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Effects of medications on incidence and risk of knee and hip joint replacement in patients with osteoarthritis: a systematic review and meta-analysis

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Abstract

Background: This systematic review and meta-analysis aimed to investigate the incidence and risk of knee and hip replacement in patients with osteoarthritis (OA) treated with different medications.

Methods: OVID MEDLINE, OVID EMBASE, Cochrane and Web of Science electronic databases were searched from inception to May 4th, 2022. Clinical trials, including randomized controlled trials, cohort studies and case–control studies, were selected. The meta-analysis effect size was estimated using either incidence with 95% confidence intervals (CIs) or odds ratio (OR)/relative risk (RR) with 95% CIs. The risk of bias and heterogeneity among studies were assessed and analyzed.

Results: Forty studies were included, involving 6,041,254 participants. The incidence of joint replacement in patients with OA varied according to the study design and treatments. The incidence of knee arthroplasty varied from 0 to 70.88%, while the incidence of hip arthroplasty varied from 11.71 to 96.43%. Compared to non-users, bisphosphonate users had a reduced risk of knee replacement (RR = 0.71, 95% CI: 0.66–0.77; adjusted hazard ratio [aHR] = 0.76, 95% CI: 0.70–0.83). Compared to intra-articular corticosteroid users, hyaluronic acid (HA) users had a higher risk of knee arthroplasty (RR = 1.76, 95% CI: 1.38–2.25). No publication bias was observed.

Conclusions: Bisphosphonate treatment is associated with a reduced risk of knee replacement. More studies are needed to validate our results due to the limited number of eligible studies and high heterogeneity among studies.

Keywords: Arthroplasty, Incidence, Osteoarthritis, Meta-analysis, Systematic review

Background

Osteoarthritis (OA) is a degenerative disease involving the cartilage and surrounding tissues, usually manifesting common clinical signs such as pain, stiffness, and swelling, which may lead to functional disability. The most commonly involved joints are those of the knee, hip, hand, facet, and foot. The age-standardized global prevalence of knee OA is 3.8%, while that of hip OA is 0.85% [1]. Approximately 10% of men and 13% of women aged over 60 years are diagnosed with symptomatic knee OA [2]. OA occurs more commonly in women than in men, with a female-to-male ratio ranging from 1.5 to 4. Since its prevalence increases with age, it is highly prevalent in the population aged over 50 years [3]. Obesity, age, female sex, and genotype are risk factors for the development of hip and knee OA [2, 4, 5].

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Knee and hip OA are ranked as the top 11th contributor to global disability and the top 38th contributor to disability-adjusted life years (DALYs), which significantly affects patients' psychological state [3] and places a substantial economic burden on the family and society [1]. Pharmacological treatment for OA includes acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, intra-articular steroid injections, viscosupplementation, chondroitin, glucosamine, and bisphosphonates [5–7]. Acetaminophen and NSAIDs are major choices for OA to relieve pain, while COX-2 inhibitors are used if NSAIDs are contraindicated. Intra-articular steroid injections are effective in reducing pain and improving function through anti-inflammatory and antinociceptive actions. Intra-articular injection of hyaluronic acid (HA) or its derivatives, is a form of viscosupplementation that is used to alleviate symptoms and improve function. Chondroitin and glucosamine are disease-modifying agents in OA [8, 9]. Bisphosphonates effectively reduce pain and slow structural progression in patients with OA [10, 11].

Globally, symptomatic OA most commonly develops in large weight-bearing joints such as the knee and hip. Arthroplasty is an effective way to improve pain, disability, physical activity, and quality of life when conservative measures fail to control pain and improve joint function [6, 12, 13]. Patients with OA has a higher risk for arthroplasty. Among females patients, the incidence of hip replacement is 52.7%, while the incidence of knee replacement is 17.9%. Among male patients, the incidence of hip replacement is 37.7%, while the incidence of knee replacement is 11.8%. In general population, the incidence of hip replacement and knee replacement is 2.34% and 4.55%, respectively [14, 15]. However, it is unclear whether the increased arthroplasty rate in patients with OA is related to drug treatment. Accumulating evidence is available on the incidence and risk of arthroplasty in patients with OA who are on different pharmacological treatments. Hence, this systematic review and meta-analysis was performed to evaluate the incidence and risk of knee or hip joint replacement in patients with OA treated with NSAIDs, HA, glucosamine, chondroitin, bisphosphonate, or corticosteroids.

Materials and methods

We conducted a systematic review and meta-analysis to investigate the incidence and risk of knee or hip joint replacement in patients with OA treated pharmacologically, while adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [16]. The predefined study protocol can be solicited from the supplementary attach (Additional file 2).

Eligibility criteria

We included studies that met the following criteria: (1) the study population included patients with OA of the knee or hip; (2) treatment intervention including HA, NSAIDs, glucosamine, chondroitin, bisphosphonates, and corticosteroids; (3) comparator treatment including placebo, no comparator treatment, or any treatment; (4) outcomes including arthroplasty of the knee or hip, such as total knee arthroplasty, total hip arthroplasty, unicompartmental knee arthroplasty, and patellofemoral joint arthroplasty; (5) study design including a randomized controlled trial (RCT), cohort study, or case–control study.

Duplicate studies, letters, correspondences, and study protocols were excluded. Studies that were not reported in English or Chinese were excluded during selection.

Search strategy

To perform systematic retrieval, the electronic databases OVID MEDLINE, OVID EMBASE, Cochrane and Web of Science were searched from inception to May 4th, 2022 by using a Medical Subject Headings term and a keyword. The search terms were "osteoarthritis," "hyaluronic acid," "NSAIDs," "glucosamine," "chondroitin," "bisphosphonate," "corticosteroid," "arthroplasty," "RCT," "cohort study," and "case–control study." The detailed search strategy is provided in the Additional file 1. The reference lists of the included studies were manually checked to identify potentially eligible studies.

Study selection

Studies were selected using a two-step screening process. First, the studies were screened using titles and abstracts, following which they were screened by full-text review. The references retrieved from the electronic databases were introduced to Endnote (USA). After removing duplicates, the studies were exported to Microsoft Office Access 2013 (USA) for preliminary screening by titles and abstracts based on our study selection criteria. The full texts of the remaining studies from the first screening were downloaded for further screening based on the study eligibility criteria. Reference lists of the included studies were manually checked. Two authors independently screened the studies, and any disagreement was resolved via discussion or adjudication by a third reviewer, if necessary.

Data extraction

Two authors independently collected data on the first author's family name, country, study design, OA site, follow-up time, number of arthroplasty cases, number of participants, and treatments. If a study reported results at different time points, data from the longest follow-up period were used. Any disagreement on data extraction was resolved via discussion or adjudication by a third reviewer, if necessary.

Methodological quality assessment

The risk of bias of RCTs was assessed using the Jadad scale, which focuses on randomization, double blinding, drop out, and loss of follow-up [17]. For randomization and double blinding, reporting with an appropriate method scored as 2, reporting without an appropriate method scored as 1, and no reporting was scored as 0. For drop-out and loss of follow-up, detailed reporting was scored as 1, while no reporting was scored as 0. Therefore, the highest score was 5, and a score of ≥ 3 was considered as being at a low risk of bias.

The methodological quality assessment of cohort studies and case–control studies was conducted using the Newcastle–Ottawa quality assessment scale (NOS) [18]. A total of three domains—selection, comparability, and exposure—with eight numbered items yielded the highest total score of 9. For selection and exposure, each of seven numbered items was scored as 1 if the answer was yes, while for comparability, a maximum score of 2 was given for a numbered item. Studies with a score ≥ 6 were considered high-quality studies.

Two authors performed the methodological quality assessment, and any disagreement was resolved via discussion or adjudication by a third reviewer, if necessary.

Data analysis

We performed data analyses using RevMan software (version 5.1.3, the Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen), and a random effect model was applied regardless of heterogeneity. The incidence of athroplasty in each study was listed. We used the random effect inverse variance model to pool the risks of arthroplasty in different treatments. Adjusted estimates namely adjusted hazard ratio (aHR) and adjusted OR (aOR), and their 95% CIs reported from cohort and case–control studies were pooled using the random effect inverse variance model. We first log-transformed the point estimate and 95% CIs and pooled the log-estimate and its associated standard error in such analyses. Data from more than 2 studies were summarized.

According to the Cochrane Handbook recommendations, we assessed clinical diversity across studies through statistical heterogeneity using I^2 and p values. I^2 values of 25%, 50%, and 75% represented low, moderate, and high heterogeneity, respectively [19]. For each of the above analyses, we conducted stratified subgroup analyses according to the arthroplasty site and treatment. Sensitivity analysis was performed by excluding studies one by one to identify the potential source of heterogeneity. We assessed the risk of publication bias using funnel plots and used Egger's test to quantify the p value when the funnel plot was visually asymmetrical by Stata (version 16.0, USA).

Results

Study selection

A total of 4642 studies were retrieved from the electronic databases of OVID MEDLINE (n = 598), OVID EMBASE (n = 2141), Cochrane (n = 1528) and Web of Science (n = 375). After excluding 1797 duplicates, 2845 studies underwent the first screening by titles and abstracts. After excluding 2,703 irrelevant studies, 142 reviews underwent full-text review. Finally, 40 studies were included [20–59]. (Fig. 1).

Characteristics of the included studies

Of the 40 eligible studies, eight were RCTs [33, 40, 42, 46, 50, 57–59] comprising 231 arthroplasty cases and 4790 participants; 27 were cohort studies [20–28, 31,

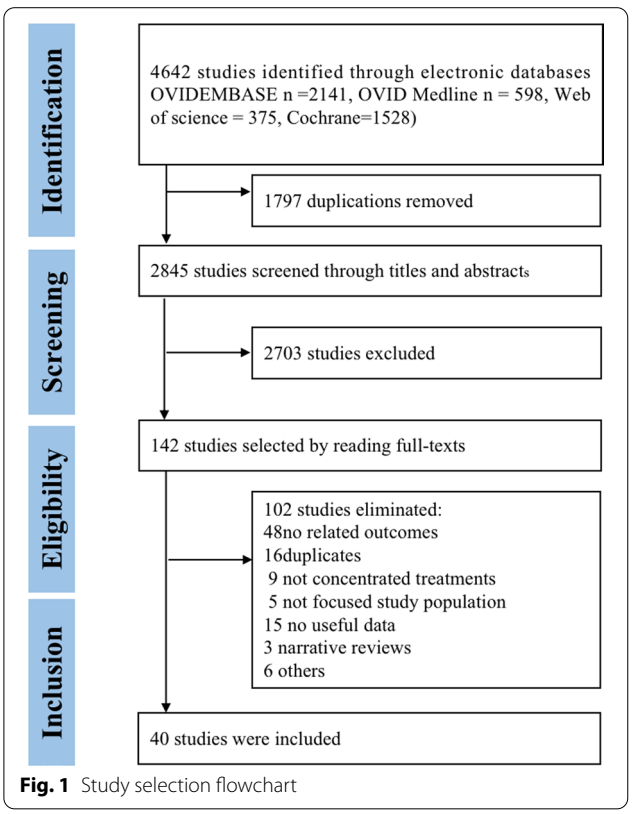

Fig. 1 Study selection flowchart

32, 34–39, 43, 44, 48, 49, 52–56] including over 597,451 arthroplasty cases and over 5,959,704 participants; and 5 were case–control studies [29, 41, 45, 47, 51] including 27,045 arthroplasty cases and 76,760 participants. Fourteen studies were from the USA, five were from Canada, four were from France, and four were from the Netherlands. The remaining studies were reported from other countries, such as Finland, Belgium, China, Italy, Japan, Norway, Romania, Thailand, and the UK. While 22 studies reported on knee OA, 11 studies reported on hip OA, and 7 studies reported on knee and hip OA. The follow-up time ranged from 0.3 years in an RCT to 9 years in a cohort study. The number of arthroplasty cases varied from 0 in an RCT to 6706 in a cohort study. The number of participants ranged from 12 in an RCT to 123,791 in a cohort study (Additional file 1: Tables S1–S3).

Methodological quality

Four RCTs had a Jadad score of ≥ 3, indicating a low risk of bias, while the remaining 4 RCTs had a Jadad score of < 3, showing a high risk of bias. Of the 27 cohort studies, 25 studies had a NOS score of ≥ 6, indicating high study quality, while 2 studies were rated as being of low quality (NOS score < 6). All five case–control studies were considered high-quality studies (Additional file 1: Tables S1–S3).

Demographic data

Among the 40 included studies, only 5 studies were conducted in Asian. In Asian patients with knee/hip osteoarthritis, the incidence of knee arthroplasty varied from 0 to 22.3%. Only one RCT demonstrated the incidence of hip arthroplasty, which was 23.33%. Among European knee/hip osteoarthritis population, the incidence of knee arthroplasty varied from 0 to 70.88%, while the incidence of hip arthroplasty varied from 4.61 to 96.43%. In most studies, female patients were dominant, with the proportion of female patients ranging from 49.1 to 91.9%.

Incidence of arthroplasty

Since the heterogeneity of the meta-analysis of the incidence of arthroplasty was high and could not be reduced by subgroup analysis, we enumerated the incidence rate reported in each study rather than combine them.

Intra-articular corticosteroids

Five studies, including 5 cohort studies and 1 case–control studies, were involved to present the incidence of knee/hip arthroplasty in patients with intra-articular corticosteroids treatment. Since the subjects of Villoutreix's study were patients with rapidly destructive hip osteoarthritis, the incidence of hip athroplasty was 96.43% [54]. In other studies, the incidence of knee athroplasty varied from 6.9 to 37.1%, while the incidence of hip athroplasty was from 43.96 to 72.22%. (shown in Table 1 and Additional file 1: Table S1).

Hyaluronic acid

The incidence of knee/hip arthroplasty in patients with intra-articular hyalurionic acid treatment was demonstrated in 15 studies (14 cohort studies and 1 RCT). The incidence of knee athroplasty varied from 4.96 to 39.21%, while the incidence of hip athroplasty was from 18.18 to 49.17%. In Gaston's cohort study, the invention treatment was synthetic hyaluronic acid (Suplasyn™) [53]. Sodium Hyaluronate was used in Turajane's and Migliore's studies, but the molecular weight of sodium hyaluronate was different (500–730 kDa in Turajane's study and 1500–2000 kDa in Migliore's study) [43, 48]. In three cohort studies, Hylan G-F 20 was used [22, 37, 44]. (Shown in Table 1 and Additional file 1: Table S1).

Bisphosphonates

The incidence of knee/hip arthroplasty in patients with bisphosphonates treatment was demonstrated in 4 studies (2 cohort studies and 2 RCT). The incidence of knee athroplasty varied from 3.66 to 15.00%, while the incidence of hip athroplasty was 23.33%. In Turajane's and Nishii's RCT study, patients in intervention group was treated with Alendronate combined with calcium [33, 42]. In Fu's study, Alendronate, Ibandronate and Zoledronate users were enrolled [35]. The types of bisphosphonates were not mentioned in Neogi study [27]. (Shown in Table 1 and Additional file 1: Table S1).

Symptomatic slow acting drugs for osteoarthritis (SYSADOA)

The incidence of knee/hip arthroplasty in patients with SYSADOA treatment was demonstrated in 4 studies (1 cohort study, 1 case–control study and 2 RCTs). The incidence of knee athroplasty varied from 0 to 31.10%. Only one study demonstrated the incidence of hip arthroplasty, which was 11.71%. Among the 4 studies, patients in Bruyere's and Rozendaal's studies were treated glucosamine sulfate (1500 mg daily), while chondroitin sulphate (Condrosan, 800 mg/day) was used in Wildi's study [46, 50, 52]. In Dorais' study, patients were treated glucosamine or chondroitin sulfate [29]. (Shown in Table 1 and Additional file 1: Table S1).

NSAIDs

The incidence of knee/hip arthroplasty in patients with NSAIDs treatment was demonstrated in 12 studies (3 cohort studies, 5 case–control studies and 4 RCTs).

Table 1 Incidence of arthroplasty in OA patients with medications

Study	Study design	Follow-up (month)	Sites of OA	NO. of arthroplasty (n)	Incidence (%)
Intra-articular corticosteroids					
Ward 2021 [20]	Cohort study	67	Knee	139,529/387,702	35.99
Zeng 2019 [23]	Cohort study	48	Knee	33/148	22.30
Delbarre 2017 [36]	Cohort study	44	Knee	366/5306	6.90
Walter 2019 [24]	Cohort study	NA	Hip	49/113	43.36
Villoutreix 2006 [54]	Cohort study	≥6	Hip	27/28	96.43
Pope 2008 [51]	Case–control study	24	Hip	26/36	72.22
Pope 2008 [51]	Case–control study	24	Knee	46/124	37.10
Hyaluronic acid					
Ward 2021 [20]	Cohort study	67	Knee	73,436/187,268	39.21
Concoff 2021 [21]	Cohort study	24	Knee	52,212/181,631	28.75
Ong 2019 [22]	Cohort study	24	Knee	8315/56,093	14.82
Dasa2018 [30]	Cohort study	36	Knee	44/887	4.96
Bowman 2018 [31]	Cohort study	27	Knee	20/102	19.61
Annaniemi 2018 [32]	Cohort study	17	Knee	31/86	36.05
Delbarre 2016 [39]	Cohort study	42	Knee	1296/9476	13.68
Turajane 2009 [48]	Cohort study	54	Knee	52/183	28.42
Migliore 2012 [44]	Cohort study	48	Hip	32/176	18.18
van den Bekerom 2008 [49]	Cohort study	36	Hip	59/120	49.17
Gaston 2007 [53]	Cohort study	6	Hip	4/15	26.67
Turajane 2017 [48]	RCT	12	Knee	3/20	15.00
Ong 2019b [22]	Cohort study	24	Knee	8315/56,093	14.82
Boutefnouchet 2017 [37]	Cohort study	60	Knee	26/82	31.70
Migliore 2012 [43]	Cohort study	60	Hip	84/224	37.50
Bisphosphonates					
Neogi 2018 [27]	Cohort study	3	Knee	138/2006	6.88
Fu 2017 [35]	Cohort study	14	Knee	595/16,276	3.66
Turajane 2017 [33]	RCT	12	Knee	3/20	15.00
Nishii 2013 [42]	RCT	24	Hip	7/30	23.33
SYSADOA					
Bruyere 2008 [52]	Cohort study	62	Knee	9/144	6.25
Dorais 2018 [29]	Case–control study	52	Knee	88/283	31.10
Wildi 2011 [46]	RCT	6	Knee	0/35	0.00
Rozendaal 2008 [50]	RCT	24	Hip	13/111	11.71
NSAIDs					
Hafezi-Nejad 2016 [38]	Cohort study	96	Knee	29/173	16.76
Reijman 2005 [55]	Cohort study	79	Knee	13/874	1.49
Reijman 2005 [55]	Cohort study	79	Hip	116/2514	4.61
Gossec 2005 [56]	Cohort study	24	Hip	139/331	41.99
Dorais 2018 [29]	Case–control study	52	Knee	101/276	36.59
Klop 2012 [45]	Case–control study	91	Knee	706/996	70.88
Raynauld 2011 [47]	Case–control study	56	Knee	18/123	14.63
Arends 2017 [41]	Case–control study	≤6	Knee/hip	105/266	39.47
Klop 2012 [45]	Case–control study	91	Hip	1099/1586	69.29
Pope 2008 [51]	Case–control study	24	Knee/hip	366/542	67.53
Balanescu 2012 [59]	RCT	8	Knee/hip	1/152	0.66
Schnitzer 2015 [40]	RCT	16	Knee/hip	25/539	4.64
Ekman 2014 [58]	RCT	6	Knee/hip	1/211	0.47
ALHO 1988 [57]	RCT	3–6	Hip	38/252	15.08

Table 1 (continued)

RCT randomized controlled trial, *NO.* number, *CI* confidence interval, *NSAIDs* nonsteroidal anti-inflammatory drugs, *NA* not available, *SYSADOA* symptomatic slow acting drugs for osteoarthritis

The incidence of knee athroplasty varied from 1.49 to 70.88%. The incidence of hip athroplasty varied from 4.61 to 69.29%. The incidence of hip/knee athroplasty varied from 0.47 to 67.53%. Coxibs were the intervention drug in one study, and the incidence of knee athroplasty in this study was 10.94% [45]. Licofelone was the intervention drug in another study, and the incidence of knee and hip athroplasty in this study was 70.88% and 69.29% respectively [47]. Naproxen was the intervention drug in 3 studies [47, 57, 58]. The types of NSAIDs were not available in other 7 studies. (Shown in Table 1 and Additional file 1: Table S1).

Risk of arthroplasty

Evidence from RCTs

Compared to tanezumab, NSAIDs (OR = 1.21, 95% CI: 0.74–1.97, $I^2 = 0$), or naproxen (OR = 2.00, 95% CI: 0.21–19.3, $I^2 = 0$, 1/417 vs. 1/834, n = 2) did not increase the overall risk of arthroplasty, regardless of OA site. The number of arthroplasties and the total number of participants were 26 and 956, respectively, in the NSAID group and 44 and 1,917, respectively, in the tanezumab group. Compared to the placebo, NSAIDs (OR = 1.07, 95% CI: 0.29–3.96, $I^2 = 41$, 83/1495 vs. 47/1500, n = 3) and naproxen (OR = 0.35, 95% CI: 0.05–2.30, $I^2 = 0$, 1/417 vs. 4/417, n = 2) did not elevate the risk of knee or hip arthroplasty in patients with OA (Table 2, Additional file 1: Fig. S5, Additional file 1: Fig. S7).

Evidence from cohort studies

Compared to non-users, bisphosphonate users had a 29% decreased risk of knee arthroplasty (RR = 0.71, 95% CI: 0.66–0.77, $I^2 = 0$, 733/18,282 vs. 6876/125,797, n = 2). Compared to non-users, HA was not associated with the risk of arthroplasty (RR = 2.27, 95% CI: 0.86–5.94, n = 5). Compared to intra-articular corticosteroid users, hyaluronic acid (HA) users had a higher risk of knee arthroplasty (RR = 1.76, 95% CI: 1.38–2.25). Nevertheless, glucocorticoid users did not have a decreased risk of arthroplasty (RR = 1.96, 95% CI: 0.57–6.75, n = 2) compared to non-users. (Table 2, Figs. 2, 3, 4, 5).

Evidence from case–control studies

With respect to knee/hip OA, compared to non-users, NSAID users did not evaluate the risk of arthroplasty (OR = 1.68, 95% CI: 0.69–4.08, $I^2 = 97$, n = 4). (Table 2,

Table 2 Pooled data of arthroplasty risk in OA patients

Comparison	Site	NO. of study	Treatment group	Comparator group	Heterogeneity		Random, OR/RR [95% CI]
			NO. of arthroplasty (n)	NO. of arthroplasty (n)	I^2 (%)	P	
RCT							
NSAIDs versus tanezumab	Knee/hip	3	26/956	44/1917	0	0.58	1.21 [0.74, 1.97]
Naproxen versus tanezumab	Knee/hip	2	1/417	1/834	0	0.34	2.00 [0.21, 19.3]
NSAIDs versus placebo	Knee/hip	3	83/1495	47/1500	41	0.19	1.07 [0.29, 3.96]
Naproxen versus placebo	Knee/hip	2	1/417	4/417	0	0.65	0.35 [0.05, 2.30]
Cohort study							
CS (yes vs. no)	Knee	2	NA	NA	79	0.03	1.96 [0.57, 6.75]
HA (yes vs. no)	Knee	5	NA	NA	100	< 0.00001	2.27 [0.86, 5.94]
HA versus CS	Knee	2	NA	NA	83	0.02	1.76 [1.38, 2.25]
Bis (yes vs. no)	Knee	2	733/18282	6876/125797	0	0.74	0.71 [0.66, 0.77]
Case–control study							
NSAIDs (yes vs. no)	Knee/hip	4	2377/3666	24,593/72734	97	< 0.00001	1.68 [0.69, 4.08]
Naproxen (yes vs. no)	Knee/hip	2	69/172	382/579	87	0.006	0.80 [0.17, 3.65]
NSAIDs (yes vs. no)	Knee	2	807/1272	9155/27170	96	< 0.00001	2.96 [1.13, 7.79]

RCT randomized controlled trial, *NO.* number, *CI* confidence interval, *NSAIDs* nonsteroidal anti-inflammatory drugs, *NA* not available, *CS* corticosteroids, *HA* hyaluronic acid, *Bis* bisphosphonates, *SYSADOA* symptomatic slow acting drugs for osteoarthritis

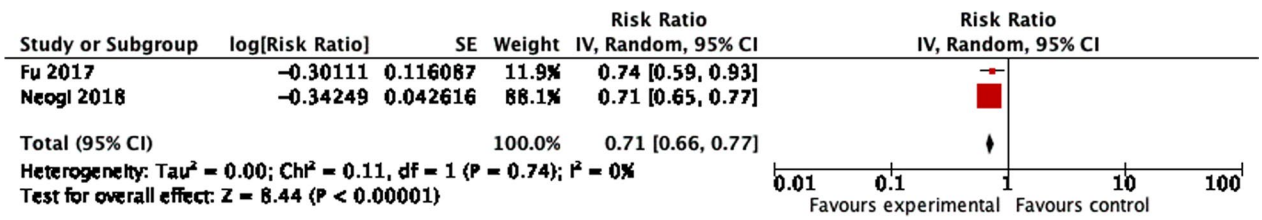

Fig. 2 Forest plot of the association between the risk of knee arthroplasty and bisphosphonate treatment in cohort studies

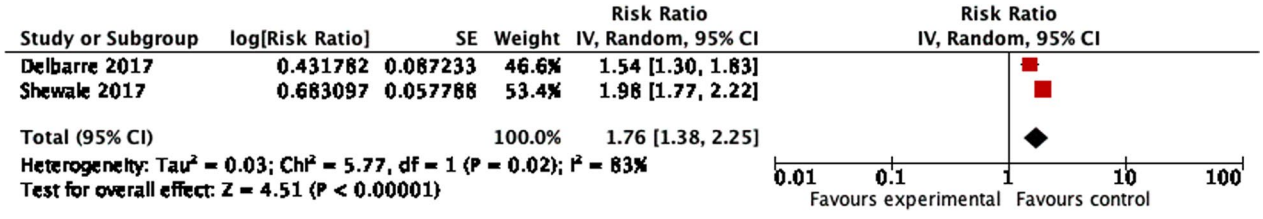

Fig. 3 Forest plot of the comparison of the effects of corticosteroid and hyaluronic acid treatment on the incidence of knee arthroplasty in cohort studies

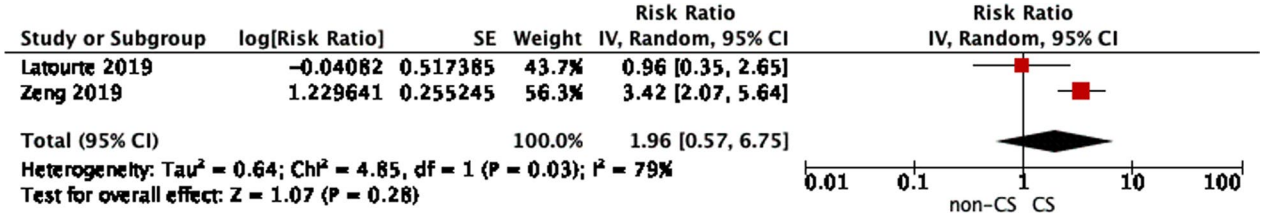

Fig. 4 Forest plot of the association between the risk of knee arthroplasty and corticosteroid treatment in cohort studies

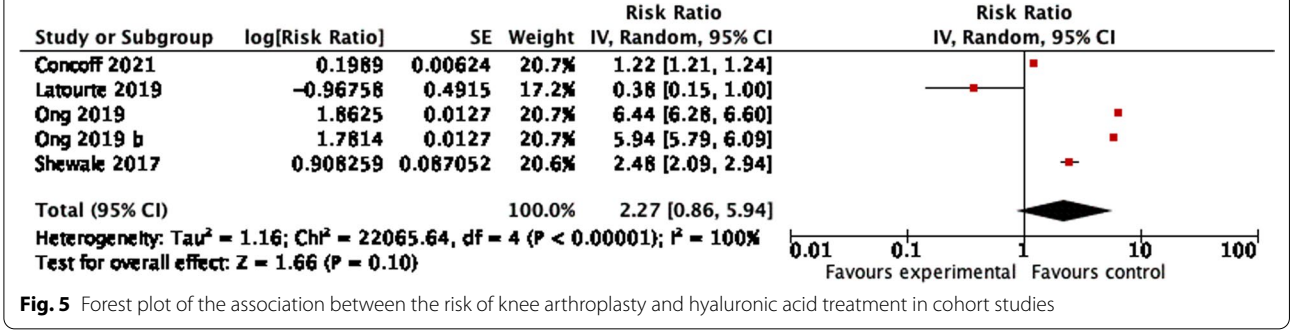

Fig. 5 Forest plot of the association between the risk of knee arthroplasty and hyaluronic acid treatment in cohort studies

Additional file 1: Fig. S4) Naproxen users did not reduce the risk of hip/knee arthroplasty (OR = 0.08, 95% CI: 0.17–3.65, $I^2 = 87$, n = 2). With respect to knee OA, compared to non-users, NSAID users had an increased risk of arthroplasty (OR = 2.96, 95% CI: 1.13–7.79, I2 = 96, 807/1272 vs. 9155/27170, n = 2) (Table 2).

Publication bias

Funnel plots were asymmetrical in the analysis of the association of NSAIDs treatment in case–control studies as well as HA treatment in cohort studies, and the values of Egger's test > 0.05, respectively. Other funnel plots of the association between the incidence of knee/hip arthroplasty and pharmacological treatments were

symmetrical. Therefore, publication bias was considered unlikely (Additional file 1: Figs. S1–S3).

Heterogeneity source

Heterogeneity was observed in meta-analysis of cohort studies. Excluding studies one by one did not reveal any apparent possible heterogeneity.

Discussion

This systematic review and meta-analysis scrutinized all available evidence to investigate the incidence and risk of knee or hip arthroplasty in patients with OA treated with NSAIDs, HA, **SYSADO,** bisphosphonates, or corticosteroids. The incidence of arthroplasty varied across study design and treatment, with the highest incidence of knee replacement of 70.88% reported by a case–control study in coxib-treated patients with OA, and the lowest incidence of knee arthroplasty of 0%, reported by a RCT in Condrosan-treated patients. Compared to non-users, bisphosphonate users had a reduced risk of knee replacement (RR = 0.71, 95% CI: 0.66–0.77; aHR = 0.76, 95% CI: 0.70–0.83). Compared to intra-articular corticosteroid users, hyaluronic acid (HA) users had a lower risk of knee arthroplasty (RR = 1.76, 95% CI: 1.38–2.25). NSAID use was associated with an increased risk of knee replacement (OR = 2.96, 95% CI: 1.13–7.79).

We found that bisphosphonate users had a reduced risk of knee replacement compared to non-users. Bisphosphonates, commonly indicated as osteoporosis treatment, inhibit the activity of osteoclasts by inhibiting the development of osteoclast progenitors and suppressing local bone turnover after attaching to hydroxyapatite binding sites on bony surfaces, particularly those undergoing active bone resorption, thus repressing bone resorption [60, 61]. In OA, subchondral bone metabolism is defective, and increased subchondral bone turnover may lead to pain, which could be alleviated by targeting osteoclasts. However, the use of bisphosphonates in reducing knee arthroplasty is controversial [62]. Li et al. stated that Neogi et al. ignored the sociocultural factor in their study, which might affect the choice and accessibility of arthroplasty for patients with OA. Further investigations are needed to clarify the beneficial role of bisphosphonates in reducing arthroplasty due to the limited number of eligible studies in this meta-analysis.

Our study demonstrated that compared to the non-users, NSAID users have a higher risk of knee arthoplasty. This may be because NSAIDs users had a lower perception in joint pain and disease activity, resulting in poor joint protection from hazardous positions, activities and weight bearings. In addition, patients who are willing to use NSAIDs may be more inclined to receive joint replacement therapy [37].

Our study demonstrated that HA could not reduce the risk of knee/hip arthroplasty. And compared with intra-articular CS therapy, HA treatment elevated the risk of joint replacement. Some studies reported HA could delay the time of arthroplasty [36, 42]. According to a previous study, HA combined with intra-articular CS could reduce joint pain earlier than HA alone. Though clinical parameters improved after combined therapy, the cartilage damage remained [63].

We included three study designs in our systematic review and meta-analysis. While the incidence of arthroplasty was low in RCTs, it was high in case–control studies despite the use of the same drug. RCTs provided imprecise estimates due to the very low event rate and short follow-up duration, while cohort and case–control studies provided accurate information on the incidence and potential risk of arthroplasty given their ability to capture large patient data and outcomes over a long duration [64]. A retrospective cohort study can detect more adverse events than other study designs, such as a cross-sectional design [65].

This study has several limitations. High heterogeneity existed among the cohort and case-control studies. Subgroup analysis according to treatment and OA site did not significantly reduce heterogeneity, which could be explained by the diverse study populations and treatments. As participants from all over the world were represented in the study, there were economic, racial and cultural disparities, which greatly influenced the patients' choice for arthroplasty [61]. The differences in the female-to-male ratios and disease severity of the studied patients with OA might have also contributed to the high heterogeneity [66]. Therefore, additional investigations such as subgroup analysis by follow-up time, sex ratio, and disease severity could not be performed.

Conclusion

In conclusion, the incidence of knee and hip arthroplasty was found to vary across different treatments and study designs. Compared with no treatment, treatment with bisphosphonates reduced the risk of knee replacement, while NSAIDs and HA users had an increased risk of knee replacement. However, more studies are needed to validate our results due to the limited number of eligible studies and high heterogeneity among studies.

Abbreviations

OA: Osteoarthritis; DALYs: Disability-adjusted life years; NSAIDs: Nonsteroidal anti-inflammatory drugs; SYSADOA: Symptomatic slow acting drugs for osteoarthritis; HA: Hyaluronic acid.

Supplementary Information

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Additional file 1. The supplementary tables and figures.

Additional file 2. Predefined protocol of the study.

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Not applicable.

Author contributions
QX, GY and YC conceived the study, YC and BC designed the study forms, and GY and QX guided this study. BC searched the literature; YC, YT, HL, and YH screened the studies for inclusion and extracted data; YT, HL, and YH assessed methodological quality; YC and GY organized data. All authors drafted and revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
All data are available in the manuscript and Additional materials.

Declarations

Ethics approval and consent to participate
This study does not involve with ethics as it is a systematic review and meta-analysis.

Consent for publication
No patient involved.

Competing interests
All authors do not have any conflicts of interest to disclose.

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