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Very early osteoarthritis changes sensitively fluid flow properties of articular cartilage

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ABSTRACT

In this study, fibril-reinforced poroelastic (FRPE) modeling was used for rabbit knee after anterior cruciate ligament transection (ACLT) to assess how the mechanical properties of collagen, proteoglycans, and fluid in articular cartilage change in early osteoarthritis, and how site-specific these changes are.

Unilateral ACLT was performed in eight skeletally mature, female New Zealand white rabbits. A separate control (CTRL) group consisted of knee joints of five non-operated rabbits. Animals were sacrificed at four weeks after ACLT and cartilage-on-bone samples from femoral groove, medial and lateral femoral condyles, and tibial plateaus were harvested. A stress–relaxation protocol in indentation geometry was applied and the FRPE model was fitted to the experimental force–time curve by minimizing the mean absolute error between experiment and simulation. The optimized parameters were: fibril network modulus (E_f), representing the collagen network; non-fibrillar matrix modulus (E_{nf}), representing the PG matrix; and permeability (k), representing fluid flow.

Permeability was increased significantly in the ACLT group compared to the CTRL group knees at all sites except for the medial tibial plateau. ACLT also caused a decrease in the E_f at all sites except for the medial and lateral tibial plateaus. The E_{nf} of the ACLT group knees was altered only for the lateral femoral condyle.

The results of this study suggest that early osteoarthritis primarily affects cartilage permeability and impairs the collagen network stiffness in a site-specific manner. These findings from early osteoarthritis indicate that fluid flow velocity in articular cartilage may change prior to quantifiable structural alterations in the tissue.

1. Introduction

Biomechanical properties of articular cartilage, and the interaction between tissue constituents (primarily collagen, proteoglycans, fluid), contribute strongly to the knee joint function. Interstitial water contributes to the dynamic/instantaneous stiffness of cartilage, while collagen fibers (type II) primarily provide tensile stiffness (Mow and Hayes, 1991). Under prolonged loading conditions, fluid escapes from the cartilage and the proteoglycan (PG) content and integrity determines the equilibrium stiffness. Osteoarthritis (OA) changes the properties of the cartilage constituents. The very first changes in the mechanical behavior of cartilage are caused by the disruption of the collagen fibers, PG loss, and increases in cartilage water content. These changes cause an increase in permeability and a decrease in the dynamic and equilibrium stiffness (Sah et al., 1997; Setton et al., 1994).

Animal model studies are essential in the study of very early osteoarthritic degeneration in the knee joint (Altman and Dean, 1990; Han et al., 2010; Intema et al., 2010; Rogart et al., 1999; Turunen et al., 2013; Yoshioka et al., 1996). Anterior cruciate ligament transection (ACLT) (the Pond–Nuki model (Pond and Nuki, 1973)) in rabbits is a widely recognized method to induce OA in the knee (Altman and Dean, 1990; Laverty et al., 2010; Sah et al., 1997; Stoop et al., 2001; Vignon et al., 1984, 1987). Following ACLT, anterior tibial displacement and internal tibial rotation are increased, loading patterns in the knee are changed, and degenerative changes in the metabolism and structure of cartilage take place (Li et al., 2006; Lohmander et al., 2007). The first signs of cartilage deterioration have been reported four weeks after ACLT in the rabbit knee (Altman and Dean, 1990; Turunen et al., 2013; Yoshioka et al., 1996). Earlier studies investigating the effects of ACLT on degenerative changes of cartilage have usually concentrated on one or two sites (Altman and Dean, 1990; Han et al.,

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Table 1
Summary of significant changes ($p < 0.05$) in the structure and elastic modulus of early osteoarthritic cartilage. Tissues were characterized 4 weeks after ACLT and the parameters (except Mankin score) have been calculated from 5–10% of tissue thickness (indentation depth of the present study). These values present percent differences between groups. In this comparison, the ACLT group samples have been compared to the control group samples and in the brackets are the contralateral compared to the control group results. (Makela et al., 2014).

Structural/mechanical parameter	Femoral condyle		Tibial plateau		Femoral groove
	Lat	*Med*	*Lat*	*Med*	
Collagen content	+10%	+10%	ns	ns	−13% (−18%)
Collagen orientation angle	+59% (+24%)	+11% (+15%)	+21% (+28%)	+38% (+36%)	+76% (+97%)
Proteoglycan content	−38%	−34%	−14%	−16%	−19%
Mankin score (absolute change)	+3.8	+4.8	ns	+1.7 (+1.4)	+1.1
Equilibrium modulus	ns	−69%	−81%	ns	ns
Dynamic modulus	−71% (-65%)	−69% (−46%)	ns	ns	ns
+/− ACLT vs. CTRL					
(+)/(-) C-L vs. CTRL					

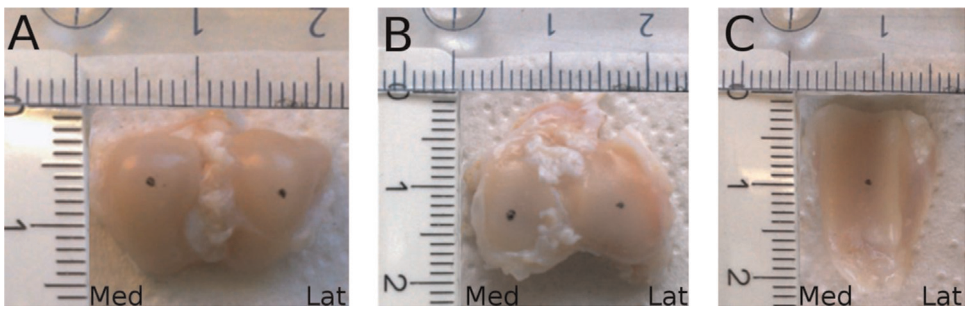

Fig. 1. Analyzed locations in the lapine knee joints with left hand side being the medial. Articular cartilage samples in the lateral and medial femoral condyles (A), tibial plateaus (B), and femoral groove (C). Indentation locations are marked with black dots and the ruler scale is in centimeters (Makela et al., 2014).

2010; Intema et al., 2010; Rogart et al., 1999; Sah et al., 1997; Setton et al., 1994; Turunen et al., 2013; Yoshioka et al., 1996); and many of the mechanical and permeability tests have been conducted in an unconfined or confined geometry, where the cartilage is detached from the underlying bone. Furthermore, the mechanical changes have usually been calculated using elastic models without knowledge of fluid properties. Also, ACLT studies have been conducted typically using the contralateral side joint for control (Altman et al., 1984; Carney et al., 1984; Guilak et al., 1994; Sah et al., 1997; Setton et al., 1994; Stoop et al., 2001; Turunen et al., 2013; Vignon et al., 1984). However, there is ample evidence of changes in the contralateral knee of unilateral ACLT intervention (Han et al., 2010; Makela et al., 2014; Shymkiw et al., 2001).

In a previous study, we found substantial site-specific changes in cartilage properties already 4 weeks after ACLT in rabbits (Table 1) (Makela et al., 2014). Microscopic and spectroscopic methods showed degenerative alterations of cartilage due to ACLT primarily in the superficial PG content and collagen orientation. In some locations, tissue alterations were observed also deeper in the tissue. Also, collagen content was changed primarily in the deep tissue. However, mechanical alterations in cartilage (tissue modulus) due to ACLT were observed only in a few locations. Detailed mechanical alterations in the major tissue constituents (collagen, PGs, fluid) in this animal model of early OA remained still unknown.

In this study, we use fibril-reinforced poroelastic modeling, together with experimental indentation testing, to study the effects of early OA (4 weeks post ACLT) on the mechanical properties of the collagen fibrils (fibril network modulus), PGs (non-fibrillar matrix modulus) and fluid (permeability) in a site-specific manner. We hypothesize that due to significant alterations in the collagen network architecture in this animal model (Table 1), alteration in the fibril network modulus is observed sensitively and in a highly site-specific manner (was not observed earlier using a simple elastic analysis). Furthermore, since tissue permeability has been earlier shown to be related to both collagen and PGs (Julkunen et al., 2007; Makela et al., 2012; Maroudas and Bullough, 1968; Mizrahi et al., 1986), and since those structural components were altered in this animal model (Table 1), cartilage permeability is hypothesized to change more sensitively than any other parameter. This is a first attempt at using computational modeling in conjunction with experimental indentation testing to determine very early osteoarthritic changes in the mechanical characteristics of different tissue constituents in lapine knee articular cartilage.

2. Methods

2.1. Samples and processing

This animal model study was carried out using skeletally mature, female New Zealand white rabbits (Oryctolagus cuniculus, age 14 months). Unilateral ACLT was performed in eight rabbits and the contralateral joints were used for analysis as a contralateral (C-L) group. In order to exclude possible effects of ACL transection, ten knee joints from five non-operated rabbits were also used as a separate control group (CTRL). All animals were sacrificed at 4 weeks following ACLT. Cartilage-on-bone samples were harvested and biomechanical measurements were conducted on the medial (med) and lateral (lat) femoral condyles and tibial plateaus in the center of the weight-bearing areas and on the femoral groove in the center of the contact area with the patella for the knee in its neutrally flexed position (Julkunen et al., 2009a; Makela et al., 2014; Wei et al., 1998) (Fig. 1, see more details from Makela et al. (2014) and Florea et al. (2014) where the same samples were used). There were no significant differences ($p > 0.05$) in sample thicknesses between ACLT, C-L and CTRL groups. ACLT procedures for rabbits were approved by the Animal Ethics committee at the University of Calgary and the guidelines of the Canadian Council on Animal Care were followed. More details are presented in the Supplementary material.

2.2. Biomechanical measurements

Biomechanical measurements were conducted using a custom made, high-precision material testing device (Korhonen et al., 2002a, 2002b) (resolution: 0.1 µm, 0.005 N). Each sample was glued onto the measurement chamber at the

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