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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.

Keywords

Biomechanics; Mechanobiology; Intervertebral disc degeneration; Continuum mixture theory; Finite element method; Modeling; Biophysics

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Conflict of interest statement

No financial support or benefits have been or will be received from any commercial source related directly or indirectly to the scientific work reported in this manuscript.

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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. (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. (Laible et al., 1993). Ferguson et al. (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 a solute phase (ions, nutrients, cytokines, etc.) (Lai et al., 1991). Later, Huang and Gu (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. (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.

Methods

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:

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

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:

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

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 moles of charge per mole of GAG in the tissue (Bashir et al., 1999):

$$C^F = 2C^{GAG}, \quad (3)$$

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

$$Q^F = 2Q^{GAG}, \quad (4)$$

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

$$C^+ = C^- + C^F, \quad (5)$$

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

$$Q^+ = Q^- + Q^F, \quad (6)$$

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

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.

Material properties

The values of Lamé 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).

The cell density at the healthy state (ρ_0^{cell}) was 4000 cells/mm³ in NP and 9000 cells/mm³ in AF (Maroudas et al., 1975). The distributions of the fixed charge density and the water content at the healthy state were from a 27 years old, healthy lumbar disc (Urban and Maroudas, 1979). The fixed charge density at the healthy state in NP was assumed to be homogeneous, with a value of 0.3425 M. It linearly decreased from 0.3425 to 0.1634 M from the innermost AF to the outermost AF regions. The water content (volume fraction) at the healthy state was 0.85 in the NP, and linearly decreased from 0.85 to 0.7 from the innermost AF region to the outermost AF regions.

The GAG degradation rate (λ_2) is related to the half-life (τ) of GAG turnover, by $\lambda_2 = \ln 2 / \tau$, where the value of τ is equal to 11 years for IVD tissues (Sivan et al., 2006). Q^{GAG} was assumed to be zero in mature, healthy discs (before the process of disc degeneration starts), see Eq. (2). Thus, the value of GAG synthesis rate per cell λ_1 could be estimated by the following relationship: $\lambda_1 = \lambda_2 c_0^{GAG} / \rho_0^{cell}$, where c_0^{GAG} and ρ_0^{cell} were the GAG content and cell density at the healthy state within the mature, healthy disc before degeneration.

The loss of the PG content within the disc during the progression of disc degeneration may change the amount of solid mass. However, to what extent the solid mass may change is not clear and no data is available yet in the literature. Since the disc degeneration is a very slow process for most cases, in this study, we assumed that the rate of change in solid mass was zero.

Boundary conditions

The top surface ($z=0.95$ cm) of the vertebra was set to move freely in the axial direction while constrained in the horizontal directions (i.e., the displacements were zero in the horizontal directions). The difference in the axial stress (between current and healthy state) was set to be zero on this surface. *There was no relative motion for solid phase at the disc-vertebra interface ($z=0.45$ cm). The lateral surfaces of AF and vertebra were set to be traction free. The mid-sagittal plane ($x=0$) and the mid-axial plane ($z=0$) were assumed to be symmetric plane. An impermeable boundary condition was used at the interface between AF and vertebra, while free draining boundary condition was used at the interface between NP and vertebra as well as at the AF periphery (Zhu et al., 2012).*

Due to limited information on endplate properties available in the literature, in this study, we decided to vary the concentrations of nutrients at the NP-vertebra interface to simulate the effect of endplate on nutrition supply to the disc. The effect of the thin layer of endplate on water flow in the disc in the current case was not believed to be significant because the degenerative process in this case is very slow (no fluid pressurization effect). For other cases (such as a disc under dynamic loading), it is important to include the endplate in the model (Zhu et al., 2012).

Simulation of disc degeneration

The disc degeneration was simulated by the reduction of the nutrition supply at the disc boundaries. *In order to calculate the initial conditions for glucose, oxygen, lactate, ions, and other signals in the healthy disc (before degeneration)*, the disc was initially equilibrated under the normal nutritional boundary conditions: the glucose concentration was 4 mM at the NP top boundary, and 5 mM on the AF periphery; the oxygen concentration was 5.1 KPa at the NP top boundary, and 5.8 KPa on the AF periphery; and the lactate concentration was 0.8 mM at the NP top boundary, and 0.9 mM on the AF periphery (Selard et al., 2003). The initial *guessed values* for glucose, oxygen, lactate, sodium, and chloride concentrations within the disc were 4 mM, 5.1 KPa, 0 mM, 150 mM, and 150 mM, respectively. After reaching equilibrium (about 10 days), *the distributions of nutrients, lactate, and ions in the disc were used as the initial conditions for the disc*. The glucose and oxygen concentrations at disc boundaries were then decreased linearly to the targeted levels in 3 days. *Cases with different rates of nutrition reduction were also investigated (see Discussion)*. The beginning of the glucose and oxygen concentrations decrease was marked as the start-point of the degeneration process ($t=0$).

The case in which glucose concentrations were 1 mM at NP-vertebra interface and 1.5 mM at AF periphery; and oxygen levels were 1.275 KPa at the NP-vertebra interface and 1.74 KPa at AF periphery were presented.

Results

Fixed charge density

In the healthy state, the fixed charge density distribution in the disc was shown in Figure 2A ('Before degeneration'). With the progression of disc degeneration, the fixed charge density decreased significantly in the NP and the inner to middle AF regions (Fig. 2), with the inner to middle AF regions near the mid-plane ($z=0$) experienced the most severe loss of fixed charged density (Fig. 2).

Fluid pressure

Changes in fluid pressure and its distributions with disc degenerative progression were similar to those for the fixed charge density change (Fig. 3). The NP and the inner to middle AF regions experienced a significant decrease in the fluid pressure, with the largest decrease shown in the inner to middle AF regions (Fig. 3).

Water content

The water content decreased in the NP and inner to middle AF regions, while it did not change significantly in the outer AF regions (Fig. 4).

Von Mises stress

As mentioned earlier, all the stresses reported in this study were the difference in values between current state and healthy state. It was shown that the Von Mises stress increased with the degenerative progression (Fig. 5). The increases in the outer AF region were seen larger than that in the rest of the regions (Fig. 5).

Deformation

The disc volume decreased by 7.2%, 11.7%, and 15.4% after 10, 20, 40 years of degeneration, respectively (Fig. 6). The disc height decreased with the degenerative progression, with 6.0%, 9.9%, and 13.0% after 10, 20, 40 years of degeneration, respectively. The disc was also shown to shrink radially inward toward the center (Fig. 6).

Discussion

In this work, the temporal and spatial changes of disc composition and mechanical signals undergoing disc degenerative progression were numerically investigated, using a 3D finite element model which was newly developed based on the extended cell activity coupled triphasic mixture theory (Gu et al., 2014; Zhu et al., 2012). This numerical model has been validated by comparing the *predicted GAG and water* contents in the degenerated discs to those experimental results, see Zhu et al. (Gu et al., 2014). To the best of our knowledge, the current study was the first numerical study for the quantitative prediction of changes in temporal-spatial distribution of mechanical signals within the human IVDs along the progression of degeneration.

In this study, the disc degeneration was initiated by decreased nutrition supply, one of the primary factors leading to the disc degeneration (Urban and Roberts, 2003). Decreased nutrition supply causes cell death (Bibby and Urban, 2004; Gu et al., 2014), and reduce cellular metabolic and biosynthetic rate of PG (Bibby et al., 2005). The decrease in PG content concomitantly reduces the amount of fixed charge density attached to its GAG chains on PG within the disc (Fig. 2). This leads to the reduction of the counter-ion (e.g., sodium ion) concentration and the osmolarity in the disc. Consequently, the fluid pressure is decreased (Fig. 3), causing less swelling of the disc and lower water content in the disc (Fig. 4).

The fluid pressure is highest in the NP region at healthy condition (Adams et al., 2000; Adams et al., 1996; Iatridis et al., 2003), and decreases gradually with the disc degeneration (Adams et al., 1996; Johannessen and Elliott, 2005; Sato et al., 1999). The largest fluid pressure was seen shifted from the NP region toward the inner and middle AF regions, especially in the region posterior to the NP in the degenerated discs (Adams et al., 2000; Adams et al., 1996). Our model well predicts such variation of pressure distribution from healthy to degenerative states, see Figure 3B (I).

The results of Von Mises stress distributions indicate that the shear stress increases significantly in the AF region with the progression of disc degeneration (Fig. 5). The high shear stresses may cause AF delamination (Goel et al., 1995; Gregory et al., 2011; Marshall and McGill, 2010).

In our study, both the volume and disc height decreased with the disc degeneration progression, this is consistent with the experimental findings (Kaner et al., 2014; Pelloquin et al., 2014; Pfirrmann et al., 2006). The volume decrease was mainly caused by the reduction in the swelling pressure and the loss of the water in the disc, especially in the NP region and the inner AF regions (Fig. 2), causing the disc to shrink inwards.

Since little quantitative information on nutrition boundary conditions in human discs in vivo is available in the literature, thus, in our current study, a case of reduced nutrition supply was chosen, as an example, to simulate disc degeneration process and to investigate the coupled biophysical events in the disc during the degeneration progress. We also investigated the effects of different rate of nutrition reduction on the process of disc degeneration (Fig. 7). Our simulations indicate that the rate of nutrition reduction has a significant effect on the onset of cell death (Fig. 7B), but not the long-term GAG and water contents in the disc (Figs. 7C and 7D).

In our simulations, the GAG synthesis rate (λ_1) per cell was estimated by $\lambda_1 = \lambda_2 c_0^{GAG} / \rho_0^{cell}$, where c_0^{GAG} and ρ_0^{cell} are the equilibrium GAG content and cell density within the mature, healthy disc before degeneration. So the value of λ_1 varies from the region within the disc. Our calculated values for GAG synthesis rate (λ_1), averaged over the NP, the inner AF, and the outer AF regions, are 0.911×10^{-5} , 0.66×10^{-5} , and 0.35×10^{-5} mmol/g dry weight/hr, respectively. These values are within the range of experimental data for GAG synthesis of human lumbar disc cells in vitro (Handa et al., 1997).

Both the GAG synthesis rate (λ_1) and degradation rate (λ_2) in discs vary with degenerative progress (Bayliss et al., 1988; Sivan et al., 2006). In our simulations, we assumed the values of λ_1 and λ_2 to be constant over time. This simplification may overestimate the time period needed for disc to reach new equilibrium after the reduction of nutrition supply at disc boundary.

Another limitation is that the change of the mechanical properties with the alteration of disc composition along disc degeneration was not considered in this model. In our current simulations, mechanical properties of degenerated discs were used. This assumption on the mechanical properties may have an influence on the rate of the degeneration process and signals in the disc. The limitation may be overcome in our future studies by incorporating a new constitutive model for hydration-dependent mechanical properties in soft biological tissues (Gao and Gu, 2014).

The anisotropy of the mechanical behavior and transport properties were not considered in this study. These simplifications may influence the distributions of the fluid pressure, deformation, and stresses within the AF region.

Moreover, in this study, the mechanical loading on the disc is assumed to be constant over time (equal to the mechanical loading on the disc at the healthy state). This does not truly reflect the real situation in human discs because the mechanical loading on discs could vary with aging or degeneration. These effects will be taken into consideration in our future studies.

In summary, the temporal and spatial distributions of fixed charge density, fluid pressure, water content, Von Mises stress, and disc deformation in the human disc were numerically simulated with a 3D finite element model developed based on the cell activity coupled mechano-electrochemical multiphase mixture theory. *This model has been validated by comparing the predicted distributions of GAG and water contents in the disc to those*

reported in the literature (Gu et al., 2014). Our results showed how the nutrition deprivation affects the cell viability, the tissue components (GAG and water contents), the tissue swelling pressure, the mechanical stress (e.g., Von Mises stress), and deformation. Knowledge of the spatial and temporal variations of the mechanical signals in the extracellular microenvironment is important for the understanding of the mechanobiology in the disc.

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Figure 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).

Figure 2.

(A) 3D distributions of fixed charge density (normalized by 0.15 M) within the disc before degeneration, after 10 years, 20 years, and 40 years, of degeneration. (B) The variations of fixed charge density (normalized by 0.15 M) with the progression of disc degeneration: (I) in the sagittal direction (averaged over the disc thickness) at $x=0$; (II) in the coronal direction (averaged over the disc thickness) at $y=0$; and (III) in the axial direction (averaged over the horizontal plane in the NP).

Figure 3.

(A) 3D distributions of fluid pressure (normalized by 0.372 MPa) before degeneration, after degeneration for 10 years, 20 years, and 40 years within the disc. (B) The variations of fluid pressure (normalized by 0.372 MPa) with the progression of disc degeneration: (I) in the sagittal direction (averaged over the disc thickness) at $x=0$; (II) in the coronal direction (averaged over the disc thickness) at $y=0$; and (III) in the axial direction (averaged over the x - y plane in the NP).

Figure 4.

(A) 3D distributions of water content (volume fraction) within the disc, before degeneration, and after 10 years, 20 years, and 40 years of degeneration. (B) The variations of water content (volume fraction) with the progression of degeneration: (I) in the sagittal direction (averaged over the disc thickness) at $x=0$; (II) in the coronal direction (averaged over the disc thickness) at $y=0$; and (III) in the axial direction (averaged over the x - y plane in the NP).

Figure 5.

(A) 3D distributions of Von Mises stress within the disc (normalized by 0.372 MPa) before degeneration, and after 10 years, 20 years, and 40 years of degeneration. (B) The variations of Von Mises stress (normalized by 0.372 MPa) with the progression of disc degeneration: (I) in the sagittal direction (averaged over the disc thickness) at $x=0$; (II) in the coronal direction (averaged over the disc thickness) at $y=0$; and (III) in the axial direction (averaged over the x - y plane in the NP).

Figure 6. Disc deformation (magnified by 3 times) before degeneration, after 10 years, 20 years, and 40 years of degeneration.

Figure 7.

Effect of rate of nutrition reduction at disc boundary on the temporal variation of (A) overall glucose concentration (normalized by 0.5 mM), (B) overall cell density (normalized by the value at healthy state), (C) overall GAG content, and (D) overall water content (normalized by the value at healthy state) in the disc (per unit of tissue volume at the reference configuration). Nutrition levels are reduced to the same target values in 3, 30, and 300 days.