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RE: Talks BJ, Fernquest S, Palmer A, et al. 2019. No evidence of systemic inflammation in symptomatic patients with femoroacetabular impingement

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Author Contributions

CLM and AB wrote and edited the letter, and approved the final version.

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Dear Professor Sandell,

We are writing in regards to an article by Talks and colleagues [1] that was recently published in the Journal of Orthopaedic Surgery. The stated aim of the study was to "determine whether there was evidence of systemic inflammation in patients with FAI, defined by sFLCs, and whether this correlated with markers of disease severity." The article measured serum free light chains (sFLCs) in 115 patients with femoroacetabular impingement (FAI), with 57 patients undergoing surgical intervention and 58 receiving physiotherapy. The authors did not include a cohort of demographically matched athletes that do not have FAI. The study found that the

baseline levels of sFLCs in all patients was 30.36±9.23 mg/L, and at follow-up the levels in the surgical intervention was 29.48±7.85 mg/L and 31.68±9.61 mg/L. Based on no observed change in sFLC levels in response to surgical or conservative interventions, the authors concluded that no systemic inflammation was present in patients with FAI.

We would like to acknowledge the authors on performing a biomarkers study in 115 patients with FAI. The sample size is impressive, and we need more well-powered studies with diverse patient populations. We also appreciate the importance of identifying factors that can help in predicting appropriate candidates for surgical versus conservative treatment. The data in this paper that showed an improvement in patient reported outcomes in surgical but not conservative treated patients is an important contribution to the FAI literature. We do, however, have concerns about conclusions the authors made regarding inflammation and FAI.

A previous study from our lab in athletes with FAI demonstrated that, compared to age- and activity-matched athletes without FAI, those with FAI had a 24% increase in circulating levels of cartilage oligomeric matrix protein (COMP) and a nearly three-fold elevation in circulating levels of C-reactive protein (CRP) [2]. COMP has been used as a marker of cartilage turnover in patients with osteoarthritis (OA), and CRP has been used as a marker of inflammation in OA and many other chronic conditions [3]. Additionally, biopsies of tissue from patients undergoing FAI corrective surgery have shown clear signs of local inflammation in the hip joint [4-6]. While there was a fair amount of variability in CRP levels in our study, and we only had N=19 subjects in the control and N=10 in the FAI cohort, given the evidence of local inflammation in FAI and OA, and studies demonstrating systemic inflammation in patients with OA, we do think inflammation likely plays a role in symptoms associated with FAI.

The topic of inflammation in FAI is important in understanding the etiology and treatment options for the condition, but we do not think the paper by Talks and colleagues measure a clinically meaningful marker of inflammation in an athletic population. sFLCs are produced by activated plasma cells, and are commonly used in the diagnosis and monitoring of multiple myeloma [7]. As the authors point out, there are some indications that sFLCs can be useful in monitoring rheumatoid arthritis (RA), but no studies have evaluated sFLCs in OA. Outside of multiple myeloma and RA, other studies in the literature that use sFLCs to monitor disease progression focus on various other cancers and severe systemic diseases. For these conditions, there is a clear suspected role for a plasma cell response in the disease pathology. Elias-Jones and colleagues [6] evaluated the presence of various immune cell populations in patients with FAI and observed virtually no $CD3^+$ T-lymphocytes in labral biopsies, although a robust innate immune response was present. Based on the lack of an adaptive immune cell presence in patients with FAI, and general observations of the adaptive immune system in other musculoskeletal injuries and diseases, we would not anticipate plasma cells to be activated at a substantial level in the case of otherwise healthy athletes with FAI.

Since there is no evidence that sFLCs are useful biomarkers of inflammation outside of autoimmune disease or severe systemic diseases, the available data does not support Talks and colleagues' rejection of inflammation in FAI. Furthermore, an absence of reduction in sFLCs after surgical intervention is not synonymous with absence of baseline inflammation. Although we continue to understand the pathophysiology of hip impingement, based on the best available evidence we hold that reducing inflammation should continue to be a clinical objective in the treatment of patients with FAI.

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