Can intra-articular cytokine profiling predict the development of knee pain? Four-year follow-up of asymptomatic controls

+1,4 Cuellar, JM; 2,4 Scuderi, GJ; 3,4 Golish SR; 1,4 Cuellar VG; 2 Song Y; 4 Hanna LS

INTRODUCTION:
Knee pain represents a plethora of etiologies, many of which remain obscured initially by traditional diagnostic modalities. Analysis of synovial fluid may provide insight into the early molecular milieu preceding pain. Biomarkers predictive of development of pain may lend insight into the pathophysiology of various conditions, and could be useful clinically as a diagnostic tool as well as therapeutic targets.

METHODS:
Synovial fluid was collected from 43 asymptomatic knees, including 17 asymptomatic volunteers and 26 patients undergoing arthroscopy on the contralateral symptomatic knee. The concentrations of 17 inflammatory cytokines were measured using a multiplex bead immunoassay. The patients were followed for a minimum of four years and asked to rate their knee pain using a visual analog scale (VAS). Baseline cytokine levels were compared and underwent statistical analysis in patients with and without pain at the four-year follow-up point to determine if any differences could be observed from cytokine levels at baseline. IRB approval was obtained prior to study initiation.

RESULTS:
Cytokine concentrations of interferon-gamma (IFN-g) and monocyte chemotactic protein-1 (MCP-1) were significantly elevated in patients that were initially asymptomatic but developed subsequent knee pain four years later. Patients that did not develop knee pain did not have significant levels of any cytokines. At baseline, all 43 knees had no clinically significant pain (VAS<2). At 4-year follow-up 10 knees (23%) had clinically significant pain (VAS greater than 2). Between the pain and no-pain groups, there were significant differences in IFN-g (p=0.001) and MCP-1 (p=0.044) but not in interleukin-16 (IL-16; p=0.077) or macrophage inflammatory protein 1-beta (MIP-1B; p=0.077) levels (Mann-Whitney U test). For IFN-g, the optimal cutoff of 19.4 pg/ml yielded a sensitivity of 90.0% and a specificity of 84.2% for pain. The area-under-the-curve (AUC) was 0.85 (±0.07) (p<0.001).

DISCUSSION:
In the present study we have observed that MCP-1 and IFN-g immunoreactivity in the knee synovial fluid of asymptomatic subjects were significantly greater in asymptomatic knees that developed non-traumatic pain than those that remained asymptomatic. IFN-g has a high sensitivity and specificity for detecting knee pain and may be able to predict the development of non-traumatic knee pain. The IFN-g signal was shown in our recent studies to represent a novel protein-protein complex of fibronectin and the aggrecan G3 domain.

SIGNIFICANCE:
Measurement of inflammatory biomarkers in knee synovial fluid from asymptomatic patients may predict the development of future symptoms. Further studies are needed to determine whether this represents early osteoarthritis, and if so, may enable earlier clinical interventions in the future.

REFERENCES: