concentrations between severity and the joint affected (P=0.015 unadjusted P=0.018 adjusted; Fig 1 a & b). No interactions were determined for SPD, SPM or the total polyamine concentration. There was no difference observed between ROA and no ROA for any of the polyamines or the total polyamine concentration (PUT P=0.801, SPD P=0.838, SPM P= 0.853, total polyamine concentration P=0.795).
Conclusions: This pilot study indicated that measurement of polyamine concentrations in plasma of volunteers with osteoarthritis is reproducible. Few studies investigating polyamine concentrations in OA have been performed previously and ours is the first study to utilise plasma samples to determine systemic plasma concentrations in OA. Our data suggest that there are a number of different OA phenotypes, particularly highlighted by the differences between hip and knee OA. Further study of polyamine concentrations in OA needs to be carried out with larger numbers of patients.

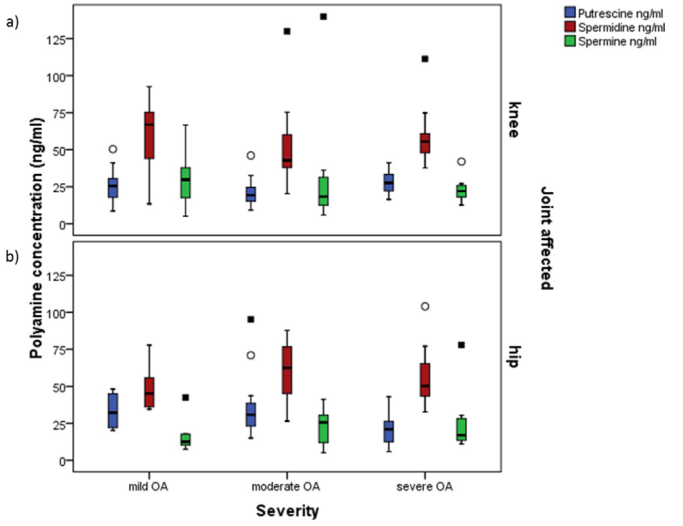

Figure 1. Analysis of polyamine concentrations in plasma samples from volunteers with varying degrees of osteoarthritis severity, divided by affected joint.

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CCL3 AS SERUM BIOMARKER IN PATIENTS WITH KNEE OSTEOARTHITIS: A CROSS-SECTIONAL STUDY

Z. Zhang, X. Zhao, W. Liao. *First affiliated Hosp. of Sun Yat-sen Univ, Guangzhou, China*

Purpose: Inflammation is widely accepted to be an essential part of osteoarthritis, chemokines as mediators of chemoattraction (chemotaxis) are known to play a pivotal role in this process. However, its role in osteoarthritis biomarker is rarely reported. The aim of this cross-sectional study is to explore the ability of chemokines in serum to identify the degree of knee osteoarthritis.
Methods: There are altogether 284 knee healthy subjects and 338 osteoarthritis patients participated in this project between September, 2012 and December, 2013. According to the inclusion and exclusion criteria, 47 early and 59 later knee osteoarthritis patients and 75 knee healthy subjects were finally enrolled. Samples were collected prior to any treatment. The promising chemokines, CCL3, CCL4, CXCL1 and CXCL8/ IL8, and four well studied proinflammatory cytokines, IL1β, IL6, TNFα and resistin, were quantified using suspension array. Preoperative radiography, magnetic resonance imaging and arthroscopy findings were compared with suspension array results. And the outcomes were presented in a statistical way.
Results: In all serum chemokines and cytokines tested, serum CCL3 and IL8 were the two best predictors of early osteoarthritis occurred (area under the curve =0.769 and 0.765, respectively). Serum CCL3 was highly specificity to early knee osteoarthritis, especially to pre-radiography patients, whereas serum IL8 showed low specificity but high sensitivity. Significant difference in serum CXCL1, IL8, CCL3, CCL4 and resistin were presented among knee OA patients with different KL grades. Although the difference did not meet statistical significance, elevated CCL3, CCL4 levels in serum were associated with the severity of high burden knee osteoarthritis. Additional, test results from suspension array were corrected well with those from ELISA.
Conclusions: Serum IL8 was a promising diagnostic biomarker for early knee osteoarthritis. And serum CCL4 was suggested can give well reflection on burden of knee osteoarthritis. Serum CCL3, moreover, was performed excellent in both sides.

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ESTABLISHING A KNEE PRESERVATION REGISTRY TO FOLLOW PATIENTS WITH DEGENERATIVE JOINT DISEASE

A. Szulc, H. Murphy, C.K. Nathasingh, E. Lee, A. Payne, I. Inneh, H.-G. Wisniewski, R. Iorio, L. Jazrawi, J. Slover, J. Samuels, E.J. Strauss, P.A. Band. *NYU-Hosp. for Joint Disease, New York, NY, USA*

Purpose: The Joint Preservation Registry (JPR) is a prospective, pragmatic, observational study, designed to identify clinical and biochemical markers of osteoarthritis (OA) phenotype, status and progression. Because the time course of degenerative joint disease is highly variable, the optimal treatment for an individual patient is clinically determined by multiple factors, and highly variable between both clinicians and patients. Few large data sets are available studying the ways that clinicians and patients handle this uncertainty, particularly with respect to the timing of surgical intervention. To address this gap in knowledge, the JPR was established to follow consenting patients who present with knee symptoms to physicians at the center for musculoskeletal care of a large tertiary care medical center. The JPR also is intended to evaluate whether synovial fluid biomarkers previously found to be predictive of radiologic progression and knee replacement over a 3-year period, are also predictive of pain score progression over shorter time periods, and useful for optimizing treatment pathways.
Methods: Patients presenting with knee-related complaints were recruited into a Knee Preservation Registry, asked to consent to regular follow-up by email or phone every 6-12 months, and to allow any biospecimens collected during the course of their standard care to be retained in a bio-repository for future analyses. Participating investigators included both physicians and surgeons from the divisions of Sports Medicine, Rheumatology, and Adult Reconstruction. Inclusion criteria were deliberately broad to enable a diverse patient population, ranging from recent acute injury to advanced degenerative disease, and including patients with comorbidities. The registry is observational and captures demographics, medical history, anthropometrics, diagnosis codes, treatments, imaging, and patient-reported outcome (PRO), with much of the data directly retrieved from the medical record. Synovial fluid (SF) biomarker analysis and PRO score collection at regular follow-up are the only study-related procedures. Patients will be followed for 5 years from the time of enrollment.
Results: From September 2012 to July 2014, 813 patients (M = 340, F = 473) were recruited for the registry. The average age at enrollment was 52.3 years. SF was aspirated from 167 subjects (225 knees, 57 bilateral, 111 unilateral), for a total of 302 unique SF samples in the current bio-repository which represents 21% of the total population that was sampled. The same percentage of patients with effusion was noted to be the same (21%) among men and women. Distribution of diagnoses, defined by ICD-9, was 72% for osteoarthritis (OA), 10% for acute injuries, and 18% for other non-OA complaints. Approximately half of the enrolled patients have reached the 6-12 month follow-up.
Conclusions: To our knowledge, this is the first pragmatic registry for knee OA patients that are not scheduled for knee replacement. The information captured by our registry can be used to study disease phenotypes as they relate to treatment alternatives, including ethnic, racial, socioeconomic and gender disparities. Ultimately we hope to establish evidence-based treatment pathways using a combination of biomarkers, PRO scores and advanced imaging to customize the treatment of OA to individual patient needs and preferences, and to assist surgeons in determining the appropriate timing for joint replacement.

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SEGREGATING OA PATIENTS WITH AND WITHOUT JOINT INFLAMMATION USING TWO BIOMARKERS OF CONNECTIVE TISSUE INFLAMMATION

A.-C. Bay-Jensen, I. Byrjalsen, A. Bihlet, K. Musa, B.J. Riis, C. Christiansen, M.A. Karsdal. *Nordic BioSci. A/S, Herlev, Denmark*

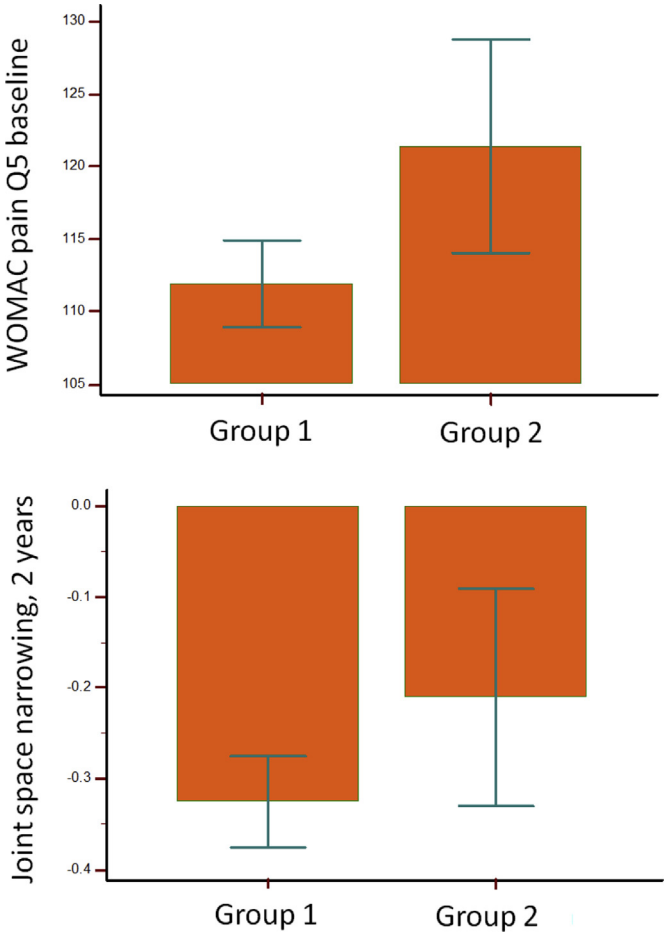
Purpose: We have recently identified the presence fragments of CRP, generated by matrix metalloproteinases (MMPs). C-reactive protein (CRP) is an acute phase reactant, involved in both acute and chronic inflammatory diseases. CRP is produced mainly by the liver upon elevated levels

of cytokines such as IL-6. From the liver CRP is transported back to the inflamed tissue where it binds its receptors and thereby accumulated by the tissue. These fragments are released from the tissue as MMPs are upregulated in response to pro-inflammatory induction. C3M is a biomarker of type II collagen remodeling, which is released from the synovial membrane with induced with pro-inflammatory cytokines. The aim of the study was to investigate whether the level of the protein fingerprint CRPM together with the tissue turnover biomarker C3M could segregate OA patients with and without inflammatory arthritis.

Methods: CRPM and C3M were measured in the serum of knee OA patients taking part of the two phase III RCTs (NCT00486434 and NCT00704847). Baseline and 2 year follow-up pain questionnaires and radiography were recorded for each patient. An array of additional biomarkers were measure; C1M, C2M, CTX-II, CTX-I and osteocalcin. The biomarkers were plotted against each other (figure) and cut-offs were set based on reference value and difference between clinical measures and biomarkers in the two patient groups were analyzed by Mann-Whitney.

Results: Patients were separated into 2 groups; 1) patient with low CRPM and low C3M, and 2) patients with either high CRPM or high C3M, or with both high. 16% of the patients were found group 2. Several of the measures were higher in group 2: Cartilage degradation (C2M) and connective tissue degradation (C1M) were significantly higher ($p=0.0037$, $p<0.0001$, respectively), as well as WOMAC subscale question Q5 ($p=0.0191$). There was no group difference in KL score or JSW nor in CTX-I, CTX-II and osteocalcin. Group 1 patients (low in both CRPM and C3M) progressed structurally more group 1 patients ($p=0.046$).

Conclusions: We found that different of the two inflammatory markers could facilitate patient segregation. This may have many implications, however most importantly in the identification of more OA patients with the right diagnosis, inflammatory vs. non-inflammatory disease, which may benefit from a given treatment.



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INTRAARTICULAR INJECTION OF ADIPOSE MESENCHYMAL STEM CELLS OVER HYALURONIC ACID AND COLLAGEN TYPE II CLEAVAGE NEOEPITOPE IN THE TREATMENT OF OSTEOARTHRITIS IN DOGS

M. Rubio Zaragoza †,‡, B. Cuervo Serrato †,‡, J. J. Sopena Juncosa †,‡, R. Cugat Bertomeu §,‡, A. Tvarijonaviciute §, J. J. Ceron Madrigal ¶, J. M. Carrillo Poveda †,‡. † *Univ. CEU Cardenal Herrera, Alfara del Patriarca, Spain;* ‡ *Garcia Cugat Fndn., Barcelona, Spain;* § *Artroscopia GC, Barcelona, Spain;* ‖ *Univ. Murcia, Espinardo, Spain;* ¶ *Univ. de Murcia, Espinardo, Spain*

Purpose: Osteoarthritis (OA) is a very common degenerative disease affecting the articular cartilage in both human and veterinary medicine.

While conventional treatments like physiotherapy or drugs offer temporary relief of clinical symptoms, restoration of normal cartilage function has been difficult to achieve. Moreover, in severe cases of osteoarthritis total articular replacement may be required.

The regenerative medicine offers exciting possibilities for treating OA. The mesenchymal stem cells are candidates for use in this pathology because they offer exciting possibilities to differentiate into other tissue lineages, and have significant effects on regeneration and/or maintenance of articular cartilage, reducing pain and increasing the articular functionality.

The aim of this study was to evaluate the effectiveness of the application of mesenchymal stem cells derived from inguinal adipose tissue (aMSC) in the treatment of degenerative joint disease in the elbow, hip and knee of the canine species.

Methods: This was a serial clinical multi-center study that included a total of 26 healthy dogs weighting more than 15 kg, with OA documented by X-Rays and clinical findings. The joints affected were distributed in 17 hips, 4 knees and 5 elbows.

The dogs were treated with one 2 ml intra-articular injection of aMSCs containing 30 millions of aMSC obtained by Dog-Stem® method, following conventional protocol for all joints.

The variables evaluated were a radiological assessment of the affected joints (mild, moderate or severe), functional limitation (measurement scale: 0 to 23 points), and joint mobility (measurement scale: 0 to 7 points), as well as serum hyaluronic acid (HA) and collagen type II cleavage neoepitope (C2C) concentration.

In addition, owners completed a questionnaire on satisfaction with treatment and the perception of pain in their pets with a visual analogue scale (VAS).

All these variables were measured at baseline (just before applying the treatment) and one, three and six months after treatment.

Results: The average age and weight of the patients were 58±40 months (age range: 8-135 months), and 35,1±14,0 kg (weigh range: 18,1-66,2 kg), respectively. There were 17 males and 9 females, 10 of them were spayed.

The radiographic grade of OA remained constant over time.

With respect to other parameters like functional limitation, joint mobility, owner satisfaction, VAS and serum C2C and HA (Figure 1 and 2, respectively), there was improvement from the first month to six months after treatment. No adverse effects were observed during the study.

Conclusions: The application of a single intra-articular injection of aMSCs, demonstrate improvement of the clinical signs and symptoms of OA, decreasing pain and improving joint function with no adverse effects and no radiographic changes, with an increase in HA and a decrease in the C2C serum levels. Stem cells are established as a safe and promising therapeutic option besides the capacity to regenerate damaged tissues and organs and there are great expectations for the future.