Title: A Biomarker Stress Test for Detection of Early Osteoarthritis

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Study Protocol:

General Study Plan: Subjects will be assigned a variable-stiffness shoe to wear for 6 months. Subjects will have gait testing and an OA stress test (serum collection before and after a 30-minute walking activity) at the baseline visit to determine the immediate effects of the shoes on joint mechanics and will return at 6 months for a second OA stress test and gait test.

Intervention: The intervention shoe is a normal-appearing commercially available athletic shoe with a specially designed sole. The lateral aspect of the sole is made of a stiffer material than the medial aspect of the sole (lateral sole 1.4 times stiffer than medial sole). Previous studies have revealed that a shoe of this kind can reduce medial compartment loading. Patients will be asked to use the shoe during their active portion of the day and provide a report of daily usage.

Collection of Serum Samples (OA Stress Test): Subjects will be asked to limit their physical activity for 36 hours prior to testing. Tests will begin between 8:00 and 9:00 am, and subjects will be required to limit their activity between the time they wake up and the beginning of study activities. Blood samples (5mL or 1 teaspoon) will be obtained by trained personnel immediately before, immediately after, 0.5, 1.5, 3.5, and 5.5 hours after a 30-minute walking exercise. For the walking exercise, subjects will walk at their self-selected speed for 30 minutes on a level surface while an activity monitor records the number of steps, cadence, and total distance walked during the task. Following the walking exercise, subjects will remain in a seated position with minimal physical activity until after the final blood draw. A thin catheter in a vein of the subject's forearm will be used so that only one venipuncture will be required for all blood samples. Blood specimens will be centrifuged to separate serum, aliquoted, and frozen to -80^{o}C within 1 hour of collection.

Gait Analysis: Each subject will be tested bilaterally in their own personal walking shoe, a constant-stiffness control shoe, and the variable-stiffness intervention shoe, to determine the immediate and long-term (6 month) effects of the variable-stiffness shoes on joint mechanics. Subjects will be instructed to perform three walking trials at a comfortable speed (normal), slower than normal, and faster than normal. A 10-camera optoelectronic system for 3d motion analysis (Qualisys Medical AB; Gothenburg, Sweden) will be used to collect marker data. Ground reaction force data will be collected using a multi-component force plate placed in the center of the walkway (Bertec Corporation; Columbus, OH). All data will be collected at a frequency of 120 Hz.

The point cluster technique (PCT) marker protocol will be used for gait analysis to measure the movements of the underlying femur and tibia. The intersegmental forces and moments at the knee will be calculated through an inverse dynamics approach. A link model of the segments of interest will be used, assuming the inertial properties for each rigid segment to be lumped at its center of mass, symmetry of the segment along the main inertia axis, and negligible angular velocity and acceleration along the longitudinal axis. The peak external knee adduction moment will be calculated as the maximum moment during stance phase. Average moment values for each speed and subject combination will be calculated. Moments will be normalized to bodyweight and height (%Bw*Ht) to allow for comparison between subjects. Pain will be quantified at baseline and at the time of the 6 month follow-up by Western Ontario and McMaster Universities (WOMAC) pain scores.

Statistical Analysis Plan:

Changes from baseline in peak knee adduction moment and in response of serum levels of biomarkers to a mechanical stimulus in an early knee OA population will be tested after 6 months of load-modification through variable-stiffness shoe wear. The analysis will test for significant differences in the biomarker levels and knee adduction moment between baseline and 6 months. Data will be checked for normality, and a paired Student's T-Test will be used for normally distributed data, or a non-parametric alternative such as the paired-sample Wilcoxon Signed Rank Test will be used if normality checks show that the data is not normally distributed. Analysis of covariance (or non-parametric alternative) may be used to test the influence of potential covariates such as pain, age, gender, and BMI.