High Levels of Synovial Inflammatory Cytokines at Time of Articular Fracture are Associated with Poorer Long Term Clinical Outcomes

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Purpose: Despite optimal surgical treatment, posttraumatic osteoarthritis (PTOA) can still occur following articular fracture repair. There is an increased understanding of the role of local inflammation in the joint as a primary mediator of PTOA in a chronic setting, but this dysregulated inflammation likely begins at the time of injury. Our hypothesis is that synovial fluid biomarker levels at the time of injury will be associated with long-term clinical outcomes.

Methods: Patients with acute articular fractures were prospectively enrolled for synovial fluid analysis from 2011 to 2018. Joint aspiration samples were collected within 24 hours of injury. Biomarkers interleukin (IL)-1β, IL-1RA, IL-6, IL-8, IL-10, and matrix metalloproteinase (MMP)-1, -3, and -13 were quantified from the synovial fluid using a human inflammatory cytokine multiplex panel. Biomarker concentrations were normalized using Box Cox transformation for each fracture type. Based on recent pilon fracture outcomes literature, patients were classified as high or low functioning based on Patient-Reported Outcomes Measurement Information System (PROMIS) Physical Function score of 46. Groups of interest were then compared utilizing 2-tailed independent t tests.

Results: 113 patients were enrolled and underwent primary synovial fluid biomarker analysis. 78 patients (28 ankle fractures, 20 pilon fractures, and 30 plateau fractures) had greater than 1 year clinical follow-up (mean 5.1 years, range 1-9.7 years) with recorded functional outcome scores. The low functioning group had statistically higher quantities of IL-8 (1.19 vs 0.88, P = 0.01), MMP-1 (1.21 vs 0.88, P = 0.003), and MMP-3 (1.19 vs 0.93, P = 0.04) at the time of their injury. Eight patients had either ankle fusion (n = 3) or knee arthroplasty (n = 5) for end-stage PTOA. This subset of patients had higher levels of inflammatory biomarkers IL-1β (1.25 vs 1.00, P = 0.19), IL-1RA (1.14 vs 0.99 P = 0.42), IL-6 (1.31 vs 1.03, P = 0.11), IL-8 (1.29 vs 0.99, P = 0.13), IL-10 (1.22 vs 1.01, P = 0.31), and MMP-3 (1.14 vs 1.04, P = 0.63), but these failed to reach statistical significance.

Conclusion: Patients with PTOA and worse functional outcomes following articular fractures demonstrated higher profiles of inflammatory cytokines at the time of injury. To our knowledge, this is the first study to directly connect inflammatory markers with clinical outcomes in PTOA following articular fracture. This suggests the pathologic inflammatory process that leads to PTOA begins at time of injury likely due to patient and injury factors and presents a window for possible pharmacologic intervention.