SPECIAL ARTICLE: EPIDEMIOLOGY OF THE RHEUMATIC DISEASES

Knee Osteoarthritis in Obese Women With Cardiometabolic Clustering

MARYFRAN SOWERS, CARRIE A. KARVONEN-GUTIERREZ, RIANN PALMIERI-SMITH,
JON A. JACOBSON, YEBIN JIANG, AND JAMES A. ASHTON-MILLER

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-

bolic 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 were 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 semi-flexed 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. Apart from 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 time. 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 for each trial, and the torque (in Nm) for 3 successful trials was averaged.

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 [m^2]). 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/m^2, or obese: BMI ≥30 kg/m^2) 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

<table>
<tr><td colspan="1">

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

</td></tr>
</table>

Measures
Self-reported DM, use of DM medications, or glucose level >126 mg/dl†
CRP level ≥2 mg/liter‡
HDL cholesterol ≤45 mg/dl or LDL cholesterol >160 mg/dl§
Triglycerides ≥200 mg/dl‡
Waist:hip ratio ≥0.81 cm¶
Systolic BP >135 mm Hg, diastolic BP >85 mm Hg, or use of high-BP medications#

* DM = diabetes mellitus; CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; BP = blood pressure.
† Per the American Diabetes Association recommendation (32).
‡ Per the previously used cut point for elevated high-sensitivity CRP level (33,34).
§ Per the Adult Treatment Panel III (ATP-III) recommendations (35) for high/very high LDL cholesterol and high triglycerides. ATP-III recommendations are for HDL cholesterol <40 mg/dl, but given recent evidence of the importance of high HDL cholesterol values, we chose a slightly higher cut point.
¶ Per the World Health Organization clinical risk categories of waist:hip ratio (36).
# Values represent the upper end of the range considered prehypertensive by the American Heart Association.

groups defined by the combinations of the presence or absence of knee OA/cardiometabolic group or physical functioning/cardiometabolic group. Regression analyses were used to evaluate the association of the difference in JSW in models that also included variables for obesity/cardiometabolic 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 cardiometabolic defects had significantly different median (interquartile range [IQR]) BMI values (26.81 [3.72] kg/m^2 and 23.76 [4.66] kg/m^2, 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/m^2) and without (32.97 [7.17] kg/m^2) cardiometabolic defects ($P = 0.06$).

Cardiometabolic clustering, obesity, and knee OA. There was a higher knee OA prevalence in obese women with cardiometabolic clustering (23.2%) compared with the referent group of nonobese women without cardiometabolic clustering (4.7%), with an odds ratio (OR) of 6.2 (95% CI 2.93–13.07) (Table 3). Obese women without cardiometabolic 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 cardiometabolic clustering did not have a significantly greater OR of having knee OA than nonobese women without cardiometabolic clustering.

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

Table 2. Age, cardiometabolic factors, and JSW measurements in women with and without radiographic-defined knee OA from MBHMS visit 11*

	No knee OA (n = 429)	Knee OA (n = 53)	*P*†
Age, years	47.0 (8.0)	50.0 (5.0)	< 0.0001‡
Weight, kg	70.6 (23.2)	92.9 (24.8)	< 0.0001‡
BMI, kg/m^2	27.3 (8.4)	35.6 (11.1)	< 0.0001‡
Waist:hip ratio, cm	0.81 (0.10)	0.86 (0.08)	0.0001‡
Glucose level, mg/dl	95.0 (13.0)	100.0 (14.0)	0.02‡
CRP level, mg/liter	0.19 (0.33)	0.33 (0.36)	0.002‡
Lipids levels, mg/dl			
HDL cholesterol	54.0 (18.0)	49.0 (14.0)	0.03‡
LDL cholesterol	138.0 (45.0)	132.5 (43.0)	0.27
Triglycerides	117.0 (79.0)	141.0 (116.0)	0.01‡
BP, mm Hg			
Systolic	117.5 (19.0)	126.0 (17.5)	< 0.0001‡
Diastolic	78.0 (12.0)	80.0 (9.0)	0.0004‡
JSW, mm			
Medial	4.27 (1.02)	4.39 (1.27)	0.67
Lateral	5.55 (1.12)	6.28 (1.61)	< 0.0001‡
Difference	1.32 (1.11)	2.01 (1.81)	< 0.0001‡

* 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 ($P < 0.05$).

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*

	With knee OA, no. (%)	OR (95% CI)†
Nonobese (BMI <30 kg/m²)		
Without clustering (n = 212)	10 (4.7)	Reference group
With clustering (n = 85)	5 (5.9)	1.28 (0.43–3.87)
Obese (BMI ≥30 kg/m²)		
Without clustering (n = 47)	6 (12.8)	3.00 (1.03–8.71)‡
With clustering (n = 138)	32 (23.2)	6.20 (2.93–13.07)§

* 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.
‡ $P < 0.05$.
§ $P < 0.0001$.

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 $P = 0.004$; versus obese without cardiometabolic clustering $P = 0.03$; versus obese with cardiometabolic clustering $P < 0.0001$). 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.

Competitive modeling of biomechanic and metabolic components. To examine the potential effect of obesity generating biomechanic and metabolic components simultaneously, the statistical models included variables representing obesity/cardiometabolic status and the lateral–medial JSW difference; all models were adjusted for age. Both JSW difference and obesity/cardiometabolic status were associated with knee OA. After adjustment for age, a 1-mm increase in JSW difference was associated with 2.1 times greater odds of having knee OA (95% CI 1.59–2.89), and those who were obese with cardiometabolic clustering had 4.5 times greater odds of having knee OA (95% CI 1.88–11.00) compared with the referent group of nonobese women without cardiometabolic clustering.

Although obesity/cardiometabolic status was associated with persistent knee joint pain, JSW difference was not. Those who were obese with cardiometabolic clustering had 2.5 times greater odds of having persistent knee pain (95% CI 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 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*

	Nonobese (BMI <30 kg/m²)		Obese (BMI ≥30 kg/m²)	
	No clustering (n = 212)	Clustering (n = 85)	No clustering (n = 47)	Clustering (n = 138)
Knee joint pain				
Persistent during last 3 years	47 (22.2)†	24 (28.2)†	12 (25.5)†	60 (43.5)
If yes, present during half of last month	34 (16.0)	17 (20.0)	6 (13.0)	49 (35.5)

* 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.

Table 5. At MBHMS visit 11, the participants in SF-36 physical functioning categories by obesity category and cardiometabolic clustering*

SF-36 physical functioning category	Nonobese (BMI <30 kg/m^2)				Obese (BMI ≥30 kg/m^2)			
	No clustering (n = 212)		Clustering (n = 85)		No clustering (n = 47)		Clustering (n = 138)	
Not limited	171	80.7†	53	62.4	29	61.7	71	51.5
Moderately limited	36	17.0	27	31.8	16	34.0	53	38.4
Substantially limited	5	2.4	5	5.9	2	4.3	14	10.1

* 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 ($P < 0.05$).

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 or-

gans. 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 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

	Nonobese (body mass index <30 kg/m^2)		Obese (body mass index ≥30 kg/m^2)		
	No defects*	Cardiometabolic defects†	No defects	Cardiometabolic defects‡	P overall
Timed stair climb, seconds	15.80 ± 0.21	16.26 ± 0.35	16.36 ± 0.46§	18.10 ± 0.30¶	0.0001
Timed walk, seconds	7.94 ± 0.07#	8.26 ± 0.11**	8.24 ± 0.15	8.58 ± 0.09#	0.0001
Velocity, cm/second	174.03 ± 1.65¶	167.64 ± 2.46**	164.45 ± 3.36**	159.70 ± 1.90#	0.0001
2-pound lift, seconds	1.58 ± 0.03	1.61 ± 0.04	1.58 ± 0.05§	1.74 ± 0.04¶	0.001
Quadriceps strength/average torque, Nm	71.59 ± 1.61††	68.81 ± 2.41††	84.82 ± 4.06‡‡	80.77 ± 2.22#	0.0001
Grip strength, kg	26.13 ± 0.52#	23.46 ± 0.74**	25.92 ± 1.09	26.42 ± 0.66#	0.02
Forward reach, cm	34.87 ± 0.42#	32.98 ± 0.63**	34.54 ± 0.87	33.18 ± 0.49	0.02
Sit-to-rise time, seconds	1.00 ± 0.02	0.99 ± 0.03	1.01 ± 0.04	1.08 ± 0.03	0.06

* 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 with 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 antiinflammatory 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 biomechanic alignment in relation to radiographic-defined OA of the knee. We also hypothesized that these metabolic and biomechanic 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

REFERENCES

1. Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly: the Framingham Osteoarthritis Study. Arthritis Rheum 1987;30:914−8.
2. Murphy L, Schwartz TA, Helmick CG, Renner JB, Tudor G,

Koch G, et al. Lifetime risk of symptomatic knee osteoarthritis. Arthritis Rheum 2008;59:1207–13.

3. Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM, et al. Osteoarthritis: new insights. Ann Intern Med 2000;137:221–7.

4. Hart DJ, Spector TD. The relationship of obesity, fat distribution and osteoarthritis in women in the general population: the Chingford Study. J Rheumatol 1993;20:331–5.

5. Cicuttini FM, Baker JR, Spector TD. The association of obesity with osteoarthritis of the hand and knee in women: a twin study. J Rheumatol 1996;23:1221–6.

6. Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman B, Aliabadi P, et al. Risk factors for incident radiographic knee osteoarthritis in the elderly: the Framingham Study. Arthritis Rheum 1997;40:728–33.

7. Davis MA, Ettinger WH, Neuhaus JM, Mallon KP. Knee osteoarthritis and physical functioning: evidence from the NHANES1 Epidemiologic Follow-up Study. J Rheumatol 1991;18:591–8.

8. Elder SH, Kimura JH, Soslowsky LJ, Lavagnino M, Goldstein S. Effect of compressive loading on chondrocyte differentiation in agarose cultures of chick limb-bud cells. J Orthopaed Res 2000;18:78–86.

9. Sowers M, Jannausch M, Stein E, Jamadar D, Hochberg M, Lachance L. C-reactive protein as a biomarker of emergent osteoarthritis. Osteoarthritis Cartilage 2002;10:595–601.

10. Hart DJ, Doyle DV, Spector TD. Association between metabolic factors and knee osteoarthritis in women: the Chingford Study. J Rheumatol 1995;22:1118–23.

11. Acheson RM, Collart AB. New Haven survey of joint diseases. XVII. Relationship between some systemic characteristics and osteoarthritis in a general population. Ann Rheum Dis 1975;34:379–87.

12. Davis MA, Ettinger WH, Neuhaus JM. The role of metabolic factors and blood pressure in the association of obesity with osteoarthritis of the knee. J Rheumatol 1988;15:1827–32.

13. Anderson JJ, Felson DT. Factors associated with osteoarthritis of the knee in the first national Health and Nutrition Examination Survey (HANES I): evidence for an association with overweight, race, and physical demands of work. Am J Epidemiol 1988;128:179–89.

14. Spector TD, Hart DJ, Nandra D, Doyle DV, Mackillop N, Gallimore JR, et al. Low-level increases in serum C-reactive protein are present in early osteoarthritis of the knee and predict progressive disease. Arthritis Rheum 1997;40:723–7.

15. Sharif M, Shepstone L, Elson CJ, Dieppe PA, Kirwan JR. Increased serum C-reactive protein may reflect events that precede radiographic progression in osteoarthritis of the knee. Ann Rheum Dis 2000;59:71–4.

16. Engstrom G, Gerhardsson de Verdier M, Rollof J, Nilsson PM, Lohmander LS. C-reactive protein, metabolic syndrome and incidence of severe hip and knee osteoarthritis: a population-based cohort study. Osteoarthritis Cartilage 2009;17:168–73.

17. Kraus VB, Stabler TV, Luta G, Renner JB, Dragomir AD, Jordan JM. Interpretation of serum C-reactive protein (CRP) levels for cardiovascular disease risk is complicated by race, pulmonary disease, body mass index, gender, and osteoarthritis. Osteoarthritis Cartilage 2007;15:966–71.

18. Dahaghin S, Bierma-Zeinstra SM, Koes BW, Hazes JM, Pols HA. Do metabolic factors add to the effect of overweight on hand osteoarthritis? The Rotterdam Study. Ann Rheum Dis 2007;66:916–20.

19. Brouwer GM, van Tol AW, Bergink AP, Belo JN, Bernsen RM, Reijman M, et al. Association between valgus and varus alignment and the development and progression of radiographic osteoarthritis of the knee. Arthritis Rheum 2007;56:1204–11.

20. Cahue S, Dunlop D, Hayes K, Song J, Torres L, Sharma L. Varus–valgus alignment in the progression of patellofemoral osteoarthritis. Arthritis Rheum 2004;50:2184–90.

21. Kobayashi T, Yoshihara Y, Yamada H, Fujikawa K. Procollagen IIC-peptide as a marker for assessing mechanical risk factors of knee osteoarthritis: effect of obesity and varus alignment. Ann Rheum Dis 2000;59:982–4.

22. Andriacchi TP, Mundermann A. The role of ambulatory mechanics in the initiation and progression of knee osteoarthritis. Curr Opin Rheumatol 2006;18:514–8.

23. Buckland-Wright C. Protocols for precise radio-anatomical positioning of the tibiofemoral and patellofemoral compartments of the knee. Osteoarthritis Cartilage 1995;3 Suppl A:71–80.

24. Kellgren JH, Lawrence JS. The epidemiology of chronic rheumatism. Vol. II. Atlas of standard radiographs of arthritis. Philadelphia: FA Davis; 1963.

25. Ware JE Jr, Sherbourne CD. The MOS 36-item Short-Form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–83.

26. Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Underwood T, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. Br Med J 1992;305:160–4.

27. McHorney CA, Ware JE, Raczek AE. The MOS 36-item short form health survey (SF-36). II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993;31:247–63.

28. McHorney CA, Ware JE, Lu RJ, Sherbourne CE. The MOS 36-item short for health survey (SF-36). III. Tests of data quality, scaling, assumption and reliability among diverse patient groups. Med Care 1994;32:40–66.

29. Nagi SZ. An epidemiology of disability among adults in the United States. Milbank Mem Fund Q Health Soc 1976;54:439–67.

30. Warnick GR, Albers JJ. A comprehensive evaluation of heparin-manganese precipitation procedure for estimating high-density lipoprotein cholesterol. J Lipid Res 1978;19:65–76.

31. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499–502.

32. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2004;27 Suppl 1:S5–10.

33. Michos ED, Blumenthal RS. Prevalence of low low-density lipoprotein cholesterol with elevated high sensitivity C-reactive protein in the US: implications of the JUPITER (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin) study. J Am Coll Cardiol 2009;53:931–5.

34. Ridker PM, Danielson E, Fonesca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–207.

35. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.

36. World Health Organization. Obesity: preventing and managing the global epidemic. Geneva (Switzerland): WHO; 2000.

37. Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J, et al. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometaboilc risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999–2004). Arch Intern Med 2008;16B:1617–24.

38. Wildman RP, Mancuso P, Wang C, Kim M, Scherer PE, Sowers MR. Adipocytokine and ghrelin levels in relation to cardiovascular disease risk factors in women at midlife: longitudinal associations. Int J Obes (Lond) 2008;32:740–8.

39. Caro JF, Sinha MK, Kolaczynski JW, Zhang PL, Considine RV. Leptin: the tale of an obesity gene. Diabetes 1996;45:1455–62.

40. Elmquist JK, Maratos-Flier E, Saper CB, Flier JS. Unravelling the central nervous system pathways underlying responses to leptin. Nat Neurosci 1998;1:445–50.

41. Dumond H, Presle N, Terlain B, Mainard D, Loeuille D, Netter P, et al. Evidence for a key role of leptin in osteoarthritis. Arthritis Rheum 2003;48:3118–29.

42. Kume K, Satomura K, Nishisho S, Kitaoka E, Yamanouchi K,

Tobiume S, et al. Potential role of leptin in endochondral ossification. J Histochem Cytochem 2002;50:159–69.

43. Figenschau Y, Knutsen G, Shahazcydi S, Johansen O, Svein-bjornson B. Human articular chondrocytes express functional leptin receptors. Biochem Biophys Res Commun 2001;287: 190–7.

44. Scharstuhl A, Glansbeck HL, van Beuningen HM, Vitters EL, van der Kraan PM, van den Berg WB. Inhibition of endoge-nous TGF-b during experimental osteoarthritis prevents os-teophyte formation and impairs cartilage repair. J Immunol 2002;169:507–14.

45. Glansbeck GL, van Beuningen HM, Vitters EL, van der Kraan PM, van den Berg WB. Stimulation of articular cartilage repair in established arthritis by local administration of transporting growth factor-β into murine knee joints. Lab Invest 1998;78: 133–42.

46. Grimaud E, Heymann D, Redini F. Recent advances in TGF-β effects on chondrocyte metabolism: potential therapeutic roles of TGF-β in cartilage disorders. Cytokine Growth Factor Rev 2002;13:241–57.

47. Fantuzzi G. Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol 2005;115:911–9.

48. Okamoto Y, Kihara S, Funahashi T, Matsuzawa Y, Libby P. Adiponectin: a key adipocytokine in metabolic syndrome. Clin Sci 2006;110:267–78.

49. Chen TH, Chen L, Hsieh MS, Chang CP, Chou DT, Tsai SH. Evidence for a protective role for adiponectin in osteoarthri-tis. Biochim Biophys Acta 2006;1762:711–8.

50. Schaffler A, Ehling A, Neumann E, Herfarth H, Tarner I, Scholmerich J, et al. Adipocytokines in synovial fluid [letter]. JAMA 2003;290:1709–10.

51. Gegout PP, Francin PJ, Mainard D, Presle N. Adipokines in osteoarthritis: friends or foes of cartilage homeostasis? Joint Bone Spine 2008;75:669–71.

52. Presle N, Pottie P, Dumond H, Guillaume C, Lapicque F, Pallu S, et al. Differential distribution of adipokines between serum and synovial fluid in patients with osteoarthritis: contribution of joint tissues to their articular production. Osteoarthritis Cartilage 2006;14:690–5.

53. Lago R, Gomez R, Otero M, Lago F, Gallego R, Dieguez C, et al. A new player in cartilage homeostasis: adiponectin in-duces nitric oxide synthase type II and pro-inflammatory cytokines in chondrocytes. Osteoarthritis Cartilage 2008; 16:1101–9.

54. Tang CH, Chiu YC, Tan TW, Yang RS, Fu WM. Adiponectin enhances IL-6 production in human synovial fibroblast via an AdipoR1 receptor, AMPK, p38, and NF-kB pathway. J Immu-nol 2007;179:5483–92.

55. Ehling A, Schaffler A, Herfarth H, Tarner IH, Anders S, Distler O, et al. The potential of adiponectin in driving arthritis. J Immunol 2006;176:4468–78.

56. Wearing SC, Henning EM, Bryne NM, Steele JR, Hills AP. Musculoskeletal disorders associated with obesity: a biome-chanical perspective. Obes Rev 2006;7:239–50.

57. Messier SP, Ettinger WH, Doyle TE, Morgan T, James MK, O'Toole ML, et al. Obesity: effects on gait in an osteoarthritic population. J Appl Biomech 1996;12:161–72.

58. Browning RC, Kram R. Effects of obesity on the biomechanics of walking at different speeds. Med Sci Sports Exerc 2007;9: 1632–41.

59. Sharma L, Lou C, Cahue S, Dunlop DD. The mechanism of the effect of obesity in knee osteoarthritis: the mediating role of malalignment. Arthritis Rheum 2000;43:568–75.