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Simulation of the Progression of Intervertebral Disc Degeneration due to Decreased Nutrition Supply

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Abstract

Study Design—Simulate the progression of human disc degeneration.

Objective—The objective of this study was to quantitatively analyze and simulate the changes in cell density, nutrition level, proteoglycan content, water content, and volume change during human disc degeneration using a numerical method.

Summary of Background Data—Understanding the etiology and progression of intervertebral disc (IVD) degeneration is crucial for developing effective treatment strategies for IVD-degeneration related diseases. During tissue degeneration, the disc undergoes losses of cell viability and activities, changes in extracellular matrix composition and structure, and compromise of the tissue-level integrity and function, which is significantly influenced by the inter-coupled biological, chemical, electrical, and mechanical signals in the disc. Characterizing these signals in human discs in vivo is difficult.

Methods—A realistic 3D finite element model of the human IVD was developed based on biomechano-electrochemical continuum mixture theory. The theoretical framework and the constitutive relationships were all biophysics based. All the material properties were obtained from experimental results. The cell-mediated disc degeneration process caused by lowered nutrition levels at disc boundaries was simulated and validated by comparing with experimental results.

Results—Cell density reached equilibrium state in 30 days after reduced nutrition supply at the disc boundary, while the proteoglycan (PG) and water contents reached a new equilibrium state in 55 years. The simulated results for the distributions of PG and water contents within the disc were consistent with the results measured in the literature, except for the distribution of PG content in the sagittal direction.

Conclusions—Poor nutrition supply has a long-term effect on disc degeneration.

Keywords

Biomechanics; Mechanobiology; Continuum mixture theory; Finite element method; modeling; Biophysics

Introduction

Spinal diseases (e.g., low back pain, spinal stenosis, segmental instability, spondylolisthesis, etc.) are a major socio-economic concern in the United States, affecting millions of people annually. For example, the low back pain alone costs approximately 100~200 billion dollars annually (including medical expenditures and loss of work ability).¹ Intervertebral disc (IVD) degeneration has been implicated in potentially playing a role in these diseases.² During degeneration, the disc undergoes a cascade of changes in biological, chemical, electrical, and mechanical events, leading to the loss of cellularity and compromised cellular activities, reduction of proteoglycan (PG) and water contents, decrease in disc volume, and resultantly the failure in tissue-level structure and functions.³⁻⁸ Consequently, the ability of the discs to support and transport mechanical loading is significantly reduced.

The disc cells play a vital role in maintaining the IVD structure and function.⁹ The cells live in a complicated mechano-electrochemical environment, and their activities and viability are regulated by mechanical signals (e.g., deformation, stress, and fluid flow), electrical signals (e.g., streaming potential and current), and biochemical signals (e.g., osmotic pressure, glucose levels, pH, and growth factors) within the environment.^{10,11} The cells synthesize both the anabolic components for matrix maintenance and the catabolic molecules responsible for matrix breakdown.¹² In the healthy condition, the balance between anabolic and catabolic activities is maintained by the cells. Disruption of this balance can result in failure of tissue-level structure and function.^{13,14}

Although a large number of experimental studies have been conducted to investigate the extracellular environment and cellular activities related to disc degeneration^{6,9,15-22}, they have limitations when applied to delineate human discs in vivo due to: (1) the much slower process in human disc degeneration (in years) than that in the cell and animal experiments (in days or months)^{23,24}; (2) inability to precisely measure the exact nature of the mechanical, electrical, chemical environment that the tissue experiences in human body in vivo; and (3) the difference in nutritional and mechanical environment in animal disc versus human disc.⁹

Mathematical modeling and simulation may serve as a supplement tool for investigating disc degeneration in human discs. Currently, the published theoretical or numerical studies on IVD usually focus on one or two specific aspects of these processes, i.e., mechanical, chemical or biological events,²⁵ which constrain the revelation of intrinsic dynamics in human IVDs because mechanical chemical and biological events occur simultaneously in vivo. The other aspect is that the disc performance has been studied at a fixed condition, i.e. healthy or degenerated, thus cannot characterize the progression of growth and/or degeneration disease.²⁶

So far, there are no theoretical or numerical methods capable of characterizing the complicated couplings among the biological, chemical, electrical, and mechanical events within the IVD during tissue degeneration or growth under various conditions. Knowledge of these coupled events is important for understanding IVD degeneration as well as developing new diagnostic and therapeutic techniques for disc degeneration. The objective of this study was to quantitatively analyze and simulate the changes in cell density, nutrition level, proteoglycan content, water content, and volume change with the progression of human disc degeneration using a numerical method. A finite element model was developed based on a multiphasic theory for the IVD.²⁷ This model was used to investigate the changes in cell density, extracellular environment, and tissue composition (PG and water contents) during progression of human disc degeneration.

Methods

The theoretical model is extended from the cell-activity coupled mechano-electrochemical model²⁷, which is developed based on the triphasic theory.^{28–30} The disc is modeled as an inhomogeneous, porous, mixture consisting of a charged solid phase (with cells and PG fixed to the solid phase), a fluid (i.e., water) phase, and a solute phase [with different species of sodium ion Na^+ (+), chloride ion Cl^- (–), glucose (g), oxygen (o), and lactate (l)]. In the model, the PG content is estimated by the chondroitin sulfated GAG content. The conservation of mass for GAG is:

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

where C^{GAG} is the molar concentration (per tissue volume) of GAG, $\mathbf{v}^s$ is the velocity of solid matrix, and Q^{GAG} is the synthetic/degradation rate of GAG (per tissue volume).

The rate of GAG synthesis/degradation is assumed to be related to the cell density and GAG content by:

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

where λ_1 is the GAG synthesis rate per cell and λ_2 is the GAG degradation rate. The value of λ_2 is related to the half-life of GAG turnover reported in literature.³¹ Q^{GAG} is assumed to be zero in discs under a normal/healthy condition before the process of disc degeneration starts. Thus,

$$\lambda_1 = \lambda_2 C_0^{GAG} / \rho_0^{cell}, \quad (3)$$

where C_0^{GAG} and ρ_0^{cell} are the GAG content and cell density at healthy state prior to the degeneration process.

In the model, the electroneutrality is satisfied by²⁸:

$$C^+ = C^- + C^F, \quad (4)$$

where C^+ and C^- are the concentrations of sodium ion and chloride ion, respectively; and C^F is the fixed charge density which is related to GAG concentration by assuming 2 moles of charge per mole of GAG in the tissue³²:

$$C^F = 2C^{GAG}, \quad (5)$$

From Eq. (4), it follows that

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

where Q^+ is the chemical reaction rate for sodium, Q^- is the rate for chloride, and Q^F is the rate for the fixed charge density with $Q^F = 2Q^{GAG}$ because of Eq. (5).

Thus, the biological, chemical, electrical, and mechanical events are coupled in the disc.

The geometry of the disc used in this study was extracted from a non-degenerated human L2-3 disc (male, non-degenerated), with a size of 27 mm anterior-posteriorly, 44 mm laterally, and 9 mm in height, see Fig. 1A. The disc was considered as an inhomogeneous material with two distinct regions, namely, NP and AF. In this study, the disc was attached to the vertebra with the thickness of 5 mm (Fig. 1B). The vertebra was modeled as a single-phase solid with linear elastic mechanical properties. A nonlinear cell-activity-coupled, mechano-electrochemical continuum mixture theory based finite element model was developed and used for the analysis and simulation of the biological, chemical, electrical, and mechanical events in the disc during degeneration. In this theoretical model, the configuration of the disc at healthy condition was chosen as a reference configuration, and all solid stresses were those above their corresponding values in the disc before degeneration. 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.³³ To reduce the computation cost, only the upper right quarter of the IVD was modeled due to the symmetry²⁷, see Fig. 1B. The mesh consisted of 7888 sextic order, hexahedral Lagrange elements. The boundary conditions were similar to those reported in Zhu et al.²⁷, except for the load boundary condition in the axial direction. The axial load was assumed to be constant during disc degeneration.

The distribution of mechanical properties in the disc was inhomogeneous and values were assigned based on experimental results.^{34–36} That is, the two Lamé constants of elasticity (i.e., λ and μ) for each region were: $\lambda=0.391$ MPa in the NP, in the AF, it linearly increased from 0.391 to 1.009 MPa from innermost to outermost AF; $\mu=0.009$ MPa in the NP; and it linearly increased from 0.009 to 0.291 MPa from innermost to outermost AF. The mechanical property of the vertebra was set to $\lambda=86.5$ MPa, and $\mu=57.7$ MPa, according to the experimental results.³⁷

The initial cell viability was set to be 4000 cells/mm³ in NP and 9000 cells/mm³ in AF, obtained from experimental measurements.³⁸ The initial distribution of the fixed charge density and the water content distribution were from a 27 years old, healthy lumbar disc³⁹: with fixed charge density of 0.3425 M in the NP, linearly decreasing from 0.3425 to 0.1634

M from innermost to outermost AF; and the water content (volume fraction) of 0.85 in the NP, and linearly decreasing from 0.85 to 0.7 from innermost to outermost AF. Other material properties, boundary conditions and initial conditions can be seen in Zhu et al.²⁷

For the healthy human disc, the glucose concentration measured was 4 mM, and 5 mM, and the oxygen concentration 5.1 KPa and 5.8 KPa at the NP-CEP boundary and the AF periphery, respectively.⁴⁰ The disc was initially equilibrated at this nutrition level. After reaching equilibrium in 10 days, the glucose levels at boundaries were then linearly decreased to 1.2 mM on the NP-CEP boundary and to 3.0 mM on the AF periphery in 3 days. The recoding of the degeneration started at the beginning of the glucose level decrease ($t=0$). The half-life of the PG turnover was set to be 11 years.^{31,41}

Results

The degenerative changes in cell density content and glucose concentration

The cell density and glucose concentration distribution with disc degeneration are shown in Figs. 2 A and B. At this nutrition boundary condition cell death began close to the NP-AF interface in the lateral regions (Fig. 2A), where the lowest glucose concentration was found (Fig. 2B). The decrease of cell density then extended toward the center of the NP, in regions where glucose concentration was lower than the threshold value (i.e., 0.5 mM²³) (Fig. 2B). The cell density distribution reached a steady state (defined as its relative change being less than 0.005% per day) in about 30 days (Figs. 2A and 3). The glucose concentration was decreased first, and then recovered in the initially decreased region (Fig. 2B). The glucose concentration distribution then reached new equilibrium in about 40 days (<0.005% per day). The PG content [estimated by chondroitin sulfated glycosaminoglycan (GAG) content] distribution with disc degeneration is shown in Fig. 2C. A decrease in PG content began to take place around 100 days after the glucose level was decreased, starting from the mid-plane near the NP-AF interface in the lateral regions toward the center of the NP. The loss of PG content was observed in the NP region under lowered nutrition supply condition. The relative PG content change (percent of current value to the value at healthy state) averaged over the whole discs is shown in Fig 3. It was found that the PG content decreased exponentially in time, and reached a steady state (defined as its relative change being less than 0.005% per year) after 55 years of degeneration.

The degenerative changes in water content

The variation of the water content distribution with the progression of disc degeneration is presented in Fig. 2D. Variation of spatial distributions of water content followed a similar pattern to the changes of the PG distribution. However, in the temporal scale, it lagged behind the PG content change (Figs. 2D and 3). The decrease of water content started after 300 days of degeneration. The relative water content change (percent of current value to the value at healthy state) averaged over the whole disc is shown in Fig 3. There was an 8.91% decrease in water content after 55 years. This disc volume decreased with the progression of the disc degeneration, Fig. 3. After 55 years there was a 9.08% reduction in the disc volume. Simulated distributions of GAG and water contents in the disc after 27 years (around 54 years of age) are consistent with the experimental results of human discs (averaged 54 years

old) reported by Iatridis et al.⁷ (Fig. 4), except for the distribution of GAG content in the sagittal direction (Fig. 4A).

Discussion

A cell-activity-coupled, mechano-electro-chemical mixture theory based numerical method was developed to study biological, chemical, electrical, and mechanical events within the tissue during disc degeneration. Our predicted spatial and temporal distributions of the PG and water contents are consistent with experimental data reported in the literature, except for the distribution of GAG content in the sagittal direction (Fig. 4).

Proteoglycan is a significant matrix component which plays a crucial role in disc integrity and compressive supporting function.^{42,43} As PG content decreases with time in the disc, associated fixed charge density decreases in the disc, resulting in a loss of swelling pressure and loss of water content.^{42,43} The reduction of water content (or disc volume) (Figs. 2D and 3) results in a smaller tissue pore size for transport of water, ions, nutrients and lactate, leading to lower values of solute diffusivity, hydraulic permeability, and electrical conductivity^{44–46}). Reduced tissue diffusivity further deteriorates nutrition supply to disc cells, leading to lower metabolic and synthetic activities and lower number of cells in the disc. The change in the water content in the disc lags behind the change in PG content because it takes time for the water to diffuse out the disc, since the value of hydraulic permeability is very small even in healthy discs tissues [e.g., $(0.9 \pm 0.43) \times 10^{-15} \text{ m}^4/\text{N} \cdot \text{s}$ in the human NP⁴⁷ and $0.17 \times 10^{-15} \text{ m}^4/\text{N} \cdot \text{s}$ in the human AF⁴⁸]. The decrease of the hydraulic permeability further decreases the rate of the water flow thus slowing water loss.

The experimental results for the rates of GAG synthesis in nucleus Pulposus (NP), inner annulus fibrosus (AF), and outer AF were reported to be (mean $\pm$ SD): $(2.6 \pm 3.5) \times 10^{-5}$, $(2.9 \pm 4.2) \times 10^{-5}$, and $(1.1 \pm 0.9) \times 10^{-5} \text{ mmol/g dry weight/hr}$, respectively.⁴¹ In our simulations, the rate of GAG synthesis varied from outer AF to inner AF regions (Eq. 3). Our calculated rates of GAG synthesis [from Eq. (3)] averaged over the NP, inner AF, and outer AF regions are 0.911×10^{-5} , 0.66×10^{-5} , and $0.35 \times 10^{-5} \text{ mmol/g dry weight/hr}$, respectively. These values are within the range of the experimental results.⁴¹

Glucose concentration was found to be the limiting factor for survival of cells.²³ It was also reported that pH lower than 6.8 would have a negative effect on the cell viability.^{23,49,50} In this study, the minimum pH in the disc over time was found to be 7.08, located within the most severely degenerated region (i.e., on the mid-plane in the inner AF region, see Fig. 5A). The minimum pH value in the case where both glucose and the oxygen levels were reduced was also higher than 6.8, see Fig. 5B. Thus, no direct relationship between cell viability and the pH was included in our model.²⁷ It was also found that the pH value (within the degenerated region) increases with the progression of degeneration. This is caused by the reduction of the lactate concentration within this region. Since the cell numbers within this region decreased significantly, both the production rate and the concentration of the lactate within this region decreased correspondingly (see Figs. 5 C and D).

This was the first report to numerically investigate complicated nonlinear interactions among biological, chemical, electrical, and mechanical events occurred in the disc during the progression of tissue degeneration. The lack of nutrition supply to the disc could have a long-term effect (up to 55 years) on disc degeneration, for the simulated case in this study.

The results and findings from this study are useful for developing new diagnostic techniques for detecting early disc degeneration. When combined with patient-specific MRI data for disc geometry and tissue water content, this numerical model can be used for evaluating disc degeneration status, predicting long-term disc degeneration, and designing optimal treatment strategies of disc degeneration on a patient-specific basis. For instance, an injection of growth factors into the disc has been proposed as a method for treatment of disc degeneration.⁵¹ Our model can be used to quantitatively analyze and simulate the outcomes of this treatment; and consequently optimize the parameters (such as growth factor concentration, injection flow rate and duration) used in this method.

There are some limitations in this model. One limitation of the model is that the change of the material mechanical properties (e.g., the aggregate modulus, Poisson's ratio) with disc degeneration was not considered in this model due to the unavailability of data, nor was the anisotropy of the AF. The discrepancies in the distribution of GAG content in the sagittal direction between our simulation and the experimental result seen in Fig. 4A might be caused by these simplifications, and will be further investigated. In addition, the lactate concentration at the disc periphery was assumed to be constant (does not change with disc degeneration). These simplifications would influence the distributions of the mechanical stress, strain, and pH values.

Conclusions

Analysis and simulation of the progression of human disc degeneration in response to a reduced glucose level have been conducted. The results of predicted PG and water content distributions are consistent with experimental results reported in the literature, except for the distribution of GAG content in the sagittal direction. This study has provided the new insight into complicated interactions among biological, chemical, electrical, and mechanical events in the disc over time, and a powerful tool for developing and optimizing new diagnostic and treatment strategies for disc degeneration.

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Key Points

- A numerical method was developed for the simulation and prediction of human disc degeneration progression. This numerical model was based on the cell-activity incorporated mechano-electro-chemical mixture theory.
- The model was used to simulate the spatial and temporal alterations of the cell viability, nutrition level, pH value, proteoglycan content, water content, disc volume during the disc degeneration progression caused by poor nutrition.
- The simulated results of the proteoglycan and water content compared well with experimental results in the literature.
- The cell density reached equilibrium state in 30 days after reduced nutrition supply at the disc boundary, while the proteoglycan and water contents reached a new equilibrium state in 55 years.

Figure 1.

(A) Geometry and size of the disc from human lumbar spine (L2-3, male, non-degenerated; vertebra is not shown). (B) Schematic of the right-upper quarter of the disc and the vertebra used in the simulations.

Figure 2.

(A) Changes of cell density (normalized to the corresponding value at the healthy state before degeneration) distribution over time. (B) Changes of glucose concentration distribution (unit: mM). (C) GAG content change with degeneration, (unit: μg GAG weight per mg dry tissue weight). (D) Water content change with degeneration (water volume per tissue volume).

Figure 3.

The temporal change of normalized cell density, GAG content, and water content, averaged on the whole disc region.

Figure 4.

Comparisons between our predicted results and the experimental results from Iatridis et al.⁷ of the 54 years old human lumbar disc: (A) GAG content and (B) Water content in the sagittal direction, (C) GAG content and (D) Water content in the coronal direction.

Figure 5.

Changes of the distributions of pH value and Lactate concentration in the disc. (A) pH value distribution for the case where the glucose concentration was reduced alone by 70% on NP-CEP boundary and 40% on AF periphery. (B) pH value distribution for the case where both glucose and oxygen concentrations were reduced by 70% on NP-CEP boundary and 40% on AF periphery. (C) Lactate concentration distribution for the case where the glucose concentration was reduced alone by 70% on NP-CEP boundary and 40% on AF periphery. (D) Lactate concentration distribution for the case where both glucose and oxygen concentrations were reduced by 70% on NP-CEP boundary and 40% on AF periphery.