (1,717) | 0.0008 |
| Lower arm/wrist/hand | 5.3 (177) | 5.2 (3,161) | 0.83 |
| Spine/tailbone | 2.9 (99) | 2.2 (1,336) | 0.004 |

our alternative definition of diabetes and found no significant variation in the results. We also used a cutoff of age 39 yr for diagnosis of diabetes instead of 20 yr and found no variation in the results. We then included only women who had baseline BMD measurements and added baseline hip BMD to the model. The addition of baseline hip BMD had little effect on the risk of any fracture and increased the risk of hip/pelvis/upper leg fractures despite the higher mean BMD for women with diabetes. We next ran the any-fracture model for those with type 2 diabetes who used insulin at baseline and found an increased risk of any fracture [relative risk (RR) 1.58, 95% confidence interval (CI) 1.18–2.11]. Finally, we stratified women by race [non-Hispanic white (NHW), black] to determine whether the risk varied. Using the same multivariate model described above, we found a somewhat higher risk of any fracture for black women with diabetes (RR 1.33, 95% CI 1.00–1.75), compared with that for NHW women with diabetes (RR 1.18, 95% CI 1.08–1.29).

**TABLE 4.** Adjusted RRs and 95% CIs for fracture among women with diabetes, compared with those without diabetes

| Site | RR (95% CI) |
|---|---|
| Any fracture | |
| Age | 1.29 (1.20, 1.38) |
| Age, weight, height, falls[a] | 1.22 (1.14, 1.31) |
| Multivariate[b] | 1.20 (1.11, 1.30) |
| Multivariate, BL hip BMD[c] | 1.24 (0.96, 1.63) |
| Hip/pelvis/upper leg | |
| Age | 1.41 (1.17, 1.70) |
| Age, weight, height, falls[a] | 1.55 (1.28, 1.87) |
| Multivariate[b] | 1.46 (1.17, 1.83) |
| Multivariate, BL hip BMD[c] | 1.82 (0.90, 3.64) |
| Lower leg/ankle/knee | |
| Age | 1.34 (1.16, 1.55) |
| Age, weight, height, falls[a] | 1.15 (0.99, 1.34) |
| Multivariate[b] | 1.13 (0.95, 1.34) |
| Multivariate, BL hip BMD[c] | 1.31 (0.76, 2.24) |
| Foot | |
| Age | 1.44 (1.21, 1.71) |
| Age, weight, height, falls[a] | 1.39 (1.16, 1.66) |
| Multivariate[b] | 1.32 (1.07, 1.62) |
| Multivariate, BL hip BMD[c] | 1.27 (0.61, 2.64) |
| Upper arm/shoulder/elbow | |
| Age | 1.30 (1.07, 1.56) |
| Age, weight, height, falls[a] | 1.15 (0.95, 1.39) |
| Multivariate[b] | 1.13 (0.90, 1.41) |
| Multivariate, BL hip BMD[c] | 0.90 (0.39, 2.07) |
| Lower arm/wrist/hand | |
| Age | 0.98 (0.84, 1.15) |
| Age, weight, height, falls[a] | 0.95 (0.81, 1.12) |
| Multivariate[b] | 1.02 (0.85, 1.22) |
| Multivariate, BL hip BMD[c] | 1.27 (0.71, 2.25) |
| Spine/tailbone | |
| Age | 1.28 (1.04, 1.56) |
| Age, weight, height, falls[a] | 1.27 (1.04, 1.56) |
| Multivariate[b] | 1.27 (1.00, 1.61) |
| Multivariate, BL hip BMD[c] | 1.57 (0.72, 3.44) |

BL, Baseline.

[a] Defined as three or more falls in past year at baseline, two or more falls in last 6 months during follow-up.

[b] Adjusted for age; ethnicity; weight; height; time-dependent history of falls; previous fracture; history of osteoporosis; trouble seeing at baseline; alcohol or tobacco use; calcium and vitamin D intake; exercise; bisphosphonate, estrogen, steroid, insulin, SERM, or thyroid hormone use.

[c] Includes only BMD participants.

## Discussion

The results of this study confirm the conclusion that postmenopausal women with diabetes are at an increased risk of fractures overall and an increased risk of hip, foot, and spine fractures separately. We found that women with diabetes had a 20% (RR 1.20, 95% CI 1.11–1.30) increased risk of having any fracture during an average of 7 yr of follow-up. The WHI-OS substantially adds to the literature on the risk of fracture among women with diabetes. Our study demonstrates that diabetes is a risk factor for fractures in black women, who are generally at lower risk than NHW women (RR 1.33 for black women *vs.* 1.18 for NHW). Due to the large number of women in the study, we are able to compare rates of fracture at multiple sites. Women with diabetes had a 46% increased risk of having a fracture of the hip/pelvis/upper leg (RR 1.46, 95% CI 1.17–1.83) and were approximately 30% more likely to report a fracture of the foot or spine. We were also able to explore the contribution of BMD on fracture risk. In the subset with baseline BMD, the increased risk of fracture remained despite the higher baseline BMD in these women. These increased risks remained after adjustment of other known fracture risk factors.

Our results support the findings of previous studies. When older women with diabetes were compared with women without diabetes in the Study of Osteoporotic Fractures, a 30–39% increased risk of a nonvertebral fracture was found (noninsulin user: RR 1.30, 95% CI 1.10–1.53; insulin user: RR 1.39, 95% CI 0.97–1.98) (19). Specific fracture types that were found to be increased in the Study of Osteoporotic Fractures included hip, proximal humerus, foot, and ankle fractures; as in our study, distal forearm fractures were not increased. In the Iowa Women's Health Study, women with type 2 diabetes had a higher risk of hip fracture (RR 1.70, 95% CI 1.21–2.38) than women without diabetes after adjustment for multiple risk factors (11). Similar findings were seen in the Health ABC study, which found a 23% increased risk of hip fracture (RR 1.23, 95% CI 0.82–1.86) (21). This increased risk has also been demonstrated among Hispanic women (20) and Norwegian women (9, 10).

The underlying mechanism is not clear. Women with diabetes often suffer from neuropathy and retinopathy and thus are at greater risk of falls and the fractures that may result from these falls. In the WHI-OS cohort, more women with diabetes reported falls at baseline and during follow-up (44 *vs.* 32%), and more women with diabetes reported moderate or severe trouble seeing at baseline (11 *vs.* 5%). How-

ever, women with diabetes remained at greater risk for a fracture, even after adjustment for falls and difficulty seeing. It is possible that the women with diabetes experienced more severe falls or falls resulting from a different mechanism and thus have a higher risk of injury in any given fall or that they experienced a greater load on their bones from their increased weight. WHI-OS does not collect information on the severity or the mechanism of the fall. In a study on the mechanism of arm fractures, wrist fractures were more likely to result from falls that were obliquely forward, whereas upper arm injuries were associated equally with forward and lateral falls (30). Although the women with diabetes in our study had more falls, it is possible that the mechanism of the fall was such that they were less able to break their fall with their hand, thus decreasing their risk of wrist fractures.

Our study and others have reported increased BMD in women with diabetes, perhaps caused by the increased body weight during adolescence and early 20s, the years of peak bone formation. Thus, the increased risk does not appear to be due to an increased risk of osteoporosis. It is possible that the BMD of women with diabetes may be overestimated due to measurement error caused by the increased BMI (31, 32). We did find an increase in spine BMD over time in both groups. This is a common finding attributable to an increase in aortic calcifications, osteophytes, and other degenerative changes rather than an actual gain in bone mass (33, 34). Animal models have indicated that although the bone density is greater in diabetes, the bone structure is more fragile, with fractures occurring under a smaller load and the bones exhibiting reduced mechanical indices (35). The higher serum level of glucose in women with diabetes may result in a larger concentration of advanced glycation end products in collagen-containing tissues such as bone (36). Advanced glycation end products have been associated with decreased strength in human cadaver femurs (37). Thus, women with diabetes may be more likely to suffer a fracture from a fall or minor trauma due to the decreased bone strength. There may be increased bone loss in women with diabetes due to lower levels of IGF-I (38), hypercalciuria secondary to elevated glucose in the urine (39), or increased inflammation (40). In the subsample of women with diabetes who underwent bone density testing, we found a similar increased risk of any fracture despite the increased bone density of the women with diabetes at baseline.

It is not clear what can be done to prevent the increased fracture rate seen among women with diabetes. Observational studies have found a greater risk of fractures among women with diabetes that have higher fasting glucose levels (22), suggesting that better control of blood glucose may reduce the risk. One study that examined the effect of alendronate on BMD found it to be effective in increasing bone density in women with diabetes (41). However, this study was limited to women who had a low bone density at baseline. Additional studies testing methods to prevent fractures in postmenopausal diabetic women are needed, including studies that assess biochemical markers of bone turnover.

There are several limitations to this study. There was no confirmation of the self-reported diabetes diagnosis with medical records, as was also the case with most previous studies. Based on baseline fasting glucose levels greater than 125 mg/dl in women who did not self-report diabetes, 3% of women in the WHI-OS had undiagnosed diabetes. We tested a variety of definitions of diabetes in sensitivity analysis and had similar results, regardless of the definition used. The women with diabetes who participate in the WHI-OS may be healthier than the general population and thus not representative of all women with diabetes. There may be under- or overreporting of fractures. To minimize bias in the comparison of fracture rates, it is most important to identify false-positive reports and achieve a high specificity in the adjudication of fractures. With 100% specificity, underascertainment will not attenuate RR estimates (42). For hip fractures, central adjudication eliminated virtually all false-positive reports, and we can therefore be most confident of a lack of bias in this outcome. As described in *Subjects and Methods*, a validation study of fracture was conducted in the WHI-OS (27). Whereas this study did not examine results separately for women with and without diabetes, there is no reason to believe that there would be a systematic difference. Women with diabetes may see physicians more frequently than women without and consequently may have clinical vertebral fractures diagnosed more frequently. Whereas we did see a higher rate of vertebral fractures in women with diabetes, the consistently higher rates of fractures at all sites make this less likely. Finally, no measurements of visual acuity or neuropathy were available, and it was necessary to rely on self-report. Diabetic women may underreport decreased visual acuity, which is a known risk factor for fractures (43).

### *Conclusion*

In conclusion, we found an elevated risk of any fractures in women with diabetes and an elevated risk of hip, foot, and spine fracture, supporting the findings of other studies. The underlying mechanism of this is unclear and is likely multifactorial. Women with diabetes did suffer more falls at baseline and follow-up, but the increased risk remained after adjustment. Similarly, in the subsample of women with measures of BMD, women with diabetes had an increased baseline bone density but continued to have an increased risk of fracture, supporting a possible structural change of the bone. Further research on the underlying mechanisms of the fracture and development of techniques to mitigate the fracture risk such as blood glucose control in women with diabetes is needed.

## Acknowledgments

Following is a short list of WHI investigators. Program office: National Heart, Lung, and Blood Institute (Bethesda, MD), Barbara Alving, Jacques Rossouw, Shari Ludlam, Linda Pottern, Joan McGowan, Leslie Ford, and Nancy Geller. Clinical coordinating center: Fred Hutchinson Cancer Research Center (Seattle, WA), Ross Prentice, Garnet Anderson, Andrea LaCroix, Charles L. Kooperberg, Ruth E. Patterson, Anne McTiernan; Wake Forest University School of Medicine (Winston-Salem, NC), Sally Shumaker; Medical Research Labs (Highland Heights, KY), Evan Stein; University of California, San Francisco (San Francisco, CA), Steven Cummings. Clinical centers: Albert Einstein College of Medicine (Bronx, NY), Sylvia Wassertheil-Smoller; Baylor College of Medicine (Houston, TX), Jennifer Hays; Brigham and Women's Hospital, Harvard Medical School (Boston, MA), JoAnn Manson; Brown University (Providence, RI), Annlouise R. Assaf; Emory University (Atlanta, GA), Law-

rence Phillips; Fred Hutchinson Cancer Research Center (Seattle, WA), Shirley Beresford; George Washington University Medical Center (Washington, DC), Judith Hsia; Harbor-UCLA Research and Education Institute (Torrance, CA), Rowan Chlebowski; Kaiser Permanente Center for Health Research (Portland, OR), Evelyn Whitlock; Kaiser Permanente Division of Research (Oakland, CA), Bette Caan; Medical College of Wisconsin (Milwaukee, WI), Jane Morley Kotchen; MedStar Research Institute/Howard University (Washington, DC), Barbara V. Howard; Northwestern University (Chicago/Evanston, IL), Linda Van Horn; Rush Medical Center (Chicago, IL), Henry Black; Stanford Prevention Research Center (Stanford, CA), Marcia L. Stefanick; State University of New York at Stony Brook (Stony Brook, NY) Dorothy Lane; The Ohio State University (Columbus, OH), Rebecca Jackson; University of Alabama at Birmingham (Birmingham, AL), Cora E. Lewis; University of Arizona (Tucson/Phoenix, AZ), Tamsen Bassford; University at Buffalo (Buffalo, NY), Jean Wactawski-Wende; University of California, Davis (Sacramento, CA), John Robbins; University of California, Irvine (CA), F. Allan Hubbell; University of California, Los Angeles (Los Angeles, CA), Howard Judd; University of California, San Diego (La Jolla/Chula Vista, CA), Robert D. Langer; University of Cincinnati (Cincinnati, OH), Margery Gass; University of Florida (Gainesville/Jacksonville, FL), Marian Limacher; University of Hawaii (Honolulu, HI), David Curb; University of Iowa (Iowa City/Davenport, IA), Robert Wallace; University of Massachusetts/Fallon Clinic (Worcester, MA), Judith Ockene; University of Medicine and Dentistry of New Jersey (Newark, NJ), Norman Lasser; University of Miami (Miami, FL), Mary Jo O'Sullivan; University of Minnesota (Minneapolis, MN), Karen Margolis; University of Nevada (Reno, NV), Robert Brunner; University of North Carolina (Chapel Hill, NC), Gerardo Heiss; University of Pittsburgh (Pittsburgh, PA), Lewis Kuller; University of Tennessee (Memphis, TN), Karen C. Johnson; University of Texas Health Science Center (San Antonio, TX), Robert Brzyski; University of Wisconsin (Madison, WI), Gloria E. Sarto; Wake Forest University School of Medicine (Winston-Salem, NC), Denise Bonds; Wayne State University School of Medicine/Hutzel Hospital (Detroit, MI), Susan Hendrix.

Received March 20, 2006. Accepted June 15, 2006.

Address all correspondence and requests for reprints to: Denise E. Bonds, M.D., M.P.H., Department of Epidemiology and Prevention, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, North Carolina 27157. E-mail: dbonds@wfubmc.edu.

This work was supported by the National Heart, Lung, and Blood Institute and the General Clinical Research Center program of the National Center for Research Resources, Department of Health and Human Services.

Disclosure statement: The authors have nothing to disclose.

## References

1. **Johnell O, Kanis JA, Oden A, Sernbo I, Redlund-Johnell I, Petterson C, De Laet C, Jonsson B** 2004 Mortality after osteoporotic fractures. Osteoporos Int 15:38–42
2. **Tosteson AN, Gabriel SE, Grove MR, Moncur MM, Kneeland TS, Melton 3rd LJ** 2001 Impact of hip and vertebral fractures on quality-adjusted life years. Osteoporos Int 12:1042–1049
3. **Jiang HX, Majumdar SR, Dick DA, Moreau M, Raso J, Otto DD, Johnston DW** 2005 Development and initial validation of a risk score for predicting in-hospital and 1-year mortality in patients with hip fractures. J Bone Miner Res 20:494–500
4. **Kroger H, Tuppurainen M, Honkanen R, Alhava E, Saarikoski S** 1994 Bone mineral density and risk factors for osteoporosis—a population-based study of 1600 perimenopausal women. Calcif Tissue Int 55:1–7
5. **Johnell O, Gullberg B, Kanis JA, Allander E, Elffors L, Dequeker J, Dilsen G, Gennari C, Lopes Vaz A, Lyritis G, Mazzuoli G, Miravet L, Passeri M, Cano RP, Rapado A, Ribot C** 1995 Risk factors for hip fracture in European women: the MEDOS Study. Mediterranean Osteoporosis Study. J Bone Miner Res 10:1802–1815
6. **Heap J, Murray MA, Miller SC, Jalili T, Moyer-Mileur LJ** 2004 Alterations in bone characteristics associated with glycemic control in adolescents with type 1 diabetes mellitus. J Pediatr 144:56–62
7. **Liu EY, Wactawski-Wende J, Donahue RP, Dmochowski J, Hovey KM, Quattrin T** 2003 Does low bone mineral density start in post-teenage years in women with type 1 diabetes? Diabetes Care 26:2365–2369
8. **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
9. **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
10. **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
11. **Nicodemus KK, Folsom AR** 2001 Type 1 and type 2 diabetes and incident hip fractures in postmenopausal women. Diabetes Care 24:1192–1197
12. **Isaia GC, Ardissone P, Di Stefano M, Ferrari D, Martina V, Porta M, Tagliabue M, Molinatti GM** 1999 Bone metabolism in type 2 diabetes mellitus. Acta Diabetol 36:35–38
13. **Barrett-Connor E, Holbrook TL** 1992 Sex differences in osteoporosis in older adults with non-insulin-dependent diabetes mellitus. JAMA 268:3333–3337
14. **van Daele PL, Stolk RP, Burger H, Algra D, Grobbee DE, Hofman A, Birkenhager JC, Pols HA** 1995 Bone density in non-insulin-dependent diabetes mellitus. The Rotterdam Study. Ann Intern Med 122:409–414
15. **Schwartz AV, Hillier TA, Sellmeyer DE, Resnick HE, Gregg E, Ensrud KE, Schreiner PJ, Margolis KL, Cauley JA, Nevitt MC, Black DM, Cummings SR** 2002 Older women with diabetes have a higher risk of falls: a prospective study. Diabetes Care 25:1749–1754
16. **Hampson G, Evans C, Petitt RJ, Evans WD, Woodhead SJ, Peters JR, Ralston SH** 1998 Bone mineral density, collagen type 1$\alpha$1 genotypes and bone turnover in premenopausal women with diabetes mellitus. Diabetologia 41:1314–1320
17. **Hirano Y, Kishimoto H, Hagino H, Teshima R** 1999 The change of bone mineral density in secondary osteoporosis and vertebral fracture incidence. J Bone Miner Metab 17:119–124
18. **Luetters CM, Keegan TH, Sidney S, Quesenberry CP, Prill M, Sternfeld B, Kelsey J** 2004 Risk factors for foot fracture among individuals aged 45 years and older. Osteoporos Int 15:957–963
19. **Schwartz AV, Sellmeyer DE, Ensrud KE, Cauley JA, Tabor HK, Schreiner PJ, Jamal SA, Black DM, Cummings SR** 2001 Older women with diabetes have an increased risk of fracture: a prospective study. J Clin Endocrinol Metab 86:32–38
20. **Ottenbacher KJ, Ostir GV, Peek MK, Goodwin JS, Markides KS** 2002 Diabetes mellitus as a risk factor for hip fracture in Mexican American older adults. J Gerontol A Biol Sci Med Sci 57:M648–M653
21. **Strotmeyer ES, Cauley JA, Schwartz AV, Nevitt MC, Resnick HE, Bauer DC, Tylavsky FA, de Rekeneire N, Harris TB, Newman AB** 2005 Nontraumatic fracture risk with diabetes mellitus and impaired fasting glucose in older white and black adults: the health, aging, and body composition study. Arch Intern Med 165:1612–1617
22. **Ivers RQ, Cumming RG, Mitchell P, Peduto AJ** 2001 Diabetes and risk of fracture: the Blue Mountains Eye Study. Diabetes Care 24:1198–1203
23. **Carnevale V, Romagnoli E, D'Erasmo E** 2004 Skeletal involvement in patients with diabetes mellitus. Diabetes Metab Res Rev 20:196–204
24. **Langer RD, White E, Lewis CE, Kotchen JM, Hendrix SL, Trevisan M** 2003 The Women's Health Initiative Observational Study: baseline characteristics of participants and reliability of baseline measures. Ann Epidemiol 13:S107–S121
25. **Curb JD, McTiernan A, Heckbert SR, Kooperberg C, Stanford J, Nevitt M, Johnson KC, Proulx-Burns L, Pastore L, Criqui M, Daugherty S** 2003 Outcomes ascertainment and adjudication methods in the Women's Health Initiative. Ann Epidemiol 13:S122–S128
26. **The Women's Health Initiative Study Group** 1998 Design of the Women's Health Initiative clinical trial and observational study. Control Clin Trials 19:61–109
27. **Chen Z, Kooperberg C, Pettinger MB, Bassford T, Cauley JA, LaCroix AZ, Lewis CE, Kipersztok S, Borne C, Jackson RD** 2004 Validity of self-report for fractures among a multiethnic cohort of postmenopausal women: results from the Women's Health Initiative observational study and clinical trials. Menopause 11:264–274
28. **Gluer CC, Faulkner KG, Estilo MJ, Engelke K, Rosin J, Genant HK** 1993 Quality assurance for bone densitometry research studies: concept and impact. Osteoporos Int 3:227–235
29. **Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett Jr DR, Schmitz KH, Emplaincourt PO, Jacobs Jr DR, Leon AS** 2000 Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 32:S498–S504
30. **Palvanen M, Kannus P, Parkkari J, Pitkajarvi T, Pasanen M, Vuori I, Jarvinen M** 2000 The injury mechanisms of osteoporotic upper extremity fractures among older adults: a controlled study of 287 consecutive patients and their 108 controls. Osteoporos Int 11:822–831
31. **Bolotin HH, Sievanen H, Grashuis JL** 2003 Patient-specific DXA bone mineral density inaccuracies: quantitative effects of nonuniform extraosseous fat distributions. J Bone Miner Res 18:1020–1027
32. **Hangartner TN, Johnston CC** 1990 Influence of fat on bone measurements with dual-energy absorptiometry. Bone Miner 9:71–81
33. **Dawson-Hughes B, Dallal GE** 1990 Effect of radiographic abnormalities on rate of bone loss from the spine. Calcif Tissue Int 46:280–281
34. **Greenspan SL, Maitland LA, Myers ER, Krasnow MB, Kido TH** 1994 Femoral bone loss progresses with age: a longitudinal study in women over age 65. J Bone Miner Res 9:1959–1965

35. **Reddy GK, Stehno-Bittel L, Hamade S, Enwemeka CS** 2001 The biomechanical integrity of bone in experimental diabetes. Diabetes Res Clin Pract 54:1–8
36. **Paul RG, Bailey AJ** 1996 Glycation of collagen: the basis of its central role in the late complications of ageing and diabetes. Int J Biochem Cell Biol 28:1297–1310
37. **Wang X, Shen X, Li X, Agrawal CM** 2002 Age-related changes in the collagen network and toughness of bone. Bone 31:1–7
38. **Jehle PM, Jehle DR, Mohan S, Bohm BO** 1998 Serum levels of insulin-like growth factor system components and relationship to bone metabolism in type 1 and type 2 diabetes mellitus patients. J Endocrinol 159:297–306
39. **Raskin P, Stevenson MR, Barilla DE, Pak CY** 1978 The hypercalciuria of diabetes mellitus: its amelioration with insulin. Clin Endocrinol (Oxf) 9:329–335
40. **Pickup JC, Crook MA** 1998 Is type II diabetes mellitus a disease of the innate immune system? Diabetologia 41:1241–1248
41. **Keegan TH, Schwartz AV, Bauer DC, Sellmeyer DE, Kelsey JL** 2004 Effect of alendronate on bone mineral density and biochemical markers of bone turnover in type 2 diabetic women: the fracture intervention trial. Diabetes Care 27:1547–1553
42. **White E** 1986 The effect of misclassification of disease status in follow-up studies: implications for selecting disease classification criteria. Am J Epidemiol 124:816–825
43. **Dargent-Molina P, Favier F, Grandjean H, Baudoin C, Schott AM, Hausherr E, Meunier PJ, Breart G** 1996 Fall-related factors and risk of hip fracture: the EPIDOS prospective study. Lancet 348:145–149

**JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.**