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A numerical model for metabolism, metabolite transport and edema in the human cornea

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Highlights

- Metabolism-swelling coupling in the human cornea is modeled by a multiphasic model.
- Primary mechanisms of corneal edema are described by a unified theory.
- Predictions of corneal edema due to hypoxia are validated against clinical data.
- Metabolite transport plays crucial rules in maintaining corneal hydration.

Abstract

When metabolic function in tissues such as brain, intervertebral disc and cornea is modified by disease processes or surgical intervention, the tissue may respond by swelling, a condition with significant clinical implications. A swelling response to metabolic change also signifies a change in the biomechanical behavior of the tissue. The connection between the metabolic and biomechanical states of the tissue is a complex and open problem. In this work we propose a multiphasic theory applicable to the human cornea. The model has three principal elements. The first is a diffusion–reaction model for cellular metabolism with reactions modeling aerobic respiration and anaerobic fermentation. The second element describes how metabolism-based ion production in the corneal stroma and active ion transport in the corneal endothelium modify the tissue osmotic pressure. Finally, the coupling between osmotic pressure and mechanical expansion of the tissue is described. The proposed model is assessed by predicting oxygen depletion and corneal edema due to contact lens wear, and by comparing the results with direct clinical measurements. To illustrate the interactions between metabolism and biomechanics under more extreme metabolic conditions, the model is used to predict the hypoxia and consequent swelling response of the cornea resulting from the introduction of an impermeable lamellar inlay (implant). The results confirm the importance of maintaining unhindered transport of metabolic species in the human cornea.

Keywords: Corneal metabolism; Corneal edema; Metabolism-swelling coupling; Endothelial active transport; Mixture theory; Corneal biomechanics

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1. Introduction

Swelling of tissue, as well as the biomechanical effects of the swelling, has numerous clinical implications. Swelling, or edema, can result from an inflammation, a local change of hydration (fluid buildup) or both and can be caused by traumatic injury, disease or disturbance of normal metabolic function [1–4]. For example, in the brain, hypoxia (low oxygen concentration) caused by a lack of blood flow after stroke can lead to cell death and swelling, which may further damage the tissue [3]. In the intervertebral disc, low glucose availability results in degenerative changes to the tissue by lowering the cells' ability to synthesize and maintain the extracellular matrix [1,5,6]. In the cornea, normal tissue hydration is vital to transparency [2]; edema of the cornea will cause the tissue to become opaque resulting in blindness [7].

There are two primary situations in which corneal tissue may become edematous: (i) disease of the endothelium, for example Fuch's dystrophy [8], which reduces the effectiveness of active trans-endothelial ion transport, and (ii) changes in cellular metabolism as observed, for example, in hypoxia [9,10]. These very different conditions both produce swelling by increasing the tissue osmotic pressure. In the first case, reduced active ion pumping increases tissue ionic concentrations and osmotic pressure. In the second case, the effect is more indirect. The cornea is avascular and the cells receive their nutrients (oxygen and glucose) by diffusive transport across the cornea. When this transport is modified, for example by introduction of a low oxygen transmissibility contact lens or an intrastromal lens, cells nearby are subject to reduced levels of metabolic nutrients and switch their metabolic pathways to emphasize anaerobic processes resulting in increased metabolic products, such as lactate and hydrogen ions, which in turn increase the osmotic pressure [10]. In this work we seek to provide a theory that can be applied to both mechanisms.

The essential modeling components in this study are: (i) a description of metabolic species transport with consumption/production based on Monod kinetics, (ii) a theory for active endothelial ion transport whereby ions are transported out of the corneal tissue, (iii) a model for the tissue osmotic pressure as a function of ionic concentrations, and (iv) a description of the coupling of the mechanical expansion due to osmotic pressure with the tissue elasticity which may act to resist the swelling. To accomplish this at steady-state, a multiphasic model based on mixture theory [11,12] is proposed. The model describes the corneal tissue as a polyelectrolyte gel comprised of solid, fluid, ionic and non-ionic solutes. Each phase satisfies a momentum or mass conservation law with appropriate coupling mechanisms resulting from the metabolic reactions. The metabolic model describes the consumption of glucose and oxygen to produce lactic acid, hydrogen ion and carbon dioxide through Monod kinetics-based reactions [9,13] for both aerobic respiration and anaerobic fermentation and enables the modeling of acidosis resulting from hypoxia. The swelling theory accounts for the fluid and osmotic pressures, with the latter determined by the tissue's solute concentrations [2]. In order to describe the effect of active endothelial ionic transport, an enhanced Kedem–Katchalsky (KK) theory [14] is derived based on linear nonequilibrium thermodynamics, and is incorporated into the proposed framework as a boundary flux condition.

The model is validated by predicting the tissue swelling pressure *ex vivo* and by simulating corneal swelling *in vivo* under epithelial hypoxia induced by a contact lens. The model was then used for an investigation of metabolic response and edema in two clinically relevant situations. In the first, we model reduced active ion transport to simulate Fuch's endothelial dystrophy and in the second we model the introduction of a thin, perfectly impermeable intrastromal inlay into the central cornea. Early experience with impermeable or low-permeable inlays showed that anterior stromal thinning and keratolysis can result [15–18], suggesting the importance of maintaining the transport of glucose, oxygen, and metabolic products such as lactic acid. While current designs feature highly permeable hydrogel inlays, in this study we revert to the extreme case of impermeable inlays to explore the underlying metabolic response and biomechanics with a view to quantifying and understanding the conditions that lead to corneal thinning, melting and implant rejection [15,16].

2. Metabolic model

Metabolism in cells converts glucose and oxygen into energy in the form of adenosine triphosphate (ATP) and produces various by-products. The cornea is avascular so that glucose and oxygen (metabolic nutrients) reach the cells primarily by diffusion. Glucose is supplied from the aqueous humor behind the cornea and oxygen is supplied from the air in front of the cornea (or from the palpebral conjunctiva in the closed eye condition) [9,19,20]. Anaerobic