Type 1 and Type 2 Diabetes and Incident Hip Fractures in Postmenopausal Women

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OBJECTIVE — To examine whether postmenopausal women with diabetes experienced a higher incidence of hip fracture than women without diabetes.

RESEARCH DESIGN AND METHODS — A prospective cohort of 32,089 postmenopausal women residing in Iowa were surveyed by mail in 1986 and followed for 11 years. Diabetes status and other potential risk factors were assessed by questionnaires at baseline; incidence of hip fracture was ascertained by follow-up questionnaires.

RESULTS — A total of 490 hip fractures were reported over 306,900 person-years of follow-up. After adjustment for age, smoking status, estrogen use, BMI, and waist-to-hip ratio, women with type 1 diabetes ($n = 47$) were 12.25 times (95% CI 5.05–29.73) more likely to report an incident hip fracture than women without diabetes. Women with type 2 diabetes had a 1.70-fold higher risk (1.21–2.38) of incident hip fracture than women without diabetes. Longer duration of type 2 diabetes was associated with higher incidence, as was use of insulin or oral diabetes medications in women with type 2 diabetes. Furthermore, women who were initially free of diabetes but in whom diabetes developed had a relative risk of hip fracture of 1.60 (1.14–2.25) compared with women who never had diabetes.

CONCLUSIONS — Postmenopausal women who have diabetes or in whom diabetes develops are at higher risk for hip fracture than nondiabetic postmenopausal women. Strategies to prevent osteoporosis and/or falling may be especially warranted in women with diabetes.

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Although it is generally accepted that people with type 1 (juvenile-onset) diabetes have decreased bone mass relative to those without diabetes, a consensus on osteoporosis risk in people with type 2 (adult-onset) diabetes has not been reached (1–11). Studies have found that people with type 2 diabetes have increased, similar, or decreased bone mass in comparison to healthy control subjects (3–10). Few studies have examined the possible relation between diabetes and the clinical outcomes of decreased bone mass, such as hip fracture, and most previous studies have been small (11–17). Furthermore, few prospective studies have focused on postmenopausal women, who are at the greatest risk for morbidity and mortality due to hip fracture.

Therefore, we examined the relation of both type 1 and type 2 diabetes with 11-year incidence of hip fracture in a large cohort of postmenopausal women living in Iowa.

RESEARCH DESIGN AND METHODS

Data collection

The Iowa Women's Health Study is a prospective cohort study of postmenopausal women living in Iowa, focusing on the relation of diet and lifestyle with occurrence of cancers and other chronic diseases. Women between 55 and 69 years of age were randomly selected from the 1985 Iowa Department of Transportation driver's license list. Of those selected and sent a questionnaire, 41,836 women responded (42% response rate) and formed the cohort under study. Based on driver's license information, we determined that nonrespondents were, on average, 3 months younger than respondents, had slightly higher BMI (0.4 kg/m^2), and were more likely to live in a rural area (18).

The baseline questionnaire assessed diet, lifestyle, body size, family and personal medical history, and reproductive history. Diabetes status and age at diagnosis of diabetes were self-reported. We used age at diagnosis to classify women as having either type 1 or type 2 diabetes, recognizing that type 1 diabetes can develop in women after 30 years of age and type 2 diabetes can develop in women before 30 years of age. Using the baseline questionnaire (1986), we classified women as having type 1 diabetes if they were first diagnosed with diabetes at 30 years of age or younger and if they were currently using insulin ($n = 47$). Women who were first diagnosed with diabetes after 30 years of age were classified as having type 2 diabetes ($n = 1,682$). Women who did not know whether they had ever been diagnosed with diabetes, who did not know if they were taking medication for diabetes, or who did not state their age at first diagnosis of diabetes were excluded from further analyses ($n = 2,206$), as were women who reported diabetes onset before 31 years of age but who were not taking insulin ($n = 42$).

In a validation study on the Iowa cohort, Kaye et al. (19) found that 64% of self-reported cases of diabetes were confirmed by the individuals' physicians. Other researchers have found relatively high validity of diabetes self-reports (20). For women who reported having diabetes at baseline, duration of diabetes was calculated as the number of years between reported diagnosis of diabetes and 1986 (the year of the baseline questionnaire).

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

Table 1—*Distributions of selected variables by diabetes status at baseline, the Iowa Women's Health Study, 1986*

Variable	Diabetes status		
	None	Type 1	Type 2
n	30,377	47	1,682
Age (years)	61.5	60.9	62.3*
Waist-to-hip ratio	0.833	0.834	0.900*
BMI (kg/m^2)	26.7	25.8	30.5*
Alcohol consumption (g/week)	3.90	2.31	1.84*
Energy intake (kcal/day)	1,802	1,810	1,751*
Vitamin D intake (IU/day)	411	486	415
Calcium intake (g/day)	1,097	1,055	1,079
Protein intake (g/day)	80.6	81.5	84.7*
Low physical activity (%)	47.0	46.7	55.9*
Smoking status (%)			
Current	15.2	11.1	12.0
Former	19.4	22.2	21.3
Never	65.4	66.7	66.7*
Estrogen use (%)			
Current	11.4	4.4	7.8
Former	27.7	28.9	27.5
Never	60.9	66.7	64.7*

Data are *n* or %. *$P < 0.01$ for overall difference among diabetes status groups.

BMI was calculated as the participant's weight (in kilograms) divided by her height (in meters) squared. A paper tape measure was provided to each participant for recording waist (inch above umbilicus) and hip (maximum) measurements; waist-to-hip ratio was then calculated as her waist measurement (in inches) divided by her hip measurement (in inches) (21). Level of physical activity was assessed from two questions on the frequency of moderate and vigorous leisure-time physical activity. The baseline questionnaire also included a food frequency questionnaire, from which we calculated nutrient intake values (22).

Hip fractures occurring during follow-up were self-reported via four follow-up mail surveys in 1987 (91% response rate), 1989 (89% response rate), 1992 (83% response rate), and 1997 (79% response rate). Self-reporting of hip fracture incidence in our cohort has been reported to have high validity (23). A total of 1,707 women without diabetes at baseline reported newly diagnosed diabetes (presumably type 2) in the follow-up questionnaires. For primary analyses, these women were classified as not having diabetes, but a supplemental analysis considered them separately.

Statistical analyses

In addition to the exclusions for missing baseline diabetes information, women were excluded from analyses if they reported at baseline having any cancer other than skin cancer, if they had extreme daily energy intake values (<500 or >5,000 calories per day), if they failed to respond to 30 or more items on the food frequency questionnaire, or if they reported being premenopausal. The final number of participants for analysis was 32,089.

Person-years of follow-up were calculated from the completion of the baseline questionnaire until the midpoint between the date of the questionnaire in which the first hip fracture was reported and the participant's most recent previous questionnaire; for noncases, person-years of follow-up were calculated from baseline to the date of the last follow-up questionnaire or death. On average, participants contributed 9.53 years of follow-up. In the supplemental analysis involving individuals with newly diagnosed diabetes, hip fractures reported before diagnosis of diabetes were not removed because diabetes is often present long before it is diagnosed (24).

Differences in means or proportions for possible confounding variables between women with type 1 diabetes, type 2 diabetes, and no diabetes (as assessed by the baseline questionnaire) were examined using either analysis of variance or χ^2 tests. To estimate the relative risk (RR) and 95% CI of hip fracture for diabetic women versus nondiabetic women, both age- and multivariate-adjusted Cox proportional hazards regression analyses were conducted. Stepwise building of the multivariate models was performed entering one variable at a time and then testing the improvement of fit using a likelihood ratio χ^2 test ($\alpha = 0.05$). Variables that did not improve the fit of the model were not retained. The pool of potential confounding variables considered included age, BMI, waist-to-hip ratio, smoking status, pack-years of smoking, use of estrogen, use of oral contraceptives, physical activity, and intake of vitamin A, vitamin D, calcium, protein, alcohol, and caffeine. Analyses including race or ethnicity were precluded because 99.2% of respondents were Caucasian. The final multivariate model included age, BMI, waist-to-hip ratio, smoking status (current, former, never), and use of estrogen (current, former, never).

For the analyses in which only women with type 2 diabetes are shown, all women with type 1 diabetes were excluded from the reference group. Similarly, for analyses in which the RRs for women with type 1 diabetes are reported, the women with type 2 diabetes were excluded from the reference group.

RESULTS — Women who did not have diabetes and those with type 1 diabetes were slightly younger at baseline than women with type 2 diabetes (Table 1). Those who were classified as having type 2 diabetes had significantly higher mean values for BMI and waist-to-hip ratio and lower levels of physical activity than women without diabetes and women with type 1 diabetes. In addition, women with type 2 diabetes reported lower intake of alcohol and lower energy levels and higher intake of protein than women without diabetes or women with type 1 diabetes. Women with either type of diabetes were less likely than nondiabetic women to be current smokers. In addition, participants with diabetes were less likely than nondiabetic participants to be former or current users of estrogen, as found in another study (25). Although dietary factors, alcohol, and physical activity were associated with diabetes, they

Table 2—*Relative risks (95% CI) of hip fracture by diabetes status, the Iowa Women's Health Study, 1986–1997*

Diabetes status	Number of fractures	Age-adjusted RR (95% CI)	Multivariate-adjusted RR (95% CI)
No diabetes*	452	1.00	1.00
Type 1 diabetes	5	14.1 (5.85, 34.2)	12.25 (5.05, 29.7)
Type 2 diabetes	38	1.75 (1.25, 2.43)	1.70 (1.21, 2.38)
Duration of diabetes*			
No diabetes	452	1.00	1.00
Type 2 diabetes			
0–4 years	11	1.47 (0.81, 2.67)	1.44 (0.79, 2.63)
5–12 years	11	1.46 (0.80, 2.66)	1.40 (0.77, 2.57)
13–40 years	16	2.38 (1.44, 3.92)	2.30 (1.39, 3.81)
Type of diabetes treatment*			
No diabetes	452	1.00	1.00
Type 2 diabetes			
Insulin treatment	13	2.79 (1.61, 4.85)	2.66 (1.52, 4.64)
Oral agents	13	1.82 (1.05, 3.16)	1.80 (1.03, 3.16)
No pharmacologic treatment	12	1.21 (0.68, 2.14)	1.17 (0.66, 2.09)
Never used estrogen†			
Nondiabetic	296	1.00	1.00
Type 2 diabetic	26	1.74 (1.17, 2.60)	1.66 (1.10, 2.51)
Current estrogen use			
Nondiabetic	31	1.00	1.00
Type 2 diabetic	1	0.98 (0.13, 7.16)	1.17 (0.16, 8.77)
Former estrogen use			
Nondiabetic	125	1.00	1.00
Type 2 diabetic	11	1.79 (0.97, 3.32)	1.84 (0.98, 3.46)
Obese women (BMI ≥30 kg/m^2)‡			
Nondiabetic	82	1.00	1.00
Type 2 diabetic	15	1.74 (1.00, 3.02)	1.66 (0.95, 2.90)
Nonobese women (BMI <30 kg/m^2)			
Nondiabetic	370	1.00	1.00
Type 2 diabetic	23	1.87 (1.23, 2.85)	1.74 (1.14, 2.67)

*Adjusted for age, smoking (former, current, never), estrogen use (former, current, never), BMI, and waist-to-hip ratio; †adjusted for age, smoking (former, current, never), BMI, and waist-to-hip ratio; ‡adjusted for age, smoking (former, current, never), estrogen use (former, current, never), and waist-to-hip ratio.

were not associated with incidence of hip fracture and, therefore, were dropped from the final models.

Over 306,900 person-years of follow-up, 490 hip fractures were identified, for an incidence rate of 1.6 per 1,000 person-years. This rate is similar to that observed by the National Hospital Discharge Survey (26) and in Rochester, MN (27).

After adjustment for age, BMI, waist-to-hip ratio, smoking status, and use of estrogen, women with type 1 diabetes were 12.25 (95% CI 5.05–29.73) times more likely than nondiabetic women to sustain a hip fracture (Table 2).

Women with type 2 diabetes had a 1.70-fold (95% CI 1.21–2.38) higher multivariate-adjusted risk for hip fracture than women without diabetes (Table 2). Risk increased with greater duration of diabetes, so that women in the highest duration tertile of type 2 diabetes (from 13 to 40 years) had a 2.30 times higher (1.39–3.81) multivariate-adjusted risk for hip fracture relative to women without diabetes.

Women with type 2 diabetes who reported taking any medication to control their diabetes showed significantly increased risk for hip fracture relative to women without diabetes (Table 2). Multivariate-adjusted RRs were 2.66 for those who used insulin, 1.80 for those who used oral medications, and 1.17 for women who were not treated pharmacologically. Although based on small numbers, the associations of fracture with duration of diabetes and type of medication used were somewhat independent (data not shown). For example, compared with women without diabetes, the RRs of fracture were 3.62 (95% CI 1.87, 7.03) for diabetes duration 13–40 years plus use of insulin, 1.71 (0.55–5.34) for duration 5–12 years plus use of insulin, 2.09 (0.67–6.54) for duration 13–40 years plus use of oral medications, and 1.89 (0.70–4.11) for duration 5–12 years plus use of oral medications.

Among women who had never used estrogen, women with type 2 diabetes had a 1.66-fold (95% CI 1.10–2.51) higher incidence of hip fractures than nondiabetic women (Table 2). Among former users of estrogen, this RR was 1.84 (0.98–3.46), and among current users of estrogen, the RR was 1.17 (0.16–8.77); however, this latter estimate was based on few events.

Among obese women, those with type 2 diabetes had a 1.66-fold (95% CI 0.95–2.90) higher incidence of hip fracture than nondiabetic women (Table 2).

Among nonobese women, the RR was 1.74 (1.14–2.67).

In a supplemental analysis, women with newly diagnosed diabetes during follow-up had a 1.60-fold (95% CI 1.14–2.25) increased multivariate-adjusted risk for hip fracture relative to women in whom diabetes had not developed (data not shown).

In addition to hip fractures, participants reported the occurrence during follow-up of fractures of the upper arm, forearm, wrist, ribs, or vertebrae. In analyses performed post hoc, compared with nondiabetic women, women with type 2 diabetes at baseline had an adjusted RR of any self-reported fracture of 1.14 (95% CI 0.97–1.33). However, this RR was 1.28 (1.05–1.55) among nonobese women and 1.24 (1.02–1.50) among women who had never used estrogen. Overall fracture risk also was elevated, compared with nondiabetic women, in women taking insulin (RR 1.46, 95% CI 1.10–1.94) and women with greater duration of diabetes. Among the various nonhip fracture sites, the RRs of type 2 diabetes were somewhat elevated for fractures of the upper arm (1.30, 0.94–1.82), forearm (1.33, 0.80–2.19), and vertebra (1.43, 1.05–1.97), whereas those for wrist and rib fractures were not. In general, the basic pattern of higher risk for type 2 diabetes among nonobese women and women who had never used estrogen, women who used insulin, and women with long-term diabetes held for fractures of the upper arm and forearm but not vertebral fractures.

CONCLUSIONS

Type 1 diabetes

People with type 1 diabetes have been reported to have high rates of bone turnover and resorption, attributed to the effects of secondary hyperparathyroidism, hypomagnesemia, and decreased levels of 1–25-hydroxycholecalciferol (1,6,9). In addition, type 1 diabetes is associated with other risk factors for osteoporosis, such as negative protein balance and disturbances in hormonal balance (2). The complications of diabetes, such as microangiopathy or neuropathy, also may be associated with increased osteoporosis (6). The overwhelming balance of studies assessing bone density in type 1 diabetes has found decreased bone mass relative to nondiabetic control subjects (1,2,9,28). Some researchers have reported that longer duration of type 1 diabetes is correlated with decreasing bone mass (1,28). Other studies have found no association between loss of bone mass and duration of type 1 diabetes (8).

Few studies have assessed risks of fracture in people with type 1 diabetes. A case-control study found that the prevalence of fractures of the hip and distal arm in insulin-treated diabetic women, of which 33% had type 1 diabetes, was lower than in women without type 1 diabetes (12). In contrast, a prospective study (13) reported the RR for hip fractures in postmenopausal women with type 1 diabetes to be 6.9 (95% CI 2.2–21.6). However, the number of hip fractures among type 1 diabetic women was very small ($n = 3$), and the authors apparently did not control for use of hormone replacement therapy. We found that type 1 diabetic women were at 12.25-fold higher risk (5.05–29.73) for hip fracture than nondiabetic women, even after controlling for age, smoking status, BMI, waist-to-hip ratio, and estrogen replacement therapy.

Type 2 diabetes

More research has been completed on the effects of type 2 diabetes on bone mass than of type 1 diabetes. However, the findings are more inconsistent. Researchers have reported lower, equal, and greater bone mass in people with type 2 diabetes relative to diabetes-free control subjects (3–6,7,10,24,29). Part of the inconsistency could be caused by heterogeneous study groups (for example, premenopausal versus postmenopausal women or different diabetes subsets) or by potential confounding by obesity. Two studies found that individuals with type 2 diabetes had lower bone density relative to nondiabetic control subjects (3,29). However, one (3) examined people who were using insulin to control their diabetes, whereas the other (29) examined those using dietary or oral diabetes agents. Two other studies found no difference in bone density between type 2 diabetes patients and control subjects (5,24) but had small numbers of type 2 diabetic women (47 and 19, respectively); therefore, findings may not be generalizable or have suffered from low statistical power. Type 2 diabetes is generally associated with obesity, which has been associated with increased bone mass because adipose tissue produces estrogen. Bone turnover in type 2 diabetes with good metabolic control is believed to be equal to or lower than bone turnover in people without diabetes (6). Therefore, it is not surprising that some researchers have reported higher bone mass in type 2 diabetic patients relative to nondiabetic control subjects (4,7,10). Unlike type 1 diabetes, the duration of type 2 diabetes has not been found to have an association with bone mass (7).

Similarly, studies examining the association between type 2 diabetes and rates of fracture have not been consistent. Two studies reported lower rates of fracture in type 2 diabetic individuals relative to nondiabetic individuals (12,15) and no relation with duration of type 2 diabetes (12). However, both studied multiple fracture sites, and one included individuals who used insulin to control their diabetes. Five other studies found moderately higher to significantly higher rates of hip fracture among those with type 2 diabetes versus those without diabetes (11,13,14,16,17). In our cohort of postmenopausal women, we found that type 2 diabetic women have a 1.70-fold increased multivariate-adjusted risk (95% CI 1.21–2.38) of hip fracture compared with nondiabetic women. In addition, duration of diabetes beyond 13–40 years seemed to carry a much higher risk for hip fracture (RR 2.30, 95% CI 1.39–3.81).

Few studies have assessed the possible relation of type of type 2 diabetes treatment with hip fracture risk, and the results are inconsistent. One study found that risk of hip fracture was increased in type 2 diabetic women who did not use insulin, whereas type 2 diabetic women who used insulin and nondiabetic women had similarly lower hip fracture risk (17). In contrast, another recent study showed that people with type 2 diabetes who used insulin, but not those who were not treated with insulin, had a significantly higher risk for hip fracture relative to nondiabetic people (13). Menczel et al. (14) found that a higher proportion of diabetic individuals aged 75–84 years who used oral diabetes medications had osteoporosis than either individuals with diabetes who used dietary measures or individuals without diabetes. Levin et al. (8) reported that bone mass was lowest in those type 2 diabetic individuals who used oral diabetes medications, and those who used in-

sulin or dietary measures had equivalently lower bone mass relative to control subjects. Our findings show that postmenopausal women with type 2 diabetes not treated pharmacologically have a hip fracture risk similar to nondiabetic women. However, type 2 diabetic women who used oral diabetes medications were at higher risk (RR 1.80, 95% CI 1.03–3.16) and women with type 2 diabetes who used insulin were at the highest risk (2.66, 1.52–4.64) for hip fracture. Although we have no direct data on mechanisms, it seems more likely that pharmacologic treatment is a marker for diabetes severity rather than a direct contributor to hip fracture. Another possibility is that some proportion of women not being treated pharmacologically actually did not have diabetes and were misclassified.

A recent study (25) found that women with diabetes were less likely than women without diabetes to use estrogen replacement therapy, which has been shown to lower risk for hip fracture. Our findings confirm that women who have diabetes are less likely than nondiabetic women to use estrogen replacement therapy. In addition, we found that among women who had never or had formerly used estrogen, type 2 diabetic women were at higher risk for hip fracture compared with nondiabetic women. Although numbers of hip fractures were few and CIs were wide, diabetes was not a risk factor for hip fracture among women currently taking estrogen.

Obesity is associated with type 2 diabetes and with increased levels of estrogen, which may decrease hip fracture risk among obese women. In addition, it has been suggested that obesity provides cushioning for the hip in the event of a fall (17,30). Nevertheless, we found that type 2 diabetes seemed to increase the risk for hip fracture in both obese and nonobese women.

Although we were primarily interested in hip fracture, a post hoc analysis of other fracture sites indicated that women with type 2 diabetes also may be at increased risk for arm or vertebral fractures. This may be true particularly for women who are nonobese, who have never used estrogen, who use insulin, or who have diabetes of longer duration. However, the results for the other fracture sites are less definitive than for hip fracture, because relative risks associated with these fractures tended to be modest, and these fractures may be less accurately self-reported than hip fractures.

Women with diabetes that was newly diagnosed during follow-up (i.e., women with "pre-diabetes") showed similarly increased risk for incident hip fractures as women who had diabetes at baseline. To our knowledge, no other study has shown that individuals with pre–type 2 diabetes have increased risk for hip fracture. This is consistent with either decreasing bone mass or increasing tendency to fall either before or very soon after diabetes is clinically recognized in older women. Only one study, to our knowledge, has assessed hip fracture in newly diagnosed elderly individuals (13). In that study, the authors found no increase in risk for hip fracture in women diagnosed with diabetes within the past 5 years versus nondiabetic women. However, some studies have reported significant decreases in bone mass within the first few years after diagnosis of diabetes (19).

It could be that risk for hip fracture in both type 1 and type 2 diabetes is increased because of increased risk of falling and not reduced bone mass. For example, diabetic neuropathy or higher risk for hypoglycemia may increase falling. Strategies to prevent falls or increase bone mineral density might benefit older women with diabetes.

Limitations

The response rate for the baseline questionnaire was 42%, and women who had unreliable responses on the food frequency questionnaire or who had cancer at baseline were excluded. The remaining women, who formed the cohort under study, may not be completely representative of Caucasian women residing in Iowa, although information gathered on nonrespondents (see RESEARCH DESIGN AND METHODS) showed that they were very similar to respondents. In addition, because our study was conducted in Iowa, results may only be generalizable to Caucasian women. During administration of the four follow-up questionnaires, additional women were lost to follow-up and censored when lost. We could not ascertain whether any of these women suffered a hip fracture during the follow-up period; lost participants may have been at increased risk.

Hip fractures were self-reported in our study and, therefore, may suffer from some misclassification. However, Munger et al. (23) found a high correlation between self-reported fractures and medical record review in this cohort. In addition, traumatic hip fractures could not be differentiated from osteoporotic hip fractures. Nutrient intake was assessed only once; estrogen use was self-reported. Women may have changed their eating habits between baseline and end of follow-up, which we could not assess.

Diabetes status was self-reported, as in many previous large prospective studies. Although undiagnosed diabetes was not identified, our validation study suggested that participants overreported diabetes compared with physician diagnoses (19). Another study reported reasonable validity of self-reported diabetes (20). Although we could assess severity of diabetes using duration or type of treatment as an indicator of severity, better measures of glycemic control, such as glycosolated hemoglobin, were unavailable. Type 1 diabetes was defined by onset before 30 years of age and use of insulin but may have been misclassified in the absence of biochemical validation.

In summary, we found significantly higher risk for hip fracture among women with type 1 diabetes. Prevalent or newly diagnosed type 2 diabetes also increased risk, especially for women with longer duration of diabetes and those who used insulin or oral medications. Therefore, women who have diabetes may especially benefit from strategies to prevent falling and the clinical outcomes of osteoporosis, such as hip fracture.

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Author note— After this article was submitted, another large study confirmed that older women with type 2 diabetes are at increased risk of total and hip fractures (31).

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