A commentary by Philippe Hernigou, MD, is linked to the online version of this article.

Rapidly Destructive Hip Disease Following Intra-Articular Corticosteroid Injection of the Hip

Kanu Okike, MD, MPH, Ryan K. King, BA, Jason C. Merchant, MD, Eugene A. Toney, MD, Gregory Y. Lee, MD, and Hyo-Chun Yoon, MD, PhD

Investigation performed at Kaiser Moanalua Medical Center, Honolulu, Hawaii

Background: While recent reports have suggested that hip corticosteroid injections can hasten joint degeneration, there are few published data on the topic. The purpose of the present study was to evaluate for an association between corticosteroid injection and rapidly destructive hip disease (RDHD) and to determine the rate of, and risk factors for, occurrence.

Methods: This study was conducted in 2 parts. First, to assess for a potential association between hip corticosteroid injection and RDHD, a case-control analysis was performed. Patients who developed RDHD between 2013 and 2016 served as cases, whereas those who underwent total hip arthroplasty for diagnoses other than RDHD during the same period served as controls, and the exposure of interest was prior intra-articular hip corticosteroid injection. Second, in a retrospective cohort analysis, we analyzed all patients who received a fluoroscopically guided intra-articular hip corticosteroid injection at our institution from 2013 to 2016. The rate of post-injection RDHD was determined, and logistic regression was used to identify risk factors for occurrence.

Results: In the case-control analysis, hip corticosteroid injection was associated with the development of RDHD (adjusted odds ratio, 8.56 [95% confidence interval, 3.29 to 22.3], $p < 0.0001$). There was evidence of a dose-response curve, with the risk of RDHD increasing with injection dosage as well as with the number of injections received. In the retrospective cohort analysis, the rate of post-injection RDHD was 5.4% (37 of 688). Cases of post-injection RDHD were diagnosed at an average of 5.1 months following injection and were characterized by rapidly progressive joint-space narrowing, osteolysis, and collapse of the femoral head.

Conclusions: This study documents an association between hip corticosteroid injection and RDHD. While the risk of RDHD following a single low-dose (≤40 mg) triamcinolone injection is low, the risk is higher following high-dose (≥80 mg) injection and multiple injections. These findings provide information that can be used to counsel patients about the risks associated with this common procedure. In addition, caution should be taken with intra-articular hip injections utilizing ≥80 mg of corticosteroid and multiple injections.

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

Intra-articular corticosteroid injection is a common treatment for hip osteoarthritis[1-6] and other conditions[7-10]. Prior research on safety has focused on the risk of periprosthetic infection when injections are performed prior to total hip arthroplasty[11-25].

Rapidly destructive hip disease (RDHD)—also termed rapidly progressive osteoarthritis (RPOA) and rapidly destructive osteoarthritis (RDO)—is a long-recognized clinical entity characterized by rapid destruction of the hip joint[26,27]. Radiographically, this entity is characterized by rapid joint-space narrowing, deformation and ascension of the femoral head, and a relative lack of osteophytes[28-30]. While a variety of potential etiologies have been proposed, in most cases the specific cause is unknown[28,30].

In recent years, RDHD has emerged as a possible complication of intra-articular hip corticosteroid injection. In particular, this entity has now been described in 3 case reports[31-33] and 2 case series[34,35]. However, a comprehensive analysis of post-injection RDHD has yet to be performed. The purpose of the present study was to evaluate for an association between hip

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJS/G684).

corticosteroid injection and RDHD and, if present, to determine the rate of, and risk factors for, occurrence.

Materials and Methods

The present study was conducted in Kaiser Permanente Hawaii, a geographically-isolated health maintenance organization (HMO) in which members receive all of their imaging and care within the integrated health-care system. The present investigation took place in 2 parts. In the first part, a case-control analysis was performed to assess for an association between intra-articular hip corticosteroid injection and RDHD. In the second part, a retrospective cohort analysis was undertaken to determine the rate of, and the risk factors for, post-injection RDHD.

Part I: Case-Control Analysis

Study Design and Selection Criteria

To assess for an association between intra-articular hip corticosteroid injection and RDHD, an unmatched case-control study was performed. Cases were defined as all adult patients (age, ≥18 years) who underwent treatment for RDHD at our institution between 2013 and 2016. To define the control group of patients who were at risk for RDHD but did not develop it, the Kaiser Permanente Total Joint Registry was utilized. Specifically, we identified all adult patients who had undergone primary total hip arthroplasty (THA) at our institution between 2013 and 2016 and did not have evidence of RDHD on radiographs preceding the arthroplasty procedure. Patients who had undergone primary THA for femoral neck fracture and those who had undergone revision THA were excluded.

Diagnosis of RDHD

In the diagnosis of RDHD, we utilized the definition provided by Zazgyva et al.[30]. Specifically, we used the definitions of rapidly progressive osteoarthritis of the hip (RPOH) grade II ("complete disappearance of the joint space, deformed femoral head and acetabulum, ascension of the femoral head ≤0.5 cm

TABLE I Factors Potentially Associated with the Development of RDHD (Case-Control Analysis)

Characteristic	No. of Cases (N = 40)	No. of Controls (N = 717)	P Value
Age* *(yr)*	65.0 ± 9.9	65.1 ± 9.5	0.93
Sex *(no. of hips)*			0.44
Male	15 (37.5%)	313 (43.7%)	
Female	25 (62.5%)	404 (56.3%)	
ASA classification *(no. of hips)*			0.052
1	2 (5.0%)	124 (17.3%)	
2	33 (82.5%)	467 (65.1%)	
3	5 (12.5%)	126 (17.6%)	
Body mass index* *(kg/m²)*	27.9 ± 5.6	28.5 ± 5.9	0.55
Smoking status *(no. of hips)*			0.87
Never	20 (50.0%)	374 (52.2%)	
Former	17 (42.5%)	298 (41.6%)	
Current	3 (7.5%)	45 (6.3%)	
Laterality *(no. of hips)*			0.33
Right	25 (62.5%)	392 (54.7%)	
Left	15 (37.5%)	325 (45.3%)	
Prior corticosteroid injection *(no. of hips)*			<0.0001
No	5 (12.5%)	394 (55.0%)	
Yes	35 (87.5%)	323 (45.0%)	
Corticosteroid injection dose *(no. of hips)*			<0.0001
None	5 (12.5%)	394 (55.0%)	
Low-dose	6 (15.0%)	97 (13.5%)	
High-dose	29 (72.5%)	226 (31.5%)	
No. of prior corticosteroid injections *(no. of hips)*			<0.0001
0	5 (12.5%)	394 (55.0%)	
1	14 (35.0%)	182 (25.4%)	
≥2	21 (52.5%)	141 (19.7%)	

*The values are given as the mean and the standard deviation.

TABLE II Regression Analysis of Factors Associated with the Development of RDHD (Case-Control Analysis)

Characteristic	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Prior corticosteroid injection				
No†				
Yes	8.54 (3.31-22.0)	<0.0001	8.56 (3.29-22.3)	<0.0001
Corticosteroid injection dose				
None†				
Low-dose	4.87 (1.46-16.3)	0.010	5.44 (1.61-18.4)	0.007
High-dose	10.1 (3.86-26.5)	<0.0001	9.69 (3.68-25.5)	<0.0001
No. of prior corticosteroid injections				
0†				
1	6.06 (2.15-17.1)	0.0007	6.03 (2.13-17.1)	0.0007
≥2	11.7 (4.34-31.7)	<0.0001	12.0 (4.40-32.8)	<0.0001

*Estimates adjusted for age, sex, and ASA classification. †Reference category.

above the radiologic teardrop") and RPOH grade III ("complete disappearance of the joint space, partial osteolysis of the femoral head, ascension of the femoral head >0.5 cm above the radiologic teardrop") to represent RDHD[30]. In the present study, RPOH grade I as defined by Zazgyva et al. was not considered to represent RDHD as the radiographic features of that entity were too nonspecific ("partial joint space narrowing, no deformation/ascension of the femoral head")[30].

Radiographs were initially reviewed by 1 individual to identify cases that could potentially represent RDHD. For each potential case, the radiographs were then reviewed by a 5-person committee consisting of 3 orthopaedic surgeons specializing in THA and 2 radiologists specializing in musculoskeletal radiology, with discrepancies resolved by consensus. In the assessment of RDHD, inter-rater reliability was substantial (kappa = 0.67; overall agreement, 83.3%).

Data Collection

For each patient in this portion of the study, a retrospective chart review was conducted by 1 individual who was blinded to the presence or absence of RDHD (i.e., case or control status). The exposure of interest was prior hip intra-articular corticosteroid injection. Specifically, we recorded whether a corticosteroid injection had taken place and, if so, how many injections had been performed and at which dosage(s). Injections of ≤40 mg of corticosteroid were considered to be low-dose, whereas those of ≥80 mg were considered to be high-dose. For hips that received multiple injections over time, those that received low-dose injections only were categorized as "low-dose" whereas those that received ≥1 high-dose injections were categorized as "high-dose." In addition, information was collected on potential confounders, including age, sex, American Society of Anesthesiologists (ASA) classification, body mass index (BMI), and smoking status (never, former, or current).

Part II: Retrospective Cohort Analysis

Study Design and Selection Criteria

To determine the rate of, and risk factors for, RDHD following injection, a retrospective cohort analysis was performed. All adult patients (age, ≥18 years) who had received a fluoroscopically-guided intra-articular corticosteroid injection into the native hip at our facility between 2013 and 2016 were included.

TABLE III Characteristics of Hips That Underwent Intra-Articular Hip Corticosteroid Injections, 2013-2016 (Cohort Analysis) (N = 688)

Age* *(yr)*	64.2 ± 11.3
Sex *(no. of hips)*	
Male	314 (45.6%)
Female	374 (54.4%)
Body mass index* *(kg/m²)*	28.4 ± 6.4
Smoking status *(no. of hips)*	
Never	352 (51.2%)
Former	285 (41.4%)
Current	51 (7.4%)
Baseline arthritis severity† *(no. of hips)*	
No arthritis	56 (8.1%)
Mild	278 (40.4%)
Moderate	69 (10.0%)
Severe	275 (40.0%)
Laterality *(no. of hips)*	
Right	371 (53.9%)
Left	317 (46.1%)
Corticosteroid injection dose *(no. of hips)*	
Low-dose	295 (42.9%)
High-dose	393 (57.1%)
No. of corticosteroid injections *(no. of hips)*	
1	440 (64.0%)
2	146 (21.2%)
≥3	102 (14.8%)

*The values are given as the mean and the standard deviation. †Data were missing for 10 hips (1.5%).

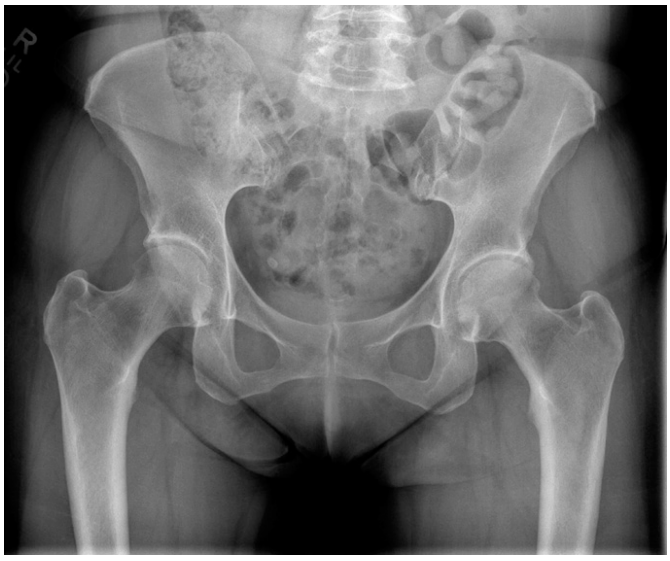

Fig. 1-A

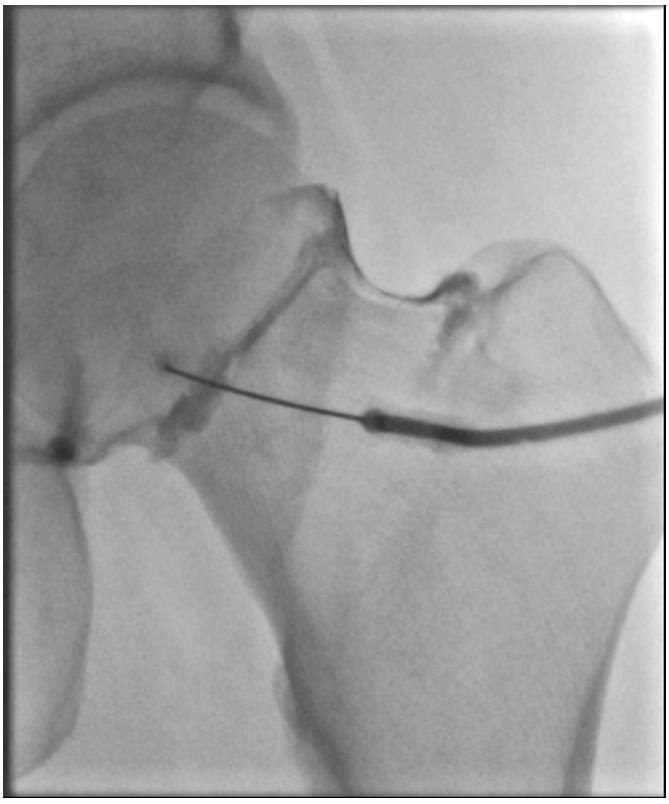

Fig. 1-B

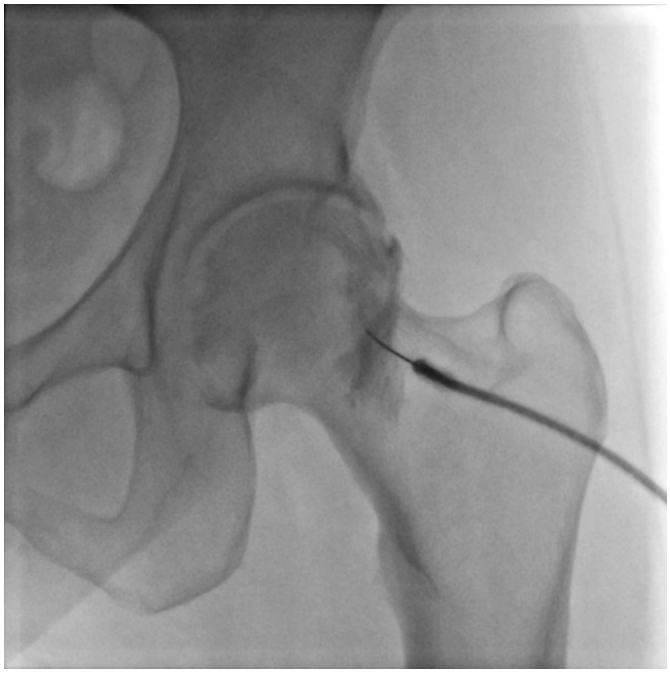

Fig. 1-C

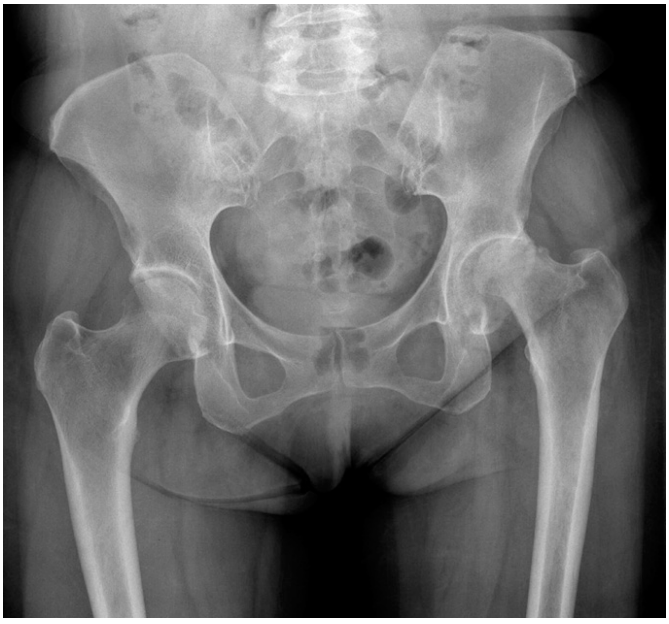

Fig. 1-D

Figs. 1-A through 1-E Case 1, a 65-year-old woman who initially presented with a 5-month history of left hip pain. **Fig. 1-A** At the time of presentation, radiographs showed mild degenerative changes. **Fig. 1-B** The patient was referred for fluoroscopy-guided intra-articular hip corticosteroid injection, performed with 40-mg triamcinolone, which relieved the pain. **Fig. 1-C** Five months later, the pain recurred and the patient underwent a second corticosteroid injection with 80-mg triamcinolone. **Fig. 1-D** Three months following the second corticosteroid injection, the patient presented to the emergency department with severe pain and inability to walk and radiographs revealed post-injection RDHD.

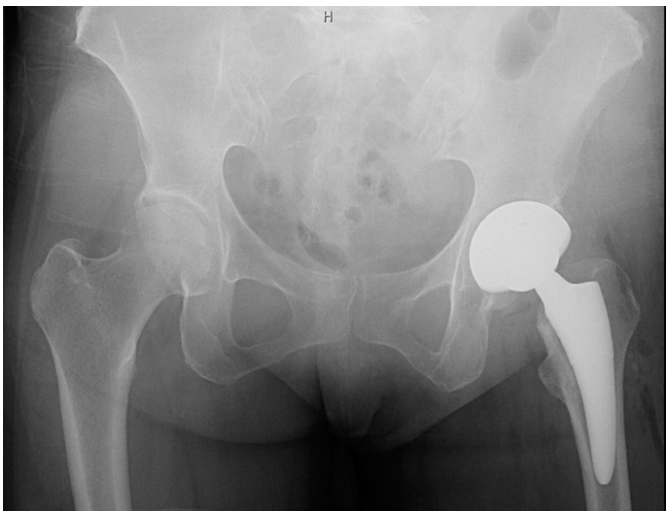

Fig. 1-E
The patient was treated with total hip arthroplasty.

Hip Injection Technique

All injections were performed by board-certified radiologists with use of fluoroscopic guidance. Following informed consent, the groin was sterilely prepared and draped and local anesthesia was achieved with 1% or 2% lidocaine. Entry into the joint space was obtained with a 20 or 22-gauge spinal needle and was confirmed on fluoroscopy via the injection of a small but variable amount of Omnipaque 240 (iohexol; GE Healthcare). The intra-articular injection was then performed with local anesthetic and corticosteroid. The vast majority of injections (99.2%; 1,117 of 1,126) were performed with 40 mg/mL triamcinolone, usually at a dose of either 1 mL (40 mg; "low dose") or 2 mL (80 mg; "high dose").

Data Collection

For each hip, the presence or absence of RDHD following corticosteroid injection was determined via the process described above. In addition, a chart review was conducted by 1 individual who was blinded to the presence or absence of RDHD. As above, information was collected on potential confounders, including age, sex, BMI, and smoking status. In addition, baseline arthritis severity was categorized as none, mild, moderate, or severe. ASA classification was not assessed in this portion of the study as it is assigned at the time of surgery and many of these patients did not undergo a surgical procedure.

Statistical Analysis

For the case-control study, univariable analysis was conducted via the chi-square test (or Fisher exact test when any cell had a value of <5) for categorical values and the unpaired t test for continuous variables. In multivariable analysis, logistic regression was used to adjust for potential confounders. Age and sex were included a priori, and the Akaike information criterion (AIC) was used to identify the optimal model. Separate models were created for each of the injection variables due to collinearity.

For the cohort study, the rate of post-injection RDHD was calculated by dividing the number of RDHD cases by the number of hips that received a corticosteroid injection during the study period. To determine the risk factors associated with its occurrence, univariable and multivariable logistic regression were performed. As above, age and sex were included a priori and the AIC was used to identify the optimal model.

For both portions of the study, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The level of significance was set at $p < 0.05$, and all tests were 2-sided. Statistical analysis was performed with use of SAS (version 9.4; SAS).

Post Hoc Analysis: Trends Over Time

Beginning in 2015, awareness of post-injection RDHD grew in our institution. As a result, orthopaedic surgeons decreased the number of intra-articular hip injections ordered and radiologists decreased the number of high-dose injections performed. In a post hoc analysis, we assessed what effect this decrease in corticosteroid injections generally, and high-dose injections specifically, had on the number of RDHD cases observed in our region. Specifically, we tallied the number of corticosteroid injections as well as the number of high-dose injections performed in each year from 2014 to 2018, along with the number of THAs performed for RDHD from 2015 to 2018 (to allow for the known time lag between injection and the development of RDHD).

Institutional Review Board

This study was approved by the Kaiser Permanente institutional review board with waiver of consent.

Source of Funding

There was no external funding source for this study.

Results

The case-control analysis involved 757 hips, including 40 cases and 717 controls. The median age was 66 years, and a slight majority of the hips (56.7%; 429 of 757) were in female patients. On univariable analysis, only factors that were related to corticosteroid injection were associated with RDHD (Table I). On multivariable analysis, hip corticosteroid injections were found to increase the likelihood of RDHD approximately 8.5-fold (adjusted OR, 8.56; 95% CI, 3.29 to 22.3; $p < 0.0001$). We also observed a dose-response effect, with low-dose injections raising the likelihood of RDHD approximately fivefold (adjusted OR, 5.44; 95% CI, 1.61 to 18.4; $p = 0.007$) and high-dose injections raising the likelihood of RDHD nearly tenfold (adjusted OR, 9.69; 95% CI, 3.68 to 25.5; $p < 0.0001$). A similar dose-response pattern was observed for the number of injections performed (Table II).

In the retrospective cohort analysis, 1,126 corticosteroid injections were performed in 688 hips (610 patients). Four hundred and forty hips received 1 injection, 146 hips had 2 injections, and 102 hips had ≥3 injections. The characteristics of the corticosteroid injection cohort are presented in Table III. There were 37 cases of post-injection RDHD, yielding a rate of 5.4% (37 of 688). Cases of post-injection RDHD were characterized by rapidly progressive joint-space narrowing as well as osteolysis, partial collapse, and ascension of the femoral head (Figs. 1-A through 2-D). In the group of 37 hips with post-

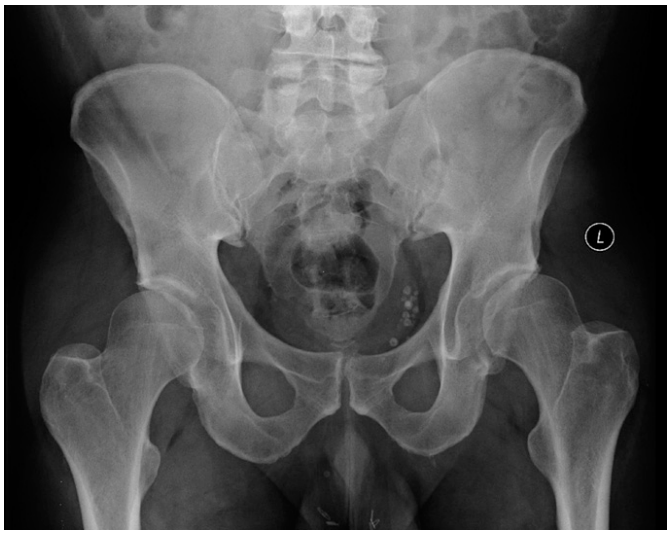

Fig. 2-A

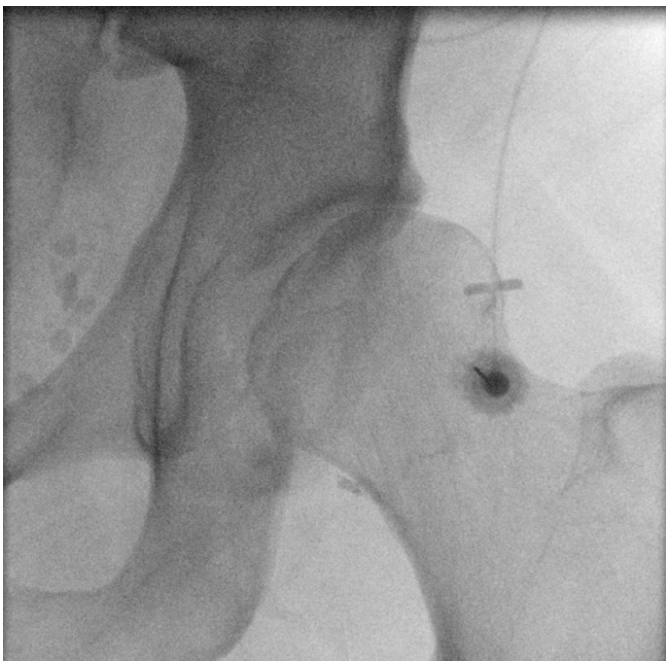

Fig. 2-B

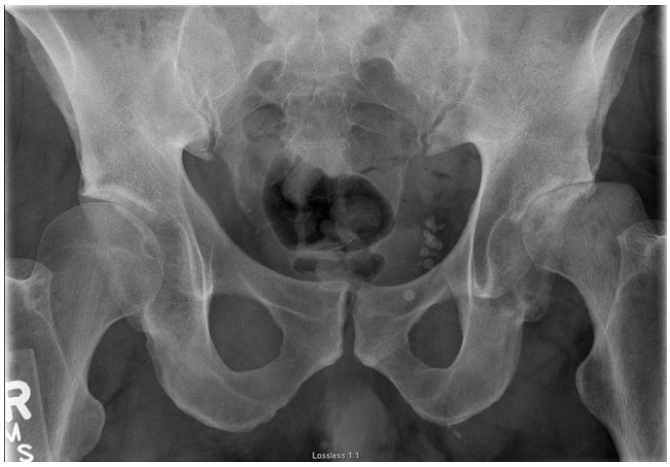

Fig. 2-C

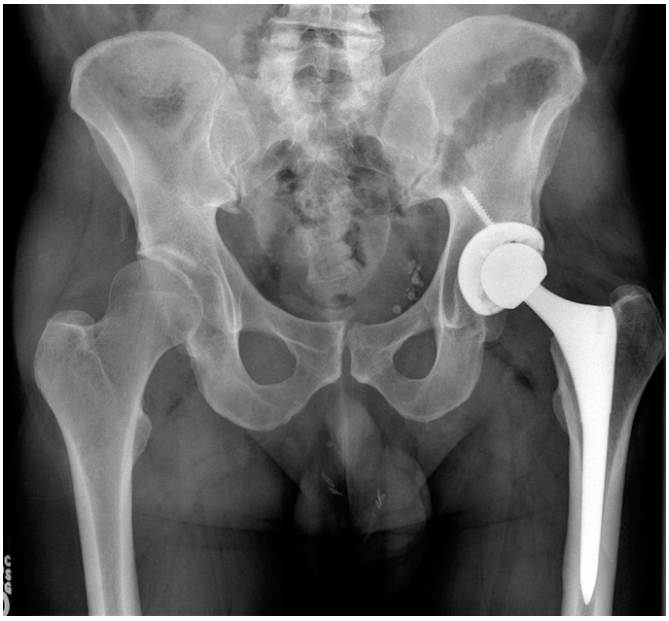

Fig. 2-D

Figs. 2-A through 2-D Case 2, a 47-year-old man who presented with a 3 to 4-month history of left hip pain. **Fig. 2-A** At the time of presentation, radiographs revealed hip dysplasia with a moderately decreased joint space. **Fig. 2-B** The patient was referred for fluoroscopy-guided intra-articular hip corticosteroid injection, which was performed with 80-mg triamcinolone. **Fig. 2-C** Three months following the injection, the patient returned with persistent left hip pain and radiographs revealed post-injection RDHD. **Fig. 2-D** The patient was treated with total hip arthroplasty.

injection RDHD, the median patient age was 66 years (range, 47 to 84 years) and there were slightly more women than men affected (23 and 14, respectively). Post-injection RDHD was diagnosed via radiographic evaluation at an average of 5.1 months after injection, and all cases were treated with total hip arthroplasty.

On univariable analysis, only the predictors related to corticosteroid injections were associated with RDHD (Table IV). With the numbers available, none of the considered predictors were found to be significant on multivariable analysis. The risks of post-injection RDHD by injection quantity and dose are presented in Table V.

Between 2014 and 2018, the number of high-dose corticosteroid injections performed at our institution declined, as did the total number of corticosteroid injections performed.

Between 2015 and 2018, we also observed a decline in the number of RDHD cases (of any etiology) treated at our institution (Fig. 3). Over this time period, the number of THAs performed for conditions other than RDHD remained relatively constant (n = 215 in 2015 versus n = 217 in 2018).

Discussion

In the case-control portion of this study, we observed an association between intra-articular hip triamcinolone injection and RDHD (adjusted OR, 8.56; 95% CI 3.29 to 22.3; $p < 0.0001$). A dose-response relationship was observed, with the risk of post-injection RDHD increasing with the dose of triamcinolone administered as well as the number of injections received. In the retrospective cohort analysis, the rate of post-injection RDHD was found to be 5.4% (37 of 688). In a post hoc analysis, we also found that the occurrence of RDHD in our region declined as the number of hip corticosteroid injections (and especially high-dose injections) was reduced.

The Bradford-Hill criteria are a group of principles that are widely used in the public-health arena when evaluating for a causal relationship between an exposure and a disease in the observational setting[36]. With regard to corticosteroid injections and RDHD, several of the Bradford-Hill criteria are met, including strength of association, biological gradient, experiment, and biologic plausibility. Specifically, the association between hip corticosteroid injection and RDHD was strong, with an adjusted odds ratio of 8.56. There is evidence of a biological gradient (also termed dose-response curve) as the risk of RDHD increased with the number of injections as well as the dose. Removal of the exposure was also shown to alter the frequency of the outcome (experiment) as the rate of RDHD (regardless of cause) was found to decrease in our region as the number of corticosteroid injections (specifically high-dose injections) was reduced.

With regard to biologic plausibility, the potential for corticosteroids to injure articular cartilage is well established. In a systematic review, Wernecke et al. concluded that intra-articular corticosteroid had a dose-dependent injurious effect on cartilage in vitro as well as in vivo[37]. In the clinical setting, corticosteroid injections have been linked to an increased risk of osteoarthritic progression in the hip[38] and knee[39,40].

While the literature on post-injection RDHD is sparse, it is increasing. In the first known report of this phenomenon[31], a 50-year-old woman with mild osteoarthritis received a single intra-articular injection of 80-mg methylprednisolone. She

TABLE IV Regression Analysis of Factors Associated with Development of Post-Injection RDHD (Cohort Analysis)

Characteristic	RDHD Rate	Univariable Analysis		Multivariable Analysis	
		OR (95% CI)	P Value	OR (95% CI)	P Value
Age	—	1.01 (0.98-1.04)	0.67	1.00 (0.97-1.04)	0.80
Sex					
Male*	4.5% (14/314)	—	—	—	—
Female	6.1% (23/374)	1.40 (0.71-2.78)	0.33	1.30 (0.64-2.64)	0.46
Body mass index	—	1.01 (0.96-1.07)	0.60		
Smoking status					
Never*	4.8% (17/352)	—	—		
Former	6.0% (17/285)	1.25 (0.63-2.50)	0.53		
Current	5.9% (3/51)	1.20 (0.35-4.36)	0.75		
Baseline arthritis severity†					
No arthritis*	3.6% (2/56)	—	—	—	—
Mild	1.4% (4/278)	0.39 (0.07-2.21)	0.29	0.40 (0.07-2.26)	0.30
Moderate	7.2% (5/69)	2.11 (0.39-11.3)	0.38	2.22 (0.41-12.2)	0.36
Severe	9.1% (25/275)	2.69 (0.62-11.7)	0.19	2.15 (0.48-9.56)	0.31
Laterality					
Right*	5.9% (22/371)	—	—		
Left	4.7% (15/317)	0.79 (0.40-1.55)	0.49		
Corticosteroid injection dose					
Low-dose*	2.7% (8/295)	—	—	—	
High-dose	7.4% (29/393)	2.86 (1.29-6.35)	0.010	2.04 (0.87-4.76)	0.10
No. of corticosteroid injections					
1*	3.6% (16/440)	—	—	—	
≥2	8.5% (21/248)	2.45 (1.25-4.79)	0.009	1.88 (0.93-3.83)	0.08

*Reference category. †Data were missing for 10 hips (1.5%).

TABLE V Risk of RDHD Following Intra-Articular Hip Corticosteroid Injection, by Injection Quantity and Dose

No. of Injections	Injection Dose	
	Low-Dose	High-Dose
1	2.1% (5/231)	5.3% (11/209)
≥2	4.7% (3/64)	9.8% (18/184)

initially reported pain relief following the procedure, but shortly thereafter developed severe pain. Three months after the injection, radiographs demonstrated "a flat and sclerotic femoral head which was subluxed superolaterally," and the patient was treated with THA[31]. The second such report involved a healthy 79-year-old man with mild osteoarthritis on radiographs[32]. He received a single intra-articular injection of 2-mL triamcinolone, which provided symptomatic relief for 2 weeks. Five weeks after the injection, he presented to the emergency department, where radiographs demonstrated "destruction of joint space in the left hip joint and destruction of the left femoral head," and he was treated with THA[32]. Most recently, Thompson and Ensrud[33] described a 72-year-old woman with moderate arthritis on radiographs who received an injection of 80-mg triamcinolone. The patient initially improved but, 1 month after injection, presented with severe pain. Radiographs revealed "left femoral head collapse and severe joint space narrowing," and the patient was treated with THA[33]. It is interesting to note that all 3 of those patients had injections that would have been categorized as "high dose" in our investigation.

We are also aware of 2 retrospective case series on this topic. In a poster presented at the 2011 Joint Meeting of the Bone Research Society and the British Orthopaedic Research Society, Mackenzie et al. reported on 103 patients who underwent hip corticosteroid injection and documented a significantly greater risk of osteonecrosis in patients who received an injection as compared with controls[35]. More recently, Kompel et al. conducted a retrospective analysis of 459 intra-articular corticosteroid injections, including 307 performed in the hip[34]. The authors documented a 10% rate of adverse joint events, including 21 cases of RPOA type 1, 2 cases of RPOA type 2, 3 cases of osteonecrosis, and 4 cases of subchondral insufficiency fracture.

The results of our investigation should be interpreted in light of our study design. Our study benefits from the fact that it was performed among members of a geographically isolated HMO who received all of their imaging and care within the integrated health-care system. In addition, cases were adjudicated by a multidisciplinary committee of orthopaedic surgeons specializing in total hip arthroplasty as well as radiologists

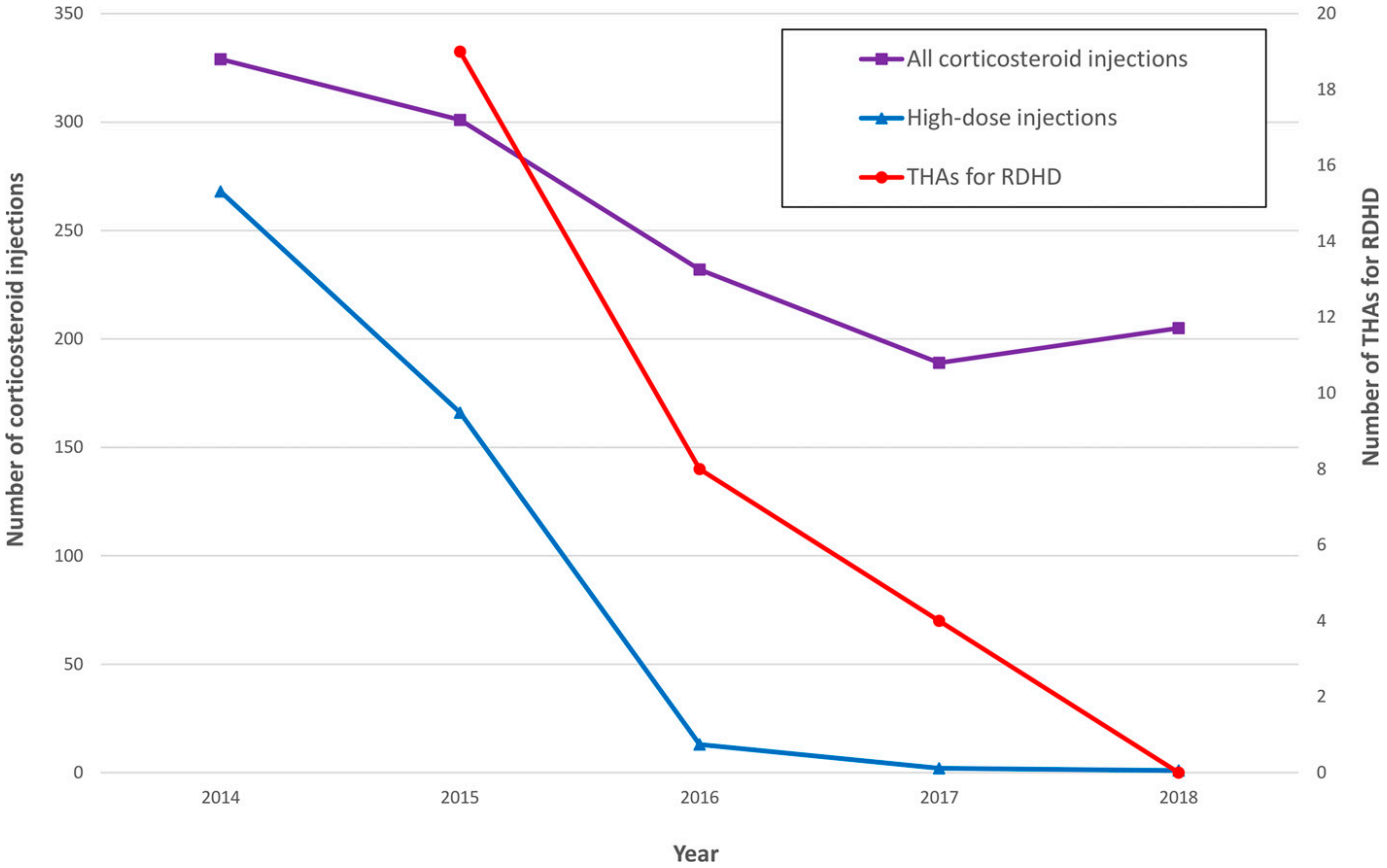

Fig. 3

Line graph showing the numbers of corticosteroid injections and total hip arthroplasty (THA) procedures for rapidly destructive hip disease (RDHD) by year.

specializing in musculoskeletal radiology. However, our investigation also had limitations. There were only 37 unique cases of post-injection RDHD; nevertheless, to our knowledge, this still represents the largest series of post-injection RDHD reported to date. As very few injections were performed with a corticosteroid other than triamcinolone, we are unable to compare the RDHD risk associated with this corticosteroid versus others. Given that our investigation was retrospective, it should be noted that our findings demonstrate association and not necessarily causation.

In summary, the present study provides evidence of an association between RDHD and intra-articular hip corticosteroid injection. While the risk of RDHD following a single, low-dose (40-mg) corticosteroid injection was relatively low (around 2%), the risk increased to 5% for patients who received either a single high-dose (80-mg) injection or multiple low-dose injections. For patients with both of these risk factors (multiple injections and high dosage), the risk of post-injection RDHD approached 10%. These findings provide information that can be used to guide clinical practice. At our institution, we have added a discussion of post-injection RDHD to the informed consent process at the time of hip corticosteroid injection. In addition, we no longer perform hip injections utilizing ≥80 mg of triamcinolone. ■

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Kanu Okike, MD, MPH[1]
Ryan K. King, BA[2]
Jason C. Merchant, MD[3]
Eugene A. Toney, MD[1]
Gregory Y. Lee, MD[1]
Hyo-Chun Yoon, MD, PhD[3]

[1]Department of Orthopaedic Surgery, Hawaii Permanente Medical Group, Honolulu, Hawaii

[2]University of Hawaii, Honolulu, Hawaii

[3]Department of Diagnostic Imaging, Hawaii Permanente Medical Group, Honolulu, Hawaii

Email for corresponding author: okike@post.harvard.edu

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