ELEVATED CRP LEVELS IN OSTEOARTHRITIS ARE ASSOCIATED WITH LOCAL INFLAMMATION

+*Pearle, A D; *Scanzello, C R; *DiCarlo E F; *Mandl, L; *Crow, M K; *Sculco, T P
+*Hospital for Special Surgery New York, NY
pearlea@hss.edu

INTRODUCTION: Previous studies have demonstrated an association between osteoarthritis (OA) progression and inflammation as measured by systemic CRP levels. However, the pathologic basis for the association between elevated CRP and more aggressive OA disease has not been established. We previously demonstrated that OA patients with histologic synovial inflammatory infiltrates had elevated CRP levels compared with OA patients without synovial inflammation[1]. The purpose of this study was to correlate the degree of synovial inflammation with CRP levels, to investigate the relationship between CRP, synovial inflammation, and synovial fluid IL-6 levels, and to establish independent predictors of CRP in OA including age, body mass index (BMI) and clinical variables.

MATERIALS AND METHODS: Patients with idiopathic OA undergoing either total hip or knee arthroplasty or knee arthroscopic debridement were identified by a single surgeon. Exclusion criteria included erosive OA, chondrocalcinosis, significant comorbities (ie DM, CAD, gout), and recent viral or bacterial inflection. Detailed demographic information, clinical history, physical examination, and intraoperative findings were recorded. Synovial samples were obtained from standardized locations and were reviewed in a blinded fashion by a single, experienced musculoskeletal pathologist. Inflammation was graded as absent, low-grade (perivascular lymphocytic infiltrates only), or high grade (perivascular and diffuse lymphocytic or lymphoplasmacytic infiltrates). Degree of synovial lining hyperplasia and vascularity were also graded histologically. Synovial fluid IL-6 levels and plasma CRP levels were measured using ELISA.

RESULTS: 59 patients with an average age of 63.2 (range 43-79) with idiopathic OA of the hip or knee were identified. CRP levels were elevated in OA patients with synovial membrane inflammatory infiltrates compared to OA patients without histologic infiltrates (4.7 mg/L vs 1.7 mg/L, p=0.003). CRP levels correlated with the degree of synovial membrane inflammatory infiltrate (r=0.42, p = 0.0015), but not with histologic vascularity or synovial lining hyperplasia. OA patients were dichotomized into two groups: high CRP (CRP level > 3 mg/L) and low CRP (CRP < 3 mg/L). The high CRP group demonstrated elevated synovial fluid IL-6 levels compared with the low CRP group (193.3 pg/ml vs 35.1pg/ml, p<0.001). There was a good and highly statistically significant correlation between synovial fluid IL-6 levels and systemic CRP levels (r=0.63, p=0.005). CRP had a weak correlation with BMI and with subjective, patient reported response to anti-inflammatory medications (r=0.31; p=0.02 and r=0.34; p=0.02, respectively). In a multivariate regression model including age, BMI, response to NSAIDs, synovial fluid IL-6, and degree of inflammatory infiltrate, synovial fluid IL-6 and degree of inflammatory infiltrate were independent predictors of CRP (p=0.02 and p=0.04, respectively).

DISCUSSION: We have demonstrated that the subgroup of OA patients with elevated systemic CRP levels is characterized by a local inflammatory component. These inflammatory findings include more intense inflammatory cell infiltrations in the synovial membrane and elevated synovial fluid IL-6 levels.

CRP, one of the most useful markers of systemic inflammation, has recently been identified as a marker of OA with clinical significance as CRP levels are modestly elevated in patients with OA as compared with normal controls[2-7]. Of greater clinical significance, in patients with OA, increased CRP levels have been associated with disease progression [6-9] as well as with clinical severity [2]. We previously demonstrated that elevated CRP levels are associated with the presence of synovial inflammatory infiltrates and that CRP levels correlated with proportions of CD4+ T cells in the synovial membrane[1]. These findings were independent of the stage of OA disease. We now demonstrate a correlation between degree of inflammatory infiltrate and CRP levels. Putting this together, these data suggest that CRP levels are associated with synovial membrane inflammatory infiltrates that are enriched with CD4+ T cells, which have been shown to have a proinflammatory phenotype[10].

IL-6 is known to be the chief regulator of CRP production and may have a role in the inflammatory OA process. IL-6 is known have direct effect on chondrocytes and stimulates T cells[11]; IL-6 knockout mice are protected from experimental inflammatory arthritis[12]; and elevated synovial fluid IL-6 levels have been associated with synovitis and degenerative changes in OA patients[13]. Our finding of a strong correlation between CRP levels and synovial fluid IL-6 levels in OA implicates synovial fluid IL-6 not only as a regulator of CRP in OA, but also as a possible mechanistic link between elevated CRP, the presence of inflammatory infiltrates, and even the more aggressive disease that has been reported in patients with elevated CRP.

Finally, because CRP is a nonspecific marker, we investigated the relationship between CRP and other factors that might influence it. In population based studies, CRP has been linked with BMI, which explained, at least in part, its association with more aggressive OA disease[7]. In this study, with a tightly controlled patient group without significant comorbidies, regression analysis demonstrated that synovial fluid IL-6 levels and synovial inflammation were independent predictors of CRP. BMI and age did not influence CRP levels.

We found that the OA subgroup with elevated CRP is characterized by elevated synovial membrane inflammation and synovial fluid IL-6 levels. Further distinguishing and defining this OA subgroup may allow for more targeted pharmaceutical and surgical intervention.

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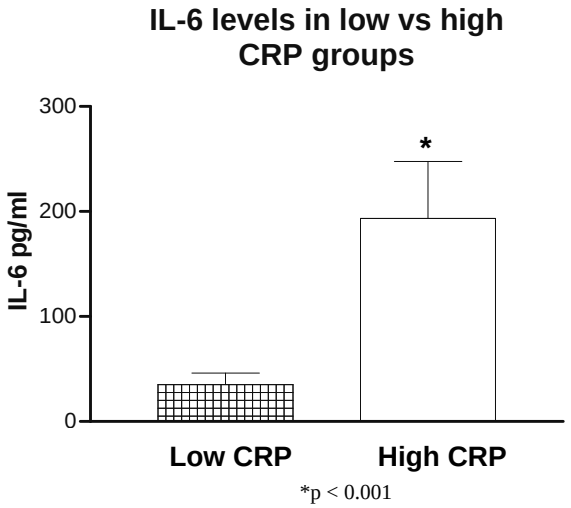

Figure 1: Elevated synovial fluid IL-6 levels in high CRP group