Knee Osteoarthritis in Obese Women With Cardiometabolic Clustering

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Objective. To assess the role of obesity and metabolic dysfunctionality with knee osteoarthritis (OA), knee joint pain, and physical functioning performance, adjusted for joint space width (JSW) asymmetry.

Methods. Knee OA was defined as a Kellgren/Lawrence score ≥2 on weight-bearing radiographs. Obesity was defined as a body mass index ≥30 kg/m². Cardiometabolic clustering classification was based on having ≥2 of the following factors: low levels of high-density lipoprotein cholesterol; elevated levels of low-density lipoprotein cholesterol, triglycerides, blood pressure, C-reactive protein, waist:hip ratio, or glucose; or diabetes mellitus. The difference between lateral and medial knee JSW was used to determine joint space asymmetry.

Results. In a sample of women (n = 482, mean age 47 years), prevalences of knee OA and persistent knee pain were 11% and 30%, respectively. The knee OA prevalence in nonobese women without cardiometabolic clustering was 4.7%, compared with 12.8% in obese women without cardiometabolic clustering and 23.2% in obese women with cardiometabolic clustering. Nonobese women without cardiometabolic clustering were less likely to perceive themselves as limited compared with women in all other obesity/cardiometabolic groups (P < 0.05). Similar associations were seen with knee pain and physical functioning measures. The inclusion of a joint space asymmetry measure was associated with knee OA but not with knee pain or physical functioning.

Conclusion. Knee OA was twice as frequent in obese women with cardiometabolic clustering compared with those without, even when considering age and joint asymmetry. Obesity/cardiometabolic clustering was also associated with persistent knee pain and impaired physical functioning.

INTRODUCTION

Osteoarthritis (OA), based on radiographs, is a highly prevalent joint disease affecting 30–50% of adults age ≥65 years (1,2). Age, female sex, obesity, and previous injury are consistently reported risk factors for OA (3). Obesity is the most conspicuous risk factor (4–7) and of great interest because it is potentially modifiable. Further, there is concern that with the increasing frequency of obesity, including the escalating frequency of morbid obesity worldwide, there will be an arthritis epidemic.

There is debate about how obesity contributes to the initiation and progression of OA; resolution of this debate could inform the selection of viable interventions. Candidate mechanisms for the contribution of obesity to joint health status include 1) an excessive and/or misdirected biomechanic load that stimulates excess osteoblast or chondrocyte biosynthesis in the bone or cartilage (8); 2) a generalized negative metabolic environment reflecting a systemic inflammatory response (9–13) or response to the secretory products of adipose tissues; or 3) both biomechanic and metabolic effects.

Hart and Spector (4) hypothesized that the association between obesity and OA in non–weight-bearing joints includes a metabolic mechanism, but the data associating OA with obesity-related metabolic factors are mixed. Some studies have reported significant associations between knee OA or hand/wrist OA and cardiovascular risk factors (uric acid and cholesterol levels and hypertension) (10,11), but other knee OA studies have failed to identify significant relationships (12,13). Although some studies have related higher concentrations of C-reactive protein to both greater prevalence and incidence of knee OA (9,14,15), not all studies have reported this (16,17).

The patterns (10,11,16,18) of association between meta-
Obesity factors and OA have led some to declare that the primary contribution of obesity to OA may be joint specific and dependent upon the degree to which obesity contributes to the mechanical loading of articular cartilage at a specific site (19–21). For example, varus knee alignment is thought to place mechanical loads, including those loads generated by excess body mass, mostly on the medial tibiofemoral compartment (22). The impact of excess body mass at this site could generate both mechanical and metabolic contributions, whereas the impact of excess body mass on hand OA may be more reflective of the metabolic contribution.

We hypothesized that obesity was associated with both a metabolic component and with joint asymmetry in relation to radiographic-defined knee OA. We also hypothesized that these metabolic and biomechanic components would be associated with knee joint pain and measures of physical functioning.

**SUBJECTS AND METHODS**

**Study population.** The Michigan Bone Health and Metabolism Study (MBHMS) is a longitudinal, population-based study conducted among women living in and around Tecumseh, Michigan. MBHMS enrollees were the daughters of the Tecumseh Community Health Study participants who, in 1988, were between the ages of 20 and 40 years, not pregnant, and premenopausal. These women were contacted using letters, telephone calls, and in-person visits, and >80% agreed to participate. In 1992, a second sampling frame based on a community census of Tecumseh was developed to include women whose parents had not participated in the Tecumseh Community Health Study. As a result, an additional 121 women in the desired age range of 24–44 years (of a possible 135 eligible) were recruited (90% participation rate). The total MBHMS cohort consists of 664 participants who ages 24–44 years in 1992. All of the women in the MBHMS cohort are white.

Although MBHMS participants have been followed annually since 1992, this report is based on data that were collected at MBHMS followup visit 11 (in 2002/2003). Included in this report is followup visit 11 data from 482 MBHMS women with readable knee radiographs (to characterize OA status), physical measures assessment and a blood/urine sample for assay of cardiometabolites (to characterize cardiometabolic obesity group), and performance-based and self-reported physical functioning information.

The University of Michigan Institutional Review Board approved the study protocol, and written informed consent was obtained from each participant.

**OA measures.** Knee radiographs were taken using semiflexed positioning (23) with General Electric radiographic equipment (model X-GE MPX-80; General Electric Medical Systems, Milwaukee, WI) and Kodak film (X-DA with Kodak rare earth-intensifying screens; Eastman Kodak, Rochester, NY). The distance was 40 inches and standard radiographic techniques were used. Radiographs were evaluated by 2 readers, with a third consensus reader for the presence of OA defined by the Kellgren/Lawrence (K/L) scale depicted in the Atlas of Standard Radiographs of Arthritis (where 0 = normal, 1 = doubtful OA, 2 = minimal OA, 3 = moderate OA, and 4 = severe OA) (24). This scale is based on the degree of osteophyte formation, joint space narrowing, sclerosis, and joint deformity. OA was defined as the presence of ≥1 knee with a grade of ≥2. Only the K/L criteria, joints were classified as uninterpretable, missing, or showing changes consistent with rheumatoid arthritis.

As a part of the quality assurance program, readers reviewed the K/L grading criteria and evaluated films that were representative of each K/L level. Then 25 knee radiographs were evaluated independently by each reader and their results were compared for consistency. After completing standardization procedures, readers independently evaluated radiographs of both knees. The scores from the 2 readers were compared and any discordant scores were reread and, if necessary, subjected to consensus evaluation. Further, a sample of 110 knee radiographs selected for use in evaluations were interleaved with newly acquired films to be reread to identify potential drift in scoring over time.

Joint space width (JSW) was measured on the medial and lateral aspects of each knee radiograph with electronic calipers. Measurement locations were ascertained by identifying the centerline of each joint using the medial and lateral tibial condyle margins and then establishing points that were 50% and 75% between the centerline and the condylar margin. Two readers measured the JSW independently, and if the difference between the 2 readers was >0.4 mm, the JSW was remeasured by the 2 readers. The absolute difference between the medial and lateral JSW at the 75% location was used as a proxy of joint asymmetry. Long films were not available to estimate the degree of varus at the knee.

**Pain and physical functioning measures.** Pain and physical functioning questionnaires are completed by MBHMS participants. The pain questions ask if there has been persistent knee joint pain during the antecedent 3 years and, if so, the participant is asked if there has been pain at least half the time in the previous month.

The Medical Outcomes Study Short Form 36 (SF-36) health survey 10-item physical function scale was used to describe women’s perception of their physical functioning limitations. This is a widely used questionnaire that has been extensively evaluated for construct validity, internal consistency, and test–retest reliability (25–28) in diverse ethnic groups and age ranges. The SF-36 includes a 3-item response (limited a lot, limited a little, or not limited at all) to the following items: vigorous activities; moderate activities; lifting or carrying groceries; climbing several flights of stairs; climbing 1 flight of stairs; bending, kneeling, or stooping; walking >1 mile; walking several blocks; walking 1 block; or requiring assistance in bathing or dressing. The SF-36 is scored using norm-based methods and transformed to have a mean ± SD of 50 ± 10 and a range of 1–100 in the general US population, with a score of 100 indicating the best physical functioning. Scores were cat-
egorized into 3 groups as follows: ≤50 points was classified as having substantial limitations, 51–85 points was classified as having moderate limitations, and 86–100 points was classified as not limited. Women categorized as having substantial limitations (≤50 points) could have reported no limitations on, at most, 5 of the 10 activities. Those classified as having moderate limitations (51–85 points) could have reported no limitations on, at most, 8 of 10 activities, thus allowing for some limitations in vigorous and moderate activities.

Velocity assessment and timed 40-foot walk. Gait and walking ability were assessed with a timed 40-foot walk, measured in seconds, that included passage over an instrumented gait mat. The gait mat provided data to characterize velocity. The participants could walk with assistive devices.

Sit-to-rise. Chair-rise performance was measured when participants rose from a standard height, armless chair. Participants were asked to fold their arms over their chest and to rise as quickly as possible. Movement time was measured by stopwatch from the onset of trunk motion on the chair to the achievement of an upright standing position. If a participant was unable to rise from the chair or sat back down before achieving a full upright stance, the rise was so noted. Results from 5 separate repetitions were averaged.

Grip and leg strength. To measure grip strength, participants were seated in a chair with their lower arm placed at a right angle to the body’s sagittal plane with the elbow in 90° of flexion. The hands were placed so that the fingers and thumb were parallel to the legs and the wrist was slightly extended to hold the dynamometer. Each participant performed 3 consecutive grip strength trials with both the dominant and nondominant hands, squeezing the dynamometer with maximum effort. Results from the 3 trials were averaged, and the participant’s average dominant grip strength was used for analysis.

A portable instrumented chair was used to measure lower leg isometric strength, measured as torque or the product of force and the torque arm length. Torque arm length is equal to the length measured between the lateral joint line of the knee and the bottom surface of the heel plus 0.0251 meters, which is the distance from the top surface of the foot trolley platform to the transducer axis. Participants were encouraged to produce maximum effort. Results from 3 trials were averaged, and the participant’s average dominant grip strength was used for analysis.

Two-pound lift. Participants were timed as they lifted a 2-pound box from the floor to waist height. The box was placed at a standard distance (8 inches) forward of the toes. Participants could either bend at the knee or waist and the modality was recorded. Inability to lift the box successfully to waist height was flagged.

Timed stair climb. Each participant was asked to climb up and down a set of 3 standard stairs 3 times, beginning with the right leg. The amount of time that each participant required to ascend the stairs, turn, and descend the stairs 3 consecutive times was measured for total movement time (29). In addition, inability to complete the stair climb (i.e., unable because of their use of a wheelchair) and the amount and type of assistance needed (e.g., handrails or a personal assistant) was recorded.

Functional reach. In the standing posture, participants were asked to do an arm’s length forward reach, and then to reach as far as possible without moving their feet. Participants held a marking pen in their hand while doing the arm’s length and forward reach, and placed a mark on a sheet of paper with each reach. The distance between the 2 marks was measured to determine the forward reach distance.

Cardiometabolic and body composition measures. Glucose was measured using a hexokinase-coupled reaction (Boehringer Mannheim Diagnostics, Indianapolis, IN). Total cholesterol and triglycerides levels were analyzed by enzymatic methods; high-density lipoprotein (HDL) cholesterol level was isolated using heparin-2M manganese chloride (30) and low-density lipoprotein (LDL) cholesterol level calculated using the Friedewald equation (31). High-sensitivity C-reactive protein level was measured using ultrasensitive rate immunonephelometry (Dade-Behring, Marburg, Germany). Two blood pressure measurements were taken using a mercury column manometer after a minimum of 5 minutes of rest with participants in the seated position, and the average of the 2 values was used. Weight and height, measured with a calibrated balance beam scale and stadiometer, were used to calculate body mass index (BMI; weight [kg]/height [m²]). Waist circumference (in cm) was measured with a nonstretching tape at the narrowest point of the midtorso at maximum inhalation. Hip circumference was measured at a point ~9 inches below the waist.

Women were classified into 1 of 4 cardiometabolic/obesity subgroups based on their obesity status (nonobese: BMI <30 kg/m², or obese: BMI ≥30 kg/m²) and the presence or absence of ≥2 cardiometabolic defects, as described in Table 1. Among those classified as having cardiometabolic defects, obese women had greater numbers of cardiometabolic defects, on average, as compared with nonobese women.

Statistical analyses. Univariate distributions of the continuous measures of body size, metabolic products, JSW, joint space difference, and physical functioning measures were examined for normality. To meet the assumptions of normality and to reduce skewness, natural log transformation was applied as necessary. The frequencies of the K/L score for OA of the knee and categorical covariates, including measures of pain and perception of physical functioning, were examined.

Knee K/L scores, pain, and measures of physical functioning were the outcome measures, and variables representing obesity/cardiometabolic status and the difference between the medial and lateral joint space were the explanatory variables. P values for comparisons between obesity/cardiometabolic groups or knee OA groups were based on the nonparametric Wilcoxon’s signed rank test for continuous variables or chi-square tests for categorical variables. Analysis of variance and analysis of covariance were used to determine the least squared means and SEs of
groups defined by the combinations of the presence or absence of knee OA/cardiovascular metabolic group or physical functioning/cardiovascular metabolic group. Regression analyses were used to evaluate the association of the difference in JSW in models that also included variables for obesity/cardiovascular metabolic status and age. P-values (2-sided tests) and 95% confidence intervals (95% CIs) were used to identify the likelihood of a true association.

RESULTS

The 2002 prevalence of radiographic-defined knee OA in the MBHMS population was 11% and the prevalence of having persistent knee pain during the previous 3 years was 30%. Women with knee OA were 3 years older, 32% heavier, and had more compromised metabolic measures than women without knee OA, with the exception of LDL cholesterol, for which there was no difference (Table 2). The 2 nonobese groups with and without cardiovascular metabolic defects had significantly different median (interquartile range [IQR]) BMI values (26.81 [3.72] kg/m² and 23.76 [4.66] kg/m², respectively; P < 0.0001), but there were no differences in the median (IQR) BMI values between the 2 obese groups with (34.82 [6.22] kg/m²) and without (32.97 [7.17] kg/m²) cardiovascular metabolic defects (P = 0.06).

Cardiovascular metabolic clustering, obesity, and knee OA. There was a higher knee OA prevalence in obese women with cardiovascular metabolic clustering (23.2%) compared with the referent group of nonobese women without cardiovascular metabolic clustering (4.7%), with an odds ratio (OR) of 6.2 (95% CI 2.93–13.07) (Table 3). Obese women without cardiovascular metabolic clustering had a knee OA prevalence of 12.8%; the OR of their having knee OA was 3.0 (95% CI 1.03–8.71) as compared with the referent group. Nonobese women with cardiovascular metabolic clustering did not have a significantly greater OR of having knee OA than nonobese women without cardiovascular metabolic clustering.

Cardiovascular metabolic clustering, obesity, and pain. Obese women with cardiovascular metabolic clustering reported significantly more persistent knee pain during the previous 3 years (P < 0.05) compared with women in the other 3 cardiovascular obesity groups (Table 4).

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**Table 1.** Measures of cardiovascular metabolic status (participants with ≥2 criteria were classified as having cardiovascular metabolic defect)*

<table>
<thead>
<tr>
<th>Measures</th>
<th>No knee OA (n = 429)</th>
<th>Knee OA (n = 53)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>47.0 (8.0)</td>
<td>50.0 (5.0)</td>
<td>&lt; 0.0001‡</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>70.6 (23.2)</td>
<td>92.9 (24.8)</td>
<td>&lt; 0.0001‡</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.3 (8.4)</td>
<td>35.6 (11.1)</td>
<td>&lt; 0.0001‡</td>
</tr>
<tr>
<td>Waist:hip ratio, cm</td>
<td>0.81 (0.10)</td>
<td>0.86 (0.08)</td>
<td>0.0001‡</td>
</tr>
<tr>
<td>Glucose level, mg/dl</td>
<td>95.0 (13.0)</td>
<td>100.0 (14.0)</td>
<td>0.02‡</td>
</tr>
<tr>
<td>CRP level, mg/liter</td>
<td>0.19 (0.33)</td>
<td>0.33 (0.36)</td>
<td>0.002‡</td>
</tr>
<tr>
<td>Lipids levels, mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>54.0 (18.0)</td>
<td>49.0 (14.0)</td>
<td>0.03‡</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>138.0 (45.0)</td>
<td>132.5 (43.0)</td>
<td>0.27</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>117.0 (79.0)</td>
<td>141.0 (116.0)</td>
<td>0.01‡</td>
</tr>
<tr>
<td>BP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>117.5 (19.0)</td>
<td>126.0 (17.5)</td>
<td>&lt; 0.0001‡</td>
</tr>
<tr>
<td>Diastolic</td>
<td>78.0 (12.0)</td>
<td>80.0 (9.0)</td>
<td>0.0004‡</td>
</tr>
<tr>
<td>JSW, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial</td>
<td>4.27 (1.02)</td>
<td>4.39 (1.27)</td>
<td>0.67</td>
</tr>
<tr>
<td>Lateral</td>
<td>5.55 (1.12)</td>
<td>6.28 (1.61)</td>
<td>&lt; 0.0001‡</td>
</tr>
<tr>
<td>Difference</td>
<td>1.32 (1.11)</td>
<td>2.01 (1.81)</td>
<td>&lt; 0.0001‡</td>
</tr>
</tbody>
</table>

* Values are the median (interquartile range). JSW = joint space width; OA = osteoarthritis; MBHMS = Michigan Bone Health and Metabolism Study; BMI = body mass index; CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; BP = blood pressure.
† For between-group comparison.
‡ Significant (P < 0.05).
The association of grip strength and obesity status varied more quadriceps torque than those who were not obese. Surprisingly, the obese women tended to have significantly greater walk times and less gait velocity than nonobese women, those with cardiometabolic clustering had significantly greater stair climb times and 2-pound lift times than those in any other category (Table 5). Among obese women with cardiometabolic clustering, obesity, and physical functioning score, compared with women in the other 3 categories (versus nonobese without cardiometabolic clustering group as the referent category. There were no differences in the distribution of perception of limitation among women in the other 3 cardiometabolic/obesity groups. Obese women with cardiometabolic clustering had a consistent 10% deficit in physical performance capacity compared with nonobese women without cardiometabolic clustering. Obese women with cardiometabolic clustering had significantly greater stair climb times and 2-pound lift times than those in any other category (Table 5). Among nonobese women, those with cardiometabolic clustering had significantly greater walk times and less gait velocity than those without cardiometabolic clustering. Not surprisingly, the obese women tended to have significantly more quadriceps torque than those who were not obese. The association of grip strength and obesity status varied by cardiometabolic status (Table 6). Women with cardiometabolic clustering (both obese and nonobese groups) had significantly shorter forward reach distances compared with nonobese women without cardiometabolic clustering.

### Cardiometabolic clustering, obesity, and physical functioning.

Nonobese women without cardiometabolic clustering were significantly more likely to perceive themselves as not limited, based on the SF-36 physical functioning score, compared with women in the other 3 categories (versus nonobese with cardiometabolic clustering OR 1.50 – 4.16) compared with the referent group. In models of physical functioning, those who were obese with cardiometabolic clustering consistently had significantly poorer functioning, but there was no association with the JSW difference measure (data not shown).

### DISCUSSION

We identified obesity as being highly associated with radiographic-defined knee OA, knee joint pain, perceived physical functioning, and multiple measures of physical functioning performance. However, although both OA and obesity were highly prevalent in this sample, it is the copresence of cardiometabolic clustering accompanying obesity that exacerbates the association with radiographic-defined knee OA, knee pain, and physical performance measures. The presence of cardiometabolic clustering among obese women is important because we identified that the prevalence of knee OA was almost twice as great in these women compared with obese women without cardiometabolic clustering. Further, there was no significant association of obesity in the pain measures or in many of the physical functioning performance measures unless

### Table 3. At MBHMS visit 11, the ORs (95% CIs) of having knee OA (K/L score ≥2) according to the presence or absence of cardiometabolic clustering within each obesity category

<table>
<thead>
<tr>
<th>Without clustering (n = 212)</th>
<th>With clustering (n = 85)</th>
<th>OR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonobese (BMI &lt;30 kg/m²)</td>
<td>10 (4.7)</td>
<td>Reference group</td>
</tr>
<tr>
<td>Obese (BMI ≥30 kg/m²)</td>
<td>5 (5.9)</td>
<td>1.28 (0.43–3.87)</td>
</tr>
<tr>
<td>Without clustering (n = 47)</td>
<td>6 (12.8)</td>
<td>3.00 (1.03–8.71)‡</td>
</tr>
<tr>
<td>With clustering (n = 138)</td>
<td>32 (23.2)</td>
<td>6.20 (2.93–13.07)§</td>
</tr>
</tbody>
</table>

* OR = odds ratio; 95% CI = 95% confidence interval; K/L = Kellgren/Lawrence. See Table 2 for additional definitions. † From an unadjusted logistic regression model with the nonobese without cardiometabolic clustering group as the referent category. ‡ P < 0.05. § P < 0.0001.

### Table 4. At MBHMS visit 11, the number of women with persistent knee joint pain in the last 3 years and knee pain in the last month, by obesity category and cardiometabolic clustering

<table>
<thead>
<tr>
<th>Knee joint pain</th>
<th>Nonobese (BMI &lt;30 kg/m²)</th>
<th>Obese (BMI ≥30 kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No clustering (n = 212)</td>
<td>Clustering (n = 85)</td>
</tr>
<tr>
<td>Persistent during last 3 years</td>
<td>47 (22.2)†</td>
<td>24 (28.2)†</td>
</tr>
<tr>
<td>If yes, present during half of last month</td>
<td>34 (16.0)</td>
<td>17 (20.0)</td>
</tr>
</tbody>
</table>

* Values are the number (percentage). See Table 2 for definitions. † Value is significantly different than for those who are obese with cardiometabolic clustering (P < 0.05). No other pairwise differences were statistically significant.
obesity was accompanied by cardiometabolic clustering. The presence of the same patterns of association of obesity with cardiometabolic clustering in relation to pain and physical performance suggests that there is internal validity in this association.

It is important to note, however, that being obese is not synonymous with the clustering of cardiometabolic risk factors. Of obese women in this sample, 25% did not have cardiometabolic clustering. Likewise, we have previously reported that approximately one-third of obese men and women of the Third National Health and Nutrition Examination Survey sample, representative of the US population, did not have evidence of cardiometabolic clustering (37).

There is substantial opportunity for obesity to have a physiologic role in the development and subsequent progression of knee OA. Recognition of the potential for this key role has emerged over the past 10 years with the understanding that adipose tissue secretes hormones with receptor-mediated action similar to other endocrine organs. We hypothesize that the observed relationship between cardiometabolic abnormalities and obesity is a reflection of the relationships between products secreted by adipose tissue and cardiovascular disease risk factors. We have published data (38) from a subset of this population in which greater increases in leptin over the menopause transition were associated with greater decreases in HDL cholesterol, and with greater increases in diastolic blood pressure, glucose, insulin, and insulin resistance (all \( P < 0.05 \)). Larger decreases in adiponectin over the menopause transition were associated with greater increases in systolic blood pressure, insulin, and insulin resistance, and with greater decreases in HDL cholesterol.

Leptin, encoded by the obesity gene (39) to reduce food intake and increase energy expenditure (40), thereby indirectly mediating body fat stores (41), was initially thought to be limited to the adipocytes, but it has been shown that osteoblasts and chondrocytes are capable of leptin synthesis and secretion (41,42), and leptin receptors have been found in articular cartilage (43). Leptin concentrations

<table>
<thead>
<tr>
<th>Table 5. At MBHMS visit 11, the participants in SF-36 physical functioning categories by obesity category and cardiometabolic clustering*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36 physical functioning category</td>
</tr>
<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Not limited</td>
</tr>
<tr>
<td>Moderately limited</td>
</tr>
<tr>
<td>Substantially limited</td>
</tr>
</tbody>
</table>

* Values are the percentage. SF-36 = Short Form 36 health survey. See Table 2 for additional definitions.
† Value is significantly different than for those in the other 3 cardiometabolic obesity categories (\( P < 0.05 \)).

<table>
<thead>
<tr>
<th>Table 6. At Michigan Bone Health and Metabolism Study visit 11, mean ± SE values (back-transformed) for performance-based physical functioning by obesity and cardiometabolic status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonobese (body mass index &lt;30 kg/m²)</td>
</tr>
<tr>
<td>--------------------------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Timed stair climb, seconds</td>
</tr>
<tr>
<td>Timed walk, seconds</td>
</tr>
<tr>
<td>Velocity, cm/second</td>
</tr>
<tr>
<td>2-pound lift, seconds</td>
</tr>
<tr>
<td>Quadriceps strength/average torque, Nm</td>
</tr>
<tr>
<td>Grip strength, kg</td>
</tr>
<tr>
<td>Forward reach, cm</td>
</tr>
<tr>
<td>Sit-to-rise time, seconds</td>
</tr>
</tbody>
</table>

* All means are significantly different (\( P < 0.05 \)) than the means for the obese with cardiometabolic clustering, except for grip strength and sit-to-rise time.
† All means are significantly different (\( P < 0.05 \)) than the means for the obese with cardiometabolic clustering, except for forward reach and sit-to-rise time.
‡ All means are significantly different (\( P < 0.05 \)) than the means for the nonobese without cardiometabolic clustering, except for grip strength and sit-to-rise time.
§ Mean is significantly different (\( P < 0.05 \)) than the mean for the obese with cardiometabolic clustering.
¶ Mean is significantly different (\( P < 0.05 \)) than the means for the nonobese and the obese without cardiometabolic clustering.
# Mean is significantly different (\( P < 0.05 \)) than the mean for the nonobese with cardiometabolic clustering.
** Mean is significantly different (\( P < 0.05 \)) than the mean for the nonobese without cardiometabolic clustering.
†† Mean is significantly different (\( P < 0.05 \)) than the mean for the obese without cardiometabolic clustering.
‡‡ Mean is significantly different (\( P < 0.05 \)) than the means for the nonobese with and the nonobese without cardiometabolic clustering.
found in the synovial fluid of people with OA correlated with their BMI. In animal models, leptin stimulated anabolic activity in chondrocytes, including induction of insulin-like growth factor 1 (IGF-1) and transforming growth factor β (TGFβ) synthesis at both the messenger RNA and protein levels. IGF-1 and TGFβ are activated in response to cartilage damage (44–46), and the anabolic activity of chondrocytes serves as a repair mechanism for damaged cartilage.

Levels of adiponectin, an adipokine associated with insulin sensitivity regulation (47,48), are low in obese individuals and in those with cardiovascular disease. Adiponectin is present in the synovial fluid (49,50), cartilage, osteophytes, infrapatellar fat pad, and menisci (51,52) of OA patients, and functional adiponectin receptors have been expressed in chondrocytes (53).

Because of the decreased levels of adiponectin among those with cardiovascular disease, adiponectin has been hypothesized to have antinflammatory effects (47); however, recent work among those with joint diseases suggests that adiponectin may, in fact, have proinflammatory effects and be involved with cartilage matrix degradation (53–55). Lago et al (53) recently demonstrated that adiponectin induced the expression of type 2 nitric oxide synthase and stimulated interleukin-6, matrix metalloproteinase 3 (MMP-3), MMP-9, and monocyte chemotactic protein 1 release.

As has been recently reviewed, the additional loading associated with obesity is almost universally believed to produce aberrant mechanics, raising stress within connective tissue structures, generating malalignment, and resulting in musculoskeletal injury (56). There are numerous mechanical theories as to how obesity can impact movement, but the evidence directly linking musculoskeletal injury to altered biomechanics in the obese is not extensive. It is thought that obesity leads to both increased gravitational and muscle forces across the knee joint, and that once cartilage degradation is present, knee OA progresses more rapidly in the presence of larger-than-normal knee loads during gait (22). Further, Messier et al (57) reported that the peak vertical ground-reaction forces increased in almost direct proportion with body weight in obese adults who were walking. Recent work by Browning and Kram in young adults (58) demonstrated that net muscle moments were significantly greater in obese versus normal-weight subjects and were due to greater ground-reaction forces in the obese group. Obesity greatly increases the biomechanic loads involved in walking, a frequently proposed therapy for obesity, and these loads increase with walking speed.

BMI has been related to knee OA severity in those with varus knees but not in those with valgus knees (59). Although those investigators concluded that much of the effect of BMI on the severity of medial tibiofemoral OA was explained by varus malalignment, the investigators statistically controlled for sex rather than reporting the association stratified by sex. The impact of obesity on the alignment of the tibiofemoral compartment may be different in men versus women because of the inherent sex difference in pelvic alignment.

We found that our proxy measure of tibiofemoral joint asymmetry (the difference between lateral and medial JSW) was significantly associated with having knee OA as a main effect concurrently with cardiometabolic status as a main effect. Interestingly, however, knee joint asymmetry was not associated with pain or physical functioning measures, whereas obesity/cardiometabolic status was associated with more pain and poorer physical functioning. This may have occurred because this joint asymmetry proxy measure was directly associated with radiographic-defined OA, and was only indirectly associated with the pain and functioning measures.

This study had several strengths and limitations. The study included a direct measure of radiographic-defined knee OA along with measures of persistent knee pain and physical performance/functioning. Further, because this population-based sample is limited to women, our findings were not complicated by the increasing evidence of the differences in body composition and cardiometabolic measures between men and women. Therefore, our findings may have a greater impact on women, the group that is at the greatest risk for knee OA. Likewise, the restricted age of our population (<60 years of age) allowed us to minimize the effects of aging, the primary risk factor for knee OA, on the cardiometabolic results. Nevertheless, the impact of cardiometabolic obesity and tibiofemoral joint asymmetry in those >60 years of age is yet to be revealed.

The major limitation of our study is that it did not include long films to assess varus alignment, and so we relied instead upon a proxy joint asymmetry measure, the difference between medial and lateral joint space.

We hypothesized that obesity was associated with both metabolic and biomechanical alignment in relation to radiographic-defined OA of the knee. We also hypothesized that these metabolic and biomechanical components would be associated with knee joint pain and measures of physical functioning. Although obesity was strongly associated with knee OA, the most prominent associations with knee OA, pain, or functioning occurred when obese women also demonstrated clustering of cardiometabolic patterning. This observation has important ramifications for the selection of both behavioral and therapeutic treatments of knee OA.

**AUTHOR CONTRIBUTIONS**

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Sowers had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Sowers, Jacobson, Jiang.

**Acquisition of data.** Sowers, Jacobson, Jiang.

**Analysis and interpretation of data.** Sowers, Karvonen-Gutierrez, Palmieri-Smith, Jacobson, Jiang, Ashton-Miller.

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