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Severity of Diabetes Mellitus and Total Hip or Knee Replacement

A Population-Based Case–Control Study

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Abstract: It is generally thought that people with diabetes mellitus (DM) are more likely to suffer from osteoarthritis (OA) due to an increased body mass index (BMI), resulting in mechanical destruction of cartilage. However, previous studies have suggested a coexisting metabolic causality.

To evaluate the risk of hip or knee replacement, as a proxy for severe OA, in patients with DM. We additionally evaluated the risk of total joint replacement (TJR) with various proxies for increased DM severity.

A population-based case–control study was performed, using the Clinical Practice Research Datalink (CPRD). Cases (n = 94,609) were defined as patients >18 years who had undergone TJR between 2000 and 2012. Controls were matched by age, gender, and general practice. Conditional logistic regression was used to estimate the risk of total knee (TKR) and total hip replacement (THR) surgery associated with use of antidiabetic drugs (ADs). We additionally stratified current AD users by proxies for DM severity.

Current AD use was significantly associated with a lower risk of TKR (OR = 0.86 (95% CI = 0.78–0.94)) and THR (OR = 0.90 (95% CI = 0.82–0.99)) compared to patients not using ADs. Moreover, risk of TKR and THR was decreased with increasing HbA1c.

This study does not support the theory that DM patients are more likely to suffer from severe OA as compared to patients without diabetes. Moreover, risk of severe OA necessitating TJR decreases with increasing DM severity. This is possibly due to dissimilarities in methodology, a decrease in eligibility for surgery, or variability of OA phenotypes.

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Abbreviations: AD = antidiabetic drug, AGEs = advanced glycation end products, BMI = body mass index, CI = confidence interval, CPRD = Clinical Practice Research Datalink, DM = diabetes mellitus, DPP = dipeptidyl peptidase, GLP = glucagon-like peptide, GLUT = glucose transporter, GP = general practitioner, GPRD = General Practice Research Database, HbA1c = glycated hemoglobin, ISAC = Independent Scientific Advisory Committee, KL = Kellgren–Lawrence, OA = osteoarthritis, OR = odds ratio, QOF = Quality and Outcomes Framework, RA = rheumatoid arthritis, ROS = reactive oxygen species, T1DM = type 1 diabetes mellitus, T2DM = type 2 diabetes mellitus, THR = total hip replacement, TJR = total joint replacement, TKR = total knee replacement, TZD = thiazolidinedione, UK = United Kingdom.

INTRODUCTION

Osteoarthritis (OA) is the most common cause of pain and disability in the United Kingdom (UK).[1] Approximately one-third of people aged 45 and over in the UK sought treatment for pain associated with OA.[1] Furthermore, between 1990 and 2010, disability due to OA has increased by 15%.[2] In patients with severe OA, total knee (TKR) and hip (THR) replacement are considered to improve the quality of life considerably.[3]

Patients with OA are more likely to suffer from diabetes mellitus (DM). DM is characterized by several metabolic problems, such as impaired glucose metabolism and obesity.

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Until recently one of the mechanisms underlying OA was considered to be an increased mechanical load on the weight-bearing joints, especially the knee, of these patients. Previous studies have shown that DM is an independent risk factor for the nonweight-bearing types of OA, suggesting a metabolic causality.[4–7] In a cross-sectional study of 202 subjects, patients with DM had an increased risk of hand or knee OA compared to patients without DM (OR 2.18 (95% CI, 1.12–4.24)).[4] Furthermore, a population-based cohort study with a 20-year follow-up in a random sample of 927 subjects showed an increased risk of total joint replacement (TJR) in type 2 DM patients compared to non-DM subjects (OR 2.1 (95% CI, 1.1–3.8)).[6] According to the Ulm osteoarthritis study, bilateral hip and knee OA was more prevalent, although not statistically significantly, in patients with DM than in patients without DM (OR 2.21 (95% CI, 0.77–6.41)).[7] Despite this, other studies show no association between OA and DM.[8,9]

From a biopathological point of view, there is an increasing body of evidence suggesting that hyperglycemia and advanced glycation end products (AGEs) play an important role in the progression of OA.[10–12] An in vitro study using chondrocytes, isolated from human cartilage, has concluded that OA chondrocytes exposed to high levels of glucose were unable to downregulate glucose transporter-1 (GLUT-1). The inability to down regulate GLUT-1 resulted in the accumulation of glucose and the production of reactive oxygen species (ROS), known for their deleterious effects in various celtypes.[10] Furthermore, AGEs have been linked to increased cartilage stiffness and a reduced capacity to repair articular cartilage.[11,12] These factors may be part of the mechanism promoting degenerative changes in the cartilage possibly facilitating the progression of OA.

Hyperglycemia and increased levels of AGEs are likely to be found in diabetic patients. Particularly poorly controlled or severe diabetic patients may be subjected to these risk factors regularly. It is therefore expected that these patients in particular are more likely to develop, or have a more severe course of OA. Subsequent progression of OA may in time lead to pain, which in severe cases can be alleviated by elective joint replacement surgery.

To date, a limited number of studies assessed the risk of OA in DM patients and showed inconsistent results. Moreover, to the best of our knowledge, none of these studies have determined the risk of OA needing TJR with increasing DM severity. The aim of this study was to evaluate the risk of TJR surgery with indicators of the severity of DM. Based on in vitro, in vivo, and clinical studies we hypothesize that DM could be associated with an increased risk of OA. Furthermore, we expect to find a higher risk of OA with increased severity of DM.

METHODS

This study protocol was approved by the Independent Scientific Advisory Committee (ISAC), protocol number: 14_054R.

Data Source

We performed a case–control study using the Clinical Practice Research Datalink (CPRD), previously known as the General Practice Research Database (GPRD). The CPRD is a large primary care database containing computerized medical records registered by over 625 general practitioners (GP) in the UK, thereby representing over 8% of the British population. This database provides information on a wide range of medical records, including diagnoses, prescriptions, referrals, and laboratory test results. We also used linked data on socioeconomic status from the Index of Multiple Deprivation for descriptive purposes.

Study Population

All patients aged 18 years or older who had undergone a primary THR or TKR surgery from January 2000 until the 31st of October 2012 were selected as cases. Patients with a diagnosis of rheumatoid arthritis (RA) or hip/knee fractures preceding the TJR surgery were excluded from analyses. All cases were matched to one control patient without a record for TJR using incidence density sampling. Cases and controls were matched by year of birth, sex, and general practice. The index date for the patients was the date of TJR surgery. This date was imputed for the matched control patient. A patient that did not undergo TJR before and at the index date of a case, but was still at risk of undergoing TJR, was matched to this specific case.

Exposure

In order to evaluate the risk between TJR surgery and DM, we determined the most recent diagnosis of Type 1 DM (T1DM) or Type 2 DM (T2DM) before the index date. If type of DM was not specified these patients were categorized as ''DM type unspecified.'' In addition, we determined the recency of exposure to antidiabetic drugs (ADs): biguanides, sulfonylureas, glitazones, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogs, glinides, and insulins, before the index date by reviewing prescriptions. Current users of these drugs comprised all patients with at least 1 recorded prescription within the 90-day period before the index date. Recent users were those with at least 1 prescription within the 180-day period before the index date, but who had stopped using these drugs $\geq$90 days before the index date. Past users were patients who had stopped using ADs more than 180 days before the index date.

Proxy indicators for the severity of DM were then defined using clinical information, lab test values, and exposure to drugs: Clinical proxies of disease severity included a history of neuropathy or retinopathy 5 years before the index date and renal function. In addition, lab tests values including HbA1c and fasting glucose were also used to determine the risk of TJR with increased severity of DM. HbA1c was stratified into the following groups: $<$6.5%, 6.5% to 7.9%, 8% to 9.4%, $\geq$9.5%. Fasting plasma glucose was stratified into the following groups: $<$6 mmol/L, 6 to 7.4 mmol/L, 7.5 to 8.9 mmol/L, $\geq$9.0 mmol/L. The most recent lab test value in the year before index date was used in this proxy. Lastly, we used proxy indicators of disease severity using longitudinal information on drug exposure according to the methods by Bazelier et al.[13] This was done by stratification of current AD users, into four treatment stages ranging from mild (Stage 1) to severe (Stage 4): Stage 1 diabetics were current users of either a biguanide or a sulfonylurea. Stage 2 diabetics comprised all patients who used these drugs simultaneously. Stage 3 diabetics used one or more drugs from the following classes: thiazolidinediones (TZD), GLP-1 analogs, DPP-4 inhibitors, or glinides, but were not on insulin treatment. Stage 4 diabetics were current users of insulin.

Covariates

We reviewed the literature to identify potential confounders for OA and TJR surgery. Factors including age, sex,

socioeconomic status, body mass index (BMI), and smoking status were used as potential confounders.[14–16] A history of diseases such as angina pectoris, acute myocardial infarction (AMI), heart failure, hemorrhagic stroke, ischemic stroke, cerebrovascular diseases, dementia, arrhythmia, peripheral vascular diseases, ulcers, and nonhip/femur fractures in the previous year were also included as potential confounders. Use of statins, loop diuretics, thiazides, NSAIDs, calcium channel blockers, beta-blockers, RAAS inhibitors, systemic glucocorticoids in the previous 6 months.[17] In all analyses potential confounders were included if they independently changed the beta-coefficient for a DM diagnosis or current AD exposure by at least 5%, or when consensus about inclusion existed within the team of researchers, supported by clinical evidence from literature.

Statistical Analysis

Conditional logistic regression analysis was used to estimate the risk of TKR and THR surgery associated with a diagnosis of DM, and clinical proxies of disease severity (SAS version 9.3, PHREG procedure). In the analyses, risk was expressed as odds ratios (OR) with corresponding 95% confidence intervals (CI). Furthermore, we estimated the risk of TKR and THR surgery associated with use of ADs. We additionally stratified current AD users by lab test and drug use proxies for disease severity. Missing data were classified as a separate category. Analyses assessing the association between prespecified treatment stages and HbA1c levels have been conducted in order to determine whether these treatment stages reflect DM severity properly. These analyses have been conducted in a set of TKR and THR control patients using an AD.

RESULTS

Baseline characteristics of TKR (n = 44,768), THR patients (n = 49,841), and their matched control subjects (n = 94,609) are presented in Table 1. On average, the subjects were approximately 70 years of age and more than 55% of them were female. In general, TKR cases were more likely to have a DM diagnosis (n = 5118) compared to TKR controls (n = 4325). TKR cases were particularly more often diagnosed with T2DM compared to controls. In contrast, THR cases were less likely to have a DM diagnosis (n = 4075) compared to controls (n = 4591), regardless of type. On average, HbA1c values were lower in the cases compared to the controls in both TKR and THR subjects. The use of ADs was higher in the TKR cases compared to their controls. This was in contrast with the THR cases, where the use of ADs was lower compared to the controls. Socio-economic status and mean fasting glucose values were similar in cases and controls in both patient groups. Mean BMI, however, was higher in cases compared to their matched controls, especially in the TKR group.

The risk of TJR surgery was 13% to 15% reduced in patients with a diagnosis of DM versus nondiabetic patients, with an OR of 0.85 (95% CI, 0.77–0.94) for TKR surgery and of 0.87 (95% CI, 0.82–0.93) for THR surgery. Risk reductions were on average more pronounced in patients with T1DM for TKR (OR 0.73; 95% CI, 0.55–0.96) but not for THR (OR 0.89; 95% CI, 0.72–1.11) surgery, as compared with non-DM patients. In T2DM patients the risk of TKR surgery (OR 0.85; 95% CI, 0.76–0.94) and THR surgery (OR 0.88; 95% CI, 0.83–0.94) was slightly decreased compared to non-DM patients. Clinical proxies of the severity of DM were mostly not associated with risk of TJR. A diagnosis of retinopathy in the 5 years before TKR yielded an OR of 1.37 (95% CI, 0.76–2.49) and an OR of 2.18 (95% CI, 1.33–3.57) for THR surgery compared to patients without diabetes. We found no differences in risk of surgery in patients with a diagnosis of neuropathy in the 5 years before TKR or THR. Risk of TKR was increased in patients with a combined diagnosis of retinopathy and a neuropathy in the 5 years before surgery (OR 2.20; 95% CI, 1.04–4.66), whereas no difference in risk of THR was found (OR 1.29; 95% CI, 0.64–2.57). Deterioration of renal function (eGFR 30–59 ml/min/1.73 m^2) was associated with a reduced risk of TKR and THR, yielding an OR of 0.69 (95% CI, 0.60–0.79) and an OR of 0.79 (95% CI, 0.71–0.87) respectively (Table 2).

The associations between current AD use and risk of TJR showed similar patterns as compared to the associations between diagnosis of DM and risk of TJR. Current AD use was significantly associated with a lower risk of TKR (OR = 0.86 (95% CI, 0.78–0.94)) and THR (OR = 0.90 (95% CI, 0.81–0.99)) compared to patients not using ADs. Moreover, risk of TKR and THR was decreased with increasing HbA1c in current AD users as compared to nonusers. More specifically, both TKR and THR patients using ADs with HbA1c values <6.5% were at equal risk of surgery as compared to nondiabetic patients, but patients using ADs with HbA1c ≥6.5 were at a lower risk of TJR. TKR (OR = 0.53 (95% CI, 0.42–0.66)) and THR (OR = 0.44 (95% CI, 0.34–0.56)) patients with HbA1c values >9.5% were approximately 50% less likely to undergo surgery. In contrast, fasting glucose levels were not associated with a change in risk of TJR. Lastly, treatment stages of current AD use were generally not associated with risk of surgery. However, patients using both a biguanide and a sulfonylurea (stage 2) were less likely to undergo surgery as compared to nondiabetic patients, with an OR of 0.75 (95% CI, 0.65–0.88) for TKR surgery and an OR of 0.80 (95% CI, 0.69–0.93) for THR surgery (Table 3).

The proportion of control subjects currently using an AD with HbA1c levels ≥9.5% increases with every step up according to the prespecified treatment stages (Table 4). The proportion of subjects with HbA1c levels <6.5% decreases with every step up.

The inverse association between DM and TJR was no longer present when taking into account the average Hb1Ac level in the previous 5 years instead of the single most recent HbA1c level (Supplementary Table 1, http://links.lww.com/MD/A987, Supplementary Table 2, http://links.lww.com/MD/A987). However, risk of TKR and THR was still decreased with increasing HbA1c levels in current AD users as compared to nonusers.

DISCUSSION

In contrast to our hypothesis, the present population-based case–control study did not show a positive association between various proxy indicators of the severity of DM and the risk of TJR surgery. On the contrary, we found 13% to 15% reduced risks between a diagnosis of DM and TJR surgery, and up to a 46% reduction with clinical proxy indicators of disease severity of DM. The use of ADs was associated with a decreased risk of TKR (OR = 0.86 (95% CI, 0.78–0.94)) and THR (OR = 0.90 (95% CI, 0.81–0.99)). Moreover, increasing DM severity, according to HbA1c levels, was associated with a lower risk of undergoing TJR surgery. In fact, patients with HbA1c values >9.5% were approximately 50% less likely to undergo surgery. When taking into account the average Hb1Ac level in the

TABLE 1. Baseline Characteristics of TJR Cases and Controls

	TKR, n = 89,536		THR, n = 99,682	
	Cases (%), n = 44,768	Controls (%), n = 44,768	Cases (%), n = 49,841	Controls (%), n = 49,841
Females	24,912 (55.6)	24,912 (55.6)	29,724 (59.6)	29,724 (59.6)
Age at index date (years, (SD))	69.5 (9.5)	69.5 (9.5)	68.8 (11.5)	68.8 (11.5)
BMI, most recent before index date (kg/m^2, mean (SD))	29.7 (5.2)	27.0 (5.1)	27.6 (5.0)	26.8 (5.0)
DM diagnosis, most recent diagnosis before index date				
DM regardless of type	5118 (11.4)	4325 (10.3)	4075 (8.2)	4591 (9.2)
Type I	149 (0.3)	211 (0.5)	189 (0.4)	243 (0.5)
Type II	4636 (10.4)	4077 (9.1)	3579 (7.2)	3979 (8.0)
Type unspecified	333 (0.7)	307 (0.7)	307 (0.6)	369 (0.7)
History of comorbidity 5 years before index date				
Retinopathy	884 (2.0)	911 (2.0)	643 (1.3)	850 (1.7)
Neuropathy	551 (1.2)	441 (1.0)	499 (1.0)	428 (0.9)
eGFR ($ml/min/1.73\,m^2$, mean (SD))	71.9 (17.9)	70.8 (17.9)	71.9 (18.9)	70.4 (18.1)
HbA1c most recent within the year before index date				
HbA1c (%, mean (SD))	6.9 (1.2)	7.1 (1.4)	6.8 (1.2)	7.2 (1.4)
<6.5%	1811 (4.0)	1422 (3.2)	1629 (3.3)	1406 (2.8)
6.5–7.9%	2331 (5.2)	1976 (4.4)	1623 (3.3)	1837 (3.7)
8–9.4%	542 (1.2)	586 (1.3)	411 (0.8)	550 (1.1)
≥9.5	189 (0.4)	299 (0.7)	133 (0.3)	310 (0.6)
Missing	39,895 (89.1)	40,485 (90.4)	46045 (92.4)	45,738 (91.8)
Fasting glucose most recent within the year before index date				
Fasting glucose (mean (SD))	5.7 (1.5)	5.7 (1.7)	5.6 (1.4)	5.7 (1.7)
<6 mmol/L	3791 (8.5)	3143 (7.0)	3351 (6.7)	3016 (6.1)
6–7.5 mmol/L	818 (1.8)	613 (1.4)	580 (1.2)	590 (1.2)
7.5–8.9 mmol/L	248 (0.6)	152 (0.3)	122 (0.2)	167 (0.3)
≥9.0 mmol/L	156 (0.3)	149 (0.3)	145 (0.3)	164 (0.3)
Missing	39,755 (88.8)	40,711 (90.9)	45,643 (91.6)	45,904 (92.1)
History of drug use within 6 months before primary TJR surgery				
All NIAD	3430 (7.7)	3075 (6.9)	2511 (5.0)	3037 (6.1)
Biguanides	2780 (6.2)	2406 (5.4)	1995 (4.0)	2388 (4.8)
Sulfonylureas	1497 (3.3)	1573 (3.5)	1206 (2.4)	1568 (3.1)
Thiazolidinediones	540 (1.2)	428 (1.0)	311 (0.6)	420 (0.8)
Glinides	38 (0.1)	28 (0.1)	18 (0.0)	26 (0.1)
GLP-1 agonists	53 (0.1)	28 (0.1)	27 (0.1)	17 (0.0)
DPP-4 inhibitors	93 (0.2)	89 (0.2)	62 (0.1)	60 (0.1)
Insulins	747 (1.7)	825 (1.8)	580 (1.2)	837 (1.7)
No. of GP consultations in the year before index date (mean (SD))	41.3 (25.7)	28.9 (26.2)	40.2 (27.0)	28.0 (26.1)
Socioeconomic status				
Low	6945 (15.5)	7120 (15.9)	8248 (16.5)	8054 (16.2)
Low–medium	7176 (16.0)	7011 (15.7)	8200 (16.5)	8015 (16.1)
Medium	5763 (12.9)	5626 (12.6)	6287 (12.6)	6113 (12.3)
Medium–high	4533 (10.1)	4451 (9.9)	4521 (9.1)	4741 (9.5)
High	3077 (6.9)	3240 (7.2)	2896 (5.8)	3191 (6.4)
Missing	17,274 (38.6)	17,320 (38.7)	19,689 (39.5)	19,727 (39.6)
History of comorbidities ever before index date				
Angina pectoris	4615 (10.3)	4309 (9.6)	4273 (8.6)	4603 (9.2)
AMI	1929 (4.3)	2336 (5.2)	2139 (4.3)	2308 (4.6)
Ischemic stroke	332 (0.7)	468 (1.0)	347 (0.7)	483 (1.0)
Hemorrhagic stroke	191 (0.4)	261 (0.6)	239 (0.5)	275 (0.6)
Valve disorders	482 (1.1)	587 (1.3)	611 (1.2)	609 (1.2)
Peripheral vascular disorders	550 (1.2)	778 (1.7)	664 (1.3)	764 (1.5)
Ulcers	3280 (7.3)	2441 (5.5)	3250 (6.5)	2815 (5.6)
Nonhip/femur fractures in the year before index date	559 (1.2)	623 (1.4)	957 (1.9)	696 (1.4)

AMI = acute myocardial infarction, BMI = body mass index, DM = diabetes mellitus, DPP-4 = dipeptidyl peptidase-4, GLP-1 = glucagon-like peptide-1, GP = general practitioner, HbA1c = glycated hemoglobin, NIAD = noninsulin antidiabetic drug, SD = standard deviation, THR = total hip replacement, TJR = total joint replacement, TKR = total knee replacement.

TABLE 2. Risk of Total Knee Replacement (TKR) and Total Hip Replacement (THR) in Current Antidiabetic Drug (AD) Users Compared With Controls by Clinical Proxies of the Severity of DM

	TKR, n = (89,536)				THR, n = (99,682)			
DM Status	**Case, n = 44,768**	**Control, n = 44,768**	**Crude OR (95% CI)**	**Fully Adjusted OR (95% CI)***	**Case, n = 49,841**	**Control, n = 49,841**	**Crude OR (95% CI)**	**Fully Adjusted OR (95% CI)†**
No	39,650	40,173	Ref	Ref	45,766	45,250	Ref	Ref
Yes	5118	4595	1.13 (1.08–1.18)	0.85 (0.77–0.94)	4075	4591	0.87 (0.84–0.91)	0.87 (0.82–0.93)
By type of DM								
Type 1	149	211	0.71 (0.58–0.88)	0.73 (0.55–0.96)	189	243	0.77 (0.64–0.93)	0.89 (0.72–1.11)
Type 2	4636	4077	1.16 (1.10–1.21)	0.85 (0.76–0.94)	3579	3979	0.89 (0.85–0.93)	0.88 (0.83–0.94)
Type unspecified	333	307	1.10 (0.94–1.29)	0.89 (0.73–1.08)	307	369	0.82 (0.71–0.96)	0.79 (0.66–0.94)
By clinical proxies for DM severity								
No neuropathy or retinopathy	4088	3588	1.16 (1.10–1.21)	0.85 (0.77–0.94)	3317	3669	0.89 (0.85–0.94)	0.86 (0.81–0.92)
Neuropathy only	169	142	1.21 (0.97–1.51)	0.79 (0.56–1.11)	146	144	1.00 (0.80–1.26)	0.88 (0.64–1.22)
Retinopathy only	789	820	0.97 (0.88–1.08)	1.37 (0.76–2.49)	578	721	0.79 (0.70–0.88)	2.18 (1.33–3.57)
Retinopathy and neuropathy	72	45	1.60 (1.11–2.33)	2.20 (1.04–4.66)	34	57	0.58 (0.38–0.89)	1.29 (0.64–2.57)
By renal function (eGFR)								
≥90 ml/min/1.73 m^2	787	568	1.42 (1.27–1.58)	1.11 (0.94–1.30)	624	553	1.12 (1.00–1.26)	1.14 (0.99–1.30)
60–89 ml/min/1.73 m^2	2602	2212	1.20 (1.13–1.27)	0.87 (0.77–0.98)	1901	2135	0.88 (0.82–0.94)	0.90 (0.83–0.97)
30–59 ml/min/1.73 m^2	1298	1376	0.95 (0.88–1.03)	0.69 (0.60–0.79)	1092	1322	0.81 (0.75–0.88)	0.79 (0.71–0.87)
15–29 ml/min/1.73 m^2	51	96	0.54 (0.38–0.75)	0.43 (0.29–0.65)	63	88	0.70 (0.51–0.97)	0.75 (0.52–1.07)
<15 ml/min/1.73 m^2	5	23	0.22 (0.08–0.59)	0.26 (0.08–0.78)	12	23	0.51 (0.25–1.03)	0.56 (0.27–1.19)
eGFR missing	375	320	1.18 (1.02–1.38)	0.95 (0.79–1.14)	383	470	0.80 (0.70–0.92)	0.78 (0.66–0.92)

AD = antidiabetic drug, CI = confidence interval, DM = diabetes mellitus, OR = odds ratio, THR = total hip replacement, TKR = total knee replacement.

*Adjusted for smoking status and BMI. Drug use in previous 6 months: statins, thiazides, calcium channel blockers, beta-blockers, RAAS inhibitors, loop diuretics, nonselective NSAIDs, COX2-selective NSAIDs. History of comorbidity ever before: acute myocardial infarction, heart failure, cerebrovascular events, ulcers, and peripheral vascular disorders. Retinopathy or neuropathy in 5 years before index date. Most recent value in previous year for HbA1c and fasting glucose. Stratified variables were excluded as confounder in the analyses stratified by that variable.

†Adjusted for smoking status and BMI. Drug use in previous 6 months: statins, thiazides, calcium channel blockers, beta-blockers, RAAS inhibitors, loop diuretics, nonselective NSAIDs, COX2-selective NSAIDs. Retinopathy and neuropathy in 5 years before index date. Most recent value in previous year for fasting glucose. Stratified variables were excluded as confounder in the analyses stratified by that variable.

previous 5 years instead of the single most recent HbA1c level, the inverse association between DM and TJR was no longer present. However, risk of TKR and THR was still decreased with increasing HbA1c levels in current AD users as compared to nonusers. Although this is probably the first study that evaluates the associations between DM as well as proxy indicators for DM severity with the risk of OA-related TJR surgery, it is not in line with previous studies that evaluated the association between (severity of) DM and OA.[4,6,7] This may be explained by mechanistic and methodological reasons.

A lacking differentiation of clinical phenotypes may explain the inverse association between AD use and OA. Previous work has suggested a division of the disease into 5 distinguishable clinical phenotypes.[18] First, a posttraumatic phenotype has been proposed. This phenotype is mainly caused by mechanical stress. Second, a metabolic phenotype, caused by mechanical stress, adipokines, hyperglycemia, and hormonal imbalance, has been suggested. Third, the aging phenotype associated with AGEs and chondrocyte senescence has been mentioned. Fourth, a genetic phenotype has been proposed.

TABLE 3. Risk of Total Knee Replacement (TKR) and Total Hip Replacement (THR) in Current Antidiabetic Drug (AD) Users Compared With Controls, Stratified by Laboratory and Drug Use Proxies for Severity of DM

	TKR, n = (89,536)				THR, n = (99,682)			
AD Use	**Case, n = 44,768**	**Control, n = 44,768**	**Crude OR (95% CI)**	**Fully adjusted OR (95% CI)***	**Case, n = 49,841**	**Control, n = 49,841**	**Crude OR (95% CI)**	**Fully adjusted OR (95% CI)†**
Never	40,896	41,237	Ref	Ref	46,853	46,304	Ref	Ref
Past	176	179	0.99 (0.81–1.22)	0.96 (0.75–1.24)	166	169	0.96 (0.78–1.20)	0.97 (0.76–1.25)
Recent	73	100	0.74 (0.54–1.00)	0.74 (0.51–1.07)	74	96	0.76 (0.56–1.04)	0.84 (0.59–1.19)
Current	3623	3252	1.12 (1.07–1.18)	0.86 (0.78–0.94)	2748	3272	0.83 (0.79–0.87)	0.90 (0.81–0.99)
By HbA1c, most recent in year before index date								
<6.5%	718	501	1.45 (1.29–1.63)	0.93 (0.81–1.07)	594	523	1.12 (0.99–1.26)	1.05 (0.92–1.21)
6.5–7.9%	1771	1489	1.20 (1.12–1.29)	0.87 (0.79–0.95)	1205	1401	0.85 (0.78–0.92)	0.88 (0.80–0.97)
8–9.4%	512	547	0.94 (0.83–1.07)	0.67 (0.58–0.78)	382	510	0.74 (0.65–0.84)	0.73 (0.63–0.86)
>9.5%	176	280	0.63 (0.52–0.76)	0.53 (0.42–0.66)	123	293	0.41 (0.33–0.51)	0.44 (0.34–0.56)
HbA1c missing	446	435	1.03 (0.90–1.18)	0.75 (0.64–0.88)	444	545	0.80 (0.71–0.91)	0.81 (0.70–0.94)
By fasting glucose, most recent in year before index date								
<6.0 mmol/L	95	83	1.16 (0.86–1.56)	0.89 (0.62–1.27)	89	91	0.96 (0.72–1.29)	0.97 (0.69–1.35)
6.0–7.4 mmol/L	163	128	1.29 (1.02–1.62)	0.88 (0.66–1.17)	105	101	1.02 (0.78–1.35)	1.15 (0.84–1.57)
7.5–8.9 mmol/L	169	90	1.91 (1.48–2.47)	1.22 (0.90–1.66)	78	103	0.75 (0.56–1.01)	0.83 (0.59–1.17)
>9.0 mmol/L	133	133	1.01 (0.79–1.28)	0.79 (0.59–1.07)	117	139	0.83 (0.64–1.06)	0.98 (0.72–1.32)
Fasting glucose missing	3063	2818	1.10 (1.04–1.16)	0.83 (0.76–0.92)	2359	2838	0.82 (0.77–0.87)	0.89 (0.81–0.98)
By treatment stages								
Stage 1: current use of biguanide or sulfonylureas only	1638	1358	1.22 (1.13–1.31)	0.90 (0.80–1.01)	1314	1389	0.93 (0.86–1.01)	0.96 (0.86–1.08)
Stage 2: current use of biguanide and sulfonylureas, but no use of other ADs	650	674	0.97 (0.87–1.08)	0.75 (0.65–0.88)	536	672	0.79 (0.70–0.88)	0.80 (0.69–0.93)
Stage 3: current use of TZD, GLP-1 analogs, DPP-4 inhibitors or glinides	618	466	1.34 (1.19–1.52)	0.89 (0.75–1.05)	356	445	0.79 (0.69–0.91)	0.84 (0.70–1.01)
Stage 4: current use of insulin	717	754	0.96 (0.86–1.06)	0.82 (0.70–0.95)	542	766	0.70 (0.62–0.78)	0.85 (0.73–1.00)

AD = antidiabetic drug, BMI = body mass index, CI = confidence interval, DM = diabetes mellitus, DPP-4 = dipeptidylpeptidase-4, GLP-1 = glucagon-like peptide-1, HbA1c = glycated hemoglobin, OR = odds ratio, THR = total hip replacement, TJR = total joint replacement, TKR = total knee replacement, TZD = thiazolidinedione.

*Adjusted for smoking status and BMI. Drug use in previous 6 months: statins, thiazides, calcium channel blockers, beta-blockers, RAAS inhibitors, loop diuretics, nonselective NSAIDs, COX2-selective NSAIDs. History of comorbidity ever before: acute myocardial infarction, heart failure, cerebrovascular events, peripheral vascular disorders, ulcers. Retinopathy or neuropathy in 5 years before TJR. Most recent value in previous year for HbA1c and fasting glucose. Stratified variables were excluded as confounder in the analyses stratified by that variable.

†Adjusted for smoking status and BMI. Drug use in previous 6 months: statins, thiazides, calcium channel blockers, beta-blockers, RAAS inhibitors, loop diuretics, nonselective NSAIDs, COX2-selective NSAIDs. Retinopathy in 5 years before TJR. Most recent value in previous year for HbA1c and fasting glucose. Stratified variables were excluded as confounder in the analyses stratified by that variable.

TABLE 4. Proportion of HbA1c Categories in Controls (No TJR)

Treatment Stages	HbA1c <6.5%, n = (%)	HbA1c 6.5–7.9%, n = (%)	HbA1c 8–9.4%, n = (%)	HbA1c ≥9.5%, n = (%)
Stage 1: current use of biguanide or sulfonylureas only	612 (26.6)	1343 (58.4)	231 (10.0)	115 (5.0)
Stage 2: current use of biguanide and sulfonylureas, but no use of other ADs	194 (16.8)	618 (53.5)	244 (21.1)	99 (8.6)
Stage 3: current use of TZD, GLP-1 analogs, DPP-4 inhibitors or glinides	134 (16.2)	449 (54.3)	150 (18.1)	94 (11.4)
Stage 4: current use of insulin	84 (6.7)	480 (38.1)	432 (34.3)	265 (21.0)

Current users of ADs are stratified by treatment stages.
AD = antidiabetic drug, DPP-4 = dipeptidylpeptidase-4, GLP-1 = glucagon-like peptide-1, HbA1c = glycated hemoglobin, TJR = total joint replacement, TZD = thiazolidinedione.

Fifth, a pain related phenotype may also exist. According to this classification, if corrected for overweight, DM may primarily be associated with metabolic OA, whereas other phenotypes have other causative features. In this study such a differentiation has not been made. We have, therefore, not exclusively included metabolic OA patients. This may explain the fact that we did not find an increased risk of TJR in DM patients compared to non-DM patients.

Dissimilarities in methodology, such as the definition of OA, between studies may be of interest. Other studies have determined OA by using the American College of Rheumatology classification criteria or by using radiographically determined Kellgren–Lawrence (KL) scores.[4,7] In this study we used TJR surgery to define severe OA. This may not reflect severity of OA as directly as KL scores, for example, but in epidemiology it has been widely used in studies assessing risk factors for severe OA.[6,19] Remarkably, a study using a definition for severe OA similar to ours reports an increased risk of OA in DM patients compared to patients without DM.[6] Still, several dissimilarities exist between our study and that by Schett and colleagues. First, their population demographics, such as mean age and sex distribution, were different compared to those in our study. On average the population included by Schett and colleagues was younger than the patients in our study. A study by King et al[20] reported increased rates of TJR at lower age. Therefore, this difference may have led to effect modification by age. After stratification by age we also found a decreased risk of surgery with increasing age.

It might be possible that, by missing out on the low risk older population, the analysis by Schett and colleagues resulted in an overall higher risk of surgery. Second, Schett and colleagues adjusted for age, sex, lifestyle factors, cholesterol and BMI, but no consideration was given toward covariates associated with hypertension. Since hypertension has also been considered to be an important component of the metabolic syndrome, possibly associated with metabolic OA, correction for this comorbidity is recommended.[21] However, when we estimated ORs without correcting for the use of antihypertensives similar ORs were found compared to analyses with adjustment for use of antihypertensives (TKR OR = 0.86 (95% CI, 0.81–0.91); THR OR = 0.90 (95% CI, 0.84–0.95)). Although evidence is limited, a combination of these methodological differences may have resulted in our deviating finding.

Although analyses were adjusted for BMI, drug use, and several comorbidities, other factors may have caused the inverse association between DM severity and the risk of OA. First, we should consider confounding by indication. Patients with DM, especially those with severe DM, are possibly less eligible for surgery due to an increased risk of surgical complications. For example, the risk of infection associated with surgery is higher in DM patients compared to patients who do not have DM.[22] More specifically, high HbA1c levels have been associated with more complications following TJR.[23,24] High HbA1c levels are particularly associated with more surgical site infections.[25] Furthermore, HbA1c levels have been associated with increased mortality rates in nonorthopedic surgical procedures.[26] Based on these increased risks surgeons may be less tempted to operate on these patients. Also, patients with DM could have complications sufficiently serious to prevent surgery, regardless of risk. The duration of DM may also be of concern. Clinically, it is difficult to determine start of DM, therefore time since first AD prescription may be used to approximate this. Furthermore, DM is known to be underdiagnosed and undertreated.[27] Therefore, we assessed the risk of TJR with a DM diagnosis (Table 2) and with the use of an AD (Table 3). Second, high HbA1c levels are associated with a decreased adherence to medication.[28] The lack of adherence may suggest care evasive behavior in general and, consequently, these patients may not be likely to visit their GPs and other healthcare providers on a regular basis. They are, therefore, less likely to undergo elective TJR. A combination of these factors may have resulted in a decreased risk of TJR in patients with increasing severity of DM compared to patients without DM.

Our study has several strengths. First, it was conducted using the world's largest primary care database representative for the British population and consequently, we were able to assess the risk in a large population of >90,000 TJR patients. Second, to our knowledge this is the first study that stratifies risk of OA by disease severity, based on HbA1c values. Third, we had detailed information on both patients and their matched controls. Fourth, medical data were routinely recorded by GPs without the presence of a study hypothesis, minimizing the possibility of recall bias. Like most observational studies, our study is not without limitations. Despite attempts to adjust for several confounders, causal interpretation of the findings will be restricted and residual confounding must be considered when interpreting the results. Furthermore, this study has focused on severe OA patients, other associations may be found in less severe subjects. The quality of proxies of disease severity may also be of concern. HbA1c levels were generally well registered

in the diabetic population analyzed in this study (83–88%), most likely due to the introduction of the Quality and Outcomes Framework (QOF) indicators for DM in 2004. The impact of missing data on HbA1c in the diabetes population was therefore probably of minor concern. Fasting glucose levels, however, are not included as one of the QOF indicators and consequently have lower registration rates (13–15%). Based on distribution of patients according to HbA1c levels, one might suggest that registration of fasting glucose is predominantly lacking in the lower fasting glucose categories (<6.0 mmol/L, 6.0–7.4 mmol/L, and 7.5–8.9 mmol/L). Considering the ORs calculated for the ''fasting glucose missing'' group, full registration of this test would probably lead in a reduction of risk in these severity categories. Misclassification of exposure may also be of concern. Use of ADs is based on prescription data registered in the CPRD. However, adherence is likely to be <100%. We may have therefore overestimated the number of patients using ADs. Assuming this is a nondifferential misclassification, and the number of AD users would in fact be lower, this would have resulted in a dilution of the true effect. Consequently, this does not explain the inverse association presented in this study. Finally, TJR could be considered to be an inadequate definition for OA. However, in epidemiology it has been used in previous studies assessing risk factors for severe OA.[6,19] With this definition we are limited to severe cases of OA, missing possible beneficial effects in earlier stages of OA.

In conclusion, in contrast to previous reports, the present study does not indicate that patients with DM are more likely to suffer from severe OA as compared to nonusers. In fact, the risk of severe OA necessitating TJR even decreases with increasing DM severity, based on HbA1c values. This unexpected result may be caused by variability of OA phenotypes, dissimilarities in methodology, or a decrease in eligibility for surgery. Our results suggest more uniform work is still needed to determine the risk of OA in DM patients. Further research may also include differentiation of OA into relevant clinical phenotypes.

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