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USE OF A NOVEL IN VIVO KNEE JOINT LOADING MODEL TO DETERMINE THE INTERPLAY BETWEEN GENETIC AND MECHANICAL FACTORS IN THE INITIATION AND PROGRESSION OF MURINE OA

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Purpose: It is known that mechanical and genetic factors contribute to OA development. Their relative contribution to the initiation and progression of OA, however, is poorly defined. Str/ort mutant mice are recognised to be genetically-prone to spontaneous OA primarily on the tibial plateau. Whether this is due to a greater mechanical predisposition to OA initiation or progression, or both, has not been addressed. We have shown that OA-like lesions can be induced selectively in the lateral femur of normal mice using our newly developed knee joint loading model. Herein, we address the hypothesis that joints which are genetically-susceptible to OA (Str/ort) are less resistant to the initiation of load-induced OA-like lesions.

Methods: To address if load-induced lesions (which develop primarily in the femur) are generated at sites of greatest mechanical challenge, we first visualised the position of the femur relative to the tibia, before and during application of 9N loads using micro-computed tomography (μCT) imaging integrated with the loading device. This allowed likely points of contact during loading to be directly visualised. To examine the effect of in vivo loading on lesion development, the right knees of 8 week-old CBA (control, non-OA prone n=9) and Str/ort (n=8) male mice were loaded 3 times/week for 2 weeks, (each episode comprised 40 cycles, 0.1Hz at 9N; De Souza et al, 2005) and mice killed 3 days thereafter. Articular cartilage lesions were scored as described by Chambers et al (2002) in multiple 6μm sections at fixed intervals across the entire joint and within each joint compartment (medial/lateral tibia/femur). In each case, right, loaded knees were compared to contra-lateral left, non-loaded knees by paired t-test.

Results: Direct visualisation of Str/ort mouse knee joints by μCT showed marked shift in the position of the femur relative to the tibia during loading. It also revealed that the lateral compartment of the knee would likely experience the most compression. Mechanical loading significantly increased OA score in the entire joint of CBA mice. In agreement with previous studies and with μCT analyses, initiation of these OA-like lesions was localised selectively to the lateral femur; no significant load-induced lesions were found in any of the other compartments in CBA mice. In contrast, such OA-like lesions were not initiated in the lateral femur of loaded Str/ort mouse knee joints. These loaded Str/ort joints, instead only showed significantly more severe lesion progression on the medial tibial plateau.

Conclusions: MicroCT imaging showed that loading in our model system likely initiates OA-like lesions at sites of greatest contact (lateral femur) in normal, non OA-prone, CBA mice. Str/ort mouse knee joints, in contrast to our stated hypothesis, are surprisingly more resistant to OA initiation at these sites of greatest mechanical challenge during loading. Str/ort mice, nonetheless, do show an accelerated progression at sites naturally susceptible to OA. These data indicate that the mechanical factors involved in OA lesion initiation and progression may differ. Indeed, OA initiation in genetically-prone mice may not necessarily be a direct result of mechanical loading, whilst progression of OA is.

BIOMECHANICAL MODELS EXPLAIN INCREASED RISKS FOR KNEE OSTEOARTHRITIS DUE TO OBESITY AND LIMB ALIGNMENT

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Purpose: Obesity is clearly associated with increased risk for incidence of knee OA; however, conflicting results have been reported regarding the importance of other factors such as knee alignment, bone properties and meniscal injuries and their interactions with obesity. These conflicting results may stem from the wide degree of variation in other potentially confounding factors in clinical trials. Computational models offer an advantage in their ability to predict detailed stress and strain patterns within multiple tissues, and also allow greater control over confounding variables. Therefore, our objective was to use finite element (FE) analyses to characterize mechanical factors resulting from increased bodyweight and malalignment and to compare these to the increased risks for onset of knee OA identified by a clinical study.

Methods: A 3D FE model of the proximal tibia was built using MR images from a normal weight adult male. Trabecular bone material properties were regionally distributed according MRI-based predictions of bone volume fractions. Tibio-meniscal-femoral pressures were distributed over the tibial cartilage/femoral cartilage contact and meniscal/tibial cartilage contact areas determined from the MR images. We investigated data from the Multicenter Osteoarthritis Study (MOST) that determined the odds of developing OA in subjects who are overweight and/or have a malalignment compared to normal weight subjects with neutral alignment. Subjects were stratified according to BMI and alignment (weight: NW=18.5-24.9, OW=25-29.9, OB=30-34.9, and very OB=35-40; alignment based on mechanical axis: varus, neutral and valgus). OA onset was defined as a radiographic K/L score ≥2 at follow-up (baseline score of 0 or 1). We estimated "clinical odds ratios" as (#OA at followup)/(# at baseline) normalized to the NW neutral prevalence, for each subgroup. According to the ISO standard, a load of 3X body weight was applied to the model, varying the magnitude for each case based on the BMI groups reported. Variations in medial/lateral contact force ratios were used to reflect the alignment differences, as these measurements are highly correlated (neutral=71/28, varus=80/20, valgus=35/65). Compressive principal stress and strain values were analyzed in medial and lateral regions of the epiphyseal trabecular bone, just distal to the subcondral bone, as well as in the articular cartilage. Average FE model results within the regions of interest were compared with the reported clinical odds ratios for OA onset, and a power-law regression analysis was performed.

Results: Higher stresses and strains are depicted throughout the tibial trabecular bone in the cases of increasing weight or malalignment compared to the normal weight case with a neutral alignment. Significant correlations were determined between the clinical odds ratios and the FE model predictions of bone stress (R2=0.89) and strain (R2=0.93). Significant, though slightly lower, correlations were also identified between cartilage stresses and clinical odds ratios (R2=0.83).

Conclusions: Our computational modeling predictions support

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