Arthritis Care & Research
Vol. 73, No. 4, April 2021, pp 540–548
DOI 10.1002/acr.24173

American College of Rheumatology
Empowering Rheumatology Professionals

Impact of Diabetes Mellitus on Knee Osteoarthritis Pain and Physical and Mental Status: Data From the Osteoarthritis Initiative

Annett Eitner,[1] Adam G. Culvenor,[2] Wolfgang Wirth,[3] Hans-Georg Schaible,[1] and Felix Eckstein[3]

Objective. Diabetes mellitus (DM) appears to increase osteoarthritic knee pain, which may be related to greater adiposity and more advanced disease status often observed in individuals with osteoarthritis (OA) and DM. We aimed to assess whether OA knee pain and health status are worse in individuals with OA and DM, independent of these potential confounders.

Methods. We included 202 OA participants with DM and 2,279 without DM from the Osteoarthritis Initiative. Knee pain was evaluated using the Knee Injury and Osteoarthritis Outcome Score (KOOS) and a numeric rating scale (NRS). Physical and mental status were assessed by the Medical Outcomes Study Short Form 12 (SF-12) questionnaire, physical component summary (PCS) score and mental component summary (MCS) score, and by the Center for Epidemiologic Studies Depression Scale (CES-D). Linear regression models assessed the influence of DM, adjusted for age, sex, body mass index (BMI), and radiographic severity.

Results. OA participants with DM reported worse knee pain and greater physical and mental issues compared with participants without DM. Individuals with DM had worse KOOS pain (β = –4.72 [95% confidence interval (95% CI) –7.22, –2.23]) and worse NRS pain (β = 0.42 [95% CI 0.04, 0.80]) independent of BMI, OA severity, age, and sex. The negative influence of DM was also apparent for SF-12 PCS (β = –3.49 [95% CI –4.73, –2.25]), SF-12 MCS (β = –1.42 [95% CI –2.57, –0.26]), and CES-D (β = 1.08 [95% CI 0.08, 2.08]).

Conclusion. Individuals with knee OA experience on average higher pain intensity and a worse physical and mental health status if they have DM. Linear regression models show that DM is a risk factor for higher pain, in addition to and independent of greater BMI and radiographic OA severity.

INTRODUCTION

Individuals with diabetes mellitus (DM) have greater rates of incident and progressive osteoarthritis (OA) compared with controls without DM (1–4). An increased risk for OA in patients with DM was found for knee and hand OA, moreso than for hip OA (3). DM has also been linked with higher rates of joint replacement, particularly at a younger age (5,6). Although the mechanisms driving the higher rates of incident and progressive OA in individuals with DM are unknown, epidemiologic and experimental data have strengthened the concept of a DM-induced OA phenotype (7,8), assuming that hyperglycemia toxicity is an important trigger of joint degradation. However, although there is much evidence for a role of metabolic factors in the development of OA (9), the

This article was prepared using an Osteoarthritis Initiative (OAI) public-use data set, and its contents do not necessarily reflect the opinions or views of the OAI Study Investigators, the NIH, or the private funding partners of the OAI. The OAI is a public–private partnership between the NIH (contracts N01-AR-2-2258, N01-AR-2-2259, N01-AR-2-2260, N01-AR-2-2261, and N01-AR-2-2262) and private funding partners (Merck Research Laboratories, Novartis Pharmaceuticals, GlaxoSmithKline, and Pfizer, Inc.) and is conducted by the OAI Study Investigators. Private sector funding for the OAI is managed by the Foundation for the NIH. The authors of this article are not part of the OAI investigative team. Dr. Culvenor's work was supported by a National Health and Medical Research Council of Australia Early Career Fellowship (Neil Hamilton Fairley Clinical Fellowship APP1121173).

ClinicalTrials.gov identifier: NCT00080171.

[1]Annett Eitner, PhD, Hans-Georg Schaible, MD: University Hospital Jena and Friedrich Schiller University, Jena, Germany; [2]Adam G. Culvenor, PhD: Paracelsus Medical University Salzburg and Nuremberg, Salzburg, Austria, and La Trobe University, Bundoora, Victoria, Australia; [3]Wolfgang Wirth, PhD, Felix Eckstein, MD: Chondrometrics, Ainring, Germany, and Paracelsus Medical University, Salzburg, Austria.

Dr. Wirth is employed part-time with Chondrometrics and is co-owner of Chondrometrics. He has received consulting fees from Galapagos (less than $10,000). Dr. Eckstein is CEO of Chondrometrics. He has received consulting fees from Merck, Novartis, Bioclinica/Synarc, Samumed, AbbVie, Tissuegene, Servier, Galapagos, Roche, and Medtronic (less than $10,000 each) and has received research support from Pfizer, Eli Lilly and Company, Merck Serono, Novartis, Stryker, AbbVie, Kolon/Tissuegene, Synarc, Ampio, BICL, Orthotrophix, Medivir, Servier, and Galapagos. No other disclosures relevant to this article were reported.

Address correspondence to Annett Eitner, PhD, Department of Trauma, Hand and Reconstructive Surgery, University Hospital Jena, Friedrich Schiller University, D-07747 Jena, Am Klinikum 1, Germany. Email: Annett.Eitner@med.uni-jena.de.

Submitted for publication May 27, 2019; accepted in revised form February 18, 2020.

SIGNIFICANCE & INNOVATIONS

- For the first time, we demonstrate, in a large cohort of 2,481 participants with osteoarthritis, the strong impact of diabetes mellitus on osteoarthritis pain and physical and mental health status.
- The impact of diabetes mellitus was independent of osteoarthritis severity, body mass index, age, and sex. Thus, the results indicate that diabetes mellitus is an independent factor of greater osteoarthritis pain and worse health status.
- The results emphasize the need to consider comorbidities in the therapy of patients with osteoarthritis.

importance of such factors is still disputed, e.g., by the authors of the prospective longitudinal Framingham study (10). In the latter study on ~1,000 patients with OA, almost all associations became weak and nonsignificant after adjustment for body mass index (BMI) (10).

Pain intensity is also higher in OA joints of individuals with DM (6,11–13). This elevated pain intensity has been linked to enhanced synovitis and increased interleukin (IL)-6 in the synovial fluid present in individuals with OA and DM (6,12). Indeed, DM is associated with systemic low-grade inflammation, increased serum levels of C-reactive protein, IL-6, and tumor necrosis factor (TNF) (14). In several organs, DM can lead to microvascular alterations and dysfunction of endothelial mitochondria, as well as stimulation of the production of reactive oxygen species and advanced glycosylated end products (15,16). These cellular alterations in synovial joints can potentially induce enhanced local inflammation of articular tissue and worsen OA pathogenesis and pain. In addition, DM can potentially influence peripheral and central pain mechanisms via induction of peripheral neuropathy and central sensitization or changes in brain activities (17). Psychological and socioeconomic factors also have an impact on OA pain (18,19).

Important aspects to be considered in the context of greater OA-related pain in patients with DM are the potentially greater BMI and radiographic progression in patients with OA and DM (4,6,12). Obesity represents an independent risk factor of incident OA (20) that is not only based on greater mechanical stress on weight-bearing joints, but also on the release of proinflammatory cytokines by adipose tissue that may contribute to structural pathology (21). Beyond that fact, obesity and radiographic OA severity are often related to OA pain (22–24). Since OA pain intensity is not always aligned with radiographic severity (25), the source of pain is difficult to identify. Hence, it is currently unclear whether the greater pain sensation reported by individuals with OA and DM (6,11–13) is due to greater BMI and radiographic OA severity of patients with DM, or whether DM induces a particular phenotype of OA, in which other pain mechanisms are in play.

Given that previous studies of the relationship between DM and OA pain were of moderate sample size only and did not adjust for radiographic OA severity (6,11–13), the current study used a large observational cohort to test the hypothesis that OA pain sensation in individuals with DM is stronger than in controls without DM, independently of BMI and radiographic disease status. Further, we explored the extent to which other measures of physical and mental health status differ between individuals with and without DM, independent of these confounders.

PATIENTS AND METHODS

Study design. The current study used data from the public Osteoarthritis Initiative (OAI) database. The OAI is a longitudinal cohort study of individuals with or at increased risk of symptomatic radiographic knee OA. A description of the cohort study design, the inclusion and exclusion criteria of participants, and an overview of collected and measured data are available at https://data-archive.nimh.nih.gov/oai/. The OAI study was conducted in compliance with the ethical principles derived from the Declaration of Helsinki and was approved by the local ethics committees at the 4 clinical OAI centers in the US. Written informed consent was obtained in those centers.

A total of 4,796 participants ages 45–79 years were recruited at the 4 clinical OAI centers. The baseline data of the OAI were used for the current cross-sectional study. OAI participants with a possible history of rheumatoid arthritis, inflammatory arthritis, or polymyalgia rheumatic and with prior total knee replacement surgery were excluded from the current analysis. Based on a self-reported diagnosis of prior DM, participants were grouped into the status of having DM or not having DM. Individuals with missing information and those with a new diagnosis of DM during OAI follow-up were excluded. Similar approaches to selecting participants with DM from the OAI have been used in analyses of cartilage degeneration (26). The knee with the greater baseline symptom status was selected for the current analysis, using the frequency of pain, aching, or stiffness reported in or around the knee for at least 1 month during the past 12 months and using the pain severity over the last month rated on a numeric rating scale (NRS). When 1 knee had more frequent pain and the contralateral knee more severe pain, the knee with the greater pain frequency was chosen. In participants with identical pain frequency in both knees, the right knee was selected for analysis. Participants with missing baseline symptom status and missing structural severity score were also excluded (Figure 1). Additionally, OAI participants with no radiographic findings of OA in the selected knee (Kellgren/Lawrence grade 0) were excluded.

Study variables. *Knee pain.* The 5 domains of the reliable and valid Knee Injury and Osteoarthritis Outcome Score (KOOS) were completed by each participant (27). Knee pain was assessed with the KOOS pain subscale (0 = worst pain, 100 = no pain), encompassing knee pain during various activities (e.g., walking, stair climbing, standing, lying) over the previous

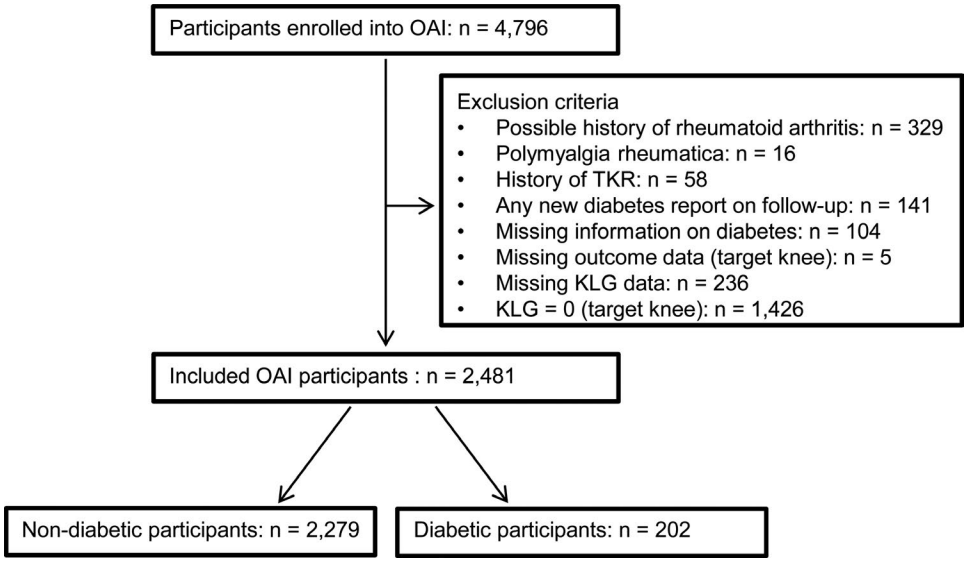

Figure 1. Selection of participants from the Osteoarthritis Initiative (OAI) database for the current study. TKR = total knee replacement; KLG = Kellgren/Lawrence grade.

7 days. Additionally, an 11-point NRS assessed a nonactivity-specific pain severity score for the past 30 days (0 = no pain, 10 = worst pain).

Physical and mental status. The Physical Activity Scale for the Elderly (PASE) was used to estimate participants' physical activity level. The PASE is an age-specific physical activity questionnaire that combines information on leisure, household, and occupational activity, especially for older people (28). The score ranges from 0 to 793, with higher scores indicating greater physical activity.

To assess general health status, the self-administered Medical Outcomes Study Short Form 12 (SF-12) questionnaire was used, one of the most extensively validated general health status instruments. The SF-12 consists of 12 questions covering physical and social functioning, emotional and mental health, and general health perception (29). This instrument was used to calculate the physical (SF-12 physical component summary [PCS] score) and mental (SF-12 mental component summary [MCS] score) summary scale scores. Both scores range from 0 to 100, with higher scores indicating better health status.

Depressive symptoms were assessed using the validated Center for Epidemiologic Studies Depression Scale (CES-D), a 20-item measure that rates symptoms associated with depression and scored from 0 to 60. Higher scores indicate more severe depressive symptoms (30). A CES-D score of ≥16 indicates the presence of clinically significant depression.

Covariates. BMI was calculated from the body weight and height, which were measured using a calibrated standard balance beam scale and a wall-mounted stadiometer. Participants were categorized into 1 of 4 BMI strata (in kg/m^2): normal weight (BMI <25), overweight (25–29.9), obese (30–34.9), and severely obese (≥35). Because there were only 9 underweight participants (BMI <18.5), these were included in the normal weight category.

The presence or absence of various comorbidities was documented (including heart failure, bypass operation, stroke, asthma, lung diseases, stomach ulcers, DM, problems with kidneys, rheumatoid arthritis, polymyalgia arthritis, liver diseases, and cancer), and the comorbidity score was calculated. Pain-related medication (including analgesics, nonsteroidal antiinflammatory drugs, opioid analgesics) was also recorded. Additionally, participants were asked about pain, aching, or stiffness in other joints in the past 30 days, including right and left hip, shoulder, elbow, wrist, hand/finger, ankle, and foot. The number of painful joints was calculated.

The Kellgren/Lawrence (K/L) grade was determined by central readers from the fixed-flexion knee radiographs (version 0.8) and used as a measure of radiographic OA severity. Details on the radiographic acquisition procedure are available at http://oai.epi-ucsf.org/datarelease/operationsManuals/RadiographicManual.pdf.

Statistical analysis. Participant characteristics are presented as median (interquartile range) due to not meeting assumptions of normality, or number (percentage) for categorical variables. The Mann-Whitney U tests and chi-square tests compared participants with and without DM, as appropriate. Box plots displayed the variations of the non-DM and DM groups in each K/L and BMI stratum. Differences between the non-DM and DM groups in each stratum were analyzed using linear regression, with adjustment for age and sex.

Multivariate linear regression analysis was used to explore the association between the presence of DM on the above variables. For each dependent variable (KOOS pain, NRS pain, PASE, SF-12 PCS, SF-12 MCS, and CES-D), 3 models were performed: one adjusting for age and sex alone, the second adjusting for age,

sex, BMI, and K/L grade, and the third adjusting for age, sex, BMI, K/L grade, pain medication, comorbidities, and the number of painful joints. The results were expressed as unstandardized coefficient (beta value) with 95% confidence interval. Sensitivity analyses were also performed with men and women separately. SPSS statistics 21 software was used for all analyses, with significance set at 0.05.

RESULTS

From a total of 4,796 OAI participants, 2,481 were included in the current analysis (Figure 1). Most individuals were scored with K/L grade = 2 (42%) (Table 1). Of the 2,481 included participants, 202 (8.14%) reported a diagnosis of DM. Participants with DM were older ($P = 0.032$) and had a greater BMI ($P < 0.001$) and a higher comorbidity score ($P < 0.001$) than participants without DM (Table 1). The K/L grade was not significantly different between both groups. The percentage of participants with DM in every K/L grade category was similar ($P = 0.175$ by chi-square test). KOOS pain, NRS pain, PASE, SF-12 PCS, and CES-D were all significantly worse for individuals with OA and DM compared to those without DM (Table 1). In all, 14.4% of participants with DM had significant depressive symptoms (CES-D ≥16), whereas only 9.1% of participants without DM had a CES-D of ≥16.

Individuals with OA and DM had significantly more comorbidities, such as heart failure, stroke, stomach ulcers, poor kidney function, or cancer (Table 2) compared to individuals without DM. The percentage of other diagnosed comorbidities, such as asthma, lung diseases, and serious liver damage was similar in both groups.

KOOS pain and NRS pain were worse in individuals with OA with a higher K/L grade or BMI (Figure 2). Importantly, across the different K/L grade categories, individuals with DM had even worse KOOS pain and greater NRS pain scores than individuals without DM (Figure 2A and 2B). Especially in subjects with severe OA (K/L grade = 4), differences of 11.1 points in the KOOS pain score and of 2.5 points in the NRS pain were recorded between subjects with DM and without DM (KOOS pain: $P = 0.014$; NRS pain: $P = 0.013$) (Figure 2). In the physical health scores of subjects with severe OA (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24173/abstract), the difference between subjects with and without DM was 49 points for PASE ($P = 0.030$) and 7.1 points for SF-12 PCS ($P = 0.030$). The mental health status of subjects with severe OA (see Supplementary Figure 2, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24173/abstract) did not differ significantly between both groups (SF-12 MCS: $P = 0.353$; CES-D: $P = 0.130$). Concerning BMI, individuals with OA and DM experienced significantly higher pain intensities in the overweight and obese category (Figure 2C and 2D).

The multivariate linear regression analysis revealed a strong and statistically significant association between the presence of DM and OA knee pain, as well as physical and mental parameters, after adjusting for age and sex. The strength of these

Table 1. Participant characteristics, including demographics, radiographic severity, pain scores, and physical and mental scores*

Characteristic	Participants without diabetes		Participants with diabetes		*P*
	No.	Value	No.	Value	
Age, years	2,279	62 (16)	202	65 (14.25)	0.032†
Sex: female/male, %	2,279	59.4/40.6	202	61.4/38.6	0.575‡
Body mass index, kg/m^2	2,277	28.6 (6.3)	201	31.6 (5.95)	<0.001†
Comorbidity score	2,270	0 (0)	201	1 (1)	<0.001†
Pain medication past 12 months, %	2,278	58.5	202	57.8	0.175‡
Kellgren/Lawrence, %					0.175‡
Grade 1	616	27.0	46	22.8	–
Grade 2	962	42.2	82	40.6	–
Grade 3	526	23.1	60	29.7	–
Grade 4	175	7.7	14	6.9	–
KOOS pain	2,277	83.3 (25)	202	75.0 (36.11)	<0.001†
NRS pain	2,273	3 (4)	202	4 (7)	0.006†
PASE	2,265	151 (110)	201	139 (105)	0.002†
SF-12 PCS	2,270	51.3 (12.3)	202	46.2 (14.8)	<0.001†
SF-12 MCS	2,270	56.0 (8.0)	202	55.8 (11.3)	0.255
CES-D	2,275	4 (8)	196	5 (8)	0.048†

* Values are the median (interquartile range) unless indicated otherwise. Mann-Whitney U test and chi-square test for categorical variables were used to compare groups. CES-D = Center for Epidemiologic Studies Depression Scale; KOOS = Knee Injury and Osteoarthritis Outcome Score; MCS = mental component summary score; NRS = numeric rating scale; PASE = Physical Activity Score for the Elderly; PCS = physical component summary score; SF-12 = Medical Outcomes Study Short Form 12.
† Statistically significant.
‡ *P* values by chi-square test.

Table 2. Comorbidities and number of painful joints of Osteoarthritis Initiative participants with and without diabetes mellitus*

	Participants without diabetes		Participants with diabetes		
	No.	%	No.	%	*P*†
Comorbidities					
Ever treated for heart failure	2,264	1.81	200	5.5	0.001‡
Operation to unclog or bypass arteries in legs	2,273	0.84	202	1.98	0.104
Stroke, cerebrovascular accident, blood clot or bleeding in brain, or transient ischemic attack	2,253	2.89	200	6.5	0.005‡
Asthma	2,238	8.13	199	10.05	0.347
Emphysema, chronic bronchitis, or chronic obstructive lung disease	2,248	1.82	192	3.65	0.081
Stomach ulcers or peptic ulcer disease	2,230	2.15	199	5.03	0.011‡
Diabetes mellitus	2,279	0	202	100	<0.001‡
Problems with kidneys, poor kidney function	2,243	0.94	196	3.06	0.006‡
Rheumatoid arthritis or inflammatory arthritis	–	0	–	0	–
Polymyalgia rheumatica	–	0	–	0	–
Cirrhosis or serious liver damage	2,264	0.27	198	0.51	0.543
Cancer, leukemia, or lymphoma	2,250	3.91	199	7.54	0.015‡
Number of painful joints, median ± IQR	2,279	2 ± 3.00	202	2 ± 2.25	0.016‡

* IQR = interquartile range.
† *P* values by chi-square test.
‡ Statistically significant.

associations was somewhat attenuated when additionally adjusted for BMI and K/L grade, but they remained statistically significant except PASE (Table 3). In model 3, after additional adjustment for pain medication, the presence or absence of several comorbidities, and the number of painful joints, the statistical analysis still revealed a statistically significant association between

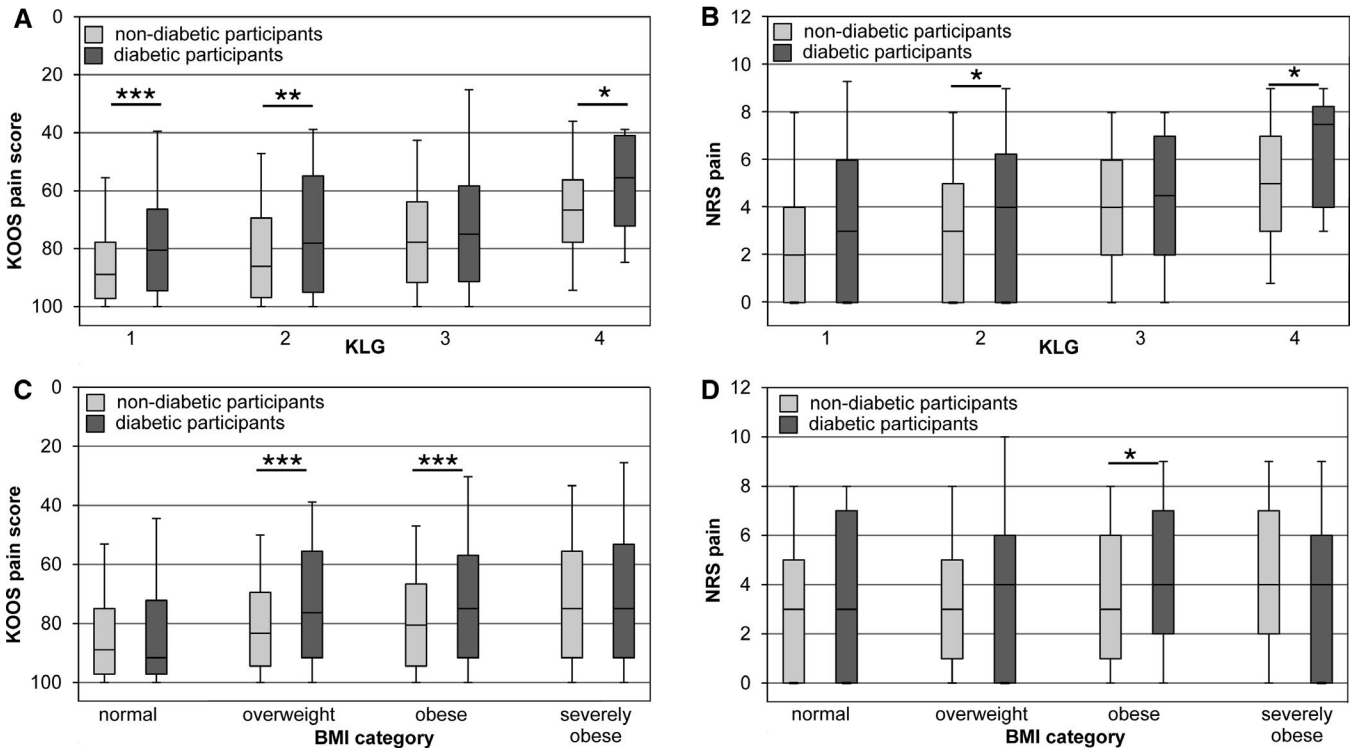

Figure 2. Distribution of Knee Injury and Osteoarthritis Outcome Score (KOOS) pain (**A** and **C**) and NRS pain (**B** and **D**) of participants without and with diabetes mellitus in each Kellgren/Lawrence grade (KLG) stratum and body mass index (BMI) category, respectively. Box plots display the median, the 25th percentile, and the 75th percentile, including whiskers that represent the 5th percentile and the 95th percentile. Differences between participants with and without diabetes mellitus were analyzed using linear regression analysis and adjusted for age and sex. * = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.005$; NRS = numeric rating scale.

Table 3. Association between the presence of diabetes mellitus and pain and physical and mental status using multivariate linear regression analysis*

	Model 1		Model 2		Model 3	
	Beta (95% CI)	*P*	Beta (95% CI)	*P*	Beta (95% CI)	*P*
KOOS pain	−6.72 (−9.31, −4.13)	<0.001†	−4.72 (−7.22, −2.23)	<0.001†	−3.32 (−5.62, −1.02)	0.005†
NRS pain	0.66 (0.27, 1.05)	0.001†	0.42 (0.04, 0.80)	0.031†	0.24 (−0.11, 0.59)	0.179
PASE	−14.52 (−25.34, −3.70)	0.009†	−10.55 (−21.51, 0.41)	0.059	−9.70 (20.92, 1.52)	0.090
SF-12 PCS	−4.88 (−6.15, −3.61)	<0.001†	−3.49 (−4.73, −2.25)	<0.001†	−2.63 (−3.81, −1.45)	<0.001†
SF-12 MCS	−1.58 (−2.71, −0.45)	0.006†	−1.42 (−2.57, −0.26)	0.016†	−1.19 (−2.36, −0.03)	0.045†
CES-D	1.49 (0.50, 2.48)	0.003†	1.08 (0.08, 2.08)	0.035†	0.73 (−0.28, 1.73)	0.156

* Model 1 was adjusted for age and sex; model 2 was adjusted for age, sex, body mass index (BMI), and Kellgren/Lawrence (K/L) grade for radiographic OA severity; model 3 was adjusted for age, sex, BMI, K/L grade, pain medication, comorbidities (including heart failure, bypass operation, stroke, asthma, lung diseases, stomach ulcers, problems with kidneys, liver diseases, and cancer), and the number of painful joints. 95% CI = 95% confidence interval; CES-D = Center for Epidemiologic Studies Depression Scale; KOOS = Knee Injury and Osteoarthritis Outcome Score; MCS = mental component summary score; NRS = numeric rating scale; PASE = Physical Activity Score for the Elderly; PCS = physical component summary score; SF-12 = Medical Outcomes Study Short Form 12.
† Statistically significant.

the presence of DM and KOOS pain ($P = 0.005$), SF-12 PCS, and SF-12 MCS (Table 3).

In sex-specific sensitivity analyses, the identified associations between the presence of DM and pain and physical and mental health status remained in woman (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24173/abstract). Some of these associations were not significant in men, likely reflecting the higher proportion of female participants (and associated statistical power). However, a significant impact of DM on the activity-related KOOS pain score and the physical parameter SF-12 PCS was detected in both females and males (see Supplementary Table 1, at http://onlinelibrary.wiley.com/doi/10.1002/acr.24173/abstract).

DISCUSSION

This study explored, for the first time, whether knee pain sensation and health status are worse in individuals with knee OA and DM, independently of age, sex, BMI, and radiographic status (K/L grade). The analysis revealed that individuals with OA and DM did in fact experience greater knee pain independent of BMI and K/L grade. Additionally, individuals with OA and DM had a worse physical and mental status compared to those without DM, independently of the above factors. The inclusion of additional possible confounders, such as other diagnosed comorbidities, painful joints, and pain medication, into the analysis confirms the association of DM and worse KOOS pain scores of knee joints in OA-affected individuals.

Our present analysis of a large cohort study extends previous data from small patient groups reporting the fact that DM increases joint pain in patients with hand and knee OA (6,11,12). But the previous reports on the impact of DM on pain sensation in OA (6,12) did not adjust for differences in K/L grade and BMI. Given that many individuals with DM are obese, with obesity as a risk factor of knee OA (4,20,31,32), and with radiographic knee OA being associated with knee pain (22,23), these studies were unable to resolve whether DM is an independent risk factor of knee OA pain.

The current study results of the unadjusted analysis showed a difference in the KOOS pain score between individuals with OA with and without DM that approached the previously reported clinically important difference of 8–10 points in the KOOS score (27). The beta values in the adjusted models suggest that this between-group difference is attenuated when adjusting for potential confounders. This finding is important to acknowledge when interpreting the findings of the current study. The current analysis included 2,481 participants from the OAI, including subjects with K/L grade ≥1. Of these, 8.14% reported having DM, which approximately matches the prevalence of DM in the US at the time of participant recruitment (33).

One of the limitations of this cross-sectional analysis is that the OAI was not designed specifically to evaluate the relationship between DM and OA outcomes. Therefore, more detailed information regarding DM disease history and blood serum analyses was not available. However, the self-reported presence of DM has a good concordance with medical record or physician diagnosis (34,35). While we attempted to control for potential confounders, there may be other variables not included in the OAI that affect the relationship between DM and pain. For example, we included the number of painful joints (such as finger, shoulder, and ankle) as a confounding factor, but the OAI holds no information about the presence of OA in these joints.

Individuals with OA and DM had a higher BMI and K/L grade score compared to controls without DM. Although BMI and K/L grade are both associated with knee pain, our results show that DM is an independent factor; there must be additional mechanisms that render individuals with DM at risk of experiencing great knee pain. Potentially, DM adversely affects local factors around the knee or peripheral or central pain processing factors, such as central sensitization (17). Further, individuals with OA and DM have been shown to exhibit greater inflammation of synovial tissue and higher concentrations of cytokines in the synovial fluid

compared to those without DM (6,12). Hyperglycemia may thus cause complications in peripheral tissues, including microvascular impairment, mitochondrial dysfunction, osmotic stress, release of proinflammatory cytokines, production of reactive oxygen species, hypoxia, and others (15). These mechanisms may damage nerve fibers in peripheral tissues and lead to painful neuropathy. The mechanism of diabetic neuropathic pain is not fully understood (36), but DM is known to cause alterations in nerve endings, including changes in voltage-gated sodium channel expression and phosphorylation (37), which may cause an abnormal activity of nociceptive fibers. Additionally, an increased level of methylglyoxal was reported in patients with DM with neuropathic pain, compared to either healthy controls or DM-affected individuals without pain (38). Methylglyoxal can depolarize nociceptive neurons, induce modifications of voltage-gated sodium channels (38), and activate neurons through transient receptor potential A1 ion channels (39).

Besides peripheral alterations, changes in the central nervous system have been described in patients with diabetic neuropathic pain and in diabetic animal models (36). These changes include activation of microglia in the spinal cord as well as central sensitization and structural changes in several areas of the brain (36,40). Further, obesity and DM may induce low-grade systemic inflammation characterized by increased C-reactive protein, circulating levels of IL-6 and TNF (14), endothelial dysfunction, and vascular inflammation (15,41). Adipose tissue is known to produce several proinflammatory mediators, including IL-1β, TNF, prostaglandin E_2, and IL-6 (42), which are known to sensitize neurons (43). Additionally, intraarticular mediators released by the infrapatellar fat pad may adversely impact the cartilage and synovium, or activate intraarticular macrophages and leukocytes (21).

Beside BMI and OA severity, various parameters seem to have an influence on OA and OA pain. Some studies have reported that female subjects have an increased risk for OA in the general population (31) and particularly among DM patients (1). Concerning OA pain and function, studies have reported sex differences, with females having higher pain sensitivities and more impaired function compared to males (44). Our results showed an impact of DM in both females and males on the activity-related KOOS pain score and the physical parameter SF-12 PCS.

Several comorbidities, such as kidney problems, heart failure, and stroke are associated with DM (45–47), but whether these comorbidities have an impact on OA pain is unclear. In the current study, the activity-related knee pain score was still significantly associated with DM, after inclusion of other diagnosed comorbidities as confounding factors. Furthermore, there is evidence that depression and psychosocial factors have an influence on the pain experience of patients with OA (19), which was not considered in the presented study.

In summary, greater inflammation, alterations in nociceptive neurons, diabetic neuropathy, and psychosocial factors may cause the presence of DM to result in more knee pain, independent of elevated BMI and radiographic OA status. In addition to OA knee pain, our current study shows that physical activities and mental health are negatively affected by DM, independent of greater BMI and K/L grade. Health-related quality of life is influenced by multiple patient and disease factors (48). DM-related complications also frequently cause negative effects on physical and mental status (49).

The current study shows that the higher BMI and advanced OA status of the participants with DM do not explain the detected differences. The inclusion of pain medication and other diagnosed comorbidities as confounders has an effect on the association of DM with PASE and CES-D, but the SF-12 PCS and SF-12 MCS are still significantly associated with the presence of DM. Gore et al (2005) showed that the negative impact of a painful diabetic neuropathy on physical and mental health was higher in patients with greater pain severity (50). The greater pain sensation in patients with OA and DM could potentially cause the impaired physical and mental functioning, but mental and social factors could also affect the pain sensation. This cross-connection between pain, physical and mental health status, and comorbidities should be further investigated. In conclusion, greater joint pain perceived by patients with OA and DM is independent of greater BMI and radiographic severity. Given greater pain and worse physical and mental health status compared with patients with OA without DM at the same radiographic disease stage, patients with knee OA and DM require particular attention in preventing and managing knee OA.

ACKNOWLEDGMENTS

The authors thank the OAI participants, investigators, technicians, funders, the OAI clinical centers, and the OAI Coordinating Center. They also thank Dr. Thomas Lehmann (Institute of Medical Statistics, Computer Sciences and Documentation, University Hospital Jena) for advice in biostatistics.

AUTHOR CONTRIBUTIONS

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

Study conception and design. Eitner, Culvenor, Schaible, Eckstein.
Acquisition of data. Wirth.
Analysis and interpretation of data. Eitner, Culvenor, Schaible, Eckstein.

REFERENCES

1. Nieves-Plaza M, Castro-Santana LE, Font YM, Mayor AM, Vila LM. Association of hand or knee osteoarthritis with diabetes mellitus in a population of Hispanics from Puerto Rico. J Clin Rheumatol 2013;19:1–6.
2. Jungmann PM, Kraus MS, Alizai H, Nardo L, Baum T, Nevitt MC, et al. Association of metabolic risk factors with cartilage degradation assessed by T2 relaxation time at the knee: data from the Osteoarthritis Initiative. Arthritis Care Res (Hoboken) 2013;65: 1942–50.

3. Louati K, Vidal C, Berenbaum F, Sellam J. Association between diabetes mellitus and osteoarthritis: systematic literature review and meta-analysis. RMD Open 2015;1:e000077.
4. Eymard F, Parsons C, Edwards MH, Petit-Dop F, Reqinster JY, Bruyère O, et al. Diabetes is a risk factor for knee osteoarthritis progression. Osteoarthritis Cartilage 2015;23:851–9.
5. King KB, Findley TW, Williams AE, Bucknell AL. Veterans with diabetes receive arthroplasty more frequently and at a younger age. Clin Orthop Relat Res 2013;471:3049–54.
6. Schett G, Kleyer A, Perricone C, Sahinbegovic E, Iagnocco A, Zwerina J, et al. Diabetes is an independent predictor for severe osteoarthritis: results from a longitudinal cohort study. Diabetes Care 2013;36:403–9.
7. Berenbaum F. Diabetes-induced osteoarthritis: from a new paradigm to a new phenotype. Ann Rheum Dis 2011;70:1354–6.
8. Dell'Isola A, Steultjens M. Classification of patients with knee osteoarthritis in clinical phenotypes: data from the osteoarthritis initiative. PloS One 2018;13:e0191045.
9. Berenbaum F, Griffin TM, Liu-Bryan R. Metabolic regulation of inflammation in osteoarthritis. Arthritis Rheumatol 2017;69:9–21.
10. Niu J, Clancy M, Aliabadi P, Vasan R, Felson DT. Metabolic syndrome, its components, and knee osteoarthritis: the Framingham Osteoarthritis Study. Arthritis Rheumatol 2017;69:1194–203.
11. Magnusson K, Hagen KB, Østerås N, Nordsletten L, Natvig B, Haugen IK. Diabetes is associated with increased hand pain in erosive hand osteoarthritis: data from a population-based study. Arthritis Care Res (Hoboken) 2015;67:187–95.
12. Eitner A, Pester J, Vogel F, Marintschev I, Lehmann T, Hofmann GO, et al. Pain sensation in human osteoarthritic knee joints is strongly enhanced by diabetes mellitus. Pain 2017;158:1743–53.
13. Calders P, Van Ginckel A. Presence of comorbidities and prognosis of clinical symptoms in knee and/or hip osteoarthritis: a systematic review and meta-analysis. Semin Arthritis Rheum 2018;47:805–13.
14. Pitsavos C, Tampourlou M, Panagiotakos DB, Skoumas Y, Chrysohoou C, Nomikos T, et al. Association between low-grade systemic inflammation and type 2 diabetes mellitus among men and women from the ATTICA study. Rev Diabet Stud 2007;4:98–104.
15. Fowler MJ. Microvascular and macrovascular complications of diabetes. Clin Diabet 2008;26:77–82.
16. Shenouda SM, Widlansky ME, Chen K, Xu G, Holbrook M, Tabit CE, et al. Altered mitochondrial dynamics contributes to endothelial dysfunction in diabetes mellitus. Circulation 2011;124:444–53.
17. Eitner A, Hofmann GO, Schaible HG. Mechanisms of osteoarthritic pain: studies in humans and experimental models. Front Mol Neurosci 2017;10:349.
18. Cleveland RJ, Luong ML, Knight JB, Schoster B, Renner JB, Jordan MJ, et al. Independent associations of socioeconomic factor with disability and pain in adults with knee osteoarthritis. BMC Musculoskelet Disord 2013;14:297.
19. Somers TJ, Keefe FJ, Godiwala N, Hoyler GH. Psychosocial factors and the pain experience of osteoarthritis patients: new findings and new directions. Curr Opin Rheumatol 2009;21:501–6.
20. Grotle M, Hagen KB, Natvig B, Dahl FA, Kvien TK. Obesity and osteoarthritis in knee, hip and/or hand: an epidemiological study in the general population with 10 years follow-up. BMC Musculoskelet Disord 2008;9:132.
21. Clockaerts S, Bastiaansen-Jenniskens YM, Runhaar J, Van Osch GJ, Van Offel JF, Verhaar JA, et al. The infrapatellar fat pad should be considered as an active osteoarthritic joint tissue: a narrative review. Osteoarthritis Cartilage 2010;18:876–82.
22. Neogi T, Felson D, Niu J, Nevitt M, Lewis CE, Aliabadi P, et al. Association between radiographic features of knee osteoarthritis and pain: results from two cohort studies. BMJ 2009;339:b2844.
23. Weiss E. Knee osteoarthritis, body mass index and pain: data from the Osteoarthritis Initiative. Rheumatology (Oxford) 2014;53:2095–9.
24. Holla JF, van der Leeden M, Knol DL, Roorda LD, van der Esch M, Voorneman RE, et al. The association of body-mass index and depressed mood with knee pain and activity limitations in knee osteoarthritis: results from the Amsterdam osteoarthritis cohort. BMC Musculoskelet Disord 2013;14:296.
25. Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. BMC Musculoskelet Disord 2008;9:116.
26. Neumann J, Hofmann FC, Heilmeier U, Ashmeik W, Tang K, Gersing AS, et al. Type 2 diabetes patients have accelerated cartilage matrix degeneration compared to diabetes free controls: data from the Osteoarthritis Initiative. Osteoarthritis Cartilage 2018;26:751–61.
27. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual Life Outcomes 2003;1:64.
28. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. J Clin Epidemiol 1993;46:153–62.
29. Ware J Jr, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220–33.
30. Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385–401.
31. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage 2010;18:24–33.
32. Manek NJ, Hart D, Spector TD, MacGregor AJ. The association of body mass index and osteoarthritis of the knee joint: an examination of genetic and environmental influences. Arthritis Rheum 2003;48:1024–9.
33. Beckles GL, Zhu J, Moonesinghe R. Diabetes: United States, 2004 and 2008. MMWR 2001;Suppl;60:90–3.
34. Robinson JR, Young TK, Roos LL, Gelskey DE. Estimating the burden of disease: comparing administrative data and self-reports. Med Care 1997;35:932–47.
35. Tisnado DM, Adams JL, Liu H, Damberg CL, Chen WP, Hu FA, et al. What is the concordance between the medical record and patient self-report as data sources for ambulatory care? Med Care 2006;44:132–40.
36. Schreiber AK, Nones CF, Reis RC, Chichorro JG, Cunha JM. Diabetic neuropathic pain: physiopathology and treatment. World J Diabetes 2015;6:432–44.
37. Hong S, Morrow TJ, Paulson PE, Isom LL, Wiley JW. Early painful diabetic neuropathy is associated with differential changes in tetrodotoxin-sensitive and -resistant sodium channels in dorsal root ganglion neurons in the rat. J Biol Chem 2004;279:29341–50.
38. Bierhaus A, Fleming T, Stoyanov S, Leffler A, Babes A, Neacsu C, et al. Methylglyoxal modification of Nav1.8 facilitates nociceptive neuron firing and causes hyperalgesia in diabetic neuropathy. Nat Med 2012;18:926–33.
39. Andersson DA, Gentry C, Light E, Vastani N, Vallortigara J, Bierhaus A, et al. Methylglyoxal evokes pain by stimulating TRPA1. PloS One 2013;8:e77986.
40. Cheng KI, Wang HC, Chuang YT, Chou CW, Tu HP, Yu YC, et al. Persistent mechanical allodynia positively correlates with an increase in activated microglia and increased P-p38 mitogen-activated protein kinase activation in streptozotocin-induced diabetic rats. Eur J Pain 2014;18:162–73.
41. Caballero AE, Bousquet-Santos K, Robles-Osorio L, Montagnani V, Soodini G, Porramatikul S, et al. Overweight Latino children and adolescents have marked endothelial dysfunction and subclinical

vascular inflammation in association with excess body fat and insulin resistance. Diabetes Care 2008;31:576–82.

42. Wisse BE. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. J Am Soc Nephrol 2004;15:2792–800.
43. Schaible HG. Nociceptive neurons detect cytokines in arthritis. Arthritis Res Ther 2014;16:470.
44. Tonelli SM, Rakel BA, Cooper NA, Angstom WL, Sluka KA. Women with knee osteoarthritis have more pain and poorer function than men, but similar physical activity prior to total knee replacement. Biol Sex Differ 2011;2:12.
45. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. Clin J Am Soc Nephrol 2017;12:2032–45.
46. Rosano GM, Vitale C, Seferovic P. Heart failure in patients with diabetes mellitus. Card Fail Rev 2017;3:52–5.
47. Chen R, Ovbiagele B, Feng W. Diabetes and stroke: epidemiology, pathophysiology, pharmaceuticals and outcomes. Am J Med Sci 2016;351:380–6.
48. Luscombe FA. Health-related quality of life measurement in type 2 diabetes. Value Health 2000;3 Suppl 1:15–28.
49. Al-Shehri AH, Taha AZ, Bahnassy AA, Salah M. Health-related quality of life in type 2 diabetic patients. Ann Saudi Med 2008;28:352–60.
50. Gore M, Brandenburg NA, Dukes E, Hoffmann DL, Tai KS, Stacey B. Pain severity in diabetic peripheral neuropathy is associated with patient functioning, symptom levels of anxiety and depression, and sleep. J Pain Symptom Manage 2005;30:374–85.