Evaluation of Early Degeneration of Cartilage in Patients with Anterior Cruciate Ligament Injury: Analysis Using Urine CTX-II Biomarker

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Introduction

• One of the main post-op sequelae of ACL injury is not completely eliminated after ligament reconstruction – osteoarthritis (OA)

• Signs and symptoms appear 10 to 15 years following ligament reconstruction, with incidence ranging from 0 to 86% of cases

• The diagnosis of OA is clinical. Imaging tests have low sensitivity and specificity for detecting early changes and monitoring disease progression

• The lack of a universal measurement standard with adequate sensitivity and specificity makes it difficult to measure the early degenerative process after injury or ACL reconstruction, making a more accurate, short-term screening modality desirable

• The use of biomarkers allows for an early, non-invasive measurement of the degenerative cartilage process. These biochemical markers of connective tissue are released into the systemic circulation and can be measured in blood, urine or synovial fluid
Introduction

• C-telopeptide of type II collagen (CTX-II) - biomarker released during the dynamic process of type II collagen degeneration (cartilage destruction)

• Initial trauma and intra-articular bleeding associated with ACL rupture are thought to cause an acute metabolic alteration cartilage and subchondral bone, resulting in the onset of the long-term degeneration of the articular cartilage

• The aim of this study - quantify the urinary concentration of CTX-II biomarker in patients who suffered an isolated ACL injury and compare concentrations found in this population with a control group

• The hypothesis of the study - urine concentrations of CTX-II biomarker will be higher in patients with ACL rupture and thus amenable to use as prognostic factor of OA development
Material and Methods

• Cross-sectional, observational, single-center study comparing CTX-II urinary biomarker in patients with ACL injury of the knee and healthy patients without knee injury (control group).

• 10 male subjects with isolated ACL lesion (Group 1 – diagnosed by clinical and MRI) x 10 males with no history of knee ligament injury (Group 2 – control)

• Inclusion criteria: male patients; between 18 and 35 years of age; with a body mass index of less than 30 kg/m$^2$; and isolated ACL lesions (1) or absence of knee injuries (2)

• Exclusion criteria: female patients; presence of degenerative knee disease; systemic, autoimmune or infectious diseases; other knee ligament injuries; history of knee surgery; lesions of the meniscus or associated cartilage
Material and Methods

• Summary statistics (mean, standard deviation, median, minimum, and maximum) were used to describe patient characteristics and biomarker concentrations within each group.

• The Mann-Whitney test was used to compare the groups in relation to the concentration of CTX-II biomarker.

• Spearman correlation was used to evaluate the relationship between injury time and the presence of urinary CTX-II biomarker. A p-value of less than 5% (0.05) and 95% confidence interval were defined as necessary for significance of the sample.
Results

• The patients in the ACL group had a mean age of 20.8 years and a mean BMI of 25 kg/m$^2$. Patients in control group had a mean age of 28.2 years and a mean BMI of 24.5 kg/m$^2$

• The individuals in ACL group presented younger age than the patients in control group 2 ($p < 0.001$) and there was no statistical difference between groups in terms of BMI ($p > 0.05$)
Results

- The mean value of the presence of CTX-II biomarker in the ACL group was $8.9 \pm 0.7$ ng/ml (range 7.7-9.8) and was higher than the average measured in the control group $6.7 \pm 2.6$ mg/ml (range 0.7 – 9.4) ($p = 0.009$)
Results
Results

• There was no difference between the time post-injury and the CTX-II biomarker level for ACL group patients. (p = 0.521; r = -0.231)
Discussion

• Our hypothesis was supported by the results of this study. Subjects with an ACL rupture were found to have a significantly higher concentration of CTX-II urine biomarker when compared to patients without injury (p = 0.009), regardless of the time post-injury.

• The difference suggests a predisposition to the development of OA in this patient population. Metabolic changes in the articular cartilage soon after the initial trauma of ACL rupture appear to predispose the patient to the degenerative knee pathology.

• Initial trauma + associated hemarthrosis = lesions of the subchondral bone and ↑ production of inflammatory cytokines (IL-6, IL-8, MMP-3 and MMP-13) → Degradation of type II collagen.
• Patients with ACL injury had higher concentrations of urinary CTX-II biomarker than those with no ACL injury (p = 0.009). However, there was no correlation between the concentration of this biomarker and the elapsed time post-injury (p > 0.05). The CTX-II biomarker may be a useful prognostic indicator for the development of OA in patients with a history of ACL injury.
References