

# **No evidence of systemic inflammation in symptomatic patients with femoroacetabular impingement**

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## **Abstract**

### **Objective**

Femoroacetabular impingement (FAI) is a common cause of hip pain and represents a major cause of early osteoarthritis. The role of systemic inflammation in pre-arthritic hip conditions remains largely unknown and uninvestigated. Serum free light chains (sFLC) are an inflammatory marker produced by B cells. This study aimed to determine whether there was evidence of systemic inflammation in patients with FAI, defined by sFLC, and whether this correlated with markers of disease severity.

### **Design**

Participants for this study were recruited from a single centre (Nuffield Orthopaedic Centre, Oxford) and were taking part in the Femoroacetabular Impingement Trial. The cohort comprised 115 individuals (38 male, 77 female, mean age 37 years): 57 individuals received surgical intervention and 58 received physiotherapy. All individuals provided patient reported outcome measures (PROMs) and serum samples at baseline and follow up 8-months post-randomisation. sFLC concentrations were measured in serum samples by immunoturbidimetry.

### **Results**

At baseline, for all individuals, mean polyclonal sFLC count was 30.36 mg/L (SD 9.232). At follow-up, the mean polyclonal sFLC levels were 31.68 mg/L (SD 9.61) in the surgical intervention cohort, and 29.48 mg/L (SD 7.85) in the physiotherapy intervention cohort. There was no significant correlation between sFLC levels and any of the PROMs, average or maximum alpha angle, or centre edge angle.

## **Conclusions**

In patients with symptomatic FAI, there was no evidence of systemic inflammation, as defined by sFLC levels, and no correlation between sFLC levels and measures of disease severity. The lack of inflammation suggests FAI is a mechanical phenomenon.

## **Manuscript Key Words**

Femoroacetabular Impingement; inflammation; serum free light chains; osteoarthritis

## **Declarations of Interest**

Arthur Bradwell founded the Binding Site Ltd. and remains a shareholder. The company manufactures free light chain and other diagnostic kits.

The rest of the authors (BT, SF, AP, JB, KP, SG) have no declarations of interest.

## **Abbreviations**

FAI: femoroacetabular impingement

sFLC: serum free light chains

PROMs: patient reported outcome measures

## Background

Osteoarthritis is a condition of progressive joint cartilage degradation resulting in potentially disabling pain and loss of function. Osteoarthritis affects 9.6% of men and 18% of women older than 60 years, predominantly involving the knee and hip joints [1].

Femoroacetabular impingement (FAI) is a common cause of hip pain, particularly in young active individuals, and represents a major cause of early osteoarthritis [2,3]. FAI is a condition of abnormal morphology of the hip joint, resulting in an aspherical femoral head or acetabular overcoverage, classified as cam or pincer impingement respectively [2]. Subsequently, abnormal contact occurs between the proximal femur and acetabulum, resulting in supraphysiologic stress of the joint, which can result in tears of the acetabular labrum and avulsion of the underlying articular cartilage [2,4]. This recurrent microtrauma of the hip causes progressive joint degeneration, culminating in hip osteoarthritis [3].

FAI is common, a recent systematic review found the prevalence (mean  $\pm$  standard deviation (SD)) of cam morphology to be  $22.4 \pm 6.2\%$  in asymptomatic individuals, increasing to  $66.4 \pm 23.5\%$  in athletes [5]. Although not all individuals with FAI progress to develop osteoarthritis, severe cam morphology is associated with a 10-fold increase in risk of total hip replacement [6] and cam deformity is observed in  $>50\%$  of individuals undergoing premature total hip replacement under the age of 50 years [7]. However, the evidence for pincer morphology causing hip osteoarthritis is controversial [8].

Traditionally, the pathogenesis of osteoarthritis was presumed to be an entirely mechanical process. Recently, local inflammation of the synovium, cartilage, and subchondral bone have also been shown to contribute to disease progression, through the production of inflammatory cytokines and matrix proteases [9]. Some studies suggest systemic inflammation could be an additional feature of the disease, with a recent systematic review showing an association between the acute phase protein C-reactive protein (CRP) and symptoms of osteoarthritis [10].

Analysis of cartilage samples harvested from patients with FAI during hip surgery has provided good evidence for local inflammation in FAI [11–13]. Real-time polymerase chain reaction has shown metabolic hyperactivity and increased expression of inflammatory genes in FAI cartilage [11,12]. Immunohistochemical staining has shown significantly greater inflammatory cell infiltration and neovascularisation in cartilage samples from patients with FAI compared to patients with osteoarthritis [13]. However, there has been little investigation of whether systemic inflammation occurs in FAI; one study showed significantly higher CRP levels in athletes with symptomatic FAI than normal controls athletes, although the participant numbers and CRP levels were modest [14].

Numerous biomarkers have been suggested for use in osteoarthritis, particularly markers of tissue degradation [9,15]; however, few studies have looked at biomarkers in pre-arthritic hip conditions, such as FAI [15]. Serum free light chains (sFLC) are inflammatory markers produced by immune cells of plasma cell lineage, they are renally cleared with a short half-life of 2-5 hours. Initial studies have demonstrated the potential of sFLC as a clinically useful biomarker across various fields [16]. In

rheumatoid arthritis, sFLC levels correlate with disease activity [17–19], and sFLC concentrations are raised 3-5 years before the clinical diagnosis of rheumatoid arthritis [20]. The role of sFLC has not yet been investigated in FAI or osteoarthritis.

The aims of this study were i) to determine whether individuals with FAI had evidence of systemic inflammation as defined by sFLC levels; and ii) to determine if sFLC levels correlated with radiological and patient reported markers of disease severity in FAI.

## **Methods**

### **Ethics**

This study was approved by Health Research Authority, National Research Ethics Services Committee South Central – Berkshire (REC reference: 13/SC/0154).

### **Cohort**

The study cohort comprised participants from the Femoroacetabular Impingement Trial (FAIT). The FAIT trial is a multi-centre two-arm randomised controlled trial comparing physiotherapy and activity modification with arthroscopic surgery for the management of symptomatic FAI [21]. Participants for this study were selected from a single centre (Nuffield Orthopaedic Centre, Oxford). Participants were aged 18 to 60 years and referred to secondary or tertiary care with symptomatic FAI confirmed clinically and with imaging (radiography and magnetic resonance imaging). Surgeons made a qualitative assessment of hip morphology to diagnose FAI. Participants were excluded if they had completed a programme of physiotherapy targeting FAI within the preceding 12 months, had received previous surgery to their symptomatic hip, or had

established osteoarthritis (Kellgren-Lawrence  $\geq 2$ ) or hip dysplasia (centre-edge angle  $< 20^\circ$  on anteroposterior pelvis radiograph).

## **Interventions**

Physiotherapy and Activity Modification (subsequently referred to as 'Physiotherapy'): a goal-based programme was developed for this trial based on the consensus opinion of the study team and existing literature. Treatment was delivered by a Specialist Physiotherapist or Advanced Physiotherapy Practitioner. The programme was tailored to individual patient needs and their desired level of function with an emphasis on muscle strengthening to improve core stability and movement control. Participants were encouraged to avoid impingement positions (extremes of hip flexion, abduction, internal rotation). Up to eight sessions were provided over a five-month period to reflect what is feasible in current National Health Service (NHS) practice.

Arthroscopic surgery: femoral and acetabular bone seen to impinge intra-operatively was excised with a burr (osteochoondroplasty) to eliminate impingement on dynamic hip flexion and internal rotation. Labral tears were repaired if possible, or otherwise debrided. Articular cartilage lesions were debrided to a stable base and in areas of full thickness cartilage loss, microfracture of the subchondral bone was performed. Participants received post-operative physiotherapy, provided as routine care in the NHS, that focused on maintaining range of movement and a graduated return to activity.

## **Outcomes**



Imaging measurements were performed using custom software by academic orthopaedic clinicians (AJRP and SF). Osteoarthritis was evaluated as the Kellgren-Lawrence Grade [22]. Dysplasia and pincer morphology were quantified using the centre edge angle on a standing anteroposterior radiograph. Cam morphology was measured as the maximal cartilage alpha angle at the 12 o'clock, 1 o'clock, 2 o'clock, and 3 o'clock position on MRI radial slices [23]. All Intraclass Correlation Coefficients for intra-observer and inter-observer reproducibility values exceeded 0.90.

Patient-reported outcome measures (PROMs) collected in this study were: Hip Outcome Score Activities of Daily Living (HOS ADL), HOS Sport subscale [24], Non-Arthritic Hip Score (NAHS) [25], and University of California, Los Angeles activity score (UCLA) [26]. Clinical assessment to examine hip range of movements, strength and impingement tests were carried out at baseline and follow up visits.

### **Serum Samples**

Fasting serum samples from individuals in both treatment arms were collected at baseline and 8-months post randomisation in a single centre (Nuffield Orthopaedic Centre, Oxford). Anonymised aliquots were shipped to the Binding Site Ltd for laboratory analysis.

### **Laboratory analysis**

There are two types of sFLC:  $\kappa$  and  $\lambda$ , polyclonal sFLC refers to the sum of  $\kappa$  and  $\lambda$  sFLC concentrations. sFLC concentrations were measured in anonymised serum samples by immunoturbidimetry, using the Freelite® sFLC assays and Optilite®

analyser (Binding Site Group Ltd, Birmingham, United Kingdom) [27]. The assays were sensitive to 0.6 mg/L for  $\kappa$  sFLC and 1.3 mg/L for  $\lambda$  sFLC concentrations.

Samples with an abnormal  $\kappa/\lambda$  ratio underwent reflex testing with capillary zone electrophoresis using the V8 E-class system (Helena Biosciences Europe, Gateshead, United Kingdom) for the quantification of paraproteins, and immunofixation and electrophoresis (Binding Site Group Ltd, Birmingham, United Kingdom), for the typing of paraproteins.

## **Statistics**

Statistical calculations were performed using STATA V.14.1 (College Station, Texas, USA). Distribution of values was examined using histograms and kernel density plots. Comparison of means was undertaken using an independent two-tailed Student's t-test for parametric data. Linear regression modelling was adopted to assess sFLC levels between groups, adjusting for the minimisation factors gender and age. Statistical significance was set at  $p < 0.05$ .

## **Results**

### **Participant demographics**

The cohort in this study comprised 115 individuals (38 male, 77 female, mean age 37 years). 57 individuals received surgical intervention, and 58 received physiotherapy. All individuals in the study cohort had symptomatic FAI and completed PROMs at baseline and follow-up. The primary pathology was isolated cam morphology FAI, which was found in 94% of individuals.

### **Marker of disease severity**

At baseline, mean HOS ADL score was 68.25 (SD 18.30), mean HOS Sport score was 49.63 (SD 23.49), mean NAHS score was 61.67 (SD 19.94), and mean UCLA was 5.32 (SD 2.65). Significant improvement was seen in all PROMs at follow-up in the surgical cohort, but not in the physiotherapy cohort (table 1).

All individuals in the study cohort received magnetic resonance and X-Ray imaging at baseline to quantify FAI morphology. At baseline, mean average cartilage alpha angle was 68.00° (SD 11.57), mean maximum cartilage alpha angle was 86.48° (SD 15.64), and mean centre edge angle was 28.82° (SD 6.94). 93 individuals had a Kellgren-Lawrence grade of 0, and 22 had a grade of 1.

### **Serum Free Light Chains**

At baseline, for all individuals, mean  $\kappa$  sFLC count was 15.71 mg/L (SD 5.02), mean  $\lambda$  sFLC count was 14.65 mg/L (SD 4.47), mean polyclonal sFLC count was 30.36 mg/L (SD 9.23, figure 1), and mean  $\kappa/\lambda$  ratio was 1.12 mg/L (SD 0.29). There was no significant difference in mean values between surgical and physiotherapy intervention groups at baseline.

At follow-up, for the surgical intervention cohort, mean  $\kappa$  sFLC count was 16.03 mg/L (SD 4.57), mean  $\lambda$  sFLC count was 15.47 mg/L (SD 6.42), mean polyclonal sFLC count was 31.68 mg/L (SD 9.61, figure 2), and mean  $\kappa/\lambda$  ratio was 1.09 mg/L (SD 0.28). There was no significant difference in mean values between baseline and follow up for surgical intervention.

At follow-up, for the physiotherapy intervention cohort, mean  $\kappa$  sFLC count was 15.43 mg/L (SD 4.23), mean  $\lambda$  sFLC count was 14.05 mg/L (SD 4.40), mean polyclonal sFLC count was 29.48 mg/L (SD 7.85, figure 2), and mean  $\kappa/\lambda$  ratio was 1.15 (SD 0.30). There was no significant difference in mean values between baseline and follow up for physiotherapy intervention (table 1).

### **Relationship between free light chains and markers of FAI disease severity**

No statistically significant correlation was seen between sFLC levels and any of the PROMs at baseline. No statistically significant correlation was observed between sFLC and average or maximum cartilage alpha angle (figure 3), or centre edge angle. There was no statistically significant difference in free light chain levels between individuals with a Kellgren Lawrence grade of 0, and those with a grade of 1 (table 2, figure 4).

Males were found to have a significantly higher  $\kappa$  sFLC than females. Males had a  $\kappa$  sFLC 2.08 mg/L higher than females ( $r^2 = 0.038$ ,  $p = 0.036$ ). However, when adjusted for age this stopped being significant ( $p=0.065$ ). There was no significant difference between males and females for  $\lambda$  sFLC, or polyclonal sFLC (table 2).

## **Discussion**

The role of systemic inflammation in pre-arthritis hip conditions remains largely unknown and uninvestigated. This study demonstrates no correlation between sFLC, as a marker of systemic inflammation, and markers of disease severity in FAI.

## Systemic inflammation

In our study, symptomatic patients with FAI did not have sFLC levels elevated outside of the normal range: at baseline patients had a mean sFLC concentration of 30.36 mg/L, which is within the normal reference range of 3.5 – 72.1 mg/L [28]. This would suggest there is no evidence of B-cell activation present in systemic inflammation in this cohort of individuals with symptomatic FAI. This finding is in contrast to the only other previous study of inflammatory markers in FAI [14]. Bedi et al. demonstrated higher CRP levels in athletes with symptomatic FAI (n=10, mean=3.15 mg/L) than control athletes (n=10, mean=0.83 mg/L); however, both the size of study and the CRP levels measured were modest. Exercise is known to effect CRP levels causing both acute increases in CRP after hard exercise and decreases in CRP with regular training; different activities have a variable impact on CRP levels [29]. Although, Bedi et al. matched the two athlete groups for activity levels using the Tegner scale, this does not provide information about the hours athletes trained for, recent athletic events, or what type of physical activity they engaged in. It is worth noting that sFLC and CRP provide independent measures of immune activation [30]: CRP is produced by the liver in response to IL-6 production by B-cells (and other immune cells), sFLC are produced directly by activated B-cells during any inflammatory process [31].

FAI represents a major cause of early osteoarthritis [7,32]. Progression to osteoarthritis has traditionally been viewed as a solely mechanical process [2], for which there are currently no prognostic biomarkers. Markers of tissue degradation such as C-terminal telopeptide of collagen type II (CTX-II) and serum cartilage

oligomeric matrix protein (COMP) have been investigated as biomarkers of osteoarthritis progression [9,15]. Urinary CTX-II and serum COMP levels have shown promise in longitudinal studies, correlating with incidence and progression of knee and hip osteoarthritis [33,34]; however, these measures lack sufficient validation for clinical use [15,35]. Recent studies have demonstrated the existence of local inflammation in FAI [11–13], suggesting that perhaps an inflammatory phenotype exists in FAI driving joint degradation, as has been proposed in osteoarthritis [36]. The presence of systemic inflammation is not supported by this study, limiting the applicability of new anti-inflammatory medications being studied in osteoarthritis to FAI [36]. However, further research into other markers of systemic inflammation is required to validate this assumption.

### **Prognostic markers**

There was no association between sFLC levels 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 (table 2). This is the first study to compare a marker of systemic inflammation with measures of disease severity, so further studies with additional inflammatory biomarkers are required for validation.

Alpha angle and PROMs are currently the gold-standard measures of disease severity in FAI, and can even predict progression to end stage disease [6,37]. Severe cam deformity, defined by an alpha angle  $>83^{\circ}$ , is associated with a 10-fold increase in risk of total hip replacement [6]. The lack of association of sFLC with either alpha angle

(figure 3) or any of the PROMs in this study (table 2), suggests that there is not an association between markers of systemic inflammation and markers of disease severity. This finding would support the argument that FAI is a mechanical phenomenon with a local inflammatory process, but no systemic inflammation.

There was significant improvement in alpha angle and all PROMs between baseline and follow up in the surgical intervention cohort (table 1). However, no corresponding change in sFLC levels was observed (figure 2), further supporting the lack of correlation between sFLC and markers of disease severity. An important consideration when using PROMs is the importance of patient characteristics, such as mental health, activity level, smoking status, and sex in determining outcomes, rather than just underlying pathophysiology [38]. Interestingly, although sFLC did not correlate with FAI symptoms in this study, CRP has previously been shown to correlate with symptoms in osteoarthritis [10]. This could be explained by systemic inflammation playing less of a role in FAI than osteoarthritis, or perhaps due to the different inflammatory pathways stimulating CRP and sFLC production.

Other radiographic measures collected were centre edge angle and Kellgren Lawrence grade of each joint. Centre edge angle is a radiographic measure of acetabular morphology, an angle  $>39^\circ$  defines a pincer deformity [39]. The lack of correlation between sFLC levels and centre edge angle supports the findings of a recent large cohort study that found no association between pincer morphology and the development of osteoarthritis [8]. Kellgren Lawrence grade is a radiographic classification of osteoarthritis [22]. Patients with established osteoarthritis were excluded from this study, leaving only patients with grade 0 or 1 joints in the study.

There was no difference in sFLC levels between individuals with Kellgren Lawrence grade 0 or 1 joints (figure 4), demonstrating that sFLC are unable to identify individuals with very early osteoarthritis.

### **Limitations of our study**

This study only looked at 115 patients with symptomatic FAI presenting to a tertiary referral centre, such a highly selected patient group has limited generalisability to the general population. Individuals with advanced osteoarthritis were excluded from this study; it is possible that systemic inflammation increases with disease progression, explaining the association of CRP with symptoms in osteoarthritis [10]. It would have been beneficial to have had an age-matched control cohort for comparison of sFLC levels with.

Systemic inflammation was only assessed using a single biomarker, sFLC, which are produced directly by activated B-cells. Although, sFLC are clinically useful in rheumatoid arthritis [17–20], it does represent a distinct inflammatory pathway to other inflammatory measures, such as CRP [30].

### **Conclusion**

FAI is a very prevalent condition and represents a major cause of early onset osteoarthritis. In patients with symptomatic FAI, there was no evidence of systematic inflammation, as defined by sFLC levels, and no correlation between sFLC levels and



measures of disease severity. This suggests that FAI is a mechanical phenomenon without any systemic inflammatory response component.

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## Tables

Table 1 – markers of disease severity and sFLC levels at baseline and follow up.

[illegible]

Table 2 – associations between markers of disease severity and polyclonal sFLC levels.

		Polyclonal sFLCs					
		Univariate regression			Multivariate regression*		
		Coefficient	R <sup>2</sup>	P value	Coefficient	R <sup>2</sup>	P value
Kellgren lawrence	1	-1.905	0.007	0.387	-2.360	0.024	0.293
	0	-	-	-	-	-	-
Average cartilage alpha angle		0.064	0.007	0.394	0.054	0.021	0.478
Max cartilage alpha angle		0.002	0.000	0.969	-0.003	0.017	0.959
Centre Edge Angle		0.087	0.004	0.486	0.065	0.017	0.609
HOS ADL		-0.013	0.001	0.788	-0.038	0.019	0.459
HOS SPORT		-0.034	0.007	0.362	-0.045	0.027	0.241
NAHS		-0.032	0.005	0.461	-0.062	0.030	0.191
UCLA		-0.038	0.000	0.922	-0.211	0.017	0.609
Gender	Male	1.678	0.007	0.362	1.451	0.014	0.435
	Female	-	-	-	-	-	-

\* age and gender as covariates (age only when comparing males with females)



Figures

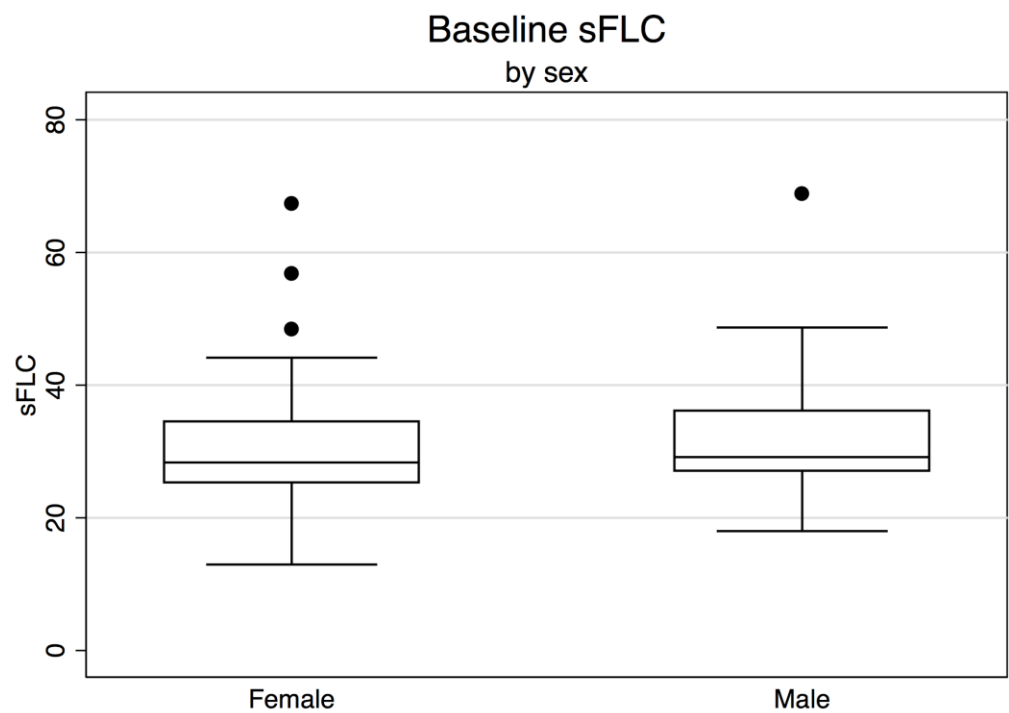


Figure 1. Baseline polyclonal sFLC levels in all male and female individuals.

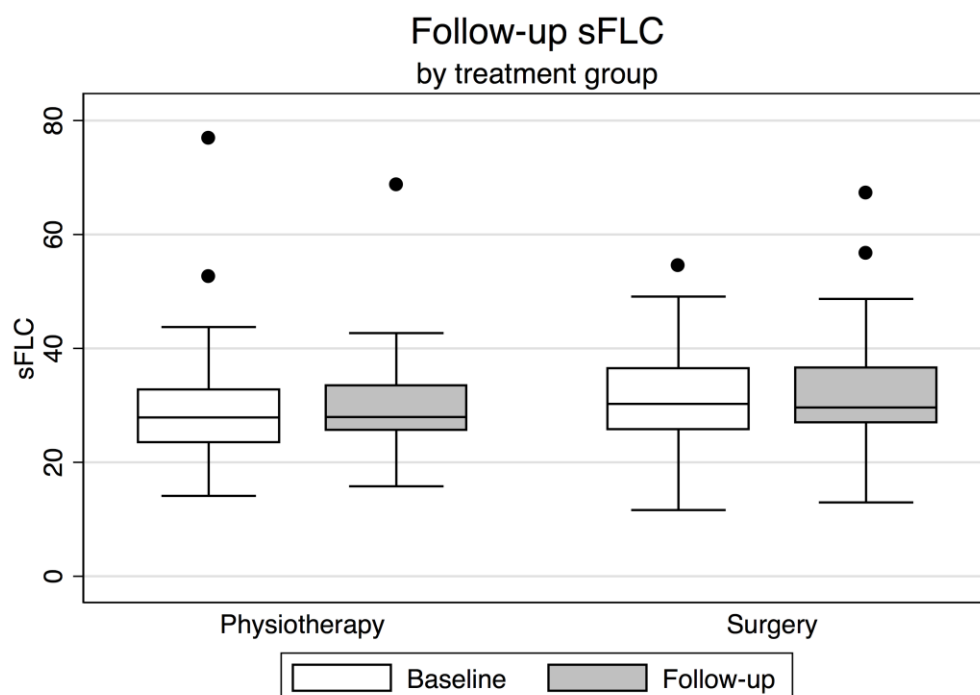


Figure 2. Baseline and follow up polyclonal sFCL levels in the physiotherapy and surgery treatment groups.

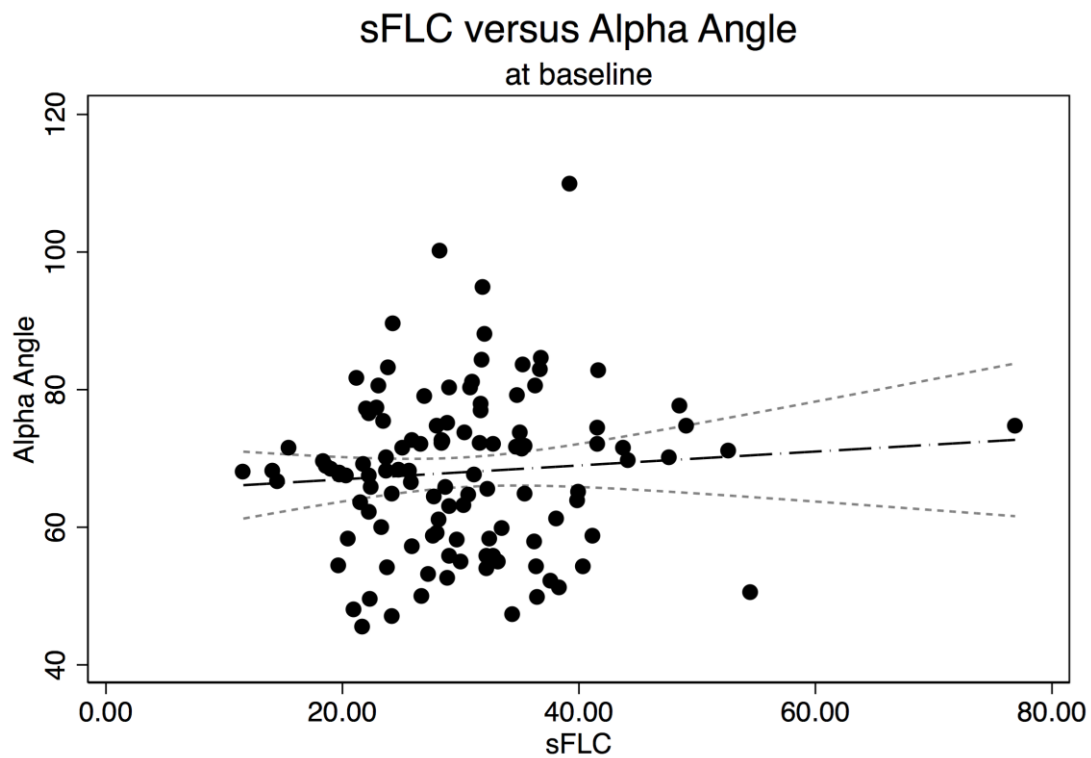


Figure 3. There was no statistically significant correlation between average or maximum alpha angle and sFLC at baseline.

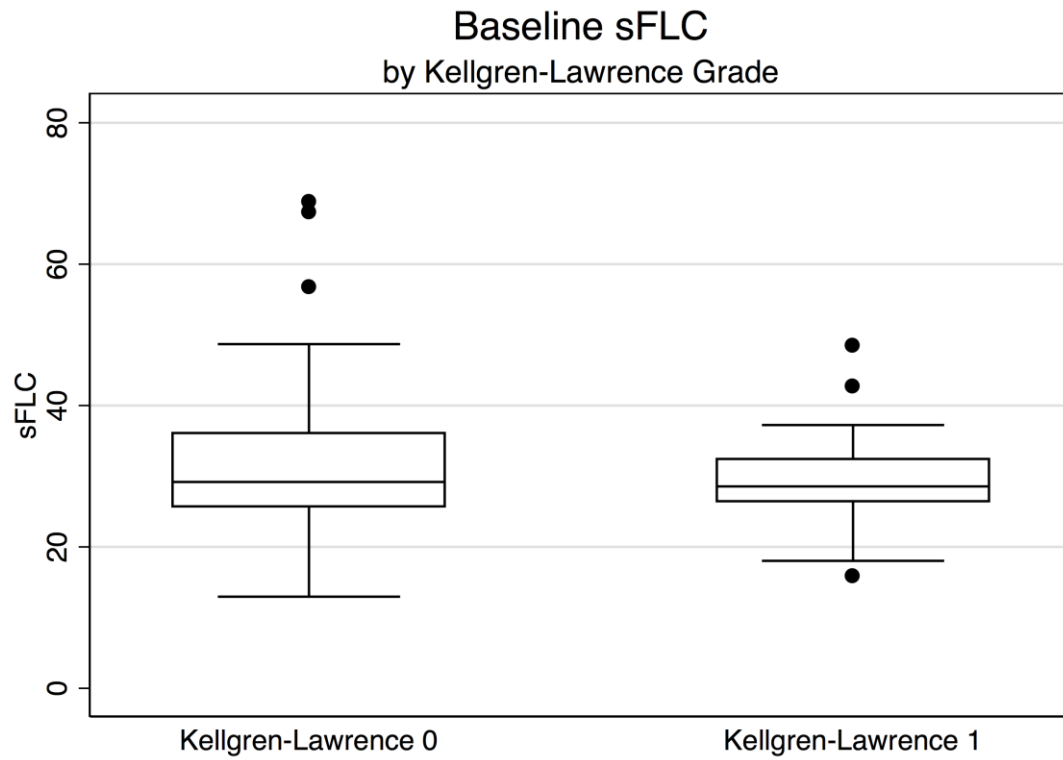


Figure 4. There was no difference in sFLC levels between patients with Kellgren-Lawrence grade 0 and 1 joints.