Identification of locations susceptible to osteoarthritis in patients with anterior cruciate ligament reconstruction: Combining knee joint computational modelling with follow-up T1p and T2 imaging

Bolcos, PO

Elsevier Ltd

https://doi.org/10.1016/j.clinbiomech.2019.08.004

Downloaded from University of Eastern Finland's eRepository
Identification of locations susceptible to osteoarthritis in patients with anterior cruciate ligament reconstruction: Combining knee joint computational modelling with follow-up T1ρ and T2 imaging

Paul O. Bolcos⁎⁎, Mika E. Mononen⁎, Matthew S. Tanaka⁎⁎, Mingrui Yang⁎, Juha-Sampo Suomalainen⁎, Mikko J. Nissi⁎⁎, Juha Töyräs⁎⁎, Benjamin Ma⁎, Xiajuan Li⁎, Rami K. Korhonen⁎⁎

⁎ Department of Applied Physics, University of Eastern Finland, POB 1627, FI-70211 Kuopio, Finland
⁎⁎ Corresponding author.
⁎⁎⁎ Correspondence to: PO Bolcos, Department of Applied Physics, University of Eastern Finland, POB 1627, FI-70211 Kuopio, Finland
E-mail addresses: paul.bolcos@uef.fi (P.O. Bolcos), rami.korhonen@uef.fi (R.K. Korhonen).

ARTICLE INFO
Keywords:
Finite-element analysis
Knee joint
Articular cartilage
Gait
Magnetic resonance imaging

ABSTRACT

Background: Finite element modelling can be used to evaluate altered loading conditions and failure locations in knee joint tissues. One limitation of this modelling approach has been experimental comparison. The aims of this proof-of-concept study were: 1) identify areas susceptible to osteoarthritis progression in anterior cruciate ligament reconstructed patients using finite element modelling; 2) compare the identified areas against changes in T2 and T1ρ values between 1-year and 3-year follow-up timepoints.

Methods: Two patient-specific finite element models of knee joints with anterior cruciate ligament reconstruction were created. The knee geometry was based on clinical magnetic resonance imaging and joint loading was obtained via motion capture. We evaluated biomechanical parameters linked with cartilage degeneration and compared the identified risk areas against T2 and T1ρ maps.

Findings: The risk areas identified by the finite element models matched the follow-up magnetic resonance imaging findings. For Patient 1, excessive values of maximum principal stresses and shear strains were observed in the posterior side of the lateral tibial and femoral cartilage. For Patient 2, high values of maximum principal stresses and shear strains of cartilage were observed in the posterior side of the medial joint compartment. For both patients, increased T2 and T1ρ values between the follow-up times were observed in the same areas.

Interpretation: Finite element models with patient-specific geometries and motions and relatively simple material models of tissues were able to identify areas susceptible to post-traumatic knee osteoarthritis. We suggest that the methodology presented here may be applied in large cohort studies.

1. Introduction

The exact mechanisms behind the onset and development of osteoarthritis (OA) are not fully understood. The incidence of OA is generally higher in patients after anterior cruciate ligament (ACL) rupture, especially with concomitant meniscal or chondral lesions (Barenius et al., 2014; Claes et al., 2013; Culvenor et al., 2015; Potter et al., 2012; Risberg et al., 2016). Additionally, a long-term follow-up study showed little difference in OA susceptibility between conservative (exercise) or surgical treatment (ACL reconstruction, ACLR) of ruptures (Lohmander et al., 2007). Postoperatively, knee OA can be present even in short-term follow-ups of ACLR (Culvenor et al., 2015; Eckstein et al., 2015; Williams et al., 2017). One of the mechanisms leading to OA for ACLR patients could be altered joint biomechanics and excessive stresses and strains experienced by articular cartilage (Gardinier et al., 2013; Konrath et al., 2017; Wellsandt et al., 2016).

This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).
High deviatoric or shear strains of cartilage non-fibrillar matrix degeneration primarily with high tensile stresses of tissue loading. Experimental and computational studies have linked swelling to proteoglycans (Duvvuri et al., 2002; Wheaton et al., 2004), while T\textsubscript{1p} relaxation time is primarily sensitive to collagen content depending on the magnetic field strength (Blumenkrantz and Majumdar, 2007; Hänninen et al., 2017; Nieminen et al., 2017). Imaging cannot assess altered biomechanics and excessive joint and tissue loading. Experimental and computational studies have linked collagen matrix degeneration primarily with high tensile stresses of collagen fibrils (Danso et al., 2014; Henao-Murillo et al., 2018; Hosseini et al., 2013; Kempson, 1982) and proteoglycan (PG) loss primarily with high deviatoric or shear strains of cartilage nonfibrillar matrix (Bonnevie et al., 2016; Ewers et al., 2001; Kelly and O'Connor, 1996; Wilson et al., 2006). This has enabled the use of finite element (FE) modelling in assessing the potential biomechanical risks for the onset and progression of OA due to collagen degeneration and/or PG loss (Gardiner et al., 2016; LaValley et al., 2017; Mononen et al., 2018; Mootanah et al., 2014). However, for better trustworthiness of the models, they should be compared against follow-up information, such as T\textsubscript{2} and T\textsubscript{1p} relaxation time maps.

In a clinical setting, the computational model has to be easy to generate and time for the converged solution has to be short. Some of the above-mentioned models applied complex materials, such as fibrillar-reinforced poro(visco)elastic, to describe articular cartilage, meniscus and ligaments (Dabiri and Li, 2015; Gu and Li, 2011; Mononen et al., 2018; Mootanah et al., 2014). This is simultaneously time consuming (in terms of implementation) and computationally demanding. Furthermore, for models that include all major knee joint structures with muscle forces, generation and simulation times become even longer (Bolcos et al., 2018; Orozco et al., 2018). Recent studies have shown that simpler FE models, in terms of geometry and motion (Bolcos et al., 2018), cartilage material properties (Klets et al., 2016) and ligament formulation (Orozco et al., 2018), produce similar results with more complex models. This enables a reduction in FE model generation and computation times. This kind of FE models for joint mechanics have not been generated before for ACLR patients with patient-specific motion. Further, to our knowledge, patient-specific OA predictions from the FE models have not been compared earlier against experimentally evaluated local changes in the knee joint cartilage, as determined by changes in T\textsubscript{2} and T\textsubscript{1p} relaxation times between follow-up timepoints.

The objectives of this proof of concept study were two-fold: (1) Using a relatively fast FE modelling approach, with a proven ability to capture mechanical responses of cartilage, to evaluate knee cartilage mechanics in patients with ACLR at 1-year follow-up, and identify areas susceptible to OA progression, due to collagen damage and/or PG loss; (2) Compare the identified areas for collagen degeneration and PG depletion against local changes in T\textsubscript{2} and T\textsubscript{1p} relaxation times between the 1-year and 3-year follow-up timepoints. Our hypothesis was that the onset and development of OA in ACLR patients is patient-specific and the areas susceptible to OA at 1-year timepoint can be identified by using FE modelling and matched with local changes in T\textsubscript{2} and T\textsubscript{1p} relaxation times of cartilage.

![Fig. 1. Workflow of the study. a) Knee joint MR image segmentation; b) Knee joint rotations and ground reaction forces from motion capture; c) FE model overview, with geometry from a) and motion from b); d) Maximum principal stress distribution on the tibial cartilage. Areas susceptible to OA are indicated in black; e) T\textsubscript{2} and T\textsubscript{1p} maps used for verifying the progression of OA.](image-url)
2. Methods

The workflow of the study is shown in Fig. 1. This study includes two patient-specific FE models of two subjects with ACLR. Information on both the knee joint geometry and motion was incorporated from manually segmented high-resolution 3D MRI images (Fig. 1a) and motion capture gait data (Fig. 1b), respectively. The included soft-tissues were femoral and tibial cartilages and menisci, with collateral (MCL & LCL) and cruciate (ACL & PCL) ligaments (Fig. 1c). The FE model results (Fig. 1d) were then compared against follow-up information: T2 and T1 maps (Fig. 1e).

2.1. Data acquisition

The magnetic resonance (MR) image acquisition and motion capture were performed at the University of California, San Francisco (UCSF). Both subjects gave informed consent and data acquisition was approved by and carried out in accordance with the rules and regulations of the Institutional Review Board under the Human Research Protection Program at UCSF. For each patient, two MR sequences were acquired at 1-year and 3-year follow-up timepoints after the ACLR surgery. Additionally, at each follow-up timepoint the subject gait data was measured using a previously established protocol (Samaan et al., 2017). The 1-year timepoint was used to predict the location susceptible to OA using FE modelling. The 3-year timepoint was used to verify the progression of OA predicted from the 1-year timepoint. Details on the MRI acquisition and motion capture are given in Supplementary Materials.

2.2. FE model construction

MRI and motion capture data were transferred to the University of Eastern Finland (UEF), where computational models were generated. There is a data transfer agreement between UCSF and UEF. The methodology used to generate the FE models was identical to a previous study (Bolcos et al., 2018), and is summarized in Supplementary materials. In that study, it was shown that simpler knee models can produce similar cartilage responses with more complex models. The FE model with motion implemented using kinetics and kinematics (forces and rotations), and without patella and quadriceps forces, produced reaction forces and contact pressures within physiological limits (Gilbert et al., 2014; Konrath et al., 2017; Kutzner et al., 2010; Pizzolato et al., 2017). Details of the material properties for each soft tissue are shown in Table 1. Simpler models are desired when the purpose is towards clinical implementation. In this study, this relatively simple approach with kinetic-kinematic motion implementation was used.

2.3. Analysis

2.3.1. T2 and T1 maps

Tibial and femoral cartilage were manually segmented from the combined multi-slice sequence at both 1-year at 3-year follow-up timepoints. The relaxation times were calculated using a two-parametric mono-exponential fit with Aedes (Niskanen, 2006) and in-house written plugins for Matlab.

2.3.2. FE analysis

Based on the experimental findings (Danso et al., 2014; Kempson, 1982; Mononen et al., 2016) and previous computer simulations (Mononen et al., 2016), maximum principal stresses above 7 MPa were assumed to trigger collagen network degeneration. Generally, experimental findings (D’lima et al., 2001; Ewers et al., 2001; Kelly and O’Connor, 1996; Loening et al., 2000; Wilson et al., 2006; Zamli and Sharif, 2011) and previous computer simulations (Hosseini et al., 2014; Mononen et al., 2018) link tissue strains above 30% with chondrocyte apoptosis and subsequent PG loss. Here, shear strains above 32% were assumed to lead to PG loss (Bonnevie et al., 2016; Hashimoto et al., 2009; Li et al., 2013). Here we evaluated:

1. $\sigma_{\text{tensile}}$ and $\gamma_{\text{abs}}$ as a function of stance. The peak values of maximum principal stress ($\sigma_{\text{tensile}}$) and absolute shear strain ($\gamma_{\text{abs}}$) were calculated on the tibiofemoral contact area (cartilage-cartilage contact area) as a function of stance.

2. $\sigma_{\text{tensile}}$ and $\gamma_{\text{abs}}$ distribution maps. To identify the locations prone to collagen network damage and/or PG loss, the $\sigma_{\text{tensile}}$ and $\gamma_{\text{abs}}$ distributions were calculated for each compartment (i.e. medial or lateral tibial/femoral cartilage). We evaluated the peak values of maximum principal stresses and absolute shear strains for each element.

2.4. Comparison of the FE model and MRI

The FE model results were verified against changes in T2 and T1p relaxation times. These are among the most established quantitative MRI parameters for articular cartilage and were shown to be highly sensitive to collagen and PG content (Duvvuri et al., 2002; Hänninen et al., 2017; Li et al., 2007; Nissi et al., 2004; Wang et al., 2016; Wheaton et al., 2004; Xia et al., 2001).

2.4.1. Total volumes

To compare the identified risk areas with follow-up information the following steps were needed:

1. For the $\sigma_{\text{tensile}}$ and $\gamma_{\text{abs}}$ distribution maps, we defined volumes-of-interest (VOI) for each compartment. The VOI was defined as the total volume in which the respective thresholds were exceeded. If neither $\sigma_{\text{tensile}}$ nor $\gamma_{\text{abs}}$ exceeded the thresholds, the VOI was defined as “0”.

2. For each VOI from step 1, we calculated the total volume of the VOI as a percentage of the total volume of each compartment, reflecting the percentage from the total volume susceptible to damage.

Table 1

| Material parameters of cartilage, meniscus and ligaments used in the FE models. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Transversely isotropic (pore)elastic | E<sub>p</sub> (MPa) | E<sub>c</sub> (MPa) | v<sub>p</sub> | v<sub>c</sub> | G<sub>c</sub> (MPa) | k (10<sup>−15</sup> m<sup>4</sup>/Ns) | e<sub>0</sub> (−) |
| Cartilage (Klets et al., 2016) | 24 | 0.46 | 0.42 | 0.06 | 12 | 1 | 4 |
| Meniscus (Danso et al., 2014; Klets et al., 2016; Vaziri et al., 2008; Wilson et al., 2004) | 20 | 159.6 | 0.30 | 0.01 | 50 | – | – |
| Bi-linear springs | Stiffness (N/mm) | Pre-strain (%) |
| ACL (Gantoi et al., 2013; Haut Donahue et al., 2002) | 380 | 5 |
| PCL (Gantoi et al., 2013; Momersteeg et al., 1995) | 200 | 5 |
| MCL (Gantoi et al., 2013; Momersteeg et al., 1995) | 100 | 4 |
| LCL (Gantoi et al., 2013; Momersteeg et al., 1995) | 100 | 4 |

Parameters: E<sub>p</sub> – in-plane Young’s modulus, E<sub>c</sub> – out-of-plane Young’s modulus, ν<sub>p</sub> – in-plane Poisson’s ratio, ν<sub>c</sub> – out-of-plane Poisson’s ratio, G<sub>c</sub> – out-of-plane shear modulus, k – permeability, e<sub>0</sub> – initial void ratio.
3. For the T2 and T1p maps, from both 1-year and 3-year follow-up timepoints we defined VOIs for each compartment. The VOI was defined as the volume of cartilage with either T2 or T1p, relaxation times above 60 ms. This value is above the literature reported value of 50 ms for healthy cartilage (Bolbos et al., 2008; Li et al., 2011; Stahl et al., 2009; Surowiec et al., 2014; Van Rosom et al., 2017). Similarly, if no relaxation time exceeded this limit, the VOI was defined as “0”.

4. For each VOI from step 3, we calculated the volume of the VOI as a percentage from the total volume of the compartment at both 1-year and 3-year follow-up timepoints.

5. From step 4, we subtracted the VOI at 3-year timepoint from the VOI at 1-year timepoint, reflecting the percentage of potentially damaged tissue from the total volume of each compartment.

Thus, we could evaluate changes in the relaxation times between 1-year and 3-year follow-up times and compare them with the areas susceptible to degeneration as predicted by the FE model. An example of steps 1–4 is shown in Supplementary materials.

2.4.2. Sagittal slices

Due to the slice thickness of 4 mm of both T2 and T1p MR images, we could not ensure the accuracy of the total volume calculated in steps 4 and 5. Therefore, a slice-by-slice comparison between the relaxation times and FE models was required. Since in the sagittal plane the resolution of the MR image was the best, sagittal slices from the 0s tensile, 0s lapse T2 and T1p maps were taken as follows:

1. For T2 and T1p maps, the sagittal slice was located in the center of the previously defined VOI. The location of this slice was approximated by calculating the number of slices to the edge of lateral side and multiplying with the slice thickness (4 mm).

2. For the 0s tensile and 0s lapse distribution maps, the sagittal slice was acquired from the same location as in step 1 (Fig. 2a and b).

3. Results

3.1. Stance

The FE model revealed that on the lateral tibial cartilage in Patient 1, 0s tensile exceeded the 7 MPa threshold for collagen degeneration through the entire stance phase (Fig. 3a), while 0s lapse values were above the threshold of 32% for PG loss between 20% and 80% of the stance phase (Fig. 3b). On the lateral femoral cartilage, the thresholds were exceeded for both 0s tensile and 0s lapse at 30–50% of the stance phase in the lateral and at ~20% in the medial joint compartments (Fig. 3g,h).

For Patient 2, 0s tensile exceeded the threshold through the entire stance phase on the medial tibial cartilage (Fig. 3c), while 0s lapse values were above the threshold for degeneration at 0–20% and 50–80% (after midstance) of the stance phase (Fig. 3f). On the lateral tibial cartilage, neither 0s tensile nor 0s lapse exceeded the degeneration thresholds (Fig. 3e,f). For the femoral cartilage, the thresholds were exceeded for both 0s tensile and 0s lapse at 30–50% of the stance phase in the lateral and at ~20% in the medial joint compartments (Fig. 3g,h).

3.2. Distribution

For Patient 1, 0s tensile exceeded the threshold of 7 MPa on the posterior side of both the lateral tibial and femoral cartilage (Fig. 4a and b). The 0s lapse values also exceeded the threshold of 32% with a similar distribution as 0s tensile (not shown). On the medial tibial and femoral cartilage, neither 0s tensile nor 0s lapse exceeded the thresholds.

For Patient 2, 0s tensile exceeded the threshold for collagen damage on the posterior side of the medial tibial and femoral cartilage (Fig. 4c and d). Further, in the lateral joint compartment, the 0s tensile values exceeded the threshold in the center of the cartilage, but the area with high values was smaller than that in the medial joint compartment. The 0s lapse values were only slightly over the threshold of proteoglycan loss (PG) if at all.

3.3. Volume change

The total volume susceptible to OA identified by the FE model matched adequately with the total volume of increased T2 and T1p relaxation times (Fig. 5). For Patient 1, the FE model revealed that in ~14% of the lateral tibial cartilage and ~7% of the lateral femoral cartilage volume, the 0s tensile values were above the threshold. The 0s lapse values were above the chosen threshold in ~6% of the lateral tibial cartilage and ~7% of the lateral femoral cartilage volume (Fig. 5a). Similarly, ~16% of the lateral tibial cartilage and ~6% of the lateral femoral cartilage volume experienced increased values for both T2 and T1p during the follow-up times. In the medial joint compartment, neither 0s tensile nor 0s lapse exceeded the thresholds. Similarly, in the medial tibial cartilage, neither T2 nor T1p were changed between the follow-up times, while in the femoral side they were increased in ~3% of the total cartilage volume (Fig. 5a).

For Patient 2, the FE model revealed high 0s tensile values in ~2% of the lateral compartment and ~3% of the medial compartment cartilage volume. High 0s lapse values were only seen at maximum of ~1% of the lateral femoral cartilage volume (Fig. 5b). Similarly, ~2.5% of the lateral tibial cartilage and ~1.5% of the lateral femoral cartilage volume experienced increased values for both T2 and T1p during the follow-up times. In the medial tibial cartilage, both T2 and T1p values

![Fig. 2. a) and b) Sagittal slice locations for the FE models. Note that slice thicknesses for both the FE models and T2/T1p maps are indicated on the right.](image-url)
In the present proof-of-concept study, two FE models of patients with ACL reconstruction were created. The knee joint geometries were based on manually segmented MRI images and the knee joint motions were based on motion capture. Each model included tibial cartilage, femoral cartilage and menisci with collateral and cruciate ligaments. To reduce model complexity and calculation times, a transversely isotropic poroelastic material was used for cartilage and a transversely isotropic elastic material for menisci. The analysis was divided in two parts. First, we identified potential failure areas for both tibial and femoral cartilage using FE modelling. Then, we compared these areas against quantitative follow-up T2_\text{abs} and T1_\text{pp} relaxation times. The potential failure areas predicted by the FE model matched adequately with the follow-up MRI information for both patients. Our results suggest that a relatively simple FE model, in terms of geometry, motion and materials, has potential to identify areas susceptible to cartilage degeneration and may be applied in a fast evaluation of subjects with traumatic ligament injuries and reconstructions.

### 4. Discussion

In the present proof-of-concept study, two FE models of patients with ACL reconstruction were created. The knee joint geometries were based on manually segmented MRI images and the knee joint motions were based on motion capture. Each model included tibial cartilage, femoral cartilage and menisci with collateral and cruciate ligaments. To reduce model complexity and calculation times, a transversely isotropic poroelastic material was used for cartilage and a transversely isotropic elastic material for menisci. The analysis was divided in two parts. First, we identified potential failure areas for both tibial and femoral cartilage using FE modelling. Then, we compared these areas against quantitative follow-up T2_\text{abs} and T1_\text{pp} relaxation times. The potential failure areas predicted by the FE model matched adequately with the follow-up MRI information for both patients. Our results suggest that a relatively simple FE model, in terms of geometry, motion and materials, has potential to identify areas susceptible to cartilage degeneration and may be applied in a fast evaluation of subjects with traumatic ligament injuries and reconstructions.

#### 3.4. Sagittal slices

For Patient 1, the FE model results and T2_\text{abs} and T1_\text{pp} maps of both the lateral (Fig. 6a) and medial (Fig. 6b) compartments showed an adequate correspondence. In the areas of the lateral compartment with high $\sigma_{\text{tensile}}$ or $\rho_{\text{abs}}$ values (dark gray areas in Fig. 6a), the T2_\text{abs} and T1_\text{pp} values were also elevated. The relaxation times more than doubled in the same areas where excessive $\sigma_{\text{tensile}}$ and/or $\rho_{\text{abs}}$ values were seen. In the medial femoral compartment, only local increases in T2_\text{abs} and T1_\text{pp} relaxation times between the follow-up timepoints were observed, while the medial tibial cartilage was unaffected. The FE model showed neither high $\sigma_{\text{tensile}}$ nor $\rho_{\text{abs}}$ values, above the chosen threshold, for either medial femoral or tibial cartilage.

For Patient 2, the FE model showed only slightly elevated $\sigma_{\text{tensile}}$ and $\rho_{\text{abs}}$ values near the cartilage surface in the lateral joint compartment (Fig. 7a), while the T2_\text{abs} and T1_\text{pp} values were close to the literature reported values for healthy cartilage. In the medial joint compartment (Fig. 7b), high $\sigma_{\text{tensile}}$ and $\rho_{\text{abs}}$ values were seen on the posterior side of the medial tibial and femoral cartilage. For the T2_\text{abs} and T1_\text{pp} relaxation times of the medial joint compartment, slightly elevated values during the follow-up were seen throughout the contacting surfaces.

#### 4.1. Patient 1

Based on the FE model results, possible collagen damage and degeneration through $\sigma_{\text{tensile}}$ was predicted to occur in both the lateral tibial (14% of the cartilage volume) and lateral femoral cartilage (7% of the cartilage volume). In agreement with the simulation results, primarily collagen-sensitive T2_\text{abs} (Nissi et al., 2004; Xia et al., 2001) more than doubled in both the lateral tibial (16% of cartilage volume) and lateral femoral cartilage (5% of cartilage volume). Moreover, the FE model revealed that the posterior side of the lateral joint compartment was the area most susceptible to collagen damage. This result was supported by the elevated T2_\text{abs} during the follow-up. In the lateral femoral cartilage, high $\rho_{\text{abs}}$ values indicated PG loss in ~7% of the volume. This result was confirmed by the elevated T1_\text{pp} during the follow-up, also in ~5% of the volume. This parameter has been considered to be mostly sensitive to PGs (Duvvuri et al., 2002). Despite high values of $\rho_{\text{abs}}$ in the lateral tibial cartilage only in ~6% of the total cartilage volume, indicating PG loss, the PG-sensitive T1_\text{pp} relaxation time was elevated in ~16% of the lateral tibial cartilage volume.

In the medial tibial cartilage, neither the FE model nor the experimental follow-up information indicated any degenerative signs by the collagen-specific ($\sigma_{\text{tensile}}$ and T2_\text{abs}) and PG-specific ($\rho_{\text{abs}}$ and T1_\text{pp}) parameters. However, in the medial femoral cartilage, despite elevated T2_\text{abs} and T1_\text{pp} values in local areas (~4% of the total volume) during the follow-up timepoints, slightly elevated values during the follow-up were seen throughout the contacting surfaces.
follow-up, the FE model did not predict tensile stresses or shear strains above the chosen thresholds. Taking into consideration that no changes were seen in the tibial compartment in any of the parameters, this increase in the femoral side may be caused by factors that could not be considered in the model. See more from limitations below.

4.2. Patient 2

Based on the FE model results, possible collagen damage and degeneration through $\sigma_{\text{tensile}}$ was predicted to occur in the medial tibial (3% of cartilage volume) and femoral cartilage (3% of cartilage volume).

---

Fig. 4. Axial views of maximum principal (tensile) stress distributions on the tibial and femoral cartilage for Patient 1 (a and b, respectively) and Patient 2 (c and d, respectively). Peak values for tensile stresses are also indicated.

Fig. 5. Degenerated volumes predicted by the FE model ($\sigma_{\text{tensile}}$ and $\gamma_{\text{abs}}$) and measured from the MRI follow-up ($T_2$ and $T_{1p}$) as a percentage of the entire cartilage volume. The volumes were calculated for the lateral and femoral tibial and femoral cartilage of Patient 1 (a) and Patient 2 (b).
Fig. 6. Sagittal slices for the FE model and corresponding sagittal T2 and T1ρ map slices at both 1-year and 3-year follow-up timepoints for the lateral and medial compartments of Patient 1 (a and b). Slice locations are indicated in Fig. 2a and arrows indicate the peak values. Note: All values above the selected degeneration thresholds in the FE models (7 MPa for tensile stress and 32% for shear strain) are shown in dark gray. T2 and T1ρ relaxation times above 100 ms are shown in dark red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 7. Sagittal slices for the FE model and corresponding sagittal T2 and T1ρ map slices at both 1-year and 3-year follow-up timepoints for the lateral and medial compartments of Patient 2 (a and b). Slice locations are indicated in Fig. 2b and arrows indicate the peak values. Note: All values above the selected degeneration threshold (7 MPa for tensile stress and 32% for shear strain for the FE model) are shown in dark gray. T2 and T1ρ relaxation times above 100 ms are shown in dark red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
were not patient-specific. One limitation is that the mechanical properties of cartilage were not patient-specific. However, the sensitivity study in Supplementary Materials indicated that, despite different material parameters of cartilage, all models identified the same locations susceptible to cartilage degeneration. Identification of locations likely to degenerate may reveal which kind of rehabilitation exercises would be the most beneficial for the patient to minimize stress and strain concentrations in locations at the highest risk for the progression of OA (Pizzolato et al., 2017).

The thresholds for defining degenerated volumes from MRI (relaxation time > 60 ms) are not unbiased, as the values depend on the specific implementation of the respective measurements (Matzat et al., 2015). Furthermore, both $T_2$ and $T_{1p}$ have demonstrated sensitivity to the orientation of the tissue in the magnetic field, complicating spatial analysis (Hänninen et al., 2017). However, in this longitudinal study, the same measurement protocol, system and analysis was used at both follow-up times, alleviating issues related to potential differences in the results.

We also acknowledge that the sensitivity of the mechanical and MRI parameters to either collagen degeneration or PG loss is not unambiguous. With only two subjects, it is difficult to correlate the FE model predictions and MRI follow-up information. Studies with higher number of patients are needed. This should allow for a comprehensive statistical analysis and help tune the threshold levels. In conjunction with the limitations presented here and in Supplementary Materials, these factors may account for some of the discrepancies between the FE model results and the follow-up information. However, this is a proof-of-concept study showing that it is possible to predict potential cartilage degeneration areas using patient-specific FE models.

4.4 Clinical application

Generation of a subject-specific computational model requires a lot of manual work and time in segmentation of soft tissues, meshing and making models to converge. In future studies, the methodology presented here should be coupled with semi-automatic or fully automatic segmentation techniques (Chandra et al., 2016; Dodin et al., 2010; Folkesson et al., 2007; Lee et al., 2014; Liukkonen et al., 2017b; Popkrok et al., 2014; Shan et al., 2014; Tamez-Pena et al., 2012; Yang et al., 2015; Yu et al., 2016) and with automated meshing tools (Rodriguez-Vila et al., 2017). As motion capture systems are not readily available in clinical settings, a simple and fast method should be developed to obtain and implement patient's gait. For instance, differences between patient-specific and population-specific (e.g. normal, early/advanced/medial OA populations) motions could be studied. If the population-specific approach would produce similar results with the patient-specific method, it could be used without motion capture. These aforementioned methods would ease the applications of the FE models in large cohort studies to identify areas susceptible to OA development

4.3 Limitations

This study has a few limitations, expanded upon in Supplementary Materials. One limitation is that the mechanical properties of cartilage were not patient-specific. However, the sensitivity study in Supplementary Materials indicated that, despite different material parameters of cartilage, all models identified the same locations susceptible to cartilage degeneration. Identification of locations likely to degenerate may reveal which kind of rehabilitation exercises would be the most beneficial for the patient to minimize stress and strain concentrations in locations at the highest risk for the progression of OA (Pizzolato et al., 2017).

The thresholds for defining degenerated volumes from MRI (relaxation time > 60 ms) are not unbiased, as the values depend on the specific implementation of the respective measurements (Matzat et al., 2015). Furthermore, both $T_2$ and $T_{1p}$ have demonstrated sensitivity to the orientation of the tissue in the magnetic field, complicating spatial analysis (Hänninen et al., 2017). However, in this longitudinal study, the same measurement protocol, system and analysis was used at both follow-up times, alleviating issues related to potential differences in the results.

We also acknowledge that the sensitivity of the mechanical and MRI parameters to either collagen degeneration or PG loss is not unambiguous. With only two subjects, it is difficult to correlate the FE model predictions and MRI follow-up information. Studies with higher number of patients are needed. This should allow for a comprehensive statistical analysis and help tune the threshold levels. In conjunction with the limitations presented here and in Supplementary Materials, these factors may account for some of the discrepancies between the FE model results and the follow-up information. However, this is a proof-of-concept study showing that it is possible to predict potential cartilage degeneration areas using patient-specific FE models.

Declaration of competing interest

The authors have no potential conflicts of interest to declare.

Acknowledgements

This project has received funding from the Doctoral Programme in Science, Technology and Computing (SCITECO) of the University of Eastern Finland, the European Research Council (ERC) under the European Union’s Horizon 2020 research and innovation programme (grant agreement No 755037), Academy of Finland (grants 285909, 307932 and 286526), Sigrid Juselius Foundation, and National Institutes of Health (NIH/NIAMS P50 AR060752). CSC-IT Center for Science, Finland, is acknowledged for providing computing resources.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinbiomech.2019.08.004.

References


Li, X., Majumdar, S., 2013. Quantitative MRI of articular cartilage and its clinical ap-


