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Intra-articular corticosteroids and the risk of knee osteoarthritis progression: results from the Osteoarthritis Initiative

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SUMMARY

Objective: A recent randomized clinical trial reported that repeated intra-articular corticosteroids (IACs) were associated with a greater cartilage loss. This study aimed to examine the relation of IACs to knee radiographic osteoarthritis (ROA) progression in a real-world setting.
Design: A cohort that initiated IACs and a comparison cohort without IACs from participants with mild to moderate knee ROA in the Osteoarthritis Initiative (OAI) were assembled (from 0-month to 48-month). Two measures of knee ROA progression were assessed during the follow-up period: (1) an increase in Kellgren and Lawrence (KL) grade by $\geq$1 grade or having a knee replacement (i.e., KL grade worsening); and (2) a decrease in joint space width (JSW) by $\geq$0.7 mm or having a knee replacement (i.e., JSW worsening). The associations of IACs initiation using a propensity-score matched cohort study and continuous IACs using marginal structural models with the risk of knee ROA progression were examined.
Results: Among 684 propensity-score matched participants at baseline (148 IACs initiators, 536 comparators), 65 knees (21.7/100 person-years) in the IACs initiation cohort and 90 knees (7.1/100 person-years) in the comparison cohort experienced KL worsening. The hazard ratios (HRs) of KL worsening from IACs initiation and continuous IACs were 3.02 (95% confidence interval [CI], 2.19–4.16) and 4.67 (95% CI, 2.92–7.47), respectively. The corresponding HRs of JSW worsening were 2.93 (95% CI, 2.13–4.02) and 3.26 (95% CI, 1.78–5.96), respectively. All HRs for continuous use of IACs were further away from the null.
Conclusions: IACs, especially continuous IACs, may be associated with an increased risk of knee ROA progression.

Introduction

Osteoarthritis (OA) is the most common joint disorder among older adults[1]. Pain from OA is a key symptom in the decision to seek medical care and an antecedent to disability. To date few safe and effective treatments for OA are available, and the main goal of clinical management remains the control of pain and improvement of both function and quality of life with the avoidance of therapeutic toxicity[2].

Intra-articular corticosteroids (IACs) are a frequently-used treatment regimen for pain relief from symptomatic knee OA as it inhibits inflammation[3,4] and reduces prostaglandin synthesis[5,6].

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While meta-analyses have reported IACs may be beneficial in relieving pain, at least for a short period of time (up to 6 weeks after IACs)[7,8], recommendations of its use in management of knee OA varies. For example, the Osteoarthritis Research Society International (OARSI), the American College of Rheumatology (ACR), and the National Institute for Health and Care Excellence (NICE) recommended or conditionally recommended IACs for patients with knee OA[9–11]; however, the American Academy of Orthopaedic Surgeons (AAOS) did not reach a conclusion on its use for the management of knee OA[12].

While previous *in vivo* studies have reported a detrimental effect of IACs on cartilage[13–15], there is a paucity of data of the effect of IACs on joint structure changes among patients with knee OA. Results from two randomized controlled trials (RCTs) assessing effect of repeated IACs on risk of knee structure change are conflicting[16,17]. One trial conducted in the early 2000's reported that repeated IACs were not associated with change in joint space width (JSW) compared with intra-articular saline[16]; and another trial conducted recently showed that repeated IACs resulted in greater loss of cartilage volume, albeit the amount of cartilage loss was small and may not be clinically meaningful, compared with intra-articular saline[17]. These findings have led clinicians to question IACs' utility in the management of knee OA[18]. To address this knowledge gap, we examined the relation of IACs to knee radiographic osteoarthritis (ROA) progression using data collected from the Osteoarthritis Initiative (OAI).

Methods

Study population

The OAI is a multi-center longitudinal observational study of risk factors for both incident and progressive knee OA. A detailed description regarding the rationale and approach of the OAI can be found at https://data-archive.nimh.nih.gov/oai/about-oai. In the current analyses, we used data collected from the 0-, 12-, 24-, 36-, and 48-month visits where the assessments of knee radiographs for progressive cohorts are publicly available.

Assessment of IACs

At 0-month and each annual follow-up visit, participants were asked “During the past 6 months, have you had an injection of steroids (cortisone, corticosteroids) in either of your knees for treatment of your arthritis?” If they answered “yes”, participants were then queried about in which knee the injection was given. The visit when the participant reported initiation of IACs was deemed as the “index visit”.

Assessment of ROA progression endpoints

Knee ROA progression was assessed using two endpoints: (1) Kellgren and Lawrence (KL) grade worsening; and (2) JSW worsening. Specifically, bilateral knee radiographs were taken at 0-month and each annual follow-up visit. KL grade at the tibiofemoral joint was assessed at the central reading center. Among knees with KL grade 2 or 3 at baseline (i.e., the nearest visit prior to the “index visit”), we defined a knee as KL grade worsening if its KL grade at a follow-up visit had increased by $\geq$1 grade compared with that at baseline or the patient had received a knee replacement. As the vast majority of patients' tibiofemoral OA occur at the medial compartment, our primary outcome regarding joint space narrowing was medial tibiofemoral JSW assessed at a fixed location along the tibial plateaus (i.e., 0.250) using a semi-automated method[19]. Two expert readers with over 50 years of combined experience independently assessed the medial tibiofemoral JSW (intraclass correlation coefficient [ICC] = 0.98 for cross-sectional analysis; ICC = 0.94 for 3-year longitudinal analysis), blinded to clinical data[20]. We defined a knee as having JSW worsening if its value at a follow-up visit decreased by $\geq$0.7 mm from baseline[21] or the patient had knee replacement during the follow-up.

Selection of index knee

We used an index knee from each participant, and selection of the index knee for KL grade or JSW worsening in the current analysis is depicted in Fig. 1. Briefly, eligible participants consisted of those who had at least one knee with a KL grade of 2 or 3 and did not report IACs use at baseline[22]. For JSW worsening, knees were ineligible if they had definite lateral joint space narrowing >1 on an ordinal 0 (i.e., normal joint width) to 3 scale according to the OARSI grades[23,24] as including those with lateral joint space narrowing may incorporate knees that have pseudo-widening (a consequence of increasing lateral joint space narrowing), or minimal tibial plateau-rim distance $\geq$6.5 mm or missing[25,26], or tibial-plateau-rim distance >2 mm of the minimal distance of all visits[25,26] or baseline JSW <0.7 mm. If a subject had two eligible knees, the one with KL grade 3 was selected as the index knee; if the KL grade for both knees was equal, then the one with the higher Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) knee pain score was selected as the index knee; if the WOMAC pain score for both knees was equal, we randomly selected one as the index knee.

Assessment of covariates

Age, sex, race, education, history of knee injury (defined as knee injured badly enough to limit ability to walk for at least 2 days), Physical Activity Scale for Elderly (PASE), non-steroidal anti-inflammatory drugs (NSAIDs), WOMAC knee pain, Charlson Comorbidity Index (CCI), and widespread pain[27] were collected at baseline. Body mass index (BMI) was computed as weight (kg)/height (m)^2. In each annual follow-up visit, data were also collected on body weight, WOMAC knee pain, knee injury, NSAIDs use, PASE, and widespread pain.

Statistical analysis

For each 1-year time block, we calculated a propensity score for each knee with the initiation of IACs (i.e., a conditional probability of initiating IACs by accounting for a vector of observed covariates[28]) using logistic regression[29,30]. Variables included in the model consisted of age, sex, race, education, BMI, history of knee injury, PASE, NSAIDs use, WOMAC knee pain score, CCI, widespread pain, and KL grade (for KL worsening) or JSW value (for JSW worsening) assessed at the visit prior to initiation of IACs. Within each time block, for each knee that initiated IACs (i.e., knee in the IACs initiation cohort) we identified up to four propensity-score matched knees that did not receive IACs (i.e., knees in the comparison cohort), and assigned the no-IACs knees with the same “index visit” as their matched knees. The absolute allowable difference in propensity score among knees in each matched set was set to be <0.005. The balance of the covariates between the IAC initiation and comparison cohorts was assessed by standardized differences[31,32].

First, we took intention-to-treat approach to examine the relation of IACs initiation to the risk of KL (JSW) worsening, assuming participants who initiated IACs remained in that group until they had outcomes or were censored. We calculated the incidence rate for KL (or JSW) worsening and plotted a cumulative incidence curve of each of these outcomes for the IACs cohort and its comparison cohort, respectively. We used cause-specific Cox proportional

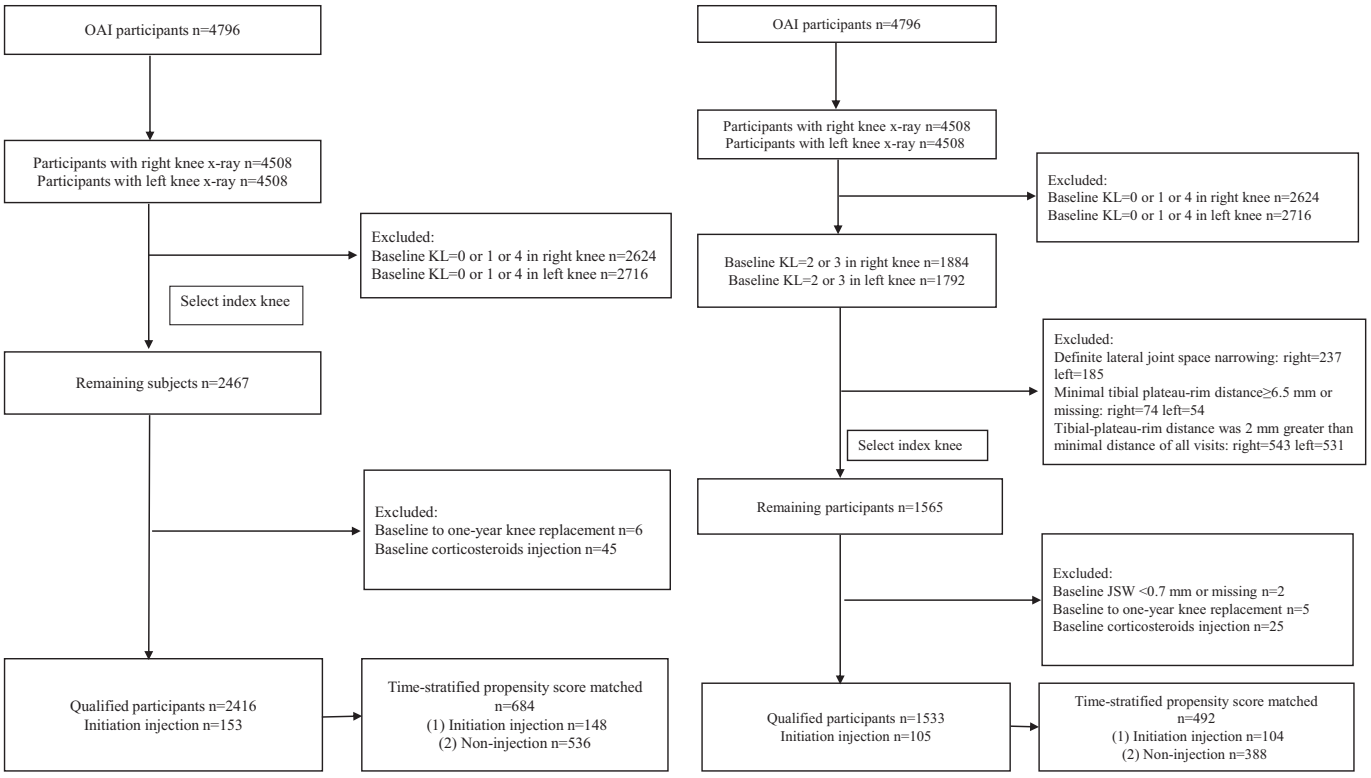


Fig. 1. Flow Chart of Participants' Selection Process for the Outcome of KL (Left) or JSW (Right) Worsening. OAI, Osteoarthritis Initiative; KL, Kellgren and Lawrence; JSW, joint space width; IACs, intra-articular corticosteroids. Each subject only contributed one knee for the current analysis. If a subject had two eligible knees, the one with KL grade 3 was selected as the index knee; if the KL grade for both knees was equal, then the one with the higher Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) knee pain score was selected as the index knee; if the WOMAC pain score for both knees was equal, we randomly selected one as the index knee.

hazards models to estimate the hazard ratio (HR) and its 95% confidence interval (CI) for the risk of KL (or JSW) worsening for IACs adjusting for competing event (i.e., death). We tested the proportional hazards assumption for each comparison cohort using the Kolmogorov supremum test[33]. If the proportional hazard assumption was violated, we conducted a weighted Cox regression to obtain a non-proportional HR[34]. Second, since participants may report IACs during some of the annual visits but not in others, to account for time-varying confounders, we performed a marginal structural model to assess the effect of continuous IACs (versus no-IACs) and the risk of KL (or JSW) worsening[35,36]. Specifically, we fitted pooled logistic models to obtain their predicted values for each person-year remaining off IACs and uncensored. We then used a SAS data step to calculate the 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 estimates the causal parameter of IACs and its robust standard error. Variables in the calculation of the propensity score were included in these models. The marginal structural models estimate the average adherence-adjusted HR of ROA progression for continuous IACs vs no-IACs during the study period[36].

Since patients with more severe knee OA are more likely to initiate and continuously receive IACs as well as are at a higher risk of ROA progression than those with less severe disease, we conducted sensitivity analyses to assess the potential impact of residual confounding. First, we applied asymmetric propensity-score trimming to exclude patients who were receiving IACs most contrary to their prediction, i.e., excluding knees with propensity scores <2.5% based on its distribution in IACs cohort and >97.5% based on its distribution in comparison cohort, respectively[37]. Second, since either propensity-score matched study design or marginal structural models may not account for unmeasured confounders, we performed quantitative sensitivity analyses to assess the minimum association that an unmeasured confounder(s) would need to have with both IACs and knee ROA progression conditional on the measured covariates in order to explain away an association observed in the current analyses[38]. Third, considering that some knees with replacement therapy may not experience KL grade (or JSW) worsening according to the criteria in the current analyses, we repeated these analyses by treating knee replacement as a competing event. Fourth, to minimize the confounding by indication we calculated the propensity score by additionally adding KL grade change (or JSW change) within 12 months before the index visit into logistic regression model. Finally, to minimize potential bias of reverse causality we performed a time-lag analysis by excluding participants with KL grade (or JSW) worsening that occurred within the same annual follow-up interval as that of IACs use.

All statistical analyses were performed by using SAS 9.4 (SAS Institute Inc., Cary, NC, USA), and a P value < 0.05 was considered being statistically significant. All tests were two-tailed.

Results

Among 2,416 knees (58.9% women, mean age: 62.6 years) eligible for the analysis for the KL grade progression, 153 initiated IACs during their follow-up visits. Of the 153, 148 knees were propensity-score matched to 536 knees that did not receive IACs (Fig. 1). Five knees were excluded from the analysis because no comparison knees could be matched according to propensity score.

The baseline characteristics of the IACs initiation cohort and comparison cohort are shown in Table I. All baseline covariates

Table I
Characteristics in propensity-score matched cohort study of intra-articular corticosteroids (IACs) for KL worsening

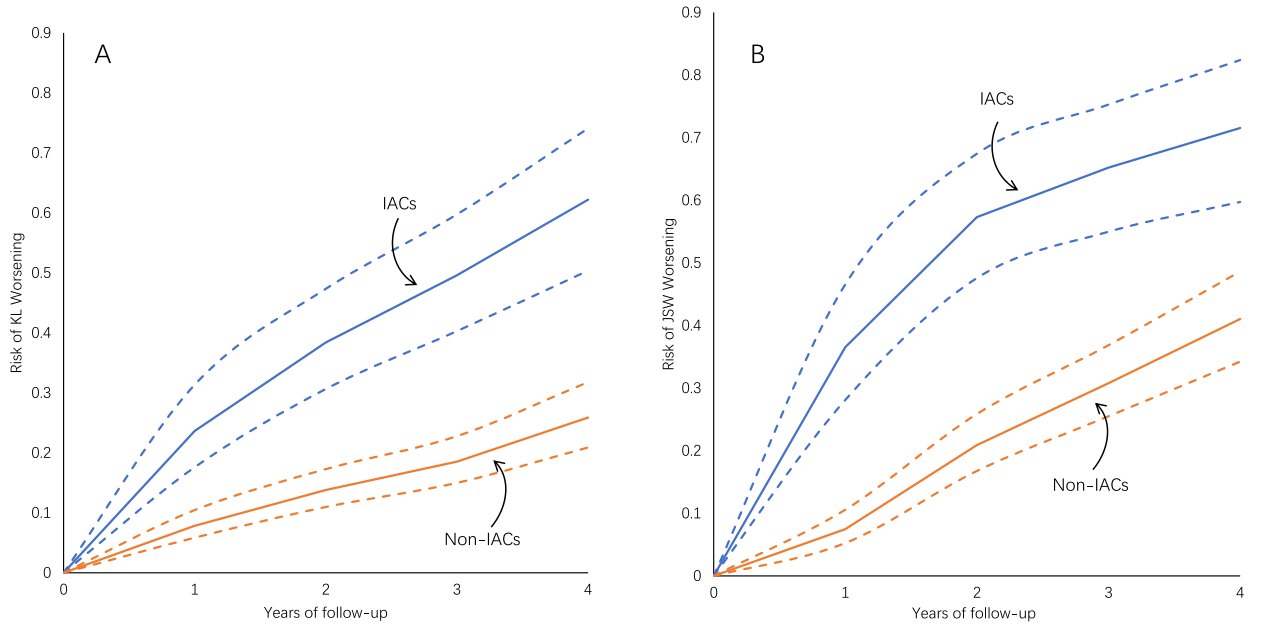
Characteristics	IACs cohort (n = 148)	Comparison cohort (n = 536)	Standardized difference
Sex (female, %)	64.2	66.8	0.055
Age (years)	64.4 ± 8.6	64.4 ± 9.1	0.003
BMI (kg/m^2)	30.3 ± 4.1	30.4 ± 5.0	0.025
Race (Whites, %)	76.4	75.4	0.023
Education (college or above, %)	83.1	78.9	0.107
Physical Activity Level (PASE)	146.0 ± 79.5	148.2 ± 80.3	0.027
Injury (yes, %)	36.5	39.7	0.067
WOMAC Knee Pain Score	4.5 ± 3.8	4.5 ± 4.2	0.001
NSAIDs Use (yes, %)	50.7	48.0	0.055
Baseline KL Grade (KL = 3, %)	52.7	53.9	0.024
Charlson Comorbidity Score	0.7 ± 1.0	0.7 ± 1.1	0.027
Widespread Pain (yes, %)	33.1	30.8	0.050

BMI, body mass index; PASE, Physical Activity Scale for Elderly; WOMAC, The Western Ontario and McMaster Universities Osteoarthritis Index; NSAIDs, non-steroidal anti-inflammatory drugs; KL, Kellgren and Lawrence; IACs, intra-articular corticosteroids.

were well-balanced between the two cohorts (i.e., standardized difference ≤0.1). During 300 person-years of follow-up, 65 knees in the IACs cohort experienced KL worsening (21.7/100 person-years), whereas 90 knees in the comparison cohort experienced KL worsening during 1,266 person-years of follow-up (7.1/100 person-years). The risk of KL worsening increased more rapidly among the knees in the IACs cohort than those in the comparison cohort (Fig. 2(A), $P < 0.001$). Compared with no-IACs, the HR of KL worsening for IACs was 3.02 (95% CI, 2.25–4.05) (Table II). The proportional hazard assumption was not violated ($P = 0.97$). The association did not change materially with propensity-score trimming (HR, 2.95; 95% CI, 2.18–3.99). A total of 62 knees (33 [22.3%] in IACs cohort, 29 [5.4%] in comparison cohort) experienced knee replacements during the follow-up. However, only one knee in IACs cohort had knee replacement during the follow-up period prior to KL worsening assessment. When knee replacement was treated as the competing event (as well as death), the HR of KL worsening for IACs was 2.54 (95% CI, 1.81–3.57).

Among 1,533 knees (60.9% women, mean age: 62.5 years) eligible for the analysis for the JSW worsening, 105 initiated IACs during their follow-up visits. Of them, 104 knees were propensity-score matched to 388 knees that did not receive IACs (Fig. 1). One knee was excluded from the analysis because no comparison knee could be identified according to propensity score matching criteria.

The baseline characteristics of the IACs cohort and its comparison cohort for JSW worsening were well-balanced (eTable 1 in the Supplement). The risk of JSW worsening was higher in the IACs cohort than that in the comparison cohort (Fig. 2(B), $P < 0.001$). Compared with no-IACs, the HR of JSW worsening for IACs was 2.92 (95% CI, 2.18–3.90) (Table II). The proportional hazard assumption was violated ($P < 0.05$). The non-proportional HR of JSW worsening for IACs was 2.77 (95% CI, 2.06–3.73). The HR obtained from propensity-score trimming did not change materially (HR, 2.66; 95% CI, 1.96–3.63). A total of 50 knees (32 [30.8%] in IACs cohort, 18 [4.6%] in comparison cohort) had knee replacements during the follow-up. Among them, seven knees had a joint replacement



No. Knees at Risk

IACs	148	88	44	20	15	104	55	27	11	9
Non-IACs	536	371	237	122	111	388	262	160	81	69

Fig. 2. A: Incidence of KL Worsening in Intra-Articular Corticosteroids Cohort and Comparison Cohort; B: Incidence of JSW Worsening in Intra-Articular Corticosteroids Cohort and Comparison Cohort. KL, Kellgren and Lawrence; JSW, joint space width; IACs, intra-articular corticosteroids.

Table II
Association between intra-articular corticosteroids (IACs) and risk of knee ROA progression

Knee ROA progression	IACs cohort		Comparison cohort		Hazard ratio† 95% CI	Continuous IACs, Hazard ratio 95% CI
	No. knees*	Incidence rate (1/100 PYs)	No. knees*	Incidence rate (1/100 PYs)		
KL Worsening	65 (148)	21.7	90 (536)	7.1	3.02 (2.25, 4.05)	4.67 (2.92, 7.47)
JSW Worsening	63 (104)	32.0	99 (388)	11.1	2.92 (2.19, 3.90)	3.26 (1.78, 5.96)

ROA, radiographic osteoarthritis; PYs, person-years; CI, confidence interval; KL, Kellgren and Lawrence; JSW, joint space width; IACs, intra-articular corticosteroids.
* Number of knees with radiographic osteoarthritis progression (total number of knees).
† Hazard ratios were adjusted for competing risk.

(five occurred in IACs cohort and two in comparison cohort) prior to JSW worsening assessment. The HR of JSW worsening attenuated slightly (HR, 2.36; 95% CI, 1.68–3.32) when knee replacement (as well as death) was treated as a competing event.

We used marginal structural models to assess the association between continuous IACs and risk of KL grade (or JSW) worsening adjusting for time-fixed and time-varying covariates. Among the 153 knees that initiated IACs use and were eligible for the KL grade worsening, 21 (13.7%) had answered "Yes" to IACs within past 6 months in two annual visits, seven (4.6%) in three visits, and two (1.3%) in four visits, respectively. Of 105 knees that initiated IACs and were eligible for JSW progression, the corresponding number (%) of knees were 15 (14.3%), six (5.7%), and one (1.0%), respectively. A total of 2,416 subjects for KL worsening and 1,533 subjects for JSW worsening were included in the marginal structural models, respectively. For KL worsening, the range of stabilized inverse-probability weights was between 0.1 and 7.7 in IACs group, and between 0.3 and 2.5 in the no-IACs group. For JSW worsening, the range of stabilized inverse-probability weights was between 0.1 and 4.3 in IACs group, and between 0.1 and 4.2 in the no-IACs group. The hazard ratios (HRs) of continuous IACs were 4.67 (95% CI, 2.92–7.47) for KL worsening and 3.26 (95% CI, 1.78–5.96) for JSW worsening, respectively. Treating knee replacement as a censored event attenuated the association of continuous IACs with either KL worsening (HR, 3.42; 95% CI, 2.07–5.63) or JSW worsening (HR, 2.69; 95% CI, 1.50–4.82).

Our sensitivity analysis indicated that a large residual confounding bias is required to completely explain away the observed association between IACs and the risk of knee ROA progression (eTable 2 and eFigure 1 in the Supplement). For example, a relative risk of an unmeasured confounder(s) with both IACs initiation and risk of KL worsening must be ≥5.49 beyond the confounders that had been adjusted for in the analysis to explain a HR of 3.02 between IACs initiation and the risk of KL worsening observed in the current study. Furthermore, results did not change materially when we additionally added KL grade change (or JSW change) prior to the index visit as a covariate into logistic regression model to calculate the propensity score (HR, 3.00, 95% CI, 1.92–4.68 for KL worsening; HR, 4.09, 95% CI, 2.68–6.23 for JSW worsening). Finally, when KL grade (or JSW) worsening that occurred within the same annual follow-up interval as that of IACs use were excluded from the analysis, initiation of IACs was still associated with an increased risk of KL grade (or JSW) worsening although the effect estimate for JSW worsening was attenuated (Table III).

Discussion

In this cohort study of knee ROA, we found that IACs may be associated with an increased risk of knee ROA progression, and the risk appeared larger with continuous IACs use. These results agree with the recent RCT, which found that repeated IACs led to larger cartilage volume loss, compared with intra-articular saline[17]. Our findings were independent of the effect of the major confounders, and remained stable in various sensitivity analyses, suggesting that the initiation of IACs and continuous IACs may have a detrimental effect on knee ROA progression.

To date, two RCTs have evaluated the effect of IACs on knee cartilage[16,17]. One study ($n = 34$ in each arm) reported no difference in mean JSW between IACs and intra-articular saline over 2 years, but the trial may have had insufficient power due to an incorrect parameter estimation when the study was planned[16]. Another trial ($n = 140$), that was adequately powered and utilized more sensitive imaging technique (i.e., magnetic resonance imaging [MRI]), demonstrated a detrimental effect of IACs on cartilage volume, although the amount of cartilage loss was small and may not be clinically meaningful[17]. However, in both trials, repeated IACs were administered to participants during the study period regardless of the flare of pain or inflammatory signs, which are the usual indications for such injections in clinical practice[39,40]. IACs have been used for pain relief among patients with knee OA for decades. Although IACs might be effective in pain relief for approximately 6 weeks in treating knee OA[7], our findings of the potential detrimental effects of IACs on knee ROA progression raise the concern of its long-term effectiveness on knee pain management, especially previous studies have shown that higher KL grade and decreased JSW were associated with knee pain[41,42]. This concern was supported by the findings that participants in the OAI who initiated IACs experienced worsening pain, stiffness, and physical functioning compared with nonusers over 2 years of follow-up[43], indicating that IACs did not appear to provide sustained symptom relief for patients with knee OA[7]. Nevertheless, since the findings were based on an observational study, we could not rule out the potential residual confounders.

Table III
Association between intra-articular corticosteroids (IACs) and risk of knee ROA progression occurring one year after IACs use

Knee ROA progression	IACs cohort		Comparison cohort		Hazard ratio† 95% CI
	No. knees*	Incidence rate (1/100 PYs)	No. knees*	Incidence rate (1/100 PYs)	
KL Worsening	30 (93)	12.2	53 (348)	5.5	2.29 (1.52, 3.46)
JSW Worsening	25 (56)	16.8	55 (200)	9.5	1.89 (1.18, 3.05)

ROA, radiographic osteoarthritis; PYs, person-years; CI, confidence interval; KL, Kellgren and Lawrence; JSW, joint space width; IACs, intra-articular corticosteroids.
* Number of knees with radiographic osteoarthritis progression (total number of knees).
† Hazard ratios were adjusted for competing risk.

Biological mechanisms linking corticosteroids to knee ROA progression are not well understood. Given the anti-inflammatory effect of corticosteroids, one would postulate that IACs may reduce the risk of knee ROA progression. However, evidence for inflammation as a predictor for knee OA progression is still inconclusive. Studies reported that MRI-detected synovitis was independently associated with incidence and progression of knee ROA[44,45]. Similarly, ultrasound-detected effusion was also a predictor of subsequent joint replacement among patients with knee OA[46]. In contrast, another study found that MRI-detected synovitis was not associated with cartilage loss in either tibiofemoral or patellofemoral compartment in knee OA[47]. Furthermore, two systematic reviews have suggested that systemic inflammation measures, such as C-reactive protein, were not associated with knee OA progression[48,49]. The present study, along with a recent RCT[17], reported IACs, especially continuous IACs, are associated with the risk of knee ROA progression. While IACs didn't prevent OA progression it does not preclude that chronic inflammation and synovitis may play a role in the pathogenesis of OA. These results are similar to the findings from previous *in vitro* and *in vivo* studies[13–15,50–56], suggesting that corticosteroids may induce chondrocyte apoptosis[55,56], decrease cell viability[50,54], suppress the expression of matrix proteins[52,53], or promote calcium pyrophosphate dihydrate crystals formation[51] that may accelerate cartilage degeneration.

The present study has several strengths. The OAI is designed to specifically assess the natural history of knee OA, including its risk factors and clinical management; thus, the findings from our study are likely to represent a real-world setting of clinical practice. Second, we selected patients who initiated IACs during the follow-up period; such a “new user” design should minimize potential selection bias on the study findings. Third, we used two different measurements to assess ROA progression, and the results are similar. Fourth, we performed several sensitivity analyses to assess potential residual confounding and reverse causality bias; and the results did not show a clinically meaningful change, indicating the robustness of our study findings. Finally, the consistency of our results with the recent RCT data[17] strengthens the validity of potential detrimental effect of IACs on cartilage.

Several limitations of our study deserve comment. First, information on IACs in the OAI was only assessed within 6 months before each annual visit, but not during the first 6 months between two annual visits, and the number of IACs was not queried. A participant who answered “yes” to IACs in only one visit does not mean he/she only received a single IACs during 12-month period. As a result, the observed HR of knee ROA progression for IACs may have overestimated the detrimental effect of a single IACs as knees categorized as having IACs in only one annual visit may actually have had multiple injections. Second, IACs in the OAI were assessed through a participant's self-report. It is possible that some participants may have mixed IACs with intra-articular hyaluronic acid or may not remember whether they have received IACs within the 6 months before follow-up visit. However, such recall bias, if occurred, would dilute the association between the continuous IACs and the risk of knee ROA progression. Third, our study comparing the risk of knee ROA progression between IACs with no-IACs was susceptible to confounding by indication. Although we used propensity-score matched design (the propensity score has an important balancing property that underlies its value for observational analysis and allows direct estimation of unconfounded risk ratios in cohort studies[57]) to address this issue, and our quantitative sensitivity analysis[38] indicated that the associations of potential residual confounder(s) with either IACs or risk of knee ROA progression must be strong (i.e., relative risk $\geq$5.0) to completely explain away the observed association, we still can not rule out bias from the residual confounding. Fourth, data on types and concentrations of IACs were not collected in the OAI; thus we were unable to examine the relation of a specific type of IACs and its dose to the risk of knee ROA progression. Finally, in our main analysis, knees that experienced KL grade (or JSW) worsening could have occurred during the same time interval as that of IACs use; thus, reverse causality bias could not be eliminated. However, when we excluded these cases from the analyses, there was still an association between IACs and risk of knee ROA progression.

Conclusions

IACs, especially continuous IACs, may be associated with an increased risk of knee ROA progression. However, such findings still warrant replication in other cohorts.

Contributors

GL and YZ are joint corresponding authors.

CZ, JW, GL and YZ had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. CZ, GL and YZ conceived the study. CZ, GL and YZ were responsible for conception of the study and drafted the manuscript. YZ and HKC were responsible for design of the study. JW, NEL, NL and YZ contributed to preparation and data analysis. NEL, DJH, HKC, TEM and HL contributed to revision of the manuscript. All the authors contributed to the interpretation of the data and critically reviewed the manuscript for publication. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Role of the funding source

The funding source had no role in the design or conduct of the study; collection, analysis, or interpretation of the data; or writing of the report.

Ethical approval

This study received approval from the medical ethical committee, and participants gave written informed consent.

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Supplementary data

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