sagittal plane features are different at baseline in those that progress to total knee arthroplasty (TKA) compared to those that do not. However, no modelling using gait biomechanics has predicted progression to TKA (a clear endpoint that includes structure and symptom aspects of progression), and structural progression prediction models only included individual frontal plane features. This study determined: i) how well individual three-dimensional (3D) lower limb biomechanical gait features discriminated between those who progress to TKA and those that do not, ii) if a multivariate model improved discrimination ability, and iii) how well gait biomechanical features that best discriminated between groups predicted progression to TKA.

Methods: 54 knee OA patients underwent baseline gait analysis where 3D lower limb motion and ground reaction forces were recorded. 3D hip, knee, and ankle angles were expressed in the joint coordinate system. External moments were calculated using inverse dynamics and amplitude-normalized to body mass (Nm/kg). Waveform shape and magnitude features were extracted using Principal Component Analysis (PCA), and waveforms were scored based on how closely they matched an extracted pattern. PC scores were used in statistical testing. Knee adduction moment (KAM) peak (Nm/kg) and impulse (Nm/kg*s) were also calculated. 5-8 years later, 26 patients reported having TKA. Receiver operating characteristic (ROC) curve analysis determined discriminative abilities of individual gait variables. Stepwise discrimination analysis determined which multivariate combinations discriminated between groups. Discriminant function scores were calculated based on multivariate models, and used as input for additional ROC curve analyses to determine which multivariate model best discriminated between groups (highest area under ROC curve). Logistic regression analysis determined predictive ability of the multivariate model with the highest discrimination.

Results: There were no significant baseline differences in demographic, clinical and spatiotemporal gait characteristics, but 3D hip, knee, and ankle gait features significantly discriminated between TKA and no-TKA groups. KAM impulse resulted in the best univariate discrimination based on area under the ROC curve (AUC=0.79) with overall shape and magnitude of KAM (KAMPC1) having the second-highest AUC. Multivariate models had higher AUCs ranging from 0.80-0.85. In all multivariate models, overall KAM magnitude (impulse or KAMPC1) was the most dominant variable for progression to TKA. The multivariate model with the highest discrimination and correct classification ability (AUC=0.85, 74.1% correct classification rate) contained KAMPC1, difference between the early stance knee flexion and late stance knee extension moments (KFMPC2), and stance ankle dorsiflexion moment (AFMPC4). Higher overall KAM magnitude, decreased knee flexion to extension moment difference, and decreased stance dorsiflexion moment were associated with progression to TKA. This model had an odds ratio of 5.7.

Conclusions: Non-frontal plane moments were predictive of progression to TKA. Multivariate models were better able to discriminate between groups than univariate models, with the best model capturing overall magnitude of loading (KAMPC1), and inability to unload the knee (KFMPC2, AFMPC4). This suggests that higher overall cartilage loading along with sustained cartilage loading were predictive of progression to TKA. These findings are consistent with animal models showing that sustained loading can lead to cartilage degradation and upregulation of inflammatory chemicals linked to knee pain. Sustained cartilage loading has not previously been identified as a risk factor for progression, and can be a new target in the development and evaluation of conservative interventions.

70
ESTABLISHMENT OF REFERENCE INTERVALS FOR OSTEOARTHRITIS RELATED BIOMARKERS – THE FNIH/OARSI OA BIOMARKERS CONSORTIUM

V. Byers Kraus †, D.E. Hargrove ‡, D.J. Hunter §, J.B. Renner ‖, J.M. Jordan ‖. †*Duke Univ., Durham, NC, USA;* ‡*LabCorp Clinical Trials, San Leandro, CA, USA;* §*Univ. of Sydney, Sydney, Australia;* ‖*Univ. of North Carolina, Chapel Hill, NC, USA*

Purpose: A Reference Interval (RI) is the central 95% range - or normal range - for endogenous analytes of a healthy person. Traditionally, reference ranges for biomarkers are established using commercially purchased "normals" including "normal" blood donors. Such "normals" are rarely adequate controls for Osteoarthritis (OA) studies as they are rarely if ever ascertained for OA status. The objective of this ancillary study was to establish reference intervals for the FNIH/OARSI panel of OA related biochemical biomarkers using biospecimens from stringently phenotyped age appropriate controls. We hypothesized that the reference interval ranges for these 'super controls' will facilitate future formal FDA qualification of the FNIH/OARSI OA-related biomarker panel for OA diagnosis and prognosis and for monitoring the efficacy of intervention.

Methods: African-American (AA) and Caucasian (C) participants were selected from the Johnston County Osteoarthritis Project (JoCo OA) population-based study of OA. From among 1518 participants with biospecimens and up to 15-years of follow-up radiographic data, and 412 with biospecimens and radiographic data at one timepoint, participants were selected who had no radiographic evidence of knee OA (Kellgren-Lawrence [KL] 0 in each knee) or hip OA (KL 0 or 1 in each hip), and no knee or hip symptoms (pain, aching or stiffness on most days). Controls further had no radiographic hand OA (GOGO definition) or spine radiographic OA (disc narrowing = 0 and anterior osteophytes no greater than 1 at same level). This yielded a total of N=129 healthy 'super control' participants with minimal or no radiographic burden of disease, two-thirds of whom had not developed OA in 15 years of observation. Baseline serum and urine samples from these individuals were analysed in duplicate for the analytes listed in Table 1. The RIs were determined with the reference intervals establishment module of EP Evaluator (Data Innovations) using transformed parametric calculations (Box-Cox transformation), which transforms the data into a Gaussian model. The SD ratio (cut-off >1.5) of the EP Evaluator partitioning test was used to determine if separate reference intervals might be justified for population subclasses based on gender or ethnicity (SD ratio calculated as the larger SD divided by smaller SD of the two subgroups, male vs female and AA vs C). Spearman correlations were used to assess for a correlation between the biomarker concentrations and age and body mass index (BMI).

Results: The sample of 129 super controls consisted of 64% women, 34% African Americans, mean age 59 (SD 8.3, range 45-95) years, mean BMI 29 (SD 5.9) kg/m2. There were no out of range high values. Out of range low values were set at just below the lower limit of detection of the assay to compute the RI. The central 95% intervals for the 18 OA-related biomarkers are provided in Table 1. Based on SD ratio >1.5, separate reference intervals may be warranted on the basis of gender for sHA, sMMP-3, sCol2-1NO2, uCTXIb/Cr, uCTXII/Cr, uNTXI/Cr, uCol2-1NO2/Cr and on the basis of race for sCS846, sCOMP, sMMP3, sCTXI, sCPII, uCTXII/Cr, and uCol2-1No2/Cr.

Conclusions: The ability to diagnose and prognose OA with biomarkers is dependent on a clear understanding of normal reference intervals. For a highly prevalent and heterogeneous disorder such as OA, the lack of ascertainment of OA status leads to misclassification of controls. These well-phenotyped controls represent a similar age demographic to that of the Osteoarthritis Initiative-FNIH main study sample so they should provide an optimal reference control for the main study. To our knowledge, no comparable 'super control' sample has ever been characterized for such an extensive panel of OA-related biomarkers.

71
LIPIDS AS MEDIATORS OF CHONDROGENESIS

N. Georgi †, B. Cillero Pastor ‡, G. Eijkel ‡, P.C. Periyasamy †, A. Kiss §, C. van Blitterswijk †, J.N. Post †, R. Heeren ‡, M. Karperien †. †*MIRA Inst. for BioMed. technology and technical medicine, Enschede, Netherlands;* ‡*FOM Inst. AMOLF, Amsterdam, Netherlands;* §*FOM Inst. AMOLF, Amsterdam, Netherlands*

Purpose: We have previously demonstrated that cartilage matrix formation is improved in pellet co-cultures of human mesenchymal stromal/stem cells (MSCs) and human primary chondrocytes (hPCs) under normoxic culture conditions (21% O2). This co-culture effect is attributed to the MSC specific expression of FGF-1. Under hypoxic culture conditions (2.5% O2), we observed that there was a decrease in chondrogenic differentiation in co-cultures as compared to the normoxic culturing conditions. For clinical applications it is plausible that co-transplantation of MSCs and chondrocytes into the defect results in improved cartilage repair. Until now it remains unclear how FGF-1 expression is regulated under the reduced oxygen level normally present in the joint. It has been underlined that hypoxia (reduced oxygen availability) and expression of