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Debate: Intra-articular steroid injections for osteoarthritis – harmful or helpful?☆,☆☆

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Abstract

Intra-articular corticosteroids injections are a widely used treatment for pain from symptomatic osteoarthritis. Systematic reviews show that the treatment effect is modest compared with intra-articular saline (often considered as placebo) and lasts for 2–4 weeks on average. Potentially as a consequence of limited therapeutic duration, repeated injections are often given up to 4 injections annually. In this context of repeat injections, recent evidence has emerged that intra-articular corticosteroids might be associated with more MRI-assessed quantitative cartilage thickness loss than saline injections. Guidelines vary in the recommendation for use of intra-articular corticosteroids. Given the frequency with which intra-articular corticosteroids injections are used, the size and scale of the population with osteoarthritis, it is critical to fully understand the benefits and drawbacks of intra-articular corticosteroids injections. That is the focus of this debate article.

Keywords

Osteoarthritis; Intra-articular; Corticosteroids; Cartilage; MRI

Introduction

Intra-articular corticosteroids (IACS) injections are a widely used treatment for pain from symptomatic osteoarthritis (OA). Systematic reviews show that the treatment effect is modest compared with intraarticular saline (often considered as placebo), and lasts for 2–4 weeks on average [1]. Potentially as a consequence of limited therapeutic duration, repeated injections are often given up to 4 injections annually [2]. In this context of

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repeat injections, recent evidence has emerged that intra-articular corticosteroids might be associated with more MRI-assessed quantitative cartilage thickness loss than saline injections [3]. Guidelines vary in the recommendation for use of IA corticosteroids [4–6]. Given the frequency with which IACS injections are used, the size and scale of the population with osteoarthritis, it is critical to fully understand the benefits and drawbacks of IACS injections. That is the focus of this debate article that was a recorded debate (available on YouTube) [7] and a podcast recording [8].

In-support

Intra-articular corticosteroids (IACS) have been used for symptom relief in patients with OA for many years. In 1951 Hollander and colleagues showed the efficacy of IACS in patients with rheumatoid arthritis, OA, and other Rheumatic and Musculoskeletal Diseases (RMDs) [9]. They advocated the use, especially in those patients when only one or a few joints were affected. From the 1950s onwards, IACS injections became quite popular. Many case series showing efficacy were published. However, discussions and controversies about the application also arose with regard to their efficacy, the most efficacious corticosteroid derivative, the preferred injection technique, and risk of complications (albeit reported to be low) such as joint destruction after repeated IACS injections [10].

To understand the potential efficacy of IACS injections, interest arose in the underlying mechanisms of action of IACS injections in osteoarthritic joints. After binding of corticosteroids to their intra-cellular receptors, a variety of anti-inflammatory effects is set into motion. In the OA joint, low grade inflammation with synovitis often plays a role. Thus, it was hypothesized that IACS injections could be efficacious by their anti-inflammatory effect. This was also supported by their speed of onset and their effect on knee temperature and circumference, as seen in the clinical case series [9]. Studies in experimental rat models of OA showed a decrease in synovitis after IACS injections [11], and underscore the hypothesis.

The anti-inflammatory mechanism of action was supported by imaging studies in patients with knee OA that received an IACS injection. Keen and colleagues showed in a randomized controlled trial (RCT) the efficacy of 80 mg methylprednisolone (versus “no intervention”) on synovial thickness and effusion as assessed by ultrasonography after 1 week [12]. The anti-inflammatory effect of IACS was also found using Dynamic contrast-enhanced MRI in two observational studies by Wenham and O’Neill and colleagues [13,14]. Also, a difference in the decrease in synovial tissue and fluid volume between those who responded and did not respond according to the OMERACT/OARSI criteria could be shown ($p<0.01$). Those who relapsed with an increase in pain also had an observed increase in synovial tissue volume during follow-up ($p=0.05$). In those who did not relapse, this observation was not made [14]. These data further support inflammation as a target of treatment.

The efficacy of IACS injections has been shown on an individual level in case series, but what about efficacy on a group level in randomized placebo-controlled clinical trials? Although IACS injections are given in any osteoarthritic peripheral joint and also in the spine, most evidence is available for the knee and hip. In 2015 Juni and colleagues

published a Cochrane review on IACS injections for knee OA including 27 trials with 1767 participants, showing a beneficial effect on pain and function after one to six weeks, however they concluded that the benefits remained unsure because of the limited quality of the trials and the heterogeneity between the trials [1]. Since then, several placebo-controlled randomized trials with low risk of bias have been performed. Also, these trials show symptomatic benefit for IACS injections at the short term. Najm and colleagues performed a recent systematic review with meta-analyses in which RCTs were summarized comparing IACS injections with placebo or active comparators, demonstrating the short-term efficacy (within 6 weeks) of IACS injections [15]. A few studies that investigated multiple steroid injections at predefined time points for one year or longer did not show long term efficacy [16]. However, in clinical practice, this is quite unusual, since IACS injections are not given when not needed. These data on efficacy are in accordance with a network meta-analysis using a Bayesian random-effects model by Bannuru and colleagues showing an effect size for IACS injections of 0.32 (0.16 to 0.47) against intra-articular placebo, which is larger than acetaminophen and NSAIDs [17].

Five randomized placebo-controlled trials have been completed in patients with hip OA, of which 4 with total 238 patients were summarized in several systematic reviews with meta-analysis. Trial duration was maximum 26 weeks, with different assessment points over time. Bannuru et al. showed a significant effect on pain but not on function [4]. However, the quality of the studies was limited with heterogeneity between studies. The efficacy of IACS injections in knee and hip OA patients was supported by using individual patient data from the OA trial bank [18]. On short-term, up to 4 weeks, clear efficacy was seen around 18 mm on a 0 to 100 pain scale. On the mid-term, up to 3 months, efficacy was clearly diminished. No efficacy for up to 1 year was seen.

Not all patients experience the beneficial effects of IACS injections. The response rates reported were between 62 and 71 percent, but there is variability in response and duration of response between patients. Many studies and systematic reviews have been undertaken to identify potential predictors, such as inflammatory signs (i.e. effusion, synovitis, skin temperature, and synovial white blood cell count), clinical characteristics (i.e. baseline symptoms including pain and duration of symptoms, local tenderness), and demographic characteristics (i.e. age, sex, and BMI). Results have been inconsistent, and thus currently no personalized medicine is possible.

Expectedly, IACS injections not only have positive effects but also side effects, however their benefits outweigh their risks. In most studies, similar side effects are reported for IACS injections as for placebo. In the large systematic review by Juni and colleagues on knee OA no differences were depicted for patients experiencing any adverse events and serious adverse events between the groups [1]. A recent trial by Conaghan and colleagues investigated triamcinolone acetonide in immediate release and extended release form and reported details on its side effects: frequent reported adverse events were arthralgia, headache and back pain, but there was no difference between triamcinolone acetate and saline-solution placebo groups [19]. Recently attention has been given to side effects on cartilage loss, especially after repeat injections after 2 years. McAlindon and colleagues reported an increased rate of cartilage loss, but not cartilage denudation or bone marrow

lesions based on semiquantitative MRI analysis [3]. Raynauld and colleagues in a similar trial did not see an effect on joint space narrowing on radiographs [20]. Also, the systematic review by McCabe and colleagues on the use of IACS injections for hip OA did not indicate a difference between the intervention and placebo groups [21]. Further potential safety issues are well known, and taken care of by the precautions taken by clinicians. Mostly feared adverse event after IACS injection is septic arthritis. However, its incidence is very low [22]. Systemic side effects can occur, since the steroid will leak out of the joint cavity, which can result in an increase in blood glucose level in patients with diabetes mellitus, and can have an effect on the hypothalamic-pituitary-adrenal-axis, with a drop in cortisol.

In conclusion, given the beneficial effects of single IACS injections for short-term symptom relief and the benign risk profile, it comes as no surprise that most recommendations and guidelines recommend IACS injections for knee OA, and some for hip OA. Most recommendations consider IACS injections as an adjunct to core treatment, including education, exercise and weight management, for relief of moderate to severe pain.

In-Opposition

IACS injections for the purpose of pain relief in OA patients are a very commonly performed procedure on a daily basis. Anecdotally, patients report some pain relief, albeit typically short-term, after such injections, particularly in the hip and knee joints. Such observations were also supported by literature evidence [15,16]. It is important to recollect, however, that the cardinal rule in medicine is "*Primum non nocere*", i.e. "first, do no harm". The important clinical question that needs to be answered is "Is IACS injection providing actual benefits to the patients or is it doing more harm (adverse joint events) than good?"

If we take the example of knee joints, pain can be caused by OA and various pathologies such as stress reactions, stress fractures, subchondral insufficiency fractures, and posterior meniscal root tears, although there currently exists no published evidence of the strength of the relationship between pain and these specific pathologies. Moreover, the precise prevalence of these pathologies in the general population is unknown. All of these pathologies may not be apparent on knee X-rays, which might otherwise be interpreted as "knee OA", and clinicians will proceed to treat the patient's pain, assuming the pain is originating from the OA alone. This is problematic because IACS injection will not be an appropriate therapeutic choice if the pain was caused by pathologies other than OA.

There is a relative paucity of literature evidence in regard to prospective and large retrospective studies investigating potential articular findings, including increased risk for adverse joint events, after treatment with IACS injection. These joint events include subchondral insufficiency fractures, osteonecrosis, and rapidly progressive OA (RPOA) type I and II affecting the hip and knee joints [23] (the latter is also known as accelerated knee OA (AKOA) [24]). RPOA is characterized as a rapid cartilage loss/chondrolysis of unknown cause, which can progress to complete destruction of the articular surface and loss of joint integrity, leading to joint destruction. On X-rays, in type I RPOA, there is a rapid progression of joint space loss (i.e. cartilage loss) at a rate of >2 mm per year or >50% of joint space loss per year [25]. In RPOA type II, there is rapid articular destruction

with accelerated bone loss not typically seen in patients with OA. It is thought there are a few radiographically detectable pathologies such as subchondral insufficiency fractures, osteonecrosis, and large subchondral cysts, are associated with RPOA type II. Atrophic phenotype of OA may be a risk factor for RPOA type II in the hip joint [26]. RPOA type II is more often observed in elderly women or in patients who had prior history of trauma of the joint [27].

Subchondral insufficiency fractures are defined as a subchondral hypointense fracture line of varying thickness and extent on MRI. Early stages of subchondral insufficiency fractures are occult on X-ray and can only be recognized on MRI. Subchondral insufficiency fractures demonstrate marked surrounding bone marrow edema pattern that is more intense than would be expected for typical OA [28] (Fig. 1). Administering an IACS injection when there is a subchondral insufficiency fracture may result in a marked decrease in pain, and potentially result in increased weight bearing. As a result, the subchondral insufficiency fracture may progress to an osteochondral defect or frank articular joint collapse, eventually leading to worse pain compared to pre-injection status, although there exists no published evidence to support this assumption.

Osteonecrosis is associated with subchondral bone plate collapse in the knee or femoral head collapse in the hip, followed by development of secondary OA. Osteonecrosis is usually occult on X-ray at early stages and can only be readily recognized on MRI. It is potentially possible that radiographically occult femoral head avascular necrosis is present in what was presumed to be “hip OA”. Multiple published reports are present in the literature showing “hip OA” patients who developed destructive avascular necrosis of femoral heads after a single IACS injection [29–31]. If a patient already has appreciable femoral head avascular necrosis without collapse, one should consider a potential risk for developing collapse of the femoral head after IACS injection, which therefore should not be performed in such patients.

Available literature evidence regarding safety and efficacy of IACS injections is somewhat limited. However, there are several papers reporting adverse effects of IACS injections into the knee and hip joints. McAlindon et al. found that IACS injections resulted in greater cartilage volume loss than did placebo injections (−0.21 mm vs. −0.10 mm; between group difference, −0.11 mm; 95%CI, −0.20 to −0.03 mm) but no significant difference in knee pain at 2-year follow-up [3]. Zeng et al. showed that, among 684 participants of Osteoarthritis Initiative at baseline (148 IACS group, 536 control group), 65 knees (21.7/100 person-years) in the IACS group and 90 knees (7.1/100 person-years) in the control group experienced worsening radiographic OA based on the radiographic readings performed in the Osteoarthritis Initiative Cohort [32]. Simeone et al. reported that 44% of the 70 patients who received IACS injections to the hip showed radiographic progression of OA (based on Kellgren and Lawrence grading of radiographic OA) and 17% developed articular surface collapse [33]. More recently, Kompel et al. showed, based on a single institution study, there were 36 (8%) total adverse joint events out of 459 IACS injections to the hip and knee joints combined [34]. RPOA type I was found in 26 (6%) patients, (Fig. 2) RPOA type II and osteonecrosis were found in 3 (0.7%) and 3 (0.7%) patients, respectively, and 4 (0.9%) patients developed subchondral insufficiency fractures after IACS injection. Another

potential adverse effect of IACS as well as local anesthetic agents which are usually injected together is chondrolysis [16,17], demonstrated in both in-vitro [35] and in-vivo studies [36].

In conclusion, IACS injections should not be routinely performed for the purpose of pain relief in OA patients. Presently, there is no established recommendation or consensus regarding imaging, clinical, or laboratory markers to screen for OA-related imaging abnormalities before the IACS injection is performed. The exact causality and natural history of aforementioned adverse joint events remain indeterminate. To answer this question, large prospective studies (ideally double-blind randomized clinical trials) evaluating the natural history of rapidly progressive OA or joint destruction in OA and after IACS injections need to be performed.

In-Support Rebuttal

This rebuttal will focus on the frequency and likelihood of RPOA and joint destruction caused by IACS injections, which are recently brought forward as important side effect and reason to consider IACS injections as harmful [34]. In a recent observational study by Kompel and colleagues in which knee and hip OA patients received an IACS injection, RPOA and joint destruction on X-rays and MRI at follow-up were reported especially in the hips, with prevalence of up to 10% [34]. This is a high percentage in patients with OA, but is not supported by results from other studies. Maybe patient selection, co-morbidities, or comedication could have played a role and confounded the results.

Also, the important question is whether there is causality between the injection and the arthropathy at follow-up in this study [34]. Temporality is a criterium that supports causality. In this observational study authors described a patient who 11 months after an IACS injection developed a collapse of the medial femoral condyle, with signs of subchondral insufficiently fracture on MRI [34]. At baseline she did not have clear OA, but she did already have a subchondral insufficiency fracture. This example makes a causal relationship between the injection and joint destruction unsure.

In case-control studies by Simeone and Zeng, it was suggested that progression of OA and collapse are seen more in the cases receiving an IACS injection [32,33], however, as also clearly pointed out by Conaghan in a letter to the editor, these studies are difficult to interpret due to confounding issues, such as confounding by indication or residual confounding [37]. Randomized controlled trials, comparing IACS injections to various types of placebo, could be helpful when it is a frequent side effect. No differences were reported between the groups with regard to these types of joint events in the trials by McAlindon and colleagues and Raynauld and colleagues [3,20], where repeated IACS injections were administered and patients were monitored for 2 years. Even in all 104 patients receiving IACS injections no articular collapse was reported. So, causality remains unsure.

The frequency of these joint events has also been evaluated in the context of their natural occurrence. RPOA of the hip is frequently described in case series by many authors since 1950’s, for instance by Rosenberg and colleagues in 1992 [38] who pointed out clearly that was in patients without earlier steroids. Also, the prevalence of insufficiency fractures is

high, nearly 3%, as shown recently in the TeMPO trial, in participants with knee pain with a presumed meniscal tear [39]. Finally, Hochberg and colleagues showed the high frequency of joint destruction and RPOA in patients on NSAIDs of 1.5% [40]. Thus, these joint events seem to be regularly taking place, regardless of the use of IACS injections.

In conclusion, given the efficacy data, and the known side effects that can be taken care of, IACS injections can be helpful for short-term symptom relief, and can be recommended in the management of knee and hip OA, as is done by many recommendations.

In-opposition rebuttal

There are three points to consider in the rebuttal. Are IACS injections efficacious? Are IACS injections safe? Is X-ray enough to understand the origin of joint pain?

First, IACS injection's efficacy seems to be debatable. It does appear to provide some short term pain relief, but there is no long term effects and mechanism of pain alleviation by IACS injections is not well understood [4]. IACS injections can suppress the inflammation but does not inhibit the underlying trigger of synovial activation, i.e. structural joint damage such as cartilage, meniscus, joint bodies, etc. Published recommendations and literature evidence also seem to provide different opinions. European League Against Rheumatism (EULAR) recommendation published in 2021 [41] includes statements about the use of IACS injection for knee osteoarthritis: "Intra-articular injection of long acting glucocorticoids is indicated for acute exacerbation of knee pain, especially if accompanied by effusion.", but for acute or recent onset swelling of the knee: "Intra-articular steroids should not be administered unless an appropriate diagnosis has been made and contraindications have been ruled out." Based on the recent meta-analysis of 15 published reports, Najm et al. found IACS injection showed a limited effect on reducing joint pain up to 6 weeks of injection, and no such benefit was observed after 6 weeks and at 24 weeks follow-up [14].

Second, safety of IACS injection does not seem so reassuring. Several studies have documented adverse events observed after IACS injections, including those secondary to injection procedure itself such as post-injection swelling, pain, and erythema [14], and those thought to be secondary to the adverse effect of IACS injections including subchondral insufficiency fractures, (Fig. 3) osteonecrosis, and RPOAs (which are all described in the earlier section of this Debate paper). Ideally, a randomized double-blind clinical trial should be performed to understand pathophysiology and natural history of these adverse joint events.

Third, X-ray is not sufficient as an imaging modality to determine whether IACS injection is indicated or not. On X-ray, all we can see is osteophytes and joint spaces (which is a surrogate for cartilage loss and meniscal extrusion), which may not be a direct cause of pain. IACS injection acts to suppress active synovitis, but synovium cannot be visualized on X-ray. The current imaging modality of choice for assessing active synovitis of a joint is color Doppler ultrasound imaging. When X-ray shows the painful hip or knee joint to be 'normal',

IACS injection should not be performed because there are potentially radiographically occult pathology, such as osteonecrosis, that may be exacerbated by IACS injection [42].

In conclusion, IACS injection has not clearly demonstrated long-term efficacy for treating joint pains in knee or hip OA. IACS injection is not totally safe, given the documented adverse joint events in the literature. Pre-injection imaging may help screening patients, but X-ray does not serve the purpose and additional imaging, i.e. MRI, should be performed. Of note, ultrasound is not good enough because it cannot show deep-seated joint structures very well such as menisci, and it cannot evaluate cartilage. IACS injection should not be performed on patients who are without evidence of active inflammation or without radiographic evidence of OA.

Declaration of Competing Interest

Ali Guermazi: Received consulting fees from Pfizer, MerckSerono, TissueGene, AstraZeneca, Novartis, Regeneron. Stockholder of Boston Imaging Core Lab, LLC.

David Hunter: Received consulting fees from Pfizer, Lilly, TLCBio, Novartis, TissueGene, Biobone.

Margreet Kloppenburg: Received Grants from IMI-APPROACH and Dutch Arthritis Society. Received royalties from Wolters Kluwer and Springer Verlag. Received consulting fees from Pfizer, Kiniksa, Flexion, Galapagos, CHDR, Novartis, UCB. Received payment or honoraria from Galapagos and Jansen. Member of OARSI board, EULAR council, and the President of Dutch Society for Rheumatology.

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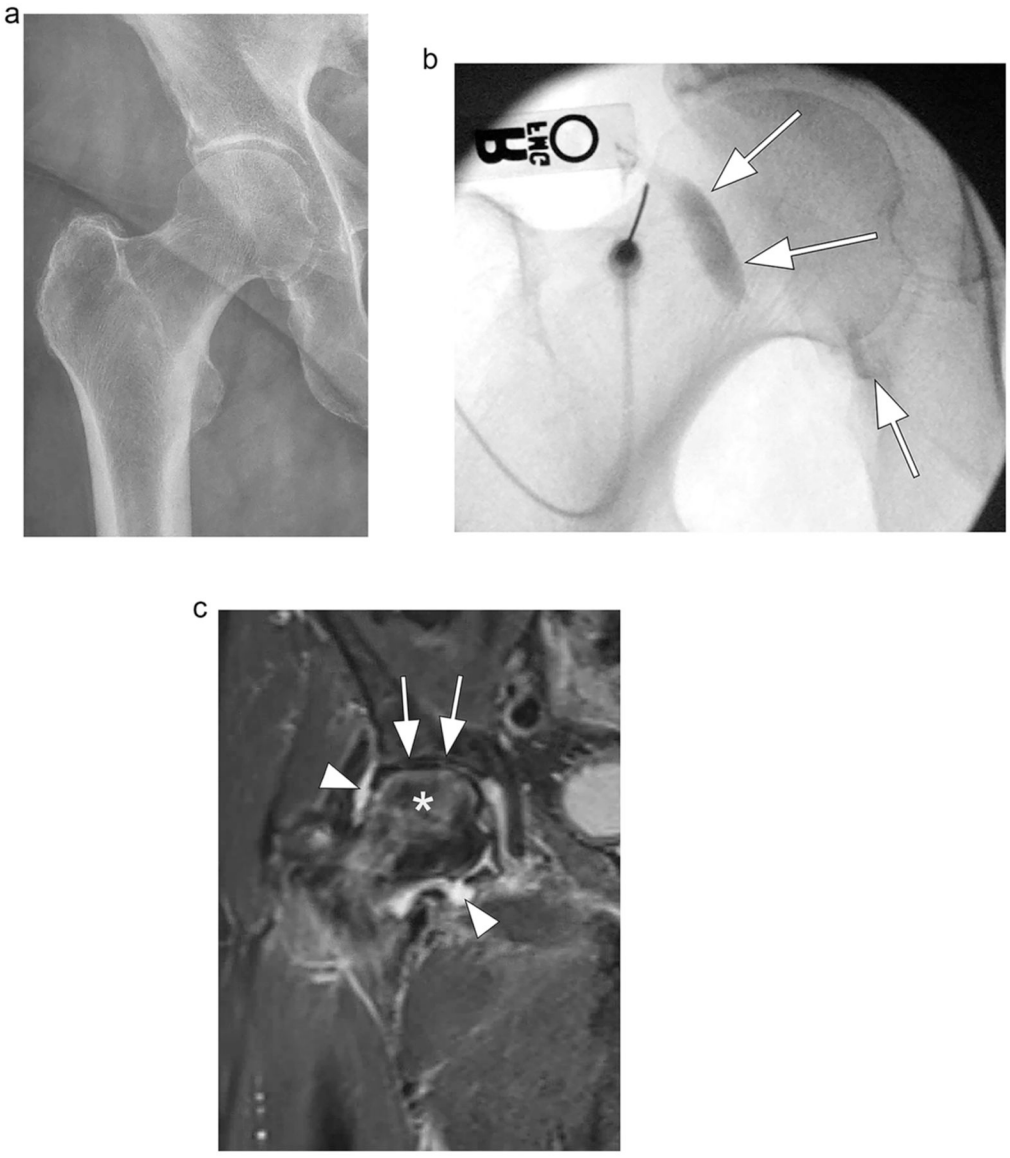

Fig. 1.

72-year-old female with right hip pain for the last 3 months. A. Anteroposterior radiograph of the right hip shows a normal hip joint morphology with no definite joint space narrowing or osteophyte. B. The patient underwent a fluoroscopy-guided injection of intraarticular corticosteroid as demonstrated by the intraarticular distribution of the contrast medium, 1 week later (arrows). C. Coronal proton density-weighted fat-suppressed MRI shows diffuse full thickness cartilage loss at the superior portion of the joint with mild deformity of the cortical contours (arrows). In addition, there is a subchondral linear hypointensity at the femoral head with diffuse accompanying bone marrow edema (asterisk) consistent with subchondral insufficiency fracture (SIF). Synovitis and joint effusion (arrowheads) are commonly observed in conjunction with SIF.

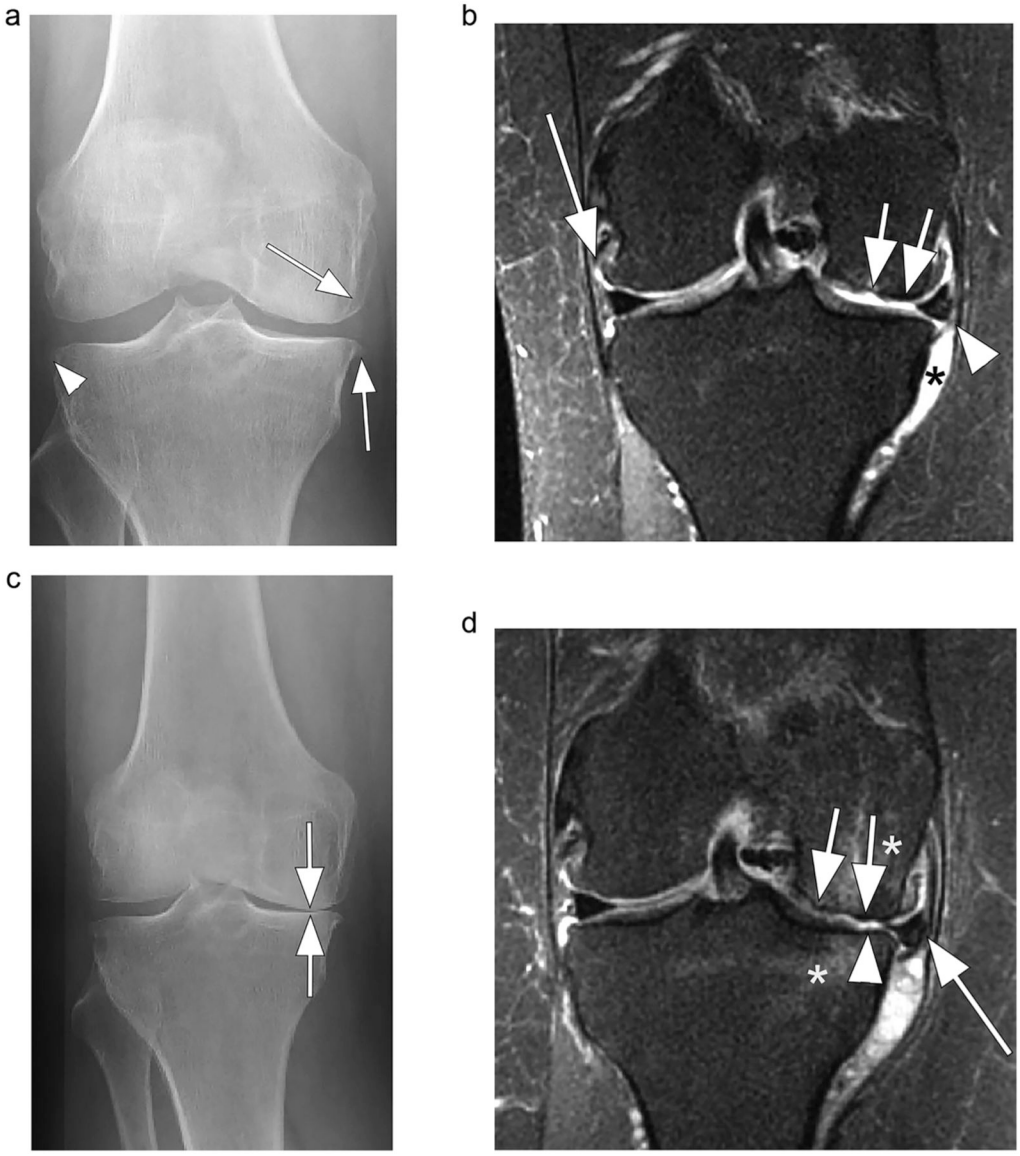

Fig. 2.

68-year-old male with right knee pain for the last 6 months. A. Anteroposterior radiograph of the right knee shows definite marginal osteophytes at the medial femur and tibia (arrows) and an equivocal osteophyte at the lateral tibia (arrowhead). There is mild joint space narrowing at the medial tibiofemoral joint. B. Corresponding coronal proton density-weighted fat-suppressed MRI shows moderate cartilage loss at the medial femoral condyle (short arrows) and moderate medial meniscus extrusion (arrowhead). In addition, there is bursitis of the medial collateral ligament bursa (asterisk). In addition to the radiograph MRI depicts an osteophyte at the lateral femur (long arrow). C. Four month after an intraarticular corticosteroid injection, anteroposterior radiograph shows marked narrowing of the medial tibiofemoral joint with bone-on-bone appearance (arrows) confirming a diagnosis of rapid progressive osteoarthritis (RPOA) type 1. D. Corresponding coronal proton density-weighted fat-suppressed MRI shows progression of medial femoral cartilage loss (short

arrows) and medial meniscal extrusion (long arrow). Incident cartilage loss is seen at the medial tibia (arrowhead). New subchondral bone marrow lesions are seen at the medial femur and tibia (asterisks).

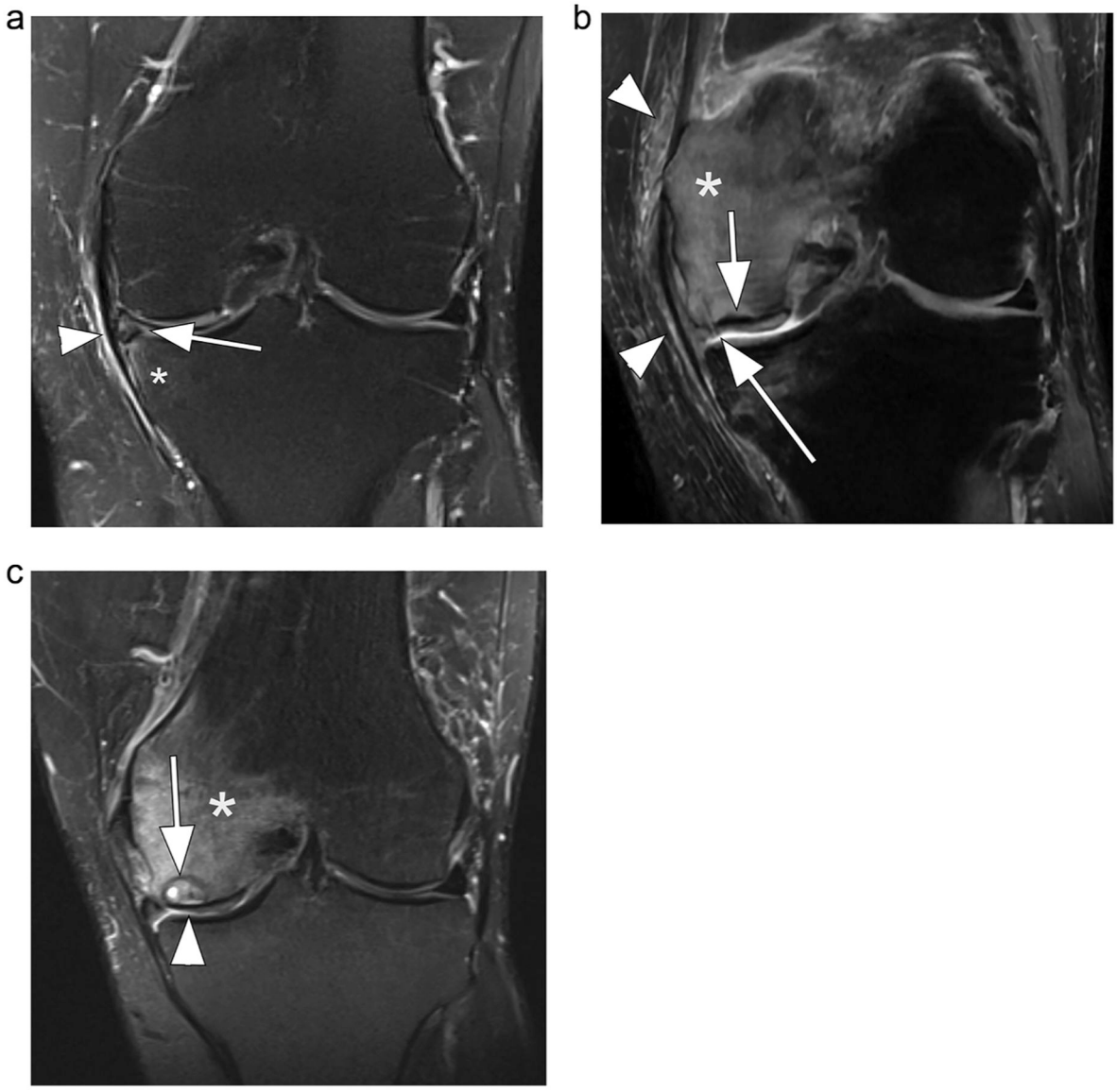

Fig. 3.

42-year-old male with partial meniscectomy 3 years previously and continuous pain. A. Coronal intermediate-weighted fat-suppressed MRI of the left knee shows new tear of the remaining medial meniscal body (arrow with adjacent subchondral bone marrow edema of the medial tibia (asterisk) and inflammation around the medial collateral ligament (arrowhead). No cartilage loss is seen. B. Five months after an intraarticular corticosteroid injection, coronal intermediate-weighted fat-suppressed MRI of the same knee shows a subchondral hypointense line at the medial femoral condyle (short arrow) with diffuse accompanying bone marrow edema (asterisk) consistent with a diagnosis of subchondral insufficiency fracture (SIF). There is increasing substance loss of the free edge of the meniscal body reflecting maceration (long arrow). In addition, there is marked soft tissue inflammation along the medial joint line commonly seen in conjunction with SIF (arrowheads). Mild deformity of the of the articular surface is observed in addition. C. Three

months later, coronal intermediate-weighted fat-suppressed MRI of the same knee shows cystic appearance of the SIF (arrow) with still large bone marrow edema (asterisk) and medial femoral cartilage loss (arrowhead).