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Use of thiazolidinediones and the risk of elective hip or knee replacement: a population based case–control study

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- No disease modifying drug exists for osteoarthritis.
- Animal studies have suggested that thiazolidinediones may be used as disease modifying osteoarthritis drugs (DMOADs).
- The disease modifying osteoarthritic effect of thiazolidinediones has not been examined in humans before.

WHAT THIS STUDY ADDS

- This is the first study assessing the potential disease modifying osteoarthritic effect of thiazolidinediones in humans.
- This study did not find any evidence for a disease modifying osteoarthritic effect of thiazolidinediones.

AIMS

Osteoarthritis (OA) is the most common musculoskeletal condition in the elderly population. However, no disease modifying drug exists for this disease. *In vivo* animal studies have suggested that thiazolidinediones (TZD) may be used as disease modifying osteoarthritis drugs (DMOADs). To our knowledge, this has not yet been examined in humans before. The aim was to determine the risk of total joint replacement (TJR) in patients using TZDs compared with diabetic patients using other antidiabetic drugs.

METHODS

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 of age who had undergone total knee (TKR) or hip replacement (THR) between 2000 and 2012. Controls were matched by age, gender and practice/surgery. Conditional logistic regression analyses were used to estimate the risk of TKR and THR with the use of TZDs in patients currently using one or more antidiabetic drugs. In order to determine effect with prolonged use, we also stratified TZD users by total number of prescriptions prior to surgery. We statistically adjusted our analyses for lifestyle factory, comorbidities and concomitant drug use.

RESULTS

There was no difference in risk of TKR (OR 1.09, 95% CI 0.93, 1.27) and THR (OR 0.92, 95% CI 0.76, 1.10) when TZD users were compared with other AD users. Furthermore, we did not find an association with prolonged use of TZDs and TJR.

CONCLUSION

Despite promising results from animal *in vivo* studies, this study did not find any evidence for a disease modifying osteoarthritic effect of TZDs.

Introduction

Osteoarthritis (OA) is the most common musculoskeletal condition in elderly people in the United Kingdom (UK). Based on 7 year consultation prevalence in general practice, it is estimated that approximately 8.8 million people, aged 45 years and over, in the UK have sought treatment for OA. [1]. This progressive disease affects the joints, causing them to become painful and thereby limiting a patient's functioning and health. Total joint replacement surgery (TJR), such as total hip replacement (THR) or total knee replacement (TKR), can substantially improve the quality of life in these patients. [2].

Patients with diabetes mellitus (DM) are more likely to suffer from OA [3]. Until recently this was related to increased prevalence of overweight in persons with DM and this with increased mechanical load on the weight-bearing joints of these patients. However, DM is also preceded by metabolic problems, such as impaired glucose metabolism. Several recent studies support the hypothesis that DM may be an independent risk factor for OA, possibly related to these and other metabolic features [4–7]. On this line, research suggests that hyperglycaemia and advanced glycation end products (AGEs) play an important role in the progression of OA [8–10]. Other factors may include dyslipidaemia and adipose tissue inflammation [11]. Dyslipidaemia may link DM to OA trough low concentrations of high density lipoprotein cholesterol [12], and increased concentrations of oxidized low density lipoprotein [13]. Adipose tissue inflammation may link DM to OA through elevated (pro-inflammatory) cytokine secretion [14] and increased adipokine concentrations [15, 16].

Peroxisome proliferator-activated receptor gamma (PPARγ) is primarily involved in the regulation of glucose and lipid metabolism. It has been associated with several conditions, such as cardiovascular diseases and DM. Additionally, previous studies have suggested that PPARγ may also play an important role in the pathogenesis of osteoarthritis [17–19]. It has been reported that PPARγ expression of chondrocytes is down regulated *in vitro,* in human OA cartilage compared with normal cartilage [11]. Furthermore, *in vivo* animal models have shown that PPARγ-deficiency is associated with an increased occurrence of a spontaneous OA phenotype [13]. Therefore, activation of PPARγ may result in a reduction of development and progression of OA. Several mechanisms have been suggested for this effect. Activation of PPARγ has been associated with a reduction of (pro) inflammatory cytokines, such as tumour necrosis factor alpha, interleukin-6, interleukin-1β and matrix metalloproteinases [20]. Interestingly, PPARγ can be activated by various therapeutic compounds, including the antidiabetic thiazolidinediones (TZD), such as rosiglitazone (withdrawn from the European market in 2010, due to an association with increased risk of myocardial infarction and death from cardiovascular causes [21]) and pioglitazone [22].

The effect of TZDs on PPARγ has been assessed in several *in vivo* animal studies. In a study using a guinea pig OA model, four treatment groups were compared: normal animals, OA animals given placebo, OA animals given a low dose (2 mg kg^{-1} day^{-1}) of pioglitazone, and OA animals given a high dose (20 mg kg^{-1} day^{-1}) pioglitazone. The high dosed guinea pigs showed a significant decrease in size and depth of macroscopic cartilage lesions compared with the OA placebo group [23]. In a similar canine model, high dose (30 mg day^{-1}) pioglitazone was also associated with a reduced development of cartilage lesions [24]. Currently, TZDs are only indicated for the treatment of DM. They can be used alone or in combination with metformin or with a sulfonylurea (SU).

To date, no disease modifying osteoarthritic drugs (DMOADs) exist. Therefore, it seemed attractive to investigate further PPARγ activation. To our knowledge, the possible disease modifying osteoarthritic effect of PPARγ activating drugs, such as TZDs, has not been studied in humans yet. Based on existing *in vitro* and *in vivo* studies, we hypothesize that patients using TZDs may have a reduced risk of severe OA and consequently have less TJRs. Furthermore, we expect to see a decreased risk of surgery with a longer duration of TZD use. Therefore, the aim of this study was to determine the risk of TJR in patients using TZDs compared with diabetic patients using other antidiabetic drugs.

Methods

The study protocol was approved by the Independent Scientific Advisory Committee (ISAC), protocol number: 14_054R. The ISAC is an expert advisory body established to provide advice on research related requests to access data provided by the Clinical Practice Research Datalink (CPRD). This body is situated in London, the UK.

Data source

A case–control study was performed using the CPRD, previously known as the General Practice Research Database (GPRD). The CPRD is a large primary care database containing medical records registered by over 625 general practitioners (GP) in the UK. It represents >8% of the British population. In the UK, GPs play a key role in the healthcare system as they are responsible for primary care and specialist referrals. Consequently, this database provides information on a wide range of medical records, including diagnoses, prescriptions, specialist referrals, laboratory test results and socioeconomic status (Index of Multiple Deprivation).

Study population

All patients aged 18 years or older who had undergone a primary THR or TKR surgery between January 2000 and the 31 October 2012 were selected as cases. This time

frame was chosen because TZDs have been registered in Europe since 2000. 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, gender and practice/surgery. The index date for the patients was the date of TJR surgery. This date was imputed for the matched control patient.

Exposure definitions

The use of TZDs and other antidiabetic drugs (AD) prior to TJR surgery was determined by reviewing dispensing information before the index date. Other ADs include all other ADs such as biguanides, SU, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, glinides and insulin. Current users of these drugs comprised all patients with at least one recorded prescription within the 90 day period before the index date. To determine whether duration of use would affect the risk of TJR, we stratified the risk of TJR in current TZD users by the number of TZD prescriptions ever before surgery. Group 1 consisted of patients with 1–4 prescriptions, group 2 with 5–8 prescriptions, group 3 with 9–14 prescriptions, group 4 with 15–29 prescriptions and group 5 with ≥30 prescriptions. [25]. On average one prescription corresponds with 4 weeks of drug use. Consequently, four and eight prescriptions will, on average, cover a duration of approximately 16 and 32 weeks respectively. More than 30 prescriptions will correspond with, on average, more than 2 years and 16 weeks of drug use.

Selection of covariates

We reviewed the literature to identify potential confounders for OA and TJR surgery. Factors including age, gender, socioeconomic status (SES), number of GP visits, body mass index (BMI), glomerular filtration rate (GFR) and smoking status were used as potential confounders [26–28]. A history of diseases such as angina pectoris, acute myocardial infarction (AMI), heart failure, arrhythmia, hypertension, haemorrhagic stroke, ischaemic stroke, cerebrovascular diseases, retinopathy and neuropathy were also included. Non-hip/femur fractures in the previous year were also included as potential confounders. Use of loop diuretics, thiazides, non-steroidal anti-inflammatory drugs (NSAIDs), calcium channel blockers, β-adrenoceptor blockers, renin-angiotensin-aldosterone system (RAAS) inhibitors, statins, systemic glucocorticoids in the previous 6 months, and the most recent laboratory test value for glycosylated haemoglobin (HbA1c) and fasting glucose in the previous year were also considered as potential confounders [29]. In all analyses potential confounders were included if they independently changed the beta-coefficient for current TZD exposure by at least 5%, or when consensus about inclusion existed within the team of researchers, supported by clinical evidence from the literature.

Statistical analysis

Conditional logistic regression analyses were used to estimate the risk of TKR and THR surgery associated with severe OA with the use of TZDs in patients currently using one or more antidiabetic drugs. Risk of surgery was compared within all diabetic patients because the underlying disease may influence the outcome. We additionally stratified current TZD users by BMI, HbA1c and fasting glucose. BMI was stratified into the following groups: <25.0 kg m^{-2}, 25–29.9 kg m^{-2}, 30–34.9 kg m^{-2}, ≥ 35.0 kg m^{-2} according to the BMI classification of the World Health Organization (WHO). HbA1c was stratified into the following groups: $<6.5\%$, 6.5–7.9%, 8–9.4%, $\geq 9.5\%$. Fasting plasma glucose was stratified into the following groups: <5 mmol l^{-1}, 5–5.9 mmol l^{-1}, 6–6.9 mmol l^{-1}, 7–7.9 mmol l^{-1}, 8–8.9 mmol l^{-1}, ≥ 9.0 mmol l^{-1}. To determine whether an effect with duration of use was present we determined the risk of TKR and THR in current TZD users stratified by number of TZD prescriptions ever before surgery. Sensitively analyses were performed to address the effect of missing key data such as HbA1c and fasting glucose. In order to determine this effect, conditional logistic regression analyses were performed excluding these variables from our statistical models. In order to address the duration of drug use we performed sensitivity analyses in which the risk of surgery was estimated with at least nine prescriptions. All analyses were conducted using SAS statistical software version 9.3.

Results

Between January 2000 and October 2012 a total of 44 768 TKR patients and 49 841 THR patients were identified (Table 1). The subjects were approximately 70 years old and 55%–60% of them were female. Both TKR and THR cases visited their GPs approximately 30% more often than their matched controls in the year prior to TJR. Furthermore, a total of 17 512 (39.1%) TKR and 12 424 (24.9%) THR cases were defined as obese (BMI $\geq$ 30 kg m^{-2}) compared with 9068 (20.2%) TKR and 9419 (18.9%) THR controls. Socio-economic status distribution was similar in both TKR and THR cases and controls. Mean estimated GFR (eGFR) and laboratory test values (HbA1c and fasting glucose) were comparable in the cases and the controls. In the TKR group there were 3623 cases and 3252 controls currently using an AD, whereas there were 2749 cases and 3272 controls in the THR group (Table 2).

TZD use was not associated with risk of TKR (odds ratio (OR) = 1.03 (95% confidence interval (CI) 0.88, 1.22)) or THR (OR 0.90, 95% CI 0.75, 1.08) compared with patients using an AD other than a TZD (Table 2). Patients with a BMI

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)
Number of GP consultations in the year prior to surgery (mean (SD))	41.3 (25.7)	28.9 (26.2)	40.2 (27.0)	28.0 (26.1)
Age at index date (years, (SD))	69.5 (9.5)	69.5 (9.5)	68.8 (11.5)	68.8 (11.5)
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)
BMI, most recent prior to TJR surgery				
BMI (kg m^{-2}, mean (SD))	29.7 (5.2)	27.0 (5.1)	27.6 (5.0)	26.8 (5.0)
<25.0 kg m^{-2}	7248 (16.2)	14 415 (32.2)	13 789 (27.7)	16 495 (33.1)
25–29.9 kg m^{-2}	16 245 (36.3)	15 243 (34.0)	17 982 (36.1)	16 524 (33.2)
30–34.9 kg m^{-2}	11 258 (25.1)	6464 (14.4)	8839 (17.7)	6647 (13.3)
≥35.0 kg m^{-2}	6254 (14.0)	2604 (5.8)	3585 (7.2)	2772 (5.6)
Missing	3763 (8.4)	6042 (13.5)	5646 (11.3)	7403 (14.9)
HbA1c most recent within the year prior to TJR surgery				
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)	46 045 (92.4)	45 738 (91.8)
Fasting glucose most recent within the year prior to TJR surgery				
Fasting glucose (mean (SD))	5.7 (1.5)	5.7 (1.7)	5.6 (1.4)	5.7 (1.7)
<6 mmol l^{-1}	3791 (8.5)	3143 (7.0)	3351 (6.7)	3016 (6.1)
6–7.5 mmol l^{-1}	818 (1.8)	613 (1.4)	580 (1.2)	590 (1.2)
7.5–8.9 mmol l^{-1}	248 (0.6)	152 (0.3)	122 (0.2)	167 (0.3)
≥9.0 mmol l^{-1}	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)
eGFR most recent within the year prior to TJR surgery				
eGFR ml min^{-1} 1.73m^{-2} (mean (SD))	71.9 (17.9)	70.8 (17.9)	71.9 (18.9)	70.4 (18.1)
eGFR ≥90	4720 (10.5)	3464 (7.7)	4998 (10.0)	3654 (7.3)
60 ≤ eGFR < 90	19 900 (44.5)	16 953 (37.9)	19 389 (38.9)	17 082 (34.3)
30 ≤ eGFR <60	8366 (18.7)	7398 (16.5)	8504 (17.1)	8028 (16.1)
15 ≤ eGFR <30	171 (0.4)	272 (0.6)	280 (0.6)	283 (0.6)
eGFR <15	23 (0.1)	53 (0.1)	49 (0.1)	71 (0.1)
eGFR missing	11 588 (25.9)	16 628 (37.1)	16 621 (33.3)	20 723 (41.6)
History of comorbidity ever before primary TJR surgery				
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)
Ischaemic stroke	332 (0.7)	468 (1.0)	347 (0.7)	483 (1.0)
Haemorrhagic 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)
Non-hip/femur fractures in the previous year	559 (1.2)	623 (1.4)	957 (1.9)	696 (1.4)
History of comorbidity 5 years before primary TJR surgery				
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)

(Continues)

Table 1
(Continued)

	TKR n = 89 536		THR n = 99 682	
	Cases (%) n = 44 768	Controls (%) n = 44 768	Cases (%) n = 49 841	Controls (%) n = 49 841
History of drug use within 6 months before primary TJR surgery				
NSAIDs	19 522 (43.6)	5773 (12.9)	22 467 (45.1)	6259 (12.6)
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)
Sulphonylureas	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-1agonists	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)

TJR total joint replacement, TKR total knee replacement, THR total hip replacement, GP General Practitioner, BMI body mass index, HbA1c glycated haemoglobin, eGFR estimated glomerular filtration rate, AMI acute myocardial infarction, NSAID non-steroidal anti-inflammatory drugs, NIAD non-insulin antidiabetic drug, GLP-1 glucagon-like peptide-1, DPP-4 dipeptidyl peptidase-4.

ranging from 30 to 34.9 kg m^{-2} (OR 1.32, 95% CI 1.02, 1.71) and those with a BMI >35 kg m^{-2} (OR 1.25, 95% CI, 0.95, 1.64) using TZDs showed a trend towards an increased risk of TKR compared with patients using other ADs. This BMI effect was not observed for the risk of THR. Furthermore, there was no trend for risk of THR and TKR with increasing HbA1c levels in TZD users compared with non-users. In fact, TZD users with HbA1c levels >9.5% had significantly lower risks of TKR (OR 0.42, 95% CI 0.20, 0.86) and THR (OR 0.34, 95% CI 0.18, 0.64) compared with patients using other ADs. No trend for risk of THR and TKR with increasing fasting glucose concentrations was found in TZD users compared with patients using other ADs. Moreover, there was no effect on risk of THR or TKR with increasing number of TZD prescriptions compared with patients using other ADs (Table 3). Patients who received up to four prescriptions of TZDs were, however, at lower risk of THR compared with patients receiving other ADs but who had never used a TZD (OR 0.32, 95% CI 0.16, 0.63).

Sensitivity analyses excluding HbA1c resulted in an OR of 0.88 (95% CI 0.73, 1.05) and an OR of 1.04 (95% CI 0.88, 1.22) for THR and TKR respectively. Sensitivity analyses excluding fasting glucose resulted in an OR of 1.04 (95% CI 0.88, 1.22) for TKR. Sensitivity analyses estimating the risk of surgery with at least nine prescriptions resulted in ORs of 0.94 (95% CI 0.77, 1.16) and 1.01 (95% CI 0.84, 1.20) for THR and TKR surgery, respectively.

Discussion

The present study showed that there was no difference in risk of TJR, associated with severe OA, when comparing TZD use to use of other ADs. Furthermore, no association with THR or TKR was found with stratification of TZD users by BMI and fasting glucose. High HbA1c levels (>9.5%) were associated with a decreased risk of surgery. Furthermore, an increase in number of TZD prescriptions was not associated with risk of TJR compared with DM patients using other ADs. Finally, sensitivity analyses excluding HbA1c and fasting glucose showed similar results compared with the analyses including HbA1c and fasting glucose as a confounder. Sensitivity analyses estimating the risk of surgery with at least nine prescription showed similar results compared with analyses including all current TZD users.

The suggested protective effect of TZDs on the development and progression of OA, based on animal *in vivo* studies, was not present in humans when we determined the risk of TKR or THR in TZD users compared with patients using other ADs. Species differences could have contributed to the deviated findings. Despite the fact that the experimental dog model has been used extensively and successfully in previous OA studies, it is unknown whether it is possible to extrapolate data from this animal model to clinical observations [30–35]. Furthermore, in a clinical setting pioglitazone is usually prescribed in doses ranging from 15 to 45 mg day^{-1}, which is comparable with the high doses used in the canine model. Unfortunately pharmacokinetic (PK) parameters of pioglitazone were not examined in the canine study. Therefore, comparison of dose and effect between the species is challenging. A separate study presented a PK profile of pioglitazone in dogs including a time to maximal concentration (t_{max}) of 0.5 h and a half-life ($t_{½}$) of 2.1 h, which are both lower than the parameters in humans (t_{max} = 2 h, $t_{½}$ = 5–6 h) [36]. This suggests that the dogs would be exposed to the drug for a shorter period of time if the same dosage was given. However, other PK and pharmacodynamic parameters may also affect the dose–effect relationship. Consequently, limitations regarding species comparison remain present.

Table 2

Use of thiazolidinediones and risk of total knee or total hip replacement in current users of antidiabetic drugs, stratified by BMI, HbA1c and fasting glucose levels

	TKR *n* = 89 536				THR *n* = 99 682			
AD use*	No. of cases *n* = 44 768	Number of controls *n* = 44 768	Crude OR (95% CI)	Fully adjusted OR[a] (95% CI)	Number of cases *n* = 49 841	Number of controls *n* = 49 841	Crude OR (95% CI)	Fully adjusted OR[b] (95% CI)
Current AD use	3623	3252			2748	3272		
AD use excl. TZD	3111	2861	ref	ref	2461	2889	ref	ref
TZD use	512	391	1.21 (1.05, 1.39)	1.03 (0.88, 1.22)	287	383	0.88 (0.75–1.04)	0.90 (0.75–1.08)
By BMI, most recent								
<25 kg/m^2	18	32	0.52 (0.29, 0.93)	0.56 (0.29, 1.06)	21	38	0.65 (0.38–1.12)	0.73 (0.41–1.30)
25–29.9 kg/m^2	114	128	0.82 (0.63, 1.06)	0.92 (0.69, 1.23)	78	119	0.77 (0.58–1.03)	0.83 (0.60–1.14)
30–34.9 kg/m^2	196	122	1.50 (1.18, 1.89)	1.32 (1.02, 1.71)	102	121	0.99 (0.76–1.30)	1.05 (0.78–1.43)
>35 kg/m^2	182	106	1.58 (1.23, 2.01)	1.25 (0.95, 1.64)	85	101	0.99 (0.74–1.34)	0.97 (0.69–1.36)
BMI missing	2	3	0.61 (0.10, 3.64)	0.72 (0.12, 4.43)	1	4	0.30 (0.03–2.68)	0.23 (0.02–2.92)
By HbA1c, most recent in previous year								
<6.5%	116	65	1.65 (1.21, 2.24)	1.26 (0.88, 1.79)	59	60	1.16 (0.81–1.67)	1.13 (0.75–1.71)
6.5–7.9%	263	192	1.26 (1.04, 1.53)	1.04 (0.83, 1.29)	131	191	0.81 (0.64–1.01)	0.80 (0.62–1.03)
8.0–9.4%	86	58	1.38 (0.98, 1.93)	1.40 (0.95, 2.06)	54	52	1.22 (0.83–1.80)	1.23 (0.80–1.89)
>9.5%	15	35	0.39 (0.21, 0.72)	0.42 (0.20, 0.86)	17	49	0.39 (0.22–0.69)	0.34 (0.18–0.64)
HbA1c missing	32	41	0.72 (0.45, 1.15)	0.61 (0.35, 1.07)	26	31	0.98 (0.58–1.66)	1.17 (0.64–2.14)
By fasting glucose, most recent in previous year								
<6.0 mmol/L	16	15	0.98 (0.48, 1.98)	0.94 (0.41, 2.19)	11	16	0.81 (0.37–1.75)	0.78 (0.33–1.86)
6.0–7.4 mmol/L	25	18	1.28 (0.69, 2.34)	1.08 (0.54, 2.18)	16	15	1.27 (0.63–2.57)	1.36 (0.61–3.05)
7.5–8.9 mmol/L	33	11	2.92 (1.43, 5.95)	2.07 (0.95, 4.51)	16	14	1.35 (0.66–2.76)	1.67 (0.74–3.77)
>9.0 mmol/L	16	17	0.87 (0.44, 1.72)	0.75 (0.33, 1.68)	14	19	0.84 (0.41–1.71)	0.97 (0.43–2.22)
Fasting glucose missing	422	330	1.18 (1.01, 1.38)	1.01 (0.85, 1.21)	230	319	0.85 (0.71–1.01)	0.85 (0.69–1.04)

*Numbers may not add up, patients not using antidiabetic drugs are not shown, but were included in the analyses. [a]Adjusted for smoking status and BMI. Drug use in previous 6 months: statins, RAAS inhibitors, non-selective NSAIDs. Most recent value in previous year for HbA1c and fasting glucose. Stratified variables were excluded as confounder in the analyses stratified by that variable. [b]Adjusted for: BMI. Drug use in previous 6 months: non-selective NSAIDs and COX2-selective NSAIDs. History of retinopathy in 5 years prior to TJR. Most recent value in previous year for HbA1c. Stratified variables were excluded as confounder in the analyses stratified by that variable. AD antidiabetic drug, TZD thiazolidinedione, TKR total knee replacement, THR total hip replacement, OR odds ratio, CI confidence interval, BMI body mass index, HbA1c glycated haemoglobin, RAAS renin-angiotensin-aldosterone system, NSAID non-steroidal anti-inflammatory drugs, COX cyclooxygenase.

Table 3

Use of TZDs and risk of total knee or total hip replacement in current users of antidiabetic drugs, stratified by number of TZD prescription before surgery

	TKR (*n* = 89 536)				THR (*n* = 99 682)			
AD use*	Number of cases *n* = 44 768	Number of controls *n* = 44 768	Crude OR (95% CI)	Fully adjusted OR[a] (95% CI)	Number of cases *n* = 49 841	Number of controls *n* = 49 841	Crude OR (95% CI)	Fully adjusted OR[b] (95% CI)
Current AD use	3623	3252			2748	3272		
AD use excluding TZD	3111	2861	ref	Ref	2461	2889	ref	ref
TZD use	512	391	1.21 (1.05, 1.39)	1.03 (0.88, 1.22)	287	383	0.88 (0.75, 1.04)	0.90 (0.75, 1.08)
By number of TZD prescriptions ever before TJR surgery								
1–4	45	47	0.88 (0.58, 1.33)	1.04 (0.65, 1.69)	15	51	0.35 (0.20, 0.62)	0.32 (0.16, 0.63)
5–8	48	29	1.53 (0.96, 2.43)	1.45 (0.86, 2.46)	38	43	1.04 (0.67, 1.62)	1.30 (0.78, 2.16)
9–14	68	50	1.25 (0.86, 1.81)	1.36 (0.87, 2.11)	34	47	0.85 (0.55, .33)	0.78 (0.47, 1.28)
15–29	157	113	1.28 (1.00, 1.63)	1.00 (0.75, 1.33)	90	97	1.09 (0.81, 1.46)	1.04 (0.75, 1.45)
≥30	194	152	1.18 (0.95, 1.48)	0.90 (0.70, 1.15)	110	145	0.89 (0.69, 1.15)	0.93 (0.70, 1.23)

*Numbers may not add up, patients not using antidiabetic drugs are not shown, but were included in the analyses. [a]Adjusted for smoking status and BMI. Drug use in previous 6 months: statins, RAAS inhibitors, non-selective NSAIDs. Most recent value in previous year for HbA1c and fasting glucose. Stratified variables were excluded as confounder in the analyses stratified by that variable. [b]Adjusted for BMI. Drug use in previous 6 months: non-selective NSAIDs and COX2-selective NSAIDs. History of retinopathy in 5 years prior to TJR. Most recent value in previous year for HbA1c. Stratified variables were excluded as confounder in the analyses stratified by that variable. TZD thiazolidinedione, AD antidiabetic drug, TKR total knee replacement, THR total hip replacement, OR odds ratio, CI confidence interval, TJR total joint replacement, RAAS renin-angiotensin-aldosterone system, NSAID non-steroidal anti-inflammatory drugs, COX cyclooxygenase

There was no difference in risk of surgery when comparing TZD use with the use of other ADs. TZDs are predominantly prescribed to patients unable to control their glucose metabolism sufficiently with use of metformin or SUs only. The TZD users may therefore be relatively severe DM patients. This may potentially result in confounding by disease severity, masking a pharmacological effect of TZDs. Additionally, severe OA patients have a reduced mobility [37], potentially resulting in a decreased ability to control their diabetes. As a result of this, severe OA patients are more likely to be prescribed a third AD, such as a TZD. Since DM has previously been associated with an increased risk of OA, the effect of this underlying disease should be taken into account. Our finding could be the result of fact that DM as such already increases the risk for OA and TZDs were not be able to counteract this effect through PPARγ activation. Stratification by HbA1c and fasting glucose, however, did not reveal an association with risk of surgery and an increasing severity of DM. In fact, patients with HbA1c values >9.5% were at lower risk of surgery. This suggests that TZDs reduce the risk of surgery in this poorly controlled diabetic population. However, it seems more likely that other factors are responsible for the reduced eligibility of surgery in patients with high HbA1c. Finally, an increase in number of TZD prescriptions was not associated with risk of TJR compared with DM patients using other ADs. These results suggest that there is no protective effect through PPARγ activation of TZD on the progression of OA.

Our study has several strengths and limitations. First, to the best of our knowledge this is the first study investigating the risk of OA with use of TZDs in a human population. We were, therefore, able to investigate the possible disease modifying osteoarthritic effect of TZDs, which has only been reported in pre-clinical studies. Second, it was conducted using the world's largest primary care database representing >8% of the British population. This enabled us to assess the risk of TJR associated with TZD use in 94 609 TJR patients. A limitation of this study is that the causal interpretation of the findings will be restricted. Although we made an effort to correct for relevant covariates, confounding is of considerable concern in an observational study. Due to limited availability of data we were unable to control for several factors, such as valgus/varus deformity, or a history of meniscus surgery or anterior cruciate ligament rupture. Furthermore, TJR could be considered to be an inadequate definition for OA. However, in epidemiology it has been widely used in previous studies assessing risk factors for severe OA [6, 38]. With this definition we are limited to severe cases of OA, missing possible beneficial effects in earlier stages of OA. Additionally, the severity of OA in the *in vivo* animal studies could be characterized as mild to moderate, limiting the comparability with the cases in our study. Finally, adherence is a concern when using large databases, such as the CPRD. Misclassification of exposure is therefore of concern [39]. Adherence to antidiabetic drugs is estimated to be approximately 70% [40]. The possible effect of TZDs may therefore be underestimated. Compensating for an underestimation would result in an OR closer to 1.0 in the case of TKR surgery and a potentially significantly lower risk of THR associated with TZD use.

In summary, we did not find any evidence supporting the hypothesis that TZDs could be used as disease modifying osteoarthritic drugs. There is no difference in risk of THR or TKR when TZD users are compared with other AD users. Finally, no duration of use effect was found with an increasing number of prescriptions. When these results will be confirmed in other observational studies, we would not recommend further clinical studies on the disease modifying osteoarthritic effect of TZDs.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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