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EFFECT OF ENDPLATE CALCIFICATION AND MECHANICAL DEFORMATION ON THE DISTRIBUTION OF GLUCOSE IN INTERVERTEBRAL DISC: A 3-D FINITE ELEMENT STUDY

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Abstract

The intervertebral disc (IVD) is avascular, receiving nutrition from surrounding vasculature. Theoretical modelling can supplement experimental results to understand nutrition to IVD more clearly. A new, 3D finite element model of the IVD was developed to investigate effects of endplate calcification and mechanical deformation on glucose distributions in IVD. The model included anatomical disc geometry, non-linear coupling of cellular metabolism with pH and oxygen concentration, and strain-dependent properties of the extracellular matrix.

Calcification was simulated by reducing endplate permeability (~79%). Mechanical loading was applied based on *in vivo* disc deformation during the transition from supine to standing positions. Three static strain conditions were considered: supine, standing, and weight-bearing standing.

Minimum glucose concentrations decreased 45% with endplate calcification, while disc deformation led to a 4.8–63% decrease, depending on the endplate condition (i.e., normal vs. calcified). Furthermore, calcification more strongly affected glucose concentrations in the nucleus compared to the annulus fibrous region. This study provides important insight into nutrient distributions in IVD under mechanical deformation.

Keywords

nutrition; transport; mechanics; diffusion; metabolism; theoretical modelling

Introduction

Low back pain is a significant economic and social burden in most industrialized countries, including the United States (NIH 1997). Although the origins of low back pain remain unclear, degeneration of the intervertebral discs (IVD) of the spine has been closely associated with the onset of the condition (Buckwalter 1995; Eyre et al. 1989; Kelsey et al. 1992; White 1981). Poor nutritional supply to the IVD is believed to be an important factor in the pathophysiology of disc degeneration (Bibby et al. 2002; Holm and Nachemson 1982; Horner and Urban 2001; Nachemson et al. 1970).

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The IVD is the largest avascular structure in the human body. It is made up of a central, gelatinous nucleus pulposus (NP) region, which is composed of randomly oriented collagen fibrils and is rich in proteoglycans (PG). The high PG content of NP allows the tissue to retain water and resist compressive forces on the disc. The NP is surrounded on its periphery by the annulus fibrosus (AF), which consists of 15 to 25 concentric lamellae composed of highly organized collagen fibers (Hickey and Hukins 1980; Marchand and Ahmed 1990). The AF acts to contain the NP tissue within the disc, and to withstand forces in the radial direction. The NP is surrounded inferiorly and superiorly by the cartilaginous endplates (CEP), which consist of a thin layer of hyaline cartilage. The CEPs separate the NP from the vertebral bodies and also serve an important role in nutritional transport into the disc, allowing for the passage of nutrients and metabolites.

Because of the lack of vasculature in the tissue, important nutrients, such as glucose and oxygen, must be transported through the extracellular matrix (ECM) of the disc from the blood vessels surrounding the AF and at the CEP-bone interface; likewise, metabolic waste products, such as lactic acid, must be transported out of the tissue for removal. Although the cell density in the tissue is low, cells require large quantities of energy in order to maintain the ECM. It has been found that, even in the presence of high oxygen concentrations, disc cells rely mainly on glycolysis (i.e., anaerobic metabolism) in order to produce energy in the form of adenosine triphosphate (ATP) (Holm et al. 1981; Ishihara and Urban 1999). Hence, it has been found that glucose is the main nutrient necessary for disc cell survival (Bibby et al. 2002; Bibby and Urban 2004; Horner and Urban 2001; Shirazi-Adl et al. 2010).

Because it is difficult to obtain *in vivo* measurements in the disc, theoretical modeling can serve as a useful tool to supplement experimental results in order to predict the *in vivo* environment. Several investigators have presented theoretical models of the disc in order to investigate the mechanical behavior of the tissue, without the inclusion of cellular metabolism, see review in (Yao and Gu 2006). More recent models of the IVD have incorporated nutrient concentrations coupled to metabolic rates, but have either presented an axisymmetric disc geometry, or have not included mechanical loading configurations (Huang and Gu 2008; Magnier et al. 2009; Selard et al. 2003; Shirazi-Adl et al. 2010; Soukane et al. 2005; Soukane et al. 2007; Soukane et al. 2009).

In order to predict the nutrient distributions in the IVD with accuracy, theoretical models must incorporate each of three main elements: (1) three-dimensional (3D) anatomical disc geometry; (2) nutrient concentrations coupled to cellular metabolic rates; and (3) *in vivo* loading or strain conditions along with strain-dependent tissue properties (e.g., porosity, permeability, diffusivity). All of these aspects are vital to providing a proper prediction of the environment within the disc *in vivo*, as well as for better understanding of the pathophysiology of disc degeneration. Therefore, in this study, we present, to our knowledge, the first finite element model of the intervertebral disc which includes all of these aspects. Using this novel model, we investigated the effects of endplate calcification, simulated by a reduction in CEP permeability, and *in vivo* mechanical strain conditions on the distribution of glucose in the disc.

Theoretical model

For this study, the theoretical framework based on the triphasic theory was extended to a new formulation (Gu et al. 1998; Huang and Gu 2008; Lai et al. 1991; Yao and Gu 2004). The following governing equations were based on the balance of linear momentum for the mixture and the conservation of mass for each of the phases or solute species:

$$\nabla \cdot \sigma = 0, \quad (1)$$

$$\nabla \cdot (v^s + J^w) = 0, \quad (2)$$

$$\frac{\partial (\phi^w c^\alpha)}{\partial t} + \nabla \cdot (J^\alpha + \phi^w c^\alpha v^s) = Q^\alpha, \quad (3)$$

where σ is the total stress of the mixture, v^s is the velocity of the solid phase, J^w and J^α are the molar fluxes of the water and solute α phases, respectively, relative to the solid phase, ϕ^w is the tissue porosity (water volume fraction), c^α is the concentration (per unit water volume) of solute α , and Q^α is the cellular metabolic rate of solute α per unit tissue volume. Note that, in Equation (3), nutrient concentrations are coupled to cellular metabolic rates.

In this study, three neutral solutes (glucose, oxygen (O_2), and lactate), sodium ion (+) and chloride ion (−) were considered. Charged ions were included as a necessary balance to the fixed negative charges on the solid matrix. The pH-dependent (Bibby et al. 2005) consumption rate of oxygen (Q^{O_2}) was based on the literature (Huang et al. 2007):

$$Q^{O_2} = - \frac{V'_{max} (pH - 4.95) c^{O_2}}{K'_m (pH - 4.95) + c^{O_2}} \rho^{cell}, \quad (4)$$

where Q^{O_2} is expressed in μM , $V'_{max} = 5.27$ nmol/million cells-hr for NP cells and 3.64 nmol/million cells-hr for AF cells, $K'_m = 3.4$ μM for NP cells and 12.3 μM for AF cells, and ρ^{cell} is the cell density. The rate of production of lactate (Q^{lac}) was based on that of NP cells in the literature (Bibby et al. 2005):

$$Q^{lac} = \exp(-2.47 + 0.93 \times pH + 0.16 \times c^{O_2} - 0.0058 \times c^{O_2^2}) \rho^{cell}, \quad (5)$$

where c^{O_2} is expressed in kPa. The oxygen concentration can be converted between kPa and μM using the solubility of oxygen in water (i.e., 1.0268×10^{-6} mol/kPa – 100 mL) (Huang and Gu 2008; Soukane et al. 2005). For sodium and chloride ions, the metabolic rates were assumed to be zero. The rate of glucose consumption is based on the assumption that glucose is primarily consumed through the process of glycolysis, in which one molecule of glucose is broken down into two lactic acid molecules; therefore, the rate of glucose consumption (Q^{glu}) was:

$$Q^{glu} = -0.5 * Q^{lac}. \quad (6)$$

An approximate linear relationship between pH and lactate was used to calculate the pH within the IVD (Bibby et al. 2005; Soukane et al. 2005):

$$pH = (-0.1 mM^{-1}) c^{lac} + 7.5 \quad (0 < c^{lac} < 30 mM). \quad (7)$$

In this study, strain-dependent tissue properties were taken into consideration. The tissue porosity, or water volume fraction, is related to the tissue dilatation, e , and the tissue porosity at reference configuration (i.e., $e = 0$), ϕ_o^w , by (Lai et al. 1991):

$$\phi^w = \frac{\phi_o^w + e}{1 + e}. \quad (8)$$

The hydraulic permeability, k , of the tissue was calculated based on the constitutive equation (Gu et al. 2003):

$$k = a \left(\frac{\phi^w}{1 - \phi^w} \right)^n, \quad (9)$$

where a and n are material constants whose values vary by region in the disc and were taken based on results in the literature for porcine AF (for AF region) (Gu and Yao 2003), agarose gels (for NP region) (Gu et al. 2003) and human articular cartilage (for CEP region) (Maroudas 1975; Yao and Gu 2004). The diffusivity of solute α , D^α , was estimated based on the constitutive relationship (Gu et al. 2004):

$$\frac{D^\alpha}{D_o^\alpha} = \exp \left[-A \left(\frac{r^\alpha}{\sqrt{k}} \right)^B \right], \quad (10)$$

where D_o^α is the diffusivity of solute α in aqueous solution, r^α is the hydrodynamic radius of solute α , and A and B are material constants previously determined for agarose gel and IVD tissues. For glucose, $D_o^{glu} = 9.2 \times 10^{-10} \text{ m}^2/\text{s}$ and $r^{glu} = 0.3 \text{ nm}$; for oxygen, $D_o^{O_2} = 3.0 \times 10^{-9} \text{ m}^2/\text{s}$ and $r^{O_2} = 0.1 \text{ nm}$; and for lactate, $D_o^{lac} = 1.28 \times 10^{-9} \text{ m}^2/\text{s}$ and $r^{lac} = 0.255 \text{ nm}$ (Huang and Gu 2008).

The averaged glucose concentration, $\bar{c}^{glu}$, in AF and NP regions was determined by:

$$\bar{c}^{glu} = \frac{\int_V c^{glu} dV}{V} \quad (11)$$

where V is the volume of the disc region (i.e., AF or NP).

Finite element analysis

In this study, we considered a 3-D anatomical geometry based on that of an L2-L3 IVD (Thompson degenerative grade I) harvested from the lumbar spine of a 41 year-old male (Figure 1a). The IVD was modeled as an inhomogeneous material consisting of three distinct regions: AF, NP and CEP. The AF and NP regions were considered to have a uniform thickness of $h = 10 \text{ mm}$. The CEP had a thickness of $h = 0.6 \text{ mm}$ and was considered to be permeable above the NP region only (i.e., completely calcified, or impermeable, above the AF). Because of symmetry with respect to the plane $x = 0$ and the plane $z = 0$, only the upper right quarter of the disc was modeled (Figure 1d).

The FEM formulation, employing the weak form, was based on the work by Sun et al. (1999) (Sun et al. 1999). The model was solved using COMSOL software (Comsol 3.2,

COMSOL, Inc., Burlington, MA). The upper right quarter of the disc was modeled with a mesh of 6927 second-order, tetrahedral Langrange elements (Figure 1c). The relative tolerance for convergence was 1×10^{-6} . All results are for the disc in the equilibrium state following application of compression (where applicable).

Tissue properties used in the model are shown in Table 1. Material properties for AF and NP are based on results for human tissue (Iatridis et al. 1997; Iatridis et al. 1999; Johannessen and Elliot 2005). For the CEP region, material properties are based on those of articular cartilage (Yao and Gu 2004). Initial solute concentrations at the tissue boundaries were the same as those used in our previous model (Huang and Gu 2008). The disc was initially equilibrated in 0.15 M NaCl (i.e., $c^+ = c^- = 0.15$ M). At the CEP boundary, $c^{glu} = 4$ mM, $c^{o2} = 5.1$ kPa and $c^{lac} = 0.8$ mM, while at the lateral AF surface, $c^{glu} = 5$ mM, $c^{o2} = 5.8$ kPa and $c^{lac} = 0.9$ mM.

The distribution of glucose in the IVD under three static deformation configurations was analyzed: (1) supine, (2) standing, and (3) weight-bearing standing. Strain (relative to the supine position) was applied to the disc using a displacement boundary condition. In the supine configuration, no strains were applied to the disc (i.e., initial geometry). The standing configuration was based on a recent *in vivo* study investigating the change in disc geometry associated with the transition from supine to standing positions (Wang et al. 2009). This transition was found to result in 16% compression (i.e., 16% reduction in disc height) in the posterior region of the disc, while the anterior region is 19% in tension (i.e., 19% increase in disc height, Figure 2). In order to investigate a weight-bearing standing configuration, we considered the same tension/compression configuration described for the standing condition, plus an additional 10% static compressive strain (i.e., the anterior region was in 9% tension, while the posterior region was 26% in compression). These configurations are illustrated in Figure 3.

The effects of endplate calcification on the distribution of nutrients in the disc were simulated by reducing the permeability of the endplate tissue. The CEP is known to become calcified during aging and degeneration (Bernick and Cailliet 1982; Nachemson et al. 1970; Roberts et al. 1993), resulting in a decrease in the nutrient exchange between the disc and the capillary bed in the adjacent vertebrae (Nguyen-minh et al. 1998; Urban et al. 2001). Since the permeability of the endplate tissue is related to the tissue water content, see Equation (9), the water content of the CEP was reduced to simulate endplate calcification; the water content of the normal CEP was considered as 0.6, while that in the 'calcified' case was 0.42 (i.e., a 30% reduction). Based on the constitutive model for hydraulic permeability (Gu et al. 2003) incorporated into the model, this reduction in tissue porosity results in a ~79% decrease in the hydraulic permeability (from $5.94 \times 10^{-17} \text{ m}^4 / \text{N}\cdot\text{s}$ to $1.24 \times 10^{-17} \text{ m}^4 / \text{N}\cdot\text{s}$). Furthermore, the solute diffusivity is also reduced due to the decreased permeability of the tissue, see Equation (10) (Gu et al. 2004). The degree to which diffusivity is reduced varies based on the size of the solute; for instance, for glucose, the 30% reduction in CEP water content results in a ~38% decrease in glucose diffusivity in CEP tissue.

Results

In general, our results showed that glucose concentrations decrease moving away from the blood supply at the disc periphery and cartilaginous endplates. Minimum glucose concentrations were found at the interface between the AF and NP regions of the disc and varied according to strain configurations (Figure 4–5). The values for minimum glucose concentration determined here (i.e., 0.41 – 0.75 mM for supine configuration) are in agreement with those measured in the AF of scoliotic discs, which were in the range of 0.5 –

2.5 mM (Bibby et al. 2002). Typical results for glucose concentrations in the disc for both the normal (left column) and 'calcified' endplate (right column) cases are shown in Figure 3.

Our results indicate that there is a 17% decrease in the minimum glucose concentration in the IVD for the 'calcified' CEP case, for which the permeability of the CEP tissue was reduced by approximately 79%. Additionally, our results show that the NP region is more strongly affected by endplate calcification as compared with the AF region of the disc. This effect is shown in Figure 4. In fact, there was a 30.6% decrease in the averaged glucose concentration, calculated using Equation (11), in the NP region for the 'calcified' case compared with normal CEP, in contrast to the 6.4% decrease in the averaged glucose concentration in the AF region.

In this study, we also investigated the effects of disc deformation on the glucose concentrations in the IVD. The *in vivo* strain conditions associated with the transition from lying to standing configuration resulted in a 4.8% decrease in the minimum glucose concentration in the disc for the normal endplate case, as compared with the supine configuration. In contrast, this standing configuration led to a 14% decrease in the minimum glucose concentration in the disc for the 'calcified' case. The standing configuration also led to an alteration in the glucose distribution in the IVD, resulting in an increase in the glucose concentration in the anterior region while that in the posterior region of the disc decreased (Figure 5).

Furthermore, disc deformation associated with weight-bearing standing conditions (i.e., an additional 10% static compressive strain added to that in standing configuration) led to a 21% decrease in the minimum glucose concentration in the disc, as compared with the standing configuration, for the normal endplate case. By comparison, the same deformation led to a 57% decrease in the minimum glucose concentration for the 'calcified' endplate case.

The change in pH distribution in the disc with varying endplate permeability and strain configurations was also investigated. The pH profile in the IVD for the normal and 'calcified' endplate conditions (in supine configuration) are shown in Figure 6. Similar to results for glucose, minimum pH values were found near the interface between the AF and NP, at the mid-plane of the disc (i.e., $z = 0$). Our results indicate that the minimum pH value in the disc decreases when the permeability of the endplate is reduced, from 6.899 in the normal CEP case, to 6.854 in the 'calcified' case. Additionally, both the standing and weight-bearing standing configurations resulted in small decreases in the minimum pH value for both CEP conditions. The minimum pH value decreased to 6.894 and 6.875 for standing and weight-bearing standing, respectively, in the normal endplate case, as compared with decreases to 6.846 and 6.821 for the 'calcified' endplate cases.

Discussion

The main objective of this study was to develop a new 3-D finite element model of the intervertebral disc, and to investigate the effects of mechanical deformation and endplate calcification on the distribution of glucose in the disc. Although only the results for glucose and pH distributions are reported here, our model is capable of simultaneously predicting stress and strain distributions in the disc, as well as the concentration distributions of other solutes (e.g., oxygen, lactate, ions).

Our results indicate that reduced permeability associated with calcification of the cartilaginous endplates leads to a significant decrease in the minimum glucose concentrations in the disc, which is similar to the results presented in previous studies (Shirazi-Adl et al. 2010; Soukane et al. 2009). The minimum concentration of glucose fell

from 0.748 mM in the normal endplate case to 0.408 mM for the 'calcified' case. The effects of reduced endplate permeability are most prominent in the NP region of the disc, as the NP receives its nutrient supply mainly from the capillary bed in the vertebral bone adjacent to the endplate (Brodin 1955; Brown and Tsaltas 1976; Holm et al. 1981; Maroudas et al. 1975; Nachemson et al. 1970; Ogata and Whiteside 1981; Urban et al. 1982). This decrease in the minimum concentration of glucose is significant as a previous study has shown that if glucose levels fall below 0.5 mM for more than 3 days, cells begin to die (Horner and Urban 2001). Endplate calcification occurs during the aging process of the disc. Although the exact mechanism of calcification is unknown, it is clear that this leads to a decrease in the transport of nutrients through the tissue (Nachemson et al. 1970). This, in turn, results in a decrease in the nutrient concentrations in the IVD, particularly in the NP region, as was seen here. Alterations in the concentrations and/or distribution of nutrients in the disc may lead to changes in the disc cellular metabolism and cell viability, which in turn would affect the function of the IVD.

Our results show that the *in vivo* deformation configuration associated with the transition from supine to standing positions (Figure 2b) results in a decrease in the minimum glucose concentration in the disc (Figures 3–5). This effect was augmented by endplate calcification; the decrease in minimum glucose concentration was more than twice as large in the 'calcified' case as compared with the normal case. Additionally, the *in vivo* standing configuration led to an alteration in the distribution of glucose in the IVD, with that in the anterior region of the disc increased during standing, while that in the posterior region decreased (see dashed line in Figure 5), compared with results for the supine configuration. Results were similar for both the normal and 'calcified' endplate cases. This alteration is a result of a change in the tissue water content caused by the unique strain configuration. The anterior region of the disc is in tension, resulting in an increase in the water content, while the posterior region of the disc is in compression, causing a reduction in water content. In fact, for AF tissue with an initial tissue water content of 0.75, a 19% tensile strain results in an increase in the water content to 0.79, while a 16% compressive strain leads to a reduced water content of 0.70. These changes give rise to an alteration in the solute diffusivity through the tissue, see Equation (10), thereby varying the glucose concentration in the disc. These findings may have clinical implications, as the majority of disc herniations have been found to occur in the posterolateral region of the disc (Martin et al. 2002). A decrease in the nutrient levels in the posterior disc during standing may lead to regional degeneration of the tissue; this degeneration may disrupt the integrity of the tissue, thereby giving rise to herniation in this region.

This study also investigated the effects of 10% static compressive strain while in the standing configuration (i.e. weight-bearing standing configuration) on the glucose concentration in the disc. Results show that this strain configuration results in decreased glucose levels in the disc, whether the endplate is normal or calcified (see Figure 4 and dotted lines in Figure 5). This result was expected, as compressive loading results in decreased water content and solute diffusivities, as discussed previously. Like the standing configuration, this weight-bearing configuration had a more pronounced effect on the minimum glucose level in the disc having endplates with reduced permeability ('calcified') (Figure 3), which had a decrease in minimum glucose concentration that was ~2.5 times greater as compared with the normal endplate case. This indicates that endplate calcification may cause more extreme glucose levels in the disc during loading, as compared to the normal, permeable endplate, leading to further degeneration of the tissue because of poor nutritional supply to disc cells.

Previous studies have also shown that the pH level in the disc tissue is an important factor in regulating cell viability and function (Horner and Urban 2001; Razaq et al. 2003).

Furthermore, the cell metabolic rates incorporated into this model are pH-dependent, see Equations (4) and (5). Therefore, we also investigated how the pH profile in the disc was affected by loading configurations and endplate calcification. Results for pH values found here are similar to results previously reported for normal and symptomatic discs (Kitano et al. 1993). It is evident that CEP calcification leads to a decrease in the pH in the disc (see Figure 6). This is a result of the build-up of lactic acid, a by-product of anaerobic metabolism, caused by reduced endplate permeability during CEP calcification. These results indicate that CEP calcification may lead to acidic conditions in the IVD, resulting in subsequent changes in cellular activity as well as a loss of cell viability. These alterations would likely be detrimental to the health of the disc, resulting in degeneration and loss of function. It should also be noted that the loading configurations investigated here also led to more acidic conditions in the tissue, again likely the result of lactic acid accumulation in the tissue. Similar to the case for glucose, the effect of compressive loading on pH was more pronounced for the 'calcified' endplate case (data not shown).

In order to predict nutrient distributions in the disc with accuracy, more information regarding nutrient consumption rates is needed. For instance, the rate of production of lactate, as well as the consumption rate of glucose, used in this study was based on results for bovine NP cells (Bibby et al. 2005). That is, metabolic rates for glucose and lactate were assumed to be the same for both AF and NP cells. Studies on the oxygen consumption rate for IVD cells have indicated a difference in metabolic rates for the two cell phenotypes (Huang et al. 2007); it is therefore likely that a difference would exist for glucose and lactate metabolism as well. However, although a recent study investigated the rate of lactate production by AF cells (Guehring et al. 2009), there is currently no quantitative relationship in the literature to describe the metabolic rates of glucose and lactate by AF cells; this information is necessary in order to predict nutrient distributions in the disc accurately. Additionally, further detailed studies on the consumption rate of glucose by IVD cells are needed, given that glucose is considered the limiting nutrient for cell viability. For example, in Equations (5) and (6), the glucose consumption rate is assumed to be dependent on the oxygen-tension level but independent of the glucose concentration. It is probable that glucose concentration levels affect the metabolic rate by disc cells, particularly at low (i.e., <0.5 mM) levels, thereby influencing the distribution of glucose in the IVD.

During degeneration, the most prominent biochemical change in the disc is a loss of proteoglycans from the matrix, resulting in an altered osmotic environment (Lyons et al. 1981; Urban and McMullin 1988). A recent study showed that the osmotic environment more strongly affected the cellular response of IVD cells, in terms of gene expression, as compared to mechanical loading alone (Wuertz et al. 2007). Therefore, a change in osmolarity may affect the rate of cellular consumption of nutrients by disc cells, thus varying the nutrient distributions in the IVD. Additionally, although the effect of mechanical strain on nutrient transport through the IVD is incorporated into this model, see Equations (8) – (10), the intrinsic effects of strain on disc cell metabolism are not known. Moreover, mechanical loading alters the extracellular osmolarity in the disc, as a result of the associated change in fixed charge density; this likely affects the cellular metabolic activity because of the changed environment. Clearly, more details regarding the effects of osmolarity and/or mechanical loading on cellular metabolic rates are necessary as this information is integral in the accurate prediction of disc *in vivo* environment and nutrient distributions.

There are a few limitations for the model presented in this study. Most notably, many of the parameters used in this study (i.e., rates of cellular metabolism, solute diffusivities) are based on results from studies using animal tissues or cells. These parameters should be determined for human IVD tissues and cells in order to predict nutrient distributions in

human discs more accurately. Also, there are few studies in the literature regarding properties of animal CEP tissue [e.g., (Accadbled et al. 2008; Ayotte et al. 2000; Setton et al. 1993)], but data regarding material properties of human endplate tissue are not available. Therefore, for convenience, material properties incorporated into the model were based on those of human articular cartilage. Additionally, the Lamé constants, λ and μ , for the cartilaginous endplates incorporated into the model were assumed to be the same for both the normal and 'calcified' cases. Changes in these properties caused by the calcification process should be incorporated into future models, in order to reflect the disc *in vivo* environment with accuracy.

It should also be noted that, in this study, analysis is limited to only a specific mechanical deformation. However, during normal daily activities, the disc is subjected to a variety of loading configurations, including static and dynamic, torsion, tension, compression, etc. The results shown here provide an example of how mechanical deformation of the disc can affect nutrient distributions in the tissue. Likewise, this study only investigated a single level of endplate calcification (or reduced tissue permeability); again, this study may serve as an example of how reduced nutritional supply at the disc periphery may alter the nutrient levels in the IVD. In the future, more complex loading or deformation configurations may be considered, as well as varying levels of endplate calcification, in order to understand more fully the nutrient distributions in the IVD *in vivo*.

In summary, we have presented a new, 3-D finite element model of the IVD which incorporates anatomical disc geometry, nutrient transport coupled to cellular metabolism, and mechanical loading conditions with strain-dependent tissue properties. This investigation showed that the decrease in permeability of cartilage endplates caused by calcification results in reduced nutrient levels in the disc, most markedly in the nucleus region. Furthermore, the results of this study also indicate that mechanical deformation causes decreased nutritional levels in the disc, and that the strain configuration resulting from the transition from supine to standing positions results in an altered glucose distribution in the IVD. This study provides important insight into nutrient distributions in the disc, and the related implications for disc degeneration and low back pain.

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References

- Accadbled F, Laffosse J-M, Ambard D, Gomez-Brouchet A, de Guazy JS, Swider P. Influence of location, fluid flow direction, and tissue maturity on the macroscopic permeability of vertebral end plates. *Spine*. 2008; 33(6):612–619. [PubMed: 18344854]
- Ayotte DC, Ito K, Perren SM, Tepic S. Direction-dependent constriction flow in a poroelastic solid: the intervertebral disc valve. *J Biomech Eng*. 2000; 122(6):587–593. [PubMed: 11192378]
- Bernick S, Cailliet R. Vertebral end-plate changes with aging of human vertebrae. *Spine*. 1982; 7(2): 97–102. [PubMed: 7089697]
- Bibby SR, Fairbank JC, Urban MR, Urban JP. Cell viability in scoliotic discs in relation to disc deformity and nutrient levels. *Spine*. 2002; 27(20):2220–2228. [PubMed: 12394897]
- Bibby SR, Urban JP. Effect of nutrient deprivation on the viability of intervertebral disc cells. *Eur Spine J*. 2004; 13(8):695–701. [PubMed: 15048560]
- Bibby SRS, Jones DA, Ripley RM, Urban JP. Metabolism of the intervertebral disc: effects of low levels of oxygen, glucose, and pH on rates of energy metabolism of bovine nucleus pulposus cells. *Spine*. 2005; 30(5):487–496. [PubMed: 15738779]

- Brodin H. Path of nutrition in articular cartilage and intervertebral disk. *Acta Ortho Scand.* 1955; 24:177.
- Brown MD, Tsaltas TT. Studies on the permeability of the intervertebral disc during skeletal maturation. *Spine.* 1976; 1:240–244.
- Buckwalter JA. Aging and degeneration of the human intervertebral disc. *Spine.* 1995; 20(11):1307–1314. [PubMed: 7660243]
- Eyre, DR.; Benya, P.; Buckwalter, J.; Caterson, B.; Heinegard, D.; Oegema, T.; Pearce, R.; Pope, M.; Urban, J. Intervertebral disk: Basic science perspectives. In: Frymoyer, JW.; Gordon, SL., editors. *New Perspectives on Low Back Pain.* American Academy of Orthopaedic Surgeons; Park Ridge, IL: 1989.
- Gu WY, Lai WM, Mow VC. A mixture theory for charged-hydrated soft tissues containing multi-electrolytes: passive transport and swelling behaviors. *Journal of Biomechanical Engineering.* 1998; 120(2):169–180. [PubMed: 10412377]
- Gu WY, Yao H. Effects of hydration and fixed charge density on fluid transport in charged hydrated soft tissue. *Annals of Biomedical Engineering.* 2003; 31(10):1162–1170. [PubMed: 14649490]
- Gu WY, Yao H, Huang C-Y, Cheung HS. New insight into deformation-dependent hydraulic permeability of gels and cartilage, and dynamic behavior of agarose gels in confined compression. *J Biomech.* 2003; 36:593–598. [PubMed: 12600349]
- Gu WY, Yao H, Vega AL, Flagler D. Diffusivity of ions in agarose gels and intervertebral disc: Effect of porosity. *Annals of Biomedical Engineering.* 2004; 32:1710–1717. [PubMed: 15675682]
- Guehring T, Wilde G, Sumner M, Grünhagen T, Karney GB, Tirlapur UK, Urban JP. Notochordal intervertebral disc cells: sensitivity to nutrient deprivation. *Arthritis Rheum.* 2009; 60(4):1026–1034. [PubMed: 19333932]
- Hickey DS, Hukins DWL. Relation between the structure of the annulus fibrosus and the function and failure of the intervertebral disc. *Spine.* 1980; 5:106–116. [PubMed: 6446156]
- Holm S, Maroudas A, Urban JP, Selstam G, Nachemson A. Nutrition of the intervertebral disc: solute transport and metabolism. *Connect.Tissue Res.* 1981; 8(2):101–119. [PubMed: 6453689]
- Holm S, Nachemson A. Nutritional changes in the canine intervertebral disc after spinal fusion. *Clin.Orthop.* 1982; 169:243–258. [PubMed: 7105584]
- Horner HA, Urban JP. 2001 Volvo Award Winner in Basic Science Studies: Effect of nutrient supply on the viability of cells from the nucleus pulposus of the intervertebral disc. *Spine.* 2001; 26(23): 2543–2549. [PubMed: 11725234]
- Huang C-Y, Gu WY. Effects of mechanical compression on metabolism and distribution of oxygen and lactate in intervertebral disc. *J.Biomech.* 2008; 41(6):1184–1196. [PubMed: 18374341]
- Huang C-Y, Yuan T-Y, Jackson AR, Hazbun L, Gu WY. Effects of low glucose concentrations on oxygen consumption rates of intervertebral disc cells. *Spine.* 2007; 32(19):2063–2069. [PubMed: 17762806]
- Iatridis JC, Kumar S, Foster RJ, Weidenbaum M, Mow VC. Shear mechanical properties of human lumbar annulus fibrosus. *J Orthop Res.* 1999; 17(5):732–737. [PubMed: 10569484]
- Iatridis JC, Setton LA, Weidenbaum M, Mow VC. Alterations in the mechanical behavior of the human lumbar nucleus pulposus with degeneration and aging. *J Orthop Res.* 1997; 15(2):318–322. [PubMed: 9167638]
- Ishihara H, Urban JP. Effects of low oxygen concentrations and metabolic inhibitors on proteoglycan and protein synthesis rates in the intervertebral disc. *J Orthop Res.* 1999; 17(6):829–835. [PubMed: 10632449]
- Johannessen W, Elliot DM. Effects of degeneration on the biphasic material properties of human nucleus pulposus in confined compression. *Spine.* 2005; 30(24):E724–E729. [PubMed: 16371889]
- Kelsey, JL.; Mundt, DF.; Golden, AL. Epidemiology of low back pain. In: Malcolm, JIV., editor. *The Lumbar Spine and Back Pain.* 4th ed.. Churchill Livingstone; New York: 1992.
- Kitano T, Zerwekh JE, Usui Y, Edwards ML, Flicker PL, Mooney V. Biochemical changes associated with the symptomatic human intervertebral disc. *Clin Orthop.* 1993; 293:372–377. [PubMed: 8339506]
- Lai WM, Hou JS, Mow VC. A triphasic theory for the swelling and deformation behaviors of articular cartilage. *J Biomech Eng.* 1991; 113(3):245–258. [PubMed: 1921350]

- Lyons G, Eisenstein SM, Sweet MB. Biochemical changes in intervertebral disc degeneration. *Biochim.Biophys.Acta*. 1981; 673(4):443–453. [PubMed: 7225426]
- Magnier C, Boiron O, Wendling-Mansuy S, Chabrand P, Deplano V. Nutrient distribution and metabolism in the intervertebral disc in the unloaded state: a parametric study. *J Biomech*. 2009; 42(2):100–108. [PubMed: 19110252]
- Marchand F, Ahmed AM. Investigation of the laminate structure of lumbar disc annulus fibrosus. *Spine*. 1990; 15(5):402–410. [PubMed: 2363068]
- Maroudas A. Biophysical chemistry of cartilaginous tissues with special reference to solute and fluid transport. *Biorheology*. 1975; 12:233–248. [PubMed: 1106795]
- Maroudas A, Stockwell RA, Nachemson A, Urban J. Factors involved in the nutrition of the human lumbar intervertebral disc: cellularity and diffusion of glucose in vitro. *J Anat*. 1975; 120(1):113–130. [PubMed: 1184452]
- Martin MD, Boxell CM, Malone DG. Pathophysiology of lumbar disc degeneration: a review of the literature. *Neurosurg Focus*. 2002; 13(2):E1.
- Nachemson A, Lewin T, Maroudas A, Freeman MA. In vitro diffusion of dye through the end-plates and the annulus fibrosus of human lumbar inter-vertebral discs. *Acta Orthop Scand*. 1970; 41(6):589–607. [PubMed: 5516549]
- Nguyen-minh C, Haughton VM, Papke RA, An H, Censky SC. Measuring diffusion of solutes into intervertebral disks with MR imaging and paramagnetic contrast medium. *AJNR Am.J Neuroradiol*. 1998; 19(9):1781–1784. [PubMed: 9802505]
- NIH. Research on low back pain and common spinal disorders. NIH Guide. 1997; 26(16)
- Ogata K, Whiteside LA. 1980 Volvo award winner in basic science. Nutritional pathways of the intervertebral disc. An experimental study using hydrogen washout technique. *Spine*. 1981; 6(3):211–216. [PubMed: 7268543]
- Razaq S, Wilkins RJ, Urban JP. The effect of extracellular pH on matrix turnover by cells of the bovine nucleus pulposus. *Eur.Spine J*. 2003; 12:341–349. [PubMed: 12883962]
- Roberts S, Menage J, Eisenstein SM. The cartilage end-plate and intervertebral disc in scoliosis: calcification and other sequelae. *J Orthop Res*. 1993; 11(5):747–757. [PubMed: 8410475]
- Roberts S, Menage J, Urban JP. Biochemical and structural properties of the cartilage end-plate and its relation to the intervertebral disc. *Spine*. 1989; 14(2):166–174. [PubMed: 2922637]
- Selard E, Shirazi-Adl A, Urban J. Finite Element Study of Nutrient Diffusion in the Human Intervertebral Disc. *Spine*. 2003; 28(17):1945–1953. [PubMed: 12973139]
- Setton LA, Zhu W, Weidenbaum M, Ratcliffe A, Mow VC. Compressive properties of the cartilaginous end-plate of the baboon lumbar spine. *J Orthop Res*. 1993; 11(2):228–239. [PubMed: 8483035]
- Shirazi-Adl A, Taheri M, Urban JP. Analysis of cell viability in intervertebral disc: Effect of endplate permeability on cell population. *J Biomech*. 2010; 43(7):1330–1336. [PubMed: 20167323]
- Soukane DM, Shirazi-Adl A, Urban J. Analysis of Nonlinear Coupled Diffusion of Oxygen and Lactic Acid in Intervertebral Discs. *Journal of Biomechanical Engineering*. 2005; 127(7):1121–1126. [PubMed: 16502654]
- Soukane DM, Shirazi-Adl A, Urban JP. Computation of coupled diffusion of oxygen, glucose and lactic acid in an intervertebral disc. *J Biomech*. 2007; 40(12):2645–2654. [PubMed: 17336990]
- Soukane DM, Shirazi-Adl A, Urban JPG. Investigation of solute concentrations in a 3D model of intervertebral disc. *Eur.Spine J*. 2009; 18:254–262.
- Sun DN, Gu WY, Guo XE, Lai WM, Mow VC. A mixed finite element formulation of triphasic mechano-electrochemical theory for charged, hydrated biological soft tissues. *International Journal for Numerical Methods in Engineering*. 1999; 45:1375–1402.
- Urban JP, Holm S, Maroudas A, Nachemson A. Nutrition of the intervertebral disc: Effect of fluid flow on solute transport. *Clin Orthop*. 1982; 170:296–302. [PubMed: 7127960]
- Urban JP, McMullin JF. Swelling pressure of the lumbar intervertebral discs: influence of age, spinal level, composition, and degeneration. *Spine*. 1988; 13(2):179–187. [PubMed: 3406838]

- Urban MR, Fairbank JC, Etherington PJ, Loh FL, Winlove CP, Urban JP. Electrochemical measurement of transport into scoliotic intervertebral discs in vivo using nitrous oxide as a tracer. *Spine*. 2001; 26(8):984–990. [PubMed: 11317125]
- Wang S, Xia Q, Passias P, Wood K, Li G. Measurement of geometric deformation of lumbar intervertebral discs under in-vivo weightbearing condition. *J Biomech*. 2009; 42(6):705–711. [PubMed: 19268946]
- White, AA. Biomechanics of lumbar spine and sacroiliac articulation: relevance to idiopathic low back pain. In: White, AA.; Gordon, SL., editors. *Symposium on Idiopathic Low Back Pain*. CV Mosby Co.; St. Louis: 1981.
- Wuertz K, Urban JPG, Klasen J, Ignatius A, Wilke H-J, Claes L, Neidlinger-Wilke C. Influence of extracellular osmolarity and mechanical stimulation on gene expression of intervertebral disc cells. *J Orthop Res*. 2007; 25:1513–1522. [PubMed: 17568421]
- Yao H, Gu WY. Three-dimensional inhomogeneous triphasic finite-element analysis of physical signals and solute transport in human intervertebral disc under axial compression. *Journal of Biomechanics*. 2007; 40(9):2071–2077. [PubMed: 17125776]
- Yao H, Gu WY. Physical signals and solute transport in human intervertebral disc during compressive stress relaxation: 3D finite element analysis. *Biorheology*. 2006; 43:323–335. [PubMed: 16912405]
- Yao H, Gu WY. Physical signals and solute transport in cartilage under dynamic unconfined compression: finite element analysis. *Annals of Biomed Engng*. 2004; 32:380–390.

Figure 1.

(a) Photograph of L2–L3 IVD used for determining disc geometry; (b) disc geometry; (c) disc mesh of upper right quarter of disc; (d) test configuration.

Figure 2.
Strain configuration on the disc for (a) supine and (b) standing conditions.

Figure 3.

Typical glucose concentrations in the IVD for the six cases investigated: (a) normal CEP, supine; (b) normal CEP, standing; (c) normal CEP, weight-bearing standing; (d) 'calcified' CEP, supine; (e) 'calcified' CEP, standing; and (f) 'calcified' CEP, weight-bearing standing. Note in (b)–(c) and (e)–(f), the deformed shape is shown, while the black outline signifies the original geometry.

Figure 4.

Minimum glucose concentration in the disc for the three loading configurations (supine, standing, and weight-bearing standing) and for normal (blue) and 'calcified' (red) endplate cases. Note the dashed line at 0.5 mM, which denotes the glucose concentration below which cells begin to die (Horner and Urban 2001).

Figure 5. Distribution of glucose in the IVD under three loading conditions (supine, standing, and weight-bearing standing) and for normal (blue) and 'calcified' (red) endplate cases along (a) the x radius ($y = z = 0$) from disc center to periphery and (b) along the y axis at $x = z = 0$ (from posterior to anterior).

Figure 6.
pH distribution in IVD for (a) normal and (b) 'calcified' endplate cases.

Table 1

IVD tissue properties used in the finite element model.

	AF	NP	CEP
ϕ_o^w	0.75 ^a	0.86 ^a	Normal: 0.60 ^b \` Calcified ^c : 0.42
ρ^{cell} (cells/mm ³) ^c	9000	4000	15000
Parameters for diffusivity ^d	A = 1.29	A = 1.25	A = 1.29
	B = 0.372	B = 0.681	B = 0.372
Parameters for hydraulic permeability	a = 0.00044 nm ² ^e	a = 0.00339 nm ² ^f	a = 0.0248 nm ² ^g
	n = 7.193 ^e	n = 3.24 ^f	n = 2.154 ^g
Lamé constants	$\lambda = 0.30 \text{ MPa}^h$	$\lambda = 15.6 \text{ kPa}^i$	$\lambda = 0.10 \text{ MPa}^j$
	$\mu = 0.10 \text{ MPa}^h$	$\mu = 0.18 \text{ kPa}^i$	$\mu = 0.20 \text{ MPa}^j$

^a(Yao and Gu 2007)^b(Roberts et al. 1989) and (Setton et al. 1993)^c(Maroudas et al. 1975)^dValues for porcine AF tissue (AF and CEP) and agarose gels (NP) (Gu et al. 2004)^eValues for porcine AF tissue (AF) (Gu and Yao 2003)^fValues for agarose gels (NP) (Gu et al. 2003)^gFrom (Yao and Gu 2004), curve-fit from Figure 9 of (Maroudas 1975)^h(Iatridis et al. 1999)ⁱCalculated from results in (Iatridis et al. 1997) and (Johannessen and Elliot 2005)^j(Yao and Gu 2004)