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Association of diabetes mellitus and biomarkers of abnormal glucose metabolism with incident radiographic knee osteoarthritis

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Abstract

OBJECTIVE.—Whether diabetes mellitus (DM) is associated with increased risk of knee osteoarthritis is uncertain. We evaluated associations of DM and biomarkers of abnormal glucose metabolism with incident radiographic knee osteoarthritis (RKO), controlling for body mass index (BMI).

METHODS.—Participants (mean age 60.6±7.8 years; mean BMI 29.1±4.9 kg/m²) were from the Multicenter Osteoarthritis Study (MOST) study and did not have RKO at baseline (Kellgren and Lawrence [KL] grade <2 bilaterally). A random sample (n=987) stratified by BMI was selected. Baseline serum fasting glucose and insulin resistance (homeostasis model of assessment [HOMA-IR]) were measured. Participants were categorized as having DM based on self-report, use of medication or fasting glucose ≥126 mg/dL. Incident RKO (KL grade ≥2 or knee replacement) was assessed at 3 follow up visits (30, 60, 84 months). Knee level pooled logistic regression

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AUTHOR CONTRIBUTIONS

Study concept and design: NEL, AVS, MW

Acquisition of data: CEL, NAS

Analysis and interpretation of data: NEL, AVS, MW, IT, TRS, MCN, DTF

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analysis was performed to obtain odds ratios (95% CI) for associations of DM status and biomarkers of abnormal glucose metabolism with incident RKOA.

RESULTS.—After adjustment for BMI, the odds of incident RKOA were not associated with baseline DM status nor with levels of fasting glucose and HOMA-IR overall and in men. In women, HOMA-IR was inversely associated with odds of incident RKOA (adjusted OR 0.80, 95% CI 0.69–0.94; $p=0.005$).

CONCLUSION.—DM and higher levels of biomarkers of abnormal glucose metabolism were not associated with increased odds of incident RKOA after adjusting for BMI in this cohort overall. A possible protective association of higher HOMA-IR with incident RKOA in women deserves further investigation.

Osteoarthritis (OA) and diabetes mellitus (DM) are common among older adults in the U.S. Knee OA causes structural changes in the joint, resulting in pain and stiffness, and is a prominent cause of global disability (1). It is estimated that 16% of adults 45 years and older develop symptomatic knee OA in the United States (2, 3). By 2018, the prevalence of knee OA is projected to reach 35% in obese individuals 60–64 years old (4). Approximately 9.3% of the population has DM in the United States, and DM is even more prevalent among older adults (25.9% of adults 65 years and older) (5). Moreover, by 2050, 55% of adults in this age group are expected to be diagnosed with DM. Type 2 DM (DM2) is more common and comprises 90–95% of all DM cases (6).

Previous epidemiological studies have suggested that OA is associated with elevated fasting glucose (7, 8) and is highly prevalent among those with DM (9–13). Proposed etiologies include advanced glycation end products, which reduce cartilage integrity (14, 15). Additionally, inflammation could contribute to changes in cartilage metabolism and integrity (14), as well as neuromuscular impairment (as a result of symmetric sensory polyneuropathy and autonomic neuropathy from long-standing DM), which could lead to muscle weakness and joint laxity (15).

However, there are few studies specifically of the association of DM and knee OA, and results have been conflicting (16, 17). Some studies of DM and knee OA have not adjusted for body mass index (BMI), even though obesity (high BMI) increases mechanical load on the knee and is a strong risk factor for both DM and OA (16–20). A meta-analysis of six studies found an increased risk of knee OA in persons with DM, but a majority of these studies did not adjust for BMI or obesity (17). A second meta-analysis of seven studies that adjusted for BMI found a small, but significant, increase in risk of OA, but this analysis pooled results from studies of knee, hip and hand OA (16). In addition, both meta-analyses pooled results from cross-sectional and prospective studies and included studies with joint replacement as the outcome, so the temporal relationship between DM and OA is uncertain (16, 17). The potential for reverse causality in cross-sectional studies (i.e., OA contributing to an increased risk of DM) has been shown (17, 21), indicating that prospective studies of the association of DM and abnormalities of glucose metabolism with the subsequent development of OA are needed to understand the contribution of DM to the risk of OA. One prospective study (22) found an increased subsequent risk of either knee or hip replacement (a surrogate for severe OA) in patients with DM after adjusting for BMI. It remains

unknown whether the presence of DM precedes development of OA when arthroplasty is the outcome.

The finding of an association between DM and OA after adjustment for BMI in some studies suggests that other aspects of DM, including metabolic abnormalities, may contribute to the risk of OA development. However, prospective studies have not found an association between hyperglycemia and either the risk of hip or knee replacement (23) or the risk of incident knee OA (24) after adjustment for BMI. A recent systematic review of abnormal glucose metabolism as a risk factor for OA reported that, of five longitudinal studies related to knee OA which adjusted for obesity, three studies reported no association, one reported a reduction in OA risk, and one reported an increase in OA risk (25). Additional prospective studies of DM and abnormalities of glucose metabolism are needed to fully elucidate their potential role in the development of OA in specific joints.

In light of these previous reports, we evaluated the association of DM and of biomarkers of abnormal glucose metabolism with incident radiographic knee osteoarthritis (RKO) of the tibiofemoral (TF) joint among participants in the Multicenter Osteoarthritis Study (MOST). We hypothesized that the presence of DM, as well as hyperglycemia and elevated insulin resistance in participants with and without DM, would be associated with increased odds of incident RKO, independent of BMI.

MATERIALS AND METHODS

Study Participants

We utilized data from MOST, which is an National Institutes of Health (NIH)-funded, community-based longitudinal cohort study of risk factors for knee OA in 3,026 men and women age 50–79 years, with or at high risk for knee OA. Eligibility for MOST included overweight or obesity (defined as weighing more than the Framingham Study medium weight for age and sex-specific group), history of knee injury that made it difficult to walk for at least one week, prior knee surgery or frequent knee pain (26, 27). The MOST clinical centers are located at the University of Alabama at Birmingham and the University of Iowa; participants were recruited from the surrounding areas. Subjects with bilateral total knee replacement (TKR), those unable to walk without assistance or who were unlikely to participate in follow-up examinations at baseline were excluded from MOST. Weight-bearing posteroanterior and lateral knee radiographs were acquired during baseline, 30-, 60- and 84-month clinic visits.

In compliance with the Helsinki Declaration, the protocol for the MOST Study was approved by Institutional Review Boards at Boston University, the University of Iowa, the University of Alabama at Birmingham and the University of California, San Francisco.

Sample Selection

To be eligible for the present analysis, MOST participants had to have two native knees free of osteoarthritis at baseline (Kellgren and Lawrence [KL] grade 0 or 1 in native knees and no KR), knee radiographs at baseline and one or more follow-up visits, and archived baseline fasting serum available. Because of a limited budget for assays, we were unable to include

all eligible participants (n=1,280). We therefore selected a random sample of 1000 from the eligible participants. The sample was stratified by decile of BMI (i.e., 100 participants [58 women and 42 men] were randomly selected from each decile of BMI). We stratified on BMI because control for this variable is essential to determine if DM is associated with OA, independent of BMI. As others have noted (28, 29), residual bias can occur if relationships with a continuous confounder are not properly modeled and a linear relationship is incorrectly assumed. Strategies to deal with nonlinear relationships, which are not uncommon in epidemiological studies of exposure-outcome associations, include ensuring that the data are spread across a wide range, as well as the use of restricted splines. Our sampling approach therefore resulted in a more even distribution of BMI across the entire range of values, which increases the precision of the adjusted odds ratios but does not add bias to the estimates of association. It also allowed us to better estimate the shape of the relationship of BMI with exposure and outcome using splines, with the goal of increased accuracy and precision of the BMI adjusted odds ratios. However, we found that the use of splines did not change the adjusted results so we did not use splines in the main analyses. The BMI groups (deciles) were used only for the selection of participants. Of these 1000 participants, 13 were excluded after we determined that they were insulin users at baseline. The final sample size for the present analysis was 987 (Figure 1).

Measurements

Participants were categorized as having DM at baseline based on the presence of at least one of the following: self-reported diagnosis of DM (“Do you have diabetes or high blood sugar?”), use of anti-diabetic medications (e.g., meglitinides, metformin, sulfonylureas, thiazolidinediones) determined by review of all prescription medications taken in the past 30 days, or a fasting glucose of ≥ 126 mg/dL.

Weight (kg) and height (mm) were measured by standard medical beam balance and wall mounted Harpenden stadiometer, respectively (30). Weight and height measurements were used to calculate BMI (kg/m^2). Self-reported health status was determined via the SF-12 Health Survey (26). Self-reported physical activity was assessed at baseline with the Physical Activity Scale for the Elderly (PASE) (31).

Fasting glucose (Unical DxC 800 Auto-analyzer (Beckman Coulter, Fullerton, CA, USA) and free insulin (Abbott Architect i1000SR immunoassay analyzer, Abbot Diagnostics, Santa Clara, CA, USA) levels at baseline were measured on all subjects. Coefficients of variation ranged from 1.4–5.6% and 2.4–2.9%, respectively. These assays were performed at the University of California, Davis Medical Center (UCDMC) clinical lab in Sacramento, CA, USA. Insulin resistance was determined with the homeostasis model of assessment – insulin resistance (HOMA-IR) formula, which is calculated as: (fasting glucose concentration [mg/dl] \times fasting insulin concentration [$\mu\text{U}/\text{ml}$])/405. HOMA-IR values have been validated as surrogate markers of insulin resistance and correlate well with insulin resistance values determined by euglycemic-insulin clamp or the frequently sampled IV glucose tolerance test (32).

Posteroanterior weight bearing knee radiographs were obtained using a Synaflexer frame (Synarc, San Francisco, CA, USA) to create a standardized knee position. All radiographs

for each participant were read together in known order by a team of experienced readers at a central location (Boston University). Readers were blind to the DM status and all clinical characteristics of the participants. Each of two readers read all radiographs from all the participants. Cases of disagreement were addressed by adjudication with a third reader (33, 34). Self-reported KR was confirmed by radiographs and/or medical records. For the purposes of this knee-level investigation, knees with incident tibiofemoral RKOA were identified separately at each visit from baseline to 84 months. A knee was defined as having this endpoint if there was at least one follow-up radiograph showing RKOA (KL grade 2 or greater) or if there had been a TKR at the time of the visit. The status of every knee was followed from baseline to 84 months. Once the criteria for incident RKOA were met, the knee was considered to have RKOA for the remainder of the study. Additionally, physical examinations of joints occurred at baseline and 30 months (26).

Statistical Analysis

Descriptive characteristics were analyzed by analysis of variance (ANOVA) for continuous variables and chi-squared test for categorical variables. Incidence of RKOA between baseline and the 84-month follow-up were evaluated as cumulative incidence.

In this study, events were discovered at clinic visits when knee radiographs were acquired, and we used pooled logistic regression to conduct a discrete time survival analysis (consecutive clinic visit at 30m, 60m or 84m). To conduct such an analysis, the data were transformed to multiple records per knee, one record per visit. If knee status was unknown (e.g., if the visit was missed or if the visit was done without imaging), the outcome was considered to be missing. Once an event occurred, all subsequent records (visits) for the affected knee were dropped from the analysis (i.e., each incidence was counted only once). Data collection continued for the other knee.

Knee level pooled logistic regression analysis (35, 36) was performed to obtain odds ratios and 95% CIs for incidence of RKOA predicted by baseline DM status, baseline fasting glucose and HOMA-IR. Generalized estimating equations were used to account for within-person correlations (between knees). Models were adjusted for age, gender, race, clinic site, visit (time to event; this variable allowed for the rate of events to change over time) and time-dependent BMI at each visit. Formal interactions for exposure*sex, as well as exposure*BMI, were examined. Missing observations (2.4% in this study) were dropped from the analysis.

Sensitivity analyses were also performed. We first examined whether excluding participants with newly reported DM (n=54) would influence the results of the analyses. Secondly, we performed the analyses in whites only (n=849) in order to remove the influence of the race. Additionally, we ran further sensitivity analyses using time-dependent DM (a combination of baseline DM and incident self-report of DM at a subsequent visit) and DM medication use, and specifically metformin use, as primary exposures. We also adjusted models for metformin use (i.e., in this sensitivity analysis, metformin use was a covariate rather than a primary exposure). Lastly, we examined the effect of physical activity by adjusting models for PASE score. All analyses were performed using SAS v9.4.

RESULTS

Among the 987 participants (mean age 60.6 ± 7.8 years, 58% female, mean BMI 29.1 ± 4.9 kg/m²), 94 (9.5%) had DM at baseline. Compared to participants without DM, participants with DM were more likely to be male, non-white and reside in Alabama. Among whites residing in Iowa, the prevalence of DM was 7.1% (5.8% in women and 9.0% in men). Among whites in Alabama, the prevalence of DM was 8.4% (7.2% in women and 10.1% in men). The prevalence of DM in blacks residing in Alabama was 23.3% (16.7% in women and 31.5% in men). There were only three black participants residing in Iowa; all were men and none had DM.

Of the 94 participants classified as having DM at baseline, 56 were taking DM medications (including 42 taking metformin), and 56 had elevated fasting glucose. Nineteen participants were classified as having DM based on self-report only, 2 had DM based on medications only, and 19 had DM based on fasting glucose levels only.

As expected, participants with DM had significantly higher fasting glucose, fasting insulin and HOMA-IR compared to participants without DM at baseline (Table 1). Additionally, participants with DM had a higher BMI and were less likely to consider their health status to be “excellent,” “very good” or “good” compared to participants without DM (Table 1).

In the cohort of 987 participants, 1972 knees were included in this analysis. Two participants did not return for follow up visits but reported by telephone contact a KR between the 60-month and 84-month visits. There were 165 (2.4%) records with a missing interim visit, and there were 365 knees (18%) that did not have 7 years of follow up.

There were 409 knees with incident RKO. Between baseline and the 84-month follow-up visit, the cumulative incidence of RKO for all knees was 23.3%; the cumulative incidence was slightly higher for knees with DM compared to knees without DM (24.0% versus 23.2%; Table 2).

The odds ratios of incident RKO by baseline DM status, baseline fasting glucose and HOMA-IR are presented in Table 3. Baseline fasting glucose and HOMA-IR were associated with increased odds of incident RKO in the unadjusted model, as well as model adjusted for age, race, clinic site and visit. After adjustment for BMI, these associations were attenuated and lost statistical significance. Fasting insulin values were highly correlated with HOMA-IR by design. As expected, the risk of incident RKO by fasting insulin mirrored the results for HOMA-IR and did not reveal any new findings (data not shown).

The only formal interaction that neared significance ($p < 0.05$) was between HOMA-IR and sex ($p = 0.12$); sex stratified results for the odds ratio for HOMA-IR and incident RKO are presented in Table 4. In women, elevated HOMA-IR was associated with lower odds of incident RKO in the model adjusted for sex, age, race, clinic site, visit and BMI. In men, elevated HOMA-IR was associated with increased odds for RKO in the model adjusted for sex, age, race, clinic site and visit. However, after adjustment for BMI, this association was attenuated and no longer statistically significant.

We repeated all analyses using participant-level incidence of RKOAs as the outcome. There were no noteworthy differences between results at the participant level and results at the knee level (data not shown). A total of 54 participants self-reported a diagnosis of DM between baseline and the 84-month follow up visit, but excluding these participants from the non-DM group did not substantially change overall results (Supplementary Table 1). Among white participants overall, there were no associations between baseline DM status, fasting glucose or HOMA-IR and odds of incident RKOAs in any of the models (Supplementary Table 2). Sensitivity analyses using time-dependent DM as the exposure and PASE score as a covariate did not substantially alter our main findings (data not shown). Metformin usage by itself was associated with a nonsignificant protective effect (OR: 0.69; 95% CI 0.43–1.09, $p=0.11$) for RKOAs, but when included as a covariate in models with HOMA-IR, the protective effect of the HOMA-IR in women was unchanged and remained significant ($p=0.007$).

DISCUSSION

This prospective analysis among older women and men with an elevated risk of developing knee OA contributes to the literature by focusing specifically on the associations between DM status (as defined by self-report, use of anti-diabetic medications or fasting glucose), and biomarkers of abnormal glucose metabolism, with odds of subsequently developing incident RKOAs. Contrary to our hypothesis, after adjustment for BMI (a strong risk factor for both DM and knee OA (16–20)) we did not find increased odds of incident RKOAs in participants with DM nor in participants with higher baseline levels of fasting glucose and HOMA-IR. Surprisingly, after adjustment for BMI, we observed a protective association of higher levels of HOMA-IR with the odds of incident RKOAs in women. This protective effect was not explained by use of diabetic medications in those with insulin resistance.

Our findings contrast with some previous studies of DM and DM-related factors and knee OA but are consistent with other studies. At least two meta-analyses have suggested an overall positive, though modest, association between the presence of DM and OA (16, 17). However, these analyses have important limitations, which include combining studies of knee, hip and hand joints, combining studies using different definitions of OA (radiographic, arthroplasty and clinical diagnosis) and pooling results from cross-sectional and prospective studies. Many of the included studies were cross-sectional and/or did not adjust for obesity (16, 17), a strong risk factor for both DM and knee OA (18–20) and important potential confounding factor. To our knowledge, there are few prospective studies of DM and knee OA outcomes, and none of incident radiographic knee OA, the focus of the present study. A recent prospective study (13) found, after BMI adjustment, that increased radiographic progression of existing knee OA was associated with baseline DM in men, but not women. Whether DM preceded the onset of knee OA in this study is not known.

Several cohort studies have explored associations between DM-related variables, including metabolic factors, and knee OA (22, 37–39). Yoshimura and colleagues analyzed impaired glucose tolerance [IGT], based on elevated serum hemoglobin A1c, and the three-year incidence and progression of RKOAs in a cohort of Japanese men and women. They found that IGT was associated with an increased incidence of RKOAs, but not with the progression

of RKOA, after adjusting for obesity and other components of the metabolic syndrome (37). In contrast, in a recent study of components of metabolic syndrome and the incidence of both RKOA and symptomatic knee OA, Niu et al. found no association between elevated fasting glucose and these knee OA outcomes (24). Similarly, in two prospective studies with knee replacement as the outcome, after adjusting for BMI, there was no association between elevated fasting glucose and knee OA (23, 38). The findings of the present analysis, along with the conflicting reports in the literature, illustrate the complexity of determining whether an independent relationship between DM and OA exists after accounting for the potentially confounding role of obesity.

Our observation of an inverse association between HOMA-IR and odds of RKOA incidence in women was unexpected and possibly spurious but was not explained by use of diabetic medications, or metformin in particular, in those with insulin resistance. We also observed a potential, though not significant, protective effect of metformin usage on incident RKOA. This aligns with recent reports (39–41). Further investigation of potential protective effects of DM and DM medications is warranted.

The association of obesity and DM with OA has suggested the existence of a metabolic syndrome-associated osteoarthritis phenotype, with potential etiologic roles in joint damage for a variety of systemic and local metabolic abnormalities, including impaired glucose metabolism, hypertension, dyslipidemia, inflammation, oxidative stress and advanced glycation end products (15, 42). Future studies should address associations of DM and OA within the broader context of metabolic OA phenotypes.

This study has several strengths, including the utilization of a prospective design to study incident RKOA while eliminating the potential for reverse causality, a well-characterized, community acquired cohort and repeated follow-up over 7 years for development of RKOA. We did not rely solely on self-report to identify participants with DM but also based DM status on use of prescription anti-diabetic medications and fasting glucose levels.

Our study also has several limitations. It is possible that some participants may have given unreliable information about fasting (e.g., overstating the number of hours they had been fasting before the blood draw) and could have been falsely classified as having DM due to elevated glucose levels). Since the study is prospective, this type of misclassification is likely to be nondifferential with respect to incident OA, which could influence the odds ratios toward the null (i.e., no association). Data on DM type were not collected in the present study. It is likely that the majority of participants with DM in the present analysis had DM2 since DM2 is more prevalent (6) and insulin users were excluded; however, it is possible that some participants had type 1 DM (DM1). The definition of knee OA in this study was based on radiographic findings only (43). Because our sample included only those without radiographic OA at baseline, there were just 14 knees with incident symptomatic OA (the combination of radiographic OA and frequent knee pain), which is too few for a separate analysis. Results may differ for incident symptomatic OA. Furthermore, this analysis was limited to tibiofemoral OA; findings may differ when taking patellofemoral or whole knee OA into account. DM has also been associated with reduced levels of osteophyte formation, possibly due to diminished availability of insulin at the cellular level or diabetic

microvascular disease attenuating proliferation (44). Potential protective effects on RKOA incidence in this study may reflect the importance of osteophytes in radiographic definitions of OA. Additionally, the MOST cohort was selected to have an elevated risk for incident RKOA and had a high BMI at baseline. (6). Thus, results of the present study may have limited generalizability since our study population does not reflect the incidence of RKOA or prevalence of DM in the general population. Finally, it is possible that our sample size was too small to detect associations between the exposure variables and RKOA; in particular, the wide confidence intervals for the baseline DM models in Table 3 suggest a certain degree of imprecision.

In this cohort of older adults with a high risk of developing knee OA, DM and higher levels of biomarkers of abnormal glucose metabolism were not associated with increased odds of incident RKOA after adjusting for BMI. We found evidence suggesting that these associations may differ by sex. In particular, a protective association of higher levels of insulin resistance (HOMA-IR) with odds of incident RKOA after BMI adjustment in women, but not men, deserves further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SIGNIFICANCE AND INNOVATION

- Osteoarthritis (OA) and diabetes mellitus (DM) are two of the most prevalent diseases worldwide.
- Meta-analyses have suggested positive associations of DM and OA, though limitations of previous studies include heterogeneity in definitions of OA and DM and lack of adjustment for body mass index (BMI) in some studies. In this prospective study, we examined associations of DM status and biomarkers of abnormal glucose metabolism specifically with incident radiographic knee OA (RKOA).
- Among older women and men with a high risk of developing knee OA, DM and biomarkers of abnormal glucose metabolism were not associated with odds of incident RKOA after adjustment for BMI.
- A possible protective association in women of greater insulin resistance (HOMA-IR) with lower odds of incident RKOA (after BMI adjustment) deserves further investigation.

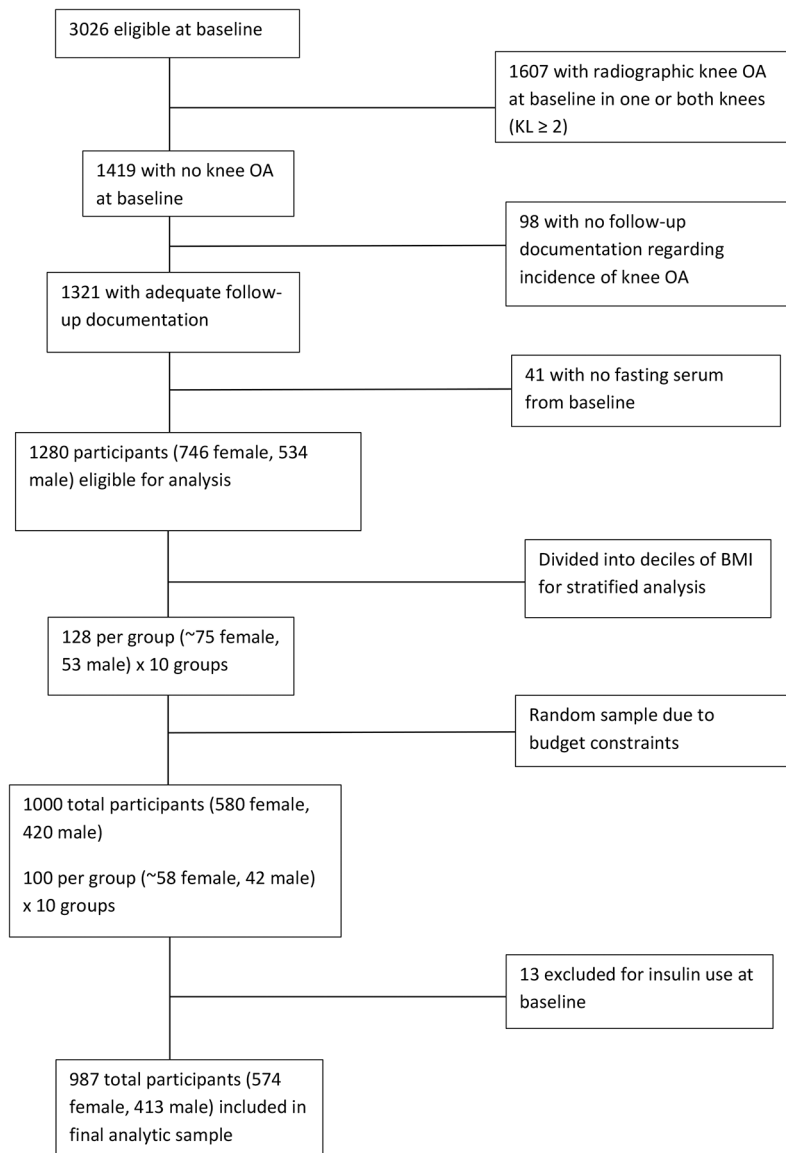


FIGURE 1:
FLOWCHART OF STUDY SAMPLE SELECTION
 KL, Kellgren & Lawrence
 OA, osteoarthritis

TABLE 1:
Descriptive characteristics at baseline,

Mean (SD) or n (%)

	No baseline DM (n=893)	Baseline DM (n=94)	P-value
Demographic characteristics			
Age (years)	60.6 (7.8)	60.7 (8.0)	0.877
Sex (female)	531 (59.5%)	43 (45.7%)	0.010
Race (white)	784 (87.8%)	65 (69.1%)	<.0001
Clinic (UAB)	425 (47.6%)	59 (62.8%)	0.005
Metabolic parameters			
Fasting blood glucose (mg/dL)	95.4 (9.2)	141.7 (45.9)	<.0001
Fasting insulin (muU/mL)	9.0 (7.6)	14.6 (10.2)	<.0001
HOMA-IR	2.2 (1.9)	5.0 (3.7)	<.0001
Anthropometric characteristics			
Weight (kg)	83.0 (15.8)	95.9 (19.0)	<.0001
Height (m)	1.7 (0.08)	1.7 (0.09)	0.1105
BMI (kg/m ²)	28.7 (4.7)	32.5 (5.2)	<.0001
General functional status			
Health status (self-assessment)			
Excellent/Very Good/Good	840 (94.1%)	73 (77.7%)	<.0001
Fair/Poor	53 (5.9%)	21 (22.3%)	
PASE (activity score)	181.5 (89.3)	197.2 (98.3)	0.1088

BMI, body mass index; DM, diabetes mellitus; HOMA-IR, homeostasis model of assessment – insulin resistance; PASE, physical activity scale for the elderly; UAB, University of Alabama at Birmingham

TABLE 2.

Knee-level incidence of radiographic knee osteoarthritis (RKOA) during 84 month follow-up

	Study sample N=1972 knees	No baseline DM N=1785 knees	Baseline DM N=187 knees
Number of knees with incident RKOA	409	368	41
Cumulative incidence (%):			
At 30 months	6.5	6.4	8.0
At 60 months	17.2	17.1	17.5
At 84 months	23.3	23.2	24.0

DM, diabetes mellitus

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TABLE 3.
Odds ratio for incidence of knee osteoarthritis (OA),

n=987 participants (1972 knees)

Model	Exposure	Odds Ratio (95% CI) and <i>P</i> for incidence of knee OA		
		Unadjusted Model	Adjusted Model ^a	Adjusted Model ^b
#1	Baseline DM status	1.06 (0.72–1.54) 0.778	1.05 (0.71–1.54) 0.813	0.79 (0.53–1.18) 0.246
#2	Fasting glucose (per 1 SD)	1.14 (1.02–1.28) 0.021	1.14 (1.01–1.27) 0.031	0.98 (0.87–1.11) 0.751
#3	HOMA-IR (per 1SD)	1.13 (1.01–1.27) 0.033	1.13 (1.00–1.27) 0.042	0.89 (0.79–1.01) 0.077

^a Adjusted for sex, age, race, clinic site and visit

^b Adjusted for sex, age, race, clinic site, visit and BMI (time-dependent)

BMI, body mass index; DM, diabetes mellitus; HOMA-IR, homeostasis model of assessment – insulin resistance

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TABLE 4.

Odds ratio for incidence of knee osteoarthritis (OA) by HOMA-IR, stratified by sex

Odds Ratio (95% CI) and <i>P</i> for incidence of knee OA					
Women, n=574			Men, n=413		
Unadjusted Model	Adjusted Model ^a	Adjusted Model ^b	Unadjusted Model	Adjusted Model ^a	Adjusted Model ^b
1.08 (0.94–1.24) 0.303	1.05 (0.91–1.22) 0.470	0.80 (0.69–0.94) 0.005	1.28 (1.05–1.56) 0.015	1.30 (1.07–1.58) 0.007	1.09 (0.89–1.33) 0.424

^a Adjusted for sex, age, race, clinic site and visit^b Adjusted for sex, age, race, clinic site, visit and BMI (time-dependent)

BMI, body mass index; DM, diabetes mellitus; HOMA-IR, homeostasis model of assessment – insulin resistance

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