ΔPresence and Degree of Matrix Metalloproteinases and Aggrecan Breakdown Products in the Setting of Acute Intra-Articular Fracture

Justin Haller, MD*; Molly McFadden, PhD; David L. Rothberg, MD; Erik Kubiak, MD; Thomas F. Higgins, MD;*
University of Utah Department of Orthopaedics, Salt Lake City, Utah, USA

Background/Purpose: Matrix metalloproteinases (MMPs) are a group of enzymes that play a role in tissue remodeling and have the ability to degrade articular cartilage. Aggrecan is a proteoglycan found in the extracellular matrix of cartilage. Proteolytic cleavage of aggrecan leads to aggrecan fragments that may be associated with cartilage degradation. Prior studies have demonstrated an association between the degree of inflammatory osteoarthritis and the presence of MMPs and presence of aggrecan breakdown products, suggesting a causative role in those diseases. The presence or absence of these compounds in the acute setting of articular fracture has not been established. Previous study of inflammatory cytokines demonstrated a local response, but did not examine these compounds. This study is designed to evaluate the presence of MMPs and aggrecan breakdown products following intra-articular tibial plateau fracture.

Methods: After IRB approval, investigators prospectively aspirated synovial fluid from the injured and uninjured knees of 45 patients between the ages of 18 and 60 years with tibial plateau fractures. Patients with open fracture, history of autoimmune disease, preexisting arthritis, or presentation greater than 24 hours from injury were excluded. The 20 patients who required spanning external fixator followed by definitive fixation were aspirated at both surgeries. The concentrations of MMP-1, -2, -3, -7, -9, -10, -12, and -13 were quantified using multiplex assays. Additionally, aggrecanase-cleaved aggrecan fragments were quantified using a sandwich ELISA (enzyme-linked immunosorbent assay) with an α-ARGS monoclonal antibody. Repeated-measures analysis of variance was used to test for differences on the log-transformed variables.

Results: We enrolled 45 patients (14 females, 31 males), with an average age of 42 years (range, 20-60). There were 24 low-energy (OTA 41B or Schatzker 1-3, all OTA 41B) tibial plateau injuries and 21 high-energy (Schatzker 4-6) tibial plateau injuries. Of the high-energy fractures, 6 were OTA 41B3 and 15 were OTA 41C. There were significantly higher concentrations of MMP-1 ($P < 0.001$), MMP-3 ($P < 0.001$), MMP-9 ($P < 0.001$), MMP-10 ($P < 0.001$), MMP-13 ($P = 0.001$), and aggrecan breakdown ($P = 0.021$) in injured knees as compared to uninjured knees. Only MMP-9 ($P = 0.05$) was found to be significantly greater in high-energy as compared to low-energy injuries. Interestingly, aggrecan breakdown ($P = 0.007$) was significantly greater in low-energy as compared to high-energy injuries. MMP-1 ($P < 0.001$), MMP-3 ($P = 0.026$), MMP-12 ($P < 0.001$), and aggrecan breakdown ($P < 0.001$) were significantly greater at the time of the second procedure at an average of 9.5 days (range, 3-21 days) from initial surgery. Conversely, the concentration of MMP-9 was significantly less at the time of the second surgery ($P = 0.005$). Both MMP-10 and MMP-7 remained elevated at the second time point, but this trend was not statistically significant. While MMP-13 was not significantly elevated in the injured compared to uninjured knee at the time of initial injury, MMP-13 was significantly elevated at the second procedure ($P < 0.001$).

Δ OTA Grant

- The FDA has not cleared this drug and/or medical device for the use described in this presentation (i.e., the drug or medical device is being discussed for an "off label" use). For full information, refer to page 600.

Conclusion: There is a significant increase in aggrecan breakdown and presence of MMPs in the acutely injured knee compared to the control knee, demonstrating the response after joint trauma to be local. In contrast to other inflammatory mediators examined, only MMP-9 was acutely elevated in high-energy as compared to low-energy injuries, suggesting that this proteinase may be associated with greater acute joint destruction. Perhaps most importantly, most of the MMPs and amount of aggrecan breakdown continued to be elevated a mean of 10 days after injury, demonstrating that the cartilage is subjected to continued interaction with matrix degenerating proteases over a week after injury. Given these data, these factors merit further investigation for a potential role in the ultimate development of posttraumatic arthritis.

See pages 99 - 147 for financial disclosure information.