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

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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,18,9,22,23 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 women25 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 colleagues24 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
inverse associations between insulin resistance and markers of bone formation, such as osteocalcin\textsuperscript{[28,29]} and osteoprotegerin\textsuperscript{[30]} and even BMD in some subpopulations\textsuperscript{[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\textsuperscript{[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.\textsuperscript{[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),\textsuperscript{[35]} and the complete MIDUS II sample was similar to the MIDUS I sample.\textsuperscript{[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.\textsuperscript{[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 Cobas Integra Analyzer (Boehringer, 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.\textsuperscript{[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, anastrozole, calcitriol, 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 (glinipiride, glipizide, Metformin, glyburide, Nateglinide, Pioglitazone, Pramlintide, Repaglinide, Rosiglitazone, or Sitagliptin) or insulin analogues (Humalog, Novolog, 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.\textsuperscript{[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\textsuperscript{[37]}:

\[
\text{HOMA-IR} = \frac{\text{fasting glucose (in mg/dL)}}{\text{fasting insulin (in μU/mL)}} \times 0.00247
\]  

Participants were said to have diabetes if they met any of the following four criteria: (1) HbA1c > 6.5%; (2) fasting glucose ≥ 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) HbA1c ≥ 5.7% < 6.5%; (2) fasting glucose < 126 mg/dL < 100 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 < 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 (L2–L4) 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/cm²).\(^4\)

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\(^2\):

\[
\begin{align*}
\text{Compression strength index} \,(\text{CSI}) & = \frac{(\text{BMD} \times \text{FNW})}{\text{Weight}} \\
\text{Bending strength index} \,(\text{BSI}) & = \frac{(\text{BMD} \times \text{FNW}^2)}{\text{FNAL} \times \text{Weight}} \\
\text{Impact strength index} \,(\text{ISI}) & = \frac{(\text{BMD} \times \text{FNW} \times \text{FNAL})}{\text{Height} \times \text{Weight}}
\end{align*}
\]

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.\(^3\)

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.\(^4\) 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.\(^4\)

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.\(^2\) 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, ≥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
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) %.

Aicipitated 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 1. Descriptive Statistics for the Analytic Sample and the Complete MIDUS II Biomarker Project Sample |
|---------------------------------------------------------------|---------------------------------------------------------------|
| Analytic sample (n = 717)                                      | MIDUS biomarker sample (n = 1255)*                             |
| 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, 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/m²)                                       | 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 (log₂ transformed)                                    | 1.36 (1.11)                                                   | 1.34 (1.13)                                            |
| Fasting glucose (mg/dL, log₂ transformed)                     | 6.65 (0.284)                                                  | 6.64 (0.281)                                           |
| Fasting insulin (μIU/mL, log₂ 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/cm²)                                         | 0.84 (0.137)                                                  | –                                                      |
| Lumbar spine (g/cm²)                                         | 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.

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

<table>
<thead>
<tr>
<th>Bone strength measure</th>
<th>Effect size per doubling of HOMA-IR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>95% confidence interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral neck BMD</td>
<td>+0.115</td>
<td>(0.047, 0.182)</td>
<td>0.001</td>
</tr>
<tr>
<td>Lumbar spine BMD</td>
<td>+0.010</td>
<td>(−0.058, 0.078)</td>
<td>0.777</td>
</tr>
<tr>
<td>Compression strength index</td>
<td>−0.342</td>
<td>(−0.405, −0.279)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bending strength index</td>
<td>−0.358</td>
<td>(−0.431, −0.284)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Impact strength index</td>
<td>−0.395</td>
<td>(−0.471, −0.319)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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, and study site.
HOMA-IR = Homeostasis Model of Assessment–Insulin Resistance; BMD = bone mineral density; BMI = body mass index.
<sup>a</sup>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<sup>24</sup> 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

<table>
<thead>
<tr>
<th>Bone strength measure</th>
<th>Prediabetes effect size (95% CI)</th>
<th>Diabetes effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral neck BMD</td>
<td>+0.114 (−0.036, +0.264)</td>
<td>+0.125 (−0.088, +0.338)</td>
</tr>
<tr>
<td>Lumbar spine BMD</td>
<td>+0.126 (−0.028, +0.280)</td>
<td>+0.022 (−0.193, +0.238)</td>
</tr>
<tr>
<td>Compression strength index</td>
<td>−0.085 (−0.232, +0.061)</td>
<td>−0.488 (−0.689, −0.288)&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bending strength index</td>
<td>−0.094 (−0.269, +0.081)</td>
<td>−0.453 (−0.680, −0.227)&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td>Impact strength index</td>
<td>−0.145 (−0.307, +0.017)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>−0.544 (−0.765, −0.323)&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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, 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.
<sup>*</sup>p < 0.10;
<sup>**</sup>p < 0.001.
range that includes both men and women. Our findings are also consistent with those from smaller studies in adolescents, young adults, bone marrow transplant patients, and diabetics 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.

These findings are in contradistinction to several previous studies that have documented higher BMD in T2DM despite the increased risk of fractures in T2DM. Our study however, suggests that hyperinsulinemia itself may in fact, be associated with lower bone mass, because fasting insulin levels (and not fasting glucose levels) were associated negatively with both BMD and composite indices of strength relative to load. Other studies have found that although BMD may be higher in T2DM, bone strength relative to load is not any higher. 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. 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. 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. It suggests that obesity and hyperinsulinemia may 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.
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