The Use of β-Blockers and the Risk of Undergoing a Knee Arthroplasty

A Nested Case-Control Study

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Background: Research has indicated that β-blockers may downregulate various inflammatory mediators that are involved in osteoarthritis (OA). The objective of this study was to analyze the likelihood of total knee arthroplasty (TKA) among patients with OA who were being treated with β-blockers.

Methods: A nested case-control study was conducted with use of clinical records from our institutional database. We included patients who attended our outpatient clinic with a history of new-onset knee pain between 2010 and 2019. The case group included individuals who had undergone primary TKA between 2018 and 2019, whereas the control group included subjects who had not undergone TKA. Controls were matched by date of birth ±2 years, sex, calendar time (first outpatient visit ±1 year), and the grade of arthritis; the control-to-case ratio was 1:1. Adherence to β-blocker use was measured with use of the proportion of days covered (PDC) (i.e.,<0.25, ≥0.25 to <0.75, ≥0.75), and the cumulative effect was measured on the basis of the total number of years of treatment with β-blockers. A binary logistic regression analysis adjusted to potential confounders was carried out to assess the risk of TKA associated with the intake of β-blockers.

Results: A total of 600 patients were included (300 in the case group and 300 in the control group). Compared with nonusers, any use of β-blockers during the follow-up period was associated with a reduction in the likelihood of undergoing TKA (adjusted odds ratio [OR], 0.51; 95% confidence interval [CI], 0.34-0.77). The adjusted ORs for the use of selective β1-blockers and nonselective β1-blockers were 0.69 (95% CI, 0.36 to 1.31) and 0.42 (95% CI, 0.24 to 0.70), respectively. The adjusted ORs for any recent use, PDC of <0.25, PDC of ≥0.25 to <0.75, and PDC of ≥0.75 were 0.65 (95% CI, 0.51 to 0.99), 0.62 (95% CI, 0.21 to 1.85), 0.32 (95% CI, 0.09 to 1.22), and 0.55 (95% CI, 0.34 to 0.88), respectively. Regarding the cumulative effect of β-blockers, the adjusted ORs for the use for <1 year, ≥1 to <5 years, and ≥5 years were 0.41 (95% CI, 0.20 to 0.85), 0.52 (95% CI, 0.21 to 1.33), and 0.36 (95% CI, 0.22 to 0.60), respectively.

Conclusions: The use of nonselective β-blockers was associated with a lower likelihood of undergoing TKA. Patients treated for prolonged periods were at a lower likelihood for undergoing TKA.

Level of Evidence: Prognostic Level III. See Instructions for Authors for a complete description of levels of evidence.

Osteoarthritis (OA) is the leading cause of musculoskeletal pain and disability in developed countries[1]. Drugs used in patients with OA, including nonsteroidal anti-inflammatory drugs (NSAIDs), opiates, glucosamine and chondroitin, corticosteroids, hyaluronic acid (HA), and platelet-rich plasma (PRP), have been shown to have different degrees of effectiveness for the treatment of knee pain related to degenerative joint disease[2-6]. However, none of these medications has been successful for preventing eventual treatment with total knee arthroplasty (TKA).

One recent study demonstrated an association between the use of β-blockers and a reduction in the cumulative risk of OA[7]. Moreover, another study showed that patients with OA who were receiving β-blockers had a lower prevalence of joint pain and consumed lower amounts of opiates[8]. These findings could be explained by a potential inhibitory effect that β-blockers may have on OA degenerative processes through the downregulation of several inflammatory mediators involved in cartilage degeneration. Cytokines and enzymes involved in the process of joint degeneration, such as interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJS/H612).

matrix metalloproteinase (MMP)-1, MMP-2, MMP-9, and MMP-13[9-11], are known to be regulated by the adrenergic signal[12-14]. Thus, downregulation of the adrenergic signal could potentially decrease cartilage degradation and delay the progression of OA.

Accordingly, we hypothesized that the use of β-blockers could slow the progression of knee OA through the suppression of inflammatory mediators involved in cartilage degeneration, indirectly reducing the need for a TKA. Accordingly, the purpose of the present study was to analyze the relationship between the use of β-blockers in patients with knee pain and the risk of undergoing a TKA as a result of advanced knee OA.

Materials and Methods

This study was approved by our institutional Ethics Board.

Data Source

We conducted a nested case-control study on patients living within our local health care area. Data were extracted from the Andalusian "Diraya Atención Hospitalaria" (DAH) single research database by the members of our research team[15]. We identified patients who had presented to our orthopaedic outpatient clinic with a history of new-onset knee pain between January 1, 2010, and December 31, 2019. Research keywords included "knee pain," "knee osteoarthritis," "knee arthropathy," and "gonalgia" (Fig. 1).

Data Collected

We collected data on patient characteristics, comorbidities, knee function, follow-up, indications for the use of β-blockers, and drugs/injections, as described below.

Patient Characteristics

Patient characteristics of interest included age, sex, and body mass index (BMI).

Comorbidities

Comorbidities of interest included the American Society of Anesthesiologists (ASA) class and a history of bronchial asthma or chronic obstructive pulmonary disease (COPD), diabetes mellitus, stroke (i.e., hemorrhagic, ischemic, and transient ischemic attack), degenerative lumbar spine disease, ipsilateral ankle and hip OA, and peripheral vascular disease.

Knee Function

Variables of interest included previous surgery involving the affected knee (i.e., arthroscopic meniscectomy/irrigation, surgical treatment of fractures around the knee joint, osteotomy/alignment surgery, and anterior cruciate ligament [ACL] reconstruction) and the grade of knee OA at the first outpatient visit according to Kellgren-Lawrence classification (determined on the side with more radiographically advanced disease in cases of bilateral involvement). All included patients had weight-bearing bilateral radiographs made with the knees in full extension; non-weight-bearing radiographs were discarded and were considered to be missing data. Rosenberg single-leg posteroanterior weight-bearing radiographs were not routinely made. None of the included patients were registered as having isolated primary severe patellofemoral disease.

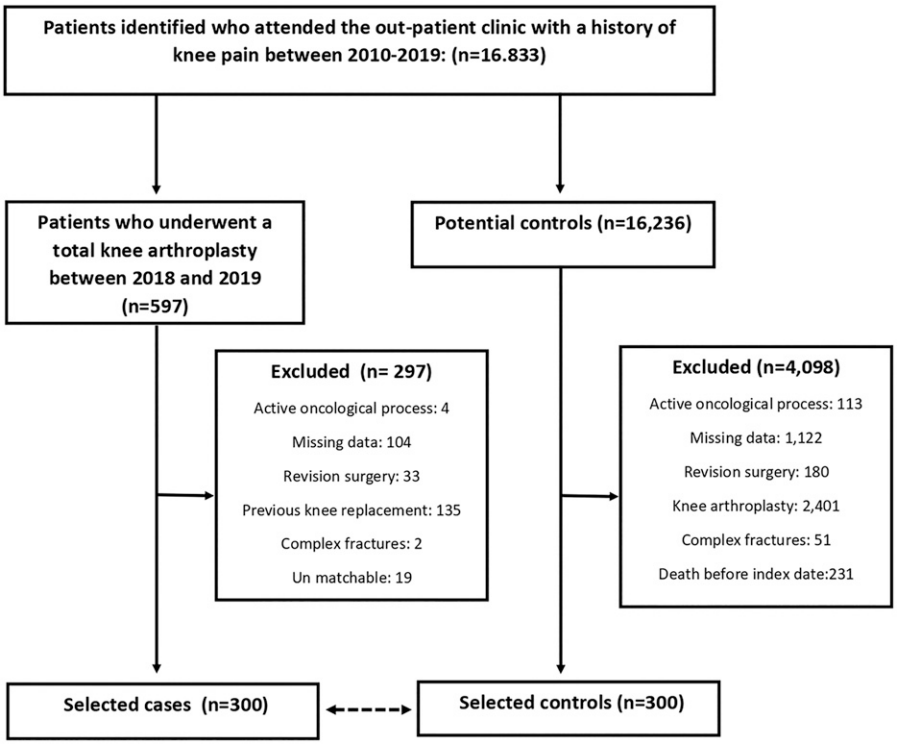

Fig. 1

Flowchart describing case and control selection.

Follow-up

Data of interest included the number of outpatient visits and the duration of follow-up.

Possible Indications for β-Blocker Use

Possible indications for the use of a β-blocker included a history of hypertension, glaucoma, ischemic heart disease (i.e., previous myocardial infarction, stable or unstable angina), heart failure (i.e., congestive heart failure, high-output failure, valvular insufficiency, hypertension, ischemic heart disease), and cardiac arrhythmias (i.e., first, second, and third-degree heart block; atrial fibrillation; supraventricular tachycardia).

Medication Use

Data of interest included the use of drugs such as β-blockers, NSAIDs, metamizole, opioids, paracetamol, diuretics, calcium channel blockers, angiotensin (I and II) receptor blockers, and adrenergic agonists as well as intra-articular injections (i.e., hyaluronic acid and corticosteroids).

Exclusions

We excluded patients with an active oncological process, those with a first outpatient visit for the evaluation of knee pain before January 1, 2010, and those who had undergone a previous contralateral TKA, revision TKA, or TKA for the treatment of a complex fracture (Fig. 1).

Case Group

The case group included patients who had undergone a primary TKA (the index date) between January 1, 2018, and December 31, 2019, and who also had presented to our clinic with a history of new-onset knee pain between January 1, 2010, and December 31, 2019. The date of the first visit to our outpatient clinic was then identified.

Our institution uses the following protocol to indicate TKA (with patients needing to fulfill all criteria): (1) a confirmed radiographic diagnosis of OA (primary or secondary) on standing radiographs, (2) advanced OA involving at least 1 of the 3 compartments of the knee, (3) severe and chronic pain, (4) substantial functional limitation affecting the performance of activities of daily living, and (5) failure of conservative measures such as the use of NSAIDs, opiates, paracetamol, metamizole, physiotherapy, infiltrations, and weight loss.

In addition, the patients had to fulfill a number of secondary criteria, including being fit for surgery, being well informed on the risks and benefits of the intervention, and having a BMI of ≤40 kg/m^2.

Control Group

The control group included patients with a history of knee pain who attended the orthopaedic outpatient clinic during the study period and who did not undergo TKA. Controls were matched to cases following incidence density sampling, in a 1:1 ratio, by date of birth ±2 years, sex, calendar time ±1 year (first visit to our outpatient clinic), and grade of arthritis (Kellgren-Lawrence grade ≤2 and >2). Controls had to be alive at least until their corresponding index date. The same exclusion criteria that were applied for the cases were applied to the controls before matching (Fig. 1).

Matching to the date of birth was performed because the prevalence of knee OA increases with age; therefore, age could act as an independent risk factor for knee OA[16]. Sex also has been described as an independent risk factor for knee OA. Moreover, in a recent study, Szilagyi et al. described how different risk factors for OA may affect men and women differently[17]. Finally, matching on calendar time was performed to provide a similar follow-up period for both groups.

Exposure to β-Blockers

β-blockers were prescribed for the treatment of cardiovascular conditions (i.e., ischemic heart disease, hypertension, cardiac arrhythmias, and heart failure) and glaucoma. Nonselective β-blockers display both β1 and β2 adrenergic antagonism, whereas selective β-blockers only display β1 antagonism. Exposure to β1-selective β-blockers (i.e., atenolol, betaxolol, bisoprolol, nebivolol) and nonselective β-blockers (i.e., propranolol, carteolol, carvedilol, nadolol, and timolol) was determined by the identification of any prescription in the digital records registered before the index date. All of the β-blockers that were identified in our cohort were administered orally, with the exception of timolol, which was prescribed as eye drops. Adherence during the follow-up period (i.e., from the first outpatient visit to the index date) was estimated by the proportion of days covered (PDC), a ratio in which the numerator was the number of days covered by the pharmacy-supplied medication and the denominator was the 2-year period before the index date (in days) (i.e., i.e.,<0.25, ≥0.25 to <0.75, ≥0.75). The cumulative effect of β-blockers was defined as the sum of the years of treatment, regardless of whether they were continuous or interrupted, with use of the following categorical variables: <1 year, 1 to 5 years, ≥5 years.

Statistical Analysis

The statistical analysis was performed with use of IBM SPSS Statistics 20.0. The Shapiro-Wilk test was performed on continuous variables. Covariate balance between the 2 study groups was analyzed with use of the standardized mean difference for continuous variables, the McNemar test for dichotomous matching variables, and the chi-square test for dichotomous non-matching variables. The artificial intelligence software Dagitty 3.0, a browser-based environment for creating, editing, and analyzing causal diagrams (Fig. 2)[18], was used to determine the best combination of variables for the logistic regression model. Dagitty 3.0 is a validated tool used to reduce potential multicollinearity, simultaneity, and selection biases in empirical studies[18]. The chi-square test and a binary logistic regression analysis adjusted for several confounding factors were used to calculate the likelihood of being treated with TKA (expressed as crude and adjusted odds ratios [ORs], respectively). Adherence to β-blocker use

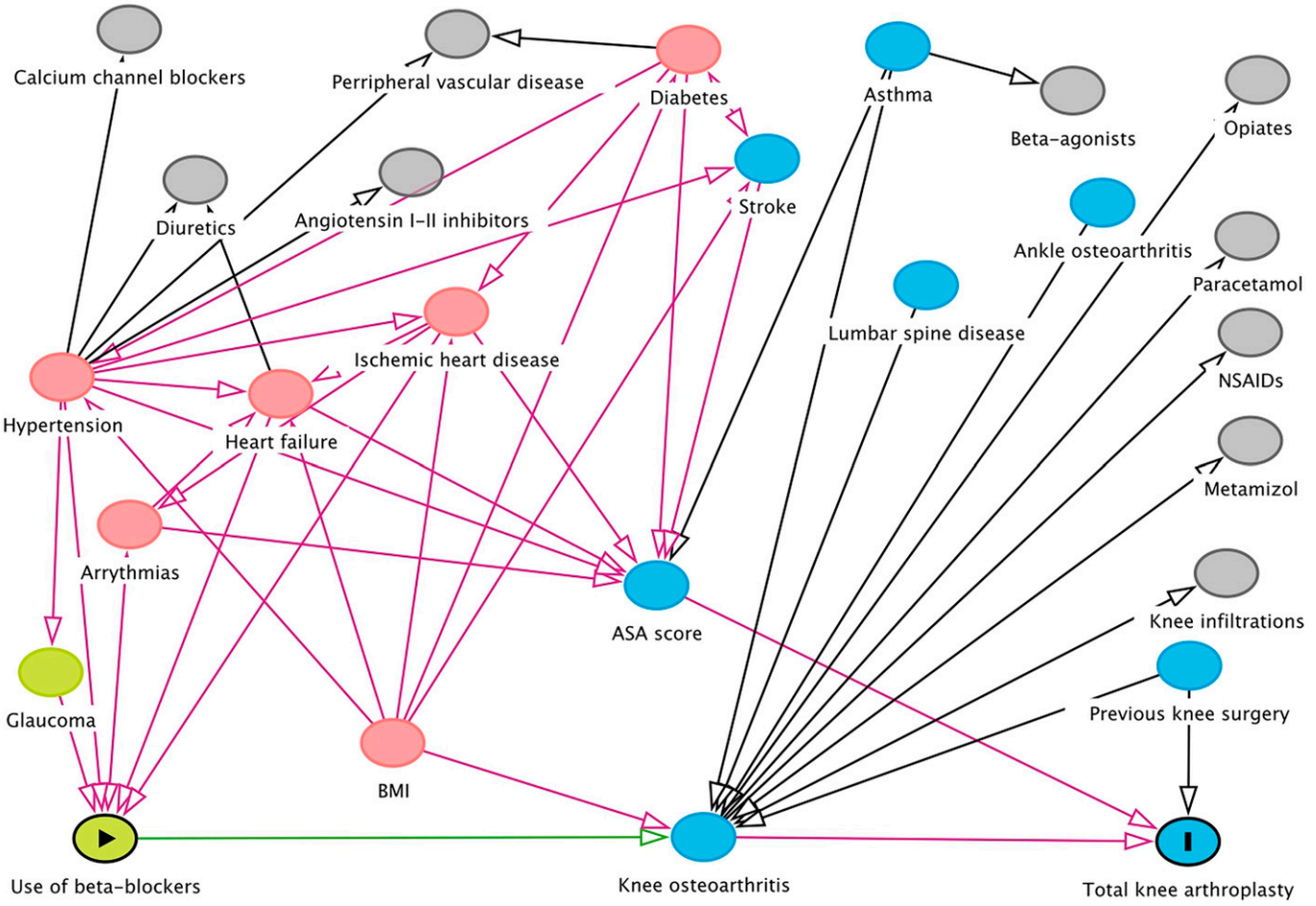

Fig. 2

Causal diagrams drawn using Dagitty 3.0 software to minimize bias in the logistic regression analysis. The use of β-blockers is the exposure variable, and TKA is the outcome variable. Blue variables = ancestor outcomes, yellow variables = ancestor exposure, pink variables = ancestor outcomes and exposures, gray variables = other variables, pink lines = biasing paths, green line = causal path, black lines = other paths.

was measured with use of the PDC, and the cumulative effect was measured as the total number of years of treatment with β-blockers.

Source of Funding

The authors did not receive any external funding for this study.

Results

A total of 16,833 patients presented to our outpatient clinic with a history of knee pain between 2010 and 2019, of whom 597 were managed with TKA between 2018 and 2019. From this initial patient sample, 297 patients (49.7%) were excluded (Fig. 1). Of those, a total of 104 patients (17.4%) in the case group were excluded because of missing data. Finally, 300 patients in the case group were matched with 300 controls who fulfilled our inclusion-exclusion criteria; each group included 87 men (29.0%) and 213 women (71.0%). The demographic and clinical features of cases and controls are presented in Table I.

The adjusted OR of undergoing TKA was 0.51 (95% confidence interval [CI], 0.34 to 0.77) for patients who had previously used any β-blocker as compared with non-users (Table II). The adjusted ORs for TKA among those who had used selective β1-blockers and nonselective β-blockers were 0.69 (95% CI, 0.36 to 1.31) and 0.42 (95% CI, 0.24 to 0.70), respectively. The adjusted ORs for TKA among the patients in the recent use, PDC <0.25, PDC ≥0.25 to <0.75, and PDC ≥0.75 categories were 0.65 (95% CI, 0.51 to 0.99), 0.62 (95% CI, 0.21 to 1.85), 0.32 (95% CI, 0.09 to 1.22), and 0.55 (95% CI, 0.34 to 0.88), respectively. Regarding the cumulative effect of β-blockers, the adjusted ORs for the use of β-blockers for <1 year, 1 to 5 years, and ≥5 years were 0.41 (95% CI, 0.20 to 0.85), 0.52 (95% CI, 0.21 to 1.33), and 0.36 (95% CI, 0.22 to 0.60), respectively (Table II). The relationship between the use of opioids and the likelihood of undergoing TKA is shown in Table III.

On the other hand, we observed that the ORs for the use of β-blockers and the intake of opioids, NSAIDs, metamizole,

TABLE I Demographic Characteristics*

	Cases (N = 300)†	Controls (N = 300)†	Standardized Mean Difference†	P Value§
Age *(yr)*	68.37 ± 6.8	68.45 ± 6.7	−0.01	—
Sex				1.000
Male	87 (29.0%)	87 (29.0%)		
Female	213 (71.0%)	213 (71.0%)		
ASA class				0.005#
≤2	223 (74.3%)	191 (63.7%)		
>2	77 (25.7%)	109 (36.3%)		
Hypertension	204 (68.0%)	212 (70.7%)		0.557
Ischemic heart disease	18 (6.0%)	23 (7.7%)		0.431
Stroke	15 (5.0%)	9 (3.0%)		0.205
Arrhythmias	37 (12.3%)	19 (6.3%)		0.011#
Diabetes mellitus	81 (27.0%)	68 (22.7%)		0.202
Heart failure	16 (5.3%)	12 (4.0%)		0.428
Peripheral vascular disease	32 (10.7%)	17 (5.7%)		0.024#
Glaucoma	10 (3.3%)	15 (5.0%)		0.307
Asthma or COPD	40 (13.3%)	46 (15.3%)		0.550
Lumbar spine disease	88 (29.3%)	158 (52.7%)		<0.001#
Ipsilateral ankle osteoarthritis	15 (5.0%)	7 (2.3%)		0.079
Ipsilateral hip arthritis	38 (12.7%)	28 (9.3%)		0.182
BMI *(kg/m²)*	31.1 ± 3.9	30.6 ± 2.4	0.16	—
Kellgren-Lawrence grade				1.000
≤2	103 (34.3%)	103 (34.3%)		—
>2	197 (65.7%)	197 (65.7%)		—
Previous knee surgery				0.008#
No	245 (81.7%)	268 (89.3%)		—
Yes	55 (18.3%)	31(10.7%)		—
Partial meniscectomy	48 (16.0%)	30 (10.0%)		—
Osteotomy/alignment surgery	2 (0.7%)	1 (0.3%)		—
ACL reconstruction	2 (0.7%)	0 (0.0%)		—
Surgical treatment of fractures around the knee joint	3 (1.0%)	0 (0.0%)		—
Duration of follow-up *(yr)*	2.1 ± 1.6	2.2 ± 1.6	0.06	—
No. of outpatient visits	3.0 ± 1.7	2.8 ± 2.0	0.11	—
Medication				
Opiates	185 (61.7%)	181 (60.3%)		0.485
NSAIDs	234 (78.0%)	227 (75.7%)		0.498
Metamizole	211 (70.3%)	212 (70.7%)		0.929
Paracetamol	276 (92.0%)	282 (94.%)		0.337
β-blockers	74 (24.7%)	104 (34.7%)		0.007#
β-agonists	76 (25.3%)	80 (26.7%)		0.879
Calcium channel blockers	69 (23.0%)	90 (30.0%)		0.061
ACEIs	129 (43.0%)	101 (33.7%)		0.016#
Diuretics	160 (53.3%)	121 (40.3%)		<0.001#
Number of infiltrations	1.1 ± 1.4	1.3 ± 1.8	0.13	—

*ASA = American Society of Anesthesiologists, BMI = body mass index, ACL = anterior cruciate ligament, COPD= chronic obstructive pulmonary disease, NSAIDs = nonsteroidal anti-inflammatory drugs, ACEIs = angiotensin-converting enzyme inhibitors and angiotensin II. †The values are presented as the mean and the standard deviation or as the number with the percentage in parentheses. ‡The balance of continuous variables was analyzed with use of the standardized mean difference between the 2 groups. §Dichotomous matched variables were compared with use of the McNemar test, and non-matched dichotomous variables were compared with use of the chi-square test. #Significant.

TABLE II Relationship Between the Use of β-Blockers and Risk of TKA*

Use of β-Blockers	Cases (N = 300)	Controls (N = 300)	Crude Odds Ratio†	Adjusted Odds Ratio‡
Non-users *(no. of patients)*	226 (75.3%)	196 (65.3%)	1	1
Any previous use of β-blockers *(no. of patients)*	74 (24.7%)	104 (34.7%)	0.62 (0.43-0.88)#	0.51 (0.34-0.77)#
Compliance with treatment§ *(no. of patients)*				
Non-users	226 (75.3%)	196 (65.3%)	1	1
Any recent use§	65 (21.7%)	81 (27.0%)	0.51 (0.31-0.82)#	0.65 (0.51-0.99)#
PDC <0.25	7 (2.3%)	4 (1.3%)	1.52 (0.43-5.26)	0.62 (0.21-1.85)
PDC ≥0.25 to <0.75	8 (2.7%)	8 (2.7%)	0.87 (0.32-2.35)	0.32 (0.09-1.22)
PDC ≥0.75	50 (16.7%)	69 (23.0%)	0.62 (0.42- 0.95)#	0.55 (0.34-0.88)#
Cumulative effect *(no. of patients)*				
Non-users	226 (75.3%)	196 (65.3%)	1	1
<1 yr	12 (4.0%)	14 (4.7%)	0.73 (0.34-1.64)	0.41 (0.20-0.85)#
1-5 yr	29 (9.7%)	24 (8.0%)	1.0 (0.59-1.86)	0.52 (0.21-1.33)
≥5 yr	33 (11.0%)	66 (22.0%)	0.44 (0.27-0.70)#	0.36 (0.22-0.60)#
β -blocker type *(no. of patients)*				
Non-users	226 (75.3%)	196 (65.3%)	1	1
β1-selective	43 (14.3%)	51 (17.0%)	0.75 (0.48-1.17)	0.69 (0.36-1.31)
Nonselective**	31 (10.3%)	53 (17.7%)	0.51 (0.31-0.82)#	0.42 (0.24-0.70)#

*PDC = proportion of days covered. †Calculated with use of the chi-square test. The 95% CI is given in parentheses. ‡Adjusted for the following potential confounders: history of arrhythmias, bronchial asthma, or chronic obstructive pulmonary disease, body mass index, heart failure, hypertension, ischemic heart disease, and previous knee surgery. The 95% CI is given in parentheses. §During the 2-year period before the index date. Nine cases and 23 controls did not take β-blockers in the 2 years before the index date. #Significant. **With or without other, selective β-blockers.

and paracetamol were 1.49 (95% CI, 1.01 to 2.20), 0.53 (95% CI, 0.36 to 0.79), 1.15 (95% CI, 0.78 to 1.69), and 1.20 (95% CI, 0.59 to 2.45), respectively.

Discussion

This study analyzed the relationship between the use of β-blockers in patients with knee pain and the likelihood of

TABLE III Relationship Between the Use of Opiates and Risk of TKA*

Use of Opiates	Cases (N = 300)	Controls (N = 300)	Crude Odds Ratio†	Adjusted Odds Ratio‡
Non-users *(no. of patients)*	115 (38.3%)	119 (39.7%)	1	1
Any previous use of opiates *(no. of patients)*	185 (61.7%)	181 (60.3%)	0.94 (0.68-1.31)	1.06 (0.74-1.52)
Compliance with treatment§ *(no. of patients)*				
Non-users	115 (38.3%)	119 (39.7%)	1	1
Any recent use†	173 (57.7%)	120 (40.0%)	1.49 (1.06-2.11)#	2.01 (1.47-2.92)#
PDC <0.25	48 (16.0%)	56 (18.7%)	0.92 (0.50-1.68)	0.73 (0.39-1.39)
PDC ≥0.25 to <0.75	69 (23.0%)	34 (11.3%)	2.18 (1.21-3.92)#	2.02 (1.09- 3.75)#
PDC ≥0.75	56 (18.7%)	30 (10.0%)	2.65 (1.61-4.35)#	2.41 (1.43-4.07)#
Cumulative effect *(no. of patients)*				
Non-users	115 (38.3%)	119 (39.7%)	1	1
<1 yr	63 (21.0%)	102 (34.0%)	0.82 (0.34-1.98)	0.70 (0.28-1.77)
1-5 yr	109 (36.3%)	69 (23.0%)	2.11 (0.87-5.09)	1.78 (0.71-4.48)
≥5 yr	13 (4.3%)	10 (3.3%)	1.34 (0.57-3.19)	1.15 (0.46-2.84)

*PDC = proportion of days covered. †Calculated with use of the chi-square test. The 95% CI is given in parentheses. ‡Adjusted for the following potential confounders: history of arrhythmias, bronchial asthma or chronic obstructive pulmonary disease, body mass index, previous use of β-blockers, heart failure, hypertension, ischemic heart disease, and previous knee surgery. The 95% CI is given in parentheses. §During the 2-year period before the index date. Twelve cases and 61 controls did not take opiates in the 2 years before the index date. #Significant.

primary knee arthroplasty. We observed that the previous use of β-blockers was associated with a lower probability of undergoing TKA. Moreover, this effect appeared to be cumulative, as patients who had been treated with β-blockers for ≥5 years had the lowest probability of TKA. Patients managed with nonselective blockers also had a lower likelihood of TKA.

β-Blockers and OA

There has been a growing interest in recent years regarding the role that β-blockers could play in the processes involving degenerative joint disease. Recent research has suggested that β-blockers could have an anti-nociceptive effect in patients with fibromyalgia, and temporomandibular pain[19]. Polymorphisms in the β2-adrenoreceptor gene have been associated with chronic pain[7]. The use of β-blockers also has been associated with less joint pain and a lower use of opioids and other types of analgesia in individuals with symptomatic hip and knee OA[8]. Accordingly, in a previous cross-sectional study on patients with hip and knee OA, the use of β-blockers was associated with lower Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scores and with a lower prevalence of articular pain[8]. However, in a more recent study involving 1,164 patients with knee OA, the use of β-blockers was not associated with a reduction in the intake of opioids[20]. In the present study, we observed that NSAIDs were less commonly used by patients being treated with β-blockers, probably to avoid NSAID-induced high blood pressure in hypertensive patients receiving β-blockers. This could explain why individuals receiving β-blockers were more likely to be treated with opioids as a more secure alternative. In the present study, we also observed that patients in the case group were more likely to use opioids in the 2 years prior to surgery as they would be expected to experience higher degrees of pain.

A recent large retrospective study suggested that the use of selective and nonselective β-blockers could reduce the cumulative risk of OA[7]. These findings are in concordance with those of our study, in which we observed a significantly lower likelihood of TKA in compliant patients and in patients who were treated with β-blockers for ≥5 years, also suggesting a cumulative effect. However, other research has shown no clinically meaningful reduction in knee pain intensity in patients with knee OA who were treated with β-blockers[20].

Previous studies have shown that the downregulation of the β-adrenergic signal could have an analgesic effect in adults with large-joint lower-limb OA[21]. This could be explained by the inhibitory effect that the adrenergic downregulation has on certain enzymes and cytokines associated with degenerative processes in the joints.

MMPs are a group of enzymes that are responsible for the degradation of the extracellular matrix[10]. Some studies have demonstrated higher MMP-2 and MMP-9 levels in patients with OA[10]. Moreover, evidence suggests that the activation of these enzymes may play a role in cartilage destruction[11]. IL-1β and TNF-α inhibit the production of type-II collagen and stimulate the production of IL-6, MMP-1, and MMP-13. In addition, IL-6 also stimulates further production MMP-1 and MMP-13. IL-17 stimulates the production of IL-1β, TNF-α, and IL-6 and inhibits the production of proteoglycans[9,22]. Accordingly, all of these proteins play important roles in the pathogenesis of OA. Therefore, their inhibition could interfere with the degenerative processes that take place in the joints.

On the other hand, recent studies have shown that β-adrenergic activation increases the expression of MMP-2 and MMP-9[12]. Moreover, the use of type-1 β-blockers for the treatment of hypertension has been associated with a significant decrease in MMP-2 levels[13]. An in vitro study demonstrated an inhibition of MMP-9 secretion in human endothelial cells that were exposed to propranolol[12]. The use of β-blockers in patients with cardiomyopathies also has been found to decrease serum levels of TGF-α and to decrease IL-10 levels in patients with heart failure[14]. For all of the above-mentioned reasons, we believe that the role of β-blockers in the management of OA could go beyond an analgesic treatment and that these drugs potentially could interfere with the degenerative processes in the cartilage. In the present study, we also observed that patients who used nonselective β-blockers had the lowest likelihood of TKA.

Strengths and Limitations

To our knowledge, this is the first nested case-control study specifically designed to analyze the relationship between the use of β-blockers and the likelihood of TKA. This study was conducted on a high-quality population-based database that covers a well-defined population. Moreover, we only included patients who had a clear history of new-onset knee pain, and those patients were matched with controls on the basis of calendar time, sex, grade of OA, and age. Our analyses of ORs were adjusted for several confounders that may affect the results.

However, this study is subject to several limitations that are common in non-experimental pharmaco-epidemiological research. The follow-up period was relatively short; therefore, we cannot assess whether these results are sustainable on the long-term. The sample sizes of the study groups were relatively small due to our restrictive inclusion criteria and matching process, which aimed to reduce the risk of any potential selection bias. We were unable to explore residual confounding around the use of β-blockers or the decision for joint replacement, and therefore the true causal link cannot be effectively explored.

Finally, the findings of the present study are only hypothesis-generating and should be confirmed in randomized controlled trials or future prospective observational studies. Nevertheless, our results could open a therapeutic window for patients with OA targeted on the downregulation of the adrenergic autonomic nervous system.

Conclusions

Our results indicate that the use of β-blockers, especially nonselective blockers, was associated with a lower likelihood of TKA. Patients treated for prolonged periods had a lower likelihood of TKA. This study provides insight to a possible relationship between the activity of the autonomic nervous system and the

progression of OA. In addition, it provides a hypothesis for the development of future therapeutic lines targeting the adrenergic system in the treatment of OA. ■

NOTE: The artificial intelligence software Dagitty 3.0, a browser-based environment for creating, editing, and analyzing causal diagrams, was used to determine the best combination of variables for the logistic regression model. Dagitty 3.0 is a validated tool used for minimizing bias in empirical studies[18].

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