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Temporal changes of mechanical signals and extracellular composition in human intervertebral disc during degenerative progression

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ABSTRACT

In this study, a three-dimensional finite element model was used to investigate the changes in tissue composition and mechanical signals within human *lumbar* intervertebral disc during the degenerative progression. This model was developed based on the cell-activity coupled mechano-electrochemical mixture theory. The disc degeneration was simulated by lowering nutrition levels at disc boundaries, and the temporal and spatial distributions of the fixed charge density, water content, fluid pressure, Von Mises stress, and disc deformation were analyzed. Results showed that fixed charge density, fluid pressure, and water content decreased significantly in the nucleus pulposus (NP) and the inner to middle annulus fibrosus (AF) regions of the degenerative disc. It was found that, with degenerative progression, the Von Mises stress (relative to that at healthy state) increased within the disc, with a larger increase in the outer AF region. Both the disc volume and height decreased with the degenerative progression. The predicted results of fluid pressure change in the NP were consistent with experimental findings in the literature. The knowledge of the variations of temporal and spatial distributions of composition and mechanical signals within the human IVDs provide a better understanding of the *progression of disc* degeneration.

1. Introduction

Low back pain is a prevalent health problem worldwide and generates huge societal and financial burdens globally [see review Hoy et al. (2012)]. The exact causes of the low back pain still remain unclear, but it is generally believed that intervertebral disc (IVD) degeneration plays a significant role in leading to this disease (Buckwalter, 1995; Freemont, 2009; Luoma et al., 2000). Nutrition deprivation, inappropriate mechanical loading, and genetic influences are the most important factors leading to the onset or exacerbation of the degenerative change in the discs [see review (Urban and Roberts, 2003)].

Proteoglycan (PG) and water are the major extracellular components in the disc, and play important roles in maintaining the structure and function of it (Gu and Yao, 2003; Iatridis et al., 2003; Perie et al., 2006b; Urban and Mcmullin, 1988). Loss of PG content during disc degeneration decreases the water content in the disc (Gu et al., 2002; Gu and Yao, 2003; Iatridis et al., 2003; Urban and Mcmullin, 1988), due to the decrease in the amount of negative charged groups on the glycosaminoglycan (GAG) chains (Urban and Maroudas, 1979). These decreases in biochemical components strongly influence the mechanical (e.g., modulus and hydraulic permeability) properties of the disc tissues.

The mechanical behaviors of the IVDs have been extensively studied experimentally [see reviews (Iatridis et al., 1996; Nachemson, 1975; Niosi and Oxland, 2004; Nixon, 1986)]. These studies have significantly advanced the understanding of the biomechanics of IVDs. Based on these data, a number of numerical models have been developed for the study of the mechanical behaviors of the IVDs and/or spinal motion segments [see a recent review (Schmidt et al., 2013)].

Early numerical models were based on single-phase assumption in which the nucleus pulposus (NP) is treated as an incompressible fluid, and the annulus fibrosus (AF) a solid material (Belytschko et al., 1974). Later Simon et al. (1985) introduced the poroelastic model of the discs in which the disc was assumed to contain a solid and a fluid phase. The fluid transport and swelling effects were later taken into consideration in the poroelastic models by Laible et al., (1993). Ferguson et al., (2004) studied the influence of fluid flow on the solute transports within the IVDs using a poroelastic model.

A triphasic model has been used to more realistically describe the mechano-electrochemical behaviors of discs (Yao and Gu, 2006, 2007), in which the disc was considered as a mixture containing a charged solid phase, an interstitial fluid phase, and

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a solute phase (ions, nutrients, cytokines, etc.) (Lai et al., 1991). Later, Huang and Gu (2008) incorporated the cell metabolisms into the triphasic model for IVD. They studied the effects of mechanical compression on the transport of nutrients and on the cell metabolisms. Cell viability was first included into the transport model for disc by Shirazi-Adl et al., (2010); the influences of nutrient environment on cell viability was investigated numerically with this model, however, this model did not include the coupled mechano-electrochemical effects on the transport of the nutrients within the disc. Recently, we developed a new constitutive model for disc cell viability and incorporated it into the triphasic model (Zhu et al., 2012). Using this model, we studied the effects of mechanical compression and disc degeneration on the cell viability within the coupled mechano-electrochemical environment.

However, to date, there seems no numerical model that is able to describe and predict continuous, temporal changes of tissue composition and extracellular mechanical signals in the disc during the degenerative progression. The knowledge of quantitative changes in these signals in the disc with degenerative progression is crucial for understanding the mechanobiology in the disc as well as for developing a new diagnostic method for detecting disc degeneration. Therefore, the objective of this study was to investigate the changes in tissue composition and mechanical signals within human *lumbar* discs during the degenerative progression with a *more* realistic three-dimensional (3D) finite element model. This model was developed based on the cell-activity coupled mechano-electrochemical mixture theory (Gu et al., 2014; Zhu et al., 2012). Using this numerical model, the temporal and spatial distributions of the PG content, water content, fluid pressure, Von Mises stress, and disc deformation were studied.

2. Methods

2.1. Theory

The disc was considered as an inhomogeneous, porous, mixture consisting of a charged solid phase (with cells and PG fixed to it), an interstitial fluid phase, and a solute phase with multiple species, including charged (e.g., sodium ion, chloride ion) and uncharged (e.g., glucose, oxygen, and lactate) solutes. In this study, the cell-activity coupled mechano-electrochemical theory (Zhu et al., 2012), which was developed based on the triphasic theory (Ateshian, 2007; Gu et al., 1998; Lai et al., 1991), was extended to include PG, a charged component in the solid matrix. The equation of mass balance for PG (estimated by GAG concentration) was described as follows:

$$\frac{\partial\left(C^{GAG}\right)}{\partial t}+\nabla\cdot\left(C^{GAG}\mathbf{v}^{s}\right)=Q^{GAG}, \tag{1}$$

where C^{GAG} is the GAG concentration (mole per tissue volume), $\mathbf{v}^{s}$ is the velocity of the solid phase, and Q^{GAG} (mole per tissue volume per time) is the rate of GAG production (or consumption), which is assumed to be dependent on the cell density and GAG content by:

$$Q^{GAG}=\lambda_1\rho^{cell}-\lambda_2 C^{GAG}. \tag{2}$$

In Eq. (2), λ_1 is the GAG synthesis rate per cell, ρ^{cell} is the cell density (per tissue volume), and λ_2 is the GAG degradation rate.

In this model, the GAG concentration was estimated by the amount of the negatively charged groups attached on the GAG chains per unit of tissue volume, i.e., the fixed charge density. The fixed charge density (C^F, mole per tissue volume) was related to GAG concentration by assuming 2 mol of charge per mole of GAG in the tissue (Bashir et al., 1999):

$$C^F=2C^{GAG}. \tag{3}$$

Obviously, the production rate of the fixed charge density (Q^F) within the tissue is related to Q^{GAG} by

$$Q^F=2Q^{GAG}. \tag{4}$$

The electroneutrality condition (Lai et al., 1991) states that:

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

where C^+ and C^- are the concentrations of sodium ion and chloride ion (per tissue volume), respectively. From Eq. (5), it follows that,

$$Q^+=Q^-+Q^F, \tag{6}$$

where Q^+ is the chemical reaction rate for sodium ions and Q^- for chloride ions.

2.2. Finite element method

A 3D finite element model was developed based on the theoretical framework. The disc was modeled as an inhomogeneous material with two distinct regions: NP and AF. The geometry of the disc was generated based on a L2-L3 human disc (male, non-degenerated, see Fig. 1A).

In the model, the disc was attached to *a part of the* vertebra (Fig. 1B) *to restrain the relative motion of solid phase on the disc–vertebra interface. Since the vertebra is about ten times stiffer than the disc, the effect of the vertebra height on disc deformation was believed to be negligible. Thus, only the small part (5 mm height) of the vertebra was included in the model to reduce the computational cost. Due to symmetry*, only the upper right quarter of the disc was modeled (Fig. 1B). The mesh consisted of 7888 sextic order, hexahedral Lagrange elements. The finite element model of the disc was developed with COMSOL software (COMSOL 4.3b, COMSOL, Inc., MA) based on the method developed by Sun et al. (Sun et al., 1999). The configuration of the disc at *mature*, healthy condition before degeneration was chosen as the reference configuration, and the total stress tensor in this study was defined as the difference in stress between current configuration and reference configuration.

2.3. Material properties

The values of Lame constants (λ and μ) in NP were $\lambda=0.391$ MPa and $\mu=0.009$ MPa; for AF, λ was linearly increased from 0.391 to 1.009 MPa and μ linearly increased from 0.009 to 0.291 MPa from the innermost AF region to the outermost AF regions, respectively (Iatridis et al., 1998; Perie et al., 2006a; Perie et al., 2005). The vertebra was modeled as a single-phase solid with linear elastic mechanical properties of $\lambda=86.5$ MPa, and $\mu=57.7$ MPa (Goldstein, 1987).

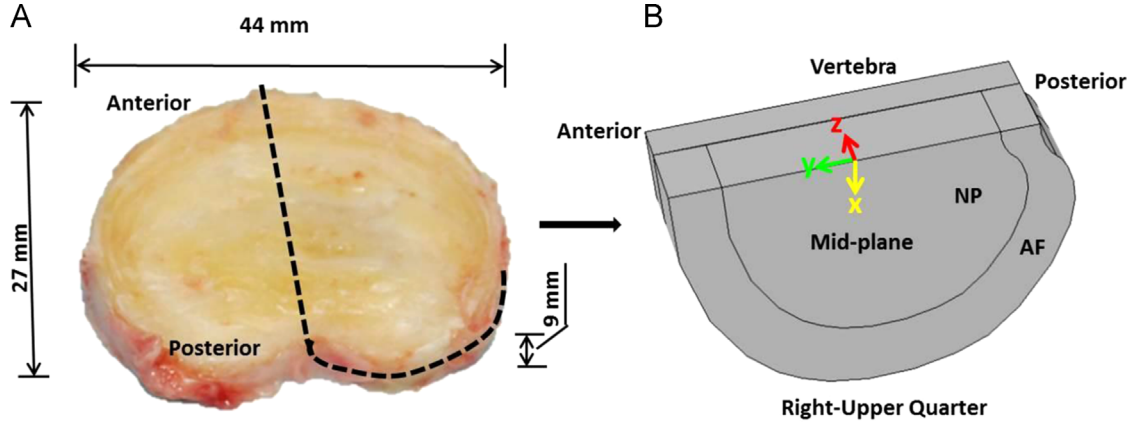

Fig. 1. (A) Geometry and size of the disc from human lumbar spine (L2-3, male, non-degenerated; vertebra is not shown) and (B) Schematic of the right–upper quarter of the disc and the vertebra used in the simulations (Gu et al., 2014; Jackson et al., 2011; Zhu et al., 2012).