

Investigación original | Diabetes y endocrinología

Prediabetes y riesgo de fracturas en mujeres de mediana edad en el Estudio Salud de la Mujer en Todo el País (Women's Health Across the Nation)

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Resumen

IMPORTANCIA No se sabe con certeza si la prediabetes está asociada a las fracturas.

OBJETIVO Evaluar si la prediabetes antes de la transición a la menopausia (MT) está asociada con la fractura incidente durante y después de la MT.

DISEÑO, ENTORNO Y PARTICIPANTES Este estudio de cohortes utilizó datos recopilados entre el 6 de enero de 1996 y el 28 de febrero de 2018 en el estudio de cohortes Study of Women's Health Across the Nation, un estudio longitudinal multicéntrico en curso, con sede en EE. UU., sobre la MT en diversas mujeres ambulatorias. El estudio incluyó a 1690 mujeres de mediana edad en premenopausia o perimenopausia temprana al inicio del estudio (que desde entonces han hecho la transición a la posmenopausia) que no tenían diabetes tipo 2 antes de la MT y que no tomaban medicamentos beneficiosos para los huesos antes de la MT. El inicio de la TM se definió como la primera visita en la perimenopausia tardía (o la primera visita posmenopáusica si las participantes pasaron directamente de la premenopausia o la perimenopausia temprana a la posmenopausia). El seguimiento medio (DE) fue de 12 (6) años. El análisis estadístico se realizó de enero a mayo de 2022.

EXPOSICIONES Proporción de visitas antes de la TM en las que las mujeres tenían prediabetes (glucosa en ayunas, 100-125 mg/dL [para convertir a milimoles por litro, multiplicar por 0,0555]), con valores que van de 0 (prediabetes en ninguna visita) a 1 (prediabetes en todas las visitas).

PRINCIPALES RESULTADOS Y MEDIDAS Tiempo hasta la primera fractura tras el inicio de la MT, con censura en el primer diagnóstico de diabetes tipo 2, inicio de medicación beneficiosa para los huesos o último seguimiento. Se utilizó la regresión de riesgos proporcionales de Cox para examinar la asociación (antes y después del ajuste por densidad mineral ósea) de la prediabetes antes de la TM con la fractura durante la TM y después de la menopausia.

RESULTADOS Este análisis incluyó a 1.690 mujeres (edad media [DE], 49,7 [3,1] años; 437 mujeres negras [25,9%], 197 chinas [11,7%], 215 japonesas [12,7%] y 841 blancas [49,8%]; índice de masa corporal [IMC] medio [DE] al inicio de la TM, 27,6 [6,6]). Un total de 225 mujeres (13,3%) tenían prediabetes en una o más visitas del estudio antes de la TM, y 1.465 mujeres (86,7%) no tenían prediabetes antes de la TM. De las 225 mujeres con prediabetes, 25 (11,1%) sufrieron una fractura, mientras que 111 de las 1.465 mujeres sin prediabetes (7,6%) sufrieron una fractura. Tras ajustar por edad, IMC y consumo de cigarrillos al inicio de la TM; fractura antes de la TM; uso de medicación perjudicial para los huesos; raza y etnia; y lugar del estudio, la prediabetes antes de la TM se asoció con más fracturas posteriores (cociente de riesgo de fractura con prediabetes en todas las visitas frente a sin visitas previas a la TM, 2,20 [IC 95%, 1,11-4,37]; $p = 0,02$). Esta asociación se mantuvo esencialmente sin cambios tras controlar la DMO al inicio de la TM.

(continued)

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Resumen (continuación)

CONCLUSIONES Y RELEVANCIA Este estudio de cohortes de mujeres de mediana edad sugiere que la prediabetes estaba asociada al riesgo de fractura. Futuras investigaciones deberán determinar si el tratamiento de la prediabetes reduce el riesgo de fractura.

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Introduction

"Diabetic bone disease" and fractures are increasingly recognized as end-organ complications of diabetes.¹⁻⁵ At the present time, whether prediabetes is also a risk factor for fractures is uncertain. Such an association is plausible; recently published data show that prediabetes is associated with lower bone turnover and worse trabecular bone microarchitecture.⁶⁻⁸ Moreover, at levels observed in individuals without type 2 diabetes, greater insulin resistance is associated with a lower bone mineral density (BMD),⁹ a lower trabecular bone score,⁸ lower indices of hip strength,^{10,11} and faster bone loss,⁸ all risk factors for fractures.

Elucidating whether prediabetes increases fracture risk is a step in understanding its clinical relevance. Although prediabetes is a risk factor for developing diabetes, clinicians disagree on how aggressively to treat it.^{12,13} Not every person with prediabetes develops type 2 diabetes, and prediabetes itself has not been definitively associated with end-organ complications. With respect to bone health, whether prediabetes is associated with fractures in the absence of prior or future progression to type 2 diabetes is unknown.

The first objective of this study was to examine whether prediabetes among midlife women is associated with subsequent fracture in the absence of type 2 diabetes. We focused on midlife, when women undergo the menopause transition (MT) and fracture risk accelerates.^{14,15} Because prediabetes may affect BMD,¹⁶ our second objective was to assess whether the potential association of prediabetes with fracture was independent of BMD.

Methods

This cohort study used data collected between January 6, 1996, and February 28, 2018, in the Study of Women's Health Across the Nation (SWAN), a multicenter cohort study of 3302 diverse, community-dwelling women. At the SWAN baseline visit, participants were 42 to 52 years of age and in premenopause (no change from usual menstrual bleeding) or early perimenopause (less predictable menstrual bleeding at least once every 3 months). Potential participants were excluded if they did not have an intact uterus and 1 or more ovaries or were using hormonal therapy or hormonal contraception. Women were recruited at 7 clinical sites: Boston, Massachusetts; Chicago, Illinois; Detroit, Michigan; Pittsburgh, Pennsylvania; Los Angeles, California; Newark, New Jersey; and Oakland, California. The SWAN Bone Cohort included 2365 women from 5 sites (excluding Chicago and Newark). Since study inception in 1996, 1 baseline visit and 16 follow-up visits have occurred at a median of 1.1 years (IQR, 1.0-1.4 years) between consecutive visits. All study volunteers provided written informed consent, and each site obtained institutional review board approval (University of Michigan; Massachusetts General Hospital; Rush University Medical Center; University of California, Davis, and Kaiser Permanente; University of California, Los Angeles; Albert Einstein College of Medicine; and University of Pittsburgh). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for observational studies.

Samples

To be included in this analysis, SWAN Bone Cohort participants needed 1 or more study visits before the MT, could not be taking a bone-beneficial medication before the MT, could not have type 2

diabetes before the MT, and needed at least 1 study visit after the start of the MT (to permit observation for fractures). Bone-beneficial medications included hormone therapy, calcitonin, calcitriol, bisphosphonates, denosumab, and parathyroid hormone. We defined the start of the MT as the first visit in late perimenopause (less predictable menstrual bleeding at least once every 3-12 months). For women who transitioned directly from premenopause or early perimenopause to postmenopause ("skipped" late perimenopause), we defined the start of the MT as the first postmenopausal visit.

Starting with 2365 SWAN Bone Cohort participants, we excluded those with no pre-MT study visits ($n = 34$), women who started a bone-beneficial medication before the MT ($n = 193$), participants with type 2 diabetes before or at the start of the MT ($n = 141$), or women without follow-up between the start of the MT and time of fracture or censoring ($n = 307$). Our resulting analysis sample included 1690 women. Mean (SD) length of follow-up was 12 (6) years. Type 2 diabetes was defined as a fasting blood glucose level of 126 mg/dL or more (to convert to millimoles per liter, multiply by 0.0555) or taking metformin, sulfonylurea, meglitinide, thiazolidinedione, dipeptidyl peptidase 4 inhibitors, glucagonlike peptide-1 receptor agonists, or insulin. Participants were censored at initiation of bone-beneficial medications, new diagnosis of type 2 diabetes, or last follow-up. We excluded women who started a bone-beneficial medication before the MT, and censored subsequent initiators to prevent potential confounding by indication.

Outcome

The outcome was time to first fracture after the start of the MT. Fracture occurrence and location were ascertained using standardized questionnaires at all study visits. Pre-SWAN fractures were recorded at the SWAN baseline visit. SWAN initiated fracture adjudication at follow-up visit 7; for the first 6 follow-up visits, fracture date was imputed as the midpoint between the participant's previous and index visits. Since adjudication began, 95% of reported fractures were confirmed. Fractures were atraumatic if they occurred after a fall from a height of less than 15.2 cm and if they did not occur during a motor vehicle accident, rapid movement, playing sports, or from impact with heavy or fast-moving projectiles. We excluded craniofacial and digital fractures but included atraumatic and traumatic fractures because both fracture types are risk factors for subsequent fractures.^{17,18}

Primary Exposure

The primary exposure was prediabetes before the MT. We modeled our prediabetes exposure as the proportion of visits from the SWAN baseline visit through the last visit before the MT at which prediabetes was present. Criteria for prediabetes were a fasting blood glucose level between 100 and 125 mg/dL and not taking a diabetes medication. The prediabetes exposure was a continuous variable with values ranging from 0 to 1, which allowed us to capture how consistently a participant had prediabetes. For example, women who never had prediabetes had an exposure value of 0, and those who had prediabetes at every visit before the MT had an exposure value of 1. Women with prediabetes at 1 or more, but not all, pre-MT visits had exposure values between 0 and 1. Consistency of prediabetes is relevant because individuals with prediabetes may not meet glycemic criteria for prediabetes at every time point over a period of several years, with up to one-third returning to normal glucose regulation altogether.¹⁹⁻²¹

Fasting blood glucose was measured at 2 different central laboratories in SWAN. Through follow-up visit 7, glucose was measured at Medical Research Laboratories (Lexington, Kentucky) using a hexokinase-coupled reaction assay (Roche; intra-assay coefficient of variability, 1.6%). Subsequent glucose measurements were performed at the University of Michigan, Ann Arbor, using the ADVIA Chemistry Glucose Hexokinase assay (intra-assay coefficient of variability, 0.7%-0.9%). A between-laboratory calibration equation was developed using 565 randomly selected values across the range of glucose results. This equation was applied to convert Medical Research Laboratories results to corresponding University of Michigan values.

Covariates

Analyses controlled for variables that were potentially associated with fracture. These variables included age at the start of the MT, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) at the start of the MT, cigarette use (yes or no) at the start of the MT, fracture before the MT (yes or no), race and ethnicity (Black, Chinese, Japanese, or White) by self-report, study site, exposure to bone-detrimental medications before the MT, and exposure to bone-detrimental medications during fracture observation. Bone-detrimental medications were oral or injectable glucocorticoids, aromatase inhibitors, gonadotropin-releasing hormone agonists, or antiepileptic medications. Exposure to these medications before the MT or during fracture observation was estimated as the proportion of visits during the respective time period at which use was reported. We adjusted for exposure to bone-detrimental medications, instead of excluding users, because very few SWAN participants took these drugs consistently over prolonged intervals.¹⁵

To address the second study objective, we adjusted for lumbar spine (LS) or femoral neck (FN) BMD at the start of the MT. Lumbar spine and FN areal BMD were measured by dual x-ray absorptiometry using Hologic Inc instruments. SWAN's protocols for cross-site calibration, cross-calibration after machine upgrades, and quality control have been described previously.²²

Statistical Analysis

Statistical analysis was conducted from January to May 2022. We assessed all continuous variables for normality. Using the Spearman rank correlation, we examined the correlations between the proportion of visits before the MT with prediabetes and the mean glucose level across pre-MT visits with prediabetes.

We conducted 2 sets of primary analyses. The first (model 1) examined whether prediabetes before the MT was associated with subsequent fracture. We used Cox proportional hazards regression with the proportion of visits before the MT with prediabetes as the primary exposure and the time to first fracture after the start of the MT as the outcome. Covariates were age, BMI, and cigarette use at the start of the MT; exposure to bone-detrimental medication before the MT or after the start of the MT; fracture before the MT; race and ethnicity; and study site. Our second set of analyses assessed whether the hypothesized association of prediabetes with fracture was independent of BMD by adding to model 1 controls for LS (model 2A) or FN (model 2B) BMD. In all models, we added quadratic terms for the continuous prediabetes exposure and BMI to test for nonlinearity in their association with fracture. Neither quadratic term made statistically significant associations and were dropped from the final models.

Because the primary exposure is a continuous variable with values ranging from 0 to 1, the hazard ratio (HR) for prediabetes generated by the Cox proportional hazards regression model is the HR for prediabetes at all pre-MT visits (exposure = 1) relative to prediabetes at no pre-MT visit (exposure = 0). Because the primary exposure is continuous and had a linear association with fracture hazard, the estimated HR (for exposure = 1) can be converted to HRs for different exposure values between 0 and 1, corresponding to an individual woman's proportion of pre-MT visits with prediabetes.

We conducted 2 sets of sensitivity analyses. First, we reran the models but used a binary exposure: any prediabetes before the MT (yes or no). Second, we reran models 1, 2A, and 2B using the original continuous prediabetes exposure but included only major nonvertebral fractures (defined in some osteoporosis therapy trials as fractures of the pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip) as outcomes.^{23,24}

All analyses were performed using Stata, version 17 (StataCorp LLC). We used a 2-tailed significance level of .05.

Results

Participant Characteristics

Table 1 shows the characteristics of the full SWAN Bone Cohort (N = 2365) and our analysis sample (n = 1690; mean [SD] age, 49.7 [3.1] years; 437 Black women [25.9%], 197 Chinese women [11.7%], 215 Japanese women [12.7%], and 841 White women [49.8%]; mean [SD] BMI at the start of the MT, 27.6 [6.6]; mean [SD] LS BMD, 1.059 [0.143] g/cm²; mean [SD] FN BMD, 0.828 [0.133] g/cm²); both were similar. Women had a median of 3 visits (IQR, 1-6 visits) before the MT. The mean (SD) proportion of pre-MT visits with prediabetes was 0.070 (0.208). Fifty-six women (3.3%) had a fracture before the MT. Mean (SD) follow-up from the start of the MT to fracture or censoring was 12 (6) years. One-hundred thirty-six (8.0%) women sustained a fracture during the MT or in postmenopause. Of the 225 women with prediabetes, 25 (11.1%) sustained a fracture, while 111 of the 1465 women without prediabetes (7.6%) sustained a fracture. Thirty-three women were censored for initiating a bone-beneficial medication, and 94 for incident diabetes.

A total of 225 participants (13.3%) had prediabetes at 1 or more study visits before the MT (Table 1). A greater proportion of Black, Chinese, or Japanese women were represented in this group. Also, among these 225 participants, the mean (SD) proportion of pre-MT visits with prediabetes was 0.524 (0.293), and prediabetes criteria were met in the majority of ($\geq 50\%$) pre-MT visits for 124 women (55.1%) or all pre-MT visits for 47 women (20.9%) women. Seventy-three participants (32.4%) did not meet prediabetes criteria at any visit after their first prediabetes visit. Spearman rank correlations between the proportion of visits before the MT with prediabetes and the mean fasting glucose level at pre-MT visits with prediabetes was 0.83. At the start of the MT, the mean (SD) BMI among women with prediabetes was 31.7 (7.0), and the mean (SD) BMD was 1.093 (0.141) g/cm² at the LS and 0.869 (0.130) g/cm² at the FN. Among participants with prediabetes, the mean (SD) follow-up from the start of the MT to the time of fracture or censoring was 10 (6) years. Twenty-five women with prediabetes (11.1%) sustained a fracture, 1 was censored for starting a bone-beneficial medication, and 62 were censored for incident type 2 diabetes.

Association of Prediabetes Before the MT With Subsequent Fractures

Having prediabetes more consistently before the MT was associated with greater rates of fracture during the MT or in postmenopause. In Cox proportional hazards regression, adjusted for age, BMI, cigarette use, bone-detrimental medications, fracture before the MT, race and ethnicity, and study site (model 1), relative to prediabetes at no pre-MT visit, prediabetes at every visit before the MT was associated with a 120% greater hazard of subsequent fracture (HR, 2.20 [95% CI, 1.11-4.37]) (Table 2). Compared with no prediabetes, HRs for prediabetes at 25%, 50%, and 75% of visits before the MT were 1.22 (95% CI, 1.03-1.45), 1.48 (95% CI, 1.05-2.09), and 1.81 (95% CI, 1.08-3.02), respectively. The observed fracture hazard of 6.3 per 1000 person-years for women with no prediabetes before the MT translated to an absolute increase of approximately 3 fractures per 1000 person-years for women who had prediabetes at half of the pre-MT visits and 7 fractures per 1000 person-years for women who had prediabetes at all pre-MT visits.

Adding additional controls for LS (model 2A) or FN (model 2B) BMD at the start of the MT did not substantially alter the magnitude or statistical significance of the association between prediabetes and fracture. Hazard ratios for prediabetes at all pre-MT visits vs no pre-MT visits in models 2A and 2B were 2.24 (95% CI, 1.12-4.46) and 2.26 (95% CI, 1.13-4.49), respectively (Table 2).

Sensitivity Analyses

Our first set of sensitivity analyses used a binary prediabetes exposure (any prediabetes before the MT) instead of the proportion of visits before the MT with prediabetes. The HR for any prediabetes before the MT were 1.94 (95% CI, 1.23-3.06) unadjusted for BMD, 2.00 (95% CI, 1.27-3.15) adjusted for LS BMD, and 2.02 (95% CI, 1.28-3.19) adjusted for FN BMD.

Table 1. Characteristics of Analysis Sample

Characteristic	Value at start of the MT ^a			
	SWAN Bone Cohort (N = 2365)	Full analysis sample (n = 1690)	Women without prediabetes before the MT (n = 1465)	Women with prediabetes at ≥1 visits before the MT (n = 225)
Time-varying characteristics				
Age, mean (SD), y	49.9 (3.2)	49.7 (3.1)	49.6 (3.1)	50.4 (3.0)
BMI, mean (SD)	28.2 (6.9)	27.6 (6.6)	27.1 (6.3)	31.7 (7.0)
Cigarette use (yes or no), No. (%)	273 (11.5)	221 (13.1)	188 (12.8)	33 (14.7)
Bone mineral density, mean (SD), g/cm ²				
Lumbar spine	1.065 (0.147)	1.059 (0.143)	1.054 (0.143)	1.093 (0.141)
Femoral neck	0.834 (0.135)	0.828 (0.133)	0.821 (0.132)	0.869 (0.130)
Fixed characteristics				
Race and ethnicity, No. (%)				
Black	665 (28.1)	437 (25.9)	368 (25.1)	69 (30.7)
Chinese	250 (10.6)	197 (11.7)	166 (11.3)	31 (13.8)
Japanese	273 (11.5)	215 (12.7)	182 (12.4)	33 (14.7)
White	1177 (49.8)	841 (49.8)	749 (51.1)	92 (40.9)
Prediabetes status ^b				
Proportion of pre-MT visits at which prediabetes criteria were met, mean (SD) ^c	0.076 (0.208)	0.070 (0.208)	NA	0.524 (0.293)
Women with prediabetes at the following proportions of pre-MT visits, No. (%)				
>0 and <0.25	59/316 (18.7)	NA	NA	35 (15.6)
≥0.25 and <0.5	100/316 (31.6)	NA	NA	66 (29.3)
≥0.5 and <0.75	95/316 (30.1)	NA	NA	71 (31.6)
≥0.75 and <1	13/316 (4.1)	NA	NA	6 (2.7)
1	49/316 (15.5)	NA	NA	47 (20.9)
Fracture before the MT, No. (%)	87 (3.7)	56 (3.3)	47 (3.2)	9 (4.0)
Fracture after the start of the MT, No. (%)	189 (8.0)	136 (8.0)	111 (7.6)	25 (11.1)
Fractures after the start of the MT by fracture site, No. (%)				
Wrist	23 (12.2)	17 (12.5)	13 (11.7)	4 (16.0)
Hip	1 (0.5)	1 (0.7)	1 (0.9)	0
Spine	2 (1.1)	2 (1.5)	2 (1.8)	0
Pelvis	2 (1.1)	2 (1.5)	2 (1.8)	0
Ribs	9 (4.8)	6 (4.4)	3 (2.7)	3 (12.0)
Upper arm or shoulder	22 (11.6)	15 (11.0)	13 (11.7)	2 (8.0)
Leg above ankle	29 (15.3)	20 (14.7)	16 (14.4)	4 (16.0)
Ankle	35 (18.5)	27 (19.9)	22 (19.8)	5 (20.0)
Hand or foot	63 (33.3)	44 (32.4)	37 (33.3)	7 (28.0)
Other	3 (1.6)	2 (1.5)	2 (1.8)	0
Exposure to bone-detrimental medications before the MT ^d				
Women reporting use of a bone-detrimental medication at ≥1 study visit before the start of the MT, No. (%)	227 (9.6)	168 (9.9)	141 (9.6)	27 (12.0)
Proportion of pre-MT visits at which bone-detrimental medication users reported use, mean (SD) ^c	0.446 (0.295)	0.457 (0.295)	0.467 (0.301)	0.403 (0.259)
Exposure to bone-detrimental medications after the start of the MT ^d				
Women reporting use of a bone-detrimental medication at ≥1 study visit after the start of the MT, No. (%)	601 (25.4)	494 (29.2)	424 (28.9)	70 (31.1)
Proportion of visits after the start of the MT at which bone-detrimental medication users reported use, mean (SD) ^c	0.224 (0.193)	0.214 (0.187)	0.218 (0.191)	0.192 (0.150)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MT, menopause transition; NA, not applicable; SWAN, Study of Women's Health Across the Nation.

^a Start of MT defined as first visit in late perimenopause (less predictable menstrual bleeding once every 3-12 months), or first visit in postmenopause if participant transitioned directly from premenopause (no change in menstrual bleeding patterns) or early perimenopause (less predictable menstrual bleeding once every 1-3 months) to postmenopause.

^b Prediabetes defined as a fasting blood glucose level between 100 and 125 mg/dL (to convert to millimoles per liter, multiply by 0.0555), without use of diabetes medication.

^c Proportion of visits at which prediabetes criteria were met or bone-detrimental medication use was reported. This was a continuous variable with values ranging from 0 to 1. For example, women without prediabetes had values of 0. Women with prediabetes at all visits before the MT had values of 1. Women with prediabetes at 1 or more, but not all, pre-MT visits had values between 0 and 1.

^d Bone-detrimental medications were oral or injectable glucocorticoids, aromatase inhibitors, gonadotropin-releasing hormone agonists, or antiepileptic medications. Participants were considered users if they reported any use (regardless of duration).

In our second set of sensitivity analyses, we retained the continuous prediabetes exposure from our primary models but considered only major nonvertebral fractures (n = 63) as outcomes. The HR for prediabetes at all vs no pre-MT visits was 2.58 (95% CI, 0.99-6.83) adjusted for BMD, 2.65 (95% CI, 1.00-7.03) adjusted for LS BMD, and 2.71 (95% CI, 1.02-7.17) adjusted for FN BMD.

Discussion

In this longitudinal cohort study of the association between prediabetes in midlife women and fractures, we found that prediabetes before the MT was associated with more subsequent fractures; having prediabetes at 50% or 100% of pre-MT visits was associated with 49% and 120% greater hazard, respectively, for fracture during the MT and in postmenopause. The observed fracture hazard of 6.3 per 1000 person-years for women with no prediabetes before the MT translated to an absolute increase of approximately 3 and 7 fractures per 1000 person-years for women who had prediabetes at half of the pre-MT visits and all pre-MT visits, respectively. This increase in fracture risk was specific to prediabetes and was not associated with overt type 2 diabetes. Similar to type 2 diabetes,¹⁻⁵ however, the prediabetes-fracture association was independent of BMD, suggesting that pathways other than BMD are associated with this risk.

Prior longitudinal analyses of prediabetes and fracture are scarce, with conflicting results.²⁵⁻²⁷ Among 5032 men and women (mean age, 74 years) from the third National Health and Nutrition Examination Survey (NHANES III) and NHANES 1999-2004, prediabetes was associated with nonsignificant trends toward greater risk of noncraniofacial fractures among Mexican American (HR, 1.20 [95% CI, 0.96-1.51]) and White (HR, 1.42 [95% CI, 0.72-2.82]) participants.²⁵ Among 5994 men (mean age, 73 years) from the Osteoporotic Fractures in Men study, impaired fasting glucose was not associated with subsequent nonvertebral fractures, before (HR, 0.95 [95% CI, 0.94-1.34]) or after (HR, 1.04 [95% CI, 0.89-1.21]) adjustment for BMD.²⁶ Last, among 5 761 785 older South Korean adults (mean age, 61 years), prediabetes was associated with a modestly greater risk of subsequent hip fracture (HR, 1.17 [95% CI, 1.11-1.23]).²⁷

Our analysis differed from previously published studies in 3 major ways. First was our prediabetes exposure, which models the consistency of prediabetes over time. This contrasts with prior studies that assessed glycemic status at 1 time point. Our finding that the proportion of visits with prediabetes had a positive, linear association with fracture suggests that more consistent prediabetes could be detrimental to fracture risk. Greater prediabetes consistency may indicate more severe prediabetes (inferred by the positive correlation between prediabetes consistency and

Table 2. Association of Prediabetes Before the MT With Subsequent Fracture During the MT and in Postmenopause^{a,b}

Model	HR (95% CI) for fracture for prediabetes at all visits vs prediabetes at no visits before the MT (n = 1690) ^a	P value
Model 1: no BMD adjustment	2.20 (1.11-4.37)	.02
Model 2A: adjusted for lumbar spine BMD	2.24 (1.12-4.46)	.02
Model 2B: adjusted for femoral neck BMD	2.26 (1.13-4.49)	.02

Abbreviations: BMD, bone mineral density; HR, hazard ratio; MT, menopause transition.

^a Hazard ratios estimated using Cox proportional hazards regression with prediabetes before the MT as the primary exposure and time to fracture after start of the MT as the outcome. Start of the MT was defined as first visit in late perimenopause (less predictable menses once every 3-12 months), or first visit in postmenopause if participant transitioned directly from premenopause (no change in menstrual bleeding patterns) or early perimenopause (less predictable menstrual bleeding once every 1-3 months) to late perimenopause. Prediabetes was modeled as proportion of visits from the Study of Women's Health Across the Nation baseline visit until last visit before the MT start that participants met prediabetes criteria. This was a continuous exposure with values ranging from 0 (prediabetes at 0 pre-MT visits) to 1 (prediabetes at all pre-MT visits). Women who had prediabetes at 1 or more, but not all, pre-MT visits had exposure values between 0 and 1. Model 1 was adjusted for age at start of the MT, body mass index at start of the MT, cigarette use at start of the MT, fracture before the MT,

use of bone-detrimental medications before the MT, use of bone-detrimental medications during fracture observation, race and ethnicity, and study site. Models 2A and 2B additionally controlled for lumbar spine or femoral neck BMD, respectively. Because the primary exposure was continuous and had a linear association with fracture hazard, the estimated HR (for exposure = 1) can be converted to HRs for different exposure values between 0 and 1, corresponding to an individual woman's proportion of pre-MT visits with prediabetes. To calculate the HR for a given proportion of visits before the MT with prediabetes, raise the HR presented to the desired proportion. Thus, the unadjusted HRs for prediabetes at 25%, 50%, or 75% of visits before the MT were 1.21 (2.20^{0.25}), 1.49 (2.20^{0.5}), and 1.81 (2.20^{0.75}), respectively.

^b Of 1690 participants, 136 sustained a fracture. Fracture sites included wrist (n = 17), hip (n = 1), spine (n = 2), pelvis (n = 2), ribs (n = 6), upper arm or shoulder (n = 15), leg above ankle (n = 20), ankle (n = 27), hand or foot (n = 44), and other (n = 2).

fasting blood glucose) and longer duration of prediabetes. Second, whereas previous studies examined older adults, we analyzed midlife women undergoing the MT, a period when insulin resistance and fracture risk accelerate.^{14,15} It may be easier to discern a prediabetes-fracture association during the MT because physiological changes are larger. Third, we designed our analysis such that the observed association of prediabetes with fracture could not be attributed to future progression to type 2 diabetes; prior studies did not censor participants at first type 2 diabetes diagnosis.

Our results add to a body of data suggesting that prediabetes is detrimental to bone health. Several recent SWAN analyses showed that prediabetes was associated with worse trabecular bone microarchitecture⁸ and that greater insulin resistance was associated with diminished bone strength¹⁰ and faster BMD loss.²² In other cohorts, prediabetes was associated with lower bone turnover,^{6,7} which can contribute to an accumulation of advanced glycation end products in bone and suboptimal bone material properties.²⁸⁻³¹

Establishing whether prediabetes is a risk factor for fractures has potential public health implications. Nearly 1 in 3 US adults has prediabetes,³² but clinicians debate the need to treat it, in part because prediabetes has not been directly linked to end-organ complications.¹³ Our results suggest that more consistently having a fasting blood glucose level in the prediabetes range before the MT may be an independent risk factor for fracture. In our cohort of midlife women, most fractures occurred at nonhip, nonvertebral sites; these fractures can confer up to a 2-fold greater risk of subsequent vertebral or hip fracture.³³⁻³⁶ Thus, for this population, prediabetes before the MT may be an early, modifiable risk factor for fracture.

Limitations

This study has several limitations. First, to maximize our fracture outcomes, we included both minimal trauma and traumatic fracture in a composite outcome. We justify this approach given the increasing recognition that both fracture types are associated with future fractures.^{17,18} Some randomized clinical trials assessing the antifracture efficacy of osteoporosis treatments now include minimal trauma and traumatic fractures as outcomes.³⁷ Second, the rates of prediabetes and fractures differed by race and ethnicity. However, we did not have sufficient power to test whether the association between prediabetes and fractures differed by race and ethnicity.

Conclusions

In this cohort study of midlife women, prediabetes before the MT was associated with greater risk of subsequent fractures during the MT and after menopause, independent of BMD. Because midlife fractures are associated with subsequent fractures in older age, future research could examine whether treating prediabetes before the MT reduces the risk of different fracture outcomes (eg, hip, vertebral, nonvertebral, major osteoporotic) in later life.

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REFERENCES

1. Shanbhogue VV, Hansen S, Frost M, Brixen K, Hermann AP. Bone disease in diabetes: another manifestation of microvascular disease? *Lancet Diabetes Endocrinol*. 2017;5(10):827-838. doi:10.1016/S2213-8587(17)30134-1
2. Khalil N, Sutton-Tyrrell K, Strotmeyer ES, et al. Menopausal bone changes and incident fractures in diabetic women: a cohort study. *Osteoporos Int*. 2011;22(5):1367-1376. doi:10.1007/s00198-010-1357-4
3. Vilaca T, Schini M, Harnan S, et al. The risk of hip and non-vertebral fractures in type 1 and type 2 diabetes: a systematic review and meta-analysis update. *Bone*. 2020;137:115457. doi:10.1016/j.bone.2020.115457

4. Koromani F, Oei L, Shevroja E, et al. Vertebral fractures in individuals with type 2 diabetes: more than skeletal complications alone. *Diabetes Care*. 2020;43(1):137-144. doi:10.2337/dci19-0925
5. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes—a meta-analysis. *Osteoporos Int*. 2007;18(4):427-444. doi:10.1007/s00198-006-0253-4
6. Jiajue R, Jiang Y, Wang O, et al. Suppressed bone turnover was associated with increased osteoporotic fracture risks in non-obese postmenopausal Chinese women with type 2 diabetes mellitus. *Osteoporos Int*. 2014;25(8):1999-2005. doi:10.1007/s00198-014-2714-5
7. Mitchell A, Fall T, Melhus H, Wolk A, Michaëlsson K, Byberg L. Type 2 diabetes in relation to hip bone density, area, and bone turnover in Swedish men and women: a cross-sectional study. *Calcif Tissue Int*. 2018;103(5):501-511. doi:10.1007/s00223-018-0446-9
8. Shieh A, Greendale GA, Cauley JA, et al. Prediabetes and insulin resistance are associated with lower trabecular bone score (TBS): cross-sectional results from the Study of Women's Health Across the Nation TBS Study. *Osteoporos Int*. 2022;33(6):1365-1372. doi:10.1007/s00198-022-06325-x
9. Shin D, Kim S, Kim KH, Lee K, Park SM. Association between insulin resistance and bone mass in men. *J Clin Endocrinol Metab*. 2014;99(3):988-995. doi:10.1210/jc.2013-3338
10. Ishii S, Cauley JA, Crandall CJ, et al. Diabetes and femoral neck strength: findings from the Hip Strength Across the Menopausal Transition Study. *J Clin Endocrinol Metab*. 2012;97(1):190-197. doi:10.1210/jc.2011-1883
11. Srikanthan P, Crandall CJ, Miller-Martinez D, et al. Insulin resistance and bone strength: findings from the Study of Midlife in the United States. *J Bone Miner Res*. 2014;29(4):796-803. doi:10.1002/jbmr.2083
12. Herman WH, Ratner RE. Metformin should be used to treat prediabetes in selected individuals. *Diabetes Care*. 2020;43(9):1988-1990. doi:10.2337/dci20-0030
13. Davidson MB. Metformin should not be used to treat prediabetes. *Diabetes Care*. 2020;43(9):1983-1987. doi:10.2337/dci19-2221
14. Greendale GA, Sowers M, Han W, et al. Bone mineral density loss in relation to the final menstrual period in a multiethnic cohort: results from the Study of Women's Health Across the Nation (SWAN). *J Bone Miner Res*. 2012;27(1):111-118. doi:10.1002/jbmr.534
15. Shieh A, Karlamangla AS, Huang MH, Han W, Greendale GA. Faster lumbar spine bone loss in midlife predicts subsequent fracture independent of starting bone mineral density. *J Clin Endocrinol Metab*. 2021;106(7):e2491-e2501. doi:10.1210/clinem/dgab279
16. Chen C, Chen Q, Nie B, et al. Trends in bone mineral density, osteoporosis, and osteopenia among U.S. adults with prediabetes, 2005-2014. *Diabetes Care*. 2020;43(5):1008-1015. doi:10.2337/dci19-1807
17. Warriner AH, Patkar NM, Yun H, Delzell E. Minor, major, low-trauma, and high-trauma fractures: what are the subsequent fracture risks and how do they vary? *Curr Osteoporos Rep*. 2011;9(3):122-128. doi:10.1007/s11914-011-0064-1
18. Cummings SR, Eastell R. Stop (mis)classifying fractures as high- or low-trauma or as fragility fractures. *Osteoporos Int*. 2020;31(6):1023-1024. doi:10.1007/s00198-020-05325-z
19. Gerstein HC, Yusuf S, Bosch J, et al; DREAM (Diabetes Reduction Assessment With Ramipril And Rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet*. 2006;368(9541):1096-1105. doi:10.1016/S0140-6736(06)69420-8
20. Gerstein HC, Mohan V, Avezum A, et al; DREAM On (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication Ongoing Follow-up) Investigators. Long-term effect of rosiglitazone and/or ramipril on the incidence of diabetes. *Diabetologia*. 2011;54(3):487-495. doi:10.1007/s00125-010-1985-4
21. Perreault L, Pan Q, Mather KJ, Watson KE, Hamman RF, Kahn SE; Diabetes Prevention Program Research Group. Effect of regression from prediabetes to normal glucose regulation on long-term reduction in diabetes risk: results from the Diabetes Prevention Program Outcomes Study. *Lancet*. 2012;379(9833):2243-2251. doi:10.1016/S0140-6736(12)60525-X
22. Shieh A, Greendale GA, Cauley JA, Srikanthan P, Karlamangla AS. Longitudinal associations of insulin resistance with change in bone mineral density in midlife women. *JCI Insight*. 2022;7(20):e162085. doi:10.1172/jci.insight.162085
23. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med*. 2016;375(16):1532-1543. doi:10.1056/NEJMoa1607948
24. Saag KG, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med*. 2017;377(15):1417-1427. doi:10.1056/NEJMoa1708322

25. Looker AC, Eberhardt MS, Saydah SH. Diabetes and fracture risk in older U.S. adults. *Bone*. 2016;82:9-15. doi:10.1016/j.bone.2014.12.008
26. Napoli N, Strotmeyer ES, Ensrud KE, et al. Fracture risk in diabetic elderly men: the MrOS study. *Diabetologia*. 2014;57(10):2057-2065. doi:10.1007/s00125-014-3289-6
27. Park HY, Han K, Kim Y, Kim YH, Sur YJ. The risk of hip fractures in individuals over 50 years old with prediabetes and type 2 diabetes—a longitudinal nationwide population-based study. *Bone*. 2021;142:115691. doi:10.1016/j.bone.2020.115691
28. Costantini S, Conte C. Bone health in diabetes and prediabetes. *World J Diabetes*. 2019;10(8):421-445. doi:10.4239/wjd.v10.i8.421
29. Furst JR, Bandeira LC, Fan W-W, et al. Advanced glycation endproducts and bone material strength in type 2 diabetes. *J Clin Endocrinol Metab*. 2016;101(6):2502-2510. doi:10.1210/jc.2016-1437
30. Dawson-Hughes B, Bouxsein M, Shea K. Bone material strength in normoglycemic and hyperglycemic Black and White older adults. *Osteoporos Int*. 2019;30(12):2429-2435. doi:10.1007/s00198-019-05140-1
31. Holloway-Kew KL, Betson A, Rufus-Membere PG, et al. Impact microindentation in men with impaired fasting glucose and type 2 diabetes. *Bone*. 2021;142:115685. doi:10.1016/j.bone.2020.115685
32. Hostalek U. Global epidemiology of prediabetes—present and future perspectives. *Clin Diabetes Endocrinol*. 2019;5:5-5. doi:10.1186/s40842-019-0080-0
33. Barrett-Connor E, Sajjan SG, Siris ES, Miller PD, Chen YT, Markson LE. Wrist fracture as a predictor of future fractures in younger versus older postmenopausal women: results from the National Osteoporosis Risk Assessment (NORA). *Osteoporos Int*. 2008;19(5):607-613. doi:10.1007/s00198-007-0508-8
34. Cerocchi I, Ghera S, Gasbarra E, Feola M, Tarantino U. The clinical significance of wrist fracture in osteoporosis. *Aging Clin Exp Res*. 2013;25(suppl 1):S81-S82. doi:10.1007/s40520-013-0083-0
35. Gehlbach S, Saag KG, Adachi JD, et al. Previous fractures at multiple sites increase the risk for subsequent fractures: the Global Longitudinal Study of Osteoporosis in Women. *J Bone Miner Res*. 2012;27(3):645-653. doi:10.1002/jbmr.1476
36. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA III, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *J Bone Miner Res*. 2000;15(4):721-739. doi:10.1359/jbmr.2000.15.4.721
37. Kendler DL, Marin F, Zerbinì CAF, et al. Effects of teriparatide and risedronate on new fractures in postmenopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet*. 2018;391(10117):230-240. doi:10.1016/S0140-6736(17)32137-2

SUPPLEMENT.

Data Sharing Statement