Regarding "Intra-Articular Injections of Hyaluronic Acid or Steroid Associated With Better Outcomes Than Platelet-Rich Plasma, Adipose Mesenchymal Stromal Cell, or Placebo in Knee Osteoarthritis: A Network Meta-analysis"

We read with great interest the recent article published in the Arthroscopy by Han et al.[1] entitled "Intra-Articular Injections of Hyaluronic Acid or Steroid Associated With Better Outcomes Than Platelet-Rich Plasma, Adipose Mesenchymal Stromal Cell, or Placebo in Knee Osteoarthritis: A Network Meta-analysis." We believe intra-articular injectables are an important aspect to study to optimize the nonoperative treatment of those with knee osteoarthritis, and the efficacy of this treatment has been the evaluated in multiple meta-analysis and network met-analysis.[2-7] We would like to thank the authors for their efforts in focusing on the issue, and we also commend the authors on performing a network meta-analysis, as we believe this is a very useful tool where multiple treatment options exist. However, we do have some concerns with the methodology that may confound our understanding on the topic, and thus, feel the conclusions may be misleading. Similar network meta-analyses on this topic have come to very different conclusions. We believe the 2 main concerns are due to the pooling of different platelet-rich plasma (PRP), hyaluronic acid (HA), and corticosteroid (CS) subtypes, as well as the mixing of different follow-up times, as both have been shown to have an effect on the clinical outcomes in osteoarthritic knees.

Our primary concern with the pooling of different PRP and HA subtypes is that these have both been shown to have different biological properties, which may impact the outcomes. Recently, there have been advances in our understanding of PRP and its biological properties. Particular attention has been paid to the leukocyte concentration regarding whether it is a pure plasma preparation or a platelet-rich fibrin matrix (PRFM). Dohan-Ehrenfest et al.[8] subgrouped PRPs into 4 categories: (1) leukocyte-poor PRP (LP-PRP), (2) leukocyte-rich PRP (LR-PRP), (3) LP-PRFM, and (4) LR-PRFM. The PRFM differs, as an anticoagulant is not added and it forms a gel-like substance, and thus it is not used as an intra-articular injection but primarily used for ligamentous healing.

In osteoarthritic knees, there are basic science studies that have shown LP-PRP can stimulate endogenous HA production and decrease cartilage catabolism, as well as suppress the inflammatory mediators and expression of their genes in synoviocytes and cartilage.[9] Cole et al.[10] found in a randomized controlled trial (RCT) that with LP-PRP there was a decrease in the proinflammatory cytokines, as measured by enzyme-linked immunosorbent assay. Although there may be concern with LR-PRP and that it may be proinflammatory based on basic science studies, Mariani et al.[11] found that this did not alter the inflammatory cytokines as measured by enzyme-linked immunosorbent assay. A recently published meta-analysis of RCTs by Belk et al.[3] found that PRP resulted in significantly improved clinical outcomes and reduced pain levels compared with HA, in contrast to the authors' findings. In addition, they showed that LP-PRP may be superior to LR-PRP and that a difference exists between the 2 PRP subtypes. Similarly, Riboh et al.[4] also determined in their network meta-analysis that LP-PRP improved outcomes compared with LP-PRP. Thus, the differing subtypes of PRP do appear to alter the outcomes, and it is incorrect to pool them, as the authors have done. The authors findings are also in disagreement with the RCTs in the literature comparing single- and multiple-PRP injections, which may stem from its pooling of different PRP subtypes. Vilchez-Cavazos et al.[5] performed a meta-analysis of these trials and determined that although there was no difference in pain at 6 months, multiple injections of PRP resulted in improved functional outcomes at 6 months.

HA and its subtypes also have differing effects in osteoarthritic joints. HA has 2 main subgroups based on its molecular weight, high-molecular weight HA (HMW-HA), and low-molecular weight HA (LMW-HA). HMW-HA has been suggested to be more efficacious, as it more closely resembles the natural HA in the knee, which is lost in an osteoarthritic joint.[12-15] Another recent network meta-analysis by Phillips et al.[6] found that HMW-HA was the most efficacious treatment for knee osteoarthritis in terms of reducing pain and improving functional outcomes. This is supported by the basic science evidence, as Elmorsy et al.[16] found in a rabbit osteoarthritis model, that HMW-HA has greater chondroprotective effects than LMW-HA.

The authors used differing time points for their analysis, pooling outcomes at 6- and 12-month follow-up. As the authors note, CS may be most efficacious in the short term, and that this effect may not be seen beyond 6 months' follow-up, and thus may have led to their earlier follow-up success.[1,17,18] However, this does not take into account the differences between standard- and extended-release CS, which may also affect the outcomes.[6,19] Many of the included RCTs not only report their outcomes at final follow-up but also at their mid-term follow-up time points, which is a strength of these trials. Therefore, it may be more appropriate for future meta-analysis and network meta-analysis to

compare the outcomes at different time points and not pool for final follow-up alone. Although CS may be most efficacious in the short term, it is unclear if they lead to long-term success, and further analyses may better determine the efficacy of these treatments over time.

While we appreciate the authors' work on this study, we believe the methodologic concerns of pooling different PRP and HA subtypes, as well different follow-up time points, may lead to incorrect conclusions being drawn from this study. We would like to echo our previous calls for greater reporting on the cytology of PRP, as it is poorly reported on and thus limits our true understanding of the area; until then, it is still unclear what we are using.[20-22]

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Accurate Assessment of the Hill-Sachs Lesion: There Is No Information About the Accuracy of Quantification of These Lesions

Optimal assessment of a Hill-Sachs lesion is an important aspect of shoulder instability management, as it is shown to be associated with recurrent dislocations.[1] A Hill-Sachs lesion is present in >84% of patients after a first-time dislocation and >88% after recurrent dislocations.[2,3] Therefore, we read "Accuracy and Reliability of Imaging Modalities for the Diagnosis and Quantification of Hill-Sachs Lesions: A Systematic Review" by Vopat et al.[4] with great interest. The authors conclude that the studies in the review demonstrate acceptable accuracy with regard to both diagnosing and quantifying Hill-Sachs lesions. However, considering the importance of this subject, we would like to argue the strength of this conclusion.

In the systematic review, 2 components are evaluated: accuracy and reliability. A clinical test or measurement with high accuracy gives a value that is close to the actual value that an observer intends to measure. A test with a high reliability demonstrates the same value when the test is repeated under the same conditions. Therefore, a test with high reliability can still have low accuracy (when the outcome is not close to the actual value). A test that is both accurate and reliable is considered valid, and the best available test under reasonable conditions is considered the gold standard.

The authors showed that the included studies report only reliability for quantifying Hill-Sachs lesions on 2- and 3-dimensional computed tomography (2D-CT and 3D-CT) and magnetic resonance imaging and angiography (MRI and MRA) and do not report accuracy for any of these modalities. With regard to quantification of Hill-Sachs lesions, they showed that only the study by Cicak et al.[5] reported accuracy for quantification of Hill-Sachs lesions on ultrasound and radiography. However, the reported 97% accuracy for ultrasound and 84% accuracy for radiography are not for quantification but for detection of Hill-Sachs lesions, with surgical findings as the reference standard (which they used as a gold standard).[5] Hence, Cicak et al. did measure volume but did not determine accuracy for their measuring method. This may also be the reason Vopat et al.[4] found possible bias in the reference standard with the QUADAS-2 tool for the study. Therefore, none of the studies seem to report accuracy for quantification of Hill-Sachs lesions, and we believe the conclusion stating that different imaging modalities show acceptable accuracy in quantifying Hill-Sachs lesions cannot be drawn.

Measuring bony lesions can be difficult, as has recently been shown for measurement of bony Bankart lesions.[6] Vopat et al.[4] discuss that the literature confirms 3D-CT as the gold standard in quantifying humeral bone loss, which is shown to be the case for identifying these lesions. However, a gold standard for quantifying lesions should consist of a modality (such as 3D-CT) in combination with a measuring method. Methods that are currently available often use 2D measurements to measure 3D volume,[6] such as a line or a circle, which was also the case in the study by Cicak et al.[5] For bony Bankart lesions, these measurements are used to determine recurrence risk; however, this concept has been challenged, as these measurements are not proven to be accurate.[6,7] The size of bony lesions is associated with recurrence, and a proper quantification can therefore be important in determining recurrence risk,[1] for example, when determining whether a Hill-Sachs lesion is on or off track.[4] 2D measurements were not proven to be accurate in quantifying bony lesions, and we believe a 3D approach is most suitable to find an appropriate gold standard.[6,8]

In conclusion, we do not believe that current evidence demonstrates how Hill-Sachs lesions can be accurately measured. In our opinion, 3D measurements may be valuable in accurately measuring the volume and relevance of a Hill-Sachs lesion.

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