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Biomechanics of Intervertebral Disc Degeneration

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Introduction

The intervertebral disc has a composite structure consisting of a gelatinous proteoglycan-rich nucleus pulposus surrounded by a collagen-rich anulus fibrosus. The proteoglycan in the nucleus pulposus provides high water content within the nucleus pulposus, and in turn, contributes to sustain large loads applied to the vertebral body. The load is distributed evenly to the anulus fibrosus through hydrostatic pressure. The fiber orientation of the anulus fibrosus is suitable to resist hoop stresses generated by the hydrostatic pressure in the healthy conditions **(see article by Grunhagen *et al*)**.

Degenerative changes in the biomechanical properties can occur in the nucleus pulposus and anulus fibrosus tissues individually. These can be shown as changes in material properties of each tissue. Degenerative changes in structural properties may be represented as consequences of these changes in material properties of the substructure of the disc. However, degenerative structural changes in the disc, such as loss of the volume of the nucleus pulposus and fissures in anulus fibrosus, can only be evaluated by analysis of structural parameters. It is important to understand how these changes affect the function of the motion segment and relate to symptoms such as low back pain (LBP) **(see article by Karppinen *et al*)**.

In this review, we will address on the degenerative changes in the material properties of nucleus pulposus and anulus fibrosus followed by the changes in structural properties of the entire disc, with an emphasis on the degenerative changes in viscoelastic properties of the whole disc. Instability of the motion segment as a consequence of the structural failure associated with the degenerative changes on the disc will be followed. Finally, instability of

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the lumbar spine, which has been considered as one of the significant causes for mechanical LBP will be reviewed.

Material Properties of the Degenerative Intervertebral Disc Components

Nucleus Pulposus

The disc degeneration process affects several of the structures differently and apparently at different times during its progression. It is important to bear in mind the impaired synthesis of the disc matrix when describing this sequence of events, as it involves all of its components at different time points.[1–4] The process is thought to start in the nucleus pulposus, exhibiting a decrease in its proteoglycan concentration[3,5–9] and gradual change in collagen type that transitions into a more fibrotic tissue.[10] These factors effectively dehydrate the nucleus pulposus down from a peak nucleus water content in the adult disc, of approximately 70 to 80%.[11] Recently, Murakami *et al* [12] quantified the difference in water content between old (3 years) and young (6 months) anulus fibrosus and nucleus pulposus tissue of rabbits, showing significant differences among them. Additionally, the nucleus pulposus GAG, DNA, aggrecan and collagen types I and II contents were significantly larger in the younger tissue. Evidence like this shows that the nucleus tissue is the most affected. Its decay constitutes perhaps one of the largest enablers of furthering disc degeneration. This transition into a more fibrotic type of tissue produces a stiffer nucleus pulposus and the ‘shock-absorbing’ properties of the disc are severely limited.

The nucleus pulposus, usually referred to as fluid,[13–17] loses its hydrostatic pressure feature.[1,18–23] A more fibrotic (increased collagen in nucleus pulposus)[10,24] tissue will not behave in the same manner as a fluid/gel nucleus pulposus. The nucleus pulposus tissue undergoes a process of stiffening by means of gradual loss of proteoglycans and change of collagens from Type II to Type I,[3,24] becoming a more fibrous and solid tissue,[25,26] which was found to amalgamate into one solid phase with the anulus fibrosus in 75% of the cases from the 6th to 8th decade in a cadaveric study by Haefeli *et al*.[10] The loss of proteoglycans originates the decrease of swelling pressure in the nucleus pulposus[27], identified as the main load-bearing mechanism in the non-degenerate nucleus pulposus.[28] As a consequence, load mechanics are altered and for a period, during the initial phase of degeneration, the disc is unstable.

Anulus Fibrosus

The mechanical behavior of the anulus fibrosus has been well documented in terms of tensile and compressive tests, but not so much in shear. Tensile behavior corresponds to the circumferential direction on the annular wall and was characterized in static and dynamic tests in order to explain its mechanism to resist hoop stresses produced by the nucleus pulposus hydrostatic pressure[29]. These two loading conditions are commonly accepted to simulate the body weight borne by the spinal column (compression) and the additional stresses seen in outward lateral bending and flexion/extension (tension). The largest strengths are usually seen when loading the lamellae in the direction of the reinforcing fibers. The arrangement of the elastic fibers plays a very important role in the overall mechanical properties of the anulus fibrosus.[30,31] Elastic anisotropy in the anulus[32] is maintained with degeneration, with posterolateral and outer lamellae regions having decreases of about 30–50% with advancing degeneration.[33–36]

However, in cases like spondylolisthesis, anterior-posterior shear seems to be the dominant failure mode and this has not been studied, as well as shear within the anulus lamellae in cases of annular failure leading to herniation. In the degenerate anulus fibrosus, the fiber patterns become disorganized, and the elastic response also varies consequently.[37,38] The elastic properties in an intact model are anisotropic and highly nonlinear[39,40]. This non-linearity, exhibited by a 'toe-region' on the stress-strain curves is common to cartilaginous tissues[41–46]. Moreover, the response of degenerate anulus fibrosus tissue has been shown to be of a two-fold increase in the toe-region modulus in tensile testing, which was correlated with age, as well as fiber realignment towards the loading direction.[47,48] Dynamic viscoelastic testing has shown that the dynamic modulus of anulus fibrosus increases with degeneration at tensile strains greater than 6%.[49] Earlier quasi-static test results from Acaroglu *et al* [33,35] described a strong influence of degeneration on elastic properties such as the Poisson's ratio, failure stress, and strain energy density of the anulus fibrosus. The work by Guerin *et al* [47] reports no other significant changes in the elastic properties of the anulus fibrosus tissue.

In addition to elastic anisotropy, permeability also has been shown to vary spatially and is influenced by age, degeneration and water content in the disc.[50] These values have been incorporated to a finite element model simulation by Natarajan *et al* [51] and they showed their effect on disc height and annular failure.

Degenerative Changes in Structural Properties of the Motion Segment

The function of the motion segment is to provide the spine with axial stability while allowing mobility.[52] The intervertebral disc is responsible for carrying enormous amounts of compressive loading while maintaining flexibility.[53] The load on the disc is mainly compressive, but it is also subjected to other types of loads such as tensile and shear stresses.[26,54] As the compressive load is subjected to the disc, hydrostatic pressure develops within the inner core of gelatinous nucleus pulposus, which pushes outward causing the outer ring of fibrous anulus fibrosus to bulge and experience tensile stress in the fibers.[55] Loads on the lumbar disc (L3/4) of volunteers performing different body postures[19,56,57] as well as disc pressures[58] have been measured *in vivo*. These studies revealed that the load on the L3/4 level disc in a sitting position and in a standing position with 20 degrees of flexion was 250% of the total body weight, although the portion of the body above the L3/4 level represented only 60%. Such large loads have been validated with mathematical models.[59,60] This suggests that the load on the lumbar disc is composed of external and internal inputs.[54] The external load is the weight of the body above the lumbar disc, and the internal load is the muscle force required to stabilize the spine under different postures. Increases in disc pressure should also be expected when a fluid is injected, as Andersson and Schultz[61] have shown, when they inquired about the effects of injecting saline in a disc, and found varied responses in cases where the injected fluid was retained, notably the large increases in pressure (up to 83%). On the other hand, a decrease in pressure was observed in the degenerated disc.[16]

A number of animal models have been established to investigate degenerative changes in structural properties of the lumbar motion segment. A commonly used mechanical damage method to cause disc degeneration is the needle puncture or stab wound. Several researchers have recently arrived at the same conclusions when reporting that the diameter of the wound has to be large enough to create degeneration.[62–64] Korecki *et al* [65,66] have shown that in an *in vitro* cyclic testing setting, bovine discs showed immediate and progressive differences in the dynamic modulus and stiffness of the anulus fibrosus tissue after puncture. Aside from the lamellar disturbances, cell viability and matrix remodeling were observed. Another animal model (ovine) of disc degeneration from induced lesions has also shown regeneration in the mid anulus fibrosus wall.[67] In a different loading condition, a murine tail model has shown also differences in the anulus fibrosus tissue as a consequence of dynamic compression, but did not achieve degenerate disc quality after long cycles of compression.[68] In all, these reports suggest that puncture injuries lead to degenerative remodeling including granulation tissue, which current image-based diagnostics methods might not be able to distinguish.[69]

MacLean *et al* [70] investigated static viscoelastic behaviors of rat caudal motion segments, vertebrae and isolated disc explants under different permeability conditions and demonstrated that differences in endplate permeability conditions had a significant effect on the viscoelastic behaviors. Johannessen *et al* [71] demonstrated a decrease in stress-relaxation after ten thousand cycles of compressive loading in adult sheep lumbar motion segments and recovery of the stress-relaxation after 18 hours of unloading in PBS solution, suggesting intervertebral disc fluid transport during loading and unloading.

Boxberger *et al* [72,73] used a degenerative disc model in rat by injection of Chondroitinase-ABC to the discs. In this model, nucleus pulposus degeneration has been successfully induced through with GAG loss as a consequence of Chondroitinase-ABC injection to the discs, which were tested in a linear viscoelastic tension/compression regime afterwards. Results showed that the dynamic stiffness was decreased at low loads. Nucleus pulposus GAG content was shown to be related to the neutral zone properties in the tension-compression cyclic tests. However, the tension and compression extremes of the load displacement curve were not. This shows that a degenerate nucleus produces hypermobility in addition to low pressures. Such distortion in load sharing leads to the development of hoop stresses in the anulus that resist compressive loads.[72,73]

Kim *et al* [74–76] used a rabbit degenerative disc model by 18-gauge needle puncture of the disc to investigate changes in dynamic viscoelastic properties of the whole disc associated with the disc degeneration. In this model, the proteoglycan content decreased and collagen content increased 4 weeks after puncture. The dynamic viscoelastic test showed a decrease in elastic and viscous properties in the punctured disc (Figure 1). The correlation study showed that the proteoglycan content positively correlated with the elastic and viscous mechanical properties and height of the disc; however, there was no correlation with the collagen content. These results suggest that the proteoglycan is a governing factor for viscoelastic properties and structural properties of the disc.

Using the same rabbit degenerative disc model and the dynamic viscoelastic testing method, Miyamoto *et al* [77] investigated effects of OP-1 injection in the lumbar disc on biomechanical and biochemical restoration of the disc. In this study, a significant increase in wet weight and proteoglycan content was observed in both nucleus pulposus and anulus fibrosus tissues of the OP-1-injected discs, compared with the lactose injected control discs, whereas an increase in collagen content was observed only in the nucleus pulposus. These results suggested that an increased proteoglycan content, induced by the injection of OP-1, resulted in tissue hydration in both the nucleus pulposus and anulus fibrosus. The results of the dynamic viscoelastic test showed that the elastic modulus has a significant positive correlation with the proteoglycan content in the nucleus pulposus and the proteoglycan and collagen content in the anulus fibrosus. Similarly, the viscous modulus was shown to have a significant positive correlation with the proteoglycan content in the nucleus pulposus and the proteoglycan and collagen content in the anulus fibrosus.

Instability of the Motion Segment Associated with Intervertebral Disc Degeneration

As disc degeneration progresses, structural failure of the disc is manifested by tears and clefts in the anulus fibrosus. These material disruptions occur in different directions and are the result of a variety of influencing factors, including altered loading of the disc. Potential relationships between osteophytes and peripheral tears were first reported by Schmorl and

Junghanns,[78] and also highlighted the fact that because of the tears, segmental instability would be affected. Farfan [79] and Kirkaldy-Willis [80] concluded that tears were by-products of torsional stresses, implicating them as initiators of the failure of other disc components in the disc degeneration cascade.

Disc fissures have been classified in three categories, depending on their morphology and anatomical position in the disc: a) peripheral tears or rim lesions, parallel to the endplates and exhibiting normally separation of the disc from the subchondral bone of the vertebral body, which with time developed b) circumferential tears that present evidence of delamination as a failure mode. Finally, c) radial tears, as it name implies, propagate in a direction perpendicular to an imaginary axis of the disc (if it is considered as a flat cylinder), which usually lead to disc herniations and expulsion of nucleus material. The literature shows few reports that address the crack propagation phenomena involved in disc tears, as it is common to report only the resulting condition (ruptured anulus, herniated disc).[38,81,82] Many of the models consider the anulus as a bulk material, but recently, more advanced models have incorporated annular layers[83] and implemented permeability and porosity[84–87], as well as the disc's osmo-viscoelastic properties.[88,89] The interlamellar structures have been deemed especially sensitive to shear stresses,[25,90,91] and the literature is lacking reports of their allegedly weaker mechanical properties. They are thought to play a predominant role when destructive processes such as delamination occur as part of herniation, as it has been attempted in analytical models of the disc[92], of anulus fibrosus tissue[93] and of individual lamellae.[94] Schollum *et al* [67,95] have been one of the few who recently analyzed in detail the interface between annular lamellae in an ovine model by subjecting thin slices of immature and mature anulus fibrosus tissue to micro-tensile tests. While their studies was mostly attempting to describe the architecture of the interlamellar interface, important differences in the response to tensile forces were shown between young and old tissue, with the older tissue exhibiting a more ordered and uniform lamellar separation than the young tissue; however the authors did not report elastic properties.

Fujiwara *et al* [7,96] studied the effect of disc degeneration graded by MRI on the segmental motion of the lumbar spine using a total of 106 motion segments obtained from 44 cadaveric lumbar spines taken from 18 females and 25 males with a mean age of 69 years. The investigators found that segmental motion increased with increasing severity of disc degeneration to grade 4 but decreased when the disc degeneration advanced up to grade 5. Such segmental motion changes were much greater in axial rotation when compared with those in lateral bending, flexion and extension, demonstrating the importance of torsional instability in diagnosing spinal instability. The results of these studies are important for understanding the kinematic property changes in relation to the types or grades of disc degeneration. The results were consistent with the previous reports and the concept of three stages of spinal degeneration: dysfunction, instability and restabilization proposed by Kirkaldy-Willis and Farfan.[97]

Instability of the Lumbar Spine Associated with Intervertebral Disc Degeneration

Segmental instability of the lumbar spine is frequently considered a cause of LBP, but instability of the spine is poorly defined and understood.[97–105] The basic concept of spinal instability is that excessive motion beyond normal constraints causes either compression or stretching of the neural elements or causes abnormal deformations of ligaments, joint capsules, annular fibers, or endplates, which are known to have a significant number of nociceptors. Even though several studies have indicated that excessive motion on flexion/extension radiographs is associated with LBP or degenerative disc disease,[106,107] other studies cite decreased motion in patients with degenerative changes and such pain.[108,109]

Lumbar segmental instability may be associated with a spectrum of clinical manifestations of degenerative changes in the intervertebral disc.[97,110–114] Intervertebral disc degeneration has been studied using MR imaging, and grades of degeneration have been reported.[111–118] The relationship between the types (or grades) of disc degeneration and kinematic characteristics of the motion segment has been studied using cadaveric spinal motion segments.[96,119–123] Despite some variation in results, likely because different loading conditions and methods of grading degenerative disc changes were used, the overall results of these studies indicate that the biomechanical characteristics of the motion segment can become altered significantly when degenerative changes develop in the intervertebral disc.

In vivo measurement of lumbar segmental movement

There have been numerous *in vivo* studies on segmental instability of the lumbar spine in which dynamic flexion/extension radiographs were used.[108,124–133] However, these dynamic radiographic techniques have been found to be inaccurate.[134,135] The errors associated with sagittal plane translational motion measurement reported in the literature range from 1 to 4 mm[134,136] or 3% to 15% of the vertebral depth.[137–139] Schaffer *et al* [135] reported surprisingly high false-positive and false-negative rates (i.e., normal translations are categorized outside of the normal range and vice versa) with significant differences between measurement methods despite very high reliability across radiographic quality, raters, and measurement. More sophisticated techniques such as biplanar stereoradiography,[140–145] centrode pattern analysis,[100,137,146–156] and traction-compression radiography,[138,157] have been introduced but have not been widely accepted. More accurate methods involve invasive techniques by inserting metal beads or spinous process wire to determine three-dimension (3-D) motion.[158–160] However, because these methods are invasive, they are not appropriate for routine use in clinical practice as well as for *in vivo* human studies. Studies on segmental instability also have been limited by other factors in addition to these problems associated with accurate measurement of segmental motion *in vivo*. For example, the range of motion measured in most of these studies is affected by the variability in voluntary efforts that the subject applies at the time of examination and also can be limited because of pain.

Other 2-D imaging methods for measuring axial rotation, as opposed to flexion/extension, have involved MR imaging of subjects in various rotated positions.[161,162] While these studies were non-invasive and controlled for voluntary motions, they could only determine changes in segmental motion around one axis. It has been suggested that coupled motions could play an important role in determining spinal instability. To measure these coupled motions, studies have been conducted to measure 3-D motions *in vivo*. More invasive techniques involve inserting wires into the spinous process of subjects to determine 3-D motion.[163] While this method has proven more accurate than radiographs, its invasive nature limits its wide spread clinical use. Other studies have used biplanar radiography, where the radiograms of the spine were taken from two directions simultaneously and 3-D motions are calculated by the positions of anatomical landmarks in corresponding images.[142,164–167] There has been some concern about the accuracy in determining anatomical landmarks for biplanar radiography, as well as a lack of equipment for this method in typical clinical settings.

To overcome some of these limitations to 3-D motion measurement, Lim *et al* [168] developed a 3-D imaging technique using dynamic computed tomography (CT) to determine 6 degree-of-freedom (3 rotations and 3 translations) transformation of individual cadaveric cervical vertebrae during motion by tracking eigenvectors of the individual vertebrae. The authors illustrated that accurate measurements (±1 mm and ±1°) can be made using CT *in vitro*. The research group expanded on this technique to measure vertebral segmental movements in human lumbar spines *in vivo* (Figure 2). Although this method was able to determine the rotations and translations of the lumbar vertebrae during motion *in vivo*, it was limited in determining transformation of the sacrum because an entire 3-D CT model of a sacrum is difficult to obtain clinically and the eigenvector analysis using a partial sacrum 3-D model caused an error of the measurement of the segmental motion at L5-S1. The same research group developed another method to determine transformation of individual vertebrae including the sacrum during motion using the 3-D CT model and a Volume-Merge method (Figure 3).[169,170] This method can determine the rotations and translations during motion even if the 3-D geometry of the bone is incomplete, as in the case of the sacrum (an assumption of the bone as a rigid body still holds) at each position. Thus, it is able to determine the transformation of the incomplete sacrum 3-D CT model with an accuracy of less than 0.1 mm in translation and 0.2° in rotation.

Relationship between instability and disc degeneration

Most patients with segmental instability have disc degeneration, but the relationship between instability and degeneration is not clear. Takeuchi *et al* [171] presented a study using MR images in which T1 relaxation time was decreased in degenerative discs and the energy dissipated to axial loading was linearly correlated with T1 relaxation time. The authors attempted to correlate the intrinsic biomechanical properties of the disc with MR imaging findings, but no information could be derived about the segmental motion characteristics from this study. Toyone *et al* [172] reported that bone marrow adjacent to the disc in patients with symptomatic lumbar segmental instability, defined by flexion more than 5° and dynamic anterior-posterior translation more than 3 mm, had decreased signals on T1 weighted spin-echo MR images or Modic type I changes. Inaccurate flexion/extension radiographs of patients were used in this study by Toyone *et al* [172] and pathogenesis of the osseous changes with disc degeneration is not known.

Results of the *in vitro* studies of segmental motion characteristics and disc degeneration done by Fujiwara *et al* [96] demonstrated that torsional motion was most significantly affected by the degenerative changes in disc and facet joints. In addition, some investigators advocate the importance of torsional loads and stability on the injuries and degeneration of the motion segments.[173–178] Torsional instability in relation to the degenerative changes in the disc had been investigated *in vivo* using the aforementioned *in vivo* 3-D measurement technique.[168] The investigators found that a relationship exists between the severity of IVD degeneration and increases in the torsional movement *in vivo*, which was previously demonstrated only in the cadaveric studies.[169,170]

Summary

A decrease in proteoglycan content and an increased collagen fiber associated with degeneration contribute changes in material properties of nucleus pulposus from a fluid-like material to a solid-like material. Changes in material properties of the anulus fibrosus tissue are also affected by water content, which is a direct consequence of proteoglycan content. Degenerative structural changes of the entire disc are well documented as are the changes in its viscoelastic properties. Decrease in proteoglycan content in the nucleus pulposus is also considered as a governing factor affecting the dynamic viscoelastic properties of the entire disc. The highest correlation between the instability and the severity of the disc degeneration in torsion, among different loading directions, indicates that the fissures in the anulus fibrosus contribute the instability. This result agrees with the concept of “degenerative cascade” proposed by Kirkaldy-Willis. Increased segmental movement with disc degeneration up to grade 4 has also been measured *in vivo*. Further investigation will still be needed to confirm whether LBP is associated with increased segmental motion. To this end, current progress made on image analysis techniques using clinical imaging modalities will be a powerful tool to investigate this challenging problem.

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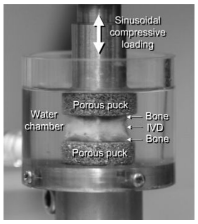

Figure 1.

Experimental test chamber for an unconfined dynamic compression experiment to record viscoelastic properties of a rabbit disc. The bone-disc-bone complex was secured between two porous pucks that prevented friction of the endplates with respect to these structures. Discs can be altered chemically to promote and recover from degeneration. Their dynamic viscoelastic properties can be assessed in this way.

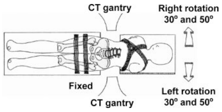

Figure 2.
Schematic of a subject’s positioning inside a CT gantry to study torso rotation. Straps hold subject onto a torso rotation apparatus and CT records evidence of coupled motion during torsion. Segmental movements are level dependent and a pattern of the segmental movement is different between healthy subjects and subjects with low back pain.

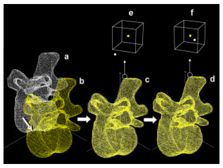

Figure 3.
Description of the Volume Merge method for analysis of segmental movement. A vertebral body in the neutral position (a) was virtually rotated and translated toward the rotated position (b). The position was refined with 0.05° and 0.05 mm increments, respectively, until the maximized volume merging was determined (d). A voxel with a dimension of 1.0×1.0×1.0 mm was created for each point of the stationary target. The number of points of the moving vertebra (white dots) that fell within the voxel of the stationary target (yellow dots) was determined and the percentage of volume merge was defined: e) no volume merge, f) volume merge achieved within the voxel region of interest.