A Numerical Tool To Study Early Osteoarthritis

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Disclosures:
C.C. van Donkelaar: None. L. Henao-Murillo: None. S.M. Hosseini: None. E.H. van den Heuvel: None. W. Wilson: None. K. Ito: 5; We receive materials for research purposes from DSM (Dyneema and loaded microbeads) and TNO (hydrogels). These are not related to the current project..

Introduction: Early signs of osteoarthritis (OA) include cartilage softening, loss of proteoglycans (PG) and collagen damage. It is unclear how these are related, and what their relative importance is for the progression of OA. Computational models provide opportunities to gain insight in such dependencies, as they allow selectively modifying one aspect and not the other. Thus, they may be used to study specific hypotheses related to cartilage degeneration. Here, we adopt a composition-based cartilage mechanics model that has been developed over the years. It uses experimental data on proteoglycan and collagen content as direct input, including their depth-varying density, fixed charge density for swelling, and the orientation of the reinforcing collagen fibrils [Wilson, 2006a]. This model has recently been extended with a description of damage development in both the ground substance and the collagen network over time as a consequence of excessive mechanical loading in each of these components [Hosseini, 2013].

Initial simulations with the damage development model suggested that collagen and ground substance damage might develop at distinct sites and in distinct patterns, depending on the magnitude of overloading [Hosseini, 2013]. The present work aims to further evaluate these initial model predictions of collagen and ground-substance damage to new sets of experimental data that were obtained for this particular purpose. Measured and predicted areas of damage after modest and severe overloading were compared, and the model was subsequently used to provide an explanation for the damage patterns that were experimentally observed.

Methods: Osteochondral plugs (7.5 mm diameter) from calf metacarpalphalangeal joints were harvested, fixed in a custom-made container filled with PBS and installed in a Zwick tensile testing machine. Subsequently, the plugs were loaded by a stainless steel indenter (diameter 2 mm), using various repeating loading protocols in which the magnitude of loading ranged between 15N and 45N and the duration of loading between 1 second and 1 hour. Force-displacement data were collected to determine tissue softening over time. After the loading regime was finished, samples were processed for histology and stained with Saffranin-O/Fast Green for evaluating PG loss, and using col2 3/4m immunostaining for monitoring the location of collagen damage.

The experiments were simulated using the computational model, in which damage (D) was implemented using a strain-history parameter. If a threshold for tensile strain in collagen fibrils was exceeded, those fibrils were assumed to become damaged, resulting in a reduction of their stiffness. Damage ranged between 0 and 1, such that at a second strain threshold, damage was complete and the fibril stiffness equaled 0 MPa. Similarly, the ground substance was developing damage and therefore reduced stiffness, when the deviatoric strain in the ground substance exceeded particular threshold values. Thus, for both the ground substance and each of the collagen fibril directions, the effective stress (σ̃) of the damaged constituent is assumed to reduce to σ̃ =σ/(1-D). Strains in subsequent loading cycles may or may not exceed the prevailing strain history parameter, and therefore damage may either progress or stabilize over time.

In a series of simulations the cartilage was indented by 10, 20, 30 or 40%, and these deformations were sustained until equilibrium was reached. From this equilibrium condition, the effects of tissue damage on the mechanical properties of the cartilage could be derived. Damage to the collagen and the ground substance were monitored over time.

Results: The experimental data (Fig 1) show that almost all PG’s are lost in the surface of the cartilage under the indenter, and that this area of PG loss gradually widens over time. For PG loss to become apparent in the histology, prolonged loading was required. Collagen damage appeared more variable, but appeared instantly and generally started below the surface. The area of damage extended towards the surface when the loading magnitude increased. Simulations predicted similar spatial and temporal patterns of damage development for both ground substance and collagen (Fig 2). In addition, it was found that under these experimental conditions, softening occurred in the cartilage, and tissue softening was also predicted to develop in the simulations (data not shown).
Figure 1. Collagen damage (left; brown staining by col2 3/4m) and PG content (right; red staining by Saffranin-O) after modest (top) and severe (bottom) loading regimes. Collagen damage starts in the transfer zone and subsequently progresses towards the surface, where the staining becomes more intense. PG loss is complete in the surface, with a sharp transition to normally stained PG in the deeper area. The zone from which PG is lost gradually extends from the surface into the deeper area.
Figure 2: Damage localization in the collagen fibre network (left) and in the ground substance (left). The spatial profile of the damage in these constituents (top) is different, with a diffuse pattern for the collagen and a sharp transition for the ground substance. Damage development over time (bottom: increasing times are shown in blue, red, green and purple) shows that the collagen damage starts below the surface, before it extends to the surface where it becomes most intense. Ground substance damage starts at the surface and extends into the deeper area, while the sharp transition from complete damage to no damage remains apparent. (Adopted from [Hosseini, 2013]).

Discussion: The spatial and temporal profiles for the predicted and the measured damage in both the collagen and the ground substance correspond very well. In particular, two characteristics show the most striking resemblance: the sharp transition in the proteoglycan network, and the initiation of collagen damage below the surface. Such patterns also correspond to data from the literature [eg Hollander, 1995; Wilson, 2006b]. These results let us believe that the model predictions are trustworthy. Further comparison for full validation of the model is ongoing. Such comparison includes comparison of damage patterns under different loading conditions. Mechanical evaluation shows softening both experimentally and computationally; thorough quantitative comparison is in progress.

We conclude that a model for cartilage damage development, which has recently been developed [Hosseini 2013], provides qualitatively reliable results considering both the spatial and the temporal development of both collagen and ground substance damage. This is a promising approach that may help to explore mechanisms of early cartilage damage development. Being able to predict the development of damage in cartilage would ultimately open ample possibilities for clinical use, such as identifying patients at risk of developing aggressive OA, or for optimizing patient-specific treatment protocols.

Significance: Osteoarthritis is a major health care problem. Earlier intervention may improve the clinical success and the quality of life for patients. In order to develop earlier intervention strategies, more insight is required in early cartilage degeneration...
and damage progression. The presented model helps to improve such insights and to test particular hypotheses.

Acknowledgments: Part of this study was financially supported by the Dutch Arthritis Foundation.

Hosseini et al, OA Cart, conditionally accepted, 2013.

ORS 2014 Annual Meeting
Poster No: 1315