# ASSOCIATION OF IMPAIRED BLOOD SUPPLY WITH PAINFUL LUMBAR DISC DEGENERATION

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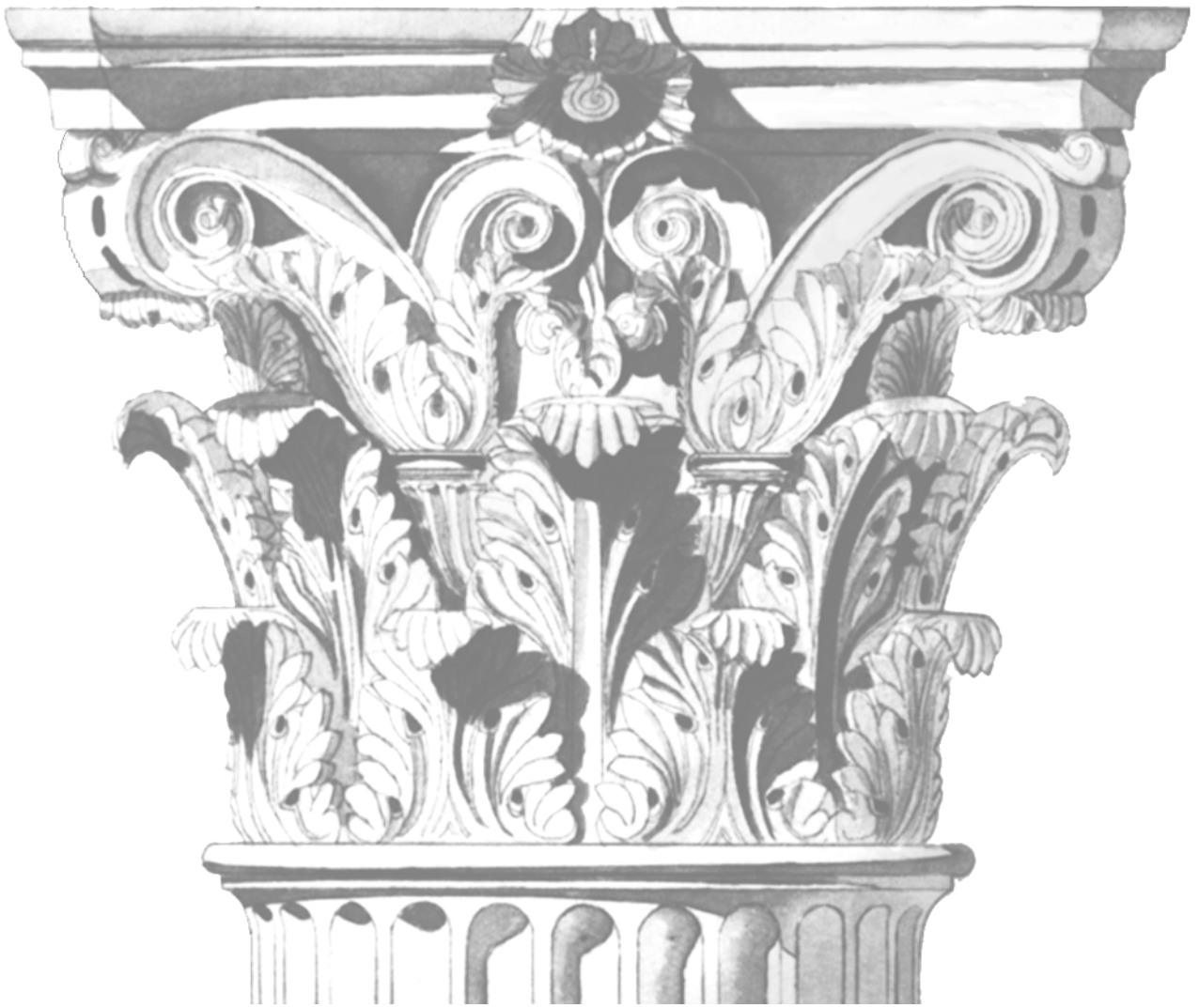

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Academic Dissertation to be presented with the assent of the Faculty of Medicine, University of Oulu, for public discussion in the Auditorium 7 of the University Hospital of Oulu, on May 23rd, 2003, at 12 noon.

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***Abstract***

The purpose of this study was to evaluate the role of diminished arterial blood flow in painful disc degeneration.

Diffusion in intervertebral discs of 37 asymptomatic adults measured by magnetic resonance imaging (MRI) and their lumbar arterial blood supply measured by magnetic resonance angiography (MRA) correlated significantly.

End plate degeneration in intervertebral discs evaluated with MRI was analysed with reference to disc distress evaluated with computed tomography (CT) discography, and a significant correlation between end plate degeneration and disc degeneration was found among 36 low back pain patients. Intradiscal pain caused by discography did not correlate with end plate degeneration.

There were significantly more atheromatous plaques in the abdominal aorta among 29 chronic low back pain patients compared to 52 asymptomatic people, especially in the age group under 50 years.

Occlusion of lumbar arteries in MRA correlated significantly with disc degeneration in MRI among 113 sciatica patients. Furthermore, the disc degeneration and the occlusion of lumbar arteries were severe among 41 sciatica patients and 41 asymptomatic people.

During a three-year follow-up, the occlusion of lumbar arteries in MRA correlated significantly with physical and mental ability measured by a self-efficacy questionnaire at every assessment point (1,2,3 years). Furthermore, the intensity of back pain at 1 year and leg pain at 2 years correlated with the occlusion of lumbar arteries. Re-stenosis of lumbar arteries within 3 years correlated significantly with medical consultations for low back pain, prolonged low back pain and prolonged sciatica during one year before the baseline assessment.

*Keywords:* diffusion-weighted MRI, disc degeneration, discography, intervertebral disc, low back pain, magnetic resonance angiography, magnetic resonance imaging, sciatica

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Oulu, May, 2003 Mauno Kurunlahti

# Abbreviations

| | |
|---|---|
| ADC | apparent diffusion coefficient |
| AF | annulus fibrosus |
| CNR | contrast-to-noise ratio |
| CSF | cerebrospinal fluid |
| CT | computed tomography |
| DDD | Dallas discogram description |
| DART | data-adaptive ray tracing |
| DWI | diffusion-weighted magnetic resonance imaging |
| EP | end plate |
| EPI | echo-planar imaging |
| FOV | field of view |
| FS | fast-spin echo |
| GE | gradient echo |
| HIZ | high-intensity zone |
| IDET | intradiscal electrothermal annuloplasty |
| IVIM | intravoxel incoherent motion |
| L | lumbar disc level |
| LBP | low back pain |
| MIP | maximum intensity projection |
| MR | magnetic resonance |
| MRI | magnetic resonance imaging |
| MRA | magnetic resonance angiography |
| MT | magnetisation transfer |
| NMR | nuclear magnetic resonance |
| NP | nucleus pulposus |
| PC | phase contrast |
| PG | proteoglycan |
| RF | radiofrequency |
| ROI | region-of-interest |
| SE | spin echo |
| SNR | signal-to-noise ratio |

| | |
|---|---|
| T | tesla |
| T1 | longitudinal relaxation time |
| T2 | transverse relaxation time |
| TE | echo time |
| TR | repetition time |
| TOF | time-of-flight |
| US | ultrasound |
| 2D | two-dimensional |
| 3D | three-dimensional |

# List of original publications

This thesis is based on the following articles, which are referred to in the text by their Roman numerals:

I Kurunlahti M, Kerttula LI, Jauhiainen J, Karppinen J, Tervonen O (2001): Correlation of Diffusion in Lumbar Intervertebral Disks with Occlusion of Lumbar Arteries: A Study in Adult volunteers. Radiology 221:779–786

II Kokkonen S, Kurunlahti M, Tervonen O, Ilkko E, Vanharanta H (2002): End-plate Degeneration Observed in Magnetic Resonance Imaging: Correlation with Pain Provocation and Disc Changes Observed in CT-Discography. Spine 27:2274–2278

III Kurunlahti M, Tervonen O, Vanharanta H, Ilkko E, and Suramo I (1999): Association of atherosclerosis with low back pain and the degree of disc degeneration. Spine 24:2080–2084

IV Kurunlahti M, Autio R, Karppinen J, Kerttula L, Niinimäki J, Ilkko E, Vanharanta H, Suramo I, Tervonen O (2003): Association between lumbar arteries and intervertebral disc degeneration among patients with low back pain and sciatica. Submitted.

V Kurunlahti M, Karppinen J, Autio R, Niinimäki J, Vanharanta H, Suramo I, Tervonen O (2003): Association between low back pain and occlusion of lumbar arteries among sciatica patients: A three years follow-up examination. Submitted.

# Contents

# 1 Introduction

Low back disorders are a major public health problem that causes individual suffering and economic losses. In the Western countries, 75–80% of people are affected by low back pain at some point during their lifetime (Andersson 1998). The cumulative lifetime prevalence of low back pain lasting for at least 2 weeks has been evaluated to be 13.8% (Deyo & Tsui-Wu 1987). Finland does not differ from the other Western countries in this respect, as the lifetime prevalence of low back pain is 77% for men and 74% for women. The corresponding figures for sciatica are 35% and 40% (Heliovaara 1988). Although the period of acute back pain is usually short, recurrences are very common, and long sick leaves due to prolonged low back pain have been granted to 17% of people in Finland (Heliovaara 1989).

Substantial progress has been made towards finding etiological factors of disc degeneration and the connection between disc degeneration and low back pain, but the results are, as yet, controversial. Degenerative changes in the lumbar spine, including intervertebral discs, are very common even in asymptomatic persons (Jarvik & Deyo 2000b). On the other hand, no clear distinction can be made between normal age-related and pathologic disc changes (Vernon-Roberts 1992).

The role of nutrition in degenerative, and even painful, disc diseases is being studied actively. *In vitro* models have shown that nutrition has an important role in cell viability and regeneration (Urban *et al.* 1977, Horner & Urban 2001). This notion was supported by the *in vivo* histologial study (Boos *et al.* 2002) which showed an absence of blood vessels in the end plate (EP) and a coincident increase of matrix breakdown, cartilage cracks, microfractures in EP and tears and clefts in nucleus pulposus (NP). In non-specific low back pain syndromes, intradiscal tears and clefts have been found to play a key role (Vanharanta *et al.* 1988a).

Atherosclerosis diminishes nutrition through reduced blood flow. Smoking has also been found to correlate with atherosclerosis as well as disc degeneration (DD) and low back pain (Frymoyer *et al.* 1983, Svensson *et al.* 1983). Some cross-sectional studies have also shown atherosclerosis to correlate with disc degeneration (Kauppila *et al.* 1994) and low back pain (Kauppila *et al.* 1997). Clinical studies on the role of blood flow in disc degeneration and low back pain are lacking, possibly because of the invasiveness of the method used to analyse blood flow to the lumbar area. Computed tomography and

new magnetic imaging methods make it possible to image the discal and end plate status as well as blood flow and even diffusion non-invasively.

In the present study, the first task was to prove that diminished blood flow really correlates with intradiscal diffusion and, ultimately, discal nutrition. Because the end plate also plays an important role as a pathway of disc nutrition, the role of end plate changes in painful disc degeneration was analysed next. After these basic studies, the role of diminished blood flow to the disc area was assessed by evaluating the calcification of the abdominal aorta and the occlusion of the lumbar artery. These results were then compared to disc degeneration and low back pain.

# 2 Review of the literature

## 2.1 Surroundings of the lumbar intervertebral disc

### *2.1.1 Anatomy of the lumbo-sacral region*

The adult lumbo-sacral vertebral column normally consists of 5 vertebrae and the sacrum, which consists of five fused sacral vertebrae (Moore KL 1985). The stability of the vertebral column is provided by ligaments, muscles, intervertebral discs and the shape of the vertebrae (Moore KL 1985). The spinal cord and the spinal nerve roots are located within the vertebral canal, with the branches locating outside the vertebral canal. The intervertebral disc connecting the vertebral bodies, the facet joints and the ligaments make up the moving spinal segment (Dwyer AP 1996).

### *2.1.2 Anatomy of the arteries supplying the disc area*

The lumbar region receives its blood supply from four pairs of lumbar arteries arising from the posterior wall of the aorta. The blood supply to the lower lumbar and lumbo-sacral area consist of the fifth lumbar artery pairs, which are supplied by branches of the middle sacral artery and branches arising from the iliolumbar artery. The middle sacral artery originates proximally from the posterior wall of the aorta just above the aortic bifurcation. The middle sacral artery as well as the fifth lumbar artery are smaller in calibre than the lumbar arteries above them (Tveten L 1976, Ratcliffe 1982). The calibre of the lumbar arteries increases slightly from lumbar artery 1 to lumbar artery 4 (Kauppila 1994). When the fifth lumbar arteries are tiny or missing, a compensatory meshwork of branches of the iliolumbar arteries is seen (Kauppila 1994). The paired iliolumbar arteries are branches of the internal iliac arteries and give off branches to, for example, the fifth lumbar vertebra (Crock & Yoshizawa 1976, Last RJ 1978, Ratcliffe 1982). These 5 lumbar artery pairs pass the vertebral columns laterally closel to the front

and side of the vertebral column, until they reach the intervertebral foramina. The arteries then break up into branches, which pass to the body wall, the spinal canal and the posterior peritoneum (Crock & Yoshizawa 1976, Ratcliffe 1982, Moore KL 1985).

The blood supply to the vertebral body comes from the periosteal branches of each segmental artery pair. Some of these branches penetrate the vertebral body near the lumbar artery, whereas some penetrate the bone adjacent to each vertebral end plate. There are also branches on the surface of discs. One big subbranch of the segmental lumbar artery to the spinal canal runs medially across the posterior surface, penetrating there the vertebral body and anastomosing with the contralateral artery. In addition to this posterior artery branch, there are two other important posterior supplying artery branches that run upwards and downwards on the posterior surface on the vertebral body, anastomosing with the artery branches of the segmental arteries above and below (Crock & Yoshizawa 1976). In addition to these anastomoses, other large anastomosing channels have been found between the two lowest lumbar segments (Ratcliffe 1982). Tiny anastomoses between the adjacent vertebrae after obliteration of the posterior anastomoses have been found in the anterolateral aspects of the vertebrae (Kauppila 1995).

### *2.1.3 Changes in lumbar artery anatomy and blood supply*

#### *2.1.3.1 Atherosclerosis*

The term ‘atherosclerosis’ refers to thick artery wall lesions. These lesions may be early, fatty streak lesions or advanced, fibrous plaque lesions (Ross R 1988). The fatty streak is an intimal lesion that stains with fat-soluble dyes, whereas the fibrous plaque is a hard intimal lesion, which may be partially or completely covered by sudanophilic deposit. Fibrous plaques often occlude the lumen of the branching artery by causing the arterial wall to thicken, and the vascular wall may also undergo degenerative changes, such as ulcerations, hemorrhages and thrombosis. It may also have X-ray-positive calcium deposits. Atheromatous lesions are usually the outcome of a long process, and the atherosclerotic obliteration of an artery is also slow, allowing time for a collateral network to develop. Subsequent development of a thrombus is also possible, and thrombosis may cause a sudden occlusion of an artery without any collateral circulation (Rogoff S.M. & Lipchik E.O. 1970, Bouissou H *et al.* 1989).

Atheromatous lesions are most commonly located around the orifices of arterial branches and bifurcations. In the abdominal aorta, these sites include the orifices of the lumbar and middle sacral arteries, the renal arteries, the inferior mesenteric artery and the bifurcation of the aorta (Rogoff S.M. & Lipchik E.O. 1970, Cluroe AD *et al.* 1992).

Atherosclerosis progresses with age, although early lesions in the abdominal aorta can already be seen in young children as well as in people over 60 years of age (Vihert 1976, Ross R 1988). In a large multicenter study, aortas from 17,300 subjects aged 10 to 99 years were evaluated (Vihert 1976). Fatty streaks were present in the abdominal aorta in

subjects aged 10–14 years. Complicated, calcified lesions appeared at 20–25 years, and 10% of the subjects had fibrous plaques in the abdominal aorta. The greatest increase in the prevalence of fibrous plaques in the abdominal aorta occurred between 30 and 45 years, and complicated lesions increased between 44 and 64 years (Vihert 1976). The results were parallel to those obtained in a Finnish study, which showed that 219 randomly selected men had marked atheromatous lesions in the abdominal aorta between 35 and 49 years of age (Särkioja T 1989). The abdominal aorta has been found to show the most pronounced atheromatous involvement (Tejada C *et al.* 1968).

### *2.1.3.2 Segmental arteries, branches and anastomoses*

The anatomy of the arteries of the lumbar region changes as the person ages. During the first two decades, small blood vessels enter the disc matrix through the cartilaginous end plates, but early in adolescence these arteries begin to regress, and they are no longer seen in adults (Coventry MB *et al.* 1945a). Especially the L5 lumbar segmental arteries as well as the medial sacralartery are occluded or tiny at advanced age (Ratcliffe 1982, Kauppila 1997). Ratcliffe found, in a clinical aortographic examination of 100 patients, large anastomoses between the lowest two lumbar segments that diminished with age (Ratcliffe 1982). These results were concordant with the histologic examination of 120 cadaveric spines, where anastomosing arteries were obliterated in older people (Hirsch C & Schajowicz F 1953). Vascularisation in the outer part of the annular disc connecting the adjacent vertebrae caused by age and disc degeneration have been found in at least three studies (Hirsch C & Schajowicz F 1953, Vernon-Roberts & Pirie 1977, Kauppila 1995). One theory concerning the mechanism of this vascular meshwork suggests that annular arteries are the outcome of the healing process of an annular tear. The other theories suggest that vascularisation consists of an anastomosing network that develops as a sequel of the occlusion of a segmental artery or its branch.

The blood supply to the lumbosacral region is segmental with tiny connecting arteries linked together in the longitudinal ligaments. After segmental occlusion, these tiny connecting arteries widen and form a collateral route to bypass obliterated segmental arteries (Rogoff S.M. & Lipchik E.O. 1970). Collaterals formed after occlusion caused by atherosclerosis of the lower aorta appear to be small and retiform (Kauppila & Tallroth 1993, Kauppila 1995) and may not compensate for the diminution of blood flow.

## 2.2 Intervertebral disc

### *2.2.1 Structure and function*

The function of the intervertebral disc as a stabiliser, a joint between vertebrae as well as a distributor and attenuator of forces of different movements (Buckwalter 1999) requires many properties, and the íntervertebral disc consists of three main components: a thin hyaline cartilage end plate and a lamellar annulus fibrosus (AF) that encircles the central gelatinous nucleus pulposus (Antoniou *et al.* 1996b, Moore 2000). The disc has a low cell density (Maroudas *et al.* 1975), but its cells play an essential role in maintaining disc health because they make and maintain the extracellular matrix. Collagens and proteoglycans (PG) are the primary structural macromolecular components of the intervertebral disc (Eyre & Muir 1976, Buckwalter 1995, Antoniou *et al.* 1996b), with collagen providing the framework of the disc and proteoglycans, through their interactions with water, giving the tissue its stiffness and resilience to compression (Eyre *et al.* 1989, Holm 1996). The disc also contains minor quantities of other molecules, e.g. serum proteins, lipids and inorganic salts.

The NP consist of a central core of highly hydrated proteoglycan matrix gel containing an irregular meshwork of mainly type II collagen fibers (80%) and minor quantities of other proteins, including collagen VI (15%), collagen IX (1–2%) and collagen XI (3%) (Eyre & Muir 1976, Eyre *et al.* 1989). The outer part of NP, where both remodelling and growth occur, is called the transitional zone. This area is also sensitive to physical forces as well as to chemical and hormonal modulation (Taylor *et al.* 1981).

Collagen is the most important component of the annulus, consisting of 10–20 concentric lamellae around the nucleus. The lamellae of the outer part of the annulus fibrosus are attached to the upper and lower vertebrae. The inner annulus lamellae are attached to the end plates. The annulus resist the radial tension induced by axial loading of the disc as stresses from torsion and flexion (Coventry MB *et al.* 1945a). In the outer part of the annulus, collagen type I increases up to 80%, whereas collagen type II is predominat near the nucleus. The annulus fibrosus also includes type V (3%), type VI (10%), type IX (1–2%) and a minor amount of type III collagen (Eyre & Muir 1976, Eyre *et al.* 1989). In articular cartilages type II collagen is typical, whereas type I collagen is typical of tendon, and it is therefore assumed that the strength of the annulus is provided by type I and the compressive component of the annulus by type II collagen.

Hyaline cartilage is the major component of the end plate, which is approximately 1 mm thick. In contrast to articular cartilage, the end plate is composed of hyaline cartilage, but there is no collagenous connection directly to the bone of the underlying vertebral bodies (Roberts *et al.* 1989). The collagen content is highest and the proteoglycan and water contents lower compared to the adjacent nuclear and annular regions (Roberts *et al.* 1989). The role of proteoglycans in the end plate is important in regulating the transport of essential solutes into and out of the disc, and a loss of proteoglycans in the end plate leads to a loss of proteoglycans from the nucleus (Roberts *et al.* 1996). In addition to serving as a semipermeable membrane that facilitates the diffusion of solutes from the

vertebra to the disc (Eyre 1979), The end plate also prevents the nucleus pulposus from bulging into the adjacent vertebral body (Moore 2000).

The adult intervertebral disc is mostly avascular, although the outer parts of the annular lamellae of degenerated discs may contain tiny collateral vessels (Kauppila 1995, Kauppila 1997). The nucleus pulposus and the inner annulus are always avascular. Similarly nerves have also been detected in the outer annulus, although no nerves have been found in the nucleus or in the inner annulus (Bogduk *et al.* 1981, Gronblad *et al.* 1991). These nerves originate from the sinuvertebral nerves in the posterior annulus, from the ventral primary ramus in the postelolateral part of the annulus and from branches of the gray rami communicans and direct branches of the ventral rami in the lateral part of annulus fibrosus (Bogduk *et al.* 1981).

### *2.2.2 Nutrition and metabolism*

The nutrition of the mainly avascular disc is complicated and a target of extensive studies. There are two main routes of nutrition. Outer annular cells obtain nutrients from blood vessels in the soft tissues around the periphery of the AF. The inner annulus and nucleus are, however, far away from the blood vessels of the vertebral body (Urban *et al.* 1978, Holm & Selstam 1982). The nutritional pathway to the inner part of the disc is a capillary network penetrating the subchondral plate of the vertebral body and terminating above the cartilaginous end plate (Eyre 1979, Holm *et al.* 1981). Nutrients are then diffused from these capillaries across the cartilaginous end plate (Roberts *et al.* 1996) and through the dense disc matrix to the cells (Urban *et al.* 1982). Thus, the nutrients are received via blood flow and diffusion (Maroudas *et al.* 1988). According to some studies, both of these nutritional pathways are affected by spinal movements and posture (Adams & Hutton 1983, Ohshima *et al.* 1989). Because of muscarine reseptors, which can influence disc nutrition under altered physiologic conditions, blood flow in the end plate is not completely passive (Wallace *et al.* 1994).

Experimental disc models have shown that the metabolism of the NP is mainly anaerobic because of the very low oxygen concentrations of the nucleus and the inner annulus (Holm *et al.* 1981). Since energy maintenance depends on anaerobic glycolysis, the critical nutrient is glucose (Holm *et al.* 1981, Ishihara & Urban 1999). The central part of the disc has a high lactate concentration and low pH levels. Cells can survive for some time under low oxygen (Horner & Urban 2001), as was also shown for articular chondrocytes (Grimshaw & Mason 2000). Under acidic concentrations, they produce very little matrix (Horner & Urban 2001), as found previously in disc explants (Ishihara & Urban 1999). Disc cells also die if low pH persists for several days, although these cells have powerful mechanisms for regulating intracellular pH (Razaq *et al.* 2000). Cells may thus survive under low levels of oxygen or at relatively acidic levels of pH, but under these conditions, the proteglycan synthesis falls steeply, (Ishihara & Urban 1999, Horner & Urban 2001), which eventually leads to a decrease of the proteoglycan concentration and, finally, to disc degeneration (Thompson *et al.* 1990). Cell density is also associated with the volume of nutrients. The role of nutritional factors as a controller of cell density has been discussed by Stairman et al (Stairmand *et al.* 1991) and earlier by

Stockwell et al (Stockwell R 1971), and it has recently been found that the concentration of nutrients drops if the cellular demand increases (Horner & Urban 2001). It is assumed that all cells in tissues have similar energy requirements and that the energy demand depends directly on cell density. The effect of mechanical events may alter the energy demand during, for example, the activity of the sodium pump, which is very sensitive to the extracellular sodium concentration (Mobasheri *et al.* 1997)and hence to the degree of fluid expression (Urban & Maroudas 1981). Mechanical loads affecting fluid expression may thus alter the energy demands, and mechanical events increasing hydrostatic pressure may also increase sodium pump activity (Hall 1999, Horner & Urban 2001). Cellular demand may also be increased by some growth factors and cytokines (Stefanovic-Racic *et al.* 1994).

In the disc, nutrient supply *in vivo* is affected by changes in the supply routes. Even under normal conditions, the gradients of oxygen (Holm *et al.* 1981)and glucose (Maroudas *et al.* 1975) are steep and the concentrations of both nutrients very low in the centre of the disc. If nutrient supply is restricted because of a reduction in end plate permeability for such reasons as end plate calcification (Roberts *et al.* 1996, Urban *et al.* 2001)or a decrease in the blood flow of the segmental lumbar arteries or their branches (Kauppila 1997), the nutrient concentration in the central region may diminish sufficiently to cause cell death (Stairmand *et al.* 1991, Urban *et al.* 2001). But even in conditions where nutrient supply is sufficient to maintain cell viability, proteoglycan synthesis may decline steeply, leading to a fall in the proteoglycan concentration and, hence, to disc degeneration (Horner & Urban 2001). The reduced nutrient supply may not be sufficient to maintain cell viability if there is an increase in cellular demand (Horner & Urban 2001).

### *2.2.3 Diffusion*

Diffusion refers to the ability of molecules at the microscopic level to move randomly in relation to their thermal energy (Gray L & MacFall J. 1998). Diffusion in the disc has been studied *in vitro* (Holm *et al.* 1981, Horner & Urban 2001) and *in vivo* (Urban *et al.* 1977, Urban *et al.* 1978). Determination of diffusion coefficients using steady-state or desorption techniques is difficult, because disc samples swell quickly and lose their proteoglycans (Maroudas *et al.* 1988). The diffusion coefficients of certain solutions in the disc have been measured by placing a spot of a radioactive tracer at one end of a thin strip of disc material (Urban *et al.* 1977). More physiologic *in vivo* measurements were made by injecting radioactive tracers into the veins of dogs, which were then sacrificed at different time intervals (Urban *et al.* 1978).

Diffusion is the main mechanism for the transport of small solutes into the intervertebral disc (Urban *et al.* 1978, Holm *et al.* 1981), because the overall direction of fluid flow, for about 16 hours daily, is mainly out of the disc (Holm 1996). There are two diffusion routes: through the outer parts of the AF and through the EP. For small uncharged solutes, such as glucose, these two routes are of equal importance, whereas for positively charged ions the end plate route is more effective (Urban *et al.* 1978). Negatively charged ion, such as sulfate, will diffuse through the periphery of the annulus.

Large uncharged solutes tend to be totally excluded from the normal disc (Moore 2000). Proton diffusion in tissues is restricted by both permeable and impermeable barriers due to cellular and fibrous structures. The parameters that mostly influence the rates of nutrient concentration are: transport of metabolites to and from cells through the disc matrix, nutrient consumption and production, disc thickness, and the exchange area (Maroudas *et al.* 1988, Stairmand *et al.* 1991). For example, degenerative changes in the permeability of the bone - end plate region limit the penetration of solutes into the disc (Roberts *et al.* 1996), and end plate calcification may also constitute an inpermeable barrier to solute transport (Roberts *et al.* 1993). The distances of diffusion are long; in adult human discs, some cells may be as much as 20 mm away from the blood supply (Moore 2000).

## 2.3 Intradiscal changes

The lumbar intervertebral disc undergoes striking changes along with age and degeneration (Buckwalter 1995). The term 'disc degeneration' (DD) is used to refer to a loss of the normal architecture of the disc due to progressive fibrosis, including a loss of gelatinous NP by desiccation and fraying (Osti & Cullum 1994), disappearance of the border between the NP and AF (Coventry MB *et al.* 1945b, Pritzker 1977) and deposition of aging pigment (Coventry MB *et al.* 1945b, Holm 1993). In the literature, the term DD has been used to describe age-related changes and pathologic, symptomatic changes. The degree of disc destruction is closely linked to age, but certain components of the disc undergo more extensive destructive alterations than others (Coventry MB *et al.* 1945c). Individual variation in DD is great (Buckwalter 1995). Substantial individual differences can be observed in the sense that young individuals may exhibit the disc of an elderly person and vice versa. Therefore, some researcher maintain that definite differentiation between purely age-related intradiscal changes and degenerative pathologic disc changes is difficult (Vernon-Roberts 1992, Boos *et al.* 2002).

### *2.3.1 Age-related and pathologic disc changes*

#### *2.3.1.1 Morphological features*

The knowledge of DD is mainly derived from an increasing number of studies on the molecular mechanisms of disc degeneration (Antoniou *et al.* 1996a, Palmgren *et al.* 1999, Pfirrmann *et al.* 2001, Antoniou *et al.* 2001, Gruber *et al.* 2001), and only a few existing studies contain information about the histological features of disc degeneration (Urban JPG 1993, Boos *et al.* 2002).

Age-related discal changes concern all structural components, but they are most extensive in the NP, where substantial increases of cell death, chondrocyte density and proliferation and granular changes are seen (Boos *et al.* 2002). During the first decade, notochordal NP disappears (Taylor & Twomey 1988), and only a few notochordal cells remain in adults (Coventry MB *et al.* 1945b). By the end of the first decade, AF also has a compact structure, the lamellae are mostly circulated, and their attachment to ligaments has started. By about 10 years of age, vascular channels through the end plate have also diminished (Coventry MB *et al.* 1945b), which feature has been described as dramatic by Boos et al (Boos *et al.* 2002). At this age, the first EP cartilace cracks are also seen (Boos *et al.* 2002).

During the second decade, the disc reaches its adult appearance. The epiphyseal ring fuses with the vertebral body and the fluid content of NP increases (Coventry MB *et al.* 1945a, Coventry MB *et al.* 1945b). Vascular channels mostly disappear by the age of 20 (Coventry MB *et al.* 1945b), contrary to the current assuption that vascular channels appear only during the fetal and early postnatal periods (Saunders JB & Inman VT 1940, Boos *et al.* 2002), and EP vascularisation disappears during the first 4 years (Wassilev W & Kuhnel W 1992).

During the third and fourth decades, the changes in the EP are similar but more numerous compared to those seen in the second decade: cartilage cracks, microfractures of adjacent subchondral bone and new formation (Boos *et al.* 2002). During the third decade, fissures in the AF are detected, followed by cellular proliferation during the fourth decade and later, and finally, invasion of blood vessels along tears and clefts, but the first rim lesions with edge neovascularisation are seen before the age of 20 years (Boos *et al.* 2002). Starting in the fourth decade, signs of structural disorganisation, including numerous clefts and fissures, are seen in the EP (Boos *et al.* 2002). During the sixth and seventh decades, microfractures and bone sclerosis are seen (Boos *et al.* 2002). Scar formation and advanced tissue destruction can be found (Boos *et al.* 2002), and the EP is finally replaced by fibrocartilage with focal necrosis (Coventry MB *et al.* 1945b). The absolute number of chondrocytes increases with age, but these are mostly non-viable cells. The volume of necrotic cells increases from about 2% in the fetus to about 50% in the adult. Annular changes are characterised by a gradual loss of the fine fibrous connective tissue meshwork and its replacement by increasingly hyalinised collagen fibers (Buckwalter 1995). Three common types of annular cleft have been described (Osti *et al.* 1992b) (Fraser R *et al.* 1993). The first type consists of rim lesions, which are assumed to be caused by trauma (Osti *et al.* 1992b) and which are discrete defects of the outer AF. The second type, i.e. circumferential tears between the layers of AF, are most commonly seen in the lateral and posterior parts of the AF, and the third type consists of radiating clefts, which extend from the NP parallel or oblique to the plane of the end plate.

Clefts and tears of the NP appeared in Coventry´s study (Coventry MB *et al.* 1945b) from the fourth decade onwards, whereas Boos et al (Boos *et al.* 2002)found NP clefts and tears as early as the second decade. From the fifth decade onwards, the nucleus becomes fibrotic, and after the sixth decade, the NP is extensively destroyed with large spaces filled by amorphous material (Coventry MB *et al.* 1945b), after which it is macroscopically difficult to distinguish the NP from the AF (Brown MD 1971).

The first significant age-related changes appear in the first decade, becoming substantial in the first half of the second decade. Vascularisation of the intervertebral disc is mostly considered to end at an early infantile age, which means that the nutritional supply is severely impaired by the ongoing growth and enlargement of the disc. The EP alternations preceded the NP changes, whereas the AF is affected in elderly individuals (Boos *et al.* 2002).

#### *2.3.1.2 Biochemical features*

Along with aging, the proteoglycan content of the nucleus decreases, proteoglycan aggregation decreases, and proteoglycans become smaller (Antoniou *et al.* 1996a), and this loss of proteoglycans in the NP is associated with degenerative changes in the disc (Eyre 1979, Tertti *et al.* 1991, Kaapa *et al.* 1994). This is assumed to lead to a decrease in the ability of the nucleus to remain hydrated (Lorentz M & Patwarhan AG 1996). With aging, qualitative changes also appear in PG's and the collagens of the NP (Kaapa *et al.* 1994), and type II collagen of the nucleus begins to resemble type I collagen (Antoniou *et al.* 1996a). Dehydration of the disc increases, and the disc becomes stiffer and less able to accommodate a large range of motion.

Collagen type X, which locates in the central region of the cartilage end plate (Moore 2000), is suggested to be involved in the calcification of cartilage (Aigner *et al.* 1998).

## 2.4 Low back pain and disc degeneration

Intradiscal pathology is assumed to play an important role in LBP syndromes (Mooney 1989). However, LBP can also be caused by the facet joint (Fairbank *et al.* 1981), the sacroiliac joint (Fortin & Aprill 1994), spondylolysis and degenerative osteophytes (Lee CK *et al.* 1988) as well as muscles and nerve roots (Sihvonen T 1992) and functional disturbance (Indahl A 1999). Furthermore, there are some rare specific causes of low back pain, such as fractures, tumours and infectious or metabolic diseases.

### *2.4.1 Causes and mechanism of low back pain due to intradiscal changes*

Radial tears are assumed to have an important role in disc pathology. Radial ruptures precede disc degeneration (Yu *et al.* 1988a, Osti *et al.* 1992a), and radial tears extending from the NP to the middle layers of the AF found by discography or MRI (Horton & Daftari 1992, Aprill C & Bogduk 1992) are also associated with local LBP (Vanharanta *et al.* 1987, Moneta *et al.* 1994) and with radiating pain (Dullerud & Johansen 1995, Ohnmeiss *et al.* 1999b). The extruded nuclear material of the disc is chemically inflammatory and neurotoxic (McCarron RF *et al.* 1987, Olmarker *et al.* 1995), and AF contains pain-sensitive nerve endings (Bogduk 1983, Coppes *et al.* 1997), which may be

irritated by these metabolites (Saal & Saal 1990). In contact with porcine nerve roots, the nuclear material induces functional changes in nerve roots (Kayama *et al.* 1996).

The susceptibility of nuclear material to extrude through annular tears has been studied in cadaveric spine segments. Age, degree of disc degeneration and spinal level have been found to influence this property (Adams & Hutton 1982). Slightly degenerated lower lumbar discs of people aged from 40 to 50 seemed to be most vulnerable (Adams & Hutton 1982). However, even younger discs may prolapse gradually when exposed to compressive loading in a flexed position (Adams & Hutton 1982). On the basis of animal studies, it is assumed that the extruded nucleus sensitises the nerve root and, in the presence of mechanical deformation, induces pain (Olmarker *et al.* 1998, Kawakami M *et al.* 2000).

The recovery of LBP is usually quite rapid. Acute non-radiating LBP resolves within 6 weeks in approximately 90% of patients. Recurrence within one year is common (Frymoyer 1988, Carey *et al.* 1995). Recovery from sciatica is, however, a slower process (Andersson *et al.* 1983). In one study, most sciatica symptoms and signs disappeared within the first 3 months, and one third of the patients had recovered fully after 1 year, though another one third had undergone surgery (Balague *et al.* 1999). In another study, only 11.4% had completely recovered by one year (Atlas SJ *et al.* 1996). Large disc herniations resorb more quickly than smaller herniations (Ito T *et al.* 1996, Ahn SH *et al.* 2000).

Despite increasing knowledge of the morphologic and biochemical features of intervertebral discs, the relationship between pathologic changes and the induction of pain remains obscure (Osti & Cullum 1994). One should remember that, depending on age, 20%–36% of asymptomatic people have disc herniations (Boden *et al.* 1990, Jensen *et al.* 1994a). On the other hand, radicular pain may also be caused by internal disc ruptures without herniation (Ohnmeiss *et al.* 1999a, Karppinen *et al.* 2001).

A positive correlation between disc degeneration and local back pain has been published in many studies (Parkkola *et al.* 1993, Erkintalo *et al.* 1995, Luoma *et al.* 2000), but no correlation was found in many others (Boden *et al.* 1990, Jensen *et al.* 1994b, Wood *et al.* 1995). In the study by Weishaupt et al. (Weishaupt *et al.* 2001), disc degeneration showed a weak positive predictive value and low specificity for a painful disc. A case-control study of LBP patients and asymptomatic subjects aged 10–49 years, showed that patients had more pronounced disc degeneration observed in MRI (Paajanen *et al.* 1997).

### *2.4.2 Determinants of low back pain and disc degeneration*

The findings on the etiognosis of intradiscal changes and back pain are largely based on cross-sectional studies (Kaplan *et al.* 1986, Riihimaki *et al.* 1989b, O'Neill *et al.* 1999). Heavy physical activities predispose to low back pain (Magora 1973) and to sciatica (Heliovaara 1989, Riihimaki *et al.* 1989a). Decreased signal intensity and bulging of the disc evaluated by MRI were found to be more common among weight lifters than other athletes in a cohort of elite athletes (Videman *et al.* 1995), and it is evident that heavy physical labour is associated with radiographically detectable lumbar disc degeneration

(Biering-Sorensen *et al.* 1985, Riihimaki *et al.* 1990). In an X-ray study of osteoporosis in persons aged 50–75 years, osteophytes in lumbar lateral radiographs were found to be associated with heavy physical activity (O'Neill *et al.* 1999). The results of an experimental study of the influence of psychosocial stress, gender and personality on mechanical loading of the lumbar spine also agreed with these findings, showing that psychosocial stress increased spine compression (Marras *et al.* 2000).

The role of cardiovascular diseases in low back pain was suggested by cadaveric studies, where calcification of the abdominal aorta was found to be associated with low back pain and DD (Kauppila & Tallroth 1993). The Framingham cohort study revealed an association between cardiovascular diseases and low back pain: lifetime low back pain as well as DD clearly correlated with atherosclerosis of the abdominal aorta (Kauppila *et al.* 1997).

Body height seemed to associate with disc degeneration in an 11-year prospective study (Heliovaara 1987), where body height was a risk factor for herniated NP in both sexes. Body height further seemed to predispose to sciatica (Hrubec & Nashold, Jr. 1975, Merriam *et al.* 1983), though opposite results have also been found (Kelsey *et al.* 1984). In a systematic review article, body weight constituted a weak positive risk for low back pain (Leboeuf-Yde 2000).

The effect of smoking on disc degeneration and on LBP and sciatica is being studied actively. According to a systematic review article, smoking was considered a minor risk factor for LBP (Leboeuf-Yde 1999). In another systematic review article, a clear association between smoking and low back pain and even the manifestation to low back pain was found (Goldberg *et al.* 2000). In recent cohort studies, smoking has been found a risk factor for low back pain (Eriksen *et al.* 1999, Power *et al.* 2001). The risk to develop low back pain between the ages of 32 and 33 years was 1.6 among smokers (Power *et al.* 2001). In a cohort study of Canadian young people, the risk to have low back pain was 2.4 among smokers, and there was also a clear association between the amount of smoking and low back pain. Smoking together with hard physical work increased the risk up to 5.5 (Eriksen *et al.* 1999). These results agreed with the results of earlier studies (Frymoyer *et al.* 1983, Deyo & Bass JE 1989), where a connection with LBP was found. It is assumed that the mechanism whereby smoking causes LBP is decreased disc metabolism; Smoking has been shown to affect disc nutrition (Holm & Nachemson 1988). On the other hand, smoking is a risk factor for atherosclerosis, which is also assumed to cause disc degeneration through diminished nutrition(Kauppila *et al.* 1994, Kauppila *et al.* 1997). One possible mechanism whereby smoking may cause low back pain is assumed to be spinal pressure, which increases during cough.

Genetic or familiar factors also play an important role in disc degeneration (Battie *et al.* 1995b, Annunen *et al.* 1999, Sambrook *et al.* 1999). In a Finnish identical twin population, a multivariate analysis model revealed genetic factors, including the early childhood environment as the most important determinant(Battie *et al.* 1995b). Family history played a significant role in a study where adolescent patients with disc herniation were compared to matched controls: the risk of developing a herniated lumbar disk before the age of 21 years was over fourfold in adolescents with a positive family history (Varlotta *et al.* 1991).

## 2.5 Imaging of the intervertebral disc

### *2.5.1 Plain radiography*

The role of plain radiography in the assessment of disc degeneration is questionable. Decreased height of the intervertebral disc is only an indirect sign of disc degeneration, indicating late shrinkage of the disc matrix (Brinckmann & Grootenboer 1991), and the validity of disc height as an indicator of early disc degeneration is questionable (Luoma *et al.* 2001). Other indicators, such as sclerosis on the end plates with osteophytes, calcification and the vacuum disc phenomenon, are also secondary or late stages of degenerative changes (Resnick 1985).

### *2.5.2 Discography*

Discography enables the evaluation of intradiscal disease in two ways: contrast medium injected into the NP helps to detect the exact location of fissures and defects in the annulus fibrosus (Vanharanta *et al.* 1988a, Tehranzadeh 1998). Secondly, pain provocation plays an important part (Vanharanta *et al.* 1988b, Moneta *et al.* 1994, Tehranzadeh 1998). When a disruption of the outer AF is present, the patient`s pain may be reproduced or aggravated by an injection of contrast agent into the NP (Moneta *et al.* 1994).

The value of discography is also under discussion nowadays (Bogduk & Modic 1996, Weishaupt *et al.* 2001). Guyer et al (Guyer & Ohnmeiss 1995) called discography the only method that directly relates a radiographic image to the patient's pain. Selby et al recognised discography as the only modality that can detect the internal disc disruption syndrome (Selby *et al.* 1987). According to some studies, the role of discography is important in differentiating painful discs from other causes of back pain as a preoperative method for discectomy (Bini *et al.* 2002) and intradiscal electrothermal annuloplasty (IDET) (Karasek & Bogduk 2000). On the other hand, some authors recommend the procedure to be limited to a strictly scientific and prospective evaluation, and until then, there is no basis for the performance of discography in clinical medicine (Nachemson 1989, Bogduk & Modic 1996). Bogduck later changed his mind and proposed that the only method for diagnosing a painful internal disruption is CT/discography (Bogduk 2002).

Discography is, however, invasive and rather time-consuming and includes a potential risk of infection and a moderate dose of radiation when combined with CT. Especially subjects with significant emotional and chronic pain problems may have long-term back symptoms after this procedure (Carragee *et al.* 2000a), and these patients may present a false positive pain provocation (Carragee *et al.* 2000c). Due to the facts mentioned above, discography is not recommendable as a screening technique (Tehranzadeh 1998). However, CT/discography can detect clinically correlative and significant pathology,

usually annular disruptions, not evident in MRI scanning (Zucherman *et al.* 1988, Osti & Fraser 1992).

### *2.5.3 Computed tomography*

The recent rapid methodological development does not only apply to MRI, but the technology of computed tomography (CT) has also reached a new stage, as the helical technology has revolutionised CT scanning (Tallroth 1998). CT is mostly used to search for nerve entrapment caused either by intervertebral disc extrusion or by spinal stenosis, but the intradiscal structure can be only grossly evaluated and its sensitivity at the early phases of disc degeneration is poor (Modic *et al.* 1988a). Reactive or secondary signs of degeneration, such as calcification, the vacuum phenomenon and sclerosis of the adjacent intervertebral body, can also be detected with CT (Modic *et al.* 1988a). Two characteristic features of CT are important: its ability to distinguish soft tissues from bone changes (Modic *et al.* 1988a) and the two- or three-dimensional reformatting (Modic *et al.* 1988a). However, the contrast sensitivity between various soft tissues is limited in CT, especially when compared to MRI (Modic *et al.* 1988a). The advantages of CT over MRI include imaging of claustrophobic patients and patients with underlying contraindications to MRI, such as patients with pacemakers, cochlear implants or intracerebral aneurysm clips. One weakness of this method is the high dose of ionising radiation, which prevents its application to non-patient populations.

### *2.5.4 Ultrasound imaging*

Ultrasound (US) is another useful imaging method for studying the structure of discs. The sensitivity and specificity of US in detecting pathologic intradiscal changes is quite high with CT as the gold standard, varying from 0.84 to 0.95 (Tolly 1984, Tervonen & Videman 1988). However, intervening abdominal tissues and bowel gas may restrict the examination of discs (Tervonen & Videman 1988). In addition, the narrowing of the disc space because of disc degeneration may also limit visibility (Tolly 1984)

### *2.5.5 Magnetic resonance imaging*

#### *2.5.5.1 Imaging techniques for the lumbar spine*

MRI is considered the most sensitive imaging method for evaluating the intervertebral disc (Modic *et al.* 1984). The advantage compared to the other image modalities is its superior contrast discrimination in evaluating soft tissue structures and its multiplanar imaging capability. Therefore, MRI is superior in the diagnosis of intervertebral disc diseases (Gibson *et al.* 1986, Gundry & Fritts 1998). In the upper parts of the spine, the

respiratory motion may cause artefacts, and to avoid or limit this, surface coils, which also provide a relatively high signal-to-noise ratio (SNR) (Axel L 1984), are used in spine imaging (Ruggieri 1999).

The sequences normally used to image lumbar spine are T1-weighted sagittal spin echo (SE) and T2-weighted sagittal fast spin echo (FSE) (Morgan & Saifuddin 1999), supplemented T1-weighted SE and/or T2-weighted FSE axial images at selected levels (Gundry & Fritts 1997). In general, T2-weighted fast-spin echo images are superior to conventional spin echo images of the lumbosacral spine because of the improved image quality resulting from the superior spatial resolution and reduced motion artefacts. Sagittal FSE T2 images with fat suppression and axial FSE T2-weighted images without fat suppression are used to assess the stenosis of the neural foramina, the central spinal canal and the lateral recess. These sequences are also useful in diagnosing the hydration status of an intervertebral disc. Other uses of these sequences are to assess the abnormal signal intensity of the disc and cancellous bone, the signal intensity of the structures surrounding the spine and disc herniation. T1-weighted SE images are used to evaluate the anatomic structure of the spine and sometimes the intensity of the vertebral body (Ross *et al.* 1993).

In the sagittal planes, disc degeneration is currently evaluated by the FSE sequence, which has replaced the conventional T2-weighted SE images (Ross *et al.* 1993, Ruggieri 1999). FSE imaging is a variation of the rapid relaxation enhancement technique, in which several steps of phase-encoding data are collected within a single TR interval. The advantages compared to conventional SE include decreased imaging times and improved resolution (Georgy & Hesselink 1994) and better SNR on T2-weighted images (Constable *et al.* 1992). The contrast-to-noise ratio (CNR) has also been shown to be better in FSE than in conventional SE images. Recent developments include shortening of the examination time and improvement of the sensitivity of the techniques (Ruggieri 1999). In the case of the lumbar spine, routine use of true T2-weighted images is possible (Ruggieri 1999) just opposite to the cervical and thoracic spine, where the cerebrospinal fluid (CSF) flow creates problems (Gundry & Fritts 1997).

Many different pulse sequences have been applied to MR imaging of the spine (Murayama *et al.* 1990, Georgy & Hesselink 1994). Fat suppression techniques are used in conjunction with gadolinium-based contrast material to improve visualisation of inflammatory and neoplastic diseases (Jinkins & Runge 1995). Paramagnetic contrast agents are also used to prove sensitivity and specificity in the evaluation of failed back surgery syndrome (Jinkins & Van 2001).

### *2.5.5.2 Intradiscal MRI findings*

The intervertebral disc undergoes marked anatomical changes over age, and the view of the spine imaged by MRI therefore also changes (Yu *et al.* 1991). The intervertebral disc is prominent during infancy, but its volume decreases at older age (Szumowski J & Simon JM 1991). The transition between NP and AF is relatively sharp in a young disc and becomes less distinct along with age (Yu *et al.* 1988a). Typically, the signal for a normal adult disc is intermediate to low in a T1-weighted image and high on a T2-

weighted image compared to adjacent bone marrow (Yu *et al.* 1988a, Morgan & Saifuddin 1999). The normal bright NP (T2 image) and the inner annulus are indistinguishable in MRI (Schiebler *et al.* 1991). The outer annulus is visualised as hypointense on all pulse sequences and is optimally demonstrated on T2-weighted FSE images (Morgan & Saifuddin 1999). A horizontal central linear focus of decreased signal intensity on T2-weighted sagittal images representing a fibrous transformation of the gelatinous matrix of the nucleus pulposus is called the intranuclear cleft (Schiebler *et al.* 1991). This is commonly seen in people aged over 30 years (Aguila *et al.* 1985). Normal adult end plates and ligamentous structures as well as the outer annulus fibrosus have low signal intensities on both T1- and T2-weighted images.

The association between symptoms and structural findings in MRI is ambiguous. Abnormal discs are frequently detected in asymptomatic subjects (Jensen *et al.* 1994a, Wood *et al.* 1995, Jarvik & Deyo 2000a). The signal loss on T2-weighted images associated with fibrotic changes and the decreased water content are often the first signs of intradiscal degenerative changes (Mirowitz SA 1996). The low signal intensity area in the anterior part of the NP, called the central dot, is found to associate with infolding of the fibers in the outer annulus. This infolding is the first phase of disc degeneration. (Schiebler *et al.* 1991). Later, the hyaline cartilage end plate is separated from the inner annulus and the nucleus (Schiebler *et al.* 1991), and fluid-filled fissures may be generated, which can be seen as high signals on T2-weighted sequences, commonly with a loss of disc height (Yu *et al.* 1988b, Cassar-Pullicino 1998). Histologic disc alternations in terms of tear and cleft formation are considered an important hallmark of disc degeneration (Yu *et al.* 1989). During degeneration, the inner annulus inverts and becomes concave, departing from its normal convex contour, and this loss of annular integrity changes the mechanical properties of the annulus and thus leads to generalised bulging with a loss of disc height (Cassar-Pullicino 1998).

Diffuse extension of the disc beyond the interspace is considered to be one of the sequels and complications of disc degeneration (Herzog 1996, Milette 2000). The terminology for disc displacement is confusing (Cassar-Pullicino 1998, Morgan & Saifuddin 1999, Milette 2000). Bulging can be defined as a disk in which the contour of the outer annulus extends in the horizontal plane beyond the edges of the disc space, which is normally greater than 50% of the disc circumference (Milette 2000). Radiological herniation usually means a focal extension of NP beyond the margin of the disc (Lee *et al.* 1988). However, it is impossible for observers of imaging studies to determine the exact nature of the material coming out of a disc space (Milette 2000). Therefore, herniations are subdivided into protrusions and extrusions, depending on the extent of the base of herniation compared with the other diameters of the herniation (Milette 2000). Extrusions can be further described as sub- or transligamentous, depending on the integrity of the posterior longitudinal ligament. In the early phase, sequestered fragments of the disc have a slightly higher signal intensity on T2-weighted images compared to the disc, and they may enhance peripherally after an injection of intravenous gadolinium (Masaryk *et al.* 1988).

Intraosseus disc herniation through a weakened vertebral end plate or the subchondral bone is called Schmorl's node. Schmorl`s nodes are strongly associated with Scheuermanns disease, which, in turn, is associated with an accelerated degenerative process in the disc (Swischuk *et al.* 1998). Intraosseus herniations, which occur

peripherally and undermine the ring epiphysis, separating it from the body of the vertebra, lead to limbus vertebrae (Swischuk *et al.* 1998).

Annular tears are classified as concentric, transverse and radial, of which radial and transverse tears may be detected in MRI (Yu *et al.* 1989). Concentric tears are found between adjacent lamellae of the annulus. Transverse tears are ruptures of Sharpey's fibers adjacent to the ring apophysis, and according to current knowledge, they are assumed to be clinically insignificant (Morgan & Saifuddin 1999). Radial tears are ruptures of the entire annulus, extending from the NP to the outer parts of the AF (Aprill C & Bogduk 1992). Aprill and Bogduk used the term 'high-intensity zone' (HIZ) to describe on T2-weighted sagittal MR images the high-signal focal area in the posterior AF surrounded by areas of low signal intensity on all sides and thus clearly separated from the nucleus (Aprill C & Bogduk 1992). Based on comparisons of MRI and discography, the HIZ has been suggested to correlate closely with pain in some studies (Aprill C & Bogduk 1992, Schellhas *et al.* 1996). Compared with discography, the association between HIZ and annular tears graded as 3, 4 and 5 and pain provocation was obvious (Lam *et al.* 2000). The role of HIZ in discogenic pain is controversial, however, as it has been found in asymptomatic subjects as well (Weishaupt *et al.* 1998, Stadnik *et al.* 1998), and its sensitivity and positive predictive value have been shown to be poor (Carragee *et al.* 2000b, Weishaupt *et al.* 2001).

Changes in the vertebral end plate are frequently associated with degenerative disc disease (Modic *et al.* 1988a, Modic *et al.* 1988b). These are usually called Modic changes. The changes were first classified into two types (Modic *et al.* 1988a, Modic *et al.* 1988b). Type 1 changes include decreased signal intensity on T1-weighted and increased signal intensity on T2-weighted images. In type 2, signal intensity is increased in both T1- and T2-weighted sequences. Type 1 changes are assumed to be a result of fibrovascular replacement of subchondral bone and type 2 changes are the manifestation of fatty replacement of subchondral bone and are considered to be chronic(Modic *et al.* 1988a, Modic *et al.* 1988b). These changes can be separated only in MRI. If bone sclerosis is extensive, signal intensities are decreased in both T1- and T2- weighted images, and this change in the end plate is called type 3 change (Modic *et al.* 1988a). In a longitudinal study, it has been demonstrated that type 1 changes often convert to type 2 (Modic *et al.* 1988a), and mixed types are also usual, accompanied by disc degeneration (Braithwaite *et al.* 1998). The role of these degenerative end-plate changes, as well as many other features among disc degeneration, is controversial. Degenerative type 1 (Toyone *et al.* 1994, Braithwaite *et al.* 1998) or type 2 changes have been shown to be associated with intradiscal back pain (Weishaupt *et al.* 2001) However, no relationship between end plate signal changes and pain provocation in discography was found in a retrospective study (Sandhu *et al.* 2000). Type 1 changes are nonspecific, and similar signal intensity changes are associated with malignancy, trauma, intraosseus herniation (Schmorl`s nodes) and infection (Morgan & Saifuddin 1999).

## 2.6 Diffusion imaging

### *2.6.1 Diffusion imaging of the intervertebral disc*

Diffusion of the intervertebral disc is studied using contrast media (Ibrahim *et al.* 1994b, Akansel *et al.* 1997) by analysing the changes in signal intensity after the injection over time. Diffusion seems to be different in healthy and degenerated discs (Nguyen-minh *et al.* 1998), and there is also a difference in the diffusion rate achieved with ionic and nonionic contrast media (Ibrahim *et al.* 1994a) and with mature and immature intervertebral discs (Ibrahim *et al.* 1995). Although a decreased diffusion rate has been suggested to be a marker of early disc degeneration (Nguyen-minh *et al.* 1997), the method is not clinically used because it requires moderate amounts of contrast medium intravenously (Nguyen-minh *et al.* 1997, Akansel *et al.* 1997). A study of diffusion tensor microscopy of the annulus fibrosus of excised porcine intervertebral discs has been presented (Hsu & Setton 1999). In that study, the diffusion anisotropy of water and the lamellar structure of the annulus fibrosus were detected with high spatial resolution.

### *2.6.2 Diffusion-weighted MR imaging*

#### *2.6.2.1 Principles*

Molecular diffusion consists of general, thermal and random displacement of molecules. This molecular diffusion together with the microcirculation of blood in the capillary network causes small motions in tissues. The distance between diffusing water molecules is only a few micrometers, and the resolution of MR imaging (DWI) is thus very high (Le Bihan 1998). Molecular motion is isotropic and occurs in all directions (Gray L & MacFall J. 1998). The term ‘intravoxel incoherent motion’ (IVIM) refers to the microscopic translations occurring in voxels on MR images (Le Bihan *et al.* 1986). IVIMs are quantified by a parameter termed ’apparent diffusion coefficient’ (ADC). The ADC is equal to the true diffusion coefficient D when diffusion is the only type of motion. However, the measured ADC values consist not only of diffusion, because perfusion contributes to the ADCs, and the reported ADC values are hence commonly higher than expected (Le Bihan *et al.* 1986). The wide scatter of ADSs in the abdominal organs (Muller *et al.* 1994) has been suggested to be due to the contribution of perfusion (Yamada *et al.* 1999). CSF flow, cardiac pulsations, restriction of possible cellular membranes and fibre packing and orientation may also contribute to ADCs (Gray L & MacFall J. 1998).

Diffusion tensor imaging characterises diffusion imaging, especially in heterogeneous and anisotropic tissues (Pierpaoli C *et al.* 1996, Gray L & MacFall J. 1998). Diffusion is measured in each voxel in each of the three directions (x,y,z), and the measurements are

averaged to generate a Trace D, which is a measure of the average of the three independent scalar elements of the diffusion tensor. The sum of the three scalar elements is known as the trace, and it is independent of direction and location. However, a full diffusion tensor measurement is quite time-consuming, requiring measurements, data acquisition and processing in at least six directions. When diffusion coefficients are measured, multiple images are acquired by applying different gradient strengths with their specific b-values. The diffusion coefficient is plotted as the natural log of the signal intensities versus the b value.

Unfortunately, DWI is very sensitive to motion, and non-diffusion-related motion is therefore usually reduced, using strong gradients of short duration (Le Bihan 1991, Le Bihan *et al.* 1992). DWI is performed by gradient pulses within any imaging pulse sequence, where the degree of diffusion weighting is based on the strength and duration of the gradient pulses (gradient factor). Software-assisted quantitative diffusion imaging can also be performed (Le Bihan *et al.* 1992). Echo-planar imaging (EPI) is the fastest clinically useful imaging technique (Edelman *et al.* 1994), and it is considered the best method for quantifying diffusion (Le Bihan *et al.* 1988).

#### *2.6.2.2 Clinical applications*

DWI is used clinically mainly to evaluate cerebral stroke (Chien *et al.* 1992, Warach *et al.* 1995). Compared to CT and conventional MR methods, DWI enables earlier and more precise detection of the location and extent of an ischemic lesion during the first critical hours after the onset of stroke. Water diffuses more slowly in ischemic regions, and DWI can visualise the cytotoxic edema associated with acute stroke within minutes of vascular occlusion (Le Bihan 1998)

Other applications are also centred round the brain. DWI is used to examine white matter (Doran *et al.* 1990, Larsson *et al.* 1992) and to differentiate between the different components of brain tumours (Le Bihan *et al.* 1992). Some studies also underline the value of DWI in studying the abdominal organs (Muller *et al.* 1994, Yamada *et al.* 1999), and a study differentiating benign from malignant vertebral fractures has also been published (Baur *et al.* 1998). Diffusion studies on the spine are quite rare because of susceptibility artefacts and spatial resolution (Ruggieri 1999).

## 2.7 Imaging of lumbar arteries

### *2.7.1 Angiography*

Angiography is still considered the most effective method to demonstrate vascular structures. In angiograms, normal arteries show a gradual and smoothly tapering

diminution in diameter. Inconsistencies in this geometric pattern are pathologic, including narrowing of vessels, filling defects, irregularity of vascular contours and partial dilatations (Rogoff S.M. & Lipchik E.O. 1970). Compared to conventional angiographies, the modern subtraction technique increases contrast sensitivity (Katzen 1995). Despite the positive features of aortography, the technique also has some limitations. The method is invasive and involves a moderate radiation dose. Contrast allergy and renal insufficiency are also at least relative contraindications for angiography.

### *2.7.2 CT arteriography*

CT arteriography is nowadays considered a promising imaging method for identifying or excluding hemodynamically significant stenoses. Its limitations are the considerable amounts of contrast medium needed (Rubin *et al.* 1995) and the noticeable radiation dose. A major advantage compared to aortoraphy is its smaller invasiveness. With the modern CT technique, using volumetric (spiral) CT scanning, the images can be reconstructed by various computed rendering techniques to generate two- (2-D) or three-dimensional (3-D) images of the blood vessels (Rubin *et al.* 1995). In a study performed by the electron beam computed tomography angiography technique, visceral branches, renal arteries and lumbar arteries were visualised in all of the 155 cases (Lehmann *et al.* 1999).

### *2.7.3 MRI angiography*

MR angiography is a term that refers to a variety of MR imaging techniques designed to produce angiographic images without the use of ionisng radiation (Sheppard 1995). The most commonly used methods of MR angiography are the time-of-flight (TOF), phase contrast (PC) and contrast-enhanced techniques (Korosec & Mistretta 1998). In the imaging of the abdominal aorta, contrast-enhanced MR angiographic methods have proved superior, but 2 D TOF is also used, particularly to demonstrate the length of occlusion and the patency of distal vessels, although the mesenteric branches are not usually adequately delineated (Smyth & Grist 1998).

The above imaging methods differ from each other. The contrast-enhancing techniques are based on the T1 shortening effects of gadolinium chelates (Smyth & Grist 1998), which enhance the contrast between the signal from the vessels and the stationary tissues. TOF achieves a contrast between flowing blood and the stationary tissues by manipulating the magnitude of the MR signal from the stationary tissues, whereas contrast using PC angiography is achieved by manipulating the phase of the MR signal. Both TOF and PC angiographies can be performed by a two-dimensional (2D) or three-dimensional (3D) acquisition scheme (Korosec & Mistretta 1998).

TOF maximises the contrast between flowing blood and stationary tissues. Static tissues are exposed to many radiofrequency pulses (RF) with a repetition time much

faster than T1, which helps to saturate these spins in stationary tissues. After saturation, magnetisation is small and the MR signal becomes low. In contrast, the signal from blood is not as much affected by cumulative RF pulses, because there is a constant flow of fresh blood into the imaging volume. The net magnetisation of these unsaturated spins (blood) is hence much greater than the saturated spins in static tissues (Sheppard 1995, Korosec & Mistretta 1998). A presaturation pulse is used to differentiate between the arterial and venous flows (Sheppard 1995). The ability of this method to enhance the contrast in slowly flowing tortuous vessels is limited, and its clinical use is mostly limited to the study of carotid arteries (Sheppard 1995).

In 2D TOF, thin slices oriented perpendicular to the vessels of interest are obtained. The data are then processed and angiographic images are obtained with maximum intensity projection (MIP) or with a data-adaptive ray-tracing (DART) algorithm (Korosec & Mistretta 1998).

# 3 Purpose of the study

The purpose of the present study was to use imaging modalities:

1. To study the correlation between diffusion in lumbar intervertebral discs and stenosis of lumbar arteries
2. To study the association between end plate degeneration and disc changes among patients with low back pain
3. To study the extent of atherosclerosis in the distal abdominal aorta in chronic low back pain patients and asymptomatic subjects and the correlation of atherosclerosis with the degree of disc degeneration.
4. To study the association between stenosis of lumbar arteries and intervertebral disc degeneration among patients with sciatica
5. To study the association between stenosis of lumbar arteries and symptoms in three-year follow-up among patients with sciatica

# 4 Patients and methods

## 4.1 Study population

All patients were recruited by physicians working in the district served by Oulu University Hospital. Most of them were referred directly from primary care. The control group population and volunteers also came from the same hospital district. All studies were approved by the local ethics committee

### *4.1.1 Low back pain patients (II,III)*

The study population consisted of patients with contiguous low back symptoms for more than one year (36 patients, aged 20–58, mean 40 years in study II and 29 patients, aged 21–58, mean 41 years in study III). All the patients had failed to improve by conservative treatment regimens without any surgical treatment. Thirteen of the patients were smokers (study III), and 11 patients were employed in jobs characterised as heavy (study III).

### *4.1.2 Controls without low back pain (III) and volunteers(I)*

The control group consisted of 52 patients, aged 20–63, mean 43 years, without low back pain collected randomly from among age- and sex-matched patients referred for abdominal CT for the evaluation of abdominal symptoms of obscure origin. Their job status was characterised as heavy in 25 cases, and there were 13 smokers in the group. None of the altogether 37 (aged 22–68, mean 38 years) asymptomatic volunteers had low back pain at the time of the study, nor had they any relevant history of back pain.

### *4.1.3 Sciatica patients and controls (IV,V)*

The study population consisted of consecutive patients with unilateral sciatic pain below the knee for 1 to 6 months referred by general practitioners to Oulu University Hospital (113 patients in study IV and 147 patients in study V). The exclusion criterion wase an earlier back operation. In study IV, a subgroup of 41 patients from the same region were chosen randomly as an age- and sex-matched control group without any low back or sciatic pain at the time of the study and without any relevant history of back pain or sciatic pain. There were 7 smokers among the sciatic patients and 6 smokers among the volunteers (study IV). The questionnaires in study V focused on leg and back pain measured on a visual analog scale (VAS), disability (Oswestry) and self-reported physical ability (self-efficacy). These questionnaires were recorded in the assessments made at one year, two years and three years. Furthermore, the number of medical consultations due to LBP or sciatica, pain duration and the number of pain episodes due to LBP or sciatica were inquired from a period of one year before the baseline assessment. The number of LBP and sciatica episodes during the follow-up was also inquired in the 1-, 2- and 3-year assessments.

## 4.2 Imaging methods

### *4.2.1 CT discography(II,III)*

Discography was performed at L3/4, L4/5 and L5/S1 for the evaluation of low back pain. All of the 87 discograms in study III were technically successful. In study II, 5 discograms of L5/S1 were technically unsuccessful, and altogether 103 intervertebral discs were evaluated. The contrast medium was injected to determine the grade of degeneration (II,III) and the level/s of painful discs (II). The pain during the injection of contrast medium was divided into three categories as follows: negative pain provocation, no pain; indifferent pain provocation, a painful injection, which induced pain different from the patient's clinical symptoms; and positive pain provocation, a painful injection with pain similar to the patient's symptoms. After the injection of contrast medum, the spine was imaged with CT with 3 mm contiguous orthogonal slices from L3 to S1 (II and III)

The extent of contrast medium in discs was evaluated in both studies, and the calcification of the abdominal aorta from L5 to S1 was evaluated in study I. The discogenic changes were graded in CT discography separately for annular disruption and degeneration according to the Dallas Discogram Description (DDD) classification (Sachs *et al.* 1987)as follows: Annular disruption: Grade 0; no contrast extension is visible beyond nucleus pulposus. Grade 1; contrast medium extends into the inner annulus. Grade 2; contrast medium extends into the outer annulus. Grade 3; contrast medium extends beyond the outer annulus. Annular degeneration: Grade 0; contrast only fills

nucleus pulposus. Grade 1 (local); contrast fills < 10% of the annulus, and grade 2 (partial); contrast fills less than 50% of the annulus. Degeneration was rated as 3 when contrast filled more than half of the annulus. The classification was performed independently by two radiologists. The interobserver error was analysed in study III, and it was 0.659 in disc degeneration and 0.856 in disc rupture. In study I, the abdominal aorta calcification from the level of the L3 vertebra to the level of the S1 vertebra was graded on the basis of the size of the biggest plaque in each imaged slice into three grades: Grade 0; no calcifications. Grade 1; aortic wall calcifications involving less than one third of the aortic circumference in a cross-sectional image of the aorta. Grade 2; aortic wall calcifications involving one third to two thirds of the aortic circumference. Grade 3; calcifications comprising more than two thirds of the aortic circumference.

### *4.2.2 Abdominal CT (III)*

The abdomen was imaged with CT with 4 mm contiguous orthogonal slices, and the images were printed on laser film, which was used for the image analysis. The lower abdominal aorta from the level of the L3 vertebra to the level of the S1 vertebra was evaluated for calcifications, which were graded on the basis of the size of the biggest plaque in each imaged slice into three grades. The evaluation and classification of atherosclerosis were made both for patients and for controls.

### *4.2.3 Magnetic resonance imaging*

#### *4.2.3.1 End plate imaging (II)*

End plate imaging was performed in study I with a 1.0 T imaging system (Magnetom Expert, Siemens, Erlangen) consisting of sagittal images with a repetition time (TR) of 4000 msec and an echo time (TE) of 95 msec (T2-weighted) or TR/TR 640/20 msec (T1-weighted). Slice thickness was 4 mm with an interslice gap of 1.0 mm and a field of view 30 cm. The end plate changes were divided into three categories according to the signal intensity of adjacent bone marrow in T1-weighted and T2-weighted images according to Modic(Modic *et al.* 1988b); 0 = no degeneration; 1 = a decreased signal on T1W and an increased signal on T2W; 2 = an increased signal on both T2W and especially T1W; 3 = a decreased signal on both T1W and T2W. The classification was performed independently by two radiologists, and the inter-observer error was 0.879.

### *4.2.3.2 Disc degeneration (I,IV)*

Disc degeneration was recorded with a 1.5 T MR unit (Signa, Echo Speed, General Electric Medical Systems, Milwaukee, Wis). The imaging was done using a phased-array surface coil. In study I, only T2-weighted fast SE sagittal images (TR/TE 6000/105 ms) were taken, whereas in study IV, T2-weighted fast SE sagittal (TR/TE 4000/95 ms) images were taken. In all images, the slice thickness/interslice gap was 4 mm/0.5 mm. The field of view was 30 × 30 cm in the sagittal and 20 × 20 cm in the axial plane. The imaging matrix was 512 × 224 in the sagittal images and 256 × 192 in the axial images.

In study I, the intervertebral discs were classified visually independently by two examiners into three groups: 0 = discs with bright signal intensity, or only a slightly blurred intranuclear cleft, 1 = discs with a normal height, but slightly decreased signal intensity, and 2 = discs with significantly decreased signal intensity and height loss indicating severe degeneration.

In study IV, intervertebral disc degeneration was also graded visually. Discs were classified in a double-blind manner from T2-weighted sagittal images into one of three categories. In category 0, signal intensity was bright and it was considered normal. In category 1, signal intensity was slightly decreased. In category 2, there was a severe loss of signal intensity in nucleus pulposus combined with normal disc height, and in category 3, there was hypointense nucleus pulposus with disc space narrowing.

The signal intensity in the disc was compared with that in the CSF (Luoma *et al.* 2001). If the opinions of the radiologists differed, a consensus was negotiated.

### *4.2.3.3 Diffusion-weighted imaging (I)*

The diffusion measurements were made during the afternoon hours (1–3 PM) using a non-phased-array, general-purpose, receive-only, flexible coil (GPFLEX) with two electronically summed surface coils. The coil could be wrapped around the patient's back to produce a relatively uniform signal throughout the region of interest (ROI). The diffusion-weighted images were obtained using a spin echo single-shot EPI sequence (effective TE about 73 ms, TR 5000 ms, slice thickness 5 mm, spacing 10 mm, FOV 40 × 20 cm, matrix size 128 × 128, 1 NEX). This yielded spatial resolutions of about 3.1 mm and 1.6 mm in the read-out and phase-encoded directions, respectively. The imaging plane chosen was axial. Diffusion weighting was obtained by adding two diffusion-sensitising gradients, one on either side of the 180° refocusing pulse. The pulse duration was $\delta = 32$ ms, the pulse interval $\Delta = 38.1$ ms, and the maximum gradient strength $G_{max} = 22$ mT/m. The gradient ramp time was 184 μs.

Phase encoding was done in the horizontal direction, and read-out was always in the vertical direction. Despite the presence of aortic and cerebrospinal fluid pulsations in the field of view, no noticeable phase-encoding ghosts could be seen in either the T2 or the diffusion-weighted axial images. The pulsations did not overlap with the intervertebral disc area. The diffusion-sensitising gradients were applied sequentially in the x, y, and z directions (z is the direction of the main magnetic field) using diffusion weighting factors (b values) of 250 and 500 s/mm$^2$. The b scale was also checked using the apparent

diffusion coefficient value ADC = $2.0*10^{-3}$ $mm^2/s$ of water at a temperature of 23°C. No susceptibility artefacts were detected in the images.

The ADC values were determined by first calculating the average intensities from a selected region of interest (ROI), separately for image sets taken with b values of 0, 250 and 500 $mm/s^2$. To optimise the SNR, rather low b values were chosen. A least-squares fit was then applied to the resulting three-point attenuation curve.

The ADC values, obtained from the slope of the fitted line, were determined in the three orthogonal directions ($ADC_x$, $ADC_y$ and $ADC_z$).

The imaging area with a sufficient signal covered by the coil was about 20 cm in the slice direction selected. Diffusion imaging was always performed after the anatomic imaging and 2 D TOF MRA, i.e. about 20 minutes after starting the MR study. The time required to perform a diffusion study was about 10 minutes.

#### *4.2.3.4 2D time-of-flight MRA (I,IV,V)*

2D TOF MRA was used to evaluate the patency of the lumbar arteries. In the studies I and IV, these arteries were evaluated as segmental pairs, which were categorised as 0 = normal vessels on both sides, 1 = one segmental artery narrowed, 2 = both segmental arteries narrowed or one or both arteries occluded. The diameters of the lumbar arteries were analysed, and the largest diameter was used as a reference. Both MIP and coronal source images were used to determine the stenosis of the lumbar arteries. The images were evaluated by two radiologists, using a GE Advantage Windows workstation. In the case of disagreement, a consensus was negotiated. MR images were obtained in the coronal direction to cover the area of the lumbar spine, using a TE of 5.1, a TR of 29, a flip angle of 60º, 256 × 512 matrix, a 30 cm FOV and a slice thickness 1.5 mm. A spatial pre-saturation pulse was placed posterior to the imaging slices in order to suppress the signal from the lumbar veins. In study V, the analysis was made using the sum of narrowed or occluded arteries as follows:

### *4.2.4 Statistical methods*

In study I, the association between the ADC values of disks, disk degeneration and the status of lumbar arteries at the same level were analysed by means of covariate and pairwise analysis (Scheffé's *post hoc* multiple-comparison test). The $\chi^2$-test was also used to calculate the correlation between the findings of CT/discography and MRI in study II and to calculate the difference between the low back pain patients and controls in the control-case studies III and IV. The association between the symptoms and the vascular lumbar artery disease was calculated with the $\chi^2$-test in study V. Because of the small number of older patients, Fisher's exact test was also used in study III. The other statistical tests used in study II were the Mann-Whitney U-test and the Kruskall-Wallis test.

# 5 Results

## 5.1 Correlation between diffusion in lumbar intervertebral discs and occlusion of lumbar arteries (I)

### *5.1.1 MRI and MRA findings in asymptomatic adults*

In a group of 37 asymptomatic adults, 108 out of 145 (74%) lumbar discs were normal, 25 (17%) were slightly degenerated (class 1), and 14 (9%) were severely degenerated (class 2). Of the lumbar artery pairs, 42 were graded as normal, 35 as grade 1 and 21 as grade 2.

### *5.1.2 Diffusion values of lumbar intervertebral discs compared with MRI and MRA findings*

The mean ADC values (x $10^{-3}$ $mm^2/s$) in normal discs (all levels) in the x, y and z directions were 1.38, 1.52 and 1.56, those in mildly degenerated discs 1.05, 1.12 and 1.21, and those in severely degenerated discs 1.06, 1.10 and 1.16, respectively. The mean ADC values (all levels) in the x, y and z directions in the discs with normal lumbar artery pairs were 1.49, 1.60 and 1.64, those in the discs with grade 1 lumbar artery pairs 1.35, 1.52 and 1.57, and those in the discs with grade 2 lumbar artery pairs 0.63, 0.66 and 0.70, respectively.

There was a significant correlation between the status of the lumbar arteries and the ADC values of the lumbar discs in the three orthogonal directions (x, y and z) at the levels L1/2, L2/3 and L3/4 and for the ADC in the x direction at L4/5 ($p < 0.001$). The correlation was less pronounced, but still significant ($p < 0.01$) for the ADCs in the y and

z directions at the L4/5 level. The results are presented in Table 1. Also, when age was controlled for, the association between the ADCs and the lumbar arteries and the correlation between the status of the lumbar arteries and the ADC values remained significant.

*Table 1. Association between ADC values (mm2/s) and the status of the lumbar arteries at L1/2–L4/5*

| | lumbar arteries 2DTOF | L1/2 (std.dev / std.error) (N = 19) | L2/3 (std.dev / std.error (N = 28) | L3/4 (std.dev / std.error) (N = 27) | L4/5 (std.dev / std.error) N = (24) |
|---|---|---|---|---|---|
| $ADC_x$ | 0 | 1.51*(0.11/0.03) | 1.50*(0.11/0.03) | 1.54*(0.10/0.02) | 1.49*(0.08/0.03) |
| | 1 | 1.27*(0.05/0.02) | 1.29*(0.04/0.01) | 1.39*(0.10/0.03) | 1.44*(0.12/0.04) |
| | 2 | 0.44*(0.21/0.15) | 0.55*(0.32/0.13) | 0.63*(0.39/0.15) | 0.69*(0.46/0.16) |
| $ADC_y$ | 0 | 1.64*(0.26/0.09) | 1.55*(0.09/0.02) | 1.67*(0.15/0.04) | 1.66**(0.10/0.03) |
| | 1 | 1.54*(0.28/0.10) | 1.45*(0.18/0.05) | 1.49*(0.16/0.05) | 1.59**(0.18/ 0.06) |
| | 2 | 0.16*(0.06/0.04) | 0.54*(0.29/0.12) | 0.55*(0.25/0.10) | 0.90**(0.59/0.21) |
| $ADC_z$ | 0 | 1.64*(0.28/0.09) | 1.61*(0.14/0.04) | 1.77*(0.19/0.05) | 1.80**(0.08/0.03) |
| | 1 | 1.54*(0.18/0.06) | 1.51*(0.29/0.09) | 1.68*(0.23/0.08) | 1.65**(0.29/0.09) |
| | 2 | 0.16*(0.03/0.02) | 0.49*(0.19/0.08) | 0.71*(0.40/0.16) | 0.92**(0.52/0.18) |

The correlation between the mean ADC values ($mm^2/s$) of the discs and the status of the lumbar arteries (2D-tof) is statistically significant (one -way ANOVA; * $p < 0.001$; ** $p < 0.01$)

Although the ADC values for all orthogonal directions decreased with increasing disc degeneration, there were no statistically significant correlations between the ADC values and the degree of disc degeneration (Table2).

*Table 2. Association between ADC values ($mm^2/s$) and disc degeneration at L1/2–L4/5*

| Disc Degeneration | | L1/2 (std.dev / std.error) (N = 19) | L2/3 (std.dev / std.error) (N = 28) | L3/4 (std.dev / std.error) (N = 27) | L4/5 (std.dev / std.error) (N = 24) |
|---|---|---|---|---|---|
| $ADC_x$ | 0 | 1.35(0.25/0.06) | 1.35+ (0.31/0.07) | 1.41(0.35/0.09) | 1.45** (0.13/0.04) |
| | 1 | 0.93(0.90/0.60) | 1.02+ (0.60/0.27) | 1.22(0.40/0.12) | 0.90** (0.56/0.19) |
| | 2 | 1.30(0.07/0.05) | 0.98+ (0.36/0.16) | 0.63(0.73/0.52) | 1.14** (0.52/0.23) |
| $ADC_y$ | 0 | 1.53(0.47/0.12) | 1.45* (0.32/0.07) | 1.53+++ (0.37/0.09) | 1.63 (0.16/0.04) |
| | 1 | 0.81(0.86/0.81) | 1.20* ( 0.47/0.21) | 1.21+++ (0.51/0.16) | 1.15 (0.67/0.24) |
| | 2 | 1.40(0.30/0.21) | 0.87* (0.55/0.24) | 1.01+++ (0.93/0.66) | 1.23 (0.50/0.23) |
| $ADC_z$ | 0 | 1.36(0.40/0.10) | 1.49++ (0.38/0.09) | 1.70(0.46/0.11) | 1.75*** (0.19/0.05) |
| | 1 | 1.02(1.18/0.83) | 1.19++ (0.56/0.25) | 1.31(0.41/0.13) | 1.13*** (0.64/0.22) |
| | 2 | 1.57(0.24/0.17) | 0.92++ (0.61/0.27) | 1.07(0.90/0.64) | 1.27*** (0.46/0.21) |

The correlation between the mean ADC values (mm2/s) of the discs and disc degeneration (one-way ANOVA) *p = 0.024; ** p = 0.028;***p = 0.016;+p = 0.085;++p = 0.051;+++p = 0.072)

The number of severely degenerated discs was small at L1–2 (n = 2) and L3–4 (n = 2), and statistical significance can therefore be reliably assessed only at the L2–3 and L4–5 levels. Even though the correlation between disc degeneration and the diffusion values

was not statistically significant, there was a trend with eight outliers: These eight severely degenerated discs had almost normal diffusion values in all directions (ADCx 1.36, ADCy 1.45, ADCz 1.54) and normal or grade 1 lumbar artery status as compared with all severely degenerated discs (1.06, 1.10 and 1.16, respectively).

## 5.2 Association between end plate degeneration and disc degeneration and discogenic pain among chronic low back pain patients (II)

### *5.2.1 End plate degeneration in MRI compared with image findings in CT discography*

There were 64 discs with normal end plate findings in MRI and 39 discs with end plate degeneration. In CT discography, six of the discs were normal in appearance, 96 showed disc degeneration, and 87 showed an annular tear. There was a positive correlation between end plate degeneration in MRI and disc degeneration in CT discography (Table3), but no correlation between end plate degeneration in MRI and disc rupture in CT discography (Table 4).

*Table 3. Correlation between end plate degeneration in MRI and disc degeneration in CT discography*

| Disc degeneration in CT discography | grade 0 | grade1 | grade2 | grade3 | Total |
|---|---|---|---|---|---|
| grade 0 | 7 | | | | 7 |
| grade 1 | 29 | 4 | 1 | | 34 |
| grade 2 | 22 | 8 | 4 | 1 | 35 |
| grade 3 | 6 | 5 | 15 | 1 | 27 |
| Total | 64 | 17 | 20 | 2 | 103 |

Pearson Chi-Square value = 40.817; df = 9; p = 0.000

*Table 4. Correlation between end plate degeneration in MRI and disc rupture in CT discography*

| Disc rupture in CT discography | grade 0 | grade1 | grade2 | grade3 | Total |
|---|---|---|---|---|---|
| grade 0 | 13 | 2 | 1 | 0 | 16 |
| grade 1 | 10 | 2 | 0 | 1 | 13 |
| grade 2 | 26 | 9 | 11 | 1 | 47 |
| grade 3 | 15 | 4 | 8 | 0 | 27 |
| Total | 64 | 17 | 20 | 2 | 103 |

Pearson Chi-Square value = 11.194; df = 9; p = 0.263

### *5.2.2 Pain provocation in discography compared with end plate degeneration in MRI and disc degeneration in CT discography*

A significant correlation was found between disc rupture and pain provocation in CT discography (Table 5), but no correlation was detected between pain provocation in CT discography and disc degeneration (Table 6) or end plate degeneration (Table 7).

*Table 5. Correlation between disc rupture and pain provocation in CT discography*

| Pain provocation in CT discography | grade 0 | grade1 | grade2 | grade3 | Total |
|---|---|---|---|---|---|
| no pain | 16 | 10 | 23 | 6 | 55 |
| indifferent pain | | 2 | 4 | 5 | 11 |
| positive pain | | 1 | 20 | 16 | 37 |
| Total | 16 | 13 | 47 | 27 | 103 |

Pearson Chi-Square value = 29.983; df = 6; p = 0.000

*Table 6. Correlation between disc degeneration and pain provocation in CT discography*

| Pain provocation in CT discography | grade 0 | grade1 | grade2 | grade3 | Total |
|---|---|---|---|---|---|
| no pain | 6 | 19 | 16 | 14 | 55 |
| indifferent pain | | 3 | 4 | 4 | 11 |
| positive pain | 1 | 12 | 15 | 9 | 37 |
| Total | 7 | 34 | 35 | 27 | 103 |

Pearson Chi-Square value = 4.550; df = 6; p = 0.603

*Table 7. Correlation between end plate degeneration in MRI and pain provocation in CT discography*

| Pain provocation in CT discography | grade 0 | grade1 | grade2 | grade3 | Total |
|---|---|---|---|---|---|
| no pain | 35 | 10 | 9 | 1 | 55 |
| indifferent pain | 7 | | 4 | | 11 |
| positive pain | 22 | 7 | 7 | 1 | 37 |
| Total | 64 | 17 | 20 | 2 | 103 |

Pearson Chi-Square value = 4.330; df = 6; p = 0.632

## 5.3 Association of atherosclerosis in the distal abdominal aorta with low back pain and degree of disc degeneration (III)

### *5.3.1 Association of calcification in the abdominal aorta in CT and degree of disk degeneration in CT discography among chronic low back pain patients*

Among 29 patients with severe chronic low back pain, no correlation between the quantity of aortic calcifications in CT and the degree of annular disruption or general degeneration in CT discography was detected.

### *5.3.2 Calcification in the abdominal aorta in CT in subjects with and without low back pain*

Aortic calcification was identified in CT in 15 (55%) of the 29 low back patients, whereas only 11 (21%) of the 52 age-matched patients without low pack pain were found to have aortic calcifications. Eleven (48%) patients aged under 50 years (n = 23) with low back pain had aortic calcifications, whereas only 3 (8%) of the 36 control patients under 50 had aortic calcifications. The percentages are presented in Table8.

*Table 8. Atherosclerotic findings in cases and controls*

| | < 50 yr | | > 50 yr | | total | |
|---|---|---|---|---|---|---|
| | With LBP (n = 23) | Without LBP (n = 36) | With LBP (n = 6) | Without LBP (n = 16) | With LBP (n = 29) | Without LBP (n = 52) |
| No. (%) of subjects with atherosclerosis | 11(48)* | 3(8)* | 5(83)† | 8(50)† | 16(55)‡ | 11(21)‡ |
| No. (%) of subjects without atherosclerosis | 12(52) | 33(92) | 1(17) | 8(50) | 13(45) | 41(79) |

* $X^{2} = 12.09419$, df = 1, P = 0.00051

† Probability was $P_1 = 0.17824$ (Fisher´s exact test)

‡ $X^2 = 9.6952$, df 1, P = 0.0185

## 5.4 Association between occlusion of lumbar arteries and intervertebral disc degeneration among patients with sciatica (IV)

### *5.4.1 Association between lumbar arteries in MRA and disc degeneration in MRI among sciatica patients (IV)*

The 113 patients had 125 discs graded as normal and 327 discs graded as degenerated in MRI (131 mild, 165 moderate, 31 severe degeneration). 107 pairs of arteries were normal and 345 pairs were narrowed. Among the degenerated discs, the grade of narrowing of lumbar arteries increased with increasing degeneration (77% in discs with mild, 85% in discs with moderate and 84% in discs with severe degeneration). The correlation between disc degeneration and the status of lumbar arteries in the whole lumbar spine (L1 to L4) was statistically significant ($p < 0.001$). When analysed by disc level, the correlation was statistically significant at the levels L2/3 ($p = 0.031$) and L3/4 ($p = 0.039$).

### *5.4.2 Occlusion of lumbar arteries observed in MRA and intervertebral disc degeneration observed in MRI of asymptomatic people compared to patients with low back pain and sciatica (IV)*

In the group of 41 sciatica patients, 164 discs and lumbar artery pairs were examined and compared to 164 discs and lumbar artery pairs of 41 volunteers. The number of degenerated discs was higher in the patients compared to the volunteers (121 vs. 73, respectively). The degree of disc degeneration was also significantly more pronounced among the sciatica patients at L2/3, L3/4 and L4/5 ($\chi^2$-test; P-values 0.01, 0.03 and 0.008, respectively).

MRA showed decreased blood flow in 74 lumbar artery pairs in the pain patients in contrast to 55 lumbar artery pairs in the volunteers (Table 9). The lumbar artery pairs of the patients were significantly more narrowed at all disc levels ($\chi^2$-test; P-values 0.001, 0.007, 0.001, 0.001, respectively).

*Table 9. Correlation of disc degeneration and status of lumbar arteries between volunteers and back pain patients*

| disc degeneration | total | | normal | | occluded | | absent | |
|---|---|---|---|---|---|---|---|---|
| | sciatica n = 164 | asympt. n = 164 | sciatica n = 90 | asympt. n = 109 | sciatica n = 45 | asympt. n = 51 | sciatica n = 29 | asympt. n = 4 |
| normal | 43/26% | 91/55% | 30/18% | 67/41% | 7/4% | 24/15% | 6/4% | 0/0% |
| mild degeneration | 55/34% | 51/31% | 32/20% | 29/18% | 14/9% | 18/11% | 9/5% | 4/2% |
| moderate degeneration | 58/35% | 22/13% | 26/16% | 13/8% | 19/12% | 9/5% | 13/8% | 0/0% |
| severe degeneration | 85% | 0/0% | 2/1% | 0/0% | 5/3% | 0/0% | 1/1% | 0/0% |

## 5.5 Association between pain symptoms and occlusion of lumbar arteries among patients with sciatica at three-year follow-up (V)

In the series of 147 patients, 688 lumbar artery pairs were examined. The baseline stenosis of lumbar arteries was associated with the intensity of back pain at 1 year ($t_1$ ) ($p = 0.036$), leg pain at 2 years ($t_2$) ($p = 0.006$) and self-reported physical ability (self-efficacy) at 1 year ($t_1$ ), 2 years ($t_2$ ) and 3 years ($t_3$) ($p = 0.005$, 0.003 and 0.007, respectively), but not with disability, previous LBP history or future pain episodes (table 10).

*Table 10. Association between stenosis of lumbar arteries and symptoms during three years*

| Symptoms | Stenosis[+] at the baseline MRI | | Stenosis[+] at 3 year MRI | |
|---|---|---|---|---|
| | Spearman's rho | Significance | Spearman's rho | Significance |
| At 1 year | | | | |
| Back pain | 0.174 | 0.036 | 0.181 | 0.036 |
| Leg pain | 0.125 | 0.133 | 0.123 | 0.157 |
| Self-efficacy | -0.232 | 0.005 | -0.204 | 0.018 |
| Oswestry | 0.107 | 0.198 | 0.107 | 0.219 |
| At 2 years | | | | |
| Back pain | 0.116 | 0.177 | 0.078 | 0.381 |
| Leg pain | 0.235 | 0.006 | 0.197 | 0.026 |
| Self-efficacy | -0.252 | 0.003 | -0.219 | 0.013 |
| Oswestry | 0.117 | 0.174 | 0.080 | 0.368 |
| At 3 years | | | | |
| Back pain | 0.064 | 0.451 | 0.001 | 0.990 |
| Leg pain | 0.129 | 0.129 | 0.075 | 0.389 |
| Self-efficacy | -0.228 | 0.007 | -0.166 | 0.055 |
| Oswestry | 0.087 | 0.307 | 0.046 | 0.596 |

[+] Stenosis is a calculated sum of the scores of the eight individual arteries. An artery was classified as narrowed if the diameter of the vessel was restricted (by at least one third) and as occluded if it was not detectable.
MRI = magnetic resonance imaging

Categorised new arterial stenosis was associated with medical consultations because of LBP during one year before the baseline assessment ($p = 0.025$) and also with prolonged LBP (over 3 months) during the year before the baseline ($p = 0.015$). The association between new stenosis and prolonged sciatica pain was weaker ($p = 0.05$) New incident arterial stenosis also correlated weakly ($p = 0.09$) with new sciatic episodes between the one-year and two-year follow-up examinations (Table11).

*Table 11. Association of new stenosis of the lumbar arteries with medical consultations and duration of LBP symptoms and sciatica*

| Period of assessment | Total | Occurrence of ≥ 2 grades of newly formed arterial occlusion between the baseline and 3-year MRI assessments* | | |
|---|---|---|---|---|
| | | n | % | p† |
| One year before baseline | | | | |
| Medical consultations due to low back pain | | | | 0.025 |
| None | 41 | 3 | 7.3 | |
| One or more | 93 | 21 | 22.6 | |
| Medical consultations due to sciatic pain | | | | 0.428 |
| None | 72 | 12 | 16.7 | |
| One or more | 62 | 12 | 19.4 | |
| From baseline to 1 year | | | | |
| Prolonged low back pain | | | | 0.015 |
| Less than 3 months | 75 | 8 | 10.7 | |
| More than 3 months | 51 | 14 | 27.5 | |
| Prolonged sciatic pain | | | | 0.053 |
| Less than 3 months | 94 | 13 | 13.8 | |
| More than 3 months | 40 | 11 | 27.5 | |
| From 1 year to 2 years | | | | |
| New low back pain episodes | | | | 0.115 |
| None to 2 | 97 | 15 | 15.5 | |
| 3 or more | 29 | 8 | 27.6 | |
| New sciatic episodes | | | | 0.362 |
| None to 2 | 105 | 18 | 17.1 | |
| 3 or more | 22 | 5 | 22.7 | |
| From 2 years to 3 years | | | | |
| New low back pain episodes | | | | 0.276 |
| None to 2 | 108 | 18 | 16.7 | |
| 3 or more | 25 | 6 | 24.0 | |
| New sciatic episodes | | | | 0.085 |
| None to 2 | 110 | 17 | 15.5 | |
| 3 or more | 23 | 7 | 30.4 | |
| Total | 134 | 24 | 17.9 | |

* A stenosis classification of no changes to one artery narrowed (or one narrowed artery occluded) vs. more pervasive stenotic changes.

† 1-sided exact significance from Fisher's test.

# 6 Discussion

The aim of the study was to evaluate the relationship between diminished blood flow and painful disc degeneration. Diffusion is one potential mechanism to connect diminished blood flow and DD. The relationship was further evaluated in a clinical series to provide information of the relationship between decreased blood flow and painful DD and, ultimately, diminished blood flow and the prognosis of painful DD. The initial hypothesis was that the effect of nutritional factors on disc degeneration would be perceived in histological and experimental studies (Horner & Urban 2001, Boos *et al.* 2002). The validity of this hypothesis has not been evaluated earlier in a clinical population. In this study, the hypothesis was evaluated in cross-sectional studies with patients and controls (I–IV) and, finally, in a follow-up survey (V).

Cross-sectional studies can be used to outline or confirm a hypothesis, but they provide limited evidence of the causality of phenomena. In addition, factors that are not measured or recorded (called confounders) further detract from the evidential power of these studies. When a cross-sectional study design is used, the level of probability achieved is an "associative" level rather than proof of a causative relationship. These limitations can be avoided in a cohort study, which, however, takes a very long time to perform and is therefore often impossible to carry out.

## 6.1 Study populations

The patient population in the present study consisted of two different groups: patients with chronic low back pain (II, III) and patients with acute sciatica. Patients with chronic LBP were selected in order to have a patient group with severe degeneration and vascular changes. This was done because the methods of examination were considered to be rather insensitive. Patients with sciatica and *a priori* new intradiscal changes were selected because experiment studies have indicated that slightly decreased flow makes the disc susceptible to tears and diminishes its regenerative potential.

In order to limit the number of confounding factors, some special exclusion criteria were used. The patients were recruited by physicians working in Oulu University Hospital's catchment area. Most patients were referred directly from primary care. The

inclusion criteria in the sciatica group (IV,V) were unilateral pain below the knee and symptom duration from 3 to 28 weeks. Clinically depressive patients, patients applying for early retirement and patients who had undergone back surgery were excluded.

The population without any low back symptoms were drawn from the same central hospital distinct without any other limitations except asymptomatic low back currently and previously. The group thus represents a general population without back symptoms. In order to minimise confounders, the patients and asymptomatic controls were matched for gender, age and smoking.

## 6.2 Methods

All images were analysed by experienced radiologist blinded to the patients' clinical status. The intra- and inter-tester reliabilities in image analysis were moderate or substantial. The MRI and MRA protocols were valid enough for evaluating disc degeneration and diffusion and narrowing of the lumbar arteries. The window levels in evaluating arterial calcifications were similar in both study groups (III). The patients were characterised using validated questionnaires (VAS, Oswestry, Self-Efficacy, NHP) (V), clinical examination (V), MRI (I,II,IV,V) and CT discography (I,III). To avoid changes in the water content and swelling pressure of NP (Adams & Hutton 1983, Urban & McMullin 1988), diffusion was imaged during the afternoons, in order to maintain the conditions similar for all measurements.

In MRA imaging, the limitation concerning the resolution of 2D TOF MRA did not allow detection of all possible collaterals. The role of collaterals in intradiscal nutrition is, however, obscure (Kauppila 1994). The ostia of the lumbar arteries are visualised by the TOF MRA method, but significant ostium stenosis can be detected as diminished blood flow in 2D TOF images. To test the validity of 2D TOF, its correlation with normal DSA arteriography, the gold standard for the evaluation of blood vessels, was evaluated and found to be good.

The axial plane was used in the measurement of ADC values. With sagittal imaging, the possibility of a partial volume effect is smaller, but imaging in sagittal slices limits the ROI size more than axial imaging does, and axial image planes were therefore chosen for the present study. In order to accurately quantify diffusion anisotropy, diffusion tensor imaging, which would allow calculation of the diffusion ellipsoid, should be carried out. However, diffusion tensor imaging was previously found to be unreliable due to noise, motion and magnetic field inhomogeneities (Kerttula *et al.* 2000). Diffusion was measured in three orthogonal directions; the z gradient being the direction of both the magnetic field and the vertical axis of the patient. Though perfusion usually contributes to the ADC values (Le Bihan *et al.* 1988), this effect was expected to be negligible in discs because of their avascularity.

In previous spinal diffusion imaging studies, steady-state sequence (Baur *et al.* 1998), spin-echo sequence (Clark *et al.* 2000) and EPI sequences (Kerttula *et al.* 2000) have been used. We used the fast acquisition method EPI (Echo Planar Imaging) sequence, which minimises motion artefacts, but is very sensitive to susceptibility artifacts. Susceptibilities have been found to be almost the same in cortical bone, water and soft

tissues (Schenk JF 1996). Thus, although various tissue-bone interfaces are located very close to the intervertebral discs, we do not suspect that they could affect the ADC values; at least we did not detect susceptibility artefacts in the images. Cerebral spinal fluid flow does not cause problems in the lumbar spine (Ruggieri 1999). The ADC values of normal discs in the present study were in very good agreement with the values presented in an earlier study on intervertebral discs (Kerttula *et al.* 2000).

In the present study, low b values, opposite to brain diffusion studies, were chosen to optimise the SNR, because the signal was too low at higher b values. The SNR of diffusion-weighted images was still rather poor. This is explained, at least partly, by the coil used and the relatively long echo time needed for diffusion imaging. The general-purpose surface coil collects signals only from a very limited source volume, and the discs are located relatively deep in the body, where the signal is already considerably attenuated. Thus, the patient's body size also affects the signal intensity. The slice thickness of 5 mm used in this study was chosen as a compromise between the SNR and the reasonably reliable positioning of the slice within the disc.

Two persons made the intradiscal injections without any measurement of or congruence with the pressure of the contrast injection, which must be regarded as a limitation.

## 6.3 Role of end plate degeneration in intradiscal changes among patients with low back pain (II)

The end plate is the main route of diffusion. The nutrition provided by arterial flow is delivered through the end plate (Roberts *et al.* 1989, Moore *et al.* 1992). MRI is the most sensitive method to show changes in the end plate, and MRI was therefore used as a method of analysing end plate degeneration. The aim in the present study was to evaluate the associations between the different end plate changes and degeneration and disc rupture. This could give information of whether the end plate degeneration occurs in an early phase of the disc damage process, in association with intradiscal ruptures, and the general disc degeneration follows later, or whether it is a single mechanism associated with general disc degeneration caused by other factors. Furthermore, the correlation between discographic pain provocation and end plate degeneration was analysed, in order to evaluate if the possible correlation could partly explain the low back pain.

A comparison between end plate degeneration in MRI and intradiscal changes revealed in discography showed end plate degeneration to be associated more clearly with long-term disc damage, i.e. degeneration, than acute disc damage, i.e. annular rupture. The primary nutritional pathway into the avascular disc is assumed to be from the subchondral vessels via the end plate (Roberts *et al.* 1989, Moore *et al.* 1992). If this route were disturbed because of a calcified endplate or occlusion of the subchondral vessels, internal disc disruption could follow (Roberts *et al.* 1989). End plate degeneration has been found to occur parallel to other disc degeneration events (Horner & Urban 2001). Histologic studies have revealed coincidence of microfractures in the end plate and intradiscal tears and clefts (Moon *et al.* 2000, Boos *et al.* 2002). It is therefore assumed that the degenerative process affecting the end plate, the NP and the AF is a

temporal sequence of nutritional deficiency (Boos *et al.* 2002). The results of these studies agreed with the present findings, which showed end plate degeneration to be more likely associated with disc degeneration than with the first phase disc damage, disc rupture.

No differences were found between the end plate degeneration categories and pain provocation, and the results were hence opposite to the previous findings (Weishaupt *et al.* 2001), which showed end plate changes to be associated with low back pain. It is yet possible that the irritation of a ruptured disc by contrast medium is such a dominant factor in producing pain that minor variables, such as possible end plate irritation, will be masked, which might explain why no evident correlation between pain provocation and end plate changes was found. On the other hand, we only evaluated intradiscal pain, and the possible end plate-originated symptoms may not be discogenic. Yet, the results showed that a significant number of positive pain provocations were associated with no end plate degeneration, which also indicates the negative role of end-plate degeneration in producing low back pain. Findings of concordant pain during discography in discs with annular ruptures support the results of previous studies showing an association between intradiscal ruptures and low back pain (Vanharanta *et al.* 1988, Moneta *et al.* 1994).

## 6.4 Arterial findings, diffusion and disc degeneration among people without low back pain (I)

The results of study I revealed a strong correlation between diminished flow in the lumbar arteries detected in MRA and apparent diffusion coefficients of the lumbar intervertebral discs. Atherosclerotic changes in the lumbar arteries have been shown to be associated with lumbar disc degeneration (Kauppila *et al.* 1997). Also, ADC values of intervertebral discs have recently been presented (Kerttula *et al.* 2000), but the present study is the first to show the clinical relevance of the changes in ADC values. The strong correlation between lumbar artery occlusion and decreased ADC values may be due to diminished intradiscal osmotic pressure. However, the diffusion coefficients obtained by MR imaging may differ from the "nutritional diffusion" through the end plates, for the diffusion coefficients may also reflect the degradation and disintegration of nucleus pulposus. The molecular nature of these findings remains unclear.

There was moderate variation in the findings on lumbar artery status between the disc levels. It has been demonstrated earlier that the correlation of atherosclerotic changes with disc degeneration was stronger at the upper compared to the lower levels of the lumbar spine (Kauppila 1994)

Surprisingly, eight intervertebral discs were severely degenerated, but the corresponding lumbar artery pairs and diffusion values were normal. This supports the previous understanding that pathogenesis of disc degeneration is multifactorial. In addition to nutritional determinants, environmental and genetic factors also play a major role in the initiation of disc degeneration (Battie *et al.* 1995a, Battie *et al. 1995b,* Annunen *et al.* 1999).

The well-being of a disc is greatly dependent on its cells (Maroudas 1988, Boos *et al.* 2002). The cell density of a disc is controlled by nutritional factors (Stairmand *et al.*

1991). During the degenerative process, considerable alterations occur in the structure and biochemistry of the intervertebral disc. The effect of altered hydration on solute transport is rather complex (Maroudas 1988), because a decrease in hydration means a lower diffusion coefficient, but, on the other hand, the height of the disc has decreased. Thus, the distances that metabolites must travel are shorter (Maroudas 1988). This may explain the findings that the ADC values did not decrease linearly during the degeneration process. It is suggested that the decreased water content as such is not likely to significantly affect the balance between the cellular requirements and metabolite transport, although its effect on the mechanical properties of the disc is obvious (Maroudas 1988).

## 6.5 Arterial findings, disc degeneration and low back pain (III,IV,V)

The major findings in the literature concerning the role of blood flow and disc degeneration can be summarised as follows. In cadaveric studies, atherosclerotic manifestations in the abdominal aorta and the lumbar arteries correlated with low back pain (Kauppila *et al.* 1997) and disc degeneration (Kauppila *et al.* 1994). In a cross-sectional cohort study, calcification of the abdominal aorta was found to correlate with disc degeneration in agreement with the present study (Kauppila *et al.* 1997). In some follow-up studies, vascular disease and LBP have been found to correlate (Penttinen 1994, Kauppila *et al.* 1997), and one post-mortem study also showed this association (Kauppila & Tallroth 1993). In epidemiological studies, low back pain and arterial disease have been found to have some common risk factors (Frymoyer & Gordon 1989, Battie *et al.* 1991). Histologic and experimental studies have revealed the association between nutritional factors and disc degeneration (Horner & Urban 2001, Boos *et al.* 2002). It has been shown anatomically that vascular buds penetrate the cartilaginous end plates on the vertebral side, but rarely communicate with the disc substance itself (Moore *et al.* 1992), and that the nutrition of discs occurs mainly via diffusion from the blood vessels into the surrounding structures (Holm *et al.* 1981, Horner H.A. & Urban J. 2001). Thus, changes in the end plate and the vessels may cause a reduction in this pathway.

The present study is the first to analyse the correlation between lumbar artery changes and disc changes in a clinical series. The results of this study may also give new information of the mechanism causing painful disc degeneration. It has been found in an experimental study that the reduction in nutrition may cause intradiscal tears and reduce the regenerative ability of cells in discs. The mechanical stress is also more likely to cause tears in conditions of reduced nutrition(Boos *et al.* 2002). This was also shown by the clinical results of the present study. These remaining tears could be a source of intradiscal pain and thus explain the difference in the degree of disc degeneration and lumbar artery occlusion between people with and without low back pain.

In the present study, there was a significant difference in the arterial findings between populations with and without low back pain. These results (III and IV) indicate that vascular changes causing insufficient blood supply in the abdominal aorta and the lumbar arteries are more common in the LBP population. Atheromatous lesions in the abdominal aorta most commonly occur around the aortic bifurcation, where the orifices of the

lumbar arteries are also located (Rogoff S.M. & Lipchik E.O. 1970, Ross R 1988). Patients with chronic low back pain were more likely to have atheromatous plaques in the abdominal aorta than patients without back pain, as analysed by CT, and this association was most distinct in the youngest patients (III). Also, when sciatica patients were compared to an asymptomatic population, intervertebral disc degeneration and narrowing of the lumbar arteries were significantly more pronounced in the sciatic population at almost every disc level (IV). In general, it can be concluded that the present study showed multiple evidence of an association between vascular changes and low back pain and disc degeneration.

Although a correlation between the arterial findings and disc degeneration was found in the sciatica group, the patients with chronic low back pain showed no association. This may be explained by the fact that the precise location of the plaques in the abdominal aorta with respect to the orifices of the lumbar arteries was not evaluated in this study, and the arterial flow to the disc area may thus also be different in cases with equal quantities of plaques. The finding may also be explained by postulating that the calcifications seen in the aorta are already late findings, while earlier predictors have initiated the disc degeneration (Boos *et al.* 2002)

There was a similar clear association between disc degeneration and lumbar artery disease among the sciatica patients. The correlation between the 2 D TOF findings and disc degeneration was not constant at all disc levels (L1/2 and L4/5). This may be due to the multifactorial nature of disc degeneration (Battie *et al.* 1995a) and also to the poor detection of possible collateral vessels by the 2D TOF technique.

In a three-year follow-up (V), physical ability (analysed by a self-efficacy questionnaire) at every assessment point (1, 2 and 3 years) and some symptoms (back pain at 1 years and leg pain at 2 years) were significantly associated with vascular disease of the lumbar arteries. Baseline lumbar artery stenosis was also associated significantly with 1 years' back pain and 2 years' leg pain. The narrowing process of lumbar arteries between 1 and 3 years was also interestingly associated with the symptoms of earlier sciatica episodes.

The results of the follow-up study showed further that, apart from definite pain, feelings of illness and decreased physical ability were also associated with lumbar artery occlusion. Self-efficacy beliefs appear to correlate with total pain behaviours {1257}. Furthermore, pain severity was also found to predict total pain behaviours {1258}, and one possible explanation of the present results thus lies in the repeated episodes of severe pain among patients with lumbar artery disease. On the other hand, the difference may be due to other atherosclerotic manifestations, and self-efficacy beliefs are thus a combination of many reasons.

The most typical natural history of LBP and sciatica is characterised by a short duration and a high remission rate (Carey *et al.* 1999, Balague *et al.* 1999). Nevertheless, there is a certain portion of patients whose pain becomes chronic (Carey *et al.* 2000), but the factors contributing to chronic pain are unknown. On the basis of this study, one possible factor causing severe, and possibly chronic, pain symptoms could be occlusion of the lumbar arteries. The results indicate that lumbar artery stenosis does not only cause DD and pain, but the presence of arterial changes makes the symptoms more severe and also has a negative effect on spontaneous healing.

In the light of earlier studies, it is not surprising that diminished blood supply has been found to associate with poor recovery and recurrence of symptoms. Apart from intradiscal causes of low back pain, however, many other causes alone or combined with intradiscal factors may influence low back pain patients' subjective symptoms and confound the present results. However, the clear association between subjective symptoms and vascular changes highlights the importance of evaluating vascular factors in the diagnosis and treatment of low back pain. Although the diagnosis of atherosclerosis and lipid metabolism and the prevention of atherosclerosis do not traditionally belong to the treatment of low back pain patients, the present study suggests a need for reconsideration.

# 7 Conclusions

1. Stenosis of lumbar arteries is significantly associated with decreased diffusion of lumbar discs and may thus play an important role as a mechanism of disc degeneration.
2. End plate degeneration is associated with disc degeneration, but not with disc rupture. Nor is end plate degeneration associated with discogenic pain caused by CT discography.
3. Atheromatous lesions in the abdominal aorta are more common and more extensive in patients with chronic low back pain than in asymptomatic people. There was no association between atheromatous lesions in the abdominal aorta and disc degeneration among chronic low back pain patients.
4. Stenosis of lumbar arteries is associated with disc degeneration among sciatica patients, and the grade of occlusion of lumbar arteries and the severity of disc degeneration are significantly higher among sciatica patients compared to asymptomatic subjects.
5. Stenosis of lumbar arteries was associated with back pain symptoms and physical activity among sciatica patients in three-year follow-up.

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