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The nutrition of the human meniscus: A computational analysis investigating the effect of vascular recession on tissue homeostasis

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ABSTRACT

The meniscus is essential to the functioning of the knee, offering load support, congruency, lubrication, and protection to the underlying cartilage. Meniscus degeneration affects ~35% of the population, and potentially leads to knee osteoarthritis. The etiology of meniscal degeneration remains to be elucidated, although many factors have been considered. However, the role of nutritional supply to meniscus cells in the pathogenesis of meniscus degeneration has been so far overlooked. Nutrients are delivered to meniscal cells through the surrounding synovial fluid and the blood vessels present in the outer region of the meniscus. During maturation, vascularization progressively recedes up to the outer 10% of the tissue, leaving the majority avascular. It has been hypothesized that vascular recession might significantly reduce the nutrient supply to cells, thus contributing to meniscus degeneration. The objective of this study was to evaluate the effect of vascular recession on nutrient levels available to meniscus cells. This was done by developing a novel computational model for meniscus homeostasis based on mixture theory. It was found that transvascular transport of nutrients in the vascularized region of the meniscus contributes to more than 40% of the glucose content in the core of the tissue. However, vascular recession does not significantly alter nutrient levels in the meniscus, reducing at most 5% of the nutrient content in the central portion of the tissue. Therefore, our analysis suggests that reduced vascularity is not likely a primary initiating source in tissue degeneration. However, it does feasibly play a key role in inability for self-repair, as seen clinically.

1. Introduction

The meniscus plays a crucial role in the functioning of the knee, offering congruency, lubrication, and bearing 45–75% of the total load on the joint (Shrive et al., 1978). Meniscus degeneration affects approximately 35% of the population (Englund et al., 2016), and is believed to be precursor of knee osteoarthritis (OA), an epidemic disease costing more than $100 billion annually in the US alone (Murphy and Helmick, 2012). The etiology of meniscus degeneration remains to be elucidated. Possible causes include aging, joint mechanical loading and presence of inflammatory cytokines in synovial fluid (Hough and Webber, 1990; Ling et al., 2016; McAlinden et al., 2001; McNulty and Guilak, 2015). To date, the role that nutritional supply to cells plays in the pathogenesis of meniscal degeneration has been overlooked.

The meniscus is fibrocartilaginous with limited vasculature which, during maturation, recedes to the outer 10–30% of the tissue (red zone), leaving the majority of the tissue avascular (white zone) (Danzig et al., 1983; McDevitt and Webber, 1990; Sweigart and Athanasiou, 2001). Delivery of essential nutrients to cells in the white zone comes from the peripheral red zone and the synovial fluid bathing the knee. In both cases, solute delivery to white zone cells occurs via diffusion, which is much slower and less efficient than transvascular transport from the adjacent blood vessels in the red zone. As a result, steep nutrient gradients are expected across the tissue, which could significantly alter cellular activity. Tissue degeneration results from an imbalance in anabolic and catabolic activity by cells in the extracellular matrix (ECM). This may be triggered by alterations in the chemical microenvironment surrounding meniscus cells, leading to a change in cellular expression, metabolism and viability. This chemical microenvironment is highly dependent on molecular supply through the ECM, particularly for avascular regions. Smillie

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postulated that inefficient nutrient supply to the white zone causes the central core of the meniscus to deteriorate with age, making the tissue more susceptible to cleavage tears (Smillie, 1978). Also, experimental studies reported that avascularity significantly hinders the ability for self-repair within the white zones, making the meniscus susceptible to permanent degenerative lesions (Makris et al., 2011). Indeed, it has been shown that meniscus fibrochondrocytes from both red and white zones are capable of matrix repair, suggesting that differences in repair seen clinically are related to the vascular supply and not intrinsic differences in cellular activity (Hennerbichler et al., 2007). The repair is facilitated by the close proximity to vasculature in the red zones, which supplies numerous important molecules, including pro-inflammatory mediators, progenitor cells, growth factors, and nutrients. Therefore, knowledge of the meniscal chemical environment could provide important insights into the mechanisms of degeneration.

Due to the difficulty in measuring *in vivo* nutrient levels, computational modeling can serve as a valuable tool to complement experimental results to better understand the *in vivo* meniscal environment. Numerous theoretical models of avascular cartilaginous tissues have been developed to investigate nutrition and homeostasis, see for instance (Schmidt et al., 2013; Sengers et al., 2005). To our knowledge, no such analogous models currently exist for the meniscus. Therefore, we present the novel computational model of the meniscus, based on the theory of the reactive mixture (Ateshian, 2007) and incorporating nutrient transport coupled to cellular metabolic rates. The model was deployed to describe the nutrition in the human meniscus. More specifically, based on Smillie's observation (Smillie, 1978), we investigated whether vascular recession may cause significant drops in the nutrient levels in the central core of the meniscus, potentially affecting cellular activity and viability. This would also be important for better understanding the regional differences in the ability for self-repair in the tissue.

2. Theoretical model

Based on its structure and composition (Makris et al., 2011), we schematize the meniscus as a mixture of an intrinsically incompressible negatively charged elastic solid phase, an inviscid fluid phase (water) containing Na^+ and Cl^- (electrolytes), and glucose, oxygen and lactate (uncharged solutes). Water and solutes access the tissue from the synovial bath surrounding the tissue or via transvascular transport through the blood vessels in the red zone. Also, nutrients can be generated or depleted as the result of fibrochondrocytes' metabolism. The theory of reactive mixtures (Ateshian, 2007) is chosen to describe the electromechanical and chemical behavior of the meniscus.

2.1. Governing equations

The governing equations (Ateshian, 2007; Gu et al., 1998; Lai et al., 1991) are adapted to the context of the meniscus:

Conservation of linear momentum for the mixture

$$\nabla \cdot \boldsymbol{\sigma} = 0, \tag{1}$$

Conservation of mass for the mixture

$$\nabla \cdot (v^s + J^w) = \hat{J}_w, \tag{2}$$

Conservation of mass for the solutes

$$\frac{\partial(\varphi^w c^\alpha)}{\partial t} + \nabla \cdot (J^\alpha + \varphi^w c^\alpha v^s) = \hat{J}_s^\alpha + R^\alpha, \tag{3}$$

Conservation of charge

$$\nabla \cdot (J^+ - J^-) = 0, \tag{4}$$

where $\boldsymbol{\sigma}$ is the total stress of the mixture; v^s is the velocity of the solid phase; J^w is the volume flux of water relative to the solid phase; $\hat{J}_w$ is the transvascular rate of water supply per unit of tissue volume; $\hat{J}_s^\alpha$ is the transvascular rate of mass supply per unit of tissue volume for the α-solute; R^α is the rate of mass supply per unit of tissue volume for the α-solute due to cellular metabolism (only for glucose, oxygen and lactate); ϕ^w is the volumetric fraction of water; c^α is the molar concentration of the α-solute, and J^α is its molar flux relative to the solid phase; J^+ and J^- are the molar fluxes of the electrolytes relative to the solid phase. Note that Eq. (2) has been derived assuming that mass terms supply from solutes are negligible when compared to the solid and fluid phase of the mixture (Ateshian, 2007). Eqs. (1)–(4) are supplemented by the electroneutrality constrain:

$$c^F + c^- = c^+, \tag{5}$$

where c^F is the molar concentration of fixed charges, and c^- and c^+ the concentrations of the electrolytes. Constitutive expressions for the solid stress, the volume flux of water and the molar fluxes of solutes are:

$$\boldsymbol{\sigma} = -p\boldsymbol{I} + \lambda tr(\boldsymbol{E})\boldsymbol{I} + 2\mu\boldsymbol{E}, \tag{6}$$

$$J^w = -k(\rho_T^w \nabla\mu^w + \sum_\alpha H^\alpha c^\alpha M^\alpha \nabla\mu^\alpha), \tag{7}$$

$$J^\alpha = H^\alpha c^\alpha J^w - \frac{D^\alpha \rho^\alpha}{RT}\nabla\mu^\alpha, \tag{8}$$

where p is the interstitial fluid pressure, $\boldsymbol{I}$ is the identity tensor, λ and μ are the Lamé constants of the solid matrix, $\boldsymbol{E}$ is the infinitesimal strain tensor for the solid matrix. Moreover, k is the hydraulic permeability, ρ^α is the apparent mass density of the solute α, and ρ_T^w is the true mass density of water. Also, H^α is the hindrance factor for the solute α, M^a its molar weight and D^α its diffusivity; R and T are the universal gas constant and the absolute temperature; μ^w and μ^α are the electrochemical potentials of water and solutes, whose expressions have been previously reported (Ateshian, 2007).

2.2. Transvascular transport

Blood vessels (arterioles and venules) are assumed to be uniformly distributed within the red zone. The subscripts 'a' and 'v' refer to arterioles and venules, respectively. The net transvascular rate of fluid flow into the tissue from the blood vessels (J_w) is given by the difference of the rate of fluid from arterioles to the ECM (J_a) and the rate of fluid flow from the ECM to the venules (J_v):

$$J_w = J_a - J_v. \tag{9}$$

According to the Starling's law (Kedem and Katchalsky, 1958; Michel, 1997), we have:

$$J_a = L_{pa} S_a \Delta p_a, \tag{10.i}$$

$$J_v = L_{pv} S_v \Delta p_v, \tag{10.ii}$$

where L_{pa} and L_{pv} are the hydraulic permeabilities of the vessels, S_a and S_v are their surface areas; Δp_a and Δp_v are defined as:

$$\Delta p_a = p_a - p, \tag{11.i}$$

$$\Delta p_v = p - p_v, \tag{11.ii}$$

where p_a and p_v are the hydrostatic pressures in the vessels. In the above expressions, the osmotic reflection coefficients have been assumed to be null, given that the solutes of interest are small (Scallan et al., 2010). Accordingly, the transvascular rate of water supply per unit of tissue volume reads:

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