95 ANALYSIS OF SYNOVIAL FLUID BIOMARKERS IN PATIENTS WITH RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, AND NORMAL DONORS

R. Kokebie[1], A. Yanke[1], A.A. Hakimiyan[1], M. Michalska[1], D.C. Rueger[2], J.A. Block[1], **S. Chubinskaya[1]**. *[1]Rush University Medical Center, Chicago, IL, USA, [2]Stryker Biotech, Hopkinton, MA, USA*

Purpose: To compare synovial fluid (SF) biomarker levels in samples from patients with rheumatoid (RA), osteoarthritis (OA), and normal organ donors for prognostic/diagnostic purposes.
Methods: Synovial fluid (SF) was collected from the knees of 45 (6 males and 39 females) OA, 22 (14 females and 8 males) RA patients and 20 (15 females and 5 males) normal organ donors. Eight biomarkers analyzed by ELISA methods were evaluated: interleukin (IL)-1, Il-6, Il-8, Il-11, leukemia inflammatory factor (LIF), cartilage oligomeric protein (COMP), osteocalcin, and osteogenic protein-1 (OP-1). Multivariate analysis assessed the effects of gender and disease activity: WOMAC scores for OA samples, and SF WBC, ESR, CRP for RA samples. Multivariant Kruskal-Wallis and Mann-Whitney Tests were used; $p < 0.05$ was considered significant.
Results: The mean ($\pm$SD) age was: 53$\pm$9 years for OA, 54$\pm$11 for RA, and 52$\pm$7 for donors. No gender differences were identified between markers. In RA SF, the levels of 4 out of 5 tested cytokines/chemokines were higher than in OA and normal SF. The most significant differences were found for Il-6 and Il-8, where Il-6 concentration was 2.5-fold higher than in OA, 2587.59$\pm$6393.69 vs. 1045.68$\pm$5451.13 ρg/ml, respectively ($p < 0.005$), and 8-fold higher than in normal, 2587.59$\pm$6393.69 vs. 339.06$\pm$906.28, respectively ($P < 0.002$). The levels of Il-8 were 8-fold higher than in OA, 6490.04$\pm$16550.74 vs 849.48 ρg/ml, respectively ($P < 0.0005$) and normal, 6490.04$\pm$16550.74 vs 788.69$\pm$837.705 ρg/ml, respectively ($P < 0.028$). The differences for Il-11 were not as substantial, especially between RA and OA samples, while it was a 5-fold difference between OA and normal SF, 654.11$\pm$1411.844 ρg/ml, respectively ($P < 0.003$). The value of Il-1 was significantly higher in normal than OA, 9.81$\pm$2.72 vs 8.56$\pm$7.06 ρg/ml, respectively ($P < 0.004$); in the RA, it was a tendency for a higher concentration of Il-1 than in OA and normal, but it did not reach significance. Surprisingly, concentration of LIF was higher in normal samples than in RA ($P < 0.044$) and OA ($P < 0.001$). The highest levels of OP-1 were found in normal SF (541.92$\pm$28.61 ng/ml), which were almost 5-fold higher than in OA (112.40$\pm$124.64) ($P < 0.001$) and more than 2-fold higher than in RA SF (202.25$\pm$149.13 ng/ml, $P < 0.001$). No differences were detected in the levels of COMP or osteocalcin between the experimental groups. Although the differences between active and inactive states of OA or RA were insignificant, for cytokines and OP-1 each state was statistically different from normal. SF from both OA and RA had higher biomarker levels than normals, regardless of disease state, though there was a trend of higher chemokine levels in less active RA, and higher Il-1, Il-6, and Il-8 levels in active OA.
Conclusions: Our findings suggest that the levels of pathophysiologically important biomarkers in SF of patients with OA and RA differ according to the mechanisms that drive each disease. Thus, Il-1, Il-11, LIF and OP-1 appear to be significant for OA; while Il-6, Il-8, and OP-1 may have significance for RA. As previously observed in cartilage, a strong negative correlation between the levels of OP-1 and Il-6 family of chemokines was seen. Larger studies are necessary to develop a biomarker algorithm that would be of diagnostic/prognostic use.

96 VASCULAR ABNORMALITIES PLAY KEY ROLES IN OSTEOARTHRITIS: IMPLICATIONS FOR DETECTION AND TREATMENT

P.A. Cheras. *Southern Cross University, Lismore, AUSTRALIA*

Purpose: Osteoarthritis (OA) is a multifactorial disease, the causes of which remain contentious. The studies presented were designed to seek evidence of vascular abnormalities in OA. These findings led to the formulation of a "Vascular Concept of OA Causation" that incorporates currently known laboratory, clinical and epidemiological data. This concept has significant implications for our approach to OA detection and treatment and has been used to develop a rudimentary approach to early OA detection.
Methods: Histological studies: Femoral heads removed from 11 OA patients at hip arthroplasty were examined histologically for evidence of microvascular thrombosis and occlusive intravascular lipid. They were compared with seven control femoral heads obtained at post mortem from donors in whom OA was excluded.
Haematological studies: Global and specific markers of coagulability, fibrinolysis, inflammation, matrix degradation and bone turnover were measured in peripheral blood from 44 patients with OA of the hip and 52 control subjects.
Use of combinations of "markers" to detect OA: A subset of 12 potential haematological markers and clinical measures was refined and applied to 45 subjects with OA and 47 control subjects to determine if the number of markers per subject could be used as a guide to discriminate between OA and non-OA subjects.
Results: Histological studies confirmed the presence of occlusive intravascular lipid and thrombosis in the vessels of the femoral head of patients with OA. These changes were not observed in the control femoral heads. The haematological studies and clinical data showed increased procoagulant tendency in OA with significantly increased blood pressure, BMI, blood lipids, platelet aggregation, clotting factors, blood viscosity and fibrinopeptide A levels. There was hypofibrinolysis as shown by prolonged euglobulin clot lysis time and raised plasminogen activator inhibitor, alpha 2 antiplasmin and LP(a) levels. Mild inflammation was demonstrated with increased levels of Il-1, TNF alpha and CRP. Leukocyte elastase degrades collagen and elastic fibres and it was elevated in OA. There were also increased levels of markers of bone turnover including ALP, BGP and DPD crosslinks. All parameters were statistically significant. Seventy percent of OA patients had four or more markers versus only 15% of controls and there was generally a combination of both increased coagulation risk and hypofibrinolysis in the osteoarthritis subjects.
These findings led to the formulation of a "Vascular Concept of OA Causation" that links vascular insufficiency to the clinical and laboratory findings in OA. Based on this we propose that anti-arthritic agents that act on the actual disease processes ought to enhance the joint microcirculation and in addition to being anti-inflammatory they should also have core activities that include anti-coagulant, fibrinolytic and lipolytic activities that will promote haemostasis.
Conclusions: Mounting evidence supports a key role for impaired blood flow in the initiation and progression of OA. Recognising the important role of vascular insufficiency in OA creates new insights that could lead to the early detection of OA. By expanding our focus to include vascular abnormalities together with inflammation, this new perspective can lead to the development of novel therapeutic targets for OA and more comprehensive approaches to treatment that have the potential to slow or halt the disease process. This concept also provides a rationale for some of the strengths and inadequacies of current pharmacological and complementary anti-arthritic medicines.

97 IS SERUM TRANSFORMING GROWTH FACTOR-BETA (TGF-β) A BIOMARKER OF RADIOGRAPHIC OSTEOARTHRITIS (rOA) AT THE KNEE AND HIP?

A.E. Nelson[1], F. Fang[2], V.B. Kraus[3], T. Stabler[3], J.B. Renner[1], C.G. Helmick[4], J.M. Jordan[1]. *[1]University of North Carolina School of Medicine, Chapel Hill, NC, USA, [2]StatWorks, Inc, RTP, NC, USA, [3]Duke University Medical Center, Durham, NC, USA, [4]Centers for Disease Control and Prevention, Atlanta, GA, USA*

Purpose: We have observed that African Americans (AA) are more likely to have osteophytes at the hip and knee compared to Whites. Elevated TGF-β has been associated with osteophyte formation in the OA joint. Therefore, the purpose of the current study was to assess the utility of serum TGF-β as a biomarker of rOA in AAs and Whites, men and women, with and without hip and knee rOA.
Methods: Baseline data from 330 participants (42% AA; 39% men) in the Johnston County Osteoarthritis Project Biomarker Substudy were used in the analysis. Natural logarithm transformation was used to produce near-normal distributions for TGF-β (lnTGF-β) in analyses. Descriptive statistics were calculated for demographic variables, knee and hip rOA (defined as K/L grade $\geqslant$ 2 at each joint), and lnTGF-β; differences were assessed by two-sample t-tests. Generalized linear models were used to obtain least squared means estimates for lnTGF-β and rOA presence, laterality (none, unilateral, or bilateral), and severity (K/L grade 0, 1 = none, K/L grade 2 = mild, K/L grade 3, 4 = moderate/severe). Models were adjusted for age, gender, race, and body mass index (BMI). Interactions by race and gender were considered significant at a p-value <0.1. Analyses were performed using SAS version 9.1 (Cary, NC).
Results: The mean age of the sample was 60.5$\pm$9.4 years, with a mean BMI of 30.3$\pm$6.9 kg/m^2; 54% had knee rOA and 22% had hip rOA. The mean for lnTGF-β was 2.82$\pm$0.34 ng/mL. Mean lnTGF-β was higher among AA participants compared to Whites ($p = 0.0085$), and women compared to men ($p = 0.0006$). There were no significant associations