Title: Reply: Normal serum free light chain concentrations in femoroacetabular impingement – evidence against a systemic inflammatory response

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Running Title: Normal sFLCs in FAI

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Letter to the Editor

14th July 2019,

Dear Professor Sandell,

We are writing in response to the letter by Mendias and Bedi, regarding our recent publication in the Journal of Orthopaedic Surgery ¹. Lately, inflammation has been acknowledged as a factor in the pathogenesis of osteoarthritis, with local inflammation contributing to disease progression ² and systemic inflammation correlating with symptom severity ³. However, the current literature predominantly suggests that femoroacetabular impingement (FAI) is a mechanical phenomenon: abnormal morphology of the hip joint exposes it to supraphysiologic stress, resulting in recurrent microtrauma of the articular cartilage, which eventually culminates in osteoarthritis of the joint ⁴⁻⁶.

In our recently published study 115 individuals (38 male, 77 female, mean age 37 years) with symptomatic FAI were randomised to receive either surgical intervention (n=58) or physiotherapy (n=58) ¹. Serum free light chain (sFLC) concentrations were measured as a marker of systemic inflammation. At baseline for all individuals, mean sFLC concentrations were 30.36 mg/L (SD 9.23). At follow-up 8-months post-randomisation, sFLC concentrations were 31.68 mg/L (SD 9.61) in the surgical intervention cohort and 29.48 mg/L (SD 7.85) in the physiotherapy cohort. These levels are within the normal reference range 3.5 – 72.1 mg/L

for sFLCs ⁷. Additionally, there was no association between sFLC concentrations and any of the measures of disease severity at baseline: average or maximum cartilage alpha angle, centre edge angle, Kellgren Lawrence grade, and patient reported outcome measures. Further, despite a significant improvement in alpha angle and patient reported outcome measures between baseline and follow up, there was no corresponding change in sFLC concentrations. These findings support the suggestion that FAI is a mechanical pathology with a local inflammatory response, but no systemic inflammation.

A limitation of this study is that we only looked at one biomarker of inflammation and further adequately powered investigation of other inflammatory markers would be useful to validate our findings. However, contrary to Mendias and Bedi we do believe sFLCs were a useful marker of inflammation to study in the FAI population. sFLCs are an inflammatory marker produced directly by activated B-cells and are renally cleared with a half-life of 2-5 hours. All inflammatory infiltrate contains a mixture of B cells that secrete FLCs and T cells that secrete IL-6 (along with other immune cells) to stimulate CRP production by the liver. In common with all biomarkers sFLCs have a lower limit of clinical sensitivity, so normal levels of sFLCs cannot exclude the possibility of low levels of inflammation; however, the inflammatory response would have to be minimal to be undetectable. sFLCs have a longer half-life following an inflammatory event than CRP, due to ongoing production by activated B-cells with a half-life of several days or longer. This makes it more likely to detect elevated sFLCs in the context of FAI.

It is important to note that despite Mendias and Bedi's assertion that CRP is a more sensitive marker of inflammation, sFLC levels have been shown to provide distinct, complementary, information on an individual's inflammatory status ⁸. As mentioned by Mendias and Bedi,

previous research on sFLCs has predominantly focussed on monoclonal haematological diseases, where they play a key role in disease diagnosis and monitoring. With time it is likely that sFLC measurements will have more general applications in the detection of inflammation, particularly in the context of impaired liver, renal, and cardiovascular function ⁹.

Medias and Bedi reference the results of their previous study comparing CRP levels in age-matched athletes (n=10, mean=3.15 mg/L) with symptomatic FAI to control athletes (n=10, mean= 0.83mg/L) ¹⁰. CRP levels in the athletes with symptomatic FAI were found to be significantly higher than the control group of athletes, which the authors interpreted as evidence of systemic inflammation in symptomatic FAI patients. Unfortunately, we did not have a control group for comparison, but we do have concerns about their conclusion of systemic inflammation being present in FAI. The absolute difference in mean CRP levels between the groups was only 2.32 mg/L, which is minimal and could be due to a number of confounding factors, particularly when considering such a small sample size. Exercise represents one such confounding factor when comparing groups of athletes; CRP levels can increase up to 22.7 mg/L (SD 15.9) after strenuous exercise ¹¹. Although Bedi et al did match the two groups' activity levels using the Tegner scale, this does not consider length of training sessions, recent athletic events, or type of physical activity, all of which can effect CRP levels ¹².

Based on the current evidence, it appears that FAI is a predominantly mechanical pathology with a local inflammatory component. Whilst this remains the case, we suggest caution should be exercised before investing valuable resources in trialling the growing range of anti-inflammatory therapeutics targeting osteoarthritis on patients with FAI ¹³.

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