Assessing Early Knee Osteoarthritis Development in Anterior Cruciate Ligament Reconstructed Individuals: A Novel Cartilage Stress Test

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INTRODUCTION: In response to mechanical load, normal articular cartilage maintains an appropriate balance of anabolic and catabolic processes. In osteoarthritic cartilage, altered mechanical loads disrupt this homeostatic state, resulting in an increase in cartilage degradation that is often present before a patient develops clinical symptoms of joint disease. Current methodologies for assessing cartilage metabolism and extracellular matrix integrity focus on serum biomarker and MRI evaluation. These approaches are not optimal in providing information on active cartilage metabolism and in-turn how cartilage will respond to load particularly in individuals at risk of early osteoarthritis (OA), such as post-anterior cruciate ligament reconstruction (ACL-R). The inability to assess the overall condition of cartilage and its response to load prevents detection of early pathologic changes in cartilage that predates clinical symptoms. Most prior studies evaluate cartilage under static loading conditions, whereas assessing the in vivo cartilage response to load would provide a more physiologic and meaningful assessment of the status of cartilage health. Such a clinical assessment can be made using a stimulus-response framework that applies quantitative biomechanical stimuli to the joint with responses determined by measurement of specific disease-related markers, such as a serum biomarker of cartilage turnover (cartilage oligomeric matrix protein, COMP). Prior stimulus response frameworks have utilized a flat walking loading paradigm which does not isolate a stress to a particular joint and has resulted in a biomarker response that is non-specific to a joint. We have developed an innovative mechanical stimulus protocol using a medial/laterally tilted treadmill allowing up to 10° of angulation while walking that can individualize the stress placed on each knee which does not occur with flat walking. The primary objective of this study was to assess biomarker responses of the ACL reconstructed knee (ACL-R) compared to the non-injured contralateral knee in an angular tilt paradigm. Our secondary objective was to determine the relationship between kinematic changes at each individual knee and serum biomarker responses.

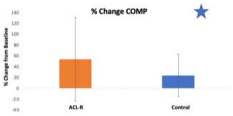
METHODS: This was a crossover sequential study that consisted of two visits and enrolled n=16 individuals with previous unilateral ACL-R performed between 2-5 years prior and without symptomatic evidence of knee OA. At each visit, participants rested for 30 minutes to establish baseline parameters. Each participant then walked for 30 minutes with a lateral angular tilt of 10°. At least 72 hours later the participant returned to the laboratory and the treadmill was tilted to the other side (the order of tilting to the ACL-R versus the contralateral knee was randomized). At each visit, while individuals were walking, blood was taken via a peripheral intravenous cannula at baseline, 15, and 30 minutes and tested for a serum biomarker of cartilage stress (COMP). At the same timepoints pain was assessed using the Numeric Pain Rating Scale (Kinematic assessment was also performed at these timepoints to track the trajectories of the pelvis, thigh, shank, and foot segments).

RESULTS:

The study cohort (n=16) had a mean age of 27.3 +/- 4.5 and was made up of 5 males and 11 females. When the healthy knee was stressed by tilt during walking, COMP concentrations increased by 20.0% from baseline. When the ACL-R was stressed, COMP concentrations increased by 57.4% ($p<0.00001$). When we compared COMP concentrations at 30 minutes, when the reconstructed knee was stressed, it was significantly more elevated than when the healthy knee was stressed ($p=0.042$). There was a significant correlation between the increase in knee adduction at mid-stance (a pathologic gait measure in osteoarthritis) in the ACL-R and change in serum COMP concentration ($r=0.532$, $p=0.03$) which was not observed in the healthy knee. In addition, knee kinematics at mid stance showed that when the healthy knee was stressed changes in knee flexion angle was correlated ($r=0.514$, $p=0.03$) to change in serum COMP concentration when the treadmill was tilted towards the contralateral side ($p=0.04$). There was no significant difference in pain during 30 minutes of walking with lateral angulation in either the ACL-R or healthy knee.

DISCUSSION AND CONCLUSION:

Our angular tilt paradigm identified increases in serum biomarker changes of cartilage stress in ACL-R (without pain) with strong relationships to pathologic gait measures of OA. This study, to our knowledge, is one of the first to find a relationship between biomarker changes and biomechanical changes at an individual knee while walking. Methodology may have significant potential in identifying knees that are at higher risk for developing OA and in-turn allow earlier intervention.



ACL-R
- 53.7% from baseline (p<0.05)
- COMP significantly more elevated at 30 min compared to control (p<0.05)

Control
- 23.7% from baseline (p<0.05)

Demographics	Mean (SD)
Participants (n)	16
Age (yr)	27.3 (4.5)
Years since surgery	2.75 +/- 2.68
Gender, No (%)	
Female	11 (68.8)
Male	5 (31.2)
Exercise Speed (MPH)	2.36

Biomechanical analysis at the end of midstance (31% gait cycle)