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ORIGINAL ARTICLE

Association of Leptin Levels With Radiographic Knee Osteoarthritis Among a Cohort of Midlife Women

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Objective. **To relate serum leptin levels to prevalent and incident radiographic knee osteoarthritis (OA) and to determine if patterns of change in longitudinal serum leptin measures differ by knee OA status over a 10-year period.**
Methods. **Participants in the Michigan Study of Women's Health Across the Nation underwent bilateral knee radiographs at baseline and followup visits 2, 4, and 11 for ascertainment of knee OA status (Kellgren/Lawrence score ≥2). Serum leptin measures were available from baseline and followup visits 1 and 3–7.**
Results. **The baseline prevalence of knee OA (mean age 46 years) was 18%; the 2-year incidence of knee OA at followup visits 2 and 4 was 18% and 14%, respectively. Serum leptin levels were associated with prevalent and incident knee OA. A 5 ng/ml increase in serum leptin level was associated with 38% higher odds of prevalent knee OA (odds ratio [OR] 1.38, 95% confidence interval [95% CI] 1.26–1.52) and 31% greater odds of incident knee OA (OR 1.31, 95% CI 1.21–1.41) after adjustment for covariates, including body mass index residuals. Leptin levels increased with time; on average, serum leptin levels increased by 0.38 ng/ml per year ($P = 0.0004$). Women with incident knee OA during the 10-year followup period had consistently higher serum leptin levels as compared to women with no knee OA during followup.**
Conclusion. **Our findings support a metabolic role of obesity in knee OA. A better understanding of the mechanisms by which increased fat mass is associated with joint damage is needed. Management of cardiometabolic dysfunction, including elevated serum leptin levels, may be beneficial in forestalling the onset or progression of knee OA.**

INTRODUCTION

As the leading cause of pain, functional limitations, and disability in the US (1), osteoarthritis (OA) is associated with decreased productivity and increased health expenditures (2). In 2003, the cost of medical care expenditures and earnings losses associated with arthritis and rheumatism was an estimated $128 billion (3). OA, a joint condition characterized by loss of articular cartilage, subchondral bone remodeling, soft tissue damage, and inflammation, affects more than 26 million US adults ages >25 years (4).

OA disproportionately afflicts women, and the prevalence rises dramatically after the menopausal transition (5,6). However, disagreements persist as to whether the menopause, the accompanying change in hormone levels, or some other physiologic processes occurring during midlife contribute to OA pathogenesis. Support for the importance of menopause-associated "estrogen deficiency" as a risk factor for knee OA has been mixed (7–11). Better characterization of the menopause transition has provided evidence that it is a time of hormonal change but also dramatic metabolic changes, including decreased energy

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Significance & Innovations

- This study is the first to examine serum leptin levels with respect to both prevalent and incident knee osteoarthritis (OA) and to relate baseline and longitudinal measures of serum leptin to subsequent OA status.
- Serum leptin levels are associated with prevalent and incident radiographic knee OA in a middle-aged population of women.
- Serum leptin levels increase with age; on average, serum leptin levels increased by 0.38 ng/ml per year ($P = 0.0004$) after adjustment for body mass index.
- We observed complete separation of estimated mean serum leptin levels over time among women with prevalent knee OA at baseline, women with incident knee OA during the 10-year followup period, and women who remained OA free during followup. Even the lowest estimated mean serum leptin levels among women with prevalent knee OA at baseline were higher than the highest estimated levels among women with incident or no knee OA during followup.

expenditure (12), changes in body composition and topology (13,14), and increased risk of metabolic syndrome (15).

Obesity is a well-documented risk factor for knee OA (16–23), and the impact of obesity on OA onset and progression is likely due to several mechanisms. Some investigators have focused on the impact of obesity as a sheer mechanical force causing increased joint loading and subsequent damage to the articular cartilage (24–26). However, associations between obesity and OA in non–weight-bearing joints such as those in the hands and/or wrists (23,27–29) suggest that additional mechanisms impact the OA–obesity relationship and emphasize the role of adipose tissue.

There is emerging evidence about the active metabolic environment of chondrocytes, including glucose transport, cholesterol efflux, and lipid metabolism (30). These findings have prompted the consideration of novel obesity-related biomarkers in studies of OA, and have suggested that there may be shared pathophysiology between OA and cardiovascular and metabolic diseases. Adipose tissue is now recognized as an endocrine organ, since adipocytes have the ability to secrete active agents, including adipokines (31). Efforts to examine the adipokines with respect to OA have focused on leptin because of its strong correlation with body size. Leptin levels in synovial fluid are correlated with the severity of knee OA (32), and leptin and its receptor have been identified in many joint tissues, including human chondrocytes, osteophytes (33,34), synovium, and infrapatellar fat pad (35).

Leptin might be an important link between obesity and OA (30,36–39), but epidemiologic evidence of such a relationship is limited, possibly because few studies of OA have leptin measures available. No studies have evaluated whether changes in leptin are associated with OA despite evidence that changes in body size are associated with joint damage (40,41). Therefore, the goal of this investigation was to describe the relationship between serum leptin measures and knee OA prevalence and incidence and to determine whether changes in serum leptin levels over time differed by OA status in a middle-aged population of women.

PATIENTS AND METHODS

The Michigan Study of Women's Health Across the Nation (SWAN) is 1 of 7 sites for SWAN, a multiethnic cohort study characterizing the menopausal transition. The Michigan SWAN population, established in 1996, is a population-based sample of women from 2 Detroit-area communities identified through a community census based on electrical utility listings. A total of 543 eligible women were recruited from the Michigan site, including 325 African American and 218 white women. Eligibility criteria at baseline included age 42–52 years, having an intact uterus, having had at least one menstrual period in the previous 3 months, no use of reproductive hormones in the previous 3 months, and self-identification with the site's designated race/ethnic group (either African American or white at the Michigan site).

At baseline (1996), women in the Michigan SWAN completed the assessment protocol common to all SWAN sites; then, a supplemental protocol, including radiographs, was implemented. Women were seen for annual followup visits, although the supplemental OA protocol was included only at baseline and followup visits 2, 4, and 11. Participation at the annual assessments has been excellent, with 80% seen at followup visit 11.

Although the number of women participating in the radiograph protocol varied by year, there were few differences among those who participated and those who did not. Race and smoker status varied with annual participation; at followup visit 2, nonparticipants were more likely to be African American and current smokers, whereas at followup visit 4, nonparticipants were more likely to be white, and at followup visit 11, current smokers were more likely to participate. The University of Michigan Institutional Review Board approved the study protocol, and written informed consent was obtained from each participant.

OA measures. Anteroposterior radiographs of the knees have been taken with weight bearing in the semiflexed position (42). Radiographs taken at baseline and followup visits 2 and 4 were obtained using General Electric Medical Systems radiograph equipment (model X-GE MPX-80). Radiographs from followup visit 11 were obtained with the AXIOM Aristos radiographic system with integrated digital flat detector technology (Siemens). Knees were scored using the Kellgren/Lawrence (K/L) grading system of the Atlas of Standard Radiographs of Arthritis (43) such that 0 = normal, 1 = doubtful OA, 2 = minimal OA, 3 = moderate OA, and 4 = severe OA. Participants with artificial knee replacements were assigned a K/L score of 4. Prevalent knee OA was defined as at least 1 knee with a

K/L score ≥2 at a given visit. Incident knee OA was defined as new knee OA (K/L score ≥2) in either knee given that the participant had a K/L score of 0 or 1 in both knees during the prior data collection cycle.

Leptin assay. The SWAN specimen collection protocol includes a fasting blood draw to provide samples for a specimen repository that is maintained at −80°C until processing. Serum leptin levels were determined spectrophotometrically using commercially-available colorimetric enzyme immunoassay kits (Millipore) and run according to the manufacturer's instructions. The coefficient of variation for duplicate samples was 3.7% and the lower limit of detection was 0.5 ng/ml. Banked serum specimens from baseline and followup visits 1 and 3–7 were assayed for leptin.

Other measures. At each annual examination, height (cm) and weight (kg) were measured using a stadiometer and a calibrated balance-beam scale, respectively, and were used to calculate body mass index (BMI). Waist (cm) and hip (cm) circumferences have been measured annually using a nonstretchable tape 3 cm above the umbilicus after a relaxed expiration and the maximum girth around the buttocks, respectively.

Menopause status was ascertained at each annual examination based on questions about bleeding patterns, current hormone use, hysterectomy, and oophorectomy. Participants were categorized as being premenopausal (regular menses with bleeding in the past 3 months), early perimenopausal (bleeding in the past 3 months but increasing irregularity in menses), late perimenopausal (bleeding in the past year but not in the past 3 months), postmenopausal (no bleeding for 12 months), hysterectomy, or unable to determine due to exogenous hormone use.

Race/ethnicity classification (African American or white) and annual current smoker status (yes/no) were determined by self-report. Age at each visit was calculated as the visit date minus birth date.

Statistical analysis. Means and SDs or frequencies and percentages of leptin levels, body size variables, and relevant covariates were examined overall and by knee OA status. The statistical significance of differences by OA status was evaluated using *t*-tests, analysis of variance, or chi-square tests.

To fully utilize the richness of the available data, including multiple measures of knee OA status and annual assessment of serum leptin through followup visit 7, three analytical approaches were employed to relate serum leptin measures and knee OA status. In the first 2 approaches, the outcome of interest was knee OA, whereas in the third approach, leptin was the outcome. First, to determine the association of leptin levels and knee OA prevalence at baseline, we examined the cross-sectional association of serum leptin and knee OA using multivariable logistic regression analysis.

Second, to determine the association of leptin levels and incident knee OA, discrete time survival analysis techniques were utilized to model the time to incident OA at followup visits 2, 4, and 11 as a function of serum leptin levels. To complete this analysis, a data set was constructed with multiple observations per participant; each row in the data set represented a study visit in which the participant was at risk of knee OA onset through followup visit 11. Once women developed knee OA, data from subsequent years of followup were not included in the data set. The discrete time logistic survival model was then estimated using logistic regression, whereby the odds ratios are the effect estimates of interest. The incidence of knee OA at each followup visit was calculated as the number of new cases of knee OA at a given visit divided by the number of women who remained at risk for knee OA. Because serum leptin levels were not available at followup visits 2 or 11, values from followup visits 1 and 7, respectively, were substituted.

Third, serum leptin levels from baseline to followup visit 7 were evaluated overall and by prevalent, incident, or no knee OA status through followup visit 11. Then, linear mixed models (PROC MIXED) with random intercepts and slopes for age were used to examine level of and change in serum leptin measures over time. OA status by time interactions in the model evaluated whether the rates of change in serum leptin measures differed between women with prevalent, incident, or no knee OA through followup visit 11. SAS PROC SGPLOT was used to graph predicted trajectories of serum leptin measures with corresponding 95% confidence intervals (95% CIs) for each knee OA group.

Due to the collinearity between body size and serum leptin ($r = 0.73$, $P < 0.0001$), all multivariable modeling included residuals of BMI as the measure of body size confounding. The BMI residual variable represents the variation in BMI that remains following simple regression of BMI on leptin. Given that serum leptin represents the metabolic component of body size, the BMI residual represents the association of body size and OA through other pathways, including mechanical loading. Interactions of the BMI residual and serum leptin were tested to assess potential effect modification of the relationship between leptin and knee OA by body size. A sensitivity analysis was conducted to examine the consistency of the results after adjustment for waist to hip ratio instead of the BMI residuals. When adjusting for waist to hip ratio, the findings remained consistent, although the estimates for leptin were attenuated by 14% (data not shown).

Model fit and final model selection were based on Akaike's information criterion and chi-square tests comparing the log-likelihood ratios between candidate models. Models were adjusted for age, race/ethnicity, menopause status (or hysterectomy [yes/no]), smoker status, and BMI residuals, as appropriate. Statistical significance was defined at an alpha level of <0.05 and all analyses were completed using SAS, version 9.3.

RESULTS

The prevalence of radiographically-defined knee OA increased over the 10-year followup period. At baseline (mean age 46 years), 18% of participants had knee OA; at followup visit 11, 66% of women had knee OA (Table 1).

Table 1. Descriptive characteristics of the Michigan Study of Women's Health Across the Nation sample at baseline, followup visit 4, and followup visit 11*

	Baseline (n = 542)	Followup visit 4 (n = 252)	Followup visit 11 (n = 387)
Age, mean ± SD years	46.1 ± 2.7	50.2 ± 2.7	56.9 ± 2.8
Weight, mean ± SD kg	85.8 ± 21.8	87.9 ± 22.1	90.1 ± 22.2
Height, mean ± SD cm	163.5 ± 6.2	162.8 ± 5.8	162.6 ± 6.2
BMI, mean ± SD kg/m^2	32.1 ± 8.0	33.2 ± 8.3	34.1 ± 8.4
Waist circumference, mean ± SD cm	94.1 ± 17.1	98.5 ± 17.6	102.3 ± 17.6
Hip circumference, mean ± SD cm	113.9 ± 16.2	115.4 ± 17.0	118.1 ± 16.9
Waist:hip ratio, mean ± SD	0.82 ± 0.07	0.85 ± 0.08	0.87 ± 0.08
Leptin level, mean ± SD ng/ml	30.6 ± 18.3	34.4 ± 20.1	–
Knee osteoarthritis, no. (%)	98 (18.1)	112 (44.4)	254 (65.6)
K/L score, no. (%)			
0	322 (59.4)	61 (24.2)	44 (11.4)
1	122 (22.5)	79 (31.3)	89 (23.0)
2	78 (14.4)	84 (33.3)	147 (38.0)
3	19 (3.5)	27 (10.7)	62 (16.0)
4	1 (0.2)	1 (0.4)	45 (11.6)
Obese (BMI ≥30 kg/m^2), no. (%)	301 (56.1)	153 (61.5)	250 (64.6)
Race/ethnicity, no. (%)			
African American	324 (59.8)	181 (71.8)	238 (61.5)
White	218 (40.2)	71 (28.2)	149 (38.5)
Menopause status, no. (%)			
Premenopausal	271 (50.3)	11 (4.4)	0 (0.0)
Early perimenopausal	268 (49.7)	104 (41.4)	12 (3.1)
Late perimenopausal	0 (0.0)	37 (14.7)	15 (3.9)
Postmenopausal	0 (0.0)	51 (20.3)	303 (78.3)
Hysterectomy	0 (0.0)	22 (8.8)	52 (13.4)
Unknown, hormone use	0 (0.0)	26 (10.4)	5 (1.3)
Hormone therapy use, no. (%)	0 (0.0)	45 (17.9)	32 (8.3)
Current smoker, no. (%)	146 (27.3)	63 (25.1)	87 (22.5)

* Sample sizes vary slightly for some variables due to data availability. BMI = body mass index; K/L = Kellgren/Lawrence.

Similarly, the prevalence of moderate to severe OA (K/L score 3 or 4) changed from 4% at baseline to 28% ten years later.

The mean baseline serum leptin level was 30.6 ng/ml. At followup visit 7, the mean serum leptin level was 38.0 ng/ml (Supplementary Table 1, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.21922/abstract); we observed a statistically significant increasing trend in serum leptin levels over time ($P < 0.0001$). Serum leptin levels were 43% higher at baseline among women with knee OA as compared to those without knee OA ($P < 0.0001$). Serum leptin levels were not different according to race/ethnicity, age, menopause status, or smoker status.

Fifty-six percent of all participants were obese at baseline in 1996–1997; by followup visit 11, the prevalence of obesity increased to 64.6%. Body size measures, with the exception of height, increased significantly over the study period and were 15–30% greater among women with knee OA as compared to those without knee OA (Table 2).

By design, 60% of participants were African American and 40% were white. In accordance with the inclusion criterion, all participants were premenopausal or early perimenopausal at baseline and were not taking exogenous hormones. By followup visit 11, most women (78%) were postmenopausal and only 8% were taking exogenous hormones. Menopause status differed by OA status at followup visit 11 ($P = 0.01$); women with OA were more likely to have had a hysterectomy as compared to women without knee OA.

The proportion of women that were current smokers declined slightly over time; at baseline, 27% of women were current smokers, whereas 23% were current smokers at followup visit 11. The proportion of current smokers was similar among women with and without knee OA at baseline; however, at followup visit 11, women with knee OA were less likely to be current smokers as compared to women without knee OA (19% versus 30%; $P = 0.01$).

Cross-sectional analysis relating leptin levels to prevalent knee OA. Baseline serum leptin levels were positively and significantly associated with prevalent knee OA (Table 3). A 5 ng/ml higher serum leptin level was associated with 38% greater odds of having knee OA after adjustment for age, race/ethnicity, menopause status, current smoker status, and BMI residuals (95% CI 1.26–1.52). African American women had 2.6 times greater odds of having knee OA at baseline as compared to white women (95% CI 1.46–4.46).

Serum leptin levels and time to incident knee OA. The 2-year incidence of knee OA at followup visits 2 and 4 was 18% and 14%, respectively. At followup visit 11, the 7-year incidence of knee OA was 47%. After adjustment

Table 2. Descriptive characteristics of the Michigan Study of Women's Health Across the Nation sample at baseline and followup visit 11 by knee OA status*

	Baseline			Followup visit 11		
	No OA	OA	*P*	No OA	OA	*P*
Age, mean ± SD years	46.1 ± 2.8	46.0 ± 2.6	0.73	56.6 ± 2.8	57.1 ± 2.8	0.07
Weight, mean ± SD kg	82.2 ± 20.0	101.8 ± 22.5	< 0.0001†	74.9 ± 15.7	98.0 ± 21.0	< 0.0001†
Height, mean ± SD cm	163.5 ± 6.2	163.3 ± 6.4	0.85	162.3 ± 6.5	162.8 ± 6.0	0.48
BMI, mean ± SD kg/m^2	30.8 ± 7.3	38.1 ± 8.5	< 0.0001†	28.4 ± 5.9	37.1 ± 7.9	< 0.0001†
Waist circumference, mean ± SD cm	91.5 ± 16.0	105.4 ± 17.5	< 0.0001†	91.1 ± 15.0	108.1 ± 16.0	< 0.0001†
Hip circumference, mean ± SD cm	111.3 ± 14.9	125.5 ± 17.1	< 0.0001†	107.1 ± 13.0	123.9 ± 15.8	< 0.0001†
Waist:hip ratio, mean ± SD	0.82 ± 0.07	0.84 ± 0.07	0.02†	0.85 ± 0.08	0.87 ± 0.08	0.003†
Leptin level, mean ± SD ng/ml	28.4 ± 17.2	40.6 ± 20.1	< 0.0001†	–	–	
Obese (BMI ≥30 kg/m^2), no. (%)	221 (50.0)	80 (84.2)	< 0.0001†	48 (36.1)	202 (79.5)	< 0.0001†
Ethnicity, no. (%)						
African American	249 (56.1)	75 (76.5)	0.0002†	75 (56.4)	163 (64.2)	0.14
White	195 (43.9)	23 (23.5)		58 (43.6)	91 (35.8)	
Menopause status, no. (%)						
Premenopausal	230 (52.2)	41 (41.8)	0.06	0 (0.0)	0 (0.0)	0.01†
Early perimenopausal	211 (47.9)	57 (58.2)		9 (6.8)	3 (1.2)	
Late perimenopausal	0 (0.0)	0 (0.0)		6 (4.5)	9 (3.5)	
Postmenopausal	0 (0.0)	0 (0.0)		105 (79.0)	198 (78.0)	
Hysterectomy	0 (0.0)	0 (0.0)		12 (9.0)	40 (15.8)	
Unknown, hormone use	0 (0.0)	0 (0.0)		1 (0.8)	4 (1.6)	
Hormone therapy use, no. (%)	0 (0.0)	0 (0.0)	N/A	13 (9.8)	19 (7.5)	0.44
Current smoker, no. (%)	121 (27.8)	25 (25.5)	0.65	40 (30.1)	47 (18.5)	0.01†

* OA = osteoarthritis; BMI = body mass index; N/A = not applicable.
† $P < 0.05$.

for baseline age, race/ethnicity, baseline smoker status, and BMI residuals, higher serum leptin levels were associated with incident knee OA (Table 4). A 5 ng/ml higher serum leptin level was associated with 31% greater odds of incident knee OA (95% CI 1.21–1.41). African American women had 52% greater odds of incident knee OA (95% CI 1.00–2.30) as compared to white women. Baseline age and current smoker status were associated with lower odds of incident knee OA. A 1-year increase in baseline age was associated with 14% decreased odds of incident knee OA (95% CI 0.83–0.88). Those who were current smokers had 52% decreased odds of having incident knee OA as compared to those who were not current smokers (95% CI 0.29–0.80).

As a sensitivity analysis, incident knee OA cases were restricted to only those individuals with a K/L score of 0 at baseline, and findings were similar. A 5 ng/ml higher serum leptin level was associated with 30% greater odds of incident knee OA (95% CI 1.18–1.44) following adjustment for covariates.

Trajectories of leptin in relation to knee OA status at followup visit 11. Serum leptin levels increased as women aged; on average, serum leptin levels increased by 0.38 ng/ml per year ($P = 0.0004$). Serum leptin levels were highest among women with prevalent knee OA at baseline

Table 3. Cross-sectional analysis of the relationship between serum leptin values and knee osteoarthritis status at the baseline visit among the Michigan Study of Women's Health Across the Nation participants, adjusted for age, body mass index residuals, race/ethnicity, menopause status, and baseline smoker status

	Odds ratio (95% confidence interval)
Leptin*	1.38 (1.26–1.52)
Age	1.00 (0.92–1.10)
African American vs. white race/ethnicity	2.55 (1.46–4.46)
Early perimenopausal vs. premenopausal	1.57 (0.95–2.60)
Current vs. not current smoker	1.05 (0.58–1.90)

* Estimate represents a 5 ng/ml change in leptin value.

Table 4. Discrete survival time analysis of the relationship between serum leptin values and incident knee osteoarthritis among the Michigan Study of Women's Health Across the Nation participants, baseline to followup visit 11, adjusted for age, body mass index residuals, race/ethnicity, and baseline smoker status

	Odds ratio (95% confidence interval)
Leptin*	1.31 (1.21–1.41)
Baseline age	0.86 (0.83–0.88)
African American race/ethnicity	1.52 (1.00–2.30)
Baseline current vs. not current smoker	0.48 (0.29–0.80)

* Estimate represents a 5 ng/ml change in leptin value.

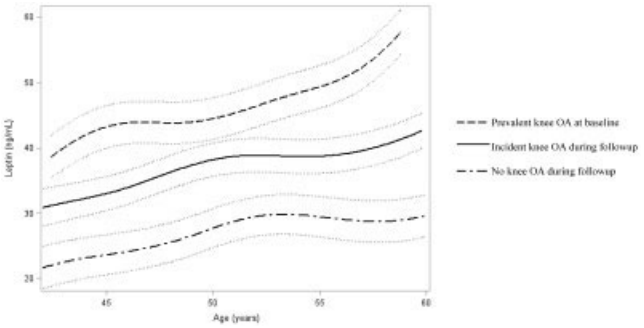

Figure 1. Predicted trajectories of serum leptin level (ng/ml) by knee osteoarthritis (OA) status among the Michigan Study of Women's Health Across the Nation (SWAN) participants, adjusted for age, body mass index residuals, race/ethnicity, hysterectomy status, and baseline smoker status.

(Figure 1). After adjustment for age, BMI residuals, race/ethnicity, hysterectomy status, and baseline smoker status, women with prevalent knee OA at baseline had serum leptin levels that were 21 ng/ml higher as compared to women that remained knee OA free throughout the 10 years of followup. Women who developed incident knee OA during followup had serum leptin levels that were 14 ng/ml higher as compared to those without knee OA. Most notably, the highest serum leptin levels among those women who never developed knee OA are still lower than those among women with knee OA. Also, the serum leptin levels among those with incident disease during the followup do not overlap with levels among those with prevalent disease at baseline. Although serum leptin levels differed by knee OA status, there was no statistically significant difference in the slope of the leptin trajectories over time among the groups.

To examine whether serum leptin levels were associated with knee OA progression, the trajectories of leptin among women with prevalent knee OA at baseline who progressed to moderate/severe knee OA at followup visit 11 were compared to those among women who did not progress. Women with prevalent knee OA who progressed had serum leptin levels that were 3.3 ng/ml higher as compared to women with prevalent knee OA who did not progress, but this difference was not statistically significant ($P = 0.35$).

DISCUSSION

Although leptin may represent an important link between obesity and knee OA (30,36–39), few epidemiologic studies have examined this hypothesis. This study is the first to examine serum leptin levels with respect to prevalent and incident knee OA and to relate longitudinal measures of serum leptin to subsequent OA status in a large population-based study. In this cohort of midlife women, higher serum leptin levels were associated with increased odds of both prevalent and incident knee OA, but the rate of change in serum leptin levels over time did not differ by knee OA status. The finding that serum leptin levels at baseline were highest among women with prevalent knee OA as compared to women with 10-year incident knee OA or no knee OA suggests that these women are the most metabolically compromised in terms of high leptin levels. Individuals with prevalent knee OA at baseline were relatively young at disease onset. We hypothesize that metabolic dysfunction may be an important risk factor for knee OA, particularly among younger individuals.

Ku et al reported that cross-sectional leptin levels (measured in synovial fluid) were related to knee OA severity among a population of knee surgery patients (32). Unlike our study, however, BMI did not differ by knee OA status, suggesting that our population and the Ku et al population differ with respect to body size. Further, the leptin levels among women in the Michigan SWAN cohort are much higher than those reported by Ku et al; 74% of the women in our study had baseline leptin levels that were higher than the upper range of values reported among the Ku et al patients (15.8 ng/ml) (32). Data from the Third National Health and Nutrition Examination Study (NHANES-III) estimate that the mean serum leptin value among women ages ≥20 years in the US is 12.7 ng/ml (44), suggesting that the Ku et al population (32) may have leptin levels lower than the general US population.

Exploration of the impact of the leptin–OA relationship among a cohort of women is of particular interest given the findings that serum leptin levels were the most important cardiometabolic biomarker for knee OA among women using data from NHANES-III (45). Further, differences in synovial leptin levels among OA patients versus controls were greater among women as compared to men (32). Leptin levels are higher among women (46–49) and correlate more strongly with subcutaneous adipose tissue (46–49), the fat depot that is proportionally larger among women as compared to men (50). Our data suggest that leptin may be an important OA biomarker among women.

Mechanistically, leptin has been associated with OA through catabolic or anabolic mechanisms. Leptin has an anabolic effect on chondrocytes and osteoblasts (33), which may be associated with repair of damaged cartilage, but also increased osteophyte development. Since the K/L scoring system reflects both joint space width (a proxy of cartilage loss) and the presence of osteophytes, the anabolic impact of leptin with respect to radiographically-defined knee OA cannot be differentiated. Leptin may also have a catabolic effect on cartilage due to its proinflammatory capabilities. Synergistic relationships of leptin and proinflammatory cytokines, including interleukin-1β (IL-1β), IL-6, IL-8, matrix metalloproteinase 9 (MMP-9), MMP-13, and nitric oxide, have been reported (33,51,52). Increased local inflammation within the joint has a catabolic role in cartilage metabolism (51). It is possible that the proinflammatory impact of leptin may be detrimental to other collagenous tissues within the joint, including the meniscus and ligaments.

Our analysis was complicated by the fact that leptin, being a product of adipose tissue, is highly correlated with all measures of body size, and greater body size is a hypothesized risk factor for knee OA through nonmetabolic mechanisms such as increased joint loading or poor muscle strength. Therefore, our analyses were adjusted for the residuals of BMI on leptin in an effort to describe the

metabolic impact of obesity (i.e., leptin) on knee OA, over and above the nonmetabolic effect of greater body size.

Utilization of hand joints may be preferable over knees as the OA phenotype for studies evaluating the metabolic impact of obesity on joint status (53). A recent study using data from NHANES-III found no association of leptin and hand OA (54). However, in the analysis from Massengale et al (54), the case definition of hand OA was based upon clinical examination in the absence of hand radiographs. Several studies have documented that radiography is superior to physical examination for the characterization of hand OA in epidemiologic studies (55–57) and that use of clinical examination may underestimate the prevalence of disease. Misclassification of OA status in this way may bias findings toward the null, which could explain the study's report of no association between leptin and hand OA.

With respect to progression of hand OA, Yusuf et al (58) reported slightly greater leptin levels (3 ng/ml) among those with progressive hand OA as compared to nonprogressive disease ($P = 0.08$). The study may have been underpowered to detect statistically significant differences in leptin levels given the relatively narrow range of leptin values in this population, which included both men and women of normal body size. In addition, all participants in the Yusuf et al cohort had OA in multiple joints, suggesting a more advanced level of disease overall. The mechanism by which leptin is associated with incident OA may be different than the mechanism by which leptin is associated with progressive OA. Taken together, the findings with respect to leptin and hand OA are not definitive and call for more work to be done exploring leptin levels among a population including both those with and without radiographic hand OA.

This study examined leptin levels with respect to knee OA prevalence and incidence in a nonclinical population. Strengths unique to this study include longitudinal leptin measures, repeated assessment of knee OA status, and information about potential confounders, including body size, menopause status, and smoking. The prevalence of knee OA continues to increase in the population, likely because of the aging of the population and the increasing proliferation of obesity. Although obesity is a known risk factor for OA, better characterization of the mechanisms through which greater fat mass is associated with joint damage will provide important information to aid in prevention and intervention strategies. We have reported here that serum leptin, an adipokine secreted by adipose tissue, is associated with knee OA prevalence and incidence over and above the nonmetabolic impact of BMI. These findings provide further evidence that body mass influences OA through a metabolic pathway and provides support for the potential utility of serum leptin as a biomarker for OA risk.

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