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Association between clinical fracture risk and type 2 diabetes mellitus among older women is mediated in part by functional impairments

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Abstract

Objective—Older women with type 2 diabetes mellitus have higher bone mineral density than those without diabetes, but a higher fracture risk. The objective of this study was to examine the role of functional impairments among older women with diabetes on incident clinical fractures.

Design—Secondary analysis of 2 large prospective cohort studies

Setting—The North Carolina Established Populations for Epidemiologic Studies of the Elderly (EPESE) and the Women's Health Initiative (WHI) clinical trials

Participants—EPESE included 2,704 community-dwelling women, age ≥ 65 years; WHI clinical trials included 68,125 postmenopausal women

Measurements—Women with diabetes at baseline were compared to women without diabetes in successive Cox proportional hazards models. Functional limitations were determined by self-reported difficulties in activities of daily living (ADLs) and physical activities.

Results—The risk of any clinical fracture during the study period was increased among women with diabetes, after controlling for age, race/ethnicity, and BMI, in both the EPESE (HR 1.36, 95% CI 1.08 – 1.72) and WHI cohorts (HR 1.29, 95% CI 1.19 – 1.39). After inclusion of

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functional limitations, the increased risk in fracture associated with diabetes decreased in both the EPESE (HR 1.25, 95% CI 0.98 – 1.59) and WHI cohorts (HR 1.21, 95% CI 1.12 – 1.31). Among those with diabetes, difficulties with moderate physical activities, such as bending/stooping, walking several blocks, and heavy house work, were significantly associated with incident fracture ($P < 0.05$).

Conclusion—Compared to those without diabetes, older women with diabetes are at increased risk of clinical fractures, independent of bone mineral density. This increased fracture risk is mediated in part by greater functional impairments in moderate physical activities. However, there still remains an unexplained residual, diabetes-associated risk for fracture.

Keywords

Diabetes mellitus; Fracture; Functional impairments

Introduction

Among older adults, the annual incidence of diabetes mellitus increased by 23% over the last 10 years, and the prevalence has increased by 62%, such that diabetes currently affects 1 in 5 persons over age 65 years (10.9 million people).^{1,2} Diabetes in older adults is associated with greater medical comorbidities, increased use of medications including central nervous system active medications, and increased falls risk.^{3,4} According to the Centers for Disease Control and Prevention, diabetes costs Americans \$116 billion in direct medical expenses and accounts for an additional \$58 billion in premature mortality and disability.¹

Older adults with diabetes have a higher average bone mineral density.⁵⁻⁸ In a meta-analysis by Vestergaard, bone mineral density Z-scores were significantly increased in both the lumbar spine (0.41 +/- 0.01) and total hip (0.27 +/- 0.01) in subjects with type 2 diabetes.⁹ Despite this increased bone density, several studies have demonstrated an increased risk of fracture.¹⁰⁻¹³ In a meta-analysis of 8 studies, Janghorbani et al. showed that adults with type 2 diabetes had a 20% higher risk (RR 1.2 95% CI: 1.0 – 1.5) for any clinical fracture, as well as an increased risk of hip fracture (RR 1.7, 95% CI: 1.3 – 2.2), compared to those without type 2 diabetes.¹⁴ Similarly, in a study by Schwartz et al., post-menopausal women with diabetes had an increased hazard ratio of 1.9 (95% CI: 1.4 – 2.5) for hip fracture, compared to women without diabetes.¹⁵ This increased fracture risk occurred despite a higher average bone density at the femoral neck among those with diabetes.

The underlying mechanism for this paradoxical observation remains unclear, but suggests the mechanism is independent of bone mineral density.^{3,16} Given diabetes' multiple systemic effects, this increased fracture risk is likely multi-factorial. One hypothesis is that patients with diabetes have more functional impairments and fall more frequently, resulting in more incident fractures. The current study was performed to examine the association between diabetes and fracture risk, and to identify functional limitations that may mediate this risk.

Methods

Data sources

Data were used from the North Carolina Established Populations for Epidemiologic Studies of the Elderly (EPESE) and the Women's Health Initiative (WHI) Clinical Trial cohort. The design of the EPESE has been reported previously.¹⁷ Briefly, the EPESE was a prospective cohort study that included community-dwelling adults aged 65 and older at the time of enrollment (1986-87) who resided in five counties in the Piedmont region of North Carolina, with in-person interviews every 3 years and annual telephone contact. The EPESE data was chosen because of the study's purposeful oversampling in blacks, who have a higher prevalence of DM, compared to whites. All participants provided informed consent prior to the enrollment in the study. The current study analysis was approved by the Institutional Review Board at Duke University Health System.

The WHI was a national health study focused on strategies for preventing heart disease, breast and colorectal cancer, and osteoporosis among postmenopausal women. Full details of the study have been previously published.^{18,19} Briefly, 68,132 postmenopausal women were enrolled at 40 centers throughout the United States from September 1993 through December 1998. Eligible women could enroll into any of three clinical trial components: 1) hormone therapy, 2) dietary modification, and 3) calcium/vitamin D. All participants were postmenopausal, age between 50 and 79 years old at time of enrollment. Participants were initially screened by telephone and then by up to 3 baseline screening visits. Demographic, medical, and social histories were obtained by self-report. Participants were mailed annual forms to update selected exposures and ascertain medical outcomes. All participants provided informed consent using materials approved by institutional review boards at each study center.

Diabetes ascertainment

In both studies, the diagnosis of diabetes was self-reported by the participants at baseline. In the EPESE study, participants were asked at the baseline interview: "Has a doctor ever told you that you had diabetes, sugar in your urine or high blood sugar?" and "Has a doctor, nurse, therapist, or medical assistant ever told you to take insulin or an injection for this?" Similarly, in the WHI clinical trial, participants were asked, "Did a doctor ever say that you had sugar diabetes or high blood sugar when you were not pregnant?"

Fracture ascertainment

In both studies, incident skeletal fractures were self-reported from subjects at each follow-up visit. In the EPESE, skeletal fracture events were obtained from surrogates, if necessary. Participants were asked whether they had had a fracture since they last completed the medical history questionnaire. For a response of "Yes" or "Suspected or possible," the participants were asked to identify the location (hip, wrist, arm, back/spine, or other). In the WHI, questions on fractures were included in the annual questionnaire. Participants were asked whether they had had a fracture since the 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). Vertebral fractures were defined as those located in the

thoracic or lumbar location. Fractures of the hands, fingers, feet, and toes were excluded from the analysis.

Other variables

In the EPESE, functional measures included the Katz Activity of Daily Living, the 3-item Rosow-Breslau functional questionnaire, the 5-item Nagi scale; these measures were collected at both in-person and follow-up telephone interviews. The Katz ADLs ranks adequacy of performance (i.e. independence) in the activities of bathing, dressing, toileting, transferring, continence, and feeding.²⁰ The Rosow-Breslau questionnaire evaluates the relative difficulty of performing high level physical tasks typically performed by community-dwelling adults (e.g. walk a half mile, walk up stairs, perform heavy housework).²¹ The Nagi scale assesses changes in function and includes specific physical movements such as moving large objects, lifting groceries, bending/stooping, writing, and reaching.²² In the WHI, functional status measures included the 36-item Short Form (SF-36). The SF-36 is a patient-reported survey of health, including domains in general health perceptions, social function, and physical function.²³ Functional impairment was defined as a response of needing help with, being limited in, or being unable to perform the functional activity.

Other potential risk factors for falls and fracture included demographics, medications, and medical comorbidities. BMD was also included for the WHI cohort; BMD ascertainment was not performed in EPESE. Demographic variables included age and race/ethnicity. Physical measurements included body mass index (BMI), using self-reported height and weight in EPESE and measured height and weight in the WHI. Comorbidities were self-reported in both studies and included a history of cerebrovascular disease, cardiovascular disease, and vision impairment. Medication factors included reported use of calcium, estrogen, corticosteroids, antihypertensive medications, and psychoactive medications including anticonvulsant and antidepressant medications. Smoking and alcohol consumption were self-reported.

Statistical Analysis

Characteristics of the study populations were described, using means and standard deviation values for continuous variables and frequencies and percentages for categorical variables. Subjects with and without diabetes were compared, using Student's t test for continuous variables and chi-square tests for categorical variables. Cox proportional hazards models were used to estimate associations between the outcome of interest (i.e. age at fracture event) and diabetes, adjusting for potential covariates and interactions. There was a significant interaction between gender and diabetes in the EPESE cohort for the outcome clinical fractures. Because the association between fracture risk and diabetes was not significant among older men in the EPESE cohort, analyses in the current report were performed for women only. Cox proportional hazards models were specified using the counting process method, with multiple observations for each subject corresponding to the interval of observation time, with updating of information at the beginning of each interval.

To evaluate the relationship between diabetes and incident fracture, a series of successive Cox proportional hazards models were run for each fracture end point. Models were run separately for each study cohort due to the difference in covariate ascertainment. In the first model, the association between the age at the fracture event and diabetes status was estimated, adjusted for age, race/ethnicity, and BMI. Next, the second multivariate model adjusted for those in the first model and additionally for functional impairments. The final, fully adjusted model included variables in the second model as well as for medical comorbidities (i.e. cardiovascular disease, cerebrovascular disease, vision impairment), alcohol and tobacco use, and medications (e.g. estrogen, corticosteroids, bisphosphonates, calcium and vitamin D).

To examine the particular functional limitations most associated with incident fractures among older women with diabetes, a Cox proportional hazards model was performed for the outcome of clinical fracture, restricted to participants with diabetes. Models included each item of the functional impairments questionnaire and were adjusted for age, race, and BMI. Functional impairments with an association $P < 0.05$ are presented.

The effect sizes associated with diabetes status and 95% confidence limits are presented for each model. All analyses were performed using SAS, version 9.3 (SAS Institute, Inc., Cary, NC).

Results

The characteristics of the study participants are presented in Table 1. At baseline, in the EPESE cohort, there were 566 women with diabetes and 2138 without diabetes. In the WHI, there were 4239 women with diabetes and 63,886 without diabetes. Because of the purposeful oversampling, the proportion of blacks in the EPESE cohort (54.5%) was higher compared to the WHI clinical trial (10.3%). Compared to the WHI participants, the women in the EPESE cohort were older and more likely to report a history of cardiovascular or cerebrovascular disease. In comparison to those without diabetes, those with diabetes were more likely to be black and with a higher BMI. Those participants with diabetes were more likely to report a history of cardiovascular and cerebrovascular disease. Older women with diabetes, in both cohorts, were more likely to report needing assistance or having difficulty with all physical activities and most ADLs (Table 2).

EPESE cohort

There were 572 incident fractures in the study period, with 173 hip fractures. The average follow-up time was 6.5 years. After adjusting for age, race, ethnicity, and BMI, women with diabetes were more likely to suffer an incident clinical fracture (HR 1.36, 95% CI: 1.08 – 1.72) [Table 3]. Though not statistically significant, there was an increased risk of hip fracture associated with diabetes (HR 1.27, 95% CI: 0.80 – 2.02). After inclusion of functional impairments, the risk of clinical fracture associated with diabetes decreased to 1.25 (95% CI: 0.98 – 1.59). Functional impairments mediated 28% of the fracture risk observed among older women with diabetes. The fracture risk associated with diabetes did not substantially differ after further addition of multiple factors including medical comorbidities and medications in the full model.

We examined the specific functional limitations among those with diabetes that were most strongly associated with incident fracture. Difficulties with moderate physical activities were significantly associated with incident fracture, specifically, housecleaning (HR 1.73, 95% CI: 1.00 – 2.99), as well as the ADL bathing/showering (HR 2.03, 95% CI: 1.16 – 3.57).

WHI cohort

There were 11,928 incident fractures in the study period, with 828 occurring among older women with diabetes. The average follow-up time was 8.1 years. Older women with diabetes (HR 1.29, 95% CI: 1.19 – 1.39) were more likely to suffer an incident clinical fracture (Table 3). After inclusion of functional impairments, the risk of clinical fracture associated with diabetes decreased to 1.21 (95% CI: 1.12 – 1.31). Functional impairments mediated 31% of the fracture risk observed among older women with diabetes. The fracture risk associated with diabetes did not substantially differ after further addition of multiple factors including medical comorbidities and medications in the full model. Also, addition of falls frequency did not substantially change the associated fracture risk (Appendix).

There were 771 incident hip fractures during the study period, with 58 occurring among older women with diabetes. The risk of hip fracture associated with diabetes was increased significantly (HR 1.45, 95% CI: 1.08 – 1.94). After inclusion of functional impairments, the hip fracture risk associated with diabetes decreased (HR 1.27, 95% CI: 0.94 – 1.71). Functional impairments mediated this associated hip fracture risk by 40%.

We examined the specific functional limitations among those with diabetes that were most strongly associated with incident fracture. Similar to the EPESE cohort, difficulties with moderate physical activities were also associated with incident fracture, specifically bending/stooping (HR 1.20, 95% CI: 1.04 – 1.38) and walking several blocks (HR 1.32, 95% CI: 1.13 – 1.55), as well as the ADL bathing/showering (HR 1.61, 95% CI: 1.09 – 2.38).

Discussion

The results of the current study show that functional impairments mediate a portion of the increased fracture risk among older women with diabetes. The current study of 2 large cohorts of older women, including an epidemiologic, community-based cohort and a large, national clinical trial, shows that older women with diabetes have a 29 – 36% increased risk of incident clinical fracture. Our study further demonstrates that functional impairments, specifically activities of moderate intensity, mediate approximately 28 – 31% of this increased fracture risk. Also, functional impairments may more strongly predict incident fracture compared to either BMD or falls frequency. This is the first study to show that a proportion of the increased fracture risk among older women with diabetes is mediated by functional limitations. Furthermore, limitations in moderate physical activities, such as housecleaning or walking several blocks, may be a useful clinical marker for incident fracture risk in this population.

Prior published studies have reported that older adults with diabetes have an increased risk of falls. In the NHANES III survey, older women with diabetes were nearly 60% more

likely to report falling and twice as likely to report a fall with injury.³ In the EPESE study, Hanlon et al. showed that diabetes was associated with an increased risk of 2 or more falls (OR 1.46, 95% CI: 1.02 – 2.08).²⁴ Though the causal mechanism by which diabetes leads to increased functional limitations and falls risk is not fully understood, it is assumed given diabetes' multiple systemic effects that the development of medical complications are a mediating factor.^{25,26} Older adults with diabetes have increased medical comorbidities, including neuropathy, visual impairment, and cardiovascular disease, which may result in greater limitations in physical function and increased falls risk.^{27,28} Older adults with diabetes are also prescribed a higher number of medications including antihypertensives and antihyperglycemics that are associated with increased falls risk. However, prior studies have suggested that falls frequency did not fully mediate fracture risk.⁵ In our study, the presence of functional impairments appear to more fully account for the increased fracture risk, and the addition of falls frequency did not substantially contribute further to the mediated effect (Appendix). This may be in part because falls are under-reported in older populations, and functional status is strongly associated with falls.

Our results are consistent with the findings of other published studies. For example, in the Health ABC study, after controlling for hip BMD and fracture risk factors, diabetes was associated with a 71% increase in incident clinical fractures (RR 1.71, 95% CI 1.11 – 2.61).¹² Similarly, in the Study of Osteoporotic Fractures, compared to women without diabetes, women with noninsulin-treated diabetes had an increased risk of non-vertebral fractures (RR 1.30, 95% CI 1.10 – 1.53) and hip fracture (RR 1.82, 95% CI 1.24 – 2.69).¹¹ As in other studies, there remained a residual increased fracture risk in the current study after adjusting for fracture risk factors. Though reduced in effect size, a residual fracture risk remained after inclusion of functional limitations as well, suggesting that either other functional limitations not assessed in these 2 cohorts may further mediate the fracture risk or other underlying mechanisms may exist, such as intrinsic changes in bone quality related to diabetes.

The limitations of the current study should be noted. This was a secondary analysis of prior prospective cohorts. The EPESE study was performed prior to the introduction of alendronate and other osteoporosis therapeutics commonly used currently. Also, there have been interval improvements in the identification and intervention of falls. However, despite possible secular changes that may have occurred in the interim between the EPESE and WHI studies, the observed effects of diabetes remain consistent in the 2 cohorts. Secondly, analyses were limited to the available data collected in each study. For example, assessment of some physical activities was not performed in the EPESE and/or WHI (e.g. difficulty with writing or handling small objects). Also, there was no assessment of BMD in the EPESE study; therefore, analyses with BMD were limited to the WHI cohort, in which only a proportion of women had a BMD thus limiting statistical inferences. Medical history of the study participants, including diabetes status, falls frequency, and fracture history, was self-reported. Prior studies have shown self-report of fracture is known to be reliable.^{29,30} However, falls may be under-reported in epidemiologic studies, and subjects are more likely to report injury-related falls.³¹ As undiagnosed diabetes is prevalent, misclassification of diabetes status may exist in the 2 study cohorts.³² Given the observed effects of diabetes on

both fracture risk and functional impairments though, such misclassifications likely resulted in attenuation of the effect sizes observed in the current study.

The current study shows older women with diabetes have a significantly increased risk of incident fracture. Furthermore, functional limitations are more common among older women with diabetes and mediate a substantial proportion of the increased fracture risk. We believe these results will assist providers in identifying older women with diabetes at risk for fracture and highlight the importance of functional assessment in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest

Elements of Financial/Personal Conflicts	*Author 1 RHL		Author 2 CFP		Author 3 CCE			
	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation		X		X		X		
Grants/Funds		X		X		X		
Honoraria		X		X		X		
Speaker Forum		X		X		X		
Consultant		X		X	X			
Stocks		X		X	X			
Royalties		X		X		X		
Expert Testimony		X		X		X		
Board Member		X		X		X		
Patents		X		X	X			
Personal Relationship		X		X		X		

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For "yes" x mark(s): give brief explanation below:

Cathleen Colon-Emeric:

-consultant to Novartis and Amgen

-Equity owner Biscardia Inc

-Inventor of 2 use patents related to bisphosphonates and cardiovascular disease

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Table 1

Baseline characteristics of the EPESE and WHI cohorts, by prior diagnosis with diabetes.

	EPESE			WHI		
	Without DM N = 2138	With DM N = 566	P	Without DM N = 6386	With DM N = 4239	P
Age (years), mean +/- SD	74.5 +/- 7.0	73.3 +/- 6.3	<0.01	61.6 +/- 7.0	63.0 +/- 6.7	<0.01
BMI (kg/m ²), mean +/- SD	25.7 +/- 5.1	27.8 +/- 5.4	<0.01	28.7 +/- 5.6	32.6 +/- 6.1	<0.01
Race, n (%)			<0.01			<0.01
White	1045 (48.9)	173 (30.6)		52834 (82.7)	2819 (66.5)	
Black	1083 (50.6)	390 (68.9)		6069 (9.5)	937 (22.1)	
Other	10 (0.5)	3 (0.5)		4983 (7.8)	483 (11.4)	
Medical history, n (%)						
Hypertension	1256 (58.7)	438 (77.4)	<0.01	20532 (32.1)	2652 (62.6)	<0.01
Cardiovascular disease	249 (11.6)	113 (20.0)	<0.01	8665 (13.6)	1048 (24.7)	<0.01
Cerebrovascular disease	116 (5.4)	96 (17.0)	<0.01	619 (1.0)	131 (3.1)	<0.01
Prior fracture	524 (24.5)	127 (22.4)	0.17	22050 (34.5)	1493 (35.2)	0.69
Cancer	241 (11.3)	69 (12.2)	0.72	2551 (4.0)	223 (5.3)	<0.01
Arthritis	--	--		28484 (44.6)	2445 (57.7)	<0.01
Tobacco use, n (%)			0.15			0.02
Current	242 (11.3)	52 (9.2)		5111 (8.0)	263 (6.2)	
Former	362 (16.9)	99 (17.5)		26129 (40.9)	1768 (41.7)	
Never	1449 (67.8)	393 (69.4)		32582 (51.0)	2200 (51.9)	
Alcohol use, n (%)			0.06			<0.01
Nondrinker	1638 (76.6)	496 (87.6)		17406 (27.2)	2355 (55.6)	
<7 drinks weekly	438 (20.5)	64 (11.3)		39072 (61.2)	1691 (39.9)	
7 drinks weekly	59 (2.8)	6 (1.1)		6895 (10.8)	148 (3.5)	
Current medications, n (%)						
Calcium	350 (16.4)	67 (11.8)	<0.01	12623 (19.8)	552 (13.0)	<0.01
Estrogen	90 (4.2)	10 (1.8)	<0.01	22580 (35.3)	1047 (24.7)	<0.01
CNS-active medication	380 (17.8)	116 (20.5)	0.14	7349 (11.5)	673 (15.9)	<0.01
Corticosteroids	60 (2.8)	15 (2.6)	0.84	99 (0.2)	13 (0.3)	0.02

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	EPESE		<i>P</i>	WHI		<i>P</i>
	Without DM N = 2138	With DM N = 566		Without DM N = 6386	With DM N = 4239	
Bisphosphonates	--	--		806 (1.3)	29 (0.7)	<0.01

Table 2

Percentage of subjects who reported needing help or having limitations with activities.

Activity	EPESE cohort			WHI cohort		
	Without DM N = 2138	With DM N = 566	P	Without DM N = 63886	With DM N = 4239	P
Eating	2.3	2.8	0.80	1.0	1.6	<0.01
Dressing	7.7	12.4	<0.01	4.9	12.1	<0.01
Bathing	10.8	16.8	<0.01	1.2	3.4	<0.01
Toileting	6.4	12.2	<0.01	--	--	
Transferring to bed	7.1	13.4	<0.01	0.5	1.6	<0.01
Grooming	5.8	9.4	0.03	--	--	
Writing/handling small objects	9.6	13.4	<0.01	--	--	
Reaching/showering	11.6	18.4	<0.01	4.9	12.1	<0.01
Lifting groceries	29.9	34.5	<0.01	28.5	48.5	<0.01
Moving furniture	31.5	41.7	<0.01	37.5	58.5	<0.01
Bending, kneeling	35.8	51.0	<0.01	54.7	74.3	<0.01
House cleaning	45.8	60.4	<0.01	85.0	92.4	<0.01
Climbing stairs	22.0	34.3	<0.01	22.3	44.4	<0.01
Walking blocks	30.6	41.0	<0.01	25.3	48.4	<0.01

Table 3
Adjusted HRs and 95% CIs for incident fracture associated with diabetes

	EPESE	WHI
Any clinical fracture		
Age, race, BMI	1.36(1.08 – 1.72)	1.29(1.19 – 1.39)
+Functional status	1.25 (0.98 – 1.59)	1.21 (1.12 – 1.31)
Full model	1.22(0.96 – 1.56)	1.20(1.11 – 1.30)
Hip fracture		
Age, race, BMI	1.27 (0.80 – 2.02)	1.45(1.08 – 1.94)
+Functional status	1.18 (0.74 – 1.90)	1.27(0.94 – 1.71)
Full model	1.08 (0.66 – 1.76)	1.28(0.95 – 1.73)
Non-hip, non-vertebral fracture		
Age, race, BMI	1.23 (0.97 – 1.56)	1.28(1.18 – 1.39)
+Functional status	1.14 (0.89 – 1.47)	1.22(1.12 – 1.32)
Full model	1.13 (0.87 – 1.46)	1.20(1.10 – 1.31)

Full model adjusts for (1) Demographics: age, race, BMI; (2) Functional status; (3) Medical history: cardiovascular disease, cerebrovascular disease, alcohol use, tobacco use, vision impairment; (4) Medications: calcium/vitamin D supplements, corticosteroids, central nervous system active medications (i.e. antidepressants, anticonvulsants, antipsychotics), osteoporosis treatment