



## Brief Report

## Response to intra-articular cortisone injections in knee osteoarthritis patients with and without effusion on ultrasound: A pilot study



Lindsey A. MacFarlane<sup>a,b,c,\*</sup>, Hanna Mass<sup>a</sup>, Jamie E. Collins<sup>a,c,e</sup>, Elena Losina<sup>a,c,d</sup>, Jeffrey N. Katz<sup>a,b,c,d,e</sup>, Antonia F. Chen<sup>c,e</sup>

<sup>a</sup> Orthopedic and Arthritis Center for Outcomes Research, Department of Orthopedic Surgery, Brigham and Women's Hospital, Boston, MA, USA

<sup>b</sup> Division of Rheumatology, Inflammation and Immunity, Brigham and Women's Hospital, Boston, MA, USA

<sup>c</sup> Harvard Medical School, Boston, MA, USA

<sup>d</sup> Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, MA, USA

<sup>e</sup> Department of Orthopedic Surgery, Brigham and Women's Hospital, Boston, MA, USA

## ARTICLE INFO

Handling Editor: H Madry

## Keywords:

Ultrasound

Effusion

Intra-articular corticosteroids

## ABSTRACT

**Objective:** Inflammation, manifesting as effusion and synovitis, is thought to contribute to pain in knee osteoarthritis (OA). We conducted a pilot study to investigate recruitment feasibility and assess whether effusion on ultrasound of the knee was associated with greater reduction in knee pain after corticosteroid injection.

**Methods:** A pilot study was conducted from 2020 to 2021 including patients  $\geq 40$  years with knee OA undergoing clinically indicated corticosteroid injections. At baseline, participants completed the Knee Injury and Osteoarthritis Outcome Score (KOOS) Pain subscale and had an ultrasound of the injected knee(s) to assess for effusion, defined as anechoic material in the suprapatellar recess. KOOS Pain was re-assessed two weeks following injection. We used mixed linear models to evaluate the change in KOOS Pain scores for knees with and without effusion to determine estimates of the magnitude of association.

**Results:** We recruited 10 participants who contributed 16 knees from 4 clinical sessions. The mean age was 68 years (standard deviation [SD] 13) and 90% were female. Six knees had effusion. At baseline, knees without effusion had greater pain (mean KOOS Pain 44, SD 19) compared to those with effusion (mean KOOS Pain 51, SD 15). Knees without effusion had a 6 point (95% CI -16, 28) greater improvement in KOOS Pain 2-weeks post injection compared to those with effusion.

**Conclusion:** This pilot study demonstrated clinic-based recruitment was feasible. We did not observe clinically important or statistically significant differences in pain relief post corticosteroid injection between knee OA patients with or without effusion.

## 1. Background

Symptomatic knee osteoarthritis (OA) is a common cause of pain and disability [1]. While OA has traditionally been regarded as a 'degenerative' disease, there is increasing interest in the role of inflammation, which may manifest as intra-articular effusion and synovitis. Inflammation has been associated with pain and progression in knee OA and is regarded as a distinct OA phenotype [1–3]. Management of OA is directed at relief of pain and pain-related functional limitations. Anti-inflammatory treatments, including oral non-steroidal anti-inflammatory drugs and intra-articular glucocorticoids, have long been

mainstays of therapy. Despite frequent clinical use, research shows variable efficacy of intra-articular steroids in relieving pain [4–6].

Patients with 'inflammatory OA,' defined by effusion-synovitis, may represent a subgroup more likely to respond to the potent anti-inflammatory properties of intra-articular glucocorticoid injections [6,7]. The ability to identify this group at the bedside could help tailor OA treatment to likelihood of benefit. Indicators of inflammation including knee effusion on exam, synovial fluid white blood cell count, and magnetic resonance imaging (MRI) evidence of effusion-synovitis have been associated with favorable response to intra-articular glucocorticoids [6–8]. Our aim is to investigate whether patients with knee OA and effusion have

\* Corresponding author. Orthopedic and Arthritis Center for Outcomes Research, Department of Orthopedic Surgery, Brigham and Women's Hospital, 60 Fenwood Road, Boston, MA 02115, USA.

E-mail address: [lmacfarlane@bwh.harvard.edu](mailto:lmacfarlane@bwh.harvard.edu) (L.A. MacFarlane).

<https://doi.org/10.1016/j.ocarto.2023.100361>

Received 18 January 2023; Accepted 6 April 2023

2665-9131/© 2023 The Author(s). Published by Elsevier Ltd on behalf of Osteoarthritis Research Society International (OARSI). This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

greater pain relief after corticosteroid injection compared to those without effusion. We used ultrasound to identify effusion as it is an inexpensive bedside procedure that has been used in previous studies [9,10]. We performed a pilot and feasibility study to 1) establish the feasibility of enrolling subjects from clinical practices and performing bedside ultrasound, and 2) obtain a first order estimate of the magnitude of association. We hypothesized that participants with knee effusion will have greater pain at baseline and greater pain relief post-injection compared to participants without effusion.

## 2. Methods

### 2.1. Study population

We performed a prospective pilot study from 2021 to 2022 of patients undergoing clinically indicated intra-articular glucocorticoid injections for symptomatic knee OA from a single site (The Brigham and Women's Hospital Arthritis Center). The participating orthopedic surgeon (AC) typically sees 20–30 patients per session at 15-min intervals. We planned on enrolling 10 patients to assess feasibility of clinic-based recruitment and gauge patient interest. Eligible patients were  $\geq 40$  years old and deemed by their orthopedic surgeon to have symptomatic knee OA. Exclusion criteria included inflammatory arthritis (i.e. rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, lupus), recent knee trauma or surgery, pregnancy and dementia. The orthopedic surgeon would alert the recruiting physician to patients who had an injection and were interested in learning about the study. Potential participants were then approached after their orthopedic visit and clinically indicated knee injection. Knee injections were performed from the anterolateral or anteromedial portals, and 4 cc of 0.25% ropivacaine along with 40 mg of triamcinolone were administered. None of the participants had knee aspiration. All participants provided informed consent. The Mass General Brigham Human Research Committee approved this study.

### 2.2. Baseline assessment

Enrolled participants completed a baseline questionnaire which included demographic information and The Knee Injury and Osteoarthritis Outcome Score (KOOS) Pain subscale to assess pain (0–100, 100 least pain) [11]. We defined the index knee as the knee injected; if bilateral knees were injected, we obtained KOOS Pain responses and ultrasound on both knees. Knee OA severity was measured using the Kellgren–Lawrence (KL) score (0–4, 4 end-stage) if weight bearing films were available for review within 2 years of the clinical visit [12].

### 2.3. Ultrasound assessment

All participants underwent musculoskeletal ultrasound of the index knee(s) for research purposes. Ultrasound was performed by a rheumatologist (LAM) using a GE NextGen LOGIQ e machine (Chicago, IL) and a 4–12 MHz transducer. Participants were supine and the knee was flexed at 30°. The probe was placed longitudinally over the suprapatellar recess (perpendicular to the femur and superior to the patella). Ultrasound settings were held constant with only depth and focus adjusted to capture the area of interest. Effusion was measured using calipers as the maximal depth in millimeters of anechoic material observed in the suprapatellar recess [13,14]. Hypochoic synovial lining tissue was not included in the effusion measurement [14]. Based on prior publications, ultrasound identified effusion was dichotomized and regarded as present if the effusion measured  $\geq 4$  mm in the longitudinal axis (perpendicular to the femur) [13].

### 2.4. Follow-up assessment

Two-weeks post intra-articular injection, patients were contacted for a follow-up questionnaire including KOOS Pain (0–100, 100 least pain)

on each injected knee and patient-reported symptom improvement and satisfaction. Participants reported knee symptoms as 1) large improvement; 2) moderate improvement; 3) slight improvement; 4) no improvement; and 5) worsened. Satisfaction was ascertained as 1) very satisfied; 2) somewhat satisfied; 3) somewhat dissatisfied; and 4) very dissatisfied. The primary outcome was the change in KOOS Pain from baseline to 2-week follow-up.

### 2.5. Statistical analysis

We first examined the correlation of continuous depth of effusion in mm on ultrasound to change in KOOS Pain from baseline to follow-up. We assessed the association between change in KOOS Pain and binary effusion (dichotomized at 4 mm) using mixed linear models to account for some participants contributing bilateral knees. We adjusted for baseline KOOS Pain. Analyses were performed using SAS 9.4 statistical software (SAS Institute Inc., Cary, NC).

## 3. Results

We recruited 10 participants contributing 16 knees from 4 orthopedic clinic sessions (average 2.5 participants/clinic) and performed ultrasound and questionnaires in a research room without disrupting clinical flow. Ultrasound was performed after the clinical visit and after the injection so as not to interfere with clinical care or decision making. Of the patients approached, one was excluded for not having knee OA and one was excluded for inflammatory arthritis. All included participants completed the baseline assessment. Nine (90%) completed the follow-up questionnaire. One participant (who received unilateral injection) could not be reached for follow-up questionnaire, leaving 15 knees for full analysis. The mean age was 68 years (standard deviation [SD] 13), mean body mass index (BMI) 28 kg/m<sup>2</sup> (SD 7), 9 (90%) were female, 1 (10%) was Black, and 9 (90%) were White. Nine participants had standing bilateral knee X-rays for review. Eighty-six percent of knees with radiograph had moderate to severe OA (KL 3 and 4) (Table 1). Five participants reported having prior cortisone injections in the knee.

Mean baseline KOOS Pain was 47 (SD 18) and mean change in KOOS Pain two-weeks post corticosteroid injection was 27 (SD 23, range –5 to 72). The mean effusion depth in mm was 4.1 (SD 4.2). Six knees in 5 participants were categorized as having an effusion ( $\geq 4$  mm) and 10 knees in 6 participants were categorized as no effusion. In knees without effusion, participants reported worse baseline pain (mean KOOS Pain 44, SD 19) than those with effusion (mean KOOS Pain 51, SD 15). Knees without effusion also had greater pain improvement post corticosteroid injection with a mean change in KOOS Pain of 32 (SD 27) versus 20 (SD

**Table 1**  
Baseline characteristics.

	Total cohort N = 10	With effusion n = 5 <sup>a</sup>	Without effusion n = 6 <sup>a</sup>
Age (years), mean (SD)	68 (13)	65 (7)	69 (16)
BMI (kg/m <sup>2</sup> ), mean (SD)	28 (7)	26 (6)	29 (8)
Female, n (%)	9 (90)	4 (80)	6 (100)
Race, n (%)			
Black	1 (10%)	0 (0)	1 (17)
White	9 (90%)	5 (100)	5 (83)
	N = 16	N = 6	N = 10
KL grade, n (%)			
0/1	0	0	0
2	2 (13)	1 (17)	1 (10)
3	3 (19)	1 (17)	2 (20)
4	9 (56)	3 (50)	6 (60)
Missing	2 (13)	1 (17)	1 (10)
KOOS pain, mean (SD)	47 (18)	51 (15)	44 (19)

BMI = body mass index, KL = Kellgren–Lawrence, KOOS = knee injury and osteoarthritis outcome score.

<sup>a</sup> One participant had one knee with effusion and one knee without effusion.

12) in those with effusion. Individual changes in pain for each knee is shown in Fig. 1. Spearman correlation between continuous effusion depth and change in KOOS Pain was weak ( $r = -0.07$  95% CI  $-0.6, 0.5$ ,  $p = 0.80$ ). After adjusting for baseline KOOS Pain in mixed linear models, the least square means for change in KOOS Pain were 32 (95% CI 14, 49) for knees without effusion and 26 (95% CI 8, 44) for those with effusion with a difference of 6 (95% CI  $-16, 28$ ). Of the 9 participants with complete data, 7 reported large improvement post-injection and 2 reported slight improvement. Accordingly, 7 were very satisfied with the procedure and 2 were somewhat satisfied.

#### 4. Discussion

We demonstrated that clinic-based recruitment that included bedside ultrasound and questionnaires was feasible in the context of a busy clinical practice. The study protocol did not disrupt clinic flow and the orthopedic surgeon and staff were not burdened by study recruitment. Patients expressed interest in the study and all enrolled were able to complete the baseline assessment. Participant follow-up was strong with 90% completing post-injection questionnaires.

We anticipated that the presence of effusion on knee ultrasound would be associated with a greater reduction in pain post corticosteroid injection. However, the difference in change in pain between those with and without effusion was neither clinically important nor statistically significant. All subjects, regardless of presence of effusion, reported a substantial decrease in pain (mean reduction of 27, SD of 23) and high satisfaction. A larger cohort will be needed to fully address the hypothesis with adequate precision.

Several other studies investigating whether inflammatory features predict response to corticosteroid injections have reported conflicting results [6,7,9,10]. In one study, clinical evidence of joint effusion on

examination and aspiration of synovial fluid was associated with greater improvement in pain after corticosteroid injection [6]. A small open label study also found an association between higher synovial fluid white blood cell counts and greater reduction in pain post corticosteroid injection [7]. However, Pendleton et al. found that while 67% of patients had at least a 20% reduction in pain at 1 week, neither effusion nor synovitis on knee ultrasound was a predictor of response to corticosteroid injections [10]. This is supported by Bevers et al. who also found that ultrasound evidence of synovial hypertrophy and effusion did not predict 'responders', defined as a numerical rating scale score  $\leq 4$  at 4-weeks post injection [9].

In this pilot study, patients without effusion had greater baseline and change in pain. Interestingly, a prior study has also noted that patients without inflammatory features (synovial hypertrophy with or without effusion) on ultrasound had statistically significantly greater improvement in pain scores 12-weeks after corticosteroid injection compared to those with inflammatory features, though no difference in pain score response was seen in those with versus without effusion on ultrasound [15]. Since the difference in pain scores between those with and without inflammatory features was not seen at the 4-week time point, the authors suggested that perhaps those with more inflammatory findings had a less durable response [15]. They also posited that perhaps the inflammatory process in some patients is 'subclinical' or 'subradiographic' and that intra-articular steroids may be better geared to modulate this 'non-inflammatory' subgroup [15]. While this may support the idea that patients with effusion have a more robust inflammatory process that is less responsive to corticosteroid injection, it also highlights the knowledge gaps in OA in terms of what drives pain in OA and how to best modulate it.

The efficacy of corticosteroids in reducing pain in knee OA has been called into question, yet the pain improvement in this pilot cohort was

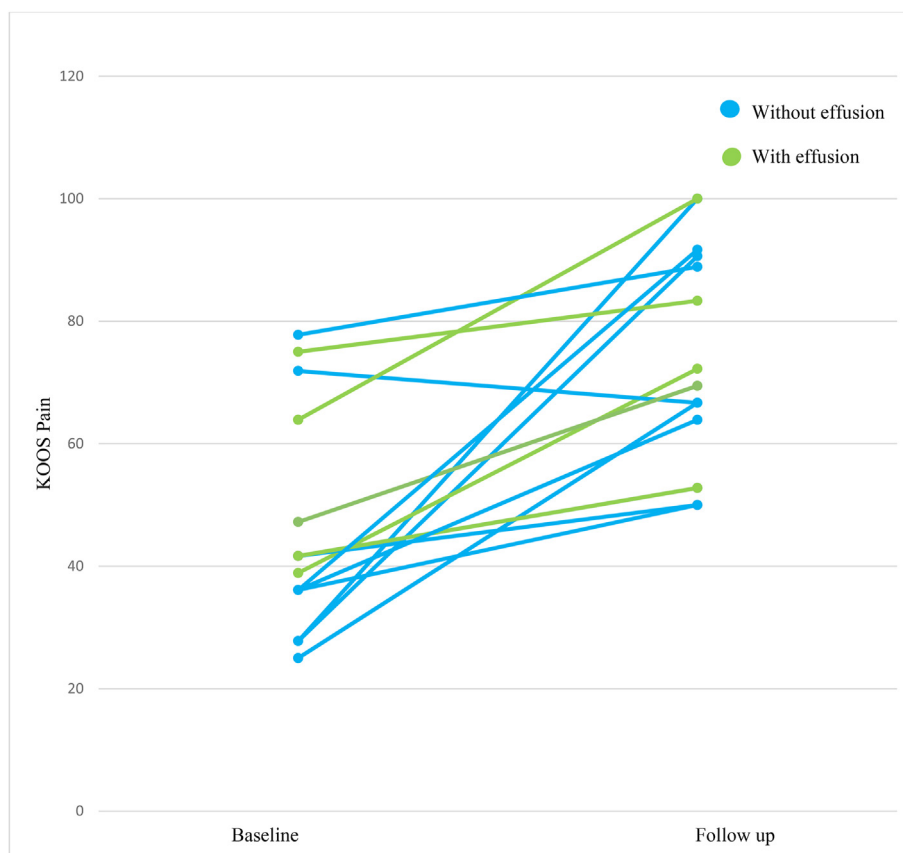


Fig. 1. Change in KOOS pain from baseline to two-week follow up, baseline and 2-week post corticosteroid injection pain scores for knees with (green) and without (blue) effusion on ultrasound.

quite large as was patient-reported satisfaction [4]. There may be several explanations for this. First, this is not a randomized trial, but a cohort of patients who have already made the choice to proceed with corticosteroid injection, some of whom were presenting for repeat injection. Thus, we may have selected for patients who had benefited from prior corticosteroid injection and would be more likely to benefit from subsequent injection. Injection procedures have substantial contextual (placebo) effects; in the absence of a sham (e.g. saline) injection we could only measure the total effect [16]. We cannot rule out that the large improvements reported were driven in part by the injection procedure itself and were not solely due to the effect of corticosteroid. The addition of a non-injected control group would be a useful comparator and will be considered for the larger study, though this design would still be subject to the potentially large placebo effect of injection.

This study has several limitations. As it was a pilot and feasibility study, we used a small convenience sample, and the majority of the participants identified as female and white. Studies including a more heterogeneous populations are warranted as our data may not be generalizable. All patients were referred by the recruiting surgeon which may lead to selection bias. Having the orthopedic surgeon alert the recruiting physician to potentially interested patients was efficient with a high yield of participants enrolling but did not allow for understanding the denominator of how many patients were potentially eligible and reasons for exclusion or lack of interest. We did not include grading of synovitis or power doppler imaging in the ultrasound protocol and realize this may better approximate synovitis or inflammation. However, we favored measuring effusion on ultrasound as this is relatively straightforward and is a prognostic feature that can be done easily at the bedside during routine clinical care. The addition of a synovitis measurement or scoring may strengthen the subsequent study. Over half of the patients had advanced (KL-4) OA and it may be that in this subset, inflammation or the presence of effusion, was not a primary driver of symptoms.

In summary, this pilot demonstrated recruitment feasibility and improvement in knee pain scores 2-weeks after intra-articular steroid injection. In this small sample we did not find a difference in post-injection pain relief between those with and without effusion. These findings and the mixed results of prior studies highlight the need for a rigorous investigation of the association between presence of inflammatory features and response to corticosteroid injection.

Author contribution: Lindsey MacFarlane: Conception and design, acquisition of data, analysis and interpretation of the data, drafting of the article, final approval and obtaining of funding. Hanna Mass: Acquisition of data, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article. Jamie Collins: Conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article. Elena Losina: Conception and design, analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article. Jeffrey Katz: conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, supervision. Antonia Chen: Conception and design, acquisition of data, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article.

### Significance and innovation

- Feasibility of recruiting patients with knee osteoarthritis undergoing cortisone injection from a busy orthopedic practice and completing bedside ultrasound
- No difference in improvement in pain 2 weeks post injection between knees with and without effusion on ultrasound

### CRedit author statement

Lindsey MacFarlane: conception and design, acquisition of data, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, obtaining of funding.

Hanna Mass: acquisition of data, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article.

Jamie Collins: conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article.

Elena Losina: conception and design, analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article.

Jeffrey Katz: conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, supervision.

Antonia Chen: conception and design, acquisition of data, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article.

### Declaration of competing interest

Dr. Collins has consulted for BICL. Dr. Katz has received research support from Biosplice. Dr. Chen has consulted for and/or received royalties from Adaptive Phage Therapeutics, Avanos, BICMD, Convatec, Ethicon, GLG, Guidepoint, Heraeus, IrriMax, Pfizer, Stryker, SLACK Incorporated, and UpToDate.

### Acknowledgement/source of funding

Source of funding: Rheumatology Research Foundation Scientific Development Award, NIH K23 AR080206-0. Funding sources did not play a role in publication process.

### References

- [1] T. Neogi, The epidemiology and impact of pain in osteoarthritis, *Osteoarthr. Cartil.* 21 (9) (2013) 1145–1153.
- [2] J.E. Collins, E. Losina, M.C. Nevitt, F.W. Roemer, A. Guermazi, J.A. Lynch, et al., Semiquantitative imaging biomarkers of knee osteoarthritis progression: data from the foundation for the national institutes of health osteoarthritis biomarkers consortium, *Arthritis Rheumatol.* 68 (10) (2016) 2422–2431.
- [3] A. Dell'Isola, R. Allan, S.L. Smith, S.S. Marreiros, M. Steultjens, Identification of clinical phenotypes in knee osteoarthritis: a systematic review of the literature, *BMC Musculoskelet. Disord.* 17 (1) (2016) 425.
- [4] T.E. McAlindon, M.P. LaValley, W.F. Harvey, L.L. Price, J.B. Driban, M. Zhang, et al., Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial, *J. Am. Med. Assoc.* 317 (19) (2017) 1967–1975.
- [5] P. Jüni, R. Hari, A.W. Rutjes, R. Fischer, M.G. Siletta, S. Reichenbach, et al., Intra-articular corticosteroid for knee osteoarthritis, *Cochrane Database Syst. Rev.* 2015 (10) (2015), Cd005328.
- [6] K. Gaffney, J. Ledingham, J.D. Perry, Intra-articular triamcinolone hexacetonide in knee osteoarthritis: factors influencing the clinical response, *Ann. Rheum. Dis.* 54 (5) (1995) 379–381.
- [7] P.S. McCabe, M.J. Parkes, N. Maricar, C.E. Hutchinson, A. Freemont, T.W. O'Neill, et al., Brief report: synovial fluid white blood cell count in knee osteoarthritis: association with structural findings and treatment response, *Arthritis Rheumatol.* 69 (1) (2017) 103–107.
- [8] T.W. O'Neill, M.J. Parkes, N. Maricar, E.J. Marjanovic, R. Hodgson, A.D. Gait, et al., Synovial tissue volume: a treatment target in knee osteoarthritis (OA), *Ann. Rheum. Dis.* 75 (1) (2016) 84–90.
- [9] K. Bevers, M.C. Zweers, J.E. Vriezekolk, J.W. Bijlsma, A.A. den Broeder, Are ultrasonographic signs of inflammation predictors for response to intra-articular glucocorticoids in knee osteoarthritis? *Clin. Exp. Rheumatol.* 32 (6) (2014) 930–934.
- [10] A. Pendleton, A. Millar, D. O'Kane, G.D. Wright, A.J. Taggart, Can sonography be used to predict the response to intra-articular corticosteroid injection in primary osteoarthritis of the knee? *Scand. J. Rheumatol.* 37 (5) (2008) 395–397.
- [11] E.M. Roos, L.S. Lohmander, The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis, *Health Qual. Life Outcomes* 1 (2003) 64.

- [12] J.H. Kellgren, J.S. Lawrence, Radiological assessment of osteo-arthritis, *Ann. Rheum. Dis.* 16 (4) (1957) 494–502.
- [13] M.A. D'Agostino, P. Conaghan, M. Le Bars, G. Baron, W. Grassi, E. Martin-Mola, et al., EULAR report on the use of ultrasonography in painful knee osteoarthritis. Part 1: prevalence of inflammation in osteoarthritis, *Ann. Rheum. Dis.* 64 (12) (2005) 1703–1709.
- [14] H.T. Philpott, T.B. Birmingham, R. Pinto, C.A. Primeau, D. Arsenault, B.A. Lanting, et al., Synovitis is associated with constant pain in knee osteoarthritis: a cross-sectional study of OMERACT knee ultrasound scores, *J. Rheumatol.* 49 (1) (2022) 89–97.
- [15] J. Chao, C. Wu, B. Sun, M.K. Hose, A. Quan, T.H. Hughes, et al., Inflammatory characteristics on ultrasound predict poorer longterm response to intraarticular corticosteroid injections in knee osteoarthritis, *J. Rheumatol.* 37 (3) (2010) 650–655.
- [16] R.R. Bannuru, T.E. McAlindon, M.C. Sullivan, J.B. Wong, D.M. Kent, C.H. Schmid, Effectiveness and implications of alternative placebo treatments: a systematic review and network meta-analysis of osteoarthritis trials, *Ann. Intern. Med.* 163 (5) (2015) 365–372.