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Metabolic osteoarthritis – Relation of diabetes and cardiovascular disease with knee osteoarthritis

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Abstract

Objective: There is an interest in identifying a metabolic OA phenotype. We therefore assessed the relation of diabetes and cardiovascular disease to prevalent and incident radiographic (ROA) and symptomatic knee osteoarthritis (SxOA).

Design: In two large cohort studies of individuals with or at risk for knee OA, the Multicenter Osteoarthritis Study (MOST) and Osteoarthritis Initiative (OAI), participants self-reported diabetes and cardiovascular disease (CVD) at baseline. We assessed the relation of baseline diabetes and CVD (exposures) to ROA and SxOA cross-sectionally and after 60 (MOST) or 48 (OAI) months of follow-up using logistic regression with GEE to account for 2 knees within an individual, adjusting for potential confounders.

Results: In MOST, 6020 knees of 3021 participants (60.1% female, mean±SD age 62.5±8.1, mean BMI 30.7±6.0, 83.3% Caucasian) were included in the analyses. In OAI, 8645 knees of 4339 participants (58.2% female, mean±SD age 61.1±9.2, mean BMI 28.6±4.8, 80.3% Caucasian) were included. We found no significant associations between prevalent diabetes or CVD and prevalent or incident ROA or SxOA. Effect estimates for prevalent ROA and SxOA ranged from 0.80 (95% CI 0.63–1.03) to 1.17 (0.91–1.51). Effect estimates for incident ROA ranged from 0.80 (0.58–1.11) to 0.88 (0.60–1.29) in MOST and from 0.75 (0.50–1.14) to 1.19 (0.81–1.74) in OAI, and for incident SxOA from 0.93 (0.65–1.31) to 1.22 (0.89–1.67) in MOST and from 0.82 (0.59–1.16) to 1.19 (0.85–1.66) in OAI).

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Contributions

Conception and design: LK, TN; Data acquisition: DF, CL, JT, MN, TN; Data analysis and interpretation: LK, NW, TN; Drafting of article: LK, TN; Critical revision for important intellectual content and final approval of the article: all authors.

Competing interest statement

Dr. Kuusalo has provided consulting services to Gilead, Pfizer, and Novartis, and reports lecture and travel fees from Abbvie, Lilly, Novartis, MSD, Orion, Pfizer, and Sanofi outside the submitted work. The other authors report no competing interests.

Conclusions: Diabetes and CVD were not associated with prevalent or incident knee OA.

Keywords

knee osteoarthritis; metabolic; diabetes; cardiovascular disease

Introduction

Knee osteoarthritis (OA), diabetes, and cardiovascular disease (CVD) are common in the aging population and frequently coexist. In addition to aging and biomechanical factors, OA is also associated with many cardiovascular risk factors, including diabetes, hypertension, obesity, and systemic low grade inflammation [1, 2], raising the potential that there is a 'metabolic OA' phenotype.

Although diabetes and hyperglycemia have been linked to accelerated cartilage degeneration [3], the relation of diabetes to knee OA is challenging to investigate as obesity is a well-established risk factor for both type 2 diabetes and knee OA [1]. Two meta-analyses found an association between type 2 diabetes and OA of various sites [2, 4]. Louati et al. analyzed 34 studies [2]. Twelve of these studies tested the association of diabetes and OA after adjustment for BMI with inconclusive results; five studies demonstrated an association whereas seven did not. Another meta-analysis by Williams et al. included ten studies, of which seven adjusted for weight or BMI [4]. In this meta-analysis, the positive association of diabetes and OA was present in the studies controlling for weight or BMI, with a similar effect estimate to that of the overall meta-analysis. However, some of the included studies were cross-sectional or case-control studies. Large, longitudinal studies of individual-level data on the association between diabetes and osteoarthritis are therefore needed to more validly examine the potential independent association between diabetes and knee OA.

Similar to diabetes, there is also a potential link between CVD and OA. Physical inactivity related to pain in knee OA may partly explain the elevated risk of cardiovascular disease observed in knee OA patients [5]. Furthermore, knee OA and CVD both correlate with obesity and aging, which are also associated with low grade systemic inflammation related to adipose tissue accumulation [6]. CVD could also be a marker for generalized atherosclerosis leading to subchondral ischemia and accelerated cartilage degeneration [7]. However, despite several studies exploring overall cardiovascular risk in knee OA patients [8, 9], CVD has not been studied as a risk factor for knee OA.

To date, it remains unclear whether diabetes and CVD predispose to knee OA or if their effects are mediated through shared risk factors. In the current study, we examined the cross-sectional and longitudinal relation of diabetes and CVD with radiographic and symptomatic knee osteoarthritis among participants of the Multicenter Osteoarthritis (MOST) study and the Osteoarthritis Initiative (OAI).

Methods

Study sample

In the current study, we analyzed data from two large cohort studies of individuals with or at high risk for knee OA. MOST enrolled 3026 subjects aged 50–79 years with, or at high risk for, radiographic or symptomatic knee OA from two study sites [10]. OAI recruited 4796 subjects aged 45-69 years from four study sites (https://oai.nih.gov). Written informed consent was obtained from all participants prior to inclusion in both studies. The studies were approved by the Institutional Review Board (IRB) of the coordinating center, University of California, San Francisco, and the IRBs of the collaborating and clinical centers.

Clinical and radiological evaluation

We used data from baseline for both cohorts. To assess longitudinal outcomes, we used data from the 60-month visit in MOST and the 48-month visit in OAI. At baseline, participants completed a modified version of the Charlson Comorbidity Index, a validated, self-reported measure of comorbid conditions. It was based on this self-reported evaluation that presence of diabetes and CVD was ascertained. Posteroanterior weight-bearing fixed flexion knee radiographs were obtained at baseline and follow-up in MOST and OAI. Radiographs for both cohorts were graded centrally at Boston University School of Medicine by two experienced readers for Kellgren and Lawrence (KL) grade. If the two readers disagreed on OA status at baseline or follow-up, the x-ray reading was adjudicated by a panel of 3 experienced readers.

Definition of exposures

We defined prevalent CVD as self-reported heart attack, stroke, transient ischemic attack, heart or leg bypass surgery, or treatment for heart failure based on the Charlson Comorbidity Questionnaire. Prevalent diabetes was defined as self-reported diagnosis of diabetes.

Definition of outcomes

Cross-sectional outcomes—In both MOST and OAI, we defined knee ROA as a KL grade ≥2 at baseline. A knee was defined as having prevalent symptomatic OA if the knee with ROA was also reported as having ‘frequent knee pain’ based on the respondent’s report of pain, aching or stiffness in or around the knee on most days of the 30 days in MOST, or on most days for at least one month during the past 12 months in OAI.

Incident outcomes—We defined incident knee ROA as a knee with KL grade 0 or 1 (no osteoarthritis) at baseline that progressed to KL grade ≥2 by 60-months in MOST and by 48-months in OAI, or underwent knee replacement during the follow-up. Incident SxOA was defined as present in a knee that did not meet criteria for SxOA at baseline but developed incident SxOA or had a knee replacement during the follow-up.

Statistical analyses

We assessed the relation of prevalent CVD and diabetes at baseline to prevalent and incident ROA and SxOA using logistic regression, with generalized estimating equations to adjust for correlations between knees within each participant. Diabetes and CVD exposure were analyzed in separate models. We adjusted the analyses for age, sex, race, BMI, history of knee injury/surgery in either knee, and physical activity at baseline. SAS 9.4 (SAS Institute) statistical package was used for the analyses.

Results

Demographics

We included 6020 knees of 3021 participants from MOST in the baseline cross-sectional analyses (60.1% female, mean±SD age 62.5±8.1, mean BMI 30.7±6.0, 83.3% Caucasian). In the OAI dataset, there were 8645 knees of 4339 participants included (58.2% female, mean±SD age 61.1±9.2, mean BMI 28.6±4.8, 80.3% Caucasian) in the cross-sectional analyses. Detailed descriptive data by exposure status for both cohorts are shown in Supplementary Tables 1–4. Number of knees excluded due to missing follow-up data or covariates is shown in Supplementary Tables 5–6.

In the cross-sectional analyses (Table 1), we found no statistically significant association between CVD or diabetes and prevalent ROA or SxOA in either MOST or OAI, with effect estimates ranging from 0.80 (95% CI 0.63–1.03) to 1.00 (0.81–1.24) for ROA in both cohorts, and 0.95 (0.75–1.20) to 1.17 (0.91–1.51) for SxOA. In the longitudinal analyses, baseline CVD or diabetes were not associated with incident ROA or SxOA (Table 2), with effect estimates ranging from 0.75 (0.50–1.14) to 1.19 (0.81–1.74) for incident ROA, and 0.82 (0.59–1.16) to 1.22 (0.89–1.67) for incident SxOA. Results without adjustment for BMI are presented in Supplementary Tables 7–8 and results stratified by obesity (BMI ≥ 30) in Supplementary Tables 9–10. We show the results of combined analyses from the two cohorts in Supplementary Table 11. In these analyses, the effect estimate for diabetes and prevalent ROA was 0.55 (0.32–0.97). As a sensitivity analysis, we analyzed also the incidence of knee ROA and SxOA in participants free of knee OA in both knees at baseline, see Supplementary Table 12.

Discussion

We evaluated the relation of diabetes and CVD to prevalent and incident knee OA in two large cohorts comprising more than 7000 individuals. To our knowledge, this represents the largest longitudinal study on this subject. We observed no relations of baseline CVD or diabetes with incident ROA or SxOA after a follow-up of 4–5 years. However, when the cohorts were combined, diabetes was associated with lower odds of prevalent ROA. We cannot, however, rule out the possibility of a Type 1 error. Hence, our results indicate that compared to strong, established knee OA risk factors such as obesity, the effects of diabetes and CVD on the development of knee OA, if present, are most likely too small to be detected even in large longitudinal studies.

Although previous research suggests that diabetes may influence the development of OA, we found no evidence of this. Although prevalent diabetes was associated with lower odds of prevalent ROA, we cannot rule out the possibility of a Type 1 error, as mentioned above, considering the number of analyses we have conducted, particularly as we cannot posit a biologic rationale for this association. Metabolic pathways are considered important in OA pathogenesis and two meta-analyses have reported associations of diabetes with OA of knee, hip and hand [2, 4]. However, in these meta-analyses, only 12 out of 34 [2] and seven out of ten [4] studies adjusted for weight, respectively. In the former meta-analysis, an association between diabetes and OA was observed in only five of the 12 BMI-adjusted studies [2]. However, diabetes remained positively associated with OA in the latter meta-analysis when only BMI-adjusted studies were included [4]. Furthermore, no evidence of an association between impaired glucose tolerance or diabetes with incident knee OA was found in a systematic review of 28 studies that included age, gender, and obesity as covariates, corroborating our results [11]. In this review by Dawson et al., the authors noted that only five of the included studies adjusted appropriately for the aforementioned confounders. Our results are also in line with a smaller study by Rogers-Soeder et al. using data from the MOST cohort while adjusting for BMI [12]. In this study, no association of diabetes, elevated fasting glucose or insulin resistance with incident radiographic knee OA was observed after a follow-up of 84 months in a sample of 987 participants [12]. The level of evidence between a link between diabetes and knee OA thereby remains low.

The prevalence of CVD and OA increase significantly with age and BMI, without necessarily being causally related. We did not detect a cross-sectional or longitudinal association between these disease states while adjusting for relevant confounders. Knee OA has been associated with elevated risk of cardiovascular disease (CVD) in the general population, possibly due to patients' reduced mobility or common risk factors [5]. Two meta-analyses have suggested that knee OA is a CVD risk factor [8, 9]. In these meta-analyses by Wang et al. and Hall et al., ten of 15 studies [8] and 14 of 15 studies adjusted for BMI, respectively [9]. However, a recent Mendelian randomization study did not provide evidence on a causal association between genetically predicted CVD risk factors, such as blood pressure and fasting plasma glucose, and OA, which was consistent with our results [13].

To date, it has remained unclear whether CVD and diabetes are associated with knee OA independent of weight as obesity significantly increases the risk of these diseases as well as the risk of knee OA [13, 14]. Obesity increases the mechanical stress on the knee. Together with age, female sex and knee injuries, it is among the best-characterized risk factors for knee OA [10, 14]. The findings of our study suggest that obesity may be one reason for the common co-occurrence of CVD or diabetes with OA.

Our study has some limitations. The ascertainment of CVD and diabetes were based on self-reported data. We had no data on participants' biochemical parameters. Although the comorbidity questionnaire used is validated, self-report may over- or underestimate the prevalence of the diseases in question, and does not provide insights into severity or duration of disease. Further, according to the 2017 Centers for Disease Control and Prevention National Diabetes Statistics, 23.8% of people with diabetes are undiagnosed [15]. Thus, the prevalence of CVD, and particularly of diabetes, is likely an underestimate in the study

sample, which could bias results toward the null. Second, although data from *in vitro* studies and animal models suggest that hyperglycaemia alters cartilage metabolism [1], the influence of diabetes as a risk factor for a slowly developing and progressing disease like OA may be difficult to detect after a follow-up of 4-5 years. On the other hand, extended follow-up time might lead to loss to follow-up which could also present a challenge for detecting possible associations. We may also have issues of depletion of susceptibles related to the fact that diabetes in particular is a chronic disease that may start in early-to-middle adult years. Thus, it may be challenging to detect the influence of diabetes on development of knee OA in older adults if diabetes influences OA onset at a younger age than studied in these samples. However, if that were the case, given the high prevalence of diabetes in the general population, one may expect to have a larger proportion of the population developing OA at a younger age than studied in these cohorts.

In summary, we found no evidence of a relation of diabetes and CVD with prevalent and incident ROA and SxOA. Metabolic abnormalities contributing to a potential metabolic OA phenotype could not be confirmed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Role of the funding source

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The OAI is a public-private partnership comprised of five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the NIH, a branch of the Department of Health and Human Services, and conducted by the OAI Study Investigators. Private funding partners include Merck Research Laboratories; Novartis Pharmaceuticals Corporation, GlaxoSmithKline; and Pfizer, Inc. Private sector funding for the OAI is managed by the Foundation for the National Institutes of Health.

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Table 1.

Cross-sectional analyses on the relation of cardiovascular disease and diabetes with radiographic and symptomatic knee OA.

	Baseline ROA in MOST			**Baseline SxOA in MOST**		
	N (knees)	**Events**	**OR* (95% CI)**	**N (knees)**	**Events**	**OR* (95% CI)**
CVD						
No	5283	2118	1.0 (reference)	5281	923	1.0 (reference)
Yes	737	357	1.00 (0.81–1.24)	734	170	1.15 (0.90–1.47)
Diabetes						
No	5428	2166	1.0 (reference)	5424	921	1.0 (reference)
Yes	558	288	0.80 (0.63–1.03)	557	159	1.09 (0.84–1.41)
	Baseline ROA in OAI			Baseline SxOA in OAI		
	N (knees)	Events	OR* (95% CI)	N (knees)	Events	OR* (95% CI)
CVD						
No	8058	3518	1.0 (reference)	8051	1655	1.0 (reference)
Yes	526	270	0.94 (0.75–1.17)	526	141	1.17 (0.91–1.51)
Diabetes						
No	7997	3462	1.0 (reference)	7990	1614	1.0 (reference)
Yes	648	348	0.86 (0.69–1.06)	648	183	0.95 (0.75–1.20)

ROA, Radiographic OA; MOST, Multicenter Osteoarthritis Study; SxOA, symptomatic OA; OR, Odds ratio; CI, confidence interval; CVD, cardiovascular disease; OAI, Osteoarthritis Initiative.

*Adjusted for age, sex, race, body mass index, history of knee injury/surgery, physical activity, and correlation between knees of each participant.

Table 2.

Longitudinal analyses on the relation of cardiovascular disease and diabetes with incident radiographic and symptomatic knee OA.

	Incident ROA at 60 months in MOST			**Incident SxOA at 60 months in MOST**		
	N (knees)	**Events**	**OR* (95% CI)**	**N (knees)**	**Events**	**OR* (95% CI)**
CVD						
No	2683	549	1.0 (reference)	3551	546	1.0 (reference)
Yes	280	53	0.80 (0.58–1.11)	401	77	1.22 (0.89–1.67)
Diabetes						
No	2699	545	1.0 (reference)	3634	559	1.0 (reference)
Yes	208	54	0.88 (0.60–1.29)	302	58	0.93 (0.65–1.31)
	Incident ROA at 48 months in OAI			Incident SxOA at 48 months in OAI		
	N (knees)	Events	OR* (95% CI)	N (knees)	Events	OR* (95% CI)
CVD						
No	4180	637	1.0 (reference)	5620	797	1.0 (reference)
Yes	225	49	1.19 (0.81–1.74)	322	64	1.19 (0.85–1.66)
Diabetes						
No	4181	641	1.0 (reference)	5618	798	1.0 (reference)
Yes	257	47	0.75 (0.50–1.14)	376	67	0.82 (0.59–1.16)

ROA, Radiographic OA; MOST, Multicenter Osteoarthritis Study; SxOA, symptomatic OA; OR, Odds ratio; CI, confidence interval; CVD, cardiovascular disease; OAI, Osteoarthritis Initiative.

*Adjusted for age, sex, race, body mass index, history of knee injury/surgery, physical activity, and correlation between knees of each participant.