Journal of Biomechanics ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

Journal of Biomechanics

journal homepage: www.elsevier.com/locate/jbiomech
www.JBiomech.com

A multi-scale finite element model for investigation of chondrocyte mechanics in normal and medial meniscectomy human knee joint during walking

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ARTICLE INFO

Article history:
Accepted 17 February 2015

Keywords:
Knee joint
Articular cartilage
Meniscectomy
Cell mechanics
Finite element analysis
Multi-scale modeling

ABSTRACT

Mechanical signals experienced by chondrocytes (articular cartilage cells) modulate cell synthesis and cartilage health. Multi-scale modeling can be used to study how forces are transferred from joint surfaces through tissues to chondrocytes. Therefore, estimation of chondrocyte behavior during certain physical activities, such as walking, could provide information about how cells respond to normal and abnormal loading in joints. In this study, a 3D multi-scale model was developed for evaluating chondrocyte and surrounding peri- and extracellular matrix responses during gait loading within healthy and medial meniscectomy knee joints. The knee joint geometry was based on MRI, whereas the input used for gait loading was obtained from the literature. Femoral and tibial cartilages were modeled as fibril-reinforced poroviscoelastic materials, whereas menisci were considered as transversely isotropic. Fluid pressures in the chondrocyte and cartilage tissue increased up to 2 MPa (an increase of 30%) in the meniscectomy joint compared to the normal, healthy joint. The elevated level of fluid pressure was observed during the entire stance phase of gait. A medial meniscectomy caused substantially larger (up to 60%) changes in maximum principal strains in the chondrocyte compared to those in the peri- or extracellular matrices. Chondrocyte volume or morphology did not change substantially due to a medial meniscectomy. Current findings suggest that during walking chondrocyte deformations are not substantially altered due to a medial meniscectomy, while abnormal joint loading exposes chondrocytes to elevated levels of fluid pressure and maximum principal strains (compared to strains in the peri- or extracellular matrices). These might contribute to cell viability and the onset of osteoarthritis.

1. Introduction

Forces experienced by knee joints during normal daily activities are transferred from joint surfaces through cartilage tissues to chondrocytes, *i.e.* articular cartilage cells (Guilak, 2000). Mechanical signals experienced by cells modulate cartilage mechanobiology and health (Guilak et al., 2006). Several previous studies suggest that the mechanical signals and deformations experienced by chondrocytes in the knee joint during daily activities play an important role in cartilage health (Abusara et al., 2011; Buschmann et al., 1999, 1995; Guilak et al., 1995; Han et al., 2012; Madden et al., 2013; Parkkinen et al., 1992; Quinn et al., 1998; Tetsunaga et al., 2011). Furthermore, abnormal loading and mechanical signals experienced by chondrocytes due to joint disorders may contribute to cell viability, and the onset and progression of osteoarthritis (OA). Quantitative evaluation of these *in vivo* cell responses can be realized by developing computational multi-scale models (Halloran et al., 2012; Sibole and Erdemir, 2012), and these models can be a useful tool for *in vivo* evaluation of local tissue and chondrocyte behavior.

Recent knee joint level finite element (FE) models incorporated both poroviscoelastic material properties of cartilage and joint loading during walking (Halonen et al., 2014, 2013; Mononen et al., 2015, 2013, 2012; Räsänen et al., 2013). Even though these models were able to evaluate the effects of the depth-dependent cartilage structure and mechanical properties on knee joint mechanics during walking (Halonen et al., 2014, 2013; Mononen et al., 2015, 2013, 2012; Räsänen et al., 2013), they did not incorporate cells. Cell level responses have been studied by applying multi-scale approaches (Guo et al., 2014; Halloran et al., 2012; Han et al., 2011; Julkunen

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http://dx.doi.org/10.1016/j.jbiomech.2015.02.043
0021-9290/

et al., 2009; Korhonen et al., 2011; Moo et al., 2012; Sibole and Erdemir, 2012; Sibole et al., 2013; Tanska et al., 2013; Varadarajan et al., 2008). However, joint loading and/or constitutive equations for cartilage were relatively simple in these models (*e.g.*, axial loading, isotropic elastic cartilage).

Bilateral and partial lateral/medial meniscectomies have been common clinical surgical treatment operations for injured and damaged menisci (Cullen et al., 2009; Hawker et al., 2008; Kim et al., 2011; Salata et al., 2010), even though the efficacy of these operations is disputed (Kirkley et al., 2008; Moseley et al., 2002; Sihvonen et al., 2013). Bilateral and partial meniscectomies have been reported to increase the risk for the onset of OA by increasing stresses and strains in the cartilage tissue (Cicuttini et al., 2002; Masouros et al., 2008; Mononen et al., 2015, 2013; Salata et al., 2010; Zielinska and Donahue, 2006). Although the normal knee joint can be valgus or varus aligned, affecting the stress distribution between lateral and medial compartments (Cooke et al., 1997, 2007; Kozanek et al., 2009; Zhai et al., 2007), higher risk for the onset of OA has typically been suggested to arise from lateral rather than medial meniscectomies (Chatain et al., 2003; Salata et al., 2010; Mononen et al., 2015, 2013). This conclusion is typically based on tissue level changes, *e.g.*, increased contact pressure of cartilage. However, possible alterations in chondrocyte responses as a result of medial meniscectomy are not known.

Thus, the aim of this study was to develop a computational multi-scale model, driven by human knee joint forces and moments, for investigating the mechanical responses of a chondrocyte in normal and meniscectomy human knee joints during gait. This study provides a novel computational method in which coupling of the joint level loading during walking with fibril-reinforced poroelastic properties of the extracellular matrix (ECM) and pericellular matrix (PCM) is employed for the investigation of chondrocyte strains, stresses and fluid pressures.

2. Materials and methods

2.1. Imaging and segmentation

The existing geometry of a left knee joint, imaged with magnetic resonance imaging (Fig. 1a), from a healthy male volunteer (28 years, 80 kg) was used in this study (Halonen et al., 2014). See the Supplementary material for more details.

2.2. Gait data

Knee joint forces (axial, medial–lateral and anterior–posterior), moments (internal–external and varus–valgus, *i.e.*, abduction–adduction) and extension–flexion angle during walking were obtained from a previous experimental study (Fig. 1c) (Kozanek et al., 2009; Kutzner et al., 2010). Based on our preliminary simulations, the internal–external moment presented in Kutzner et al. (2010) was reduced by 90% to match experimentally observed ranges of internal–external rotation (~10°) (Benoit et al., 2006; Kadaba et al., 1990; Kozanek et al., 2009; Reinschmidt et al., 1997). This was also supported by another study suggesting that passive internal–external moment of the knee is about 10–20% from the measured knee moments (Adouni et al., 2012).

2.3. FE analysis

The imported geometry was used to create a whole joint level FE model (Fig. 1b), consisting of femoral and tibial cartilages, menisci and ligaments. The medial meniscus was discarded from the meniscectomy model. Using Abaqus, femoral and tibial cartilages were meshed using first-order, 8-node porous continuum elements (type C3D8P). C3D8P elements were chosen for their good capability for contact modeling in non-uniform contacts. The average element edge lengths in the whole knee joint model were 300 and 800 μm in the axial and transversal directions at the area of interest (see Figs. 1 and 3), respectively. Similarly as before in the joint and tissue level analyses (Halonen et al., 2014, 2013; Mononen et al., 2015, 2013, 2012; Räsänen et al., 2013), we were only interested in fluid pressure in cartilage, thus, lateral and medial menisci were meshed using first-order 8-node reduced integration continuum elements without fluid (type C3D8R). Also, bones were considered as rigid and ligaments were modeled with linear springs (type SPRINGA) for computational efficacy.

Femoral and tibial cartilages were modeled as fibril-reinforced poroviscoelastic (FRPVE) materials using user-defined material script (UMAT) in Abaqus. Menisci

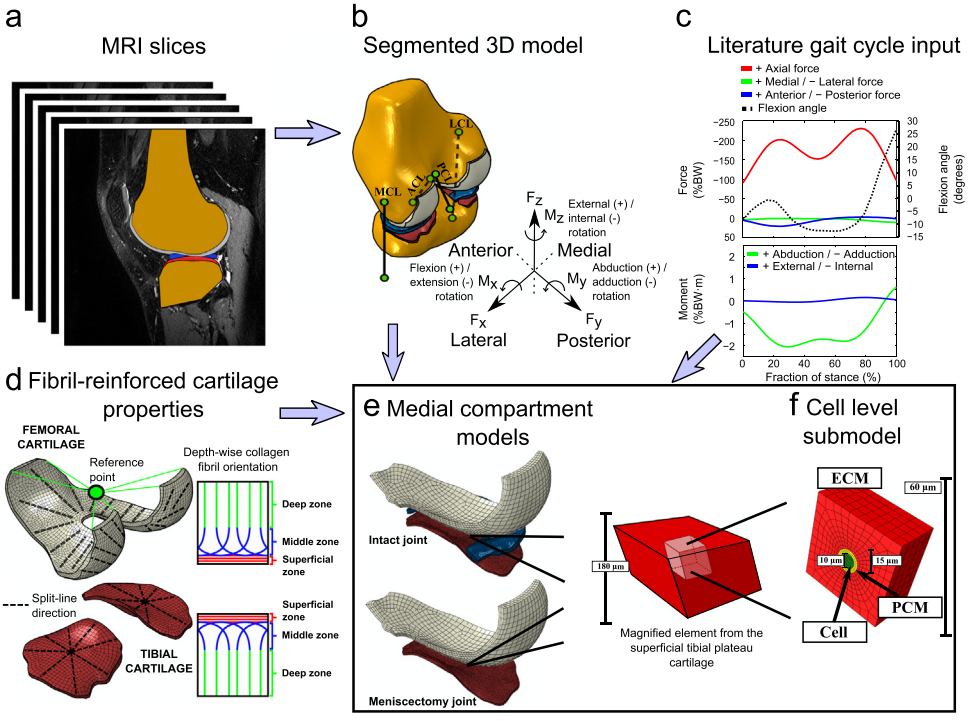

Fig. 1. (a,b) Model geometry, (c) force/moment (Kutzner et al., 2010) and extension angle (Kozanek et al., 2009) inputs used in this study. First, (c) the implemented force/moment-controlled joint movement was implemented into the intact and meniscectomy joint level FE models. Then, (d) forces and translations in the medial compartment were implemented into a more densely meshed medial compartment model. Finally, (f) a cell level submodel consisting of a single chondrocyte, and surrounding pericellular matrix (PCM) and local extracellular matrix (ECM), driven by displacements and pore pressures of the tissue level submodel, was used to evaluate stresses, strains and fluid pressures of the chondrocyte, PCM and ECM. A mesh convergence study was conducted by increasing the mesh density (8 times finer mesh) at all three levels. Meshes used in further analyses were assumed fine enough since the differences in maximum principal stresses and logarithmic strains between the models were $<5\%$.

Please cite this article as: Tanska, P., et al., A multi-scale finite element model for investigation of chondrocyte mechanics in normal and medial meniscectomy human knee joint during.... Journal of Biomechanics (2015), http://dx.doi.org/10.1016/j.jbiomech.2015.02.043