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Research letter

Association of type 2 diabetes mellitus with self-reported knee pain and clinical knee osteoarthritis: The Maastricht Study



Introduction

Osteoarthritis (OA) of the knee is a progressive disabling joint disease characterized by pain and functional limitations. The global age-standardized prevalence of radiographic knee OA in 2010 was estimated to be 3.8%, and was higher in women (4.8%) than in men (2.8%) [1].

Several epidemiological studies have identified a strong association between type 2 diabetes mellitus (T2DM) and knee OA [2,3]. As both diseases share overweight and obesity as strong common risk factors, one of the main underlying mechanisms causing OA in T2DM patients is thought to be the increased mechanical load on weight-bearing joints, especially the knees. However, the above-mentioned studies have shown that T2DM may be an independent risk factor for OA, suggesting a coexisting metabolic cause. Conversely, other studies have reported no independent association between T2DM and OA [4,5].

The mechanisms underlying pain in knee OA are still poorly understood. Perception of pain in patients with T2DM might be different partly because of their different underlying biopathology (formation of neurovascular channels in subchondral bone and articular cartilage, low-grade inflammation) and partly related to diabetic neuropathy. Therefore, it would be of value to understand whether the level of knee pain experienced by patients with T2DM is different from that of those without T2DM.

Thus, the primary aim of the present study was to evaluate the association of T2DM with knee pain and clinical knee OA. In addition, a further aim was to determine whether patients with T2DM experience different levels of pain compared with people without T2DM.

Methods

The Maastricht Study is an observational, prospective, population-based cohort study, the details of which have been published elsewhere [6]. The present report includes cross-sectional data from the first 3451 participants who completed the baseline survey between November 2010 and September 2013. The study has the approval of the institutional medical ethics committee (NL31329.068.10) and Dutch Ministry of Health, Welfare and Sport (Permit 131088-105234-PG). All participants gave their written informed consent. Information regarding drug use was available from electronic dispensing records obtained from community pharmacies. Participants not consenting to collection of their pharmacy data ($n = 163$), and those with type 1 diabetes mellitus

(T1DM; $n = 43$) or missing data for any of the covariates ($n = 507$), were excluded, leaving a total of 2738 participants (Fig. 1).

Glucose metabolism status was defined, as per the World Health Organization (WHO) 2006 criteria, by a 2-h oral glucose tolerance test (OGTT) after an overnight fast. In addition, participants taking an antihyperglycaemic drug [AD; Anatomical Therapeutic Chemical Classification System (ATC) code A10] [7] were categorized as T2DM patients regardless of glucose levels. The date of the OGTT was used as the date of inclusion. T2DM patients were stratified by HbA_{1c} ($\leq 6.0\%$, 6.1–7.0%, $> 7.0\%$) and by duration of AD treatment.

The presence of knee pain was assessed by simply asking participants whether their knee pain, which could not be due to an accident, was present for at least four of the previous six weeks (yes/no). Clinical knee OA was defined based on a modified version of the American College of Rheumatology (ACR) guidelines (Table S1; see supplementary materials associated with this article online) [8]. Participants should have experienced knee pain, and at least three of the following five criteria should apply: age > 50 years; morning stiffness (lasting < 30 min); bony tenderness; bony distortion; and no palpable warmth in the knee. In addition, participants with knee prostheses were classified as having knee OA. Severity of knee pain was scored on a visual analogue scale (VAS) ranging from 0 to 10, with 0 corresponding to “no pain” and 10 reflecting “pain as bad as it possibly could be”. Subjects missing data for any outcome were excluded from analyses of that outcome, thereby leaving a final total $n = 2719$ for knee pain analysis and $n = 2721$ for knee OA analysis (Fig. 1).

Logistic regression models were fitted to test the association between T2DM and knee pain or clinical knee OA. Odds ratios (ORs) and 95% confidence intervals (CIs) were assessed in unadjusted models and in models adjusted for body mass index (BMI). Subsequently, our analyses were also adjusted for age, gender and BMI. Finally, our fully adjusted models included the following confounders:

- age, gender, BMI, systolic (SBP) and diastolic blood pressure (DBP), smoking status, level of education, alcohol use, a physically demanding occupation and a history of activities such as running and/or jumping;
- and use of the following drugs in the six months prior to inclusion: statins, diuretics, calcium-channel blockers, beta-blockers, renin-angiotensin-aldosterone system (RAAS) inhibitors, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, bisphosphonates and systemic corticoids.

The association of T2DM with severity of self-reported knee pain in patients with clinical knee OA was assessed using a linear regression model, adjusted for the same above-mentioned confounders as in the fully adjusted logistic regression model and complemented by the following covariates: previous knee

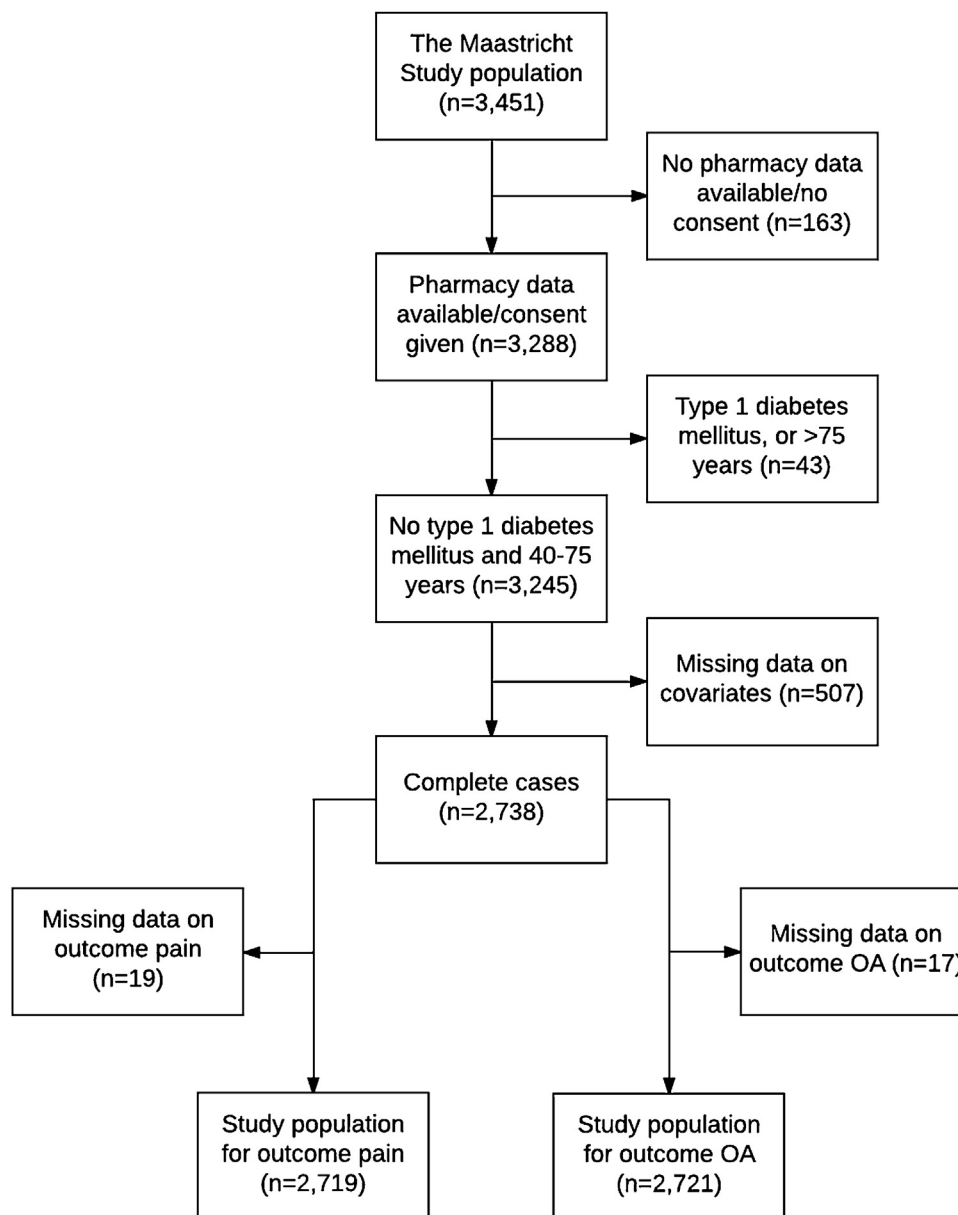


Fig. 1. Flow chart of inclusion of study participants.

surgery; previous sports-related knee injury; presence of neuropathic pain [four-item Neuropathic Pain Questionnaire (DN4) score ≥ 3], and knee alignment (valgus/varus). Statistical significance was set at $P < 0.05$, and SAS version 9.4 software (SAS Institute, Cary, NC, USA) was used for all analyses.

Results

From the study base population of 3451 participants, 2719 and 2721 cases with no missing data were available for the knee pain and knee OA analyses, respectively (Fig. 1). For the former analysis, 549/2719 (20.2%) subjects fulfilled the case definition, as did 387/2721 (14.2%) subjects for the latter analysis (Table S2; see supplementary materials associated with this article online). Participants with knee pain were, on average, 1 year older than those without knee pain (60.6 vs 59.8 years), whereas participants with knee OA were, on average, two years older than those without knee OA (62.3 vs 59.6 years). Also, participants with knee OA or knee pain had higher BMI scores than those without knee OA or

knee pain. The age and gender standardized rate of OA in T2DM patients was 21.5/100 population compared with 12.4/100 population without T2DM. The age and gender distribution of the population without T2DM was used as reference (results not shown).

Compared with having normal glucose metabolism (NGM), T2DM was not associated with knee pain after adjusting for all relevant confounders (OR: 0.89, 95% CI: 0.67–1.19). Stratification of T2DM patients by HbA_{1c} or duration of AD use showed similar results (Table S3; see supplementary materials associated with this article online). Similarly, T2DM was not associated with knee OA after adjusting for BMI (OR: 1.22, 95% CI: 0.94–1.60). In addition, after adjusting for other relevant confounders, T2DM results showed no relevant changes (OR: 0.96, 95% CI: 0.69–1.33). Stratification of T2DM patients by HbA_{1c} or duration of AD use showed similar results (Table 1).

Severity of knee pain was rated by 327/387 (84.5%) patients with knee OA, and the results were 5.1 ± 2.0 [standard deviation (SD)] and 4.8 ± 2.2 in patients with and without T2DM, respectively.

Table 1
Association of prediabetes and type 2 diabetes mellitus (T2DM) with knee osteoarthritis (OA)^a in patients stratified by HbA_{1c} and duration of antihyperglycaemic drug (AD) use.

	No knee OA (n = 2334) n (%)	Knee OA (n = 387) n (%)	OR (95% CI) unadjusted	OR (95% CI) adjusted for BMI	OR (95% CI) adjusted for age/gender/BMI	OR (95% CI) fully adjusted ^b
NGM	1383 (59.3)	182 (47.0)	Reference	Reference	Reference	Reference
Prediabetes	363 (15.6)	65 (16.8)	1.36 (0.99–1.85)	1.09 (0.80–1.49)	0.97 (0.70–1.35)	0.98 (0.70–1.37)
T2DM	588 (25.2)	140 (36.2)	1.81 (1.42–2.30)	1.22 (0.94–1.60)	1.11 (0.84–1.48)	0.96 (0.69–1.33)
HbA _{1c} levels:						
≤ 6.0%	94 (16.0)	17 (12.1)	1.37 (0.80–2.36)	1.07 (0.62–1.86)	1.00 (0.57–1.76)	0.84 (0.47–1.50)
6.1–7.0%	324 (55.1)	68 (48.6)	1.59 (1.18–2.16)	1.10 (0.80–1.52)	0.97 (0.69–1.37)	0.86 (0.59–1.26)
> 7.0%	170 (28.9)	55 (36.2)	2.46 (1.75–3.46)	1.55 (1.07–2.25)	1.47 (0.99–2.17)	1.28 (0.83–1.98)
AD use ^c						
Never	155 (26.4)	31 (22.1)	1.52 (1.00–2.30)	1.1 (0.67–1.60)	0.90 (0.57–1.40)	0.87 (0.55–1.38)
Past	24 (4.1)	6 (4.3)	1.90 (0.77–4.71)	1.2 (0.49–3.15)	1.10 (0.43–2.85)	0.95 (0.36–2.48)
Recent	25 (4.3)	5 (3.6)	1.52 (0.57–4.02)	1.3 (0.49–3.50)	1.16 (0.43–3.16)	1.04 (0.37–2.92)
Current	384 (65.3)	98 (70.0)	1.94 (1.48–2.54)	1.3 (0.96–1.74)	1.21 (0.88–1.66)	1.01 (0.70–1.47)
Duration of AD use						
≤ 879 days	101 (26.3)	20 (20.4)	1.50 (0.91–2.49)	1.0 (0.61–1.74)	1.01 (0.59–1.73)	0.87 (0.49–1.55)
880–1645 days	97 (25.3)	23 (23.5)	1.80 (1.11–2.91)	1.2 (0.72–1.98)	1.13 (0.67–1.92)	0.99 (0.56–1.73)
1646–2939 days	96 (25.0)	25 (25.5)	1.98 (1.24–3.15)	1.3 (0.82–2.16)	1.26 (0.76–2.08)	1.05 (0.60–1.83)
> 2939 days	90 (23.4)	30 (30.6)	2.53 (1.63–3.94)	1.6 (1.04–2.62)	1.45 (0.89–2.35)	1.17 (0.68–2.02)

^a According to adapted American College of Rheumatology criteria: knee pain not due to accident experienced over at least four of the last six weeks and meeting at least three of the following five criteria: age > 50 years; morning stiffness lasting < 30 min; bony tenderness; bony distortions; no palpable warmth in the knee; those with knee prostheses were classified as knee OA.

^b At time of inclusion by age, gender, BMI, education level, smoking status, alcohol use, systolic and diastolic blood pressure, a physically demanding occupation, history of activities such as running and/or jumping, and use, 6 months prior to inclusion, of statins, diuretics, calcium-channel blockers, beta-blockers, renin-aldosterone-angiotensin system (RAAS) inhibitors, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, bisphosphonates or systemic corticoids.

^c Current users defined as having at least one recorded dispensing within 90 days of inclusion date; recent users defined as taking an AD 91–180 days before inclusion, but not within 90 days of inclusion date; past users defined as stopping AD use > 180 days before inclusion date; NGM: normal glucose metabolism.

Furthermore, T2DM did not contribute to the variable severity of knee pain in either unadjusted (β : 0.28; $P = 0.23$) or adjusted (β : -0.04 ; $P = 0.88$) models (Table S4; see supplementary materials associated with this article online).

Discussion

Our present results demonstrate that patients with T2DM are more likely to experience knee pain and knee OA. However, these associations were no longer present after adjusting for BMI, reflecting the importance of overweight in the relationship between T2DM and knee pain or knee OA. In patients with knee OA, there was no difference in severity of knee pain experienced by T2DM patients compared with those without T2DM.

The association of T2DM with knee pain as reported in the present study confirms the findings of previous studies [9,10]. The association of T2DM with knee OA was strongly influenced by BMI, suggesting that T2DM does not affect knee OA independently. The inconsistency between results from the present study and other previous studies may be due to methodological differences, such as different definitions of OA, and the general difficulty of assessing duration and date of onset of knee OA and T2DM. Also, the known major role of overweight in knee OA might overrule (small) metabolic effects, although this may not apply to OA in other joints, such as those of the hand, where overweight is less likely to have any effect.

Although T2DM patients experience knee pain more often than those without T2DM, our study has shown that the severity of the experienced knee pain in patients with knee OA does not differ between subjects with and without T2DM. This may be due to the fact that our included T2DM population was relatively healthy, and their glucose metabolism was relatively well controlled. Thus, the effects of any underlying biopathological mechanisms or of diabetic neuropathy may have been limited.

Our study has several strengths. First, the Maastricht Study is characterized by an extensive phenotyping approach, making it

possible to include a wide range of potential confounders. This provides an opportunity to better assess the independent association of T2DM with knee pain and knee OA. Second, as the Maastricht Study was focused on T2DM and its comorbidities, glucose metabolism status was highly accurately defined, rendering the risk of misclassification low. Third, this was the first study to provide an insight into the different perception of severity of knee pain between those with and without T2DM.

However, there were some limitations as well. Due to the cross-sectional design of our study, causality cannot be assessed. Furthermore, as there was no measurement of crepitus during motion, the original ACR definition of clinical knee OA could not be used [8]. Nevertheless, our adapted definition was more stringent than the original (three out of five criteria were required compared with three out of six criteria in the original definition). Thus, some OA cases may have been misclassified as non-OA. However, such misclassification would be expected to be non-differential, resulting in a bias towards null. As a consequence, the effect of T2DM on OA may have been underestimated. Finally, as is the case in most studies, the date of onset and duration of T2DM are difficult to determine. In the present study, an attempt was made to approximate these data by stratifying T2DM patients by duration of AD use. However, this approximation may not reflect the actual date of disease onset as non-pharmacological lifestyle changes are usually suggested first. Nevertheless, it does provide a specific point in the course of the disease at which metabolic control can only be achieved by pharmacological treatment. Duration of knee pain or knee OA were not available and were therefore not included in our analyses.

In conclusion, T2DM patients are more likely to experience knee pain or have knee OA compared with patients with NGM, although this seems to be mostly associated with overweight rather than a metabolic effect, thereby emphasizing the importance of weight reduction as a major factor in the treatment and prevention of knee pain and knee OA. Furthermore, T2DM patients with knee OA do not experience knee pain any differently from knee OA patients without T2DM.

Author contributions

JN, AB, PE, BB, PD and FV contributed to the conception and design of the study. FV, PD, MS, AB, PE, NS and CS contributed to the acquisition of data. JN and KD contributed to analysis of data. All authors contributed to interpretation of data. JN, AB, NS and PE drafted the manuscript and all authors contributed intellectual content in revising the article. All authors gave final approval of the version to be submitted, and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosure of interest

BB's department received research grants from Pfizer and Roche, and he has occasionally received speaker's honoraria from Pfizer, Roche, AbbVie and MSD. AB's department received research grants from Amgen, AbbVie, Pfizer and Merck, and she has occasionally received speaker's honoraria from Pfizer, UCB and Sandoz. PE's department receives research grants from Stryker, Active Implants, Episurf Medical, DSM Biomedical, Regentis Biomaterials, DePuy Synthes and he has occasionally received speaker's honoraria from Biomet. PD has received unrestricted grants from NWO, the EU and the nutritional industry for research unrelated to this topic. The other authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.diabet.2018.01.013>.

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