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Menopausal bone changes and incident fractures in diabetic women: a cohort study

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Summary

The purpose of this study was to evaluate the rate of bone loss and incident fractures in women with diabetes mellitus (DM) across menopause. During menopause, DM women experienced bone mineral density (BMD) loss that was faster at hip and slower at spine and had a higher risk of fractures, perhaps because of their earlier menopause. The increasing DM epidemic will contribute to higher fracture burden.

Introduction—Women with DM have a higher risk of fractures independent of age, body mass index (BMI), and BMD. Our objective is to evaluate if women with DM experience greater bone loss and more fractures across menopause.

Methods—Two thousand one hundred seventy one women, aged 42 to 52 years at baseline (1996), enrolled in the Study of Women's Health Across the Nation (SWAN), a prospective study, with 8 years of annual follow up. One thousand three hundred forty six (62%) completed annual visit 7 (2004). Women with baseline fasting blood glucose level of ≥ 126 mg/dl and those being treated for diabetes were designated as DM. Annual assessment of menopausal stage, BMD, and urinary N-telopeptide (NTx) were carried out. Rate of change in BMD across menopause and annual self-report data for risk of incident fractures by DM status were determined.

Results—Despite higher baseline BMD at hip ($p < 0.001$), and lumbar spine ($p < 0.001$), rate of decline in BMD was faster at hip ($\beta = -0.45$ vs. -0.11 gm/cm²/year, $p < 0.001$) for DM women, compared to non-DM. However, lumbar spine bone loss was slower in women with DM as compared to non-DM women ($\beta = 0.04$ vs. -0.25 gm/cm²/year, $p = 0.004$). DM women experienced menopause 3 years earlier than non-DM women ($p = 0.002$), and age adjusted incident fractures were two fold higher in women with DM compared to non-DM (RR=2.20, 95% CI: 1.26–3.85, $p < 0.006$).

Conclusions—BMD loss is greater in hip and slower at spine in DM women during menopausal transition. Women with DM have a higher risk of fractures, perhaps because of their earlier menopause.

Keywords

Bone; Density; Diabetes; Menopause; Women

Introduction

Osteoporosis and diabetes mellitus (DM), two of the most common chronic conditions, are public health concerns. In the USA, two million osteoporotic fractures occur every year [1]. Incident DM affects 7.8% of the US population [2]. With global demographic trends of aging and obesity, the prevalence of diabetes is projected to double in the next 20 years [3].

Menopause is the most significant period for bone loss in women, when rapid metabolic and endocrine changes occur. Bone loss initiates before the last menstrual period [4]. The percent decrease in bone mineral density (BMD) in the first 5 years post-menopause can be as high as 9–13% [5]. Although menopause has a greater effect on bone loss than chronological age [6], age is also an independent risk for osteoporotic fractures [7].

DM affects bone metabolism; the relationship between DM and osteoporosis is complex, and the mechanisms underlying this association remain controversial. While low BMD is consistently observed in type 1 DM, the association is less clear in type 2 DM; both type 1 and type 2 DM have been associated with a higher risk of fractures [8]. New bone formation and bone quality (micro-architectural bone composition and characteristics of bone strength) may be impaired in DM, leading to lower mechanical strength and a propensity to fracture.

The majority of published studies involving DM and skeletal outcomes have been conducted in postmenopausal older women who were predominantly Caucasian. Prospective studies of BMD change in DM women of diverse ethnicity, across menopause, that concurrently evaluate bone biomarkers and fracture risk are lacking. The Study of Women's Health Across the Nation (SWAN) is uniquely positioned to address BMD changes across menopause. Women of Caucasian, African American, Chinese, and Japanese ethnicity have been followed annually up to 8 years in SWAN. In this analysis, we report BMD changes

and fracture risk across menopause in women with DM compared to women without DM. We tested the following hypotheses: (1) women with DM experience greater bone loss and more fractures across the menopausal transition and (2) this association may be mediated by menopause status.

Subjects and methods

Study population

SWAN began in 1996–1997 to study the health changes during mid-life in a multi-ethnic community-based cohort of 3,302 women. Eligibility criteria have been detailed elsewhere [9]. Briefly, women eligible for SWAN were aged between 42 and 52 years at baseline, had an intact uterus, had at least one intact ovary, were not currently taking hormone therapy or oral contraceptives, were not pregnant or lactating, and had ≥ 1 menstrual period in the previous 3 months.

The SWAN bone study aims to describe skeletal changes as women transition menopause and to compare associated factors across different ethnic backgrounds. In addition to recruiting Caucasian women, each of the five bone-study sites enrolled women of another ethnic group: African American (Boston, MA; Pittsburgh, PA; Detroit, MI), Chinese (Oakland, CA), and Japanese (Los Angeles, CA). Japanese women formed the referent group in the current analyses. Though the overall rate of BMD loss as previously shown in SWAN was similar among ethnic groups across menopause, Japanese women had the most rapid *lumbar* spine bone loss [10]. The rate of hip fracture in Japanese women is 50% lower than in Caucasian women, as revealed in another study [11]. Each clinical center and the data coordinating center received institutional review board approval, and all women provided written informed consent.

This analysis included data from baseline (1996) through annual visit 7 (2004) from participants who had baseline assessment of blood glucose and underwent at least one BMD measurement during the observation period. At baseline, observations from women who reported anorexia ($n=28$), reported bulimia ($n=16$), were missing information for diabetes ($n=175$), or were missing information for BMD at the total hip or lumbar spine ($n=27$) were excluded, leaving an analytic baseline sample of 2,155 women. During follow up, 386 observations from women who reported use of medication that influence bone turnover (hormone preparations, GnRH agonist therapy, or antiresorptive therapy including bisphosphonates, calcitonin, tamoxifen, raloxifene) at any visit, or reported use of steroid preparations on two consecutive visits, were censored from further analysis [10]. Observations from women who developed incident diabetes at any annual follow up visit after baseline in this cohort were censored from subsequent analysis: $n=98$ (6%) women developed DM at visit 1 and none at visit 2 because created diabetes variable was not available at visit 2 (blood glucose concentrations were not obtainable at this visit), $n=91$ (6%) at visit 3, $n=97$ (7%) at visit 4, $n=111$ (8%) at visit 5, $n=112$ (8%) at visit 6, and $n=112$ (8%) at visit 7 (1,929 total incident DM observations censored from longitudinal analysis)]. One thousand three hundred forty six women completed visit 7 (62% of the baseline cohort).

Bone mineral density measurements

BMD at the total hip and the lumbar spine were measured at baseline and annually with dual X-ray absorptiometry (DXA). Hologic QDR 2000 densitometers (Hologic, Waltham, MA, USA) were used in Pittsburgh and Oakland sites and 4500A in Boston, Detroit, and Los Angeles. Reproducibility of hip measurements was improved by using Osteodyne (Research Triangle Park, NC, USA) positioning devices [12]. Quality control protocol comprised of daily scans of anthropomorphic spine phantoms, cross-site and cross-time calibration with a

Hologic spine phantom, and an on-site review. Scans with potential problems, and 5% of all scans, were reviewed by Synarc (Waltham, MA, USA). Short-term in vivo measurement standard deviations were 0.014 g/cm² for the lumbar spine and 0.016 g/cm² (2.2 %) for the lumbar spine and femoral neck (hip), respectively [10].

Urinary N-telopeptide

Urinary N-telopeptide of type 1 collagen (NTx) was measured in singlicate using an automated immunoassay (Vitros ECI; Ortho Clinical., Rochester, NT, USA). The assay was based on competition between urinary peptide and synthetic NTx peptide coating the wells, for binding by an anti-NTx monoclonal antibody conjugated to horse radish peroxidase. The bound conjugate was measured by chemiluminescence. NTx was expressed as nanomoles of bone collagen equivalents per liter per millimole creatinine per liter (nM BCE/mM creatinine). The lower limit of detection was 10 nM BCE and intra- and inter-assay coefficients of variation were 2.75% and 4.8%, respectively, over the assay range. Samples >3,000 nM BCE were diluted 1/20 prior to measurement. Creatinine was measured on the Cobas Mira (Horiba ABX, Montpellier, France) based on the Jaffé reaction (to calculate NTx/Cr ratio). The lower limit of detection was 0.014 mM and the intra- and inter-assay coefficients of variation were 0.62% and 4.12%, respectively, across the assay range.

Ascertainment of baseline diabetes

DM was defined as [1] fasting baseline glucose level ≥ 126 mg/dl or [2] self-report of current hypoglycemic medications or insulin.

Questionnaire-based and anthropometric measurements

At baseline and at each annual visit, women underwent an interview that included menopause status checklist and socio demographic and lifestyle characteristics. Ethnicity was self-identified. Smoking was coded as never (referent), past, or current. Alcohol consumption was categorized as none vs. any alcoholic beverages per day (referent). Self-reported daily use of vitamin D and calcium supplement was ascertained as none (referent) vs. any use. Physical activity was categorized as moderate to more activity vs. less or much less (referent). Self-reported baseline health status was coded as good/fair (referent) vs. poor/unchanged, and economic status as difficulty in paying for basic necessities vs. no difficulty (referent). At baseline and annual visits, weight (kg) was measured with a balance beam scale. Medication use was ascertained and verified through an interviewer-administered questionnaire. A complete inventory was taken at baseline and subsequent annual visits that included but was not limited to use of hormone preparations, steroids, GnRH agonist therapy, and antiresorptive therapy (including bisphosphonates, calcitonin, tamoxifen, raloxifene) [10].

Assessment of fractures

At baseline, participants reported fracture and their age at the time of fracture since age 20, as ascertained by a physician. During follow-up annual visits, participants self-reported incident fractures, including the site and number of fractures since their last study visit. The reliability of self-reported fractures with medical records confirmation has been documented in several studies. In 161,809 post-menopausal women enrolled in Women Health Initiative study, the overall fracture confirmation rate between self report and medical records was 71% [13]. Nevitt et al. described that 78% of fractures were confirmed when self-reported non-spine fractures were compared with radiographs and medical reports in 9,704 elderly women [14].

Menopausal status

Menopausal status was based on self-reported menstrual cycle characteristics recalled over the past year: premenopausal (menstruation in the past 3 months with no change in menstrual regularity in past year), early peri-menopausal (menstruation in past 3 months with decreased regularity in past year), late peri-menopausal (no menstruation for 3–11 months), and post-menopausal (no menstruation for past 12 months) [15].

Role of the funding source

The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Statistical analysis

Separate linear mixed models with random intercept were run using SAS PROC MIXED to ascertain rate of change in BMD at lumbar spine, and total hip, as repeated-measure analysis. Baseline age and weight were centered at their means, percentage change in weight since baseline was computed for all follow-up visits. Statistical model building comprised of the sequential addition of one covariate to the preceeding model starting with DM, followed by the addition of age, baseline weight, percentage change in weight from baseline, smoking, lifestyle (alcoholic beverages consumed/day, physical activity, study site, health and economic status), daily supplement use (calcium and vitamin D) baseline BMD at respective bone site, ethnicity, and NTx/Cr.

DM has been associated with an earlier menopause [16,17]; thus, in the final model, we adjusted for menopausal status. We hypothesized that, if the association between DM and fracture was modified when menopause was added to the model, this would suggest that a higher fracture risk among DM women would reflect their earlier menopause. SAS PROC GLM was used to ascertain difference in age at menopause across DM status in unadjusted and multivariate adjusted models. An interaction term for DM and time, to test if change in BMD differed between DM and non-DM over time, was also included. In secondary analyses, the same modeling strategy was repeated to test if the interaction of time, DM, and menopause status predicted BMD change across menopause over time.

The relative risk of fractures by DM status was estimated using SAS PROC GENMOD as repeated measures analysis sequentially adjusting for the same covariates listed above. Analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA).

Results

Characteristics of the participants

The prevalence of DM at baseline was 5%, mean age was 46, and approximately half of participants were non-Caucasian (Table 1). Although all women at baseline were premenopausal (54%) or early peri-menopausal (46%), a significantly higher proportion of DM women had transitioned to early peri-menopausal as compared to those without DM (58% vs. 45%, respectively, $p<0.001$). Mean weight for DM women was higher than for non-DM women (95 vs. 72 kg, $p<0.001$). DM women were less likely to consume alcohol, to be economically better-off, or to be physically active ($p<0.001$ for all). Smoking status and overall health status did not differ by DM. Women with DM reported significantly less use of calcium supplements ($p=0.001$); however, use of vitamin D was similar. DM women had higher mean baseline total hip and lumbar spine BMD ($p<0.001$ for both) as compared to non-DM women. DM women were also more likely to report a history of fracture than non-DM women (26% vs. 19%, respectively, $p=0.065$).

DM and change in BMD

Over a maximum follow up of 8 years (median 3.1, interquartile range 4.1), the magnitude of decline in adjusted BMD was about fourfold higher in women with DM compared to non-DM women at the total hip ($\beta = -0.45$ vs. -0.11 gm/cm²/year, $p < 0.001$) (Table 2). However adjusted lumbar spine bone loss was significantly slower in women with DM as compared to non-DM women ($\beta = 0.04$ vs. -0.25 gm/cm²/year, $p < 0.01$). Addition of menopausal status to the models attenuated the effect slightly, but the rate of bone loss remained significantly different in DM vs. non-DM women. *Mean* BMD in the final models was significantly lower in DM women compared with non-DM women at the total hip (Table 2); however, adjusted *mean* lumbar spine BMD was significantly higher in women with DM as compared to non-DM women ($p < 0.01$ for both).

DM, menopause stage, and change in BMD

DM women reached menopause at a mean age of 49 years, compared to 52 years in non-DM women, an average of 3 years earlier in unadjusted ($p = 0.0015$) and risk-factor-adjusted models ($p = 0.0046$) (Table 3).

Rate of BMD change in women with DM vs. those without DM at various stages of menopause were compared. In adjusted models, the interaction between menopause status and DM was significant in both bone sites, implying a different rate of BMD change across the menopause by DM status (total hip $p = 0.016$, lumbar spine $p < 0.001$) (Table 3; Fig. 1).

At the total hip, a trend towards higher rate of BMD change over post-menopause was observed in women with DM ($p = 0.058$). However, at the lumbar spine, DM women experienced a significantly slower rate of BMD loss, compared to non-DM participants both during late peri-menopause and post-menopause ($p < 0.001$ for both).

Fractures

Baseline self-reported fractures ($n = 415$) since age 20 were significantly higher in women with DM compared to women without DM [30 (26%) vs. 385 (19%), $p = 0.065$], respectively. The percentage of baseline fractures at all bone sites was higher in DM women, although this difference reached statistical significance only for fractures of the lower arm (Table 1).

During 8 years of follow up, 260 incident fractures were reported overall; 232 women reported a single fracture, 12 women reported fractures on more than one visit (nine reported fractures on two different visits, two reported fractures on three visits, and one reported fracture on four separate visits). A total of 245 women reported any fracture; percentage of fractures was significantly higher in DM women compared to non-DM participants [26 (5%) vs. 219 (2%), respectively ($p < 0.0001$)]. The relative risk of incident fractures was approximately twofold higher in women with DM compared to non-DM women in age (RR=2.16, 95% CI: 1.26–3.72, $p < 0.006$), and multivariate adjusted (RR=1.85; 95% CI=1.06, 3.22, $p = 0.036$) models. However, the addition of menopausal status to the models attenuated the effect of DM on fractures (RR=1.53; 95% CI=0.76, 3.14, $p = 0.292$) [Fig. 2 (p values are not shown in the figure)].

Secondary analysis

To explore if insulin use influenced BMD loss and fracture outcomes in DM participants, we carried out a secondary analysis by excluding women who were using insulin at baseline. After insulin exclusion, rate of hip BMD loss was significantly faster in adjusted models in DM women, relative to non-DM participants ($p = 0.016$). However, in lumbar spine, women with DM experienced slower bone loss ($p = 0.040$). The relative risk of fracture in DM, compared to non-DM women, was not significant in adjusted models (RR=0.78; 95%

CI=0.27, 2.24). Even after excluding insulin users, a higher proportion of DM women suffered a fracture compared to non-DM women [10 (2.9%) vs. 266 (2.2%), respectively ($p=0.374$)], although results were not statistically significant

Discussion

The results of this study suggest that, during menopause, women with DM experience a higher risk of fracture and a rate of bone loss that is faster at the hip and slower at the spine. An earlier age of menopause in DM women was observed, which, in conjunction with their fourfold faster rate of bone loss, may contribute to a higher risk of having any fracture. The SWAN study provides further evidence that, despite their higher baseline BMD, women with DM are at greater risk of fracture. To our knowledge, this is the first longitudinal study to report a more rapid rate of hip bone loss and a higher risk of fractures in a relatively young cohort of DM women.

The observation of a higher baseline BMD supports the findings of previous studies in which a higher BMD has been observed in women with DM compared with age-matched subjects without DM, in femoral neck, lumbar spine [18], and calcaneus [19]. While low BMD is observed in type 1 DM, the relationship is less definitive in type 2 DM, with recent reviews reporting modestly higher or unchanged BMD [8]. Despite discrepancies between BMD, recent research underscores that bone formation, micro-architecture, and bone quality are affected in both types of DM [20].

Recent meta-analyses also reported a higher hip fracture risk with both type 1 and type 2 DM (RR=1.4–1.7) [8,21], although the mechanism is not well understood. DM women, regardless of the type, had significantly elevated hip fracture risk from studies in Europe [22], Canada [23], and USA [24]. The SWAN findings extend these observations to a much younger group of women.

Even though, in adults, type 2 accounts for 90–95% of all diagnosed cases of DM, information related to *longitudinal changes* in BMD in type 2 DM in women is sparse [25]. A faster rate of hip bone loss has been reported in one longitudinal study of older adults (age at least 65), in which Caucasian women with type 2 DM lost bone more rapidly at the hip relative to those without DM [26]. In a prospective evaluation of type 2 DM men and women (age 70–79) in the Health, Aging, and Body Composition Study (Health ABC), women lost more hip BMD over 4 years of follow up, despite having higher baseline BMD [27]. In another analysis from the same cohort, type 2 DM participants with fractures had lower hip BMD when compared to those without fractures [18].

These epidemiologic observations are supported by animal data, which showed that, in rodent models (diabetic mouse model, MKR), although bone density is greater in DM, bone structure is more fragile, with fractures occurring under a smaller mechanical load [28]. In other spontaneous diabetic rat models, despite having normal BMD, decreased femoral bone strength against torsion, bending, and energy absorption was noted [29]. Specifically, in type 2 DM, skeletal fragility may arise from reduced transverse bone accumulation and increased resorption, as explained in a recent study of MKR mice [28]; type 2 diabetic mice had thin long bones with 20% decreased strength ($p<0.05$) relative to controls. Micro-computed tomography and histomorphometry revealed that, although BMD was not affected, periosteal increase was impaired, cortical bone resorption was 250% faster, and bone formation was 40% reduced as compared to normal mice ($p<0.05$) [28]. Similar structural and mechanical change could play a role in DM-induced fragility in human bone.

DM could also affect bone *remodeling* by various mechanisms, including insulin deficiency and microangiopathy; higher circulating glucose levels may predispose to accumulation of

advanced glycation end products (AGE) in bone, which lead to impaired bone quality and biomechanics as studied in diabetic rats [28] and human cadaver femurs [30]. The combination of poor bone quality and microstructure and an accelerated bone loss would reduce bone strength. As observed in our study, bone fragility due to rapid bone loss cannot be calculated from DXA measure of BMD. However, newer technology, peripheral quantitative computed tomography (p-QCT), can measure volumetric density (v BMD) and skeletal properties. In a recent publication, Petit and colleagues compared tibial and radial v BMD using p-QCT in type 2 DM men 65 years, relative to those without DM [31]. There was lower bone bending strength at both tibia and radius in DM men, despite no difference in cortical vBMD at both sites.

Adjusting for menopause status attenuated the higher risk of fracture in DM women, which implies that menopause status is an intermediary in the association between DM and fracture risk. A significant difference in age at menopause was seen; DM women reached menopause on average 3 years earlier as compared to non-DM women. While premature menopause has been linked with type 1 DM [17], its association is less defined with type 2 DM [32]. Earlier menopause is an independent risk factor for fractures [7]. In a cross sectional eligibility survey of about 16,000 women for SWAN, DM was associated with premature ovarian failure, defined as menses cessation before age 40 [16]. More research is clearly needed to explore the impact of DM on age at menopause and its clinical consequences.

We found a relatively higher lumbar spine BMD and a lower rate of vertebral bone loss over time in DM women as compared to women without DM. This finding is consistent with other studies that evaluated spine BMD with DXA in female DM patients [33]. Measurements of spinal BMD with DXA are inaccurately high (radiological artifact) as extra-osseous calcification in adjacent aorta and degenerative osteo-arthritic changes are incorporated in the radiograph [34]. Moreover, individuals with DM have a higher propensity of calcification in the aorta [35], the mechanism for which is not completely understood, though AGE is proposed as a trigger [36].

We did not observe a difference in NTx/Cr, a bone resorption biomarker in DM vs. non-DM women. Previous studies have not revealed a consistent association between DM status and rates of bone change as assessed by bone turnover markers [37]. Clearly, the mechanism(s) involved in bone turnover in DM is complex, and more research is needed.

Newer hypoglycemic medications (TZD), rosiglitazone (Avandia), and pioglitazone (Actos) are associated with elevated fracture risk in white women and, for rosiglitazone, more rapid bone loss [38]. Information on the use of these drugs was not ascertained for this analysis, as they were introduced in USA in 1999 [39] after the baseline SWAN visit (1996).

Our study has several strengths, including longitudinal design. We collected comprehensive health and lifestyle data across a diverse cohort of women undergoing menopause. With almost 2,200 participants, this was the largest study with information on bone biomarker; eight annual BMD examinations at two anatomical sites. There are, however, limitations to our results; the fractures were self reported and were not confirmed radiologically, which could lead to misclassification. However, self-reported fractures have good reliability [40]; frequencies of self-reported fractures are found to be similar to those verified using radiographs. One additional limitation of this analysis is the small number of fracture events, especially in DM women. A fracture is a relatively rare endpoint; individual studies often lack power, as accrual of events takes time, more so in younger subjects. The SWAN participants are relatively young (42–52 years at baseline in 1996–1997) and are now reaching an age when incidence of osteoporotic fractures begins to increase markedly.

The current analysis was also limited by our inability to differentiate between type 1 and 2 DM. In the US, type 1 accounts for 5–10% of DM cases [25]. It is reasonable to assume that the proportions of type 1 and 2 diabetes in the SWAN are similar to the US figures. Diagnosis of DM has distinct criteria, which can be clearly conveyed to participants, which, in turn, make it easier to ascertain the validity of a self report for the diagnosis [41]. For instance, in 87,253 women 34–59 years old, enrolled in Nurses' Health Study, validation of diabetes self report with medical records was 98.4% [42]. Other researchers have also shown relatively high agreement (96.4%) between diabetes self reports and medical records [43]. In one validation study, Kaye et al. reported 64% confirmation rate between self-report of DM and participants' physicians [44].

In secondary analysis, insulin use did not explain the faster bone loss at hip in DM women. The risk persisted even when insulin users were excluded. This result is similar to observation by Levin et al., who reported that loss in bone density was seen in patients within 5 years of diagnosis of DM [45] but it did not correlate with duration of DM. This supports the hypothesis that the loss of skeletal tissue in DM reflects the underlying disease since it occurs early and is not related to severity of disease, as evidenced by the need for insulin.

In conclusion, loss in BMD is significantly greater in the hip and slower in the spine in women with DM during the menopausal transition. DM women had a higher risk of fractures than non-DM women, perhaps because of their earlier menopause. The increasing epidemic of DM may contribute to an increasing fracture burden.

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Fig. 1.

Rate of change in adjusted BMD by DM status across menopause stages. *Pre* pre-menopause, *Early peri* early peri-menopause, *Late peri* late peri-menopause, *Post* post-menopause. **p* value significant at <0.05 for comparison of BMD between DM and non-DM in respective menopause status. Data were adjusted for same variables as in Table 3. *DM* diabetes, *Non-DM* no-diabetes

Fig. 2.
Adjusted relative risk (*RR*) and 95% confidence intervals (*CI*) for incident fractures

Table 1

Baseline characteristics of women in SWAN across DM status

Characteristic (N=2,171)	DM (n=117)	Non-DM (n=2054)	p value
Age, mean (SD), year	47 (3)	46 (3)	0.329
Ethnicity, n (%)			
African American	61.7 (53)	542.6 (27)	
Caucasian	48.6 (42)	1,024.7 (50)	<0.001
Chinese	4.9 (4)	217.8 (11)	
Japanese	0.9 (1)	254.2 (12)	
Baseline menopause status, n (%)			
Pre-menopause	49.3 (42)	1,115.6 (55)	0.007
Early peri-menopause	67.4 (58)	910.5 (45)	
Difficult to pay for basics (yes), n (%)	18.7 (17)	141.4 (7)	<0.001
Weight, mean (SD), kg	95.4 (20)	71.6 (19)	<0.001
BMI, mean (SD), kg/m ²	36.2 (7)	26.7 (7)	<0.001
Alcoholic beverages/day (any vs. none), n (%)	81.8 (70)	1,021.3 (50)	<0.001
Smoking, n (%)			
Never	58.1 (50)	1177.8 (57)	
Past	30.6 (27)	534.9 (26)	0.161
Current	25.3 (21)	314.8 (15)	
Physically active, n (col %)			
Less active	45.7 (39)	374.6 (18)	<0.001
More active	66.7 (57)	1,612.2 (78)	
Health status compared to a year ago, n (%)			0.178
Better	30.1 (26)	426.3 (21)	
Same, poor, or worse	83.5 (74)	1,601.7 (79)	
Vitamin D supplement use, n (%)	36.7 (32)	800.2 (39)	0.113
Calcium supplement use, n (%)	40.2 (34)	935.7 (46)	0.016
NTx/Cr, mean (SD), nM BCE/mM creatinine ^d	33.6 (17)	34.6 (16)	0.610
Baseline BMD, mean (SD), g/cm ²			
Total hip	1.09 (0.16)	0.95 (0.14)	<0.001
Lumbar spine	1.17 (0.16)	1.07 (0.14)	<0.001
Baseline history of fractures, n (%)			
All fractures	30.3 (26)	385.4 (19)	0.065
Spinal fractures	2.9 (3)	18.1 (1)	0.070
Foot fractures	4.1 (3)	55.6 (3)	0.657
Lower arm fractures	7.3 (6)	52.6 (3)	0.029
Upper arm fractures	1.8 (2)	15.6 (1)	0.280
Hip fracture	0.0 (0)	6.7 (0.3)	0.527
Lower leg fractures	7.8 (7)	96.4 (5)	0.286

Reference group for categorical variables: smoking (referent = none), alcoholic beverages/day (referent=> = 1 drink/day), physical activity (referent = less or much less), health (referent = better), and economic status (referent = not hard to pay), supplement use (referent = none), study site (referent = Pittsburgh), and ethnicity (referent = Japanese), menopause status (referent = pre-menopause)

DM diabetes, *Non-DM* no diabetes

^aNTx/Cr is expressed as nanomoles of bone collagen equivalents per liter per millimole creatinine per liter (nM BCE/mM creatinine, corrected for creatinine level)

Table 2
Adjusted rate of BMD change/year across diabetes status between baseline and visit 7

Model	BMD (g/cm ² /yr)			
	Total hip		Lumbar spine	
	DM	Non-DM	DM	Non-DM
Unadjusted	-0.58	-0.24	<0.001	-0.27
Age ^b	-0.58	-0.24	<0.001	-0.27
Weight ^b	-0.58	-0.24	<0.001	-0.27
% Wt change ^b	-0.58	-0.32	<0.001	-0.26
Smoking ^b	-0.60	-0.32	<0.001	-0.25
Lifestyle ^{b, c}	-0.60	-0.32	<0.001	-0.26
Supplement use ^{b, d}	-0.60	-0.32	<0.001	-0.26
Respective baseline BMD ^b	-0.60	-0.32	<0.001	-0.26
Ethnicity ^b	-0.60	-0.32	<0.001	-0.25
NTx ^b	-0.60	-0.33	<0.001	-0.25
Menopause status ^b	-0.45	-0.11	<0.001	0.04
Least square means	0.928	0.938	<0.001 ^e	1.050
Standard error	0.003	0.002	-	0.004

Reference group for categorical variables: smoking (referent = none), alcoholic beverages/day (referent=>= 1 drink/day), physical activity (referent = less or much less), health (referent = better), and economic status (referent = not hard to pay), supplement use (referent = none), study site (referent = Pittsburgh), ethnicity (referent = Japanese), menopause status (referent = pre-menopause)

DM diabetes, Non-DM no-diabetes

^aP = All p values for interaction between DM status and time

^bAll models adjusted for variable that sequentially appear above

^cAdjusted for alcoholic beverages consumed/day, physical activity, study site, health and economic status

^dVitamin D, calcium

^eP = p values for difference of least squares means

Table 3

Adjusted rate of change in BMD across DM status over menopause stages

Mean age at menopause (year)	DM	Non-DM	<i>p</i> value
Unadjusted	49.1	52.4	0.002
Multivariate adjusted ^a	48.9	51.7	0.005
Adjusted rate of change in BMD across DM status			
Total hip	% Rate of BMD change/year ^b		
Menopause status ^a	DM	Non-DM	<i>p</i> value
Pre-menopause	referent	referent	referent
Early peri-menopause	0.10	0.15	0.684
Late peri-menopause	-0.37	-0.96	0.069
Post menopause	-3.16	-2.33	0.058
Lumbar spine			
Pre-menopause	Referent	Referent	Referent
Early peri-menopause	0.20	0.16	0.630
Late peri-menopause	0.45	-1.94	<0.001
Post menopause	-1.59	-3.94	<0.001

DM diabetes, *Non-DM* no-diabetes

^a All models adjusted for baseline age and weight, percent weight change, smoking (referent = none, alcoholic beverages/day (referent=> = 1 drink/day), physical activity (referent = less or much less), health (referent = better), and economic status (referent = not hard to pay), supplement use (referent = none), study site (referent = Pittsburgh), and ethnicity (referent = Japanese), menopause status (referent = pre-menopause)

^b Overall interaction between and menopause status and rate of change in BMD *p* value: total hip *p*=0.016, lumbar spine *p*=<0.001