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Influence of Osmotic Pressure Changes on the Opening of Existing Cracks in 2 Intervertebral Disc Models

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Study Design. An experimental hydrogel model and a numerical mixture model were used to investigate why the disc herniates while osmotic pressure is decreasing.

Objective. To investigate the influence of decreasing osmotic pressure on the opening of cracks in the disc.

Summary of Background Data. In the degeneration process, the disc changes structure (*i.e.,* cracks occur, and osmotic pressure decreases). Disc herniation typically develops when hydration declines, but, on the other hand, it is said that the anulus of a highly hydrated disc has a high risk of rupture. We hypothesized that disc herniation is preceded by the opening of cracks as a result of decreasing osmotic pressure.

Methods. The osmotic pressure was changed in hydrogel samples with a crack, which was visualized with a confocal laser scanning microscope (Zeiss, Göttingen, Germany). A 2-dimensional finite element mixture model simulated a decrease in osmotic pressure around a crack in a swelling material.

Results. Experiments and simulations show that a decrease in osmotic pressure results in the opening of cracks. The simulations show high effective stress concentrations around the crack tip, while the overall stress level decreases, indicating an increased risk of crack growth.

Conclusions. Decreasing osmotic pressure in a degenerating intervertebral disc enhances the opening of existing cracks, despite the concomitant decrease in anular stresses.

Key words: intervertebral disc, herniated disc, osmotic pressure, crack, finite element analysis, mixture theory, hydrogel. **Spine 2006;31:1783–1788**

Low back pain is the most common cause of disability in individuals between 20 and 50 years of age. Disorders associated with low back pain impose an economic burden similar to that of coronary heart disease and higher than that of other major health problems, such as diabetes, Alzheimer disease, and kidney diseases.[1] It is still largely unknown from what pathologies low back pain occurs, but it is believed that many cases occur from intervertebral disc problems. Two commonly known pathologies are intervertebral disc degeneration and intervertebral disc herniation. Knowledge of the causes and exact underlying processes of disc degeneration and herniation is increasing, thanks to new imaging and modeling techniques, and advances in cell biology and genetics.[1] However, the intervertebral disc seems to be poorly researched, even in comparison with other musculoskeletal systems. Because of the limited knowledge, no adequate treatment exists for low back pain occurring from disc degeneration or herniation.

The intervertebral disc, which is the primary connection between 2 subsequent vertebrae, is a complex tissue consisting of different distinct structures: the gelatinous nucleus pulposus in the center, a fibrous outer ring called anulus fibrosis, and the cartilaginous endplates that connect the disc to the vertebrae. Both the nucleus and the anulus consist of a dense collagen network embedded in a gel-like hydrophilic material, with a high water content of 70% to 80% wt/wt on average and a high internal pressure of 0.1 MPa on average in supine position.[1a] This pressure is caused by the swelling properties of the proteoglycans being resisted by tension in the anulus fibrosus and ligamentum flavum. The fixed charges in the material cause a difference in ion concentration between the material and solution, resulting in a Donnan osmotic pressure gradient. This gradient attracts water into the disc, resulting in a high water content.[2]

The collagen network, especially that of the anulus, prevents the disc from swelling freely, leading to the high internal pressure and tensile osmotic prestressing of the anulus fibers. The lower the amount of fixed charges and the higher the concentration of the external salt solution, the lower the osmotic pressure and the lower the tensile stresses in the solid material.[3] Intervertebral disc tissue has been successfully modeled as a material consisting of a solid matrix with fixed charges, representing the collagen fibers and proteoglycans, together with interstitial fluid with dissolved ions.

The intervertebral disc ages faster than most other tissues because nutrition is hampered in an avascular tissue. During aging, the disc changes its structure and composition.[1,4,5] A major structural change that occurs in the process of degeneration is a decrease in water content and osmotic pressure, mainly in the nucleus and inner anulus,[4,6,7] leading to a loss of prestressing of the collagen network in the whole disc. A possible reason for this decreasing hydration could be the loss of and changes in distribution of proteoglycans and, consequently, fixed charges.[7]

A more localized form of an intervertebral disc pathology is intervertebral disc herniation. Intervertebral disc herniation typically is a problem in individuals 30–50 years of age, which is the period of life in which

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degeneration already has occurred to some extent but in which the remodeling process to withstand the altered stresses probably has not had effect yet. This result implies that the underlying mechanisms of disc herniation and disc degeneration may be linked.

Tears, fissures, or cracks in the anulus are observed in degenerated discs.[4,8,9] Anular tears must play a major role in the damage mechanism of disc herniation. These tears could be a precursor for herniation, followed by extrusion of a fragment of nuclear material through the fissure, as was suggested by others.[10,11] One of the important questions is how such anular tears develop into full grown cracks, eventually leading to disc herniation.

It follows that both decreasing osmotic pressure and anular tears are important factors in disc degeneration. Moreover, disc degeneration likely precedes disc herniation, which indicates that a relation could exist between osmotic pressure or hydration, anular tears, and disc herniation. The influence of hydration on the propensity of a disc to prolapse was investigated before by other investigators.[12–14] These studies suggest that the intervertebral disc has a higher risk of herniation when it is fully hydrated. The outcome of these studies seems contradictory to the clinical facts because it is known that disc herniation usually occurs in intervertebral discs that, considering the age of occurrence, must be degenerated to some extent. Hence, their hydration should be decreasing.

Therefore, the objective of the present study is to elucidate the apparent paradox of, on the one hand, experimental and conceptual evidence that the anulus of a highly hydrated disc is more likely to rupture than a less hydrated disc and, on the other hand, that disc herniation typically develops in a period of life in which the hydration declines. We hypothesize that the opening and propagation of cracks results from decreasing hydration. The influence of decreasing osmotic pressure on the opening behavior of existing cracks is investigated using both an experimental hydrogel model and a numerical 4-component mixture model. The hydrogel model material is preferred above native intervertebral disc tissue because: (1) hydrogel mimics the swelling propensity of the disc,[15,16] while the complicating properties of disc tissue, such as its anisotropy, nonhomogeneity, specimen-to-specimen variability, limiting viability, and proteoglycan leakage are excluded; and (2) of the transparency of the hydrogel.

■ Materials and Methods

Experimental Setup. Experiments are performed on HEMA-sodium methacrylate hydrogel samples. This hydrogel consists of negatively charged polymer chains, water, and free ions. The charged polymer chains mimic the proteoglycan content of disc tissue.[14] Thin, cylindrically shaped hydrogel samples are stored in a NaCl solution of 0.4 M, in which they have a diameter of 14 mm and a thickness of 1.3-mm. A crack 3–6-mm long is generated in the middle of each sample by cutting through its depth with a scalpel knife, after which the sample is colored with the fluorescent dye Procion Red (Zijdelings, Tilburg, The

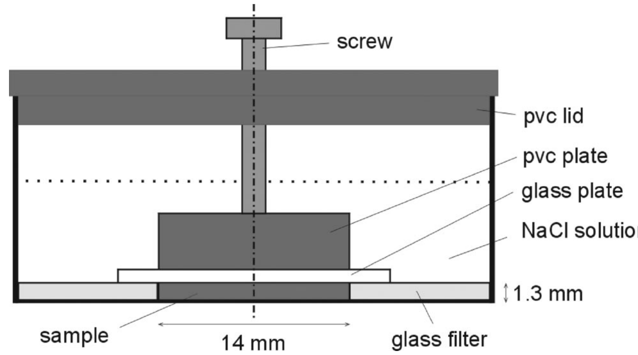

Figure 1. Experimental setup. A cross-section through 1 well indicating the colored sample (ø14 mm), NaCl solution, and system to prevent the sample from swelling: a porous glass filter surrounding the sample, a glass plate and a polyvinyl chloride plate on top and a polyvinyl chloride lid with screw.

Netherlands). There are 6 samples placed in a 6-wells culture plate together with a 0.4-M NaCl salt solution and a system to prevent the sample from changing volume when swelling (Figure 1). The decreasing osmotic pressure in the degenerating intervertebral disc is simulated in the hydrogel samples by increasing the concentration of the external salt solution.

The osmotic pressure in the sample is first brought to a physiologic level in supine position of approximately 0.1 MPa[16] by decreasing the external salt concentration from 0.4 to 0.2 M and finally to 0.15 M. This process is reversed again (*i.e.,* from 0.15 to 0.2 M and back to 0.4 M) to achieve a decrease in osmotic pressure. After each replacement, the samples are left to equilibrate overnight. Trial experiments are performed to test the setup.

The 6-wells plate is placed under a confocal laser scanning microscope (Zeiss, Göttingen, Germany) to visualize the crack. Images of the crack are collected when in equilibrium with an external salt concentration of 0.4 M (t = 0), 0.2 M (t = 1 day), 0.15 M (t = 2 days), 0.2 M (t = 3 days), and 0.4 M (t = 7 days). With these experiments, the opening behavior of the crack in the hydrogel sample as a result of changing osmotic pressure is determined.

Numerical Simulations. The finite deformation of the swelling material around a crack is simulated with a 4-component mixture model.[17] The simulated material consists of 4 different components: (1) a solid matrix with fixed charges, representing either the collagen fibers with the proteoglycans in intervertebral disc tissue or the charged polymer chains in hydrogel; (2) fluid, representing either the interstitial fluid or water; (3) monovalent cations; and (4) anions dissolved in the fluid. The 4 components interact with each other resulting in chemical, mechanical, and electrical forces. The mixture model is implemented in the finite element package SEPRAN,[18] and it is validated for intervertebral disc tissue.[3] As a result of changing external salt concentration, fixed charge density, or loading conditions, the material deforms by swelling or shrinking.

The model material is assumed isotropic and homogeneous to limit the number of material parameters. A hyperelastic, compressible neo-hookean constitutive relation is used. Both the osmotic coefficients of the material and the surrounding solution are considered in the model. The input and material parameters[19,20] of the model are given in Table 1. The deformation, electrical potential, electrochemical potentials, hydrostatic pressure, stresses, and strains throughout the material are calculated.

Table 1. Material Properties of the Model Material*

$R = 8.3145 \cdot 10^{-3}$ kN mm/mmol K	$c_i^{fc} = -2 \cdot 10^{-4}$ mmoleq/mm^3
$F = 96.4853$ c/mmol	$\nu_i^f = 0.8$
$T = 298$ K	$V^+ = 2.33$ mm^3/mmol
$c_{ex}^+ = 1.5 \cdot 10^{-4}$ mmol/mm^3	$V^- = 15.17$ mm^3/mmol
$c_{ex}^- = 1.5 \cdot 10^{-4}$ mmol/mm^3	$r = 0.4$
$H = 1.0 \cdot 10^{-3}$ GPa	$D^+ = 1.334 \cdot 10^{-3}$ mm^2/s
$E = 9.0 \cdot 10^{-4}$ GPa	$D^- = 2.032 \cdot 10^{-3}$ mm^2/s
$\nu = 0.2$	$\Gamma_{ex} = 0.9$
$G = 3.75 \cdot 10^{-4}$ GPa	$\Gamma_{in} = 0.9$
$k = 5.0 \cdot 10^{-4}$ GPa	$K_{11} = 0.28$ mm^4/kNs

*The material parameters are derived from different studies[17,18] and standard books.
D^+ and D^- are the diffusion coefficients in a free solution. "r" is the hindrance factor, accounting for the deceleration of diffusion caused by the presence of a solid. "K_{11}" denotes the permeability of the porous solid in a Darcy experiment. The molar volumes and osmotic coefficients are taken constant throughout the simulation. For simplicity reasons, the external osmotic coefficient (Γ_{ex}) is taken equal to the internal osmotic coefficient (Γ_{in}).

The left half of a rectangular sample of 2 × 0.5 mm with a 1-mm long crack in the center is modeled (Figure 2). The bottom and top are fixed in both directions to model the swelling restraint caused by the anulus fibers in the disc and adjacent vertebral bodies. Both the left side of the sample and the crack are allowed to move freely, while in contact with an external salt solution and free fluid flow is allowed. For symmetry reasons, the right side of the sample is disallowed to move in the horizontal direction, and no fluid flow between the material and exterior is allowed. The crack is assumed to be closed at an external salt concentration of 0.15 M and a fixed charge density of −0.2 moleq/L.

There are 2 types of simulations with a decrease in osmotic pressure performed: (1) the external salt concentration at the left side of the material is increased at the start of the simulation from 0.15 to 0.2 M, which is consistent with the design of the hydrogel experiment; and (2) the fixed charge density is decreased from −0.2 to −0.15 moleq/L, which is consistent with degeneration of the inner anulus of an intervertebral disc.[6] The material is left to equilibrate for 1000 seconds. By performing both types of simulations, the effect of an increase in external salt concentration is compared with the effect of a decrease in fixed charge density.

■ Results

Experiments

The geometry of the crack in the hydrogel samples is visualized at different external salt concentrations (0.4, 0.2, 0.15, 0.2, and 0.4 M) using the confocal laser scanning microscope. The trial experiments showed that the cracks did not change when the osmotic pressure was not changed. Figure 3 shows the results of one of the samples. At the start of the experiments, the external salt concentration is 0.4 M, and the crack is open. The diameter of the crack in Figure 3 is about 0.2 mm, and the length of the crack is 5.8 mm. After equilibrating the sample with a 0.2-M NaCl solution, the crack is almost closed. However, at 0.15 M, the crack is even more closed. After returning to a salt solution of 0.4 M and waiting for several days, the crack opens again to the same extent as in the beginning of the experiment. Images are also taken every hour in the period after changing the salt solution from 0.2 to 0.4 M, showing a steady increase in the diameter of the crack (Figure 4). The 5 other samples had a crack width ranging from 35 to 90 μm at an external concentration of 0.4 M and were also closed at 0.15 M. The experimental results show that a crack closes because of a decrease in external salt concentration and reopens because of an increase in external salt concentration (*i.e.*, a decreasing osmotic pressure).

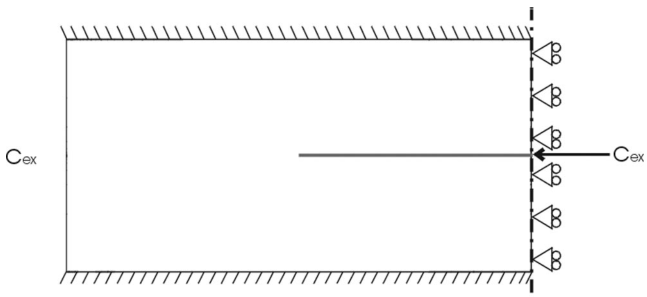

Figure 2. The sample used in the finite element simulations. The left side of the sample and crack are in contact with a salt solution of concentration (c_{ex}). The right side is a symmetry plane. The crack is indicated in red.

Numerical Simulations

Simulations are run with an increase in external salt concentration and a decrease in fixed charge density. Both methods decrease the osmotic pressure. They both result in opening of the crack. In the simulation with an increase in external salt concentration, the crack has opened to a maximum width of 0.75 μm. Decreasing the fixed charge density results in a crack width of 20 μm. Therefore, both an increase in external salt concentration from 0.15 to 0.2 M and a decrease in fixed charge density from −0.2 to −0.15 moleq/L result an in opening of the crack. The decrease in fixed charge density has a larger effect on the crack than the increase in external salt concentration.

A decrease in fixed charge density transforms the initial uniform effective stress distribution into a distribution with a high concentration of effective stress around the crack tip (Figure 5). The average effective stress level in the material decreases from $\sigma_{11}^e = \sigma_{22}^e = 0.136$ MPa in the state with high-fixed charge density to ±0.1 MPa in the state with low-fixed charge density. The stresses around the crack tip are more than 3 times as high as in the rest of the material. The simulations with increase in external salt concentration show similar results.

The largest strains are found in the simulations with a decrease in fixed charge density. These strain values show that the model is able to describe relatively large deformations, with strains up to 0.37. In both simulations, the initial strain was 0.11.

■ Discussion

Both an experimental hydrogel model and a numerical 4-component mixture model show that a decrease in osmotic pressure results in the opening of an existing crack in swelling materials. The simulations further show that this conclusion holds regardless of the method of achiev-

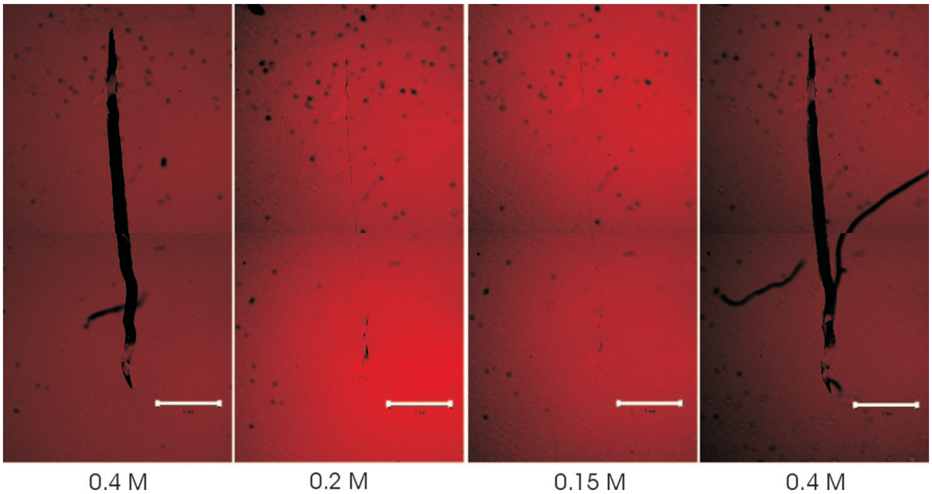

Figure 3. Confocal laser scanning microscope photographs of the crack in a hydrogel sample at different external salt concentrations: 0.4, 0.2, 0.15, and 0.4 M. The white lines each represent 1 mm. The length of the crack is 5.8 mm, and the width at 0.4 M is approximately 0.2 mm.

ing the decrease in osmotic pressure (*i.e.*, by a decrease in fixed charge density or increase in external salt concentration). Around the crack tip in the simulations, a high peak of effective stress is observed, while the overall effective stress has decreased significantly.

Translating this to the intervertebral disc, these findings imply that the decreasing proteoglycan content that is associated with degeneration results in decreased osmotic pressure and decreased overall levels of fiber prestressing, while through the very same mechanism, the crack tips in the disc are exposed to increased stress concentrations. We hypothesize that the vulnerability of the degenerating disc to herniation is caused by these local stress concentrations because it contributes to the increased risk of propagation of the cracks and, therefore, herniation (Figure 6). The importance of localized stresses in the development of intervertebral disc herniation is confirmed by other studies,[21–24] and the fact that it appeared difficult to produce experimentally a disc prolapse in the past[25–27] may substantiate our hypothesis. In addition, the opening of cracks increases the risk of fragments of nucleus material extruding through the crack, which may contribute to further opening of the cracks.[10,11] Therefore, this study proposes a new paradigm in the understanding of disc herniation: increased stress concentration around crack tips in a surrounding of decreased anular stresses.

The experiments and simulations were performed without the presence of external forces. Therefore, the proposed hypothesis implies that cracks open and stress concentrations occur without explicit contribution from external mechanical load. This result is comparable to an aging oak beam that develops cracks because of loss of turgor, even if it remains unloaded. Furthermore, this finding is consistent with the clinical observation that disc degeneration is poorly correlated with mechanical load.[28]

The positive correlation between stress and hydration as found in this study confirms the experimental findings of Simunic *et al*,[13,14] that the disc is at highest risk for disruption in the fully hydrated state (*i.e.*, in the state of maximal osmotic pressure). However, the involvement of decreasing osmotic pressure in disc herniation seems contradictory to their findings. The difference in results could suggest that the process of initiation of disc herniation, as is investigated by Simunic *et al*,[13,14] is different from the process of growing of cracks, as is investigated

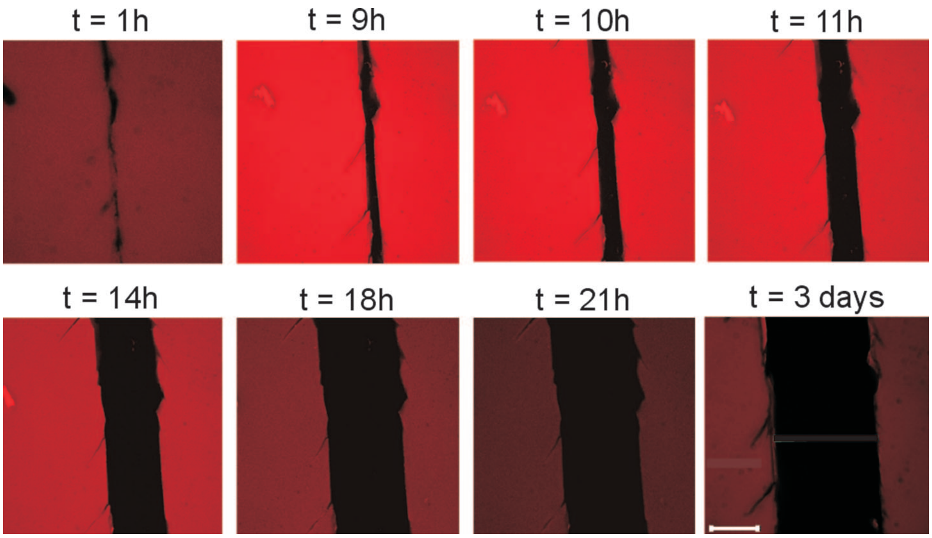

Figure 4. Confocal laser scanning microscope photographs of the crack in a hydrogel sample in the period after changing the salt solution from 0.2 to 0.4 M. The white line represents 0.1 mm. The moment of changing the salt solution is defined as t = 0. The photographs are taken at t = 1 hour, t = 9 hours, t = 10 hours, t = 11 hours, t = 14 hours, t = 16 hours, t = 18, t = 21 hours, and t = 3 days.

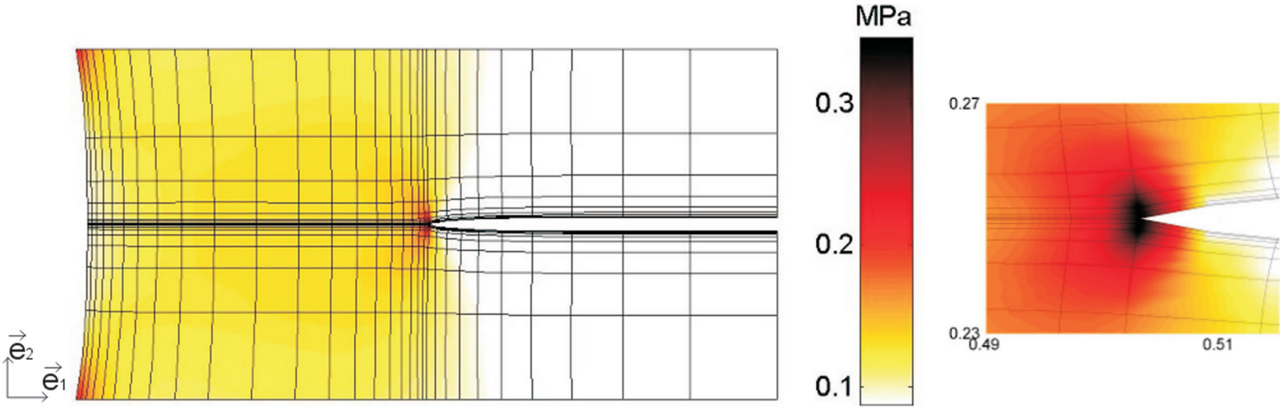

Figure 5. Simulated normal effective stress distribution (σ_{22}^{e}, in MPa) after a decrease in fixed charge density in the full sample as well as zoomed in at the crack tip. The color bar belongs to both figures. The effective stress at the start of the simulation was $\sigma_{22}^{e} = 0.136$ MPa.

in the present study. Lu *et al*[12] also concluded that disc prolapse is more likely to occur if the disc is fully hydrated. They found with their simulations that higher hydration gives higher tensile stresses in the fibers, which agrees well with the findings of the present study.

The lower average effective stress found in the present study seems contradictory to the numerical findings of Iatridis *et al*,[7] who report an increase in matrix stresses and strains with changes in fixed charge density from a healthy to a degenerate distribution. However, the increase in matrix stresses in their study is an increase in compressive axial stresses in the nucleus, whereas in the present study, the tensile effective stresses that balance the hydrostatic pressure are considered.

The conclusions in this study are based on results from models. One could question whether the models are suitable to investigate the physiologic problem of disc herniation. Hydrogel is chosen because of its resemblance with disc tissue,[15,16] while it excludes the complicating factors of disc tissue. The 4-component mixture model[17,18] is preferred above other computational models[7,29–36] because it describes the full mechano-electrochemical behavior of swelling materials in time, including the electrical potential, for finite deformations. Furthermore, this model was verified to describe the 1-dimensional behavior of dog intervertebral disc tissue reasonably well.[2] We realize that the symmetry assumption applied in the simulated sample might not be justified and may have given limitations. However, it has not affected the results significantly.

In the experimental as well as the numerical model, no fibers are considered, which is justified by the fact that we solely wanted to look at the influence of osmotic pressure on the opening of a crack, without having to consider other influences. Of course, fibers could largely influence the orientational behavior of a crack. In addition, the presence of external loads and, therefore, higher internal pressures in the disc would influence the orientational behavior of the crack. Depending on the direction of the crack, this will either help opening or prevent opening of the crack.

The sensitivity of the opening behavior of cracks to osmotic pressure is qualitatively well understood in the context of the Starling law, one of the key ingredients of

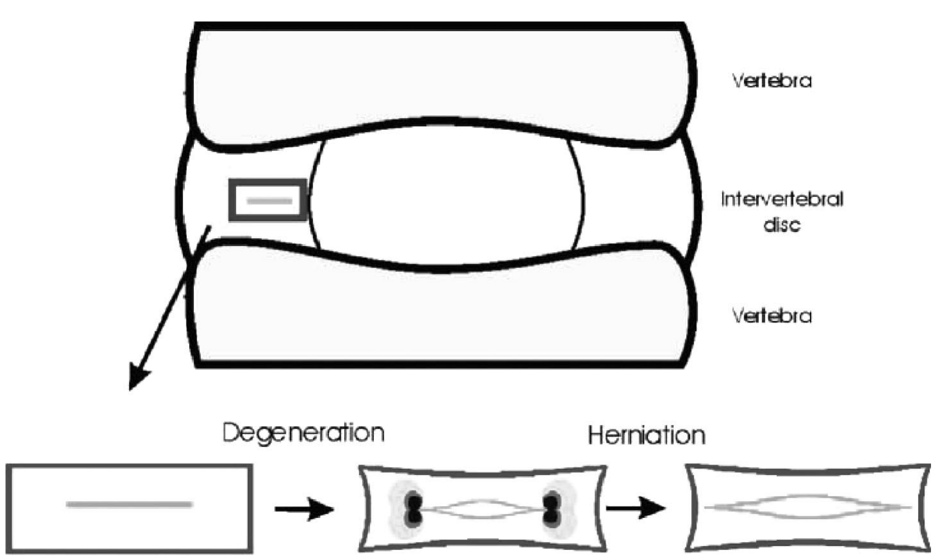

Figure 6. A degenerating disc is vulnerable to herniation because, as a result of decreasing fixed charge density and, therefore, decreasing osmotic pressure, closed cracks open and stress concentrations occur at the crack tips. The stress concentrations contribute to an increased risk of propagation of the cracks and, therefore, intervertebral disc herniation.

the mechano-electrochemical model discussed previously. This law states that the driving force of fluid flow from the crack to the medium is governed by the gradient of the chemical potential of the water. The chemical potential is the hydrostatic pressure minus the osmotic pressure. At constant osmotic pressure, fluid flows from high hydrostatic pressure to low hydrostatic pressure. At constant hydrostatic pressure, fluid flows from low osmotic pressure to high osmotic pressure. A crack in a healthy young disc is surrounded by high osmotic pressure tissue, causing the fluid to leave the crack and the crack to close. Degeneration of the tissue causes the osmotic pressure of the tissue to decrease, leading the fluid into the crack. Therefore, the crack opens.

■ Key Points

- The intervertebral disc typically herniates in a period of life in which osmotic pressure decreases. However, literature shows that the disc is at highest risk for rupture in the fully hydrated state.
- Existing cracks in swelling materials open as a result of decreasing osmotic pressure.
- Degeneration leads to decreased overall levels of fiber prestressing and increased stress concentrations at crack tips.
- Local stress concentrations at crack tips contribute to an increased risk of crack propagation and, therefore, herniation.

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