

# PRP Is Not Associated With Improved Outcomes Following Hip Femoroacetabular Impingement Surgery: Very Low-Quality Evidence Suggests Hyaluronic Acid and Cell-Based Therapies May Be Beneficial—A Systematic Review of Biological Treatments



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**Purpose:** To examine the efficacy of biologic agents in the treatment of cartilage defects associated with femoroacetabular impingement (FAI). **Methods:** PubMed, Ovid MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews were reviewed by 2 independent reviewers for eligible studies. We included randomized and nonrandomized control trials as well as uncontrolled case series and retrospective studies. Studies were excluded if they included injections of corticosteroids, papers that described technique only, review papers, and those not in the English language. Demographics, treatment type, outcome of treatment, and complications were extracted, whereas risk of bias and study quality were assessed independently using the risk of bias tool (ROB2) and effective public health practice project tool. A narrative synthesis was performed, and standardized mean differences were reported. Certainty of evidence was assessed using the GRADE approach. **Results:** Eighteen studies consisting of 1,024 patients met the inclusion criteria. Three studies involved the use of platelet-rich plasma (PRP) as an adjuvant to surgery and were included in the meta-analysis. Three studies administered hyaluronic acid (HA) as a primary treatment. Twelve involved various cell-based methods of chondrocyte stimulation for cartilage defects associated with FAI, but heterogeneity did not allow for pooling. Low-quality evidence indicates PRP is not associated with improved outcomes following surgery (mean difference  $-1.42$ , 95% confidence interval  $-3.95$  to  $1.11$ ,  $P = .27$ ). Very-low-quality evidence suggests HA (standardized mean difference  $1.15$ , 95% confidence interval  $0.64$ - $1.66$ ,  $P < .001$ ,  $Z = 4.39$ ) and cell-based therapies may improve function and pain in patients with FAI. **Conclusions:** Low-quality evidence indicates PRP is not associated with improved outcomes following hip FAI surgery, and very-low-quality evidence suggests HA and cell-based therapies may improve outcomes. **Level of Evidence:** systematic review of Level I-V studies.

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The authors report that they have no conflicts of interest in the authorship and publication of this article. Full ICMJE author disclosure forms are available for this article online, as [supplementary material](#).

Received December 2, 2021; accepted May 1, 2022.

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2666-061X/211698

<https://doi.org/10.1016/j.asmr.2022.05.002>

Femoroacetabular impingement (FAI), first described by Ganz et al.<sup>1</sup> is a bony deformity of the hip joint, either on the head–neck junction (cam impingement) or the acetabulum (pincer impingement). Excessive bone obstructs the fluid movement of the femoral head within the acetabulum during motion. This causes subsequent damage to the underlying structures, mainly the labrum and articular cartilage.<sup>1</sup> Due to the poor regenerative properties of the articular cartilage, tissue damage may be irreversible and progressive.<sup>2</sup> Surgical intervention that removes the obstructing bone and repairs labral and chondral tissue using sutures has been shown to be a safe and viable treatment option with good clinical outcomes in the

short to medium term.<sup>3</sup> Conservative approaches to date have focused mainly on activity modification, strength and rehabilitation, and education, with a limited evidence base reporting improved clinical outcomes in the short term.<sup>4</sup>

More recently, the role of biologic agents in the treatment of hip pathology is being examined.<sup>5</sup> Biologics are autologous or synthetically derived biological substances that may have the ability to promote healing by providing concentrated levels of biological material necessary for synthesis of new tissue. A number of biologic treatments have been used in orthopaedics to treat disorders, in particular osteoarthritis, and mainly include platelet-rich plasma (PRP), hyaluronic acid (HA), and cell-based therapies.<sup>5</sup> PRP is an autologous compound containing growth factors and other molecules that stimulate cell proliferation. It is produced by centrifuging the patient's own blood to separate each component, following which the platelets are injected into the injured site.<sup>5</sup> To date, different preparation methods of PRP have been used with different component combinations,<sup>6</sup> and no clear optimal preparation has been determined.<sup>7</sup> HA is produced by chondrocytes and synoviocytes, and provides much of the lubrication properties of synovial fluid within joints.<sup>5</sup> The efficacy of HA in comparison with other treatments including PRP and placebo is conflicting within the literature.<sup>8,9</sup>

The interest in using cell-based therapies for the treatment of cartilage degeneration is increasing and involves the introduction of new cells to a lesion which stimulates the growth and restoration of cartilage.<sup>10</sup> A variety of methods have been described and involve harvesting and manipulation of autologous cell products that are then reintroduced into the lesion to promote cartilage growth and return homeostasis.<sup>5</sup>

The use of biologic treatments has grown in popularity in sports medicine,<sup>11</sup> and although there is an expanding global market for their use, their efficacy remains ambiguous. The purpose of the study was to examine the efficacy of biologic agents in the treatment of cartilage defects associated with femoroacetabular impingement. The hypothesis was that the use of biologic agents would lead to superior outcomes in treatment of symptomatic FAI compared with surgical or conservative approaches that do not include biologics.

## Methods

Although this review was not registered before commencement, the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for reporting of systematic reviews was followed.<sup>12</sup>

### Eligibility Criteria

For this analysis, we considered the population to be anyone diagnosed with FAI and subsequent

comorbidities, including cartilage defects and labral tears. The intervention was any biologic agent used either as a primary, nonsurgical treatment or as an adjuvant to surgery. The outcome in this instance was an improvement in hip function, as measured by patient-reported outcomes, and pain scoring such as the visual analog scale. Any other outcome measure used by the original author to measure improvement following treatment, for example, swelling, also was included. All follow-up times were included. As this is an emerging area of research, we included randomized and nonrandomized control trials as well as uncontrolled case series and retrospective studies. This was to provide the reader with all available research on the topic and draw clear conclusions as to the efficacy of treatments. Studies that were not written in English, those with the use of intra-articular injections for diagnostic purposes, and review articles were excluded. For the purpose of this review, studies that incorporated corticosteroids solely for pain relief and patients with a Tönnis grade  $\geq 2$  (established osteoarthritis) were also excluded.<sup>13</sup> We did not include conference abstracts in this review, as they are not subject to the same rigors of peer-review for publication.

### Information Sources

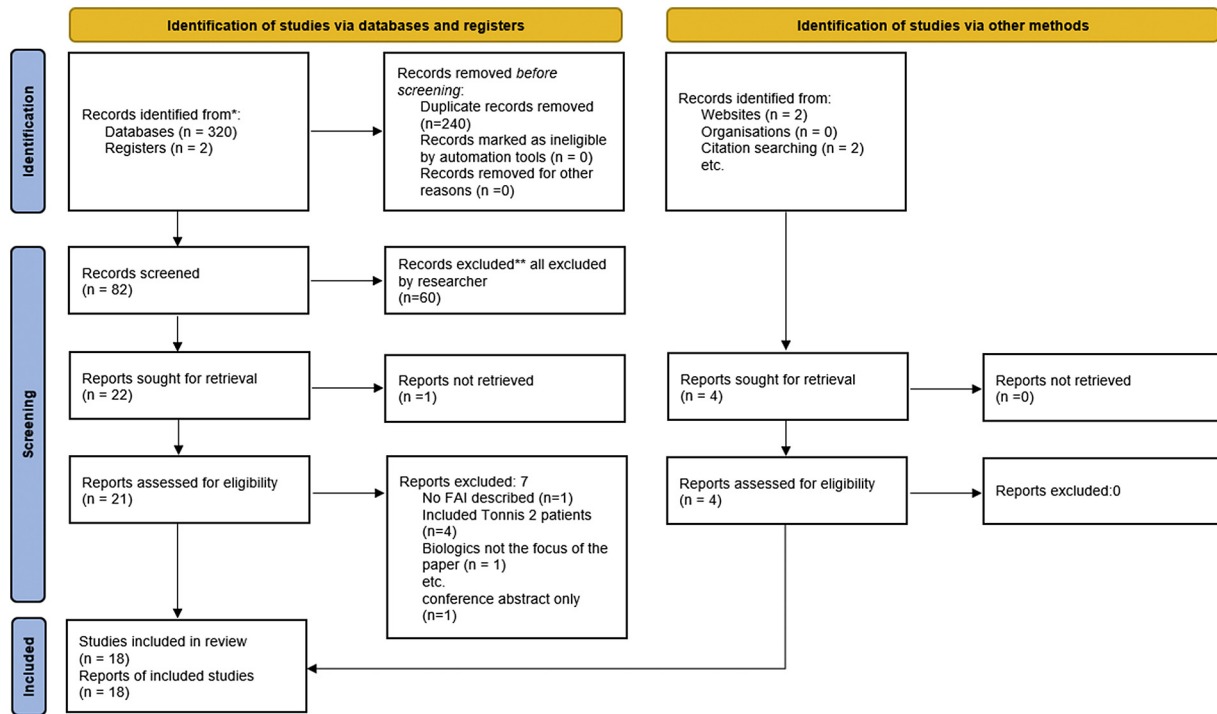
Between August 2020 and November 2020, we conducted 2 electronic searches of PubMed, Ovid MEDLINE, EMBASE, Cochrane Central Register of Controlled, Trials and the Cochrane Database of Systematic Reviews.

### Search Strategy

Two reviewers (K.M. and D.F.) who were blinded to the other's results individually performed the search and determined which studies should be included or excluded. Boolean logic was used with the following Medical Subject Heading terms included femoroacetabular impingement, arthroscopy, biological products, platelet-rich plasma, hyaluronic acid, bone marrow concentrate, mesenchymal stem cells, and injection. No limits were applied to the search criteria. The full search strategy is included in [Appendix 1](#), available at [www.arthroscopyjournal.org](http://www.arthroscopyjournal.org).

### Selection Process and Data Extraction

First, titles were screened for eligibility, following which abstracts were screened, and finally full-text articles were screened ([Fig 1](#)). To assess reviewer agreement on final study inclusion, Cohen kappa<sup>14</sup> was used. In this instance the kappa statistic was calculated as 0.744 ( $P < .001$ ), indicating substantial agreement between reviewers. Only 2 instances occurred whereby reviewers differed with respect to inclusion. In this case, a third reviewer (P.C.) was consulted. Data were extracted by the main author (K.M.) on 2 occasions



**Fig 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection. (FAI, femoroacetabular impingement.)

from selected papers and included author, year of publication, study design (including the use of a control/comparison group), number of participants, sex, age, FAI diagnosis, treatment, complications (if reported), the outcome tool used to measure effectiveness of treatment, longest follow-up, and statistical outcomes of each study. Whether the authors reported a conflict of interest was also recorded. Authors were contacted if raw data relevant to the review were missing from the original papers.

### Assessment of Bias and Study Quality

Risk of bias was assessed independently by both reviewers who were again blinded until bias and quality assessments had been completed; in instances in which results differed, the third reviewer assessed the study. Randomized control trials were assessed for risk of bias using the revised Cochrane risk of bias tool.<sup>15</sup> As we included retrospective studies and studies that did not include a control group in this review, the ROB2 and ROBINS-1 were not applicable to assess the risk of bias. The quality of these studies, therefore, was assessed using the Effective Public Health Practice Project (EPHPP) tool.<sup>16</sup> The individual judgments for each domain are presented in [Appendix Tables 1-3](#), available at [www.arthroscopyjournal.org](http://www.arthroscopyjournal.org). The certainty of evidence also was assessed using the Grades of Recommendation, Assessment, Development and Evaluation (GRADEpro GDT, McMaster University, 2020).<sup>17</sup>

### Effect Measures and Synthesis Methods

Where methodologic homogeneity allowed, data were pooled for meta-analysis for each outcome domain (function and pain). Review Manager (Version 5.4.1; The Cochrane Collaboration, 2020) was used to conduct synthesis. For continuous data, where the same outcome measure was used, mean difference (MD) was calculated to measure treatment effect in a fixed model approach. Alternatively, if different outcome tools were used, a random effects model was employed, and the standardized mean difference (SMD) was calculated. Forest plots with tests of overall effect were generated to visually represent estimates of treatment effect. Heterogeneity, which represents the variation between individual trials, was calculated as the  $I^2$  statistic.  $I^2$  measures the proportion of variation in the combined estimates due to study variance. An  $I^2$  value of 0% represents maximal consistency between the results of individual trials, conversely, an  $I^2$  value of 100% indicates maximal inconsistency between trials.

In cases of extreme heterogeneity, where pooling was not appropriate, a narrative synthesis was conducted and the Synthesis Without Meta-Analysis guidelines were followed.<sup>18</sup> Interventions were grouped according to broader treatment similarities and treatment aims and/or study designs. For example, studies involving cell-based biologics may use different biologic agents but the overall theoretical approach, which is to occlude a cartilage defect using a biologic agent that stimulates

**Table 1.** Study Characteristics

| Author                                 | Year | Study Design and LOE                                  | Control | Treatment          | Patients, n  | Age Range, y | M/F     | FAI Type:<br>Cam/Pincer/Mixed | Outcome<br>Domain(s) | Outcome Tool(s)                        | Longest<br>Follow-up |
|--|------|---|---------|--------------------|--------------|--------------|---------|-------------------------------|----------------------|--|----------------------|
| Platelet-rich plasma                   |      |   |         |                    |              |              |         |                               |                      |  |                      |
| Lafrance et al. <sup>20</sup>          | 2015 | Prospective RCT<br>LOE II                             | Yes     | PRP<br>Saline      | 35           | 18-63        | NR      | 17/18/0                       | Function             | NAHS, mHHS, HOS                        | 1 y                  |
| Rafols et al. <sup>21</sup>            | 2015 | Prospective RCT<br>LOE II                             | Yes     | PRP<br>No PRP      | 57           | 16-52        | 30/27   | 24/0/33                       | Function             | mHHS                                   | 2 y                  |
| Redmond et al. <sup>22</sup>           | 2015 | Prospective RCT<br>LOE II                             | Yes     | PRP<br>Bupivacaine | 306          | x 36         | 103/203 | NR                            | Pain<br>Function     | VAS mHHS, NAHS,<br>HOS                 | 2 y                  |
| Hyaluronic acid                        |      |   |         |                    |              |              |         |                               |                      |  |                      |
| Abate et al. <sup>23</sup>             | 2014 | Prospective case series<br>LOE IV                     | No      | HA                 | 20 (23 hips) | 26-57        | 13/7    | 17/6/0                        | Pain<br>Function     | VAS<br>HHS, Lequesne index             | 1 y                  |
| Lee et al. <sup>24</sup>               | 2016 | Prospective randomized<br>cross over study<br>LOE III | No      | HA<br>Steroid      | 30           | 24-51        | 11/19   | 12/6/12                       | Function             | HOOS                                   | 12 wk                |
| Ometti et al. <sup>25</sup>            | 2020 | Prospective case series<br>LOE IV                     | No      | HA derivative      | 19 (21 hips) | 36-56        | 5/14    | 14/3/4                        | Pain<br>Function     | VAS,<br>HHS, Lequesne<br>index, TALS   | 1 y                  |
| Cell-based Therapies                   |      |   |         |                    |              |              |         |                               |                      |  |                      |
| Flickert et al. <sup>28</sup>          | 2014 | Retrospective case<br>series<br>LOE IV                | No      | MACT               | 6            | 25-45        | 5/1     | 5/0/0<br>1 traumatic cause    | Function             | mHHS, NAHS, SF-36                      | 1 y                  |
| Mancini &<br>Fontana <sup>33</sup>     | 2014 | Retrospective cohort<br>study<br>LOE IV               | No      | AMIC<br>MACI       | 57           | 19-50        | 25/32   | 37/29/9                       | Function             | mHHS                                   | 5 y                  |
| Fontana & de<br>Girolamo <sup>29</sup> | 2015 | Retrospective case-<br>control<br>LOE IV              | Yes     | AMIC<br>Mf         | 147          | 18-55        | 91/56   | 101/19/27                     | Function             | mHHS                                   | 5 y                  |
| Körsmeier<br>et al. <sup>31</sup>      | 2016 | Prospective case series<br>LOE IV                     | No      | ACT 3D             | 16           | 20-47        | 14/2    | 16/0/0                        | Function             | NAHS, WOMAC                            | Average 16 mo        |
| Tahoun et al. <sup>35</sup>            | 2017 | Prospective case series<br>LOE IV                     | No      | BST-Cargel         | 13           | 25-50        | 10/3    | 8/0/5                         | Function             | HOS                                    | 2 y                  |
| Their et al. <sup>36</sup>             | 2017 | Prospective case series<br>LOE IV                     | No      | ACI                | 13           | 22-43        | 13/0    | 10/1/2                        | Function             | iHOT-33, NAHS, EQ-5D                   | 1 y                  |
| Their et al. <sup>37</sup>             | 2017 | Prospective case series<br>LOE IV                     | No      | MACI               | 29           | 18-45        | 27/2    | 20/1/6<br>2 traumatic causes  | Function             | iHOT-33, NAHS, EQ-5D                   | 2 y                  |
| de Girolamo<br>et al. <sup>27</sup>    | 2018 | Retrospective case<br>-control<br>LOE IV              | Yes     | AMIC<br>Mf         | 109          | 18-55        | 64/45   | 73/17/19                      | Function             | mHHS,<br>conversion to THR             | 8 y                  |
| Kruger et al. <sup>32</sup>            | 2018 | Prospective case series<br>LOE IV                     | No      | ACI                | 31           | 18-49        | 27/4    | 7/0/25                        | Function             | mHHS, iHOT-33,<br>subjective hip value | 3 y                  |
| Rivera et al. <sup>34</sup>            | 2019 | Prospective cohort<br>study<br>LOE III                | Yes     | BMC<br>No BMC      | 80           | x 42 y       | 53/27   | 70/5/5                        | Pain<br>Function     | VAS mHHS, iHOT-33                      | 2 y                  |

(continued)

**Table 1.** Continued

| Author                             | Year | Study Design and LOE                     | Control | Treatment  | Patients, n | Age Range, y | M/F   | Cam/Pincer/Mixed | FAI Type: | Outcome Domain(s) | Outcome Tool(s)                    | Longest Follow-up |
|------------------------------------|------|--|---------|------------|-------------|--------------|-------|------------------|-----------|-------------------|------------------------------------|-------------------|
| Bretschneider et al. <sup>26</sup> | 2020 | Prospective case series<br>LOE IV        | No      | MACT       | 21          | 20-53        | 17/4  | NR               | NR        | Function          | iHOT-33, EQ-5D-5L,<br>EQ-5D-5L-VAS | 1 y               |
| Ivone et al. <sup>30</sup>         | 2020 | Retrospective case<br>-control<br>LOE IV | Yes     | Mf<br>MATT | 35          | 19-59        | 21/14 | 25/6/4           | 25/6/4    | Function          | mHHS                               | 2 y               |

LOE, Level of Evidence; M, male; F, female; FAI, femoroacetabular impingement; RCT, randomized control trial; PRP, platelet-rich plasma; NR, not reported; NAHS, Nonarthritic Hip Score; (m)HHS, (modified) Harris Hip Score; HOS, Hip Outcome Scale; VAS, visual analog scale; HA, hyaluronic acid; HOOS, hip Disability and Osteoarthritis Outcome Score; TALS, Tegner activity level scale; MACT, matrix-associated chondrocyte transplantation; SF-36, Short-form 36 Health Survey; AMIC, autologous matrix-induced chondrogenesis; MACI, matrix-induced autologous chondrocyte implant; Mf, microfracture; ACT, autologous chondrocyte transplantation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; BST-Cargel, chitosan-based implant; ACL, autologous chondrocyte implantation; iHOT-33, 33-item International Hip Outcome Tool; EQ-5D, EuroQol group score; THR, total hip replacement; BMC, bone marrow concentrate; MATT, microfragmented autologous adipose tissue transplantation.

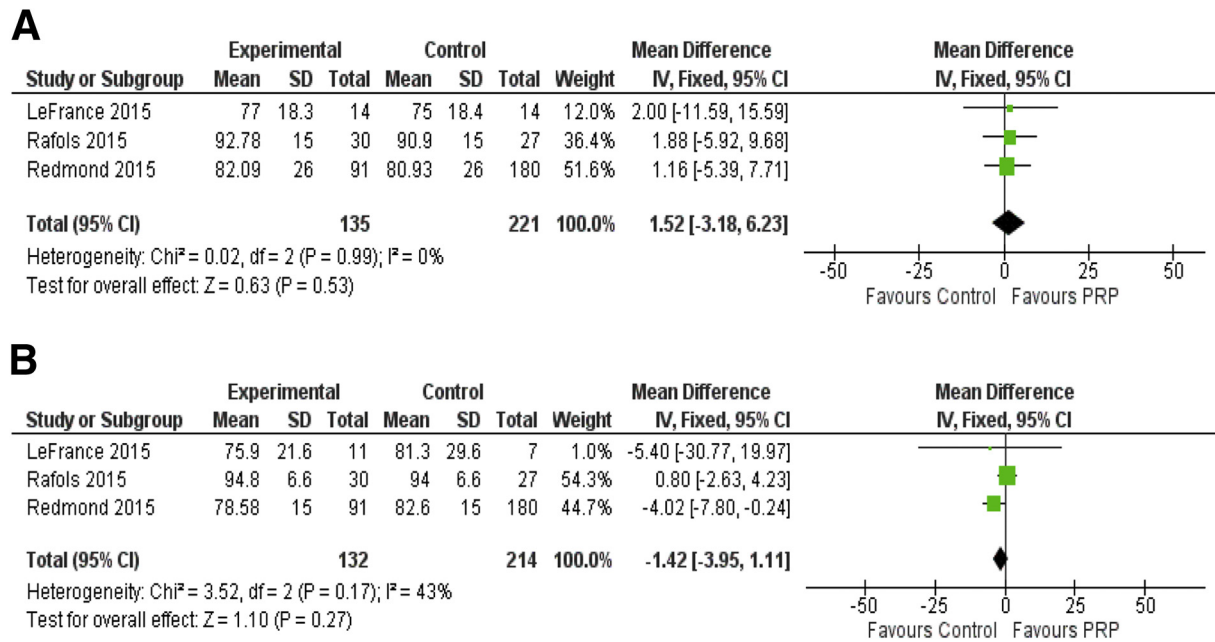
cartilage repair, is similar across studies. SMD was used as a measure of intervention effect. In line with the treatment aim, all studies were included in the narrative synthesis and no limits (e.g., study design/bias) were placed on the synthesis. When dealing with multiplicity (more than one outcome tool used in a study to measure treatment effect), decision rules were employed to select the most relevant outcome measures for synthesis. In this instance, 2 rules were applied in a ranked order. The first was to select an outcome with established content validity in the literature, and the second, if applicable, to select the same outcome that was used in other papers in the review so that in as many cases as possible the same outcome tool was used. Heterogeneity for included studies in the narrative synthesis was accounted for visually using the forest plots. Studies were grouped according to potential effect modifiers such as study design and if applicable evidence certainty. Full GRADE summary of findings tables are located in the [Appendix Figures 1-3](#), available at [www.arthroscopyjournal.org](http://www.arthroscopyjournal.org)). For both the narrative synthesis and meta-analysis, in cases of multiple observations, the longest follow up point was considered for the analysis.<sup>19</sup> Finally, complications were reported as a percentage of the total patients treated with a particular treatment type. For consistency, data are presented in tables and visually using forest plots with studies grouped together by treatment type in chronological order. Reporting bias was assessed using funnel plots generated in Review Manager and are located in the [Appendix Figures 1-3](#), available at [www.arthroscopyjournal.org](http://www.arthroscopyjournal.org).

## Results

### Study Characteristics and Patient Populations

Eighteen studies met the inclusion criteria for this review; each was published between 2014 and 2020 from countries which included the United States, Chile, Italy, South Korea, Germany, and Spain. Three studies used PRP<sup>20-22</sup> in conjunction with surgery, 3 used HA as a primary treatment,<sup>23-25</sup> and 12 applied different methods of cell therapies as an adjuvant to surgery for cartilage defects<sup>26-37</sup> ([Table 1](#)). Thirteen studies were prospective<sup>20-26,31,32,35-37</sup> and 5 were retrospective<sup>27-30,33</sup> with 7 of the studies including a control group.<sup>20-22,27,29,30,34</sup> Randomization of patients allocated to treatment or control groups occurred in 3 of these studies.<sup>20-22</sup> Five studies reported a conflict of interest.<sup>20,22,27,29,36</sup> The conflict of interests were 1 or more authors were consultants/had financial relationships with medical device companies involved in providing materials for the study (3 studies), 1 or more author would receive benefits for personal or professional use from a commercial party





All PRP injections were adjuvant to surgery. The studies indicate no difference in patient reported outcome improvements compared no PRP (longest follow up; 2 years)

**Fig 2.** Risk of bias judgments for randomized controlled trials.

related either directly or indirectly to the subject material (1 study), and 1 or more authors were paid consultants who receive payment for manuscript preparation from the pharmaceutical company who provided the biologic material for the study (1 study).

In total, 1,024 patients were included, consisting of 529 male and 460 female patients; one study did not report sex. The age ranged from 16 to 63 years across the studies. A cam deformity was reported in 456 cases, pincer in 111, and mixed in 151; in 3 cases FAI was caused by a traumatic event (that was not explained by the authors<sup>28,37</sup>); and 2 studies did not report the prevalence of bony deformities.<sup>22,26</sup> All patients were general population, and no studies reported including special populations such as athletes specifically. Twelve patient-reported outcome measures in 2 outcome domains (pain and function) were used across the studies, which consisted of Harris Hip/modified Harris Hip Score, Nonarthritic Hip Score, visual analog scale, International Hip Outcome Tool, EuroQol group score, Hip Outcome Score, Lesquesne Index, Hip Disability and Osteoarthritis Outcome Score, SF-36, Western Ontario and McMaster Universities Osteoarthritis Index, Tegner activity level scale, and subjective hip value. Seven other variables relative to treatment effectiveness were examined and included labral integration, edema, effusion, pain, morphine use and nonsteroidal anti-inflammatory use, and conversion to

total hip replacement. The average number of follow-up assessments with patients was  $3.5 \pm 2$  follow-ups, ranging from 3 months to 8 years postsurgery.

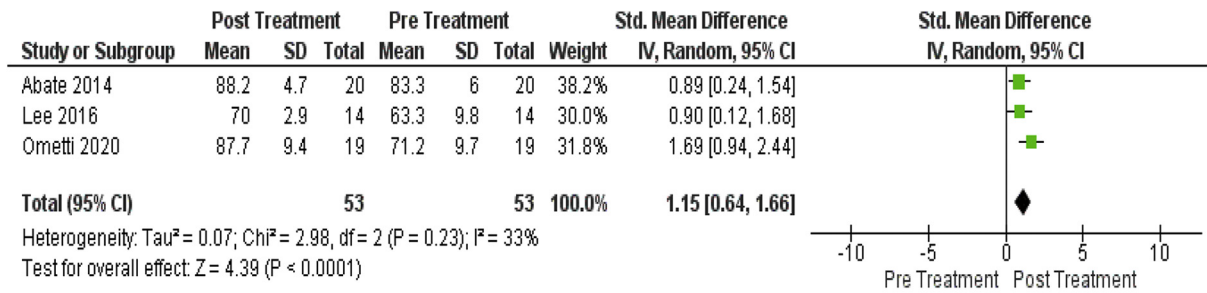
### Risk of Bias and Quality Results

Of the 18 studies included in the risk of bias assessment and quality assessment, the 2 reviewers agreed on ratings for 17 studies, with the final study subsequently rated by a third reviewer. The randomized controlled trials were thought to have some concerns regarding bias, but none were high risk (Fig 2).

Ten studies were rated as weak using the EPHPP tool<sup>23-26,28,31,32,35-37</sup> and 5 were rated as moderate.<sup>27,29,30,33,34</sup> The main areas where studies were rated as weak on the EPHPP tool was for confounders and blinding (Appendix Tables 1-3, available at [www.arthroscopyjournal.org](http://www.arthroscopyjournal.org)). Only one study using HA blinded both patients and surgeons to injection type. The rest of the studies made no reference to blinding. Studies also were rated as weak for confounding factors. This was evident in 2-step surgical procedures, whereby authors did not discuss the results or implications of initial procedures which removed bony deformities and repaired labral tissue.

### Effect of PRP

Given that all 3 studies involving PRP were randomized controlled trials, each study was initially rated as



HA was administered in the absence of surgery without a control comparison. The studies indicate post-treatment improvements in patient reported outcomes compared to baseline (longest follow up; 1 year)

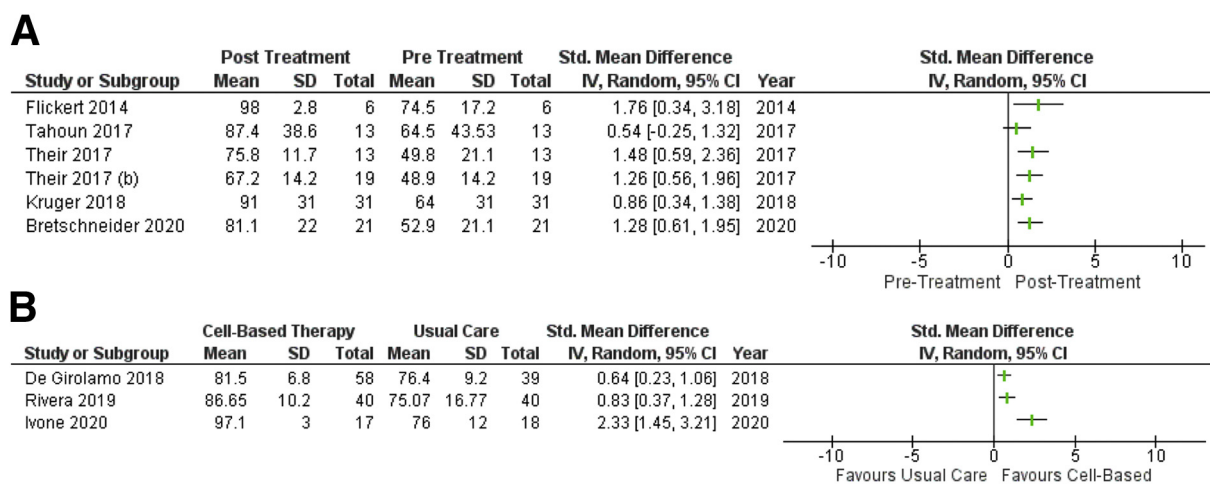
**Fig 3.** A forest plot showing the effect of platelet-rich plasma (PRP) compared with control on (A) early (<6 months) and (B) late (>6 months) postoperative hip function as measured by the modified Harris Hip Score. (CI, confidence interval; IV, inverse variance; SD, standard deviation.)

“high quality” on the GRADE scale (Appendix Figures 1-3, available at [www.arthroscopyjournal.org](http://www.arthroscopyjournal.org)). The evidence was downgraded, however, owing to inconsistencies in sex distributions, approach to the capsule following surgery, complications reporting, and lack of detail in PRP preparation, which not all studies detailed. Similar outcome reporting and time frames among the studies using PRP allowed for synthesis of treatment effect using a fixed model approach for function with early (<6 months) and later (>6 months) comparisons. Low-quality evidence indicated that PRP following surgery did not result in superior outcomes compared with control substances in either the short-term (MD 1.52, 95% confidence interval [CI] -3.18 to 6.23, P = .53, Z = 0.63) or longer-term (MD -1.42, 95% CI -3.95 to 6.23, P = .27, Z = 1.10). This is visually represented in Figure 3, A and B.

Owing to the small number of studies involved, and the inclusion of 2 time points, a sensitivity analysis was not undertaken.

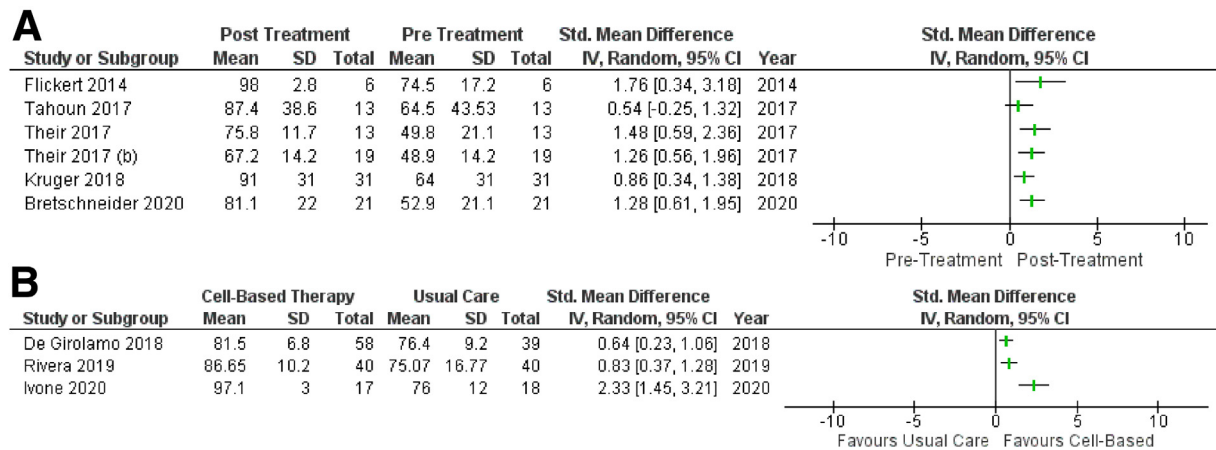
**Effect of HA**

The evidence for HA was considered very low quality (Appendix Figures 1-3, available at [www.arthroscopyjournal.org](http://www.arthroscopyjournal.org)), and none included a control group and so were included as a pre- to post-treatment comparison. Results indicated improvements in function (Fig 4) following treatment with HA (SMD 1.15, 95% CI 0.64-1.66, P < .001, Z = 4.39). Two studies used VAS to assess pain. Abate et al.<sup>23</sup> reported significant improvements in pain scoring (SMD -3.12, 95% CI -4.09 to -2.14, P = .002) at the latest follow-up. This was also the case in the study by Ometti et al.,<sup>25</sup> who demonstrated significant improvements in pain



All cell-based therapies were adjuvant to surgery. The studies indicate potential post-treatment improvements in patient reported outcomes compared to baseline or compared to no cell-based treatment (longest follow up; 8 years)

**Fig 4.** A forest plot showing changes from pretreatment to postfunction treatment using hyaluronic acid (HA). (CI, confidence interval; IV, inverse variance; SD, standard deviation.)



**Fig 5.** A Forest plot showing the effect of cell-based therapies on function from pretreatment to post-treatment (A) and in comparison with usual therapy with respect to postoperative function (B). (CI, confidence interval; IV, inverse variance; SD, standard deviation.)

following HA (SMD  $-2.71$ , 95% CI  $-3.59$  to  $-1.83$ ,  $P \leq .001$ ) at final follow-up.

### Effect of Cell-Based Therapies

All cell-based studies were observational in nature and therefore considered low quality of evidence (Appendix Figs 1-3, available at [www.arthroscopyjournal.org](http://www.arthroscopyjournal.org)) and were further downgraded to very low evidence due to risk of bias, given the lack of blinding and potential publication bias. Studies were grouped together by study design for synthesis in which studies that did not include a comparison group were included on one forest plot in a pretreatment to post-treatment comparison (Fig 5A) and those with a comparison group were included on another, in a post-treatment comparison (Fig 5B). Not all cell-based therapies studies are included in forest plots, however; Körsmeier et al.<sup>31</sup> and Fontana and Girolamo<sup>29</sup> did not report any raw information beyond the  $P$  value. Fontana and Girolamo<sup>29</sup> were also not included on the forest plot, as the population overlaps with a follow-up paper published in 2018, which is included in the plot. Mancini and Fontana<sup>33</sup> compared 2 types of biological treatments to each other (autologous matrix-induced chondrogenesis vs matrix-induced autologous chondrocyte implant) and reported no difference between the groups at longest follow-up (SMD 0.00, 95% CI  $-0.52$  to  $0.52$ ,  $P > .05$ ). Rivera et al.<sup>34</sup> reported on pain outcomes following intervention and demonstrated a significant improvement in pain scoring at latest follow-up (SMD  $-0.97$ , 95% CI  $-1.43$  to  $-0.50$ ,  $P < .001$ ).

### Complications

Six of 18 studies (33%) did not make reference to complications in their papers.<sup>20,21,25,29,34,35</sup> The PRP studies included 398 patients. One study defined conversion to total hip replacement (THR) and

reoperations as a complication<sup>22</sup> and reported 4 THR in the PRP group and 10 THR in control group, with 11 revision procedures in the PRP group and 13 revisions in the control group. There was no statistical difference in these distributions. The remaining studies did not report complications. A total of 69 patients were included in the HA studies, and there were 3 cases of pain<sup>23,24</sup> (4.3%) at the injection site, 1 case of itching (1.4%), and 1 case of swelling at the site (1.4%).<sup>24</sup>

Of the cell-based therapy studies, which included 557 patients, 5 studies totaling 261 patients (47%)<sup>27,30,32,33,37</sup> did not observe any complications from the procedures. There were 4 cases of neuropraxia (0.7%), which did not surpass 12 weeks in any case.<sup>31,36</sup> There was one incidence of bacterial arthritis (0.2%), which developed 6 days after matrix-associated chondrocyte transplantation (MACT) and was treated with antibiotics.<sup>26</sup> A further patient treated with MACT was diagnosed with and treated for persistent arthralgia (0.2%) at 8 months due to adhesions that were removed.<sup>26</sup> One patient reported disturbed wound healing (0.2%) during harvesting of the cartilage cylinders in an index procedure.<sup>31</sup> There was 1 case of hypoesthesia (0.2%) in both feet of the patient,<sup>28</sup> and 1 patient (0.2%) reported pain in scrotum with redness, but no infection was recorded.<sup>28</sup>

## Discussion

Low-quality evidence indicates that PRP as an adjunct to surgery does not improve function or pain compared with surgery without PRP. Very low-quality evidence suggests HA improves pain and function in patients with FAI. Very low-quality evidence would also indicate cell-based treatments for cartilage defects can improve function and pain in hip surgery for FAI. Although HA and cell-based therapies may appear to



improve symptoms, their efficacy should be viewed in light of the quality of evidence, and caution is advised.

### Platelet-Rich Plasma

PRP has grown in popularity in recent years for a variety of injuries, including soft-tissue and joint-related osteoarthritis (OA).<sup>38</sup> A recent meta-analysis by Filardo et al.<sup>39</sup> examined the effectiveness of PRP injections when compared with both placebo and HA treatments. They report improvements in function and pain following PRP treatment compared with steroid and HA injections and concluded that the use of PRP goes beyond a placebo effect, although the clinical significance of PRP may not be apparent until longer follow up. In this review, we found no clear benefit from PRP use after surgery for FAI both in early and later follow-up. Capsular closure following hip arthroscopy is an important consideration when administering PRP; by not repairing the capsule, it is possible for the PRP amalgam to simply leak out from the joint following delivery.<sup>40</sup> Of the studies included here, only 1 study carried out routine capsular closure, another study carried out the procedure on select cases based on surgeon discretion, and the remaining study made no reference to capsular closure. It is therefore not possible to determine whether the PRP remained within the targeted area, and this could account for lack of improvements seen. Although outside the search time frame of the current review, a recent study detailing the results of a randomized control trial using PRP where capsular closure was routinely carried out; Foo et al.<sup>41</sup> did not find any significant benefits to PRP injection compared with placebo at any time point (last follow-up 5 years postoperatively) on any outcome measure. Specific complications from PRP use were not reported in any of the studies included; however, Redmond et al.<sup>22</sup> did examine differences in the rate of conversion to THR and reoperation and described this as a complication. The lack of reporting of complications can underestimate the harm of a treatment and overestimate the benefit and should be included. None of the 3 studies suggested a potential bias due to differences between the participants at the time of allocation to treatment protocols within any of the studies. Between studies, similar outcome measures were used, with similar age ranges from adolescents to middle-aged adults. It must be noted, however, between studies there were differences in FAI types. Redmond et al.<sup>22</sup> did not report the type of FAI diagnosed. Furthermore, there were differences in gender distributions across the studies. While Rafols et al.<sup>21</sup> had an evenly distributed cohort. Redmond et al.<sup>22</sup> had twice as many females as males and LaFrance et al.<sup>20</sup> did not report the number of male or female patients. Sex has been identified an influencing factor in PRP efficacy

studies in patients with OA, as no sex subanalysis was undertaken in this analysis, it is unclear whether the same is true for FAI.<sup>42</sup> It is uncertain whether differences in FAI type are likely to alter the overall conclusions of the evidence, given the PRP was administered as part of the corrective surgery, and the patients were not arthritic at the time.

### Hyaluronic Acid

Arthritic joints display HA of a reduced molecular weight compared with healthy joints. This reduces overall lubrication of the joint by diminishing the viscoelastic properties of synovial fluid.<sup>43</sup> Wu et al.<sup>44</sup> reported that although HA injections could improve function and pain compared with baseline in patients with hip OA, HA did not result in superior outcomes compared with control solutions. FAI is considered as a precursor to OA,<sup>45</sup> and the results of this review would echo these findings. We found that for FAI, HA can improve pain and function in patients, but given the certainty of the evidence was very low, and the absence of a control group in each of the available studies, a placebo effect must be considered. Second, in the study by Abate et al.,<sup>23</sup> patients also were advised to refrain from activities that aggravate symptoms. Activity modification has been shown to improve symptoms in patients with FAI and is a well-recognized component of conservative interventions.<sup>46-49</sup> It is therefore not possible to determine in this instance whether the improvements noted were due to HA or activity modification. The associated complications of HA appear to be low and superficial in nature, mostly related to the injection itself rather than the HA.

### Cell-Based Therapies

A number of cell-based approaches to cartilage defects associated with FAI are presented here and a large heterogeneity was observed. Considering this heterogeneity and low study quality, the results indicated a positive effect of cell-based therapies on outcomes following surgery for FAI. One of the major confounding factors common across these studies was the influence of bony deformity correction and labral repair. Biologic substances to repair cartilage defects in conjunction with removal of the obstructing bone could represent the next stage in hip-preservation surgery, but whether the combined effect of these approaches outweighs the benefits of solely removing the bone and repairing the labrum to warrant the extended procedure times or in some cases, second procedures, could not be determined from the studies. While the aim of cell-based therapies is to stimulate the regrowth of cartilage, determining the level of cartilage regeneration it is not always possible. Of the studies reported here, Bretschneider et al.<sup>26</sup> did, however, include

magnetic resonance imaging assessments at follow-up and reported complete integration of the implant for 80% of patients at 12 months following treatment with MACT. Using bone marrow concentrate treatments for cartilage lesions of the knee, Gobbi et al.<sup>50,51</sup> observed that  $\geq 80\%$  of patients had complete cartilage regeneration at follow-up.

Before the introduction of biologics for cartilage regeneration, microfracture was used to stimulate cartilage growth in patients with FAI. This technique in conjunction with bony correction and labral repair yields favorable results in the midterm to long term, although careful patient selection is advised.<sup>52,53</sup> In this review, autologous matrix-induced chondrogenesis and microfragmented adipose tissue transplantation appeared to have superior outcomes compared with microfracture alone, as demonstrated with large SMD in the 2 studies in which this difference could be calculated.

The complications associated with cell-based therapies were also low, with 5 studies not observing any complications. There is always risk of contamination in surgical procedures, which is then increased when second procedures are required, as was seen in the case of bacterial arthritis following MACT transplantation. Although not a complication, Krueger et al.<sup>32</sup> reported 2 incidences of failed cell cultivation that required another cell-harvesting procedure, resulting in 3 surgical procedures for 2 patients. Future research requires control groups and adequate blinding where possible to improve the scientific rigor of the literature. Based on this review, it is also recommended that future researchers standardize FAI diagnosis, detail the preparation of treatments used, particularly PRP, and include more transparent reporting on the effects of all treatments included, this is most applicable to 2-step procedures.

### Limitations

The current review has inherent limitations due to the low quality of evidence available for inclusion. Owing to the emerging nature of the subject matter, greater quality control trials are lacking; however, all available evidence was included in the review. Observational studies are necessary, however, for advancing medical treatments, as they can provide information regarding the benefit or harm of a treatment and offer a rationale for a randomised control trial. We also included papers that used biologics as either a primary treatment or in conjunction with surgery. Given the aim was to determine the efficacy of biologics in the treatment of FAI, it was determined that inclusion of all treatments was necessary despite the obvious differences in surgical and conservative approaches for FAI. By including all the information available on biologics for FAI, we provide clinicians with an in-depth analysis

of the current available literature, and a succinct analysis of the quality.

This review aimed to assess the efficacy of biologics in the treatment of FAI, although the imprecise FAI diagnosis in the studies included in the review is problematic. Recent consensus among clinicians and researchers is that a triad of symptoms, clinical findings, and radiologic parameters is necessary for a diagnosis of FAI.<sup>54</sup> To further compound this uncertainty, the dearth of radiologic parameters such as alpha angles and center edge angles does not allow for determination of either the extent of bony deformity and/or the level of correction implemented which will influence outcomes following surgery.<sup>55</sup> The observational studies also were limited by lack of blinding and confounding factors.

Summarizing effect estimates in a narrative synthesis does not allow for differences in sample sizes across studies or heterogeneity in follow-up times. For standardized reporting, we used the longest follow-up as suggested in the Cochrane handbook, but caution is advised when comparing outcomes of longer duration compared to shorter follow up times.

### Conclusions

Low-quality evidence indicates PRP is not associated with improved outcomes following hip FAI surgery, and very low-quality evidence suggests HA and cell-based therapies may improve outcomes.

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## Appendix 1. Search Terms

**((((Femoroacetabular impingement) OR (femoroacetabular impingement syndrome)) AND (((arthroscopy) OR (surgery)) OR (treatment)) OR (procedure))) AND ((((((biological products) OR (biologics)) OR (platelet rich plasma)) OR (Hyaluronic acid)) OR (bone marrow concentrate)) OR (mesenchymal stem cells)) OR (injection))**

("femoracetabular impingement"[MeSH Terms] OR ("femoracetabular"[All Fields] AND "impingement"[All Fields]) OR "femoracetabular impingement"[All Fields] OR ("femoracetabular"[All Fields] AND "impingement"[All Fields]) OR "femoroacetabular impingement"[All Fields] OR ("femoracetabular impingement"[MeSH Terms] OR ("femoracetabular"[All Fields] AND "impingement"[All Fields]) OR "femoracetabular impingement"[All Fields] OR ("femoracetabular"[All Fields] AND "impingement"[All Fields] AND "syndrome"[All Fields]) OR "femoroacetabular impingement syndrome"[All Fields])) AND ("arthroscopy"[MeSH Terms] OR "arthroscopy"[All Fields] OR "arthroscopies"[All Fields] OR ("surgery"[MeSH Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms] OR "surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "general surgery"[MeSH Terms] OR ("general"[All Fields] AND "surgery"[All Fields]) OR "general surgery"[All Fields] OR "surgery s"[All Fields] OR "surgeries"[All Fields] OR "surgeries"[All Fields]) OR ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "treatment-s"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "treatment s"[All Fields]) OR ("methods"[MeSH Terms] OR "methods"[All Fields] OR "procedure"[All Fields] OR "methods"[MeSH Subheading] OR "procedures"[All Fields] OR "procedural"[All Fields] OR "procedurally"[All Fields] OR "procedure s"[All Fields])) AND ("biological products"[MeSH Terms] OR ("biological"[All Fields] AND "products"[All Fields]) OR "biological products"[All Fields] OR ("biological products"[MeSH Terms] OR ("biological"[All Fields] AND "products"[All Fields]) OR "biological products"[All Fields] OR "biologic"[All Fields] OR "biologicals"[All Fields] OR "biological factors"[MeSH Terms] OR ("biological"[All Fields] AND "factors"[All Fields]) OR "biological factors"[All Fields] OR "biologics"[All Fields] OR "biologically"[All Fields] OR "biology"[MeSH Terms] OR "biology"[All Fields] OR "biological"[All Fields]) OR ("platelet rich plasma"[MeSH Terms] OR ("platelet rich"[All Fields] AND "plasma"[All Fields]) OR "platelet rich plasma"[All Fields] OR ("platelet"[All Fields] AND "rich"[All Fields] AND "plasma"[All Fields]) OR "platelet rich plasma"[All Fields]) OR

("hyaluronic acid"[MeSH Terms] OR ("hyaluronic"[All Fields] AND "acid"[All Fields]) OR "hyaluronic acid"[All Fields]) OR ("bone marrow"[MeSH Terms] OR ("bone"[All Fields] AND "marrow"[All Fields]) OR "bone marrow"[All Fields]) AND ("concentrate"[All Fields] OR "concentrated"[All Fields] OR "concentrates"[All Fields] OR "concentrating"[All Fields] OR "concentration"[All Fields] OR "concentrations"[All Fields])) OR ("mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields]) OR ("inject"[All Fields] OR "injectability"[All Fields] OR "injectant"[All Fields] OR "injectants"[All Fields] OR "injectate"[All Fields] OR "injectates"[All Fields] OR "injected"[All Fields] OR "injectible"[All Fields] OR "injectibles"[All Fields] OR "injecting"[All Fields] OR "injections"[MeSH Terms] OR "injections"[All Fields] OR "injectable"[All Fields] OR "injectables"[All Fields] OR "injection"[All Fields] OR "injects"[All Fields]))

### Translations

**Femoroacetabular impingement:** "femoracetabular impingement"[MeSH Terms] OR ("femoracetabular"[All Fields] AND "impingement"[All Fields]) OR "femoracetabular impingement"[All Fields] OR ("femoracetabular"[All Fields] AND "impingement"[All Fields]) OR "femoroacetabular impingement"[All Fields]

**femoroacetabular impingement syndrome:** "femoracetabular impingement"[MeSH Terms] OR ("femoracetabular"[All Fields] AND "impingement"[All Fields]) OR "femoracetabular impingement"[All Fields] OR ("femoracetabular"[All Fields] AND "impingement"[All Fields] AND "syndrome"[All Fields]) OR "femoroacetabular impingement syndrome"[All Fields]

**arthroscopy:** "arthroscopy"[MeSH Terms] OR "arthroscopy"[All Fields] OR "arthroscopies"[All Fields]

**surgery:** "surgery"[Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "general surgery"[MeSH Terms] OR ("general"[All Fields] AND "surgery"[All Fields]) OR "general surgery"[All Fields] OR "surgery's"[All Fields] OR "surgeries"[All Fields] OR "surgeries"[All Fields]

**treatment:** "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "treatments"[All Fields] OR "therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "treatment's"[All Fields]

**procedure:** "methods"[MeSH Terms] OR "method-s"[All Fields] OR "procedure"[All Fields] OR "method-s"[Subheading] OR "procedures"[All Fields] OR "procedural"[All Fields] OR "procedurally"[All Fields] OR "procedure's"[All Fields]

**biological products:** "biological products"[MeSH Terms] OR ("biological"[All Fields] AND "products"[All Fields]) OR "biological products"[All Fields]

**biologics:** "biological products"[MeSH Terms] OR ("biological"[All Fields] AND "products"[All Fields]) OR "biological products"[All Fields] OR "biologic"[All Fields] OR "biologicals"[All Fields] OR "biological factors"[MeSH Terms] OR ("biological"[All Fields] AND "factors"[All Fields]) OR "biological factors"[All Fields] OR "biologics"[All Fields] OR "biologically"[All Fields] OR "biology"[MeSH Terms] OR "biology"[All Fields] OR "biological"[All Fields]

**platelet rich plasma:** "platelet-rich plasma"[MeSH Terms] OR ("platelet-rich"[All Fields] AND "plasma"[All Fields]) OR "platelet-rich plasma"[All Fields] OR ("platelet"[All Fields] AND "rich"[All Fields] AND "plasma"[All Fields]) OR "platelet rich plasma"[All Fields]

**Hyaluronic acid:** "hyaluronic acid"[MeSH Terms] OR ("hyaluronic"[All Fields] AND "acid"[All Fields]) OR "hyaluronic acid"[All Fields]

**bone marrow:** "bone marrow"[MeSH Terms] OR ("bone"[All Fields] AND "marrow"[All Fields]) OR "bone marrow"[All Fields]

**concentrate:** "concentrate"[All Fields] OR "concentrated"[All Fields] OR "concentrates"[All Fields] OR "concentrating"[All Fields] OR "concentration"[All Fields] OR "concentrations"[All Fields]

**mesenchymal stem cells:** "mesenchymal stem cells"[MeSH Terms] OR ("mesenchymal"[All Fields] AND "stem"[All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields]

**injection:** "inject"[All Fields] OR "injectability"[All Fields] OR "injectant"[All Fields] OR "injectants"[All Fields] OR "injectate"[All Fields] OR "injectates"[All Fields] OR "injected"[All Fields] OR "injectible"[All Fields] OR "injectibles"[All Fields] OR "injecting"[All Fields] OR "injections"[MeSH Terms] OR "injections"[All Fields] OR "injectable"[All Fields] OR "injectables"[All Fields] OR "injection"[All Fields] OR "injects"[All Fields]

**Appendix Table 1. Summary of Findings for PRP Analysis**

**Author(s):** LaFrance, Rafols, Redmond

**Question:** PRP compared with placebo for early and late outcomes in patients undergoing surgery for femoroacetabular impingement

| Certainty Assessment  |                   |              |               |              |             |                      | No. Patients |         | Effect            |  | Certainty | Importance |
|---|-------------------|--------------|---------------|--------------|-------------|----------------------|--------------|---------|-------------------|--|-----------|------------|
| No. Studies   | Study Design      | Risk of Bias | Inconsistency | Indirectness | Imprecision | Other Considerations | PRP          | Placebo | Relative (95% CI) | Absolute (95% CI)                          |           |            |
| Early follow-up (function) (assessed with: mHHS; scale from: 0 to 100)    |                   |              |               |              |             |                      |              |         |                   |  |           |            |
| 3   | Randomized trials | Not serious  | Very serious* | Not serious  | Not serious | None                 | 135          | 221     | —                 | MD 1.52 higher (3.18 lower to 6.23 higher) | ⊕⊕○○ Low  | IMPORTANT  |
| Late follow-up (function) (assessed with: mHHS; scale from: 0 to 100)     |                   |              |               |              |             |                      |              |         |                   |  |           |            |
| 3   | Randomized trials | Not serious  | Very serious* | Not serious  | Not serious | None                 | 132          | 214     | —                 | MD 1.42 lower (3.95 lower to 1.11 higher)  | ⊕⊕○○ Low  | IMPORTANT  |
| Pain (follow-up: mean 24 months; assessed with: VAS; scale from: 0 to 10) |                   |              |               |              |             |                      |              |         |                   |  |           |            |
| 1   | Randomized trials | Not serious  | Very serious  | Not serious  | Not serious | None                 | 104          | 202     | —                 | 0 (0 to 0)                                 | ⊕⊕○○ Low  | IMPORTANT  |

CI, confidence interval; MD, mean difference; mHHS, modified Harris Hip Score; PRP, platelet-rich plasma; VAS, visual analog scale.  
 \*Inconsistencies in PRP preparation, routine capsular closure, sex, and complications.

**Appendix 2 Table 2. Summary of Findings for HA Analysis**

**Author(s):** Abate, Lee, and Ometti

**Question:** Does HA improve function and pain in patients with femoroacetabular impingement

| Certainty Assessment                            |                       |                      |                      |              |             |   | No. Patients |     | Effect            |  | Certainty     | Importance |
|---|-----------------------|----------------------|----------------------|--------------|-------------|---|--------------|-----|-------------------|--|---------------|------------|
| No. Studies                                     | Study Design          | Risk of Bias         | Inconsistency        | Indirectness | Imprecision | Other Considerations  | HA           | n/a | Relative (95% CI) | Absolute (95% CI)                            |               |            |
| Function  |                       |                      |                      |              |             |   |              |     |                   |  |               |            |
| 3   | Observational studies | Serious*             | Serious <sup>†</sup> | Not serious  | Not serious | Publication bias strongly suspected strong association <sup>‡</sup> | 53           |     | —                 | SMD 1.15 higher (0.64 higher to 1.66 higher) | ⊕○○○ VERY LOW | IMPORTANT  |
| Pain (follow-up: 12 months; assessed with: VAS) |                       |                      |                      |              |             |   |              |     |                   |  |               |            |
| 2   | Observational studies | Serious <sup>§</sup> | Not serious          | Not serious  | Not serious | Publication bias strongly suspected <sup>  </sup>                   | 39           |     | —                 | SMD 2.89 SD lower (3.55 lower to 2.24 lower) | ⊕○○○ VERY LOW | IMPORTANT  |

CI, confidence interval; HA, hyaluronic acid; n/a, not available; SMD, standardized mean difference; VAS, visual analog scale.

\*Lack of control groups and lack of blinding.

<sup>†</sup>Study by Lee et al. (2016) includes crossover patients but no washout period.

<sup>‡</sup>See funnel plot.

<sup>§</sup>Lack of blinding.

<sup>||</sup>Lack of control groups and lack of blinding.

### Appendix Table 3. Summary of Findings for Cell-Based Therapies Analysis

**Author(s):** Flickert, Korsmeier, Tahoun, Their (a), Their (b), Kuger, Breschneider, Fontana, De Girolamo, Rivera, Ivone, Mancini,

**Question:** Do cell-based therapies in conjunction with surgery improve function and pain in patients with femoroacetabular impingement

**Setting:** primary care

| Certainty Assessment   |                       |                      |               |              |             |  | No. Patients                   |            | Effect            |   | Certainty        | Importance |  |
|--|-----------------------|----------------------|---------------|--------------|-------------|--|--------------------------------|------------|-------------------|---|------------------|------------|--|
| No. Studies  | Study Design          | Risk of Bias         | Inconsistency | Indirectness | Imprecision | Other Considerations                             | Effect of Cell-Based Therapies | Usual Care | Relative (95% CI) | Absolute (95% CI)   |                  |            |  |
| Effect of cell-based therapies: no control arm (function)            |                       |                      |               |              |             |  |                                |            |                   |   |                  |            |  |
| 7  | Observational studies | Serious <sup>*</sup> | Not serious   | Not serious  | Not serious | Publication bias strongly suspected <sup>†</sup> | 103                            | 0          | –                 | Not pooled  | ⊕○○○<br>VERY LOW | IMPORTANT  |  |
| Effect of cell-based therapies with a comparison group (Function)    |                       |                      |               |              |             |  |                                |            |                   |   |                  |            |  |
| 4  | Observational studies | Serious <sup>‡</sup> | Not serious   | Not serious  | Not serious | None   | 115                            | 97         | –                 | Not pooled  | ⊕○○○<br>VERY LOW | IMPORTANT  |  |
| Pain (follow-up: 24 months; assessed with: VAS; scale from: 0 to 10) |                       |                      |               |              |             |  |                                |            |                   |   |                  |            |  |
| 1  | Observational studies | Serious <sup>§</sup> | Not serious   | Not serious  | Not serious | None   | 40                             | 40         | –                 | SMD 0.97<br>SD<br>lower<br>(1.43<br>lower to<br>0.5<br>lower) | ⊕○○○<br>VERY LOW | IMPORTANT  |  |

CI, confidence interval; SMD, standardized mean difference; VAS, visual analog scale.

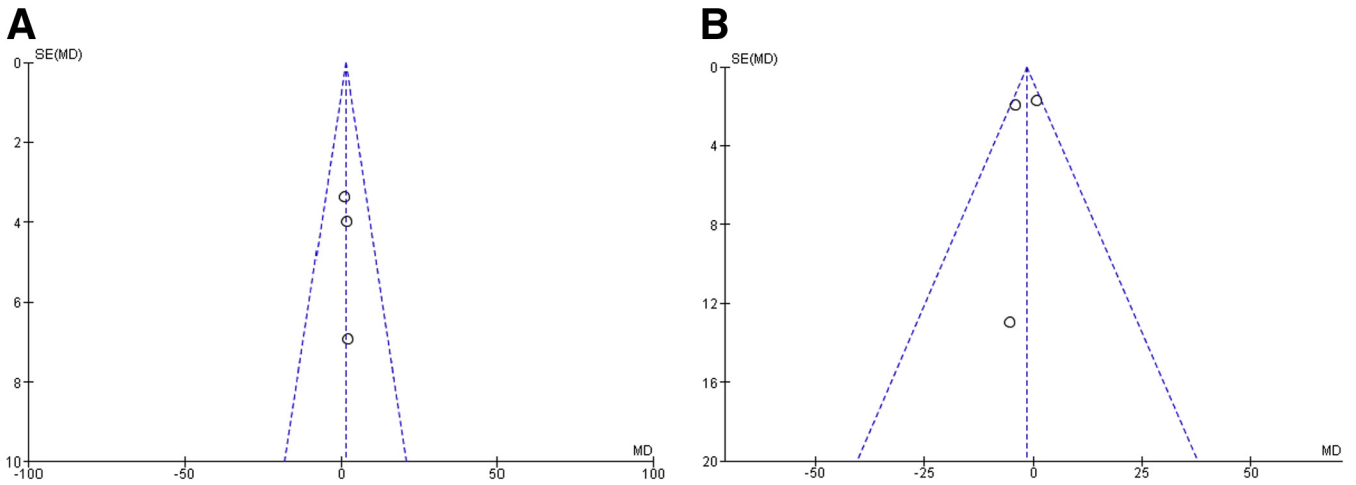
<sup>\*</sup>Lack of blinding throughout, no control groups and retrospective in nature.

<sup>†</sup>See funnel plot; all studies indicate positive results.

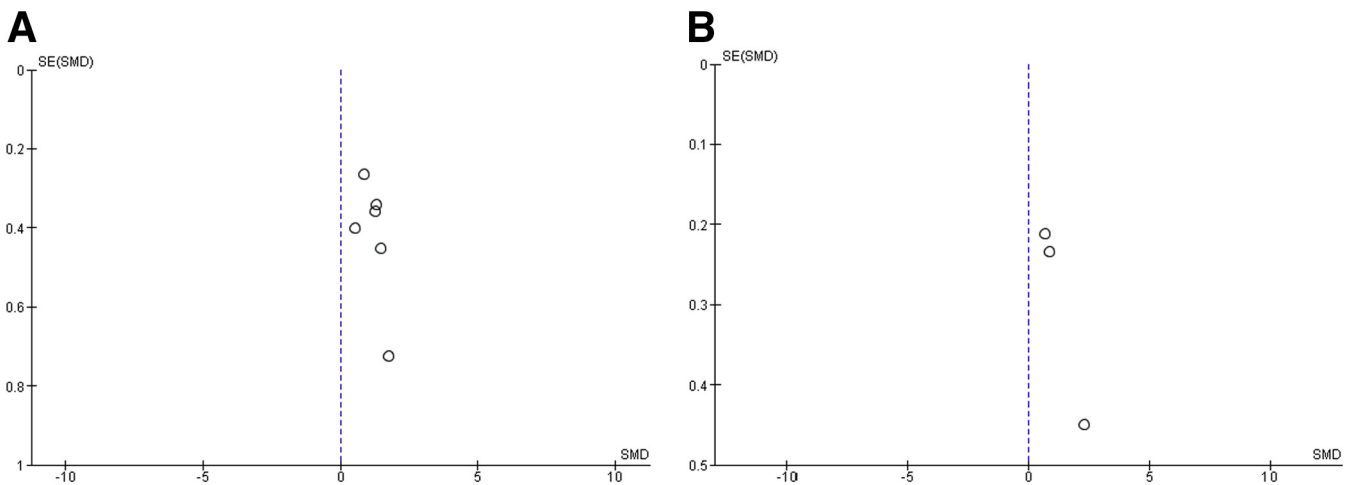
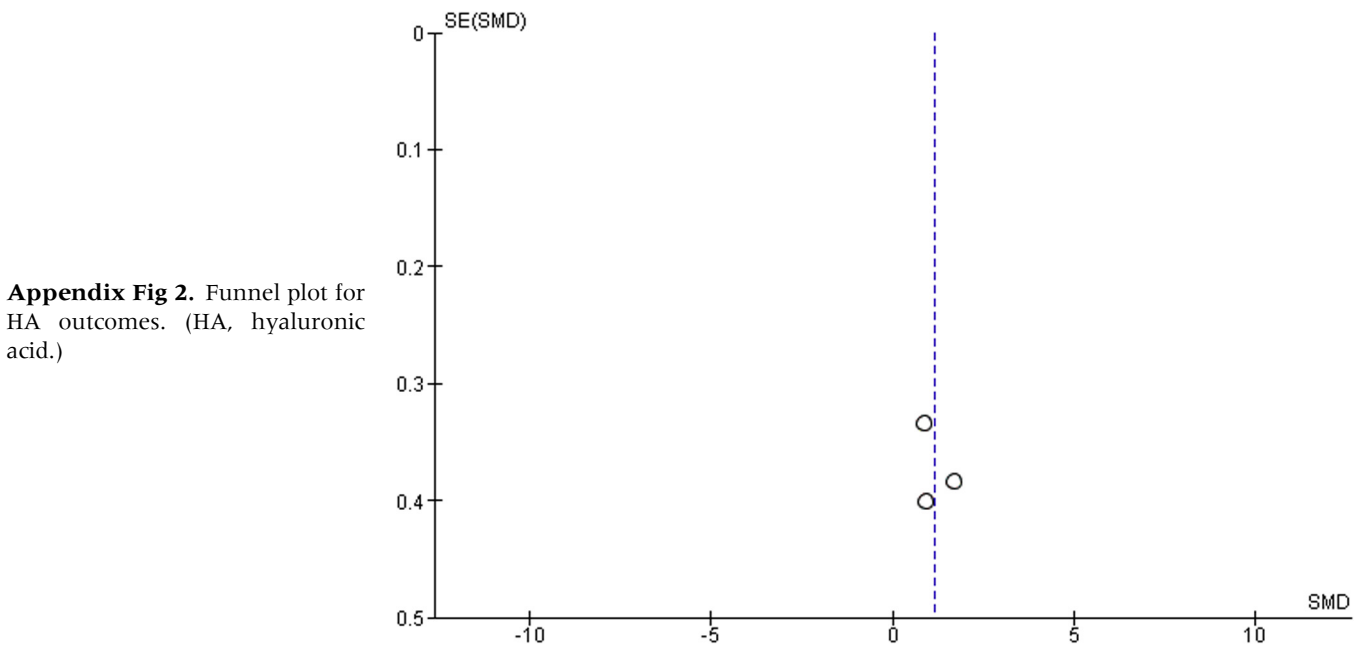
<sup>‡</sup>No randomization and retrospective in nature, no blinding.

<sup>§</sup>See previous comment.





**Appendix Fig 1.** (A) Funnel plot for early PRP outcomes. (B) Funnel plot for late PRP outcomes. (PRP, platelet-rich plasma.)



**Appendix Fig 3.** (A) Funnel plot for cell-based studies with no comparison group. (B) Funnel plot for cell-based studies with comparison group.