Variation in Knee Shape Predicts the Future Onset of Radiographic Knee Osteoarthritis (RKOA) and this Variation is Different in Males Compared to Females

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Introduction: Osteoarthritis (OA) is the most common form of arthritis and, as the major cause of activity limitation and physical disability in older people, is a tremendous public health concern. While it is well known that the burden of knee OA is significantly greater in women as compared to men [1], the exact etiology of this sex difference is not well understood. It has been hypothesized that the complex interaction between risk factors (varus alignment, joint congruency, cartilage thickness, and soft tissue damage), and knee joint mechanics, particularly mechanical stress in the cartilage, is largely responsible for disease pathology [2]. Since stress in the cartilage is highly dependent upon the geometry of the joint, among other biomechanical and physiological factors, it is not surprising that imaging biomarkers based on high fidelity bone shape descriptors are significantly different in individuals who are at risk of developing radiographic knee OA (RKOA) and those who are not [3], and that baseline subchondral bone shape is a significant predictor of the onset of RKOA 12-months prior to onset [4]. We tested the hypothesis that high fidelity descriptors of distal femur subchondral bone shape are significant predictors of future RKOA and that these shape descriptors are different in males compared to females.

Methods: The OAI is a multi-center, longitudinal, observational cohort study focused on identifying biomarkers for the development or progression of knee OA conducted at four clinical centers with 3D knee MRI image data are collected for both knees for each participant using identical dedicated 3.0 Tesla Siemens MRI scanners. The OAI cohort consists of 1,389 subjects in the Progression subcohort, 3,285 subjects in the Incidence subcohort, and 122 individuals in the Control subcohort (http://www.oai.ucsf.edu/). From an ongoing case-control longitudinal OAI study, we identified a group of subjects within the OAI Incidence subcohort that presented with no signs of knee OA per the OAI definition (KL=0 in both knees) at baseline and at the 36- or 48-month visit (control group; n=32). We have also identified age, and sex matched subjects from the OAI Incidence subcohort who presented with no signs of knee OA at baseline (KL=0 in both knees) who then went on to develop knee OA (KL>=2 in any knee) by the 36- or 48 month visit (case group; n=32). Baseline axial MRI image data sets were processed to extract the distal femur bone surface [5] and a statistical shape model (SSM)of the distal femur representing the entire cohort (n=64) was constructed using established methods [3]. We tested for differences in mean SSM weighting factors (WFs) between the case and control groups and between males and females (JMP Pro, v.10, SAS Institute, Cary, NC). Using stepwise logistic regression (JMP Pro, v.10, SAS Institute, Cary, NC) we tested the ability of baseline SSM weight factors to predict the future onset of RKOA at least three years post baseline imaging for the whole cohort and for males and females.
separately. Sensitivity and specificity of the resulting predictions of future RKOA were quantified using the area under the receiver operating characteristic curve (ROC AUC).

**Results:** A total of six distal femur SSM WFs (WFs 3, 13, 26, 32, 42, and 52) were significantly different between case and control knees for males. Three SSM WFs (WF 8, 21, 50) were significantly different between case and control knees for females. Using stepwise logistic regression, with case or control status as the outcome variable, three SSM WFs were selected for males (WFs 3, 27, 32) and six SSM WFs were selected for females (WFs 8, 22, 27, 29, 40, 50). The resulting area under the ROC curve for the logistic model using the three selected SSM WFs for males was 1.0 and the AUC for the model constructed from the six SSM WFs for females was 0.975.

**Discussion:** We have shown that baseline high fidelity descriptions of knee shape are significantly different between individual knees that go on to develop RKOA at least three years later compared to knees that remain disease free over this time period. Furthermore, there are differences between men and women in the baseline distal femur shapes of those who go on to develop future RKOA compared to those who do not. Distal femur subchondral bone shape variability associated with future onset of RKOA appears to be more complex in females compared to males since the number of shape variables (6 WFs) used to construct an accurate predictive model for females was larger than the number of shape models required to construct an accurate predictive model for males (3 WFs). While, on average, the incident knees generally had higher condylar curvature and greater varus orientation, knee shape differences between cases and controls are much more complex and cannot be easily described using gross discrete measures (Fig. 1). These results warrant further investigation to determine how the identified subchondral bone shape variations affect knee mechanics, particularly the stresses encountered within the knee cartilage and subchondral bone.

**Significance:** Subchondral knee bone shape differs significantly between knees that later developed RKOA and those that did not. This difference is detectable at least three years prior to the onset of RKOA. In addition the high fidelity SSM parameters describing these differences are not the same for men compared to women. Predictions of the future onset of RKOA can be made with high specificity and sensitivity using independent, high fidelity, shape descriptors of the distal femur.
Figure 1. Differences in the subchondral bone shape of case compared to control knees are highly complex and cannot be fully described using simple, discrete measures of knee shape. Independent, high fidelity SSM WFs describing these differences are highly predictive of future onset of knee OA.