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Thiazide diuretics and risk of knee replacement surgery among patients with knee osteoarthritis: a general population-based cohort study

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SUMMARY

Objective: Thiazide diuretic use is associated with higher bone mineral density (BMD) and possibly lower serum magnesium levels than loop diuretic use, and both high BMD and low serum magnesium have been linked to high prevalent knee osteoarthritis. This study aimed to compare the risk of a clinically relevant endpoint, knee replacement (KR) surgery, among initiators of thiazide and loop diuretics.

Design: Among patients aged ≥50 years with a diagnosis of knee osteoarthritis in The Health Improvement Network (THIN) in United Kingdom, we conducted a propensity score-matched cohort study to examine the relation of thiazide diuretic initiation vs loop diuretic initiation to the risk of KR over 5 years.

Results: Among thiazide and loop diuretic initiators (n = 3,488 for each group; mean age: 73 years; female ratio: 59%), 359 (28.6/1,000 person-years) and 283 (24.1/1,000 person-years) KRs occurred during the follow-up period, respectively. The hazard ratio (HR) of KR for thiazide diuretic initiation vs loop diuretic initiation was 1.26 (95% confidence interval [CI]: 1.08–1.47). The adherence-adjusted HR of KR for continuous use of thiazide diuretics was 1.44 (95% CI: 1.21–1.72).

Conclusions: In this population-based cohort of patients with knee osteoarthritis, thiazide diuretic use was associated with a higher risk of KR than loop diuretic use. This association may potentially be due to thiazide diuretics' effect on BMD and serum magnesium.

Introduction

High bone mineral density (BMD) and low serum magnesium levels are both associated with a high prevalence of knee osteoarthritis (OA)[1–3]. High BMD is also associated with an increased risk of incident knee OA but may protect against knee OA progression[4]. Such a paradoxical phenomenon is not fully understood, though selection bias due to conditioning on an intermediate stage of knee OA has been postulated as one potential explanation. Identifying risk factors of knee OA progression would provide insightful

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guidance for secondary prevention of this disabling disease; however, owing to methodological (e.g., confounding by indication and index event bias) and logistic (e.g., repeated assessment of BMD or serum magnesium level) challenges, few, if any, studies have examined the effect of changes in either BMD or serum magnesium on the risk of knee OA progression due to exposure to incident extraneous factors (e.g., medication use) occurring after knee OA diagnosis.

Diuretics are commonly-used medications with an acceptable side–effect profile[4]. There is increasing evidence for a beneficial effect of thiazide diuretic therapy in preserving BMD[5]. In contrast, loop diuretics have been found to decrease BMD[6]. In addition, there is increasing recognition of the potential effect of diuretic use on lowering serum magnesium levels[4,7,8]; the effect appears to be greater for thiazide than loop diuretics[9,10]. Of relevance, the Rotterdam Study recently reported that serum magnesium levels were lower among thiazide users but higher among loop diuretic users than nonusers of either medications[9].

Since diuretics are often used for relatively long periods of time, and thiazide and loop diuretics may have different impact on BMD and serum magnesium levels, initiation of these two medications could serve as a potential indicator for changes in BMD and serum magnesium levels[4,7–9]. Assessment of their relation to the risk of end stage knee OA should shed light on our understanding of the role of both BMD and magnesium in knee OA progression. We conducted a sequential propensity score-matched cohort study to compare the risk of the clinically relevant endpoint of knee replacement (KR) surgery among patients with knee OA who initiated thiazide vs those who initiated loop diuretics.

Methods

Data source

We used The Health Improvement Network (THIN), an electronic medical record database from general practitioners in United Kingdom[10]. THIN contains health information on approximately 17 million patients from 770 general practices in the UK, and previous study has shown that THIN is representative of the UK population in terms of patient demographics and the prevalence of common illnesses[11]. During consultation with patients, health information is recorded by general practitioners using a computerized system. The information includes socio-demographics, anthropometrics, lifestyle factors, details from general practice visits, diagnoses from specialists' referrals as well as hospital admissions, and results of laboratory tests. The Read classification system is used to code specific diagnoses. Prescription medications are coded based on a drug dictionary in BNF code and ATC code formats from the Multilex classification system[12]. Scientific Review Committee for the THIN database and the Institutional Review Board at Xiangya Hospital approved this study, with waiver of informed consent.

Study population

We identified knee OA based on Read codes (i.e., a coded thesaurus of clinical terms) that have been used in the National Health Service in the UK since 1985. Read codes provide a standard vocabulary for clinicians to record findings and procedures of the patients when they receive health and social care. We identified knee OA based on the following Read codes: N053611 (patellofemoral osteoarthritis), N05z611 (knee osteoarthritis not otherwise specified), N05zL00 (osteoarthritis not otherwise specified, of knee), and N05zM00 (osteoarthritis not otherwise specified, of tibio-fibular joint). We included individuals ($\geq$50 years) who had a diagnosis of knee OA by Read codes between January 2000 and December 2016. Patients with OA coded only as general, without specifying the knee, were ineligible for the current analysis. We also excluded subjects who had KR prior to knee OA diagnosis, or who were deemed unlikely to be a candidate for KR (i.e., history of joint infection or comorbidities with poor prognosis [end-stage renal disease on dialysis, severe pulmonary disease requiring supplemental oxygen, or any cancer])[10]. In addition, we introduced a 3-month exposure lag period to exclude subjects with KR within 3 months after entering the study cohort because KRs that occur right after the initiation of diuretic were likely to have been scheduled before initiation of the medication.

Assessment of exposure and active comparator

We identified individuals who initiated thiazide or loop diuretics through the following ATC codes: C03AA01 (Bendroflumethiazide), C03AA04 (Chlorothiazide), C03BA04 (Chlortalidone), C03BA12 (Clorexolone), C03AA03 (Hydrochlorothiazide), C03AA02 (Hydroflumethiazide), C03BA11 (Indapamide), C03BA05 (Mefruside), C03AA08 (Methyclothiazide), C03BA08 (Metolazone), C03AA05 (Polythiazide), and C03BA10 (Xipamide) for thiazide diuretics; C03CA02 (Bumetanide), C03CC01 (Etacrynic), C03CA01 (Furosemide), C03CA03 (Piretanide), and C03CA04 (Torasemide) for loop diuretics, and BNF (thiazide diuretics: 2.2.1; loop diuretics: 2.2.2). The "initiation" of thiazide or loop diuretic was defined as the first prescription of thiazide or loop diuretic after the knee OA diagnosis during the study period in THIN database. Subjects with a history of prescription of thiazide or loop diuretic before entering the study were considered prevalent users and excluded from the study. In addition, subjects were required to be continuously enrolled with the general practice for $\geq$ 1 year in THIN database before the date of first prescription date of either thiazide or loop diuretic (i.e., index date).

Assessment of outcome

The outcome was the first (i.e., incident) primary KR that occurred 3 months after initiation of either thiazide or loop diuretics during the follow-up period. Primary KR included both total and partial KR, identified by Read codes. Previous studies have used this approach to identify KRs in THIN and Clinical Practice Research Datalink (a similar database to THIN)[10,13–15].

Sequential propensity score-matched cohorts

We conducted a sequential propensity score-matched cohort study to compare the risk of KR among thiazide diuretic initiators with that among loop diuretic initiators. Propensity score is the probability of treatment assignment (e.g., thiazide initiation) conditional on observed baseline characteristics. Propensity score matching is used to mitigate the effects of confounding by indication, especially in the presence of a large number of covariates, in epidemiological studies[16]. We divided calendar time into 1-year blocks from 2000 to 2016 (i.e., 17 blocks). Specifically, subjects were allocated into 17 blocks based on their index date, which was based on the date of initiation of either their thiazide or loop diuretic. For example, subjects whose initiation date fell between January 1, 2000 and December 31, 2000 would be allocated into the first (year-2000) time block. Within each time block, we assembled a cohort of thiazide initiators, defined as patients who started thiazide during that time block, and a comparator cohort of matched loop diuretic initiators, who started loop diuretic during the same time block. We conducted propensity score matching within each time block using a greedy matching algorithm[17], i.e., for each thiazide initiator, an initiator of a loop diuretic with the closest

propensity score was selected as a comparator from the same time block. Propensity scores (i.e., predicted probability of thiazide initiation) were estimated using logistic regression separately for each time block. The variables included in the model consisted of sociodemographic factors (age at index date, sex, the Townsend Deprivation Index score[18]), body mass index (BMI), duration of osteoarthritis prior to the index date, lifestyle factors (smoking status, and alcohol use), comorbidities and medication use

Table I
Baseline Characteristics of Propensity Score-matched Knee Osteoarthritis Patients (≥50 years) Initiating Thiazide or Loop Diuretics

Variable list	Thiazide diuretics (n = 3,488)	Loop diuretics (n = 3,488)	Standard difference
Demographics			
Age, mean (SD), y	72.6 (9.0)	72.5 (9.6)	0.010
Socioeconomic deprivation index score*, mean (SD)	2.8 (1.3)	2.8 (1.3)	0.018
Female (%)	59.1	58.4	0.015
OA duration, mean (SD), y	7.4 (6.6)	7.5 (6.7)	0.010
BMI, mean (SD), kg/m^2	29.9 (6.0)	29.8 (6.3)	0.010
Lifestyle factors			
Drinking (%)			0.025
None	24.6	23.9	
Past	3.6	3.2	
Current	71.8	72.8	
Smoking (%)			0.006
None	54.6	54.9	
Past	33.3	33.1	
Current	12.0	12.0	
Comorbidity (%)			
Chronic kidney diseases	8.2	8.3	0.003
Congestive heart failure	2.4	2.7	0.018
Hypertension	59.5	59.8	0.007
Atrial fibrillation	7.9	8.3	0.014
Chronic obstructive pulmonary disease	6.7	7.0	0.011
Myocardial infarction	6.5	6.5	<0.001
Peripheral vascular disease	2.4	2.7	0.015
Angina	14.4	14.5	0.003
Diabetes	19.0	19.3	0.007
Venous thromboembolism	5.1	5.3	0.012
Hyperlipidemia	17.2	17.8	0.016
Ischemic heart disease	20.1	20.2	0.004
Liver disease	2.6	2.8	0.012
Pneumonia or infection	8.5	7.7	0.026
Stroke	5.8	5.3	0.021
Transient ischemic attack	5.9	5.4	0.021
Varicose veins	15.2	15.8	0.017
Depression	14.6	14.2	0.012
Dementia	1.4	1.5	0.002
Fall	17.4	17.9	0.012
Fracture	11.5	11.2	0.010
Peptic ulcer	8.7	9.3	0.021
Osteoporosis	10.0	10.1	0.004
Rheumatic arthritis	2.2	2.2	0.004
Medication (%)			
ACE inhibitors	38.0	38.4	0.007
Beta receptor inhibitors	36.0	36.3	0.006
Calcium channel blockers	39.9	39.6	0.006
Angiotensin receptor blockers	11.4	11.4	<0.001
Statins	42.6	42.8	0.005
Anticoagulants	8.7	9.5	0.031
Antidiabetic medicine	14.6	14.9	0.009
Insulin	3.5	3.6	0.005
Aspirin	44.2	43.2	0.020
Glucocorticoids	25.7	25.0	0.017
Nitrates	17.9	18.4	0.013
NSAIDs	86.0	85.7	0.008
Opioids	45.4	44.5	0.020
Estrogen	11.9	12.7	0.025
Bisphosphonates	8.6	8.4	0.005
PPIs	50.1	49.7	0.007
H2 blockers	27.7	28.2	0.010
Healthcare utilization, mean (SD)			
Hospitalizations†	0.4 (0.9)	0.4 (0.9)	0.010
General practice visits†	7.8 (5.8)	7.9 (6.4)	0.025
Specialist referrals†	0.6 (1.1)	0.6 (1.1)	0.003

BMI, body mass index; n, number; y, years; SD, standard deviation; NSAIDs, non-steroidal anti-inflammatory drugs; ACE, angiotensin converting enzyme; OA, osteoarthritis; PPIs, proton pump inhibitors; H2, histamine-2.

* The Socio-Economic Deprivation Index was measured by the Townsend Deprivation Index, which was grouped into quintiles from 1 (least deprived) to 5 (most deprived).

† Frequency during the past 1 year.

recorded in THIN at any time prior to the index date, and healthcare utilization during the 1 year before the index date (see Table I). Comorbidities and medication use were assessed from the date subjects entered into THIN until their index date.

Statistical analysis

We compared the baseline characteristics of the two cohorts (i.e., thiazide diuretic initiators and loop diuretic initiators). The follow-up time for each subject began from the index date until the date of KR, death, age of 90, date of disenrollment in THIN, or the end of the fifth year of follow-up (because approximately 90% of subjects' diuretics prescriptions were for 5 years or less), whichever occurred first. We calculated the cumulative incidence rate of KR to depict the risk of KR for each cohort accounting for the competing risk of death[19]. The absolute rate difference (RD) in KR was estimated between the thiazide cohort and loop diuretic cohort. Since the two compared cohorts were balanced at baseline, we were able to calculate the crude RD between two groups. The following formula was used for RD (95% confidence interval [CI]) calculation: RD = rate (exposed) - rate (non-exposed); $SE_{RD} = \sqrt{\frac{a}{PT_a^2} + \frac{b}{PT_b^2}}$, where a and b refer to the number of events in each cohort, PT_a and PT_b refer to the total person-time accumulated in each cohort, and 95% CI: RD ± 1.96*SE_{RD}. We fitted cause-specific Cox proportional hazard models to examine the relation of thiazide vs loop diuretic initiation to the hazard of KR while accounting for the competing risk of death[19].

To account for time-varying exposures and confounders, we performed a marginal structural model to estimate the average adherence-adjusted hazard ratio (HR) of KR for continuous use of thiazide vs loop diuretic use[20]. Specifically, time-varying exposures and confounders were updated each year. We fit pooled logistic regression models to obtain their predicted values for each person-year remaining off thiazide diuretic prescription and uncensored. We then used a SAS data step to calculate stabilized inverse-probability weights for each person-year from the predicted values of the previous models. Last, we used generalized estimating equations to fit the final weighted pooled logistic model that estimated the causal parameter and its robust standard error. Variables in the calculation of the propensity score were included in these models.

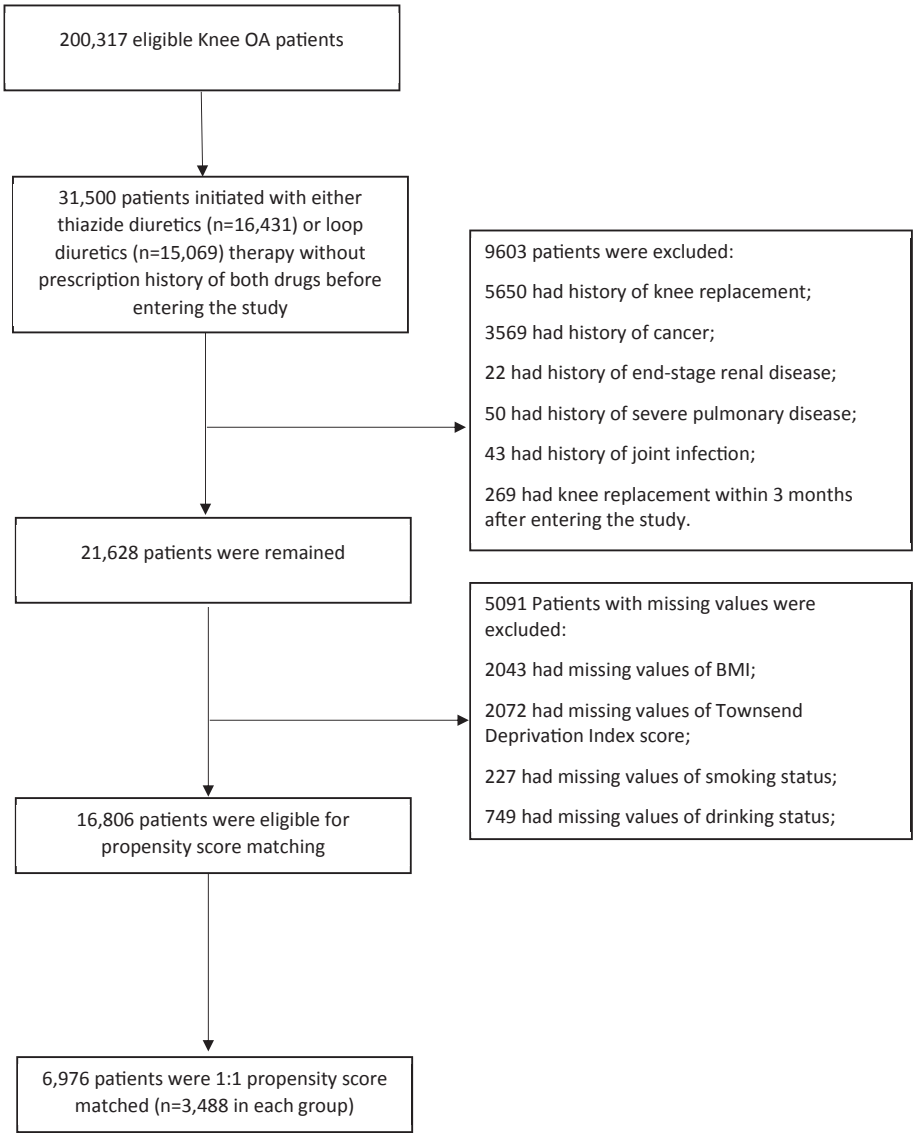

Fig. 1. Selection process of included subjects.

We performed several sensitivity analyses. First, to further minimize potential confounding by indication, we conducted the analyses by excluding patients with chronic kidney disease. Second, we used asymmetric trimming to exclude patients whose propensity score was <2.5th percentile of the propensity score of the exposure (thiazide) cohort and >97.5th percentile of the propensity score of the comparison cohort (loop diuretics); thus, patients who were treated with the agent most contrary to prediction were excluded from the analyses to minimize potential unmeasured confounders. Third, we performed an analysis among subjects who were enrolled in THIN for at least 1 year without a diagnosis of OA prior to inclusion in the study sample (i.e., incident OA[10]) to minimize potential misclassification of the duration of OA. Fourth, since the analyses may not fully adjust for potential confounders we performed quantitative sensitivity analyses to assess the minimum unmeasured confounding effect that would need to explain away an association observed in the main analyses conditional on the included covariates[21].

In addition, we conducted a nested case–control study to assess the dose–response relationship between number of prescriptions of thiazides and risk of KR using risk set sampling[22]. Specifically, for each case of KR, we created a risk set that included up to 10 controls who were alive and free of KR when a KR case occurred and matched by sex, year of entry into study, age of entry into study (within ±1 year), and propensity-score (within a caliper of ±0.1). The number of prescriptions of thiazides was calculated from the date of thiazide initiation to the date the case (i.e., KR) and matched controls (assigned the same date as their matched case) were identified. We divided number of prescriptions of thiazides into three categories: non-use of thiazides, 1–5, and ≥six prescriptions of thiazides. We estimated the relation of each thiazide prescription category to the risk of KR using conditional logistic regression and tested a dose–response relationship by number of thiazide prescriptions.

All *P*-values were two-sided. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

In total,200,317 subjects with knee OA met our inclusion criteria. Of them 16,431 initiated a thiazide diuretic and 15,069 initiated a loop diuretic. We excluded 9,334 subjects who were deemed unlikely to be a candidate for KR, 269 subjects who had KR within 3 months after initiation of the diuretic because KRs that occur during this period were likely to have been scheduled before initiation of the medication, and 5,091 subjects who had missing information on BMI, Townsend Deprivation Index Score, smoking status and alcohol drinking. Of the remaining (n = 16,806) 3,488 initiators of thiazide were successfully propensity score-matched to the same number of initiators of loop diuretic (Fig. 1). The baseline characteristics of the two propensity score-matched cohorts are shown in Table I. The mean age was 73 years, and slightly more than 40% were men. The characteristics of the thiazide cohort and its matched comparison loop diuretic cohort were well-balanced, with all standardized differences being < 0.1[23].

The cumulative incidence of KR was higher in the thiazide cohort than in the loop diuretic cohort (Fig. 2). As shown in Table II, 359 kRs (28.6/1,000 person-years) occurred in the thiazide cohort and 283 (24.1/1,000 person-years) occurred in the loop diuretic cohort over 5 years of follow-up. The RD of incident KR in the thiazide cohort vs that in the loop diuretic cohort was 4.5 (95% CI: 1.08 to 1.47) per 1,000 person-years and the corresponding HR was 1.26 (95% CI: 1.08 to 1.47). The adherence-adjusted HR of KR for continuous use of thiazide was 1.44 (95% CI: 1.21 to 1.72).

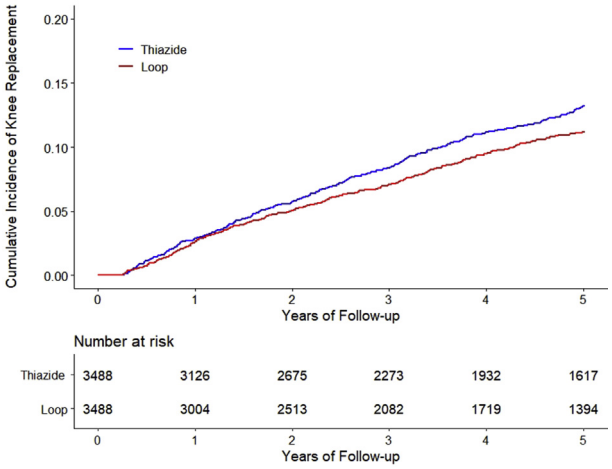

Fig. 2. Time to Knee Replacement over Five Years for the Propensity Score-Matched Cohorts of Knee Osteoarthritis Patients with Thiazide Diuretic Initiation compared with Initiation of Loop Diuretic, adjusting for Competing Risk of Death.

The results from various sensitivity analyses are presented in Table II. Exclusion of subjects with chronic kidney disease (HR = 1.27, 95% CI: 1.08 to 1.49), extreme propensity scores (HR = 1.30, 95% CI: 1.11 to 1.52), or restricting to subjects with incident knee OA (HR = 1.23, 95% CI: 1.02 to 1.48) did not change the association materially. Furthermore, to completely nullify the observed associations (e.g., HR = 1.23 for the smallest effect estimate), the association of residual confounder(s) with either thiazide or with KR should be ≥ an odds ratio of 1.76. Such a strong residual confounder(s) seems unlikely given that many known confounders have been accounted for in the propensity score-matched design.

The odds of KR increased with longer duration of thiazide use (Table III). Compared with non-use of thiazide, multivariable-adjusted odds ratios (ORs) of KR were 1.16 (95% CI: 0.90 to 1.48) and 1.28 (95% CI: 1.03 to 1.58) for 1–5 and ≥six prescriptions of thiazide, respectively (P for trend = 0.04).

Discussion

We found that the risk of KR was higher among thiazide initiators than those of loop diuretic initiators, and long-term use of

Table II
Association between thiazide diuretic initiation and incidence of knee replacement surgery comparing with loop diuretic initiation

	Thiazide diuretics	Loop diuretics
Total population*		
Subject (n)	3,488	3,488
Incident knee replacement (n)	359	283
Mean follow-up (year)	3.6	3.4
Rate (1,000 person-years)	28.6	24.1
RD (1,000 person-years, 95% CI)	4.5 (0.4, 8.5)	0.00 (reference)
HR (95% CI)†	1.26 (1.08, 1.47)	1.00 (reference)
Adherence-adjusted, HR (95% CI)†	1.44 (1.21, 1.72)	1.00 (reference)
Excluding CKD, HR (95% CI)†	1.27 (1.08, 1.49)	1.00 (reference)
PS trimming, HR (95% CI)†	1.30 (1.11, 1.52)	1.00 (reference)
Incident OA, HR (95% CI)†	1.23 (1.02, 1.48)	1.00 (reference)

HR, hazard ratio; n, number; RD, rate difference; PS, propensity score; 95% CI, 95% confidence interval; CKD, chronic kidney disease.

* Thiazide initiation also showed a higher risk of knee replacement compared with initiation of loop diuretics (hazard ratio = 1.26, 95% confidence interval: 1.10 to 1.44) without restricting to 5-year follow-up.

† Hazard ratios were adjusted for competing event (death).

Table III
Dose–response association between thiazide diuretic initiation and incidence of knee replacement surgery

	Cases*	Controls	Odds Ratio (95% CI)
Total number	599	2,446	–
Non-use of thiazide (n)	227	1,039	1.00 (reference)
1-5 prescriptions of thiazide (n)	140	560	1.16 (0.90, 1.48)
6 or more prescriptions of thiazide (n)	232	847	1.28 (1.03, 1.58)

95% CI, 95% confidence interval; n, number.
* Incident knee replacement.

thiazide was associated with even higher risk of KR than loop diuretics. Our findings were independent of the major confounders and remained stable in various sensitivity analyses, suggesting that the observed associations were robust.

Possible explanations

While the biological mechanisms linking thiazide use to the risk of KR are not fully understood, differential impacts of thiazide vs loop diuretics on changes in both BMD and serum magnesium levels may partly explain these findings. First, randomized controlled trial (RCT) demonstrated that thiazide preserved BMD[5], loop diuretics decreased BMD[6]. Many studies have shown that high BMD is associated with prevalent and incident knee OA; however, its association with knee OA progression remains controversial. One explanation for such paradoxical phenomena is related to the fact that BMD is a chronic risk factor. Observational studies of the association of BMD with the risk of knee OA progression among subjects with mild-to-moderate knee OA are in effect adjusting for an intermediate stage of disease (i.e., mild-to-moderate knee OA). Such studies are affected by collider bias (index event bias) and are susceptible to potential selection bias.

Second, previous studies have shown that chronic use of either thiazide or loop diuretics increases magnesium excretion; however, the degree of magnesium depletion from thiazide use appears to be greater than loop diuretic use[4,7–9]. Recently, the Rotterdam Study reported that thiazide use was associated with lower whereas loop diuretic use with higher serum magnesium levels than nonuse, respectively[7]. An animal study demonstrated that intra-articular magnesium sulfate attenuated the development of OA[24], and several cross-sectional clinical studies have found that low levels of serum magnesium were associated with high prevalence of knee OA[2,3]. In addition, magnesium is an antagonist of N-methyl-D-aspartate receptors, which plays an important role in nociceptive transmission, modulation and sensitization of pain[25]. Indeed, results from a meta-analysis demonstrated that systemic administration of magnesium was effective in minimizing postoperative pain[26]. Thus, thiazide diuretics could increase the risk of KR by decreasing serum magnesium levels.

Strengths and limitations

Several characteristics of our study are worth noting. First, BMD or serum magnesium are both chronic factors; thus, they likely occur prior to the occurrence of knee OA. Observational studies of the effects of a prevalent exposure on disease progression are susceptible to potential selection bias. To mitigate this kind of bias, we examined initiation of diuretics after knee OA diagnosis, whereby both BMD and serum magnesium levels may be altered by these medications after knee OA diagnosis. Second, in contrast to observational studies that compared users of anti-osteoporotic drugs or magnesium-supplement with non-users, we assembled two comparative cohorts who initiated different types of diuretics to minimize confounding by indication.

Third, we postulated that an increased risk of KR among thiazide users may be through its impact on BMD and/or serum magnesium; however, we can't verify these mechanisms owing to lack of BMD or serum magnesium data in THIN. Fourth, although previous studies have used Read codes to define symptomatic knee OA in THIN[27,28] and KR has been generally accepted as a "hard" outcome in cohort studies of knee OA[10,14,29,30], we were unable to confirm a diagnosis of radiographic knee OA and to assess the radiographic progression of knee OA since knee image data were not available in THIN. Nonetheless, 96% of primary KRs are performed for knee OA[31], though we acknowledge that there is potential for individuals qualifying for KR but not undergoing the procedure due to other factors such as personal preference. In addition, we excluded patients with rheumatoid arthritis (2.2% in thiazide diuretics group and 2.2% in loop diuretics group according to Table I), the result did not change materially (HR = 1.25, 95% CI: 1.07 to 1.47). Fifth, though we took the propensity score-matching method including many comorbidities as covariates to control for potential confounding bias, as in any observational study we cannot rule out residual confounding. Finally, the current study was conducted using UK data. The differences in health care systems between UK and other countries may limit the generalizability of our study findings. Thus, future studies conducted outside UK are warranted to verify the findings.

Clinical and research implications

The present findings may have clinical implications. If replicated and determined to be causal, these findings suggest that thiazide diuretics use may have an unfavorable effect on knee OA progression. In addition, this study may shed light on our understanding of the biological mechanisms linking thiazide use to the risk of knee OA progression. If future studies could collect data on thiazide use, BMD, serum levels of magnesium, as well as changes in knee structures and symptoms, we could assess to what extend the effect of thiazide use on the risk of knee OA progression is mediated via effects on BMD or magnesium levels; such insight could help guide the development of targeted treatment strategies for knee OA prevention and progression.

Conclusions

In this population-based cohort of patients with knee OA, thiazide diuretic use was associated with a higher risk of KR than loop diuretic use. Such an association may potentially be due to thiazide diuretics' effect on BMD and serum magnesium.

Contributions

JW, TN, RT, AZF, CZ, DM, HKC, GL and YZ made substantial contributions to the conception and design of the study. JW conducted the data cleaning, and data analysis. All authors contributed to the interpretation of results. JW and CZ wrote the first draft. All authors contributed to the revision of the manuscript. YZ and GL has full access to the data and takes responsibility for the content and guarantees the integrity and accuracy of the work undertaken. All authors have read, provided critical feedback on intellectual content and approved the final manuscript.

Conflict of interest

None.

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Ethical approval

The Institutional Review Board approved this study, with waiver of informed consent.

Scientific approval

This study was approved by the THIN Scientific Review Committee (18THIN073).

Transparency

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Supplementary data

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