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A numerical model to study mechanically induced initiation and progression of damage in articular cartilage

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SUMMARY

Objective: Proteoglycan (PG) loss and surface roughening, early signs of osteoarthritis (OA), are likely preceded by softening of the ground substance and the collagen network. Insight in their relative importance to progression of OA may assist the development of treatment strategies for early OA. To support interpretation of experimental data, a numerical model is proposed that can predict damage progression in cartilage over time, as a consequence of excessive mechanical loading. The objective is to assess the interaction between ground substance softening and collagen fiber damage using this model.
Design: An established cartilage mechanics model is extended with the assumption that excessive strains may damage the ground substance or the collagen network, resulting in softening of the overstrained constituent. During subsequent loading cycles the strain may or may not cross a threshold, resulting in damage to stabilize or to progress. To evaluate how softening of the ground substance and collagen may interact, damage progression is computed when either one of them, or both together are allowed to occur during stepwise increased loading.
Results: Softening in the ground substance was predicted to localize in the superficial and transitional zone and resulted in cartilage softening. Collagen damage was most prominent in the superficial zone, with more diffuse damage penetrating deeper into the tissue, resulting in adverse strain gradients. Effects were more pronounced if both constituents developed damage in parallel.
Conclusion: Ground substance softening and collagen damage have distinct effects on cartilage mechanopathology, and damage in either one of them may promote each other.

Introduction

Articular cartilage derives this biomechanical function from the constitution of its extracellular matrix (ECM), which consists of a strongly hydrated ground substance, mainly consisting of proteoglycans (PGs), reinforced by a tension-resistant fibrillar collagen network. The PGs attract water through osmotic pressure, therewith resisting compression and straining the collagen. Unfortunately, this load bearing construction may become damaged when cartilage is subjected to excessive mechanical conditions, and such damage is likely to progress into osteoarthritis (OA)[1–4]. Early signs of OA include PG loss and cartilage surface roughening, which proceed into fibrillation with cracks penetrating deeper into the tissue at later stages[5–9]. It is apparent that these changes reduce tissue stiffness under tension[8,10,11], compression and shear, and increase permeability[12]. It has become apparent that initial damage may start before PGs are lost and the surface roughens. As a consequence of loading with an indenter, collagen damage was detected below the cartilage surface, but it did not necessarily become apparent at the surface[13]. Similar loading conditions were later associated with cartilage softening[14]. These effects may corroborate with observations of damage to the collagen fiber structure at the microscopic scale in early OA tissue[5,15,16]. However, softening also occurred without detectible collagen damage or loss of PGs from the tissue. Therefore, it was proposed that softening may result from damage to the PG-rich ground substance[14], or from the interaction between PGs and collagen at the microscopic scale[17,18].

Because together they determine the mechanical properties of articular cartilage, softening or either the ground substance or the collagen network may affect the strains experienced by the other. However, the importance of such interaction to the progression of

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cartilage damage is unknown. Various mechanisms can be postulated. Softening of the ground substance may reduce the compressive properties of the cartilage and this may subsequently put the collagen network at risk of overstraining. Alternatively, softening of the collagen network may allow the ground substance to attract more water, resulting in local tissue swelling. This may further weaken the tissue, which could result in excessive straining during mechanical loading. Indeed, OA was found to develop in animals that were treated with either collagenases or stromelysins[19,20], indicating that both PGs and collagen are essential to joint homeostasis. Yet, these studies did not reveal the mechanism by which softening of the PGs and collagen network may interact, and effects not related to tissue mechanics such as inflammation, may have played a role.

Therefore, the importance of softening in the ground substance, damage to the collagen network, and the possible interaction between these two for the progression of cartilage damage remains speculative. Yet, such insight may be useful for future development of therapies to treat early OA. To explore these effects experimentally is challenging. Therefore, a numerical approach is adopted, using a composition based model that includes collagen fiber-reinforcement, ground substance stiffness and tissue swelling due to PGs, and constitutes a physiological organization of the collagen structure and a depth dependent collagen and PG density[21,22]. To study progression of cartilage damage with this model requires extension, such that softening of the collagen network and of the ground substance may progress independently over time as a result of mechanical conditions in the tissue.

The objective of the present study is to present such damage progression model, and to employ it to explore whether and how damage in the PG-rich ground substance may advance damage in the collagen network and vice versa. For this purpose, simulations are compared in which cartilage is excessively loaded under four hypothetical conditions. The first condition is when no damage is allowed to develop in the cartilage as a reference. Second, damage is only allowed to develop in the fibrillar network. Third, damage only develops in the ground substance. Fourth, damage may develop in both the fiber network and the ground substance.

Materials and methods

Cartilage mechanics model

A composition-based, fiber-reinforced, poroviscoelastic biphasic swelling model is adopted[21,23,24], in which cartilage is assumed to consist of a porous solid matrix saturated with water. The solid consists of a PG-rich ground substance and a fibrillar part representing the collagen network. The ground substance has a particular stiffness and contains fixed negative charges associated with the PGs, which induce osmotic swelling. The viscoelastic fibrillar network is implemented in 2D as a collection of two primary and four secondary fiber directions per integration point. The primary fiber directions are oriented such that they represent the arcade-like organization and bend in opposite directions close to the surface. A less dense network of random fibrils in the tissue is represented by the four secondary fibers compartments, which run in vertical, horizontal and two oblique directions. The relative density of the primary fibers has previously been determined to be 3.009 times that of the secondary fiber directions, and has been taken into account in the collagen density ρ_c^i per fiber direction i (Eq. (1))[23]. The total stress ($\boldsymbol{\sigma}_{tot}$) in the cartilage is then determined by the combination of hydrostatic, non-fibrillar and fibrillar matrix stresses and osmotic pressure ($\Delta\pi$) (Eq. (1)).

$$\boldsymbol{\sigma}_{tot} = -p\mathbf{I} + n_{s,0}\left(\left(1-\sum_{i=1}^{totf}\rho_c^i\right)\boldsymbol{\sigma}_{nf} + \sum_{i=1}^{totf}\rho_c^i\boldsymbol{\sigma}_f^i\right) - \Delta\pi\mathbf{I} \tag{1}$$

where p is the hydrostatic pressure, $\mathbf{I}$ is the unit tensor, $n_{s,0}$ is the initial solid volume fraction, $\boldsymbol{\sigma}_{nf}$ is the Cauchy stress in the non-fibrillar matrix, σ_f^i is the fiber Cauchy stress in the ith fiber with respect to the global coordinate system, ρ_c^i is the volume fraction of the collagen fibers in the ith direction with respect to the total volume of the solid matrix and $\Delta\pi$ is the osmotic pressure gradient. The non-fibrillar and fibrillar stress terms are defined per unit area of the non-fibrillar and fibrillar areas respectively.

The non-fibrillar matrix stress can be calculated by the following formula, which depends on the amount of deformation, the amount of solid and shear modulus G_m[21,23]:

$$\boldsymbol{\sigma}_{nf} = -\frac{1}{6}\frac{\ln(J)}{J}G_m\mathbf{I}\left[-1+\frac{3(J+n_{s,0})}{(-J+n_{s,0})}+\frac{3\ln(J)Jn_{s,0}}{(-J+n_{s,0})^2}\right] + \frac{G_m}{J}\left(\mathbf{F}\cdot\mathbf{F}^T - J^{2/3}\mathbf{I}\right) \tag{2}$$

where J is the determinant of the deformation tensor $\boldsymbol{F}$.

The fiber Cauchy stress tensor is as follows:

$$\boldsymbol{\sigma}_f = \frac{\lambda}{J}P_f\vec{e}_f\vec{e}_f \tag{3}$$

where λ is the elongation of the fiber, P_f is the first Piola–Kirchhoff stress, and e_f is the current fiber direction. The total Cauchy stress of the fibers is expressed as a function of the deformed surface that a fiber works on. The viscoelastic behavior of the collagen fiber was represented by the two-parameter exponential stress–strain relationship springs S_1, parallel to a spring S_2 in series with a linear dashpot with dashpot constant η. The strain dependent stresses P_1 and P_2 in springs S_1 and S_2 are calculated as:

$$\begin{aligned} P_1 &= E_1\left(e^{k_1\varepsilon_f}-1\right) \quad \text{for } \varepsilon_f > 0 \\ P_2 &= E_2\left(e^{k_2\varepsilon_e}-1\right) = \eta\dot{\varepsilon_v} \quad \text{for } \varepsilon_e > 0 \end{aligned} \tag{4}$$

with E_1, E_2, k_1 and k_2 positive material constants, ε_f the total fiber strain, ε_e the strain in spring S_2 and ε_v the dashpot strain. Fibers are assumed to withstand tension (positive strains), but not compression. The total fiber stress P_f is the summation of P_1 and P_2[23].

The values of the model parameters used are[23]: $E_1 = 4.316$ MPa, $E_2 = 19.97$ MPa, $k_1 = 16.85$, $k_2 = 41.49$, $\eta = 1.424 \times 10^5$ MPa s, $G_m = 0.903$ MPa.

For formulations of the osmotic pressure and strain dependent permeability the reader is referred to Wilson *et al.*[23].

Damage model

The mechanics model is extended with a description of damage. Basically, it is assumed that when the deviatoric strain value in the ground substance exceeds a particular threshold, this would soften the matrix. For the fiber network, it is assumed that when the strain in the direction of the fibers exceeds a threshold, these fibers soften. As there may be a distribution of strains in the ground substance or in the collagen fibers, softening accumulates over time when during subsequent cycles a larger portion of the ground substance or fibers become damaged.

This theory is implemented using a damage parameter D, which represents the relative amount of damaged material and has a value