Prospective Study of Diabetes and Risk of Hip Fracture

The Nurses' Health Study

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OBJECTIVE — The purpose of this study was to determine whether women with type 1 and type 2 diabetes are at higher risk of hip fractures.

RESEARCH DESIGN AND METHODS — A total of 109,983 women aged 34–59 years in 1980 were followed through 2002 for the occurrence of hip fracture. At baseline and through biennial follow-up, women were asked about their history and treatment of diabetes and other potential risk factors for hip fracture.

RESULTS — During 2.22 million person-years of follow-up, 1,398 women had a hip fracture. Compared with women without diabetes, the age-adjusted relative risk (RRs) of hip fracture was 7.1 (95% CI 4.4–11.4) for women with type 1 diabetes and 1.7 (1.4–2.0) for those with type 2 diabetes. After further adjustment for BMI, smoking, physical activity, menopausal status, daily intake of calcium, vitamin D, protein, and postmenopausal hormone use, the multivariate RR of incident hip fracture in individuals with type 1 diabetes compared with individuals without diabetes was 6.4 (3.9–10.3) and with type 2 diabetes was 2.2 (1.8–2.7). The RRs increased with longer duration of type 2 diabetes (3.1 [2.3–4.0] for ≥12 years compared with no diabetes, *P* for trend < 0.001) and ever use of insulin.

CONCLUSIONS — These data indicate that both type 1 and type 2 diabetes are associated with an increased risk of hip fracture. The results of this study highlight the need for fracture-prevention strategies in women with diabetes.

Diabetes Care 29:1573–1578, 2006

The role of diabetes as a risk factor for osteoporosis and fracture remains unsettled. Bone mineral density (BMD) appears to be reduced in patients with type 1 diabetes in most (1–4) but not all studies (5,6). There have also been conflicting reports about BMD in patients with type 2 diabetes (3,4,7–18); in some studies BMD was reduced (7,9), whereas in other studies BMD was increased (8,10–12) or unchanged (13–18). Uncertainty also exists about the relationship between diabetes and fracture incidence. Only a few studies have examined the risk of fracture in people with type 1 diabetes (9,14–16,19,20); the risk of hip fracture appeared to be increased in some (9,14,19,20) but not all studies (15,16). Studies of the association between type 2 diabetes and the risk of fracture also demonstrated inconsistent conclusions (4,8,9,11,12,21–25). Several of these studies showed a positive association (12,22–25), whereas others reported no association (4,8,9) or even an inverse relation (11,21). However, most of these studies have been conducted with relatively small numbers of participants, have had limited ability to adjust for potential confounders, or were not able to distinguish between type 1 and type 2 diabetes (24,25). Given the conflicting results in previous studies, we used the large ongoing Nurses' Health Study (NHS) to examine the risk of hip fracture in women with type 1 or type 2 diabetes.

RESEARCH DESIGN AND METHODS

— The NHS is an ongoing cohort that was established in 1976 when 121,701 female registered nurses 30–55 years of age and residing in one of 11 states completed a mailed questionnaire on their health status and on various potential risk factors for diabetes, cancers, cardiovascular disease, and other chronic diseases. Of this cohort, ~98% are white. Participants receive follow-up questionnaires biennially to update information on demographic, anthropometric, and lifestyle factors and on newly diagnosed diseases including hip fracture. The follow-up rate still exceeds 90% for every 2-year period. The study was approved by the Human Research Committees at the Harvard School of Public Health and Brigham and Women's Hospital.

Ascertainment of fracture

Incident cases of hip fracture that occurred before 1 June 2002 were identified from questionnaires mailed to participants biennially after 1980. Although we relied on self-reports of hip fractures, we expected reliable information in a cohort of registered nurses. Validity was demonstrated in a small validation study in which all 30 reported hip fractures were confirmed by medical records (26). Fractures due to major trauma such as a motor vehicle accident were excluded.

Ascertainment of diabetes

Cases of diabetes were identified from baseline and biennial follow-up questionnaires. When women reported that diabetes had been diagnosed by a physician, confirmation was based on responses to a supplementary questionnaire about complications, diagnostic tests, and treatments. Confirmation criteria conformed

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Received for publication 24 February 2006 and accepted in revised form 18 April 2006.

Abbreviations: BMD, bone mineral density; NHS, Nurses' Health Study; SOF, Studies of Osteoporotic Fractures.

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

DOI: 10.2337/dc06-0440

Table 1—*Age-adjusted characteristics* of women (109,983) by diabetes status in the NHS, 1980–2002*

Characteristic	Without diabetes	Type 1 diabetes	Type 2 diabetes
n	101,343	292	8,348
Age (years)	55.9 ± 9.4	54.7 ± 9.3	61.7 ± 8.2
Age at hip fracture (years)	65.6 ± 8.3	65.3 ± 7.4	68.6 ± 7.2
Height (cm)	164 ± 6	164 ± 6	163 ± 6
Waist-to-hip ratio	0.78 ± 0.07	0.79 ± 0.08	0.84 ± 0.09
BMI at age 18 (kg/m^2)	20.6 ± 3.1	20.5 ± 3.3	22.1 ± 4.4
BMI, current (kg/m^2)	25.6 ± 4.9	24.2 ± 4.5	31.0 ± 6.4
Weight change since age 18 (kg)	11.6 ± 12.0	7.4 ± 11.4	21.0 ± 16.0
Follow-up duration (years)	20.0 ± 4.3	18.3 ± 5.4	20.4 ± 3.4
Duration of diabetes (years)	—	32.7 ± 12.9	16.3 ± 9.3
Glycemic index	52 ± 4	52 ± 4	53 ± 4
Daily alcohol intake (g)	5.8 ± 10.1	4.4 ± 9.2	2.4 ± 7.3
Daily caffeine intake (mg)	295 ± 240	338 ± 268	252 ± 226
Daily vitamin K intake (μg)	181 ± 105	191 ± 120	186 ± 111
Daily vitamin A intake (μg)	2,266 ± 1,719	2,380 ± 1,831	2,246 ± 1,524
Daily vitamin D intake (μg)	8.9 ± 6.8	9.6 ± 6.8	9.2 ± 6.6
Daily calcium intake (mg)	988 ± 517	1,003 ± 484	964 ± 491
Daily protein intake (g)	74 ± 14	79 ± 16	79 ± 14
Daily calorie intake (kcal)	1,707 ± 533	1,732 ± 521	1,720 ± 546
Physical activity (h/week)	2.8 ± 3.0	2.7 ± 3.2	2.3 ± 2.9
Thiazide diuretics use (%)	12.0	13.0	25.0
Current smoker (%)	18.0	16.0	17.0
Postmenopause (%)	65.0	67.0	67.0
Postmenopausal hormone use (%)	35.0	31.0	26.0
History of osteoporosis (%)	8.0	11.0	9.0

Data are means ± SD unless otherwise indicated. *Values were calculated over person-time of the entire follow-up period and were adjusted to the age distribution of the study population.

to guidelines of the National Diabetes Data Group (27) until 1997 and to revised criteria of the American Diabetes Association from 1998 forward (28). A validation study found 98.4% concordance of our nurse participants' reports of type 2 diabetes with medical records (29). Only women with definite type 1 and type 2 diabetes were considered in this analysis. We estimated duration of diabetes by subtracting the date of diagnosis from the date of last completed questionnaire. We obtained information on drug treatment for diabetes from the supplementary questionnaire. Using the baseline questionnaire, we classified women as having type 1 diabetes if diabetes was first diagnosed at ≤30 years of age and if they were currently using insulin or were ketosis prone (n = 292). Women whose diabetes was first diagnosed at >30 years of age were classified as having type 2 diabetes (n = 8,348). A total of 6,883 women without diabetes at baseline reported newly diagnosed type 2 diabetes in the biennial follow-up questionnaires.

Covariates

Information on age, body size, smoking status, weight change, alcohol intake, diet and physical activity, family and personal medical history, and postmenopausal hormone therapy was collected at the baseline and through biennial questionnaires. Every 2–4 years, we sent a semiquantitative food frequency questionnaire to the participants, from which we calculated nutrient intake values. Although the NHS cohort started in 1976, this analysis was begun in 1980 (referred to as baseline) when the food frequency questionnaire was first included. We calculated BMI as the ratio of weight in kilograms to the square of height in meters, the latter being assessed at 1976 only. Self-reports of body weight have been highly correlated with technician-measured weights (r = 0.96) (30). Waist and hip circumferences were self-reported in 1986 and 1996. Self-reports of waist and hip circumference have been reasonably correlated with the average of two technician measurements of waist and hip circumference (r = 0.89 for waist and 0.84 for hip) (31). The number of hours of leisure time physical activity per week was assessed in 1986, 1988, 1992, 1994, 1996, 1998, and 2000. Physical activity reported on the questionnaire was highly correlated with activity recorded in diaries (32).

Women who reported diabetes that was not confirmed were excluded from the analyses (n = 842). Participants were also excluded if they did not report their height or weight or reported, at baseline, having any disease or conditions known to affect fracture risk (e.g., cancer other than skin cancer or heart disease and stroke) (n = 10,876). This left a study population of 109,983 women with a mean ± SD age of 56.1 ± 9.4 years.

Analysis

Incidence was expressed as the number of cases of hip fracture per 100,000 person-years of follow-up beginning on the date of completion of the baseline questionnaire in 1980 and continuing until the occurrence of a hip fracture, the date of the last completed follow-up questionnaire, death, or end of follow-up on 1 June 2002, whichever came first. To describe the association between diabetes and risk of hip fracture we used two types of statistical analyses: age-adjusted relative risks (RRs) based on incidence rates and multivariate-adjusted RRs from Cox's proportional hazard model using the SAS computer package (version 9.0; SAS Institute, Cary, NC). We considered the following covariates in the multivariate-adjusted analyses: current BMI, BMI at age 18, weight change from age 18 to current, waist-to-hip ratio, menopausal status and use of postmenopausal hormones, smoking, physical activity, history of osteoporosis, use of thiazide diuretics, dietary glycemic index, and daily consumption of calcium, vitamin D, protein, retinol, vitamin K, alcohol, and caffeine. To clarify the role of BMI further, we also conducted an analysis including the interaction terms of BMI as a continuous variable with type 2 diabetes in the "full" model.

RESULTS — Differences in distribution of several age-adjusted characteristics among 101,343 (92.1%) women without diabetes, 292 (0.3%) with type 1 diabetes, and 8,348 (7.6%) with type 2 diabetes are shown in Table 1. As expected, women with type 2 diabetes were older; had higher age-adjusted current BMI and at age 18, waist-to-hip ratio, and

Table 2—*Incidence rates and RRs of hip fracture by diabetes status, duration of diabetes, and treatment in the NHS, 1980–2002*

Variables	*n*	Incidence/100,000 person-years	Age-adjusted RR	Age- and BMI-adjusted RR	Multivariate-adjusted RR
Nondiabetes	1,255	59	1.0	1.0	1.0
Type 1 diabetes	18	383	7.1 (4.4–11.4)*	6.4 (4.0–10.3)*	6.4 (3.9–10.3)*
Type 2 diabetes	125	153	1.7 (1.4–2.0)*	2.3 (1.9–2.7)*	2.2 (1.8–2.7)*
Type 2 diabetes <5 years	34	107	1.3 (0.9–1.9)	1.8 (1.3–2.6)*	1.7 (1.2–2.4)*
Type 2 diabetes 5–11 years	34	127	1.4 (1.0–1.9)	1.9 (1.3–2.7)*	1.8 (1.3–2.6)*
Type 2 diabetes ≥12 years	57	248	2.4 (1.8–3.1)*	3.1 (2.3–4.1)*	3.1 (2.3–4.0)*
Type 2 diabetes treatment					
Nondiabetes	1,255	59	1.0	1.0	1.0
Never used insulin	83	133	1.4 (1.1–1.8)*	1.9 (1.5–2.4)*	1.9 (1.5–2.3)*
Ever used insulin	36	209	2.4 (1.8–3.5)*	3.4 (2.4–4.8)*	3.4 (2.4–4.7)*

Total number of cases is not the same for each variable because of missing values. RRs (95% CI) were calculated by the Cox proportional hazard model, adjusted for age, BMI, physical activity, menopausal status and estrogen use, smoking and daily intake of calcium, vitamin D, and protein. *$P < 0.001$.

weight gain; were less likely to be alcohol drinkers; consumed less caffeine; were more likely to use thiazide diuretics and less likely to use postmenopausal hormones; and had slightly lower physical activity than those without diabetes and those with type 1 diabetes. In addition, women with either type of diabetes were less likely than women without diabetes to be users of estrogen. The mean ± SD age of hip fracture was 65.6 ± 8.3 years for nondiabetic subjects, 65.3 ± 7.4 years for type 1 diabetic subjects, and 68.6 ± 7.2 years for type 2 diabetic subjects. Of the 8,348 women with type 2 diabetes, 1,379 (16.5%) reported ever using insulin.

Incidence

During the follow-up, a total of 1,398 (1.2%) incident cases of hip fracture occurred during 2.22 million person-years of follow-up. The overall incidence of subsequent hip fracture was 63 (95% CI 60–66) per 100,000 person-years. Of the 292 women who had type 1 diabetes but were free of hip fracture at baseline, 18 subsequently had a hip fracture, giving an incidence of 383 (206–560) per 100,000 person-years. This was higher than the incidence rates seen for type 2 diabetes, which is 153 (126–180) per 100,000 person-years. Of the 1,379 women with type 2 diabetes who had ever used insulin and were free of hip fracture at baseline, 36 subsequently had hip fracture, giving an incidence of 209 (141–278) per 100,000 person-years. This was higher than the incidence rates seen for women with type 2 diabetes who never used insulin, which is 133 (104–162) per 100,000 person-years (Table 2).

Risk factors

Compared with women without diabetes, the age-adjusted risk of hip fracture was sevenfold higher in those with type 1 diabetes (RR 7.1 [95% CI 4.4–11.4]) and 70% higher in those with type 2 diabetes (1.7 [1.4–2.0]) in age-adjusted models. When women with type 2 diabetes were divided based on insulin use, both those who used (2.4 [1.8–3.5]) and did not use (1.4 [1.1–1.8]) insulin had a greater risk of hip fracture than women without diabetes (Table 2). Controlling for age and BMI slightly reduced the relationship between type 1 diabetes and hip fracture (6.4 [4.0–10.3]) but increased the RR of hip fracture associated with type 2 diabetes (2.3 [1.9–2.7]) compared with the model adjusted for age alone. In a multivariate model, the additional adjustment for other time-dependent covariates did not appreciably alter the relationship between either type of diabetes and fracture risk compared with the model adjusted for age and BMI (Table 2). Women with a longer duration of type 2 diabetes tended to have a higher risk of fracture than did diabetic subjects with a shorter duration of diabetes (3.1 [2.3–4.0], for ≥12 years compared with no diabetes, *P* for trend < 0.001).

The association between type 2 diabetes and hip fracture was similar among obese and nonobese women (Table 3). Also, in both obese and nonobese women with type 2 diabetes, the risk of fracture increased with increasing duration of diabetes.

CONCLUSIONS — In this 22-year follow-up study, both type 1 and type 2 diabetes were associated with a signifi-

Table 3—*Incidence rates and RRs of hip fracture by obesity in the NHS, 1980–2002.*

Variables	*n*	Incidence/ 100,000 person-years	Age-adjusted RR	Multivariate-adjusted RR
Obese women (BMI ≥30 kg/m^2)				
Nondiabetes	79	34	1.0	1.0
Type 2 diabetes	41	107	2.3 (1.5–3.3)*	2.2 (1.4–3.3)*
Type 2 diabetes <5 years	11	72	1.8 (0.9–3.3)	1.9 (1.0–3.8)
Type 2 diabetes 5–11 years	10	76	1.6 (0.8–3.1)	1.6 (0.8–3.1)
Type 2 diabetes ≥12 years	20	204	3.7 (2.2–6.0)*	3.0 (1.7–5.2)*
Nonobese women (BMI <30 kg/m^2)				
Nondiabetes	1,085	61	1.0	1.0
Type 2 diabetes	79	202	1.9 (1.5–2.4)*	2.5 (1.9–3.1)*
Type 2 diabetes <5 years	23	155	1.5 (1.0–2.3)*	2.1 (1.4–3.2)*
Type 2 diabetes 5–11 years	23	190	1.7 (1.2–2.6)*	2.3 (1.5–3.5)*
Type 2 diabetes ≥12 years	33	273	2.4 (1.7–3.4)*	3.0 (2.1–4.3)*

Total number of cases is not the same for each variable because of missing values. RRs (95% CI) were calculated by the Cox proportional hazard model, adjusted for age, BMI, physical activity, menopausal status and estrogen use, smoking and daily intake of calcium, vitamin D, and protein. *$P < 0.001$.

cantly higher risk of hip fracture in women; the association with type 1 diabetes was stronger. Few studies have assessed risks of fracture in individuals with type 1 diabetes, and the results are inconsistent. A case-control study found that the prevalence of hip and wrist fractures in insulin-treated diabetic women, of whom 33% had type 1 diabetes, was lower than that in women without type 1 diabetes (16). In another case-control study, however, no greater risk of fracture was found in patients with type 1 or type 2 diabetes than in matched control subjects (15). The Studies of Osteoporotic Fractures (SOF) found that type 1 diabetes was associated with an increased risk of foot fractures (33) and proximal humerus fractures (23). However, diabetes was not associated with an increased risk of hip fracture (7). In contrast, a Norwegian prospective study reported that the RR for hip fracture in postmenopausal women with type 1 diabetes was 6.9 (95% CI 2.2–21.6) (14), but the number of hip fractures among women with type 1 diabetes was very small ($n = 3$). A large Danish case-control study showed that type 1 and type 2 diabetes were associated with an increased risk of any fracture and hip fracture, but it was not possible to adjust for BMI (20). In a study similar to ours, the Iowa Women's Health Study, those with type 1 diabetes were 12.3 (5.1–29.7) times more likely to report an incident hip fracture than women without diabetes, after control for age, smoking status, BMI, waist-to-hip ratio, and hormone replacement therapy (9). A Swedish population-based retrospective study reported increased risk in both men and women with type 1 diabetes, but in this study the ability to adjust for potential confounders was limited (19). We found that women with type 1 diabetes had a 6.4 (3.9–10.3) times higher risk of hip fracture than women without diabetes, even after controlling for age, BMI, physical activity, smoking, postmenopausal hormone use, menopause status, vitamin D, calcium, and protein intake.

More studies have examined the effect of type 2 diabetes on bone fracture, also with inconsistent results. Although the SOF found that type 2 diabetes was associated with increased risk of foot (33) and proximal humerus fractures (23), another SOF report suggested an increased risk of hip fracture in women with diabetes not treated with insulin; after adjustment for obesity the RR was 1.6 (95% CI 0.9–2.7) (7). Also, the SOF reported an increased risk of hip and proximal humerus fractures in older women with type 2 diabetes, despite having higher BMD (12). In a case-control study among elderly people in Oslo, there was a nonsignificant increased risk for hip fracture in those with diabetes (34), whereas in a Danish study there was no increased risk in diabetic women treated with insulin compared with the general population (16). Studies in Norway also showed a strong association between diabetes and risk of hip fracture in both women and men, although it was not possible to distinguish between type 1 and type 2 diabetes (14,24). In the Blue Mountains Eye Study, insulin-treated type 2 diabetes but not tablet- or diet-treated type 2 diabetes was associated with an increased risk of fracture (8). At the Mayo Clinic, the risk of ankle fractures was elevated among women with diabetes, but a higher risk for other fracture sites was not found (15). These results, however, were not adjusted for body size or BMD. Melchior et al. (16) found no differences in rates of hip and Colles' fracture among women with diabetes who were being treated with insulin compared with women without diabetes. In a large cross-sectional study from Rotterdam, women with type 2 diabetes had a lower frequency of self-reported nonspine fracture in the preceding 5 years than women without diabetes (11,35). In this study both men and women with type 2 diabetes had higher mean BMD than subjects without diabetes, even after adjustment for obesity. We found that women with type 2 diabetes had a 2.2 (1.8–2.7) times higher multivariate-adjusted risk of hip fracture than women without diabetes.

The mechanisms whereby diabetes exerts negative effects on fracture risk are not entirely clear. Putative mechanisms include lower BMD, weight loss, metabolic acidosis, and hyperglycemia in type 1 diabetes, whereas vision loss and neuropathy may be of greater importance in type 2 diabetes. Moreover, a link between microvascular complications of type 1 diabetes and long-term bone loss has been reported (36), notably between neuropathy and decreased BMD of the femoral neck (6). Another possible cause of the increased risk of hip fracture in both type 1 and type 2 diabetes is diabetes-related comorbidity (8,37,38), such as diabetic retinopathy, peripheral neuropathy, cerebral stroke, or hypoglycemia, which may increase the risk of falling. The combination of poor bone quality and frequent falls would be expected to increase the risk of fracture independent of BMD.

We found that the incidence of hip fracture was higher in patients with insulin-treated type 2 diabetes than in non–insulin-treated patients. Although we have no direct data on mechanisms, insulin treatment may indicate a more severe disease process rather than be a direct contributor to hip fracture. A higher incidence of hip fracture among insulin-treated patients could be attributable to a younger age at onset, to more difficult metabolic control than in non–insulin-treated type 2 diabetes or to episodes of hypoglycemia. Insulin may have an anabolic effect on bone (28,35), but the role of insulin in fracture risk is uncertain. This role warrants further study.

In this study, duration of type 2 diabetes was associated with the incidence of hip fracture, supporting the results of other studies (8,9), albeit not all studies (20). The strong association with duration may largely explain the substantially greater RR among women with type 1 diabetes. Measures of duration of diabetes are subject to error, and type 2 diabetes remains undiagnosed for years in many individuals; this error would tend to weaken associations with duration and could have accounted for the lack of an apparent relation in some studies.

Obesity is associated with type 2 diabetes and with increased levels of estrogen, which may decrease hip fracture risk among obese women. In addition, obesity provides cushioning for the hip in the event of a fall (7). However, our findings confirm other studies (9) in which type 2 diabetes increased the risk for hip fracture regardless of obesity.

Consistent with previous studies (9,39), we found that women with diabetes were less likely than women without diabetes to use hormone replacement therapy, which has been shown to lower the risk for hip fracture. However, the positive association between diabetes and hip fracture remained, even after adjustment for hormone replacement therapy, and a significant positive association was observed among never users (data not shown).

The strengths of this study include the prospective cohort design, large sample size, long-term follow-up, and detailed information on potential confounding factors, such as weight change, smoking, body size, exogenous estrogen, alcohol consumption, and diet. Selection and information bias were unlikely because of

the prospective design and high rate of follow-up. However, the NHS was not undertaken primarily to determine risk factors for fracture. Thus, because there were no measures of BMD, neuromuscular impairment, history of fractures at baseline, family history of fractures, or cognitive impairment we cannot evaluate whether the increased hip fracture risk was mediated by reduced bone mass or by complications of diabetes predisposing to trauma, such as retinopathy, cerebral stroke, and peripheral neuropathy. Hip fracture was based on self-report, although the validity has been shown to be high (26). Because diabetes was determined by self-report and confirmed through a diagnostic supplementary questionnaire, those participants identified as not having diabetes probably included some women with undiagnosed type 2 diabetes. However, these misclassifications would tend to reduce rather than increase the significance of differences between diabetes and hip fracture. Some women with type 2 diabetes may have been misclassified as having type 1 diabetes, and some with late onset type 1 diabetes may have been included in our group of women with type 2 diabetes, but again this could not have accounted for the differences in risk. Another limitation was the fact that study participants were mainly white, and results may not apply to the broader population of women, especially to other racial/ethnic groups.

In summary, our study indicates that women with type 1 or type 2 diabetes are at increased risk for hip fracture. These findings highlight the need for fracture prevention efforts in individuals with diabetes.

Acknowledgments— This work was supported by National Institutes of Health Grants DK58845 and P01CA87969.

We are grateful to Tricia Li for computer technical assistance. This study could not have been conducted without the contribution of the nurses who participated.

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