ORIGINAL ARTICLE

JBMR®

Insulin Resistance and Bone Strength: Findings From the Study of Midlife in the United States

Preethi Srikanthan,[1] Carolyn J Crandall,[1] Dana Miller-Martinez,[1] Teresa E Seeman,[1] Gail A Greendale,[1] Neil Binkley,[2] and Arun S Karlamangla[1]

[1]Department of Medicine, David Geffen School of Medicine at University of California, Los Angeles (UCLA), Los Angeles, CA, USA
[2]Osteoporosis Clinical Center, University of Wisconsin-Madison, Madison, WI, USA

ABSTRACT

Although several studies have noted increased fracture risk in individuals with type 2 diabetes mellitus (T2DM), the pathophysiologic mechanisms underlying this association are not known. We hypothesize that insulin resistance (the key pathology in T2DM) negatively influences bone remodeling and leads to reduced bone strength. Data for this study came from 717 participants in the Biomarker Project of the Midlife in the United States Study (MIDUS II). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated from fasting morning blood glucose and insulin levels. Projected 2D (areal) bone mineral density (BMD) was measured in the lumbar spine and left hip using dual-energy X-ray absorptiometry (DXA). Femoral neck axis length and width were measured from the hip DXA scans, and combined with BMD and body weight and height to create composite indices of femoral neck strength relative to load in three different failure modes: compression, bending, and impact. We used multiple linear regressions to examine the relationship between HOMA-IR and bone strength, adjusted for age, gender, race/ethnicity, menopausal transition stage (in women), and study site. Greater HOMA-IR was associated with lower values of all three composite indices of femoral neck strength relative to load, but was not associated with BMD in the femoral neck. Every doubling of HOMA-IR was associated with a 0.34 to 0.40 SD decrement in the strength indices ($p < 0.001$). On their own, higher levels of fasting insulin (but not of glucose) were independently associated with lower bone strength. Our study confirms that greater insulin resistance is related to lower femoral neck strength relative to load. Further, we note that hyperinsulinemia, rather than hyperglycemia, underlies this relationship. Although cross-sectional associations do not prove causality, our findings do suggest that insulin resistance and in particular, hyperinsulinemia, may negatively affect bone strength relative to load. © 2014 American Society for Bone and Mineral Research.

KEY WORDS: INSULIN RESISTANCE; BONE STRENGTH

Introduction

Osteoporotic fractures represent a significant morbidity and financial cost burden to individuals and society.[1,2] The scope of this problem is expected to increase worldwide with the graying of the population and is likely to be exacerbated by the rapidly increasing prevalence of type 2 diabetes mellitus (T2DM) in both developed and developing economies.[3–5] Indeed, multiple studies have noted the increased fracture risk in individuals with T2DM.[6–9]

The pathophysiology underlying this increase in fracture risk in T2DM is not well understood. For instance, low bone mineral density (BMD) is a major risk factor for fracture, yet BMD in diabetics is greater than that in nondiabetic individuals.[8,10–12] But T2DM is also associated with greater body weight, which can increase fracture risk by several mechanisms, including increasing the forces on bone during a fall.[13–19] Greater body weight is also expected to increase BMD by the impact of skeletal loading on osteoblast differentiation and activity.[20,21] However, the pathophysiology of T2DM may negatively influence bone formation,[8,9,22,23] so that although BMD is increased in T2DM in response to increased skeletal loading, it is not increased enough relative to the increased impact forces in a fall.

Consistent with this hypothesis, composite indices of femoral neck strength relative to load are indeed lower in midlife women with diabetes than in nondiabetic women.[24] The composite strength indices combine femoral neck areal BMD and size obtained from dual-energy X ray absorptiometry (DXA) hip scans with body size to gauge strength relative to load (impact forces) as may be borne during a fall.[25] They are inversely associated with incident hip fracture risk in community-dwelling older white women[25] and in young U.S. white and Chinese men and women,[26] and unlike BMD, predict fragility fracture risk in middle-aged women without requiring knowledge of the woman's race/ethnicity.[27]

Ishii and colleagues[24] also noted a significant inverse association between insulin resistance (measured using the Homeostatic Model of Insulin Resistance [HOMA-IR]) and composite indices for bone strength in a multiethnic sample of premenopausal women. A few small studies have also found

Received in original form March 29, 2013; revised form July 30, 2013; accepted August 13, 2013. Accepted manuscript online August 26, 2013.
Address correspondence to: Preethi Srikanthan, MD, MS, University of California, Los Angeles, David Geffen School of Medicine, BOX 951679, A2-237 CHS, Los Angeles, CA 90095-1679, USA. E-mail: psrikanthan@mednet.ucla.edu

Journal of Bone and Mineral Research, Vol. 29, No. 4, April 2014, pp 796–803
DOI: 10.1002/jbmr.2083

inverse associations between insulin resistance and markers of bone formation, such as osteocalcin,[28,29] osteoprotegerin,[30] and even BMD in some subpopulations.[31–33]

We therefore hypothesized that insulin resistance plays a key role in the increased fracture risk observed in T2DM, and used data from a national midlife sample to examine the association between insulin resistance and bone strength. Thus we hope to extend the results of Ishii and colleagues[24] to a population of men and women, and uniquely, we used DXA-derived femoral bone strength relative to load, in addition to BMD, as markers of bone strength.

Subjects and Methods

Data came from the second wave of the Midlife in the United States Study (MIDUS II), which included blood and urine assays for biomarkers and bone scans for a subsample of the overall MIDUS II cohort. The MIDUS II study, initiated in 1995, was designed to determine how social, psychological, and behavioral factors interrelate to influence mental and physical health. The first wave (MIDUS I) collected sociodemographic and psychosocial data on 7108 English-speaking, noninstitutionalized American adults residing in the contiguous 48 states, ages 25 to 74 years, whose household included at least one telephone (recruited by random digit dialing), with oversampling of five metropolitan areas, twin pairs, and siblings.[34] To increase the representation of African Americans from urban, low socioeconomic strata in the sample, 592 additional African American residents were recruited from Milwaukee, WI, USA, to participate in MIDUS II.

Of the 4963 participants who completed the MIDUS II survey, 3191 participants were deemed medically safe to travel. Of them, 1255 agreed to participate in the MIDUS II biomarker project, which required a 2-day commitment, including travel to one of three general clinical research centers (GCRC): the University of California at Los Angeles, Georgetown University, and the University of Wisconsin–Madison. Reasons given for nonparticipation were travel, family, and work obligations. MIDUS II Biomarker Project participants were similar to the MIDUS II sample with respect to key characteristics (eg, subjective health, chronic conditions, physical activity, alcohol use),[35] and the complete MIDUS II sample was similar to the MIDUS I sample.[36] Data were collected during a 24-hour stay at a GCRC between July 2004 and May 2009. The protocol included a medical history and physical examination (including medication review), a fasting blood draw, and DXA scans of the lumbar spine and left hip.[35] Height and weight were measured during the GCRC visit. Blood samples were frozen and shipped to a central laboratory for assays. The glycosylated hemoglobin (HbA1c) and lipid assays were performed at Meriter Labs (GML) in Madison, WI, USA using a Cobra Integra Analyzer (Roche Diagnostics, Indianapolis, IN, USA). The glucose assays were performed at ARUP Laboratories in Salt Lake City, UT, USA. Insulin assays were performed on a Siemens Advia Centaur Analyzer also at ARUP Laboratories (Siemens Medical Solutions Diagnostics, Tarrytown, NY, USA). Informed consent was provided by each participant, and each MIDUS center obtained institutional review board approval.[35]

The sample for this analysis included participants in the MIDUS II Biomarker Project with valid data on bone strength, fasting insulin, and fasting glucose. Of the 1255 participants in the MIDUS II Biomarker Project, we excluded data from 347 participants who did not have DXA scans (mainly because funding for DXA scanning at the UCLA and Georgetown sites was obtained after the Biomarker Project had commenced), an additional 15 individuals for whom data for fasting insulin and glucose data was lacking or fasting insulin values were less than or equal to 68 μU/mL, 91 participants who were taking medications known to influence bone strength (oral corticosteroids, alendronate, anastrazole, calcitonin, ibandronate, leuprolide, letrozole, raloxifene, risedronate, tamoxifen, zoledronic acid, testosterone, finasteride, or dutasteride), and 85 women whose menopause transition stage could not be determined, resulting in an analytic sample of 717.

For those models in which insulin resistance, fasting insulin, or fasting glucose were primary predictors, 83 individuals who were taking hypoglycemic medications (glimepiride, glipizide, Metformin, glyburide, Nateglinide, Pioglitazone, Pramlintide, Repaglinide, Rosiglitazone, or Sitagliptin) or insulin analogues (Humalog, Novalog, Humulin N, Novolin N, Lantus, or Levemir) were excluded, leaving an analytic sample of size 634 for these analyses.

Measurements: primary predictors

Details of the sequence and methodology of biological specimen collection in the MIDUS II Biomarker Project have been described in detail.[35] Biomarker Project participants also provided information on health conditions and medication usage. Medication information was verified by examination of medication bottles brought to the clinical research center.

Blood HbA1c measurements were obtained from fasting blood draws in the morning. Blood glucose and insulin levels measured from fasting morning blood samples were used to calculate insulin resistance by the HOMA-IR, which is approximated using the formula below[37]:

$$\text{HOMA-IR} = \text{fasting glucose (in mg/dL)} \times \text{fasting insulin (in } \mu\text{U/mL)} \times 0.00247 \quad (1)$$

Participants were said to have diabetes if they met *any* of the following four criteria: (1) HbA1c $\geq$ 6.5%; (2) fasting glucose $\geq$ 126 mg/dL; (3) reported having diabetes (categorical answer to the question "In past 12 months have you experienced or been treated for any of the following conditions: diabetes or high blood sugar?"); or (4) were taking medication(s) for diabetes including insulin analogue agents or hypoglycemic medications mentioned earlier in the Subjects and Methods section. Participants were said to have prediabetes if they met *all* of the following three criteria: (1) 5.7% $\leq$ HbA1c $<$ 6.5% OR 100 mg/dL $<$ fasting glucose $<$ 126 mg/dL; (2) did NOT report having diabetes; AND (3) were NOT taking medication(s) for diabetes. Participants were deemed to not have either prediabetes or diabetes if they met all of the following criteria: (1) HbA1c $<$ 5.7%; (2) fasting glucose $\leq$ 100 mg/dL; (3) did NOT report having diabetes; AND (4) were NOT taking medication(s) for diabetes.

Measurements: bone strength

During the GCRC visit, 2D projected (areal) BMD was measured in the lumbar spine (L_1–L_4) and left hip using DXA. DXA scans were performed using GE Healthcare Lunar Prodigy (Madison site) or Hologic 4500 (UCLA and Georgetown sites) technology.

Reading of all DXA scans was performed centrally by physicians at the University of Wisconsin DXA center. Three

times per week, and on all days on which scans were obtained, instruments were calibrated and phantom scan data were acquired. No densitometer shift or drift occurred during the course of this study. For BMD cross-calibration across the three clinical sites, a phantom was scanned 10 times on the densitometers at each of the three study sites. The linear regression equation developed from these calibration scans was used to correct BMD values from two of the three sites to make the data comparable across study sites. The recalibrated BMD values at the lumbar spine and left hip were reported in units of grams per square centimeters(g/cm^2).[38]

Femoral neck axis length (FNAL), the distance along the femoral neck axis from the lateral margin of the base of the greater trochanter to the apex of the femoral head, and femoral neck width (FNW), the smallest thickness of the femoral neck along any line perpendicular to the femoral neck axis, were measured from the hip scans using software provided by the scanner manufacturers. Composite indices of femoral neck strength relative to load were created using the following formulas[25]:

$$\text{Compression strength index (CSI)} = (\text{BMD} \times \text{FNW})/\text{Weight} \quad (2)$$

$$\text{Bending strength index (BSI)} = (\text{BMD} \times \text{FNW}^2)/(\text{FNAL} \times \text{Weight}) \quad (3)$$

$$\text{Impact strength index (ISI)} = (\text{BMD} \times \text{FNW} \times \text{FNAL})/(\text{Height} \times \text{Weight}) \quad (4)$$

All three indices were recorded in units of grams per kilogram per meter (g/kg-m). Because BMD was measured in grams per square centimeter, FNW and FNAL in centimeters, weight in kilograms, and height in meters, we scaled CSI and BSI by 100 to obtain values in units of grams per kilogram per meter (g/kg-m). CSI reflects the ability of the femoral neck to withstand an axial compressive load, BSI reflects its ability to withstand bending forces, and ISI reflects the ability of the femoral neck to absorb the potential energy in a fall from standing height.

Measurements: covariates

Information regarding age and gender was obtained from self-reports. Gender/race/ethnicity was self-identified as white, Black/African American, other, or multiracial. From self-reported menstrual patterns and use (in the last year) of sex steroid hormones (from self-report and examination of medication bottles brought to the clinical research center), we classified each female participant's menopause transition stage as one of the following: premenopausal (no change in regularity of menses), early perimenopausal (had menses in last 3 months with change in regularity of menses), late perimenopausal (last menses 3–12 months previously with change in regularity of menses), postmenopausal (no menses in prior 12 months) not taking menopausal hormone therapy, and postmenopausal taking menopausal hormone therapy.[39]

Men were categorized by age into three categories: younger than 50 years, 50 to 59 years, and 60 years or older. The choice of age categories in men was guided by previous observations that substantial age-related bone loss in men does not start until age 50 years.[40] Further, the age categories chosen in men also age-matched the oldest group of men to the postmenopausal women, because only 0.3% of occurrences of spontaneous menopause take place at or after 59 years of age.[41]

Statistical analyses

We used multiple linear regression to examine the associations of HOMA-IR (which was log-transformed to reduce skew in the distribution, using base 2 log transformation to facilitate interpretation), prediabetes, and diabetes with bone strength measures, adjusted for age, gender, menopause transition stage, race (black versus non-black), and study site. We treated log-transformed HOMA-IR as a continuous predictor because the relationship between log HOMA-IR and bone strength indices has been noted to be linear.[24] To allow for age-related changes in bone strength being different in men and in women, we used gender-specific coding for age. We included the categorical age variable for men ($<$50 years, 50–59 years, $\geq$60 years) as well as two continuous variables—one that tracked age in men 60 years and older, and another that tracked age in women who were late perimenopausal or postmenopausal and not taking menopausal hormone therapy.

Bone strength measures examined as dependent variables were BMD in the lumbar spine; BMD in the femoral neck; and the three composite indices of femoral neck strength relative to load: CSI, BSI, and ISI. Because increased body weight is associated with insulin resistance and because body weight also influences bone deposition, the models were run with and without adjustment for body mass index (BMI). BMI was calculated as weight (kilograms) divided by the square of height (meters), and was included in the models as a three different terms: continuous (linear) term, a squared term (BMI^2), and a race interaction term (BMI $\times$ race) to allow for potentially different effects of BMI by race.

We tested for effect modification by gender, by including interactions between gender and the primary predictor(s). Further, as the relationship between HOMA-IR and bone strength may be different in prediabetics and diabetics compared to nondiabetics, we included interaction terms HOMAIR $\times$ prediabetes and HOMAIR $\times$ diabetes to test for effect modification by diabetes and prediabetes statuses. In supplementary analyses aimed at shedding light on the independent roles of insulinemia and glycemia, fasting serum insulin (base 2 log transformed) and fasting serum glucose (base 2 log transformed) were included together in the models in place of HOMA-IR.

All models accounted for within-family correlations using STATA's cluster option. STATA SE version 10.1 (StataCorp LP, College Station, TX, USA) was used for all analyses.

Results

The study sample was similar to the complete MIDUS II Biomarker Project sample with respect to age, BMI, HOMA-IR, prediabetes, and diabetes prevalence (Table 1). The most common reasons for exclusion of Biomarker Project participants from the analysis sample were missing hip DXA scans (from the UCLA and Georgetown sites where DXA scans were added late to the protocol due to funding limitations) and unclassifiable menopause transition stage in women. Therefore, compared to the Biomarker sample, the study sample had a smaller proportion of women and a larger proportion of African Americans (because the new urban African American participants from Milwaukee

Table 1. Descriptive Statistics for the Analytic Sample and the Complete MIDUS II Biomarker Project Sample

	Analytic sample ($n = 717$)	MIDUS biomarker sample ($n = 1255$)[a]
Age (years)	56.8 (11.3)	57.3 (11.5)
Race		
Black	23.7%	17.7%*
Non-black	76.3%	82.3%
Study site		
University of California, Los Angeles, Los Angeles, CA, USA	30.8%	34.5%*
University of Wisconsin–Madison, Madison, WI, USA	55.9%	42.5%
Georgetown University, Washington, DC, USA	13.3%	23.0%
Body weight (kg)	86.5 (20.5)	84.7 (20.3)*
Body mass index (kg/m^2)	30.0 (6.65)	29.8 (6.6)
Gender		
Male	48.4%	43.2%*
Female	51.6%	56.8%
Age in men (years)		
<50	32.3%	28.8%*
50–59	29.4%	28.2%
≥ 60	38.3%	43.0%
Women by menopause transition stage		
Premenopausal	17.0%	12.7%*
Early perimenopausal	14.3%	9.84%
Late perimenopausal or postmenopausal, no hormones	58.7%	65.7%
Postmenopausal taking hormones	10.0%	11.8%
HOMA-IR ($\log_2$ transformed)	1.36 (1.11)	1.34 (1.13)
Fasting glucose (mg/dL, $\log_2$ transformed)	6.65 (0.284)	6.64 (0.281)
Fasting insulin (μIU/mL, $\log_2$ transformed)	3.37 (0.990)	3.36 (1.00)
Blood HbA1c (%)	6.13 (1.25)	6.09 (1.16)
Prediabetic	54.4%	54.7%
Diabetic	19.7%	20.1%
Bone mineral density		
Femoral neck (g/cm^2)	0.84 (0.137)	–
Lumbar spine (g/cm^2)	1.06 (0.18)	–
Femoral neck composite strength indices		
Compression strength index (g/kg-m)	3.60 (0.867)	–
Bending strength index (g/kg-m)	1.22 (0.276)	–
Impact strength index (g/kg-m)	0.206 (0.044)	–

Values are mean (SD) or percentage.

MIDUS = Study of Midlife in the United States; HOMA-IR = Homeostasis Model of Assessment–Insulin Resistance; HbA1c = glycosylated hemoglobin; g/kg-m = grams per kilogram per meter.

[a]Most common reasons for exclusion of MIDUS II Biomarker Project participants from the study sample were missing bone scans ($n = 348$), use of medications known to influence bone ($n = 94$), and unclassifiable menopause transition stage ($n = 88$).

*$p < 0.05$ for t test or chi-square test comparing analytic sample to excluded sample.

were seen at the University of Wisconsin–Madison site, which collected DXA scans from the start of the Biomarker Project) (Table 1).

The average age of study participants was 56.8 years, 38% of men were 60 years or older and 59% of women were either late perimenopausal or postmenopausal and not taking menopausal hormone therapy. The mean age (SD) of men in the analytic sample was 56.53 (11.24) years and that of women was 57.12 (11.38) years.

Further, 54.4% of participants had prediabetes and 19.7% of participants had diabetes. Both prediabetes and overt diabetes were more common in older individuals and in African American participants: among diabetics, mean age was 59.5 years, 44.4% were men, and 34.7% were African American; among prediabetics, mean age was 57.7 years, 41.8% were men, and 15.5% were African American; and among those who did not have either prediabetes or overt diabetes, mean age 52.9 years, 45.3% were men, and 9.2% were African American.

In the complete sample, median and interquartile range of HOMA-IR was 2.47 (1.47–4.40), of fasting insulin was 10.0 (6.00–17.0) μIU/mL, of fasting glucose was 96 (90–105) mg/dL, and of HbA1c was 5.86 (5.60–6.24) %.

Adjusted for age, gender, race/ethnicity, menopause transition stage, and study site, greater insulin resistance was associated with higher BMD in the femoral neck but with lower values of each of the three composite indices of femoral neck strength relative to load (Table 2). With additional adjustment for BMI, greater insulin resistance was associated with lower values of all five bone strength measures, although the association with lower BMD in the femoral neck was not significant (Table 2). Every doubling of HOMA-IR was associated with a 0.09 to 0.14 SD decrement in the other four bone strength measures (Table 2).

Table 2. Adjusted Associations of HOMA-IR With Bone Strength

Bone strength measure	Effect size per doubling of HOMA-IR[a]	95% confidence interval	*p*
Femoral neck BMD	+0.115	(0.047, 0.182)	0.001
Lumbar spine BMD	+0.010	(−0.058, 0.078)	0.777
Compression strength index	−0.342	(−0.405, −0.279)	<0.001
Bending strength index	−0.358	(−0.431, −0.284)	<0.001
Impact strength index	−0.395	(−0.471, −0.319)	<0.001
After additional adjustment for BMI			
Femoral neck BMD	−0.054	(−0.133, 0.026)	0.19
Lumbar spine BMD	−0.087	(−0.171, −0.002)	0.045
Compression strength index	−0.091	(−0.153, −0.030)	=0.004
Bending strength index	−0.141	(−0.222, −0.060)	=0.001
Impact strength index	−0.124	(−0.200, −0.048)	=0.001

Values adjusted for age, sex, race/ethnicity, menopause transition stage in women, and study site.
HOMA-IR = Homeostasis Model of Assessment–Insulin Resistance; BMD = bone mineral density; BMI = body mass index.
[a]Effect size in multiples of the SD of the outcome (strength measure).

Adjusted for age, gender, race/ethnicity, menopause transition stage, and study site, prevalent diabetes (but not prevalent prediabetes) was associated with lower composite indices of femoral neck strength relative to load, but neither diabetes nor prediabetes were significantly associated with BMD in either the femoral neck or lumbar spine (Table 3). Following additional adjustment for BMI, neither prediabetes nor overt diabetes was significantly associated with any of the five strength measures (Table 3).

Gender did not modify the associations of HOMA-IR, with bone strength (all *p* values in tests of gender by HOMAIR interaction were greater than 0.24). Moreover, prediabetes and diabetes status did not modify the association of HOMA-IR with four of the five bone strength measures (all but one of the 10 *p* values in tests of prediabetes/diabetes by HOMA IR interaction were greater than 0.17). The one exception was a significant interaction between prediabetes and HOMA-IR in the association with lumbar spine BMD (interaction *p* value 0.05). Therefore, we re-ran the HOMA-IR and lumbar spine BMD model with the analytic sample restricted to prediabetics. Among prediabetics, the association was even stronger: adjusted for age, gender, race/ethnicity, menopause transition stage, study site, and BMI, every doubling of HOMA-IR was associated with a 0.15 SD decrement in lumbar spine BMD ($p = 0.01$); 95% confidence interval (−0.27 to −0.03).

Finally, when fasting insulin and fasting glucose were entered *together* into the models, higher insulin (but not glucose) was independently associated with lower bone strength. Adjusted for age, gender, race/ethnicity, menopause transition stage, study site, BMI, and fasting glucose, every doubling of fasting insulin was associated with a 0.10 to 0.18 SD decrement in each of the five bone strength measures (Table 4).

Discussion

As hypothesized, in this national sample, increased insulin resistance, prediabetes, and overt diabetes mellitus were all cross-sectionally associated with lower indices of femoral neck strength relative to load. Adjustment for BMI also unmasked an association between greater insulin resistance and lower BMD in the lumbar spine. Our study confirms and extends the findings of an inverse association between bone strength indices and insulin resistance, noted by Ishii and colleagues[24] in premenopausal women to a national sample, in a population with a wider age

Table 3. Adjusted Associations of Prediabetes and Overt Diabetes With Bone Strength

Bone strength measure	Prediabetes effect size (95% CI)	Diabetes effect size (95% CI)
Femoral neck BMD	+0.114 (−0.036, +0.264)	+0.125 (−0.088, +0.338)
Lumbar spine BMD	+0.126 (−0.028, +0.280)	+0.022 (−0.193, +0.238)
Compression strength index	−0.085 (−0.232, +0.061)	−0.488 (−0.689, −0.288)**
Bending strength index	−0.094 (−0.269, +0.081)	−0.453 (−0.680, −0.227)**
Impact strength index	−0.145 (−0.307, +0.017)*	−0.544 (−0.765, −0.323)**
After additional adjustment for BMI		
Femoral neck BMD	+0.030 (−0.111, +0.171)	−0.074 (−0.281, +0.134)
Lumbar spine BMD	+0.082 (−0.073, +0.237)	−0.066 (−0.284, +0.151)
Compression strength index	+0.072 (−0.057, +0.201)	−0.080 (−0.243, +0.082)
Bending strength index	+0.053 (−0.107, +0.213)	−0.071 (−0.266, +0.124)
Impact strength index	+0.023 (−0.114, +0.161)	−0.104 (−0.285, +0.076)

Values adjusted for age, sex, race/ethnicity, menopause transition stage in women, and study site. Effect size in multiples of the SD of the outcome (strength measure). Reference group = no diabetes.
BMD = bone mineral density; CI = confidence interval; BMI = body mass index.
*$p < 0.10$;
**$p < 0.001$.

Table 4. Independent Associations of Fasting Glucose and Fasting Insulin With Bone Strength

	Outcome				
Predictor	Femoral neck BMD	Lumbar spine BMD	Compression strength index	Bending strength index	Impact strength index
Glucose	0.339	0.282	0.175	0.204	0.185
	(−0.15, +0.83)	(−0.23, +0.80)	(−0.26, +0.61)	(−0.28, +0.68)	(−0.28, +0.65)
Insulin	0.092*	−0.018	−0.395***	−0.415***	−0.455***
	(0.01, 0.17)	(−0.10, +0.07)	(−0.47, −0.32)	(−0.50, −0.33)	(−0.54, −0.37)
After additional adjustment for BMI					
Glucose	0.348	0.284	+0.168	0.199	0.177
	(−0.12, +0.82)	(−0.22, +0.79)	(−0.18, +0.52)	(−0.21, +0.61)	(−0.20, +0.55)
Insulin	−0.099*	−0.129*	−0.121**	−0.180***	−0.158***
	(−0.19, −0.01)	(−0.23, −0.03)	(−0.19, −0.05)	(−0.27, −0.09)	(−0.25, −0.07)

Effect size in units of outcome SD per doubling of the predictor (glucose or insulin), adjusted for the other primary predictor, age, sex, race/ethnicity, menopause transition stage in women, and study site; 95% confidence intervals are shown within parentheses.

BMD = bone mineral density; BMI = body mass index.

*$p < 0.05$;

**$p < 0.01$;

***$p < 0.001$.

range that includes both men and women. Our findings are also consistent with those from smaller studies in adolescents,[42] young adults,[33] bone marrow transplant patients,[32] and diabetics[31] that have found associations between greater insulin resistance and lower BMD. These findings and ours help explain, at least partly, the increased fracture risk observed in T2DM.[6–9,43]

These findings are in contradistinction to several previous studies that have documented higher BMD in T2DM[44–46] despite the increased risk of fractures in T2DM.[6,8,10,12,43,47,48] Our study however, suggests that hyperinsulinemia itself may in fact, be associated with lower bone strength, because fasting insulin levels (and not fasting glucose levels) were associated negatively with both BMD and composite indices of strength relative to load in the femoral neck. A deleterious role for insulin on bone is also consistent with experiments in mouse models that suggest that osteoblasts are insulin target cells[49] and that insulin signaling in osteoblasts favors bone resorption. Mice deficient in osteoblast-specific insulin receptors have reduced expression of genes implicated in bone resorption (*CathepsinK* and *Tcirg1*), less acidification of bone extracellular matrix, significantly smaller resorption pits, and markedly lower serum levels of bone resorption marker, cross-linked C-telopeptide (CTX).[50] Further, it was recently noted that in Wistar rats with an obese, insulin-resistant condition induced by a 12-week high-fat diet, there was significant impairment of osteoblastic insulin signaling and osteoblast proliferation, with increased osteoblastic apoptosis culminating in osteoporosis in the jaw bone, compared to baseline, measured using micro–computed tomography (μCT) of mandibular bone.[51]

This study also adds to the accumulating evidence that it is not enough to look at BMD in isolation when assessing bone's ability to resist fracture. The importance of bone size and body size to fracture risk has been established.[47,52–56] The composite indices of femoral neck strength relative to load combine BMD with both bone size and body load and improve fracture prediction ability in both women[25,27] and men.[26] Previous studies have also noted the lower spine bone volume in T2DM subjects.[57] A recent study found that bone cross-sectional area is also lower in T2DM,[58] suggesting a deficit in periosteal apposition which is normally stimulated by skeletal loading. Other studies have found that although BMD may be higher in T2DM, bone strength relative to load is not any higher.[24,59] Taken together, these studies suggest that increased insulin resistance and/or hyperinsulinemia may interfere with the usual anabolic response in bone to skeletal loading, so that bone strength relative to load is negatively affected.

Our study has some important limitations. Foremost, it is a cross-sectional study; thus causal inferences cannot be conclusively drawn. We cannot for instance, infer that insulin resistance leads to low bone strength. An alternate explanation for our findings might be that increased bone mass leads to greater insulin sensitivity, because osteoblasts and osteocalcin appear to have a role in pancreatic function and glucose metabolism.[33,60–62] Further longitudinal studies of the temporal relationships between changes in insulin resistance and changes in bone strength are needed. Next, the composite indices of femoral neck strength are based on macroscopic measurements from DXA scans, and ignore changes in microarchitecture and quality of mineralization, both of which are thought to be adversely affected by T2DM.[63,64] Finally, previous studies have validated femoral neck strength indices measured from Hologic machine scans; this is the first time Lunar machine–based measurements of the strength indices have been examined in a research study.

Despite these limitations, our study confirms the negative association between insulin resistance and femoral neck strength that was first noted in the Study of Women and the Menopausal Transition (SWAN) cohort of women by Ishii and colleagues.[24] It suggests that obesity and hyperinsulinemia may not be bone-protective, and adds to the growing body of evidence which points to the importance of measuring bone strength relative to load, in assessing and understanding fracture risk. Further research is needed to uncover the biological mechanisms by which insulin resistance could deleteriously affect bone health.

Disclosures

All authors state that they have no conflicts of interest.

Acknowledgments

This research was supported by National Institutes of Health grant number 1R01AG033067. The MIDUS I study (Midlife in the U.S.) was supported by the John D. and Catherine T. MacArthur Foundation Research Network on Successful Midlife Development. The MIDUS II research was supported by a grant from the National Institute on Aging (P01-AG020166) to conduct a longitudinal follow-up of the MIDUS I investigation. The research was further supported by the following grants M01-RR023942 (Georgetown), M01-RR000865 (UCLA) from the General Clinical Research Centers Program and 1UL1RR025011 (UW) from the Clinical and Translational Science Award (CTSA) program of the National Center for Research Resources, National Institutes of Health. The funding sources had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors' roles: Data analysis: DMM. Data interpretation: PS, ASK, and CJC. Drafting manuscript: PS. Revising manuscript content: PS, ASK, CJC, TES, GAG, NB, and DMM. Approving final version of manuscript: PS, ASK, CJC, TES, GAG, NB, and DMM. DMM, PS, and ASK take responsibility for the integrity of the data analysis.

References

1. Becker DJ, Kilgore ML, Morrisey MA. The societal burden of osteoporosis. Curr Rheumatol Rep. 2010;12(3):186–91.
2. Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the United States. JAMA. 2009; 302(14):1573–9.
3. Barcelo A, Gregg EW, Gerzoff RB, et al. Prevalence of diabetes and intermediate hyperglycemia among adults from the first multinational study of noncommunicable diseases in six Central American countries: the Central America Diabetes Initiative (CAMDI). Diabetes Care. 2012;35(4):738–40.
4. Tan DA. Changing disease trends in the Asia-Pacific. Climacteric. 2011;14(5):529–34.
5. van Dieren S, Beulens JW, van der Schouw YT, Grobbee DE, Neal B. The global burden of diabetes and its complications: an emerging pandemic. Eur J Cardiovasc Prev Rehabil. 2010;17Suppl 1:S3–8.
6. Bonds DE, Larson JC, Schwartz AV, et al. Risk of fracture in women with type 2 diabetes: the Women's Health Initiative Observational Study. J Clin Endocrinol Metab. 2006;91(9):3404–10.
7. Strotmeyer ES, Cauley JA. Diabetes mellitus, bone mineral density, and fracture risk. Curr Opin Endocrinol Diabetes Obes. 2007;14(6): 429–35.
8. Strotmeyer ES, Cauley JA, Schwartz AV, et al. Nontraumatic fracture risk with diabetes mellitus and impaired fasting glucose in older white and black adults: the health, aging, and body composition study. Arch Intern Med. 2005;165(14):1612–7.
9. 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):427–44.
10. de Liefde II, van der Klift M, de Laet CE, van Daele PL, Hofman A, Pols HA. Bone mineral density and fracture risk in type-2 diabetes mellitus: the Rotterdam Study. Osteoporos Int. 2005;16(12):1713–20.
11. 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):1367–76.
12. Schwartz AV, Vittinghoff E, Bauer DC, et al. Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes. JAMA. 2011;305(21):2184–92.
13. Robinovitch SN, Hayes WC, McMahon TA. Prediction of femoral impact forces in falls on the hip. J Biomech Eng. 1991;113(4):366–74.
14. Beck TJ, Petit MA, Wu G, LeBoff MS, Cauley JA, Chen Z. Does obesity really make the femur stronger? BMD, geometry, and fracture incidence in the women's health initiative-observational study. J Bone Miner Res. 2009;24(8):1369–79.
15. Compston JE, Watts NB, Chapurlat R, et al. Obesity is not protective against fracture in postmenopausal women: GLOW. Am J Med. 2011;124(11):1043–50.
16. Goulding A, Grant AM, Williams SM. Bone and body composition of children and adolescents with repeated forearm fractures. J Bone Miner Res. 2005;20(12):2090–6.
17. Nielson CM, Marshall LM, Adams AL, et al. BMI and fracture risk in older men: the osteoporotic fractures in men study (MrOS). J Bone Miner Res. 2011;26(3):496–502.
18. Premaor MO, Pilbrow L, Tonkin C, Parker RA, Compston J. Obesity and fractures in postmenopausal women. J Bone Miner Res. 2010;25(2):292–7.
19. von Muhlen D, Safii S, Jassal SK, Svartberg J, Barrett-Connor E. Associations between the metabolic syndrome and bone health in older men and women: the Rancho Bernardo Study. Osteoporos Int. 2007;18(10):1337–44.
20. Bonewald LF, Johnson ML. Osteocytes, mechanosensing and Wnt signaling. Bone. 2008;42(4):606–15.
21. Ehrlich PJ, Lanyon LE. Mechanical strain and bone cell function: a review. Osteoporos Int. 2002;13(9):688–700.
22. de Paula FJ, Horowitz MC, Rosen CJ. Novel insights into the relationship between diabetes and osteoporosis. Diabetes Metab Res Rev. 2010;26(8):622–30.
23. Yaturu S. Diabetes and skeletal health. J Diabetes. 2009;1(4):246–54.
24. 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):190–7.
25. Karlamangla AS, Barrett-Connor E, Young J, Greendale GA. Hip fracture risk assessment using composite indices of femoral neck strength: the Rancho Bernardo study. Osteoporos Int. 2004;15(1): 62–70.
26. Yu N, Liu YJ, Pei Y, et al. Evaluation of compressive strength index of the femoral neck in Caucasians and Chinese. Calcif Tissue Int. 2010; 87(4):324–32.
27. Ishii S, Greendale GA, Cauley JA, et al. Fracture risk assessment without race/ethnicity information. J Clin Endocrinol Metab. 2012; 97(10):3593–602.
28. Hwang YC, Jeong IK, Ahn KJ, Chung HY. The uncarboxylated form of osteocalcin is associated with improved glucose tolerance and enhanced beta-cell function in middle-aged male subjects. Diabetes Metab Res Rev. 2009;25(8):768–72.
29. Weiler HA, Lowe J, Krahn J, Leslie WD. Osteocalcin and vitamin D status are inversely associated with homeostatic model assessment of insulin resistance in Canadian Aboriginal and white women: the First Nations Bone Health Study. J Nutr Biochem. 2013 Feb;24(2): 412–8.
30. Oh KW, Rhee EJ, Lee WY, et al. The relationship between circulating osteoprotegerin levels and bone mineral metabolism in healthy women. Clin Endocrinol (Oxf). 2004;61(2):244–9.
31. Arikan S, Tuzcu A, Bahceci M, Ozmen S, Gokalp D. Insulin resistance in type 2 diabetes mellitus may be related to bone mineral density. J Clin Densitom. 2012;15(2):186–90.
32. Faulhaber GA, Premaor MO, Moser Filho HL, Silla LM, Furlanetto TW. Low bone mineral density is associated with insulin resistance in bone marrow transplant subjects. Bone Marrow Transplant. 2009; 43(12):953–7.
33. Lucey AJ, Paschos GK, Thorsdottir I, Martinez JA, Cashman KD, Kiely M. Young overweight and obese women with lower circulating osteocalcin concentrations exhibit higher insulin resistance and concentrations of C-reactive protein. Nutr Res. 2013;33(1):67–75.
34. Brim OG, Ryff CD, Kessler RC. The MIDUS national survey: an overview. In: Brim OG, Ryff CD, Kessler RC, editors. How healthy are we? A national study of well-being at midlife. Chicago, IL: The University of Chicago Press; 2004. p.1–36. Available from: http://www.midus.wisc.edu/findings/pdfs/3.pdf.

35. Dienberg Love G, Seeman TE, Weinstein M, Ryff CD. Bioindicators in the MIDUS national study: protocol, measures, sample, and comparative context. J Aging Health. 2010;22(8):1059–80.
36. Radler BT, Ryff CD. Who participates? Accounting for longitudinal retention in the MIDUS national study of health and well-being. J Aging Health. 2010;22(3):307–31.
37. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care. 2004;27(6):1487–95.
38. Crandall CJ, Merkin SS, Seeman TE, Greendale GA, Binkley N, Karlamangla AS. Socioeconomic status over the life-course and adult bone mineral density: the Midlife in the U.S. Study. Bone. 2012; 51(1):107–13.
39. Finkelstein JS, Brockwell SE, Mehta V, et al. Bone mineral density changes during the menopause transition in a multiethnic cohort of women. J Clin Endocrinol Metab. 2008;93(3):861–8.
40. Riggs BL, Wahner HW, Dunn WL, Mazess RB, Offord KP, Melton LJ 3rd. Differential changes in bone mineral density of the appendicular and axial skeleton with aging: relationship to spinal osteoporosis. J Clin Invest. 1981;67(2):328–35.
41. Treloar AE. Menstrual cyclicity and the pre-menopause. Maturitas. 1981;3(3–4):249–64.
42. do Prado WL, de Piano A, Lazaretti-Castro M, et al. Relationship between bone mineral density, leptin and insulin concentration in Brazilian obese adolescents. J Bone Miner Metab. 2009;27(5):613–9.
43. Dobnig H, Piswanger-Solkner JC, Roth M, et al. Type 2 diabetes mellitus in nursing home patients: effects on bone turnover, bone mass, and fracture risk. J Clin Endocrinol Metab. 2006;91(9):3355–63.
44. Haffner SM, Bauer RL. The association of obesity and glucose and insulin concentrations with bone density in premenopausal and postmenopausal women. Metabolism. 1993;42(6):735–8.
45. Smythe HA. Osteoarthritis, insulin and bone density. J Rheumatol. 1987;14 Spec No: 91–3.
46. Meema HE, Meema S. The relationship of diabetes mellitus and body weight to osteoporosis in elderly females. Can Med Assoc J. 1967; 96(3):132–9.
47. Rivadeneira F, Zillikens MC, De Laet CE, et al. Femoral neck BMD is a strong predictor of hip fracture susceptibility in elderly men and women because it detects cortical bone instability: the Rotterdam Study. J Bone Miner Res. 2007;22(11):1781–90.
48. Khazai NB, Beck GR Jr, Umpierrez GE. Diabetes and fractures: an overshadowed association. Curr Opin Endocrinol Diabetes Obes. 2009;16(6):435–45.
49. Fulzele K, Riddle RC, DiGirolamo DJ, et al. Insulin receptor signaling in osteoblasts regulates postnatal bone acquisition and body composition. Cell. 2010;142(2):309–19.
50. Ferron M, Wei J, Yoshizawa T, et al. Insulin signaling in osteoblasts integrates bone remodeling and energy metabolism. Cell. 2010; 142(2):296–308.
51. Pramojanee SN, Phimphilai M, Kumphune S, Chattipakorn N, Chattipakorn SC. Decreased jaw bone density and osteoblastic insulin signaling in a model of obesity. J Dent Res. 2013;92(6):560–5.
52. Alonso CG, Curiel MD, Carranza FH, Cano RP, Perez AD. Femoral bone mineral density, neck-shaft angle and mean femoral neck width as predictors of hip fracture in men and women. Multicenter Project for Research in Osteoporosis. Osteoporos Int. 2000;11(8):714–20.
53. Faulkner KG, Wacker WK, Barden HS, et al. Femur strength index predicts hip fracture independent of bone density and hip axis length. Osteoporos Int. 2006;17(4):593–9.
54. Orwoll ES, Marshall LM, Nielson CM, et al. Finite element analysis of the proximal femur and hip fracture risk in older men. J Bone Miner Res. 2009;24(3):475–83.
55. Leslie WD, Pahlavan PS, Tsang JF, Lix LM. Prediction of hip and other osteoporotic fractures from hip geometry in a large clinical cohort. Osteoporos Int. 2009;20(10):1767–74.
56. Allolio B. Risk factors for hip fracture not related to bone mass and their therapeutic implications. Osteoporos Int. 1999;9Suppl 2: S9–16.
57. Strotmeyer ES, Cauley JA, Schwartz AV, et al. Diabetes is associated independently of body composition with BMD and bone volume in older white and black men and women: The Health, Aging, and Body Composition Study. J Bone Miner Res. 2004;19(7):1084–91.
58. Petit MA, Paudel ML, Taylor BC, et al. Bone mass and strength in older men with type 2 diabetes: the Osteoporotic Fractures in Men Study. J Bone Miner Res. 2010;25(2):285–91.
59. Melton LJ III, Riggs BL, Leibson CL, et al. A bone structural basis for fracture risk in diabetes. J Clin Endocrinol Metab. 2008;93:4804–9.
60. Amelio PD, Panico A, Spertino E, Isaia GC. Energy metabolism and the skeleton: reciprocal interplay. World J Orthop. 2012;3(11):190–8.
61. Schwetz V, Pieber T, Obermayer-Pietsch B. The endocrine role of the skeleton: background and clinical evidence. Eur J Endocrinol. 2012;166(6):959–67.
62. Lee NK, Sowa H, Hinoi E, et al. Endocrine regulation of energy metabolism by the skeleton. Cell. 2007;130(3):456–69.
63. Burghardt AJ, Issever AS, Schwartz AV, et al. High-resolution peripheral quantitative computed tomographic imaging of cortical and trabecular bone microarchitecture in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab. 2010;95(11):5045–55.
64. Saito M, Marumo K. Collagen cross-links as a determinant of bone quality: a possible explanation for bone fragility in aging, osteoporosis, and diabetes mellitus. Osteoporos Int. 2010;21(2):195–214.