



Systematic Review

Incidence of Rapidly Progressive Osteoarthritis Following Intra-articular Hip Corticosteroid Injection: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: The American Academy of Orthopedic Surgery recommends intra-articular corticosteroid injections (CSIs) for managing hip osteoarthritis (OA) based on short-term, prospective studies. Recent retrospective studies have raised concerns that CSIs may lead to rapidly progressive OA (RPOA). We sought to systematically review the literature of CSIs for hip OA to estimate the incidence of RPOA.

Methods: MEDLINE, Embase, and Cochrane Library were searched to identify original research of hip OA patients receiving CSIs. Overall, 27 articles involving 5831 patients published from 1988 to 2022 were included. Study design, patient characteristics, CSI details, follow-up, and cases of RPOA were recorded. Studies were classified by their ability to detect RPOA based on follow-up. Random effects meta-analysis was used to calculate the incidence of RPOA for studies able to detect RPOA.

Results: The meta-analytic estimate of RPOA incidence was 6% (95% confidence interval, 3%-9%) based on 10 articles classified as able to detect RPOA. RPOA definitions varied from progression of OA within 6 months to the presence of destructive changes. These studies were subject to bias from excluding patients with missing post-CSI radiographs. The remaining 17 articles were classified as unable to detect RPOA, including all of the studies cited in the American Academy of Orthopedic Surgery recommendation.

Conclusions: The incidence of RPOA after CSIs remains unknown due to variation in definitions and follow-up. While RPOA following CSIs may be 6%, many cases are not severe, and this may reflect selection bias. Further research is needed to understand whether clinically significant RPOA is incident enough to limit CSI use.

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Introduction

Hip osteoarthritis (OA) is one of the most common joint diseases in the United States and is placing an increasing burden on our health system given trends in aging and obesity [1]. While total hip

arthroplasty (THA) is considered the gold standard treatment for patients who fail nonoperative management, there are number of options prior to surgical intervention, including but not limited to analgesics, activity modification, and assist device use. While various nonoperative strategies may carry different risks and benefits, there is strong interest among patients in nonoperative options [2,3].

In 2017, the American Academy of Orthopedic Surgeons published clinical practice guidelines (CPG) on the management of hip

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OA [4]. This guideline provided a strong recommendation for corticosteroid injections (CSIs) in the management of hip OA “to improve function and reduce pain in the short-term for patients with symptomatic OA of the hip” based on short-term, prospective studies [4-7]. Recommendations made by the American College of Rheumatology and Veterans Affairs/Department of Defense also recommend the use of CSIs in the treatment of hip OA [8,9]. The American Academy of Orthopedic Surgeons guidelines list possible harms from CSIs, including “Bleeding, potential injury to adjacent structures, transient pain, allergic reaction, infection before and after total hip arthroplasty, postinjection pain flare and hyperglycemia.” Neither the CPG nor the studies cited in it list rapidly progressive OA (RPOA) as a potential adverse event.

RPOA, which is sometimes referred to as rapidly destructive OA, is a condition with more rapid progression of OA than might be typically expected [10-13]. While the etiology is poorly understood and multiple definitions exist for what defines RPOA, it can have an impressive clinical presentation in some cases with patients experiencing extreme pain and severely limited function [14]. Recent retrospective studies have raised concerns that hip CSIs may lead to RPOA [15-20]. These studies have reported various estimates of RPOA incidence of up to 20%.

Whether these retrospective studies are overestimating the incidence of RPOA or earlier randomized controlled trials with shorter follow-up may have missed cases of RPOA is unknown. We sought to systematically review the literature of CSIs for hip OA to estimate the incidence of RPOA and, as a part of this, to systemically explore whether studies are likely to detect cases of RPOA and what definitions are being used for RPOA.

Material and methods

Search strategy

A systematic review of the literature was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [21]. The protocol for this review was registered in the International Prospective Register of Systematic Reviews (identifier CRD42023393254). The MEDLINE, Embase, and Cochrane Library databases were searched from their inception to September 2022. To maximize sensitivity, medical subject headings of the terms “osteoarthritis, hip”, “intra articular” injection, and “glucocorticoids” were utilized in addition to permutations of each keyword (detailed strategy is provided in Appendix Table 1). Database-specific keywords corresponding to the medical subject headings terms outlined previously were utilized in the Embase and Cochrane Library searches to ensure the returned results were both comprehensive and comparable to the MEDLINE search. The reference lists of retrieved articles were reviewed to identify any additional relevant studies as per the inclusion and exclusion criteria as listed below.

Inclusion criteria

Studies eligible for this systematic review included English-language studies published at any time that reported on the outcomes of CSI for the treatment of hip OA. Studies that did not specifically utilize intra-articular injection of corticosteroids in human hips were excluded. Studies in which it was not possible to obtain data from the publication were excluded. Studies investigating other conditions such as rheumatoid arthritis or ankylosing spondylitis were excluded. Case reports or series with fewer than 10 patients, abstracts, conference proceedings, clinical trial updates, and commentaries were also excluded.

Literature search

The literature search identified 831 studies. All 831 studies underwent title and abstract screening. Thirty-two full-length articles were then reviewed by 2 reviewers (FS, DL) to determine if they met inclusion criteria. When disagreement occurred, resolution was reached through discussion. Three case series, 1 clinical trial update, and 1 non-OA study were excluded, yielding 27 articles from 1988 to 2022 for inclusion. (Fig. 1). Of the 27 articles, 13 were retrospective and 14 prospective [5-7,15-20,22-39]. A total of 5831 patients were identified with a range from 12 to 1471 patients. All studies used image guidance for injections with the most common aide being fluoroscopy, followed by ultrasound and radiograph. Twenty-four of the studies utilized a single, specific corticosteroid with the most commonly studied corticosteroids being triamcinolone and methylprednisolone. There was significant variation of dosing. (Table 1).

Quality assessment

Study quality was assessed using the Newcastle-Ottawa Quality Assessment Scale for cohort studies and Cochrane risk-of-bias tool for randomized trials with several studies being rated as high risk of bias (Appendix Tables 2 and 3) [40-42].

Data abstraction

Data regarding number of patients, patient demographics and clinical characteristics, type of steroid, dose of steroid, and follow-up details including length and use of imaging were recorded from each study. Details of inclusion and exclusion criteria as well as loss to follow-up or exclusion for missing imaging were recorded. Whether RPOA was mentioned was recorded for each study along with the definition used for studies mentioning this term and the number of cases recorded.

Studies were classified based on their reported follow-up as likely able detect cases of RPOA if they were to occur or not. Key determining factors in determining a study’s ability to detect RPOA were the presence of baseline and follow-up imaging as well as the duration which patients were followed. The articles were also assessed for potential unreported cases of RPOA by examining outliers within patient-level data that demonstrated significant worsening after receiving a CSI though this could only be performed a small number of studies.

Statistical analysis

Random effects meta-analysis was used to calculate the incidence of RPOA from studies classified as able to detect RPOA. A random effects model was chosen independent of empirical estimates of heterogeneity given the differences in study design. The I^2 statistic is provided to give this empirical estimate of heterogeneity. A funnel plot was created to assess for possible publication bias though as mentioned, there was also concern about bias at the study level.

Source of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Results

Based on the 10 studies classified as able to detect RPOA, the meta-analytic estimate of RPOA incidence after hip CSIs was 6%

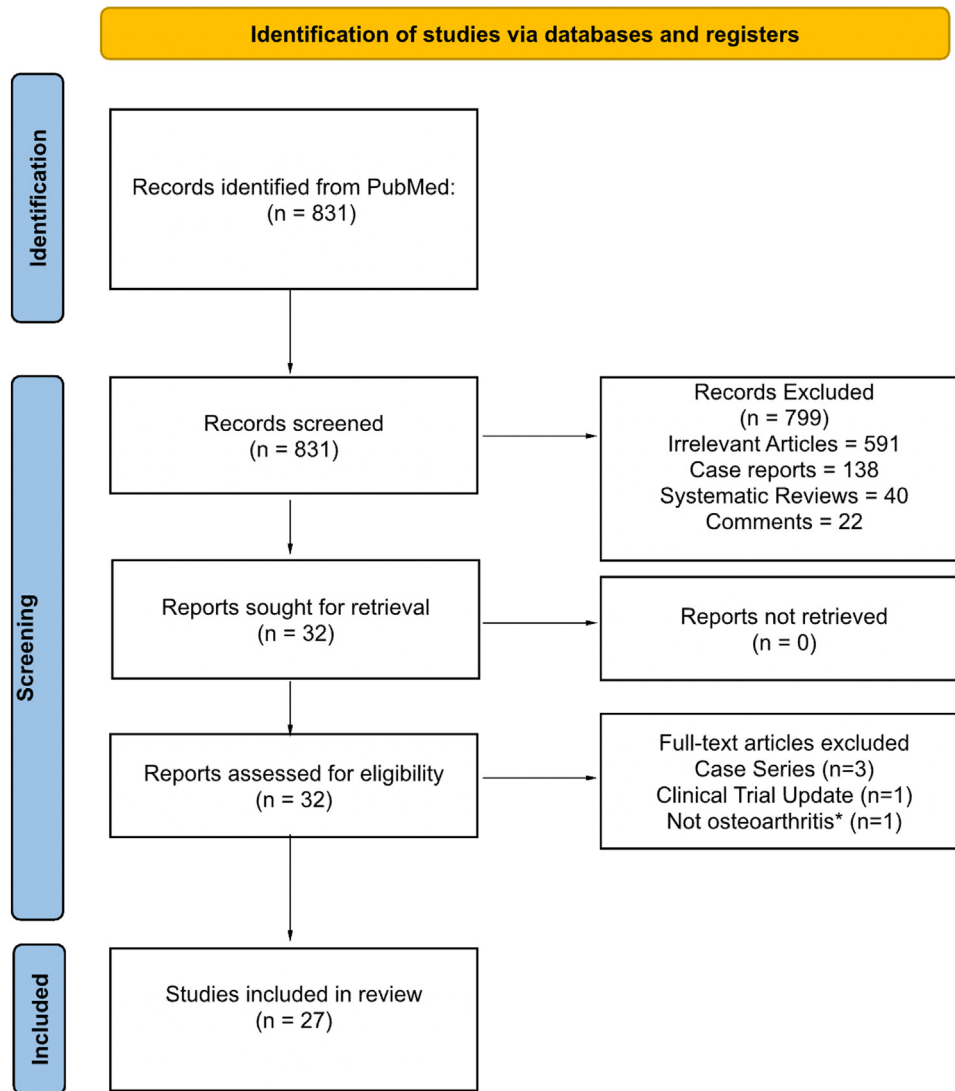


Figure 1. PRISMA flow diagram of included articles *Study explores the treatment of hip pain without a diagnosis of osteoarthritis with intra-articular steroid injections. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

with a 95% confidence interval of 3%-9% (Fig. 2). The I^2 statistic was 89% suggesting significant heterogeneity as expected. The funnel plot based on estimates from these studies displayed some asymmetry, raising concern for publication bias (Fig. 3).

Follow-up imaging

Of the 14 prospective studies, only 2 performed follow-up imaging. Plant et al. [23] obtained radiographs at 26 weeks after CSI. Micu et al. [26] obtained follow-up ultrasounds at 1 and 3 months to compare to baseline ultrasound.

Of the 13 retrospective studies, 8 contained follow-up imaging. Hess et al. [16] only included patients with a baseline radiograph up to 6 months before CSI and a follow-up radiograph up to 1 year after CSI and noted that this excluded over 80% of patients who had a hip CSI for OA. Kompel et al. [17] only included patients with follow-up radiographs after injection and noted that excluded roughly 50% of patients who had a CSI for OA. Someone et al. [37] only included patients with baseline radiographs up to 6 months prior to injection and follow-up imaging 3-12 months after injection and note that this excluded over 80% of patients who had a hip CSI for OA. The retrospective cohort from the study by Okike et al. [18] does not

present details of when follow-up imaging was obtained though this study was specifically diagnosing RPOA. Abraham et al. [39] only included patients with a baseline radiograph up to 1 year prior to injection and follow-up radiograph up to a year postinjection and do not note the number of patients excluded for lack of imaging. Boutin et al. [19] only included patients with baseline and follow-up radiographs and did not note the number of patients excluded for lack of imaging. Graf et al. [15] only included patients with follow-up imaging within 12 months of the injection and note that 35% of patients who had a hip CSI did not have additional imaging. Sanguino et al. [20] only included patients with baseline and follow-up imaging before a surgical procedure and imaging modalities included radiographs, magnetic resonance imaging, and computed tomography. This study did not note the total number of patients excluded for lack of imaging but did note that over 30% of hip CSI patients were excluded because imaging was after a surgery.

Classification of ability to detect RPOA and case definitions

All 10 of the studies with follow-up imaging were classified as possibly able to detect RPOA, while the other 17 studies without follow-up imaging were classified as unlikely to be able to detect

Table 1
Characteristics of included studies.

Study	Patients (n =)	Mean age (y)	Female (%)	Radiographic severity	Steroid with dose (mg)	Follow-up (mo)	Follow-up imaging
Prospective studies							
Flanagan, 1988 [22] ^a	12	46-79	80%	KL 3 ^g	TCM 20	12	N
Plant, 1997 [23]	45	59	77.8%	KL 3 ^g	MP 80	6	Y
Kullenberg, 2004 [24]	40	67	n/a	≥Ahlbäck 2	TCM 80	3	N
Qvistgaard, 2006 [5]	32	69	72%	KL 1-4	MP 40	3	N
Lambert, 2007 [6]	31	66	68%	KL 1-4	TCM 40	6	N
Robinson, 2007 [25]	120	64	75%	KL 3 ^g	MP 40 & 80	3	N
Micu, 2010 [26] ^b	40	63	70%	KL 3	BM 8	3	Y
Spitzer, 2010 [27]	155	61	51%	KL 2-3	MP 40	6	N
Atchia, 2011 [7]	19	67	42.1%	Croft 1-4	MP 120	2	N
Young, 2012 [28]	110	65	61%		TCM 40	3	N
Anderson, 2014 [29] ^c	47	56	63.6%		TCM 40	1	N
Subedi, 2015 [30]	100	58	64%	KL 1-4	MP 80	1.5-2	N
Jurgensmeier, 2021 [31]	26	65	64.2%	KL 2-4	TCM 80	3	N
Paskins, 2022 [32]	66	63	57%		TCM 40	6	N
Retrospective Studies							
Deshmukh, 2011 [33]	220	64	59.5%	KL 0-4	MP 80	0.5	N
Park, 2015 [32]	50	58	76%	KL 2-3	TCM 40	6	N
Hess, 2018 [16] ^d	109	54	73%	KL 2.2 ^g	TCM 40	12	Y
Lai, 2018 [35]	82	64	75.6%	Tönnis 1-3	MP 80	24	N
Kompel, 2019 [17] ^e	307	57	52.8%	KL 0-4	TCM 40	2-15	Y
Walter, 2019 [36]	113	59	68.1%	Tönnis 1.9 ^g	TCM 40 & 80	1-6	N
Simeone, 2019 [37]	70	67	63%	KL 1-4	TCM 40	3-10	Y
Okike, 2021 [18] ^f	688	64	54.4%		TCM 40 & 80		Y
Kanthawang, 2021 [38]	361	60	60.9%	KL 0-4	MP 80, TCM 40	2-7	N
Abraham, 2021 [39]	93	55	62.4%	KL 0-4	MP 40 to 80, TCM 40 to 80, BM 12	1-12	Y
Boutin, 2021 [19]	1471	62	61.3%	Croft 3.7 ^h	TCM 40 & 80	11	Y
Graf, 2022 [15]	500	57	54.5%		TCM 40	1-12	Y
Sanguino, 2022 [20] ⁱ	924	59	64%		MP 40-120, TCM 20 & 40, BM 3-12, DX 4	1-12	Y

BM, betamethasone; DX, dexamethasone; MP, methylprednisolone; NRCT, nonrandomized controlled trial; RCT, randomized controlled trial; TCM, triamcinolone.

- ^a Study provides age range without a mean age.
- ^b This study utilized ultrasound for follow-up imaging.
- ^c Study injected 47 hips from 44 patients.
- ^d 129 hips from 109 patients were studied.
- ^e Patient sex demographics only reported for adverse event group, and 218 patients did not have follow up imaging.
- ^f 688 hips from 610 patients were studied.
- ^g Mean grade of patient osteoarthritis severity.
- ^h Mean Croft score of 3.7 for patients diagnosed with RPOH and 3.1 for patients without a diagnosis of RPOH.
- ⁱ Utilized a hybrid of Zazgyva and Tönnis for grading of nonradiographic images.

RPOA. Six of the 10 studies that obtained follow-up imaging also specifically reported on assessing for RPOA. Simeone et al. [37] did report on the incidence of femoral head collapse but did not

specifically define this as RPOA, though they comment in their discussion that this may be on that spectrum. Abraham et al. [39] also reported on the incidence of femoral head collapse.

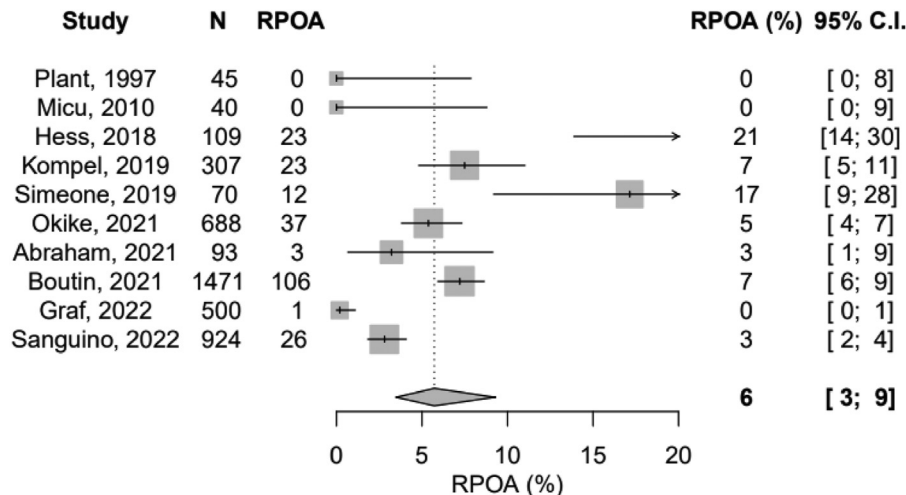


Figure 2. Forest plot of RPOA incidence based on studies classified as able to detect RPOA. RPOA, rapidly progressive osteoarthritis.

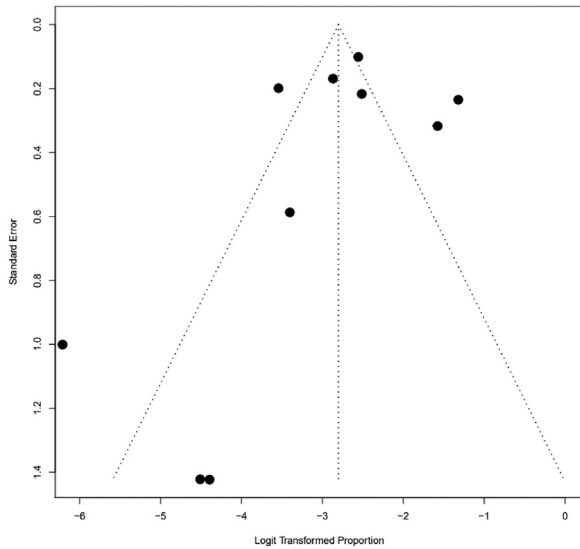


Figure 3. Funnel plot of the logit of RPOA incidence by standard error. RPOA, rapidly progressive osteoarthritis.

All studies reporting on RPOA were able to detect at least one case though the definitions of RPOA varied. There were 4 different definitions of RPOA utilized including the Lequesne definition, Roemer definition, Zazgyva, and a hybrid system based on the Tönnis and Zazgyva systems (Table 2) [10,20,43,44].

Sensitivity analysis of possible cases

Review of individual patient data suggested there may have been some cases RPOA not described as such due to limited follow-up imaging. Subedi et al. [30] identified a patient that had a 19-point decrease of their Oxford Hip Score following CSI. Jurgensmeier et al. [31] reported on a patient with a significantly worse Hip Global Health score months after CSI. Robinson et al. [25] identified 2 patients that experienced a worsening in their WOMAC pain scores greater than 75% at 6 weeks. By the 12th week, the WOMAC pain score of one patient had worsened by over 200%.

Discussion

Estimating the incidence of RPOA following CSIs for hip OA using the limited available research proved to be a challenging endeavor. This was complicated by most studies having inadequate follow-up to detect RPOA, other studies excluding a large number of patients who had a hip CSI due to lack of imaging, and then variable definitions of what constituted RPOA. Whether clinically significant RPOA following CSIs is common enough to limit use remains unknown.

The majority of prospective studies did not have follow-up imaging, which could have allowed cases of RPOA to go undetected. It is interesting that some of these studies reported on patients with a significant deterioration in their patient-reported outcome measures following CSI, which may represent cases of RPOA that lacked imaging confirmation given the study follow-up design.

The American Academy of Orthopedic Surgeons and American College of Rheumatology based their CPG recommendations on the studies by Atchia et al., Lambert et al., and Qvistgaard et al. [4-8] Similarly, the Veterans Affairs/Department of Defense CPG based their recommendation on a literature review by McCabe et al., which explores these 3 studies in addition to those by Flanagan et al. and Kullenberg et al. [9,22,24,45] These studies lacked the

design to detect RPOA, and these guidelines do not list RPOA as a potential adverse event secondary to CSI.

Conversely, retrospective studies may be overestimating the incidence of RPOA through selection bias. Exclusion of patients without a follow-up radiograph narrows the study population to those returning to clinic for a follow-up radiograph who may be more likely to have continued pain. This may artificially deflate the denominator and increase the estimated incidence.

Additionally, the lack of a clear definition of RPOA may lead to an inflated incidence, by including cases which reflect the natural progression of OA. [10,43,44]. For example, use of the definition of RPOA by Lequesne et al. or the grade I of RPOA Zazgyva et al. may represent progression of hip OA that is not of the severity that would dramatically alter the clinical care of a patient. Experiencing less impressive progression of arthritis following CSIs may not be a reason to avoid injections.

While the specific pathophysiology of RPOA is unknown, it is known to occur in the absence of CSI. For instance, in one of the larger series reported outside of North Wales, none of the 18 cases had a history of CSIs [12]. In a series of 3 patients where their RPOA had mimicked infection, none had a history of CSIs [13]. Especially for cases with femoral head collapse, there is the possibility that the underlying diagnosis was attributed to OA when in fact the case was early osteonecrosis. The study by Abraham et al. [39] discusses this concern and used magnetic resonance imaging to exclude patients with osteonecrosis. They found no association relative to a control group. Interestingly, there appear to be few reports of RPOA following CSIs for other hip pathologies such as femoroacetabular impingement [46-48].

Given all the uncertainty and clear potential for CSIs to be associated with RPOA, it is important that shared decision-making between surgeons and patients be used to guide care. Especially for cases that are likely to result in need for total hip arthroplasty, CSIs should not be considered a mandatory part of the patient evaluation and coverage of surgeries should not require failure of response to CSIs. This is an important risk for updated guidelines to

Table 2
Method of RPOA identification and definition.

Author Identifying RPOA	Method of RPOA identification	Definition
Hess Boutin Graf Kompel	Lequesne Roemer Type 1 and 2	<p>≥2 mm of chondrolysis or 50% joint space narrowing within 1 year.</p> <p>Type 1: Rapid loss of joint space within approximately 1 year without evidence of bone loss or destruction. Type 2: Abnormal bone loss or destruction in a short period of time, including limited or total collapse of at least one subchondral surface that is not a feature of conventional advanced OA.</p>
Okike	Zazgyva Grade II and III	<p>Grade I: Partial joint space narrowing without deformation or ascension of the femoral head. Grade II: Absolute disappearance of the joint space, deformity of the femoral head and acetabulum, ascension of the femoral head ≥0.5 cm above the radiographic teardrop. Grade III: Absolute disappearance of the joint space, partial osteolysis of the femoral head, ascension of the femoral head >0.5 cm above the radiographic teardrop.</p>
Sanguino Abraham Simeone	Hybrid Zazgyva & Tönnis grading system Femoral head collapse ^a	

^a Cases of Femoral head collapse were classified as RPOA in this meta-analysis though this not specifically defined in the individual articles as such.

include in the interim. Related to this decision-making is that surgery would likely need to be delayed for 3–4 months following CSIs to avoid an increased risk of infection [49–51], and it is possible that RPOA may complicate subsequent surgery [14].

Ideally, a future study would prospectively randomize a diverse group of patients with hip OA to CSI vs placebo with planned follow-up using patient-reported outcome measures and imaging at 3 mo. Including a diverse group of patients would maximize external generalizability and allow for the exploration of potential post-traumatic osteoarthritis risk factors. Radiographs should be reviewed in a blinded fashion for destructive changes using current definitions as well as changes thought to alter or compromise clinical management. If clinically significant RPOA occurs in 4% of patients following CSI and in 0.5% of patients with OA but not receiving a CSI, then 562 patients would be needed to power a superiority trial comparing CSI to placebo to 80%. Another option would be an open label study which could better estimate the incidence of RPOA after CSIs but this would have the disadvantage of not being able to establish the extent to which CSIs may be the causative factor.

Although this study may be the first meta-analysis to estimate the incidence of RPOA, it is not without limitations. Results from systematic reviews are only as strong as the studies included. Large variability in study design as well as the data reported in each study, as demonstrated by the high I^2 can, be seen among included articles. Many of the included studies did not obtain imaging. The baseline and follow-up imaging performed by Micu et al. was ultrasound, which is an unconventional imaging modality that is unlikely to be used in the diagnosis of hip OA. The follow-up duration also varied significantly from 2 weeks to 2 years. The type of steroid used, and their respective doses, varied significantly. Definitions of RPOA varied among studies that searched for this adverse event. Studies which reported on cases of RPOA may have been subject to selection bias, as the inclusion criteria requires baseline and follow-up imaging for patients receiving CSI. There was also a potential for publication bias which some studies estimating lower rates of RPOA possibly not having been published. Furthermore, systematic reviews and meta-analyses are limited in the ability to draw conclusions on adverse events due to the generally poor reporting of adverse events [52–54].

Conclusions

The incidence of RPOA after hip CSI for OA is difficult to estimate based on the available literature given the large number of studies not designed to detect this complication and considerable variation in the definitions used to identify RPOA. Future research is needed to guide recommendations on the use of CSI for hip OA, and to determine whether clinically significant RPOA is common enough to limit use.

Conflicts of Interest

The authors declare there are no conflicts of interest.

For full disclosure statements refer to <https://doi.org/10.1016/j.artd.2023.101242>.

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Appendix Table 1

Search string.

Search Engine	Search Strategy
Pubmed/ MEDLINE	((("Hip arthritis"[Text Word] OR "Hip osteoarthritis"[Text Word] OR "Hip OA"[Text Word] OR "Hip"[Text Word] OR "Arthritis of the hip"[Text Word] OR "osteoarthritis of the hip"[Text Word] OR "Rapidly Destructive Hip"[Text Word] OR "Rapid destructive osteoarthritis"[Text Word] OR "Rapidly progressive"[Text Word] OR "rapidly destructive osteoarthritis"[Text Word] OR "Rapid progressive"[Text Word] OR "rapid destructive hip"[Text Word] OR "Rapid progressive"[Text Word] OR "Arthritis of the hip"[Text Word] OR "hip arthropathy"[Text Word]) AND ("Glucocorticoids"[MeSH Terms] OR "steroid*"[Text Word] OR "corticosteroid*"[Text Word] OR "glucocorticoid*"[Text Word] OR "Methylprednisolone"[Text Word] OR "Triamcinolone"[Text Word] OR "corticoid*"[Text Word] OR "Kenalog"[Text Word] OR "DepoMedrol"[Text Word] OR "Medrol"[Text Word] OR "steroid"[Text Word] OR "steroids"[Text Word]) AND ("injections, intra articular"[MeSH Terms] OR "inject*"[Text Word] OR "intraarticular*"[Text Word] OR "intra articular*"[Text Word] OR "intra articular"[Text Word] OR "intraarticular"[Text Word] OR "intra-articular"[Text Word] OR "intra-articular injection"[Text Word] OR "intraarticular"[Text Word] OR "intra-articular"[Text Word] OR "Intra-articular injections"[Text Word]))

Appendix Table 2

Cochrane risk-of-bias tool for randomized trials (RoB 2).

Study	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
Flanagan 1988 [22]	+	+	⊗	○	○	⊗
Kullenberg 2004 [24]	+	+	⊗	+	+	⊗
Qvistgaard 2006 [5]	+	+	○	+	+	○
Lambert 2007 [6]	○	+	+	+	+	○
Spitzer 2010 [27]	+	+	+	+	+	+
Atchia 2011 [7]	+	+	+	+	+	+
Young 2012 [28]	+	+	+	+	+	+
Jurgensmeier 2021 [31]	+	+	+	+	+	+
Pakins 2022 [32]	+	+	+	+	+	+

Domains: D1: Bias arising from the randomization process. D2: Bias due to deviations from intended intervention. D3: Bias due to missing outcome data. D4: Bias in measurement of the outcome. D5: Bias in selection of the reported result.

Judgment: ⊗ High; ○ Some concerns; + Low.

Appendix Table 3
Newcastle-ottawa quality assessment scale^a.

Author & year	Selection	Comparability	Outcome
Prospective Studies			
Plant 1997 [23] ^b	***		**
Robinson 2007 [25]	****	**	***
Micu 2010 [26]	****	**	***
Anderson 2014 [29] ^b	***		*
Subedi 2015 [30]	****		*
Retrospective Studies			
Deshmukh 2011 [33]	****	*	**
Park 2015 [32]	****	**	***
Hess 2018 [16] ^b	**		***
Lai 2018 [35] ^b	***		**
Kompel 2019 [17] ^b	**		**
Walter 2019 [36] ^b	***		***
Simeone 2019 [37]	****	**	***
Okike 2021 [18]	****		***
Kanthawang 2021 [38] ^b	***		***
Abraham 2021 [39]	****	**	***
Boutin 2021 [19]	****		***
Graf 2022 [15] ^b	***		***
Sanguino 2022 [20] ^b	***		***

^a Higher number of asterisks indicates a higher quality study. A maximum of (4) asterisks may be obtained from 'Selection' category; (2) from the 'Comparability' category; (3) from the 'Outcome' category.

^b Denotes studies without comparison group.