Journal of Biomechanics ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

Journal of Biomechanics

journal homepage: www.elsevier.com/locate/jbiomech
www.JBiomech.com

Prediction of glycosaminoglycan synthesis in intervertebral disc under mechanical loading

Xin Gao [a], Qiaoqiao Zhu [b], Weiyong Gu [a,b,*]

[a] Department of Mechanical and Aerospace Engineering, University of Miami, Coral Gables, FL, USA
[b] Department of Biomedical Engineering, University of Miami, Coral Gables, FL, USA

ARTICLE INFO

Article history:
Accepted 25 May 2016

Keywords:
Intervertebral disc
Glycosaminoglycan synthesis
Mechanical stimuli
Mechanobiology
Multiscale mathematical model
Finite element analysis

ABSTRACT

The loss of glycosaminoglycan (GAG) content is a major biochemical change during intervertebral disc (IVD) degeneration. Abnormal mechanical loading is one of the major factors causing disc degeneration. In this study, a multiscale mathematical model was developed to quantify the effect of mechanical loading on GAG synthesis. This model was based on a recently developed cell volume dependent GAG synthesis theory that predicts the variation of GAG synthesis rate of a cell under the influence of mechanical stimuli, and the biphasic theory that describes the deformation of IVD under mechanical loading. The GAG synthesis (at the cell level) was coupled with the mechanical loading (at the tissue level) via a cell-matrix unit approach which established a relationship between the variation of cell dilatation and the local tissue dilatation. This multiscale mathematical model was used to predict the effect of static load (creep load) on GAG synthesis in bovine tail discs. The predicted results are in the range of experimental results. This model was also used to investigate the effect of static (0.2 MPa) and diurnal loads (0.1/0.3 MPa and 0.15/0.25 MPa in 12/12 hours shift with an average of 0.2 MPa over a cycle) on GAG synthesis. It was found that static load and diurnal loads have different effects on GAG synthesis in a diurnal cycle, and the diurnal load effects depend on the amplitude of the load. The model is important to understand the effect of mechanical loading at the tissue level on GAG synthesis at the cellular level, as well as to optimize the mechanical loading in growing engineered tissue.

1. Introduction

The initiation of intervertebral disc (IVD) degeneration is much earlier than that of other musculoskeletal tissues (Urban and Roberts, 2003). The most significant biochemical change in IVD degeneration is the loss of glycosaminoglycan (GAG) content (Lyons et al., 1981). The loss of GAG directly compromises the disc mechanical roles in the spinal system (Adams et al., 1996; Lyons et al., 1981; Urban and McMullin, 1988; Zhu et al., 2014). This is because the fixed negatively charged groups on the GAG generate a higher osmolarity within the tissue than that outside the tissue. The imbalance of osmolarity results in Donnan osmotic pressure within the tissue which contributes significantly to the load-bearing capabilities of discs (Urban and Maroudas, 1981). Abnormal mechanical loading has been thought to be a major factor that initiates the disc degeneration (Adams and Roughley, 2006; Stokes and Iatridis, 2004; Urban and Roberts, 2003). It has been suggested that cell-mediated remodeling may be the main pathway of disc degeneration initiated by abnormal mechanical loading, aside from the structure failure directly caused by mechanical loading (Setton and Chen, 2006).

During daily activities, the disc is subjected to compression, bending, torsion, and shear, and the combination of the above. The GAG synthesis within the disc has been shown to be significantly affected by mechanical loading (Chan et al., 2011; Ohshima et al., 1995; Setton and Chen, 2004). Many in-vivo and in-vitro experimental studies on the discs reveal that the effects of mechanical loading on GAG synthesis depend on the loading regimes (static or dynamical loading), magnitude, amplitude, duration, and frequency [see reviews, (Chan et al., 2011; Setton and Chen, 2004)].

The mechanism as to how the mechanical loads alter the cell biosynthetic behaviors is still unknown. This is because the mechanical loading on the tissue can induce many stimuli to the cell, including cell volume change, high level of stresses and strains arising from the deformation of extracellular matrix (ECM), high magnitude of hydrostatic pressure, shear stress caused by interstitial fluid flow, electrokinetic effects caused by the interactions between fixed charge groups and mobile charged ions, the change of nutrient level, and others (Bibby et al., 2001; Setton and

* Corresponding author at: Department of Mechanical and Aerospace Engineering, University of Miami, Coral Gables, FL, USA.

http://dx.doi.org/10.1016/j.jbiomech.2016.05.028
0021-9290/

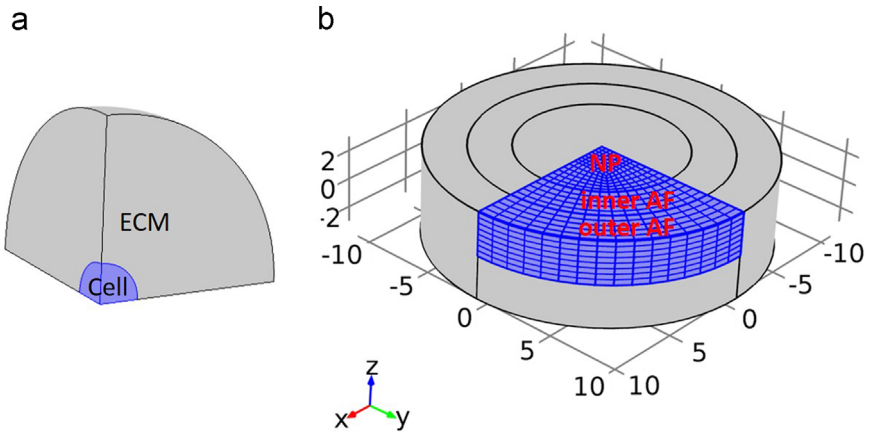

Fig. 1. Schematics of (a) cell-matrix unit; (b) bovine tail IVD. Scale unit in mm.

Chen, 2006; Urban, 2002). All of these stimuli could be a potential regulator for cell synthetic activities in the disc.

Recently, we have developed a cell volume dependent GAG synthesis theory to characterize the cell biosynthetic behavior in response to mechanical stimuli (Gao et al., 2015). The theory is based on the hypothesis that the change of cell volume is a regulator for downstream posttranslational biosynthesis (Guilak et al., 1995; O'Conor et al., 2014; Wong et al., 1997). The deviation of cell volume from its optimal state was considered as a mechanical stimulus, and it was correlated with the reduction (or decrease) of GAG synthesis rate from its maximum value. This theory has been shown to be able to predict GAG synthesis rate of isolated intervertebral disc cells under different osmotic loading conditions (Gao et al., 2015). However, there is no mathematical model available to quantify the variation of GAG synthesis rate within the disc in response to the externally applied mechanical load. The difficulty of developing such a mathematical model lies in the fact that the tissue deformation and the GAG synthesis are two events at different scale levels.

Therefore, the objective of this study was to develop a multiscale mathematical model to predict GAG synthesis within disc tissue under mechanical loading. In this study, the mathematical model was first developed and validated with experimental results, then used to investigate the GAG synthesis within the disc subjected to static and diurnal compressions.

2. Multiscale mathematical model

The multiscale mathematical model was based on cell volume dependent GAG synthesis theory (at the cell level) (Ohshima et al., 1995) and biphasic theory for cartilaginous tissues (at the tissue level) (Mow et al., 1980). In this study, it was assumed that the newly synthesized GAG binds to the solid matrix. Thus, the mass balance equation for GAG can be written as (Ateshian, 2007; Gu et al., 2014, 1998; Lai et al., 1991),

$$\frac{\partial c^{GAG}}{\partial t}+\nabla\cdot\left(\mathbf{v}^{s}c^{GAG}\right)=R^{GAG}\rho^{cell}-T^{GAG} \tag{1}$$

where c^{GAG} is the concentration of GAG (per tissue volume), $\mathbf{v}^{s}$ is the velocity of the solid matrix, R^{GAG} is GAG synthesis rate of each single cell, ρ^{cell} is the cell density (per tissue volume), and T^{GAG} is the breakdown rate of GAG (per tissue volume). Cell density changes with tissue deformation, that is, $\rho^{cell}=\rho_r^{cell}/J$, where ρ_r^{cell} is the cell density at reference state, and J is the volume ratio of tissue. $T^{GAG}$was assumed to be zero in this study because the turnover time for GAG in the IVD is about 20 years which is much longer than the duration of interest in this study (Roughley, 2004).

A cell volume dependent GAG synthesis theory was adopted to model the GAG synthetic behavior of a single cell in response to mechanical stimuli (Gao et al., 2015). In this theory, it was assumed that the relative change of GAG synthesis rate (i.e.,R^{GAG}) is proportional to the relative cell volume change (i.e., dilatation), and there is an optimal cell volume corresponding to the maximum GAG synthesis rate, mathematically,

$$\frac{R^{GAG}}{R_0^{GAG}}=1-\beta\left|\frac{V^{cell}-V_0^{cell}}{V_0^{cell}}\right|, \tag{2}$$

where R_0^{GAG} is the maximum GAG synthesis rate, V^{cell} and V_0^{cell} are the cell volumes at current and optimal states, respectively, and β is a positive parameter characterizing the effect of cell volume change on GAG synthesis rate and it was assumed to be independent of cell volume in this study. The value of β was found to be 2.41 for isolated bovine IVD cells (Gao et al., 2015), and this value was used in this study. Combining Eqs. (1) and (2) yields,

$$\frac{\partial c^{GAG}}{\partial t}+\nabla\cdot(\mathbf{v}^{s}c^{GAG})=Q\left(1-\beta\left|\frac{V^{cell}-V_0^{cell}}{V_0^{cell}}\right|\right), \tag{3}$$

where Q $(=\rho^{cell}R_0^{GAG})$ is the maximum synthesis rate per tissue volume.

In order to evaluate the change of cell volume within the matrix caused by the mechanical loading on the tissue level, a cell-matrix unit approach was adopted, in which a spherical cell is encapsulated in a larger sphere of the ECM, see Fig. 1. It was assumed that the cell-matrix composite is subjected to a uniformly distributed normal stress at the outer boundary, and the cell and matrix are attached perfectly. Therefore, the relationship between the cell dilatation, $e^{c}[=(V^{cell}-V_r^{cell})/V_r^{cell}$, where V_r^{cell} is the cell volume at the reference state], and the composite dilatation, $e(=J-1)$, can be established through this unit approach. In this study, we assumed the total cells occupy 1% of the total tissue volume (Bibby et al., 2001; Urban et al., 2000), thus the ratio between cell radius (r^{c}) and composite radius (r) is 0.215 $(=\sqrt[3]{0.01})$. The cell was modeled as a single phase linear elastic material and the matrix was modeled as a biphasic material.

The deformation of IVD under mechanical loading was modeled based on the biphasic theory (Mow et al., 1980). The mass balance equation for the mixture can be written as,

$$\nabla\cdot(\phi^{s}\mathbf{v}^{s}+\phi^{w}\mathbf{v}^{w})=0, \tag{4}$$

where $\phi^{\alpha}(\alpha=s,w)$ denotes for the volume fraction and $\mathbf{v}^{\alpha}$ for the velocity of solid and fluid phases, respectively.

The transport of the interstitial fluid within the extracellular solid matrix is characterized by Darcy's law, that is,

$$\mathbf{J}^{w}=\phi^{w}(\mathbf{v}^{w}-\mathbf{v}^{s})=-k\nabla p, \tag{5}$$

Please cite this article as: Gao, X., et al., Prediction of glycosaminoglycan synthesis in intervertebral disc under mechanical loading. Journal of Biomechanics (2016), http://dx.doi.org/10.1016/j.jbiomech.2016.05.028