Prognostic factors for recovery in radicular pain caused by lumbar disc herniation

by

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Abbreviations

AF	Annulus fibrosus
ANOVA	Analysis of variance
CC	Craniocaudal size
CI	Confidence interval
CILP	Cartilage intermediate layer protein
CNS	Central nervous system
COL	Collagen
COMT	Catechol-*O*-methyltransferase
COX	Cyclooxygenases
CPM	Conditioned pain modulation
CT	Computed tomography
DD	Disc degeneration
DDD	Degenerative disc disease
DH	Disc herniation
DNA	Deoxyribonucleic acid
DNIC	Diffuse noxious inhibition control
DRG	Dorsal root ganglion
GABA	γ-aminobutyric acid
GWA	Genome wide association
EFP	Endoneurial fluid pressure
ELISA	Enzyme-linked immunosorbent assay
EMG	Electromyography
EPs	Endplates
EPJF	Endplates junction failure
HIZ	High intensity zone
HSCL-25	Hopkins Symptom checklist
IASP	International Association of the study of Pain
IDIC	Intradiscal injection of corticosteroids
ILs	Interleukins
IFN-gamma	Interferon Gamma
IVD	Intervertebral disc
LBP	Low back pain

IL1RN	IL-1 receptor antagonist
MC	Modic changes
MMP	Matrix metalloproteinases
MPQ	Norwegian version of the McGill Pain Questionnaire
MRI	Magnetic resonance imaging
NP	Nucleus pulposus
ODI	Oswestry Disability Index
OPRM1	Opioid receptor mu 1
P. acnes	Proprionibacterium acnes
PAG	Periaqueductal gray
PFC	Prefrontal cortex
PCP	Protein gene product
PNS	Peripheral nervous system
PPT	Pressure pain threshold
QPS	Questionnaire for Psychological and Social Factors at Work
RNA	Ribonucleic acid
rmANOVA	Repeated measures analysis of variance
RVM	Rostral ventromedial medulla
SIA	Stress-induced analgesia
SLR	Straight leg raising
SNP	Single nucleotide polymorphism
SPSS	Statistical Package for the Social Sciences
TIMP	Tissue inhibitors of metalloproteinase
TNF-α	Tumour necrosis factor alpha
VAS	Visual analogue scale
VNTR	Variable number of tandem repeat
VDR	Vitamin D receptor

List of papers

The thesis is based on the following papers, which are referred to in the text by their roman numbering I-IV:

Paper I. E.I. Schistad, A. Espeland, L.M. Pedersen, L. Sandvik, J. Gjerstad, and C. Røe. Association between baseline IL-6 and one-year recovery in lumbar radicular pain. *Submitted.*

Paper II. Elina Iordanova Schistad, Line Melå Jacobsen, Cecilie Røe, and Johannes Gjerstad. The interleukin-1α gene C>T polymorphism rs1800587 is associated with increased pain intensity and decreased pressure pain thresholds in patients with lumbar radicular pain. *The Clinical Journal of Pain*. *Epub ahead of print*.

Paper III. Elina Iordanova Schistad, Ansgar Espeland, Lars Jørgen Rygh, Cecilie Røe, and Johannes Gjerstad. The influence of Modic changes on pain during one-year follow-up in patients with lumbar radicular pain. *Submitted.*

Paper IV. Maria Belland Olsen, Line Melå Jacobsen, Elina Iordanova Schistad, Linda Margareth Pedersen, Lars Jørgen Rygh, Cecilie Røe, and Johannes Gjerstad. Pain intensity the first year after lumbar disc herniation is associated with the A118G polymorphism in the opioid receptor mu 1 gene: evidence of a sex and genotype interaction. *The Journal of Neuroscience.* 2012 Jul 18;32(29):9831-4.

Summary

Lumbar radicular pain constitutes only 5%-10% of low back pain conditions, but it accounts for 33% of the sick leave and 47% of the disability benefits due to back pain in Norway. Previous data show that the recovery from lumbar radicular pain may be influenced by physical, psychosocial, surgery-related and clinical factors. In addition, genetic factors can influence on the development of disc degeneration and the recovery after symptomatic disc herniation.

The fact that inflammation contributes to the pathogenesis of disc herniation and radicular pain is now well established. The inflammatory response, initiated from the annulus fibrosus in case of disc herniation, may lead to increased levels of pro-inflammatory interleukins (ILs) close to nerve roots. This inflammatory process could also promote Modic changes.

In this thesis, the role of such cytokines and genetic factors in recovery from lumbar radicular pain was addressed. The present data demonstrated a significant association between the inflammatory serum cytokine IL-6 and functional recovery from symptomatic disc herniation. Moreover, the genotype IL-1α C>T rs1800587 increased the risk of persistent pain 1-year after disc herniation. Regarding the radiological factors, we showed that type I Modic changes influences the short-term clinical outcome in patients with low back pain and radicular pain. A sex dependent effect of the opioid receptor mu 1 (OPRM1 A118G) rs1799971 genotype on recovery after disc herniation was also identified.

It is concluded that inflammatory, radiological and genetic factors may be important for the recovery after lumbar disc herniation.

Norsk sammendrag (Summary in Norwegian)

Radikulær utstrålende smerte på bakgrunn av skiveherniering representerer kun 5%-10% av alle korsryggsmerter, men står for 33% av sykefraværet og 47% av uføretrygden relatert til slike ryggplager i Norge. Tidligere studier har vist at fysiske, psykososiale, kirurgirelaterte og kliniske faktorer påvirker sykdomsforløp ved lumbal skiveherniering. I tillegg kan genetiske faktorer ha betydning for utvikling av skivedegenerasjon og sykdomsforløp etter skiveherniering.

Patogenesen ved prolapsbetinget radikulær utstrålende smerte omfatter både inflammatorisk og mekanisk nerverotspåvirkning. Inflammasjon igangsettes av annulus ruptur som ofte fører til skiveherniering med frisettelse av en rekke proinflammatoriske stoffer bl.a. interleukiner (ILer) som påvirker nerverøttene. Det er også vist at denne proinflammatoriske prosessen fremmer dannelse av Modic forandringer.

I dette arbeidet er betydning av inflammatoriske og genetiske faktorer for sykdomsforløp ved symptomgivende skiveherniering studert. Våre resultater viste en signifikant assosiasjon mellom det inflammatoriske serum cytokinet IL-6 og gjenvinning av funksjon. Videre, ble det vist at genotypen IL-1α C>T rs1800587 økte risikoen for vedvarende smerter ved ett års oppfølging. Når det gjelder radiologiske faktorer, ble Modic type I forandringer vist å påvirke første del av forløpet hos pasientene med radikulær utstrålende smerte. En kjønnsavhengig effekt av opioid receptor mu 1 (OPRM1) A118G rs1799971 genotypen for smerte og funksjon etter lumbalt skiveprolaps ble også vist.

Det konkluderes med at inflammatoriske, radiologiske og genetiske faktorer har betydning for sykdomsforløp ved radikulær utstrålende smerte etter lumbal skiveherniering.

1. Introduction

1.1 Definitions and terminology

The International Association for the Study of Pain (IASP) defines *pain* as: "…**an unpleasant sensory and emotional experience, associated with actual or potential tissue damage, or described in terms of such damage**" [123, 124]. Thus pain is an experience with sensory, cognitive, and emotional components. The evolutionary function of pain perception is primarily detection of tissue damage. High-intensity heat, mechanical stimuli or chemicals that can produce such tissue damage are termed "noxious stimuli", and are selectively detected by specific transducers called nociceptors localized at the peripheral nerve terminals.

Nociception refers to the neural process by which noxious stimuli are detected by the nervous system. In contrast, the term pain is reserved for the psychological experience. Still, pain unpleasantness serves as a signal allowing avoidance of stimuli that can damage tissue. Thus, pain is an important physiological mechanism that increases the chance of survival. Unfortunately, pain can outlive its usefulness as a warning system, and can instead become chronic and debilitating. The transition to chronic pain involves mechanisms of peripheral and central sensitisation. Pain, similar to most experiences, can also be affected by psychosocial factors [84, 170]. Better understanding of the neurophysiologic mechanisms involved in the development and maintenance of pain will probably improve future treatment of chronic pain conditions [118, 119].

Pain is often classified as nociceptive, inflammatory, neuropathic and noninflammatory/non-neuropathic pain [103, 184]. *Nociceptive pain* arises from damage to non-neural tissue causing activation of nociceptors. *Inflammatory pain* is also a response to tissue damage eliciting an immune response and inflammation which activates the nociceptors. Inflammatory pain may overlap with nociceptive pain, but do not involve nerve damage [184]. *Neuropathic pain* is in contrast defined as pain caused by a lesion or disease of the somatosensory nervous system [113, 168]. In neuropathic pain the warning system of the body itself is damaged. This neural damage results in sensory deficits and may in some patients leads to inappropriate nociceptive signaling to the brain that induces pain. Another pain category is *noninflammatory/non-neuropathic pain*, such as in fibromyalgia, tension-

type headache, irritable bowel syndrome, or temporomandibular disorder [103].

The term *Low back pain (LBP)* is used for pain localized in the low back, irrespectively of causes [172]. The term chronic LBP is used for duration of pain above 3 months [129]. LBP may be source of referred pain. *Referred pain* is pain in a region of the body topographically distinct from the region in which the actual source of pain is located. Referred pain from lumbar spine is initiated by activation of nerve endings innervating spinal structures such as discs, zygapophysial joints, or sacroiliac joints. The proposed mechanism of referral is convergence of nociceptive afferents on second-order neurons in the spinal cord. The pattern of referred pain in the lower limb corresponds to the segmental innervation of deep tissues in the lower limb, such as muscles and joints [21].

Radicular pain, in contrast, is caused by activation of the nerve roots. This form of radiating pain has also been called sciatica. The taxonomy of the IASP recommends replacement of sciatica with the term "radicular pain" [21]. Moreover, radicular pain should not be mixed with the term radiculopathy. Notably, *radiculopathy* is characterized by objective signs of loss of neurological function (loss of sensory and/or motor function and/or diminished reflexes) as a result of conduction block in axons of a spinal nerve or its roots, but is not necessarily associated with pain. Still, radiculopathy and radicular pain commonly occur together and may also be caused by the same lesion. The present thesis will focus on radicular pain and associated LBP due to disc herniation (DH).

1.2 Epidemiology and clinical presentation of lumbar radicular pain

A large variation in the prevalence of lumbar radicular pain is reported in the literature due to a lack of strict definitive criteria [99, 161]. Several studies report a lifetime prevalence of 14–40% for leg pain associated with back problems, but do not distinguish true radicular pain from the more common referred pain [67]. However, if stricter definitions of radicular pain are used the prevalence rate may be approximately 2% [38, 189]. Although lumbar radicular pain constitutes only 5–10% of LBP conditions [97], sick leave and disability benefits due to radicular pain account for 33% and 47%, respectively, of all back pain conditions in Norway [23].

Lumbar radicular pain is characterized by radiating pain in an area of the leg typically

innervated by one nerve root in the lumbar or sacral spine [95], and is evoked by ectopic discharges emanating from a dorsal root or its ganglion [124]. Radicular pain is typically caused by DH, but can also be due to mechanical compression of the nerve by a bone spur (osteophytes), thickening of surrounding ligaments or disc protrusion in case of lateral spinal stenosis. Patients with lumbar radicular pain often have LBP. Other less common causes of radilar pain are tumours or infections. Scoliosis can cause the nerves on one side of the spine to become compressed by the abnormal curve of the spine.

The clinical presentation of lumbar radicular pain varies depending on the type and level of DH in lumbar spine and the affected nerve roots. Patients will often have pain in the lumbar region that radiates to one or both legs. Such leg pain is described typically as burning, stabbing, or shooting and is often exacerbated by coughing and sneezing. In radiculopathy, however, neurological signs are present such as weakness, numbness, or reflexive changes [165]. Clinical presentation for lumbar radicular pain, following a specific pain patterns in lower limbs, is well described and usually involves the L3, L4, L5 or S1 root [73]. DH often causes severe LBP.

Diagnosis: The diagnosis of a lumbar radicular pain is based on symptoms and clinical examination findings. The neurologic examination, which includes an assessment of sensory, motor function and deep tendon reflexes in lower limbs and nerve stretch tests as straight leg raising (SLR), crossed SLR, reverse SLR, is important. However, the diagnostic accuracy of the SLR and crossed SLR tests is limited by its low specificity and sensitivity, respectively [37, 174]. Examination of a patient suspicious of cauda equine syndrome includes testing anal sphincter tonus and bladder function.

The diagnosis of radicular pain due to DH may be confirmed by magnetic resonance imaging (MRI), alternatively computed tomography (CT) or CT myelography of lumbar spine. An MRI is more informative than CT because it also identifies other intraspinal pathologies. DH is defined on MRI as a localized displacement of disc material and can be classified as protrusion (mostly “focal” protrusions, not a “bulging” disc), extrusions (ruptured annulus fibrosus) or sequestrations (herniated disc material has no continuity with the disc of origin) [32, 46]. Electromyography (EMG)/neurography provide a more detailed assessment of nerve dysfunction, and is useful in diagnosis of radiculopathy.

Prognosis and treatment: The majority of patients with radicular pain due to DH have spontaneous regression of symptoms [13, 179]. Patients with persistent radicular pain lasting more than 8 weeks, neurological deficits (sensory changes, muscle weakness or depressed or absent deep tendon reflexes) and corresponding MRI findings of DH in the anticipated location may be assessed for surgical treatment. The surgery involves mostly partial removal of the herniated disc (microdiscectomy), rarely complete removal of the disc (discectomy). The utility of surgery for symptomatic lumbar DH is reviewed briefly. There is considerable evidence on the clinical effectiveness of DH surgery in patients that do not respond to conservative management [57]. Conservative treatment usually consists of activity guidance during the acute phase of symptomatic DH, use of analgesics and adjuvant analgesics, brief cognitive intervention, exercises and physiotherapy [110].

1.3 The intervertebral disc

1.3.1 The normal anatomy

The intervertebral disc (IVD) consists of the circumferential annulus fibrosus (*AF)* encapsulating the central nucleus pulposus (*NP)*. The third component of the IVD is the vertebral *endplate (EP)*, which comprises two layers of cartilage covering the top and bottom aspects of each disc.

The AF consists of collagen Type I oblique fibres aligned in a lamellae. Within the lamella, the collagen fibres run parallel to one other, starting from the vertebra below and ending at the vertebra above. Each fiber forms a 65-70° angle from the vertical. Annulus cells are mostly elongated fibroblasts, some lying parallel to the lamellae and some rounded in shape. AF cells synthesize mostly proteoglycans and collagen [60]. The main proteoglycan in the IVD is aggrecan, which has high glycosaminoglycan content.

The NP is a semifluid mucoid material, which consists of 70–90% water, although the exact proportion varies with age. Proteoglycans are the next major component, and they constitute approximately 65% of the dry weight of the NP. The water of the NP is contained within the domains of these proteoglycans. The majority of the proteoglycans are in the form of freely dispersed proteoglycan units that lack a functional binding site that would enable them to aggregate with hyaluronic acid, and only approximately 25% of the proteoglycans occur in an

aggregated form. Interspersed through the proteoglycan medium are thin fibrils of type II collagen, which serve to hold proteoglycan aggregates together. The mixture of proteoglycan units, aggregates and collagen fibres within the NP is referred to collectively as the matrix of the NP. Embedded in the proteoglycan medium of the NP are cartilage cells (chondrocytes) and some primitive notochordal cells, which disappear after approximately 10 years of age. The fluid nature of the NP allows it to be deformable under physical stress, but at the same time not compressible. Thus, under extreme loads, the NP deforms and distributes the weight in all directions, minimizing physical and structural damage.

The intervertebral disc is the largest avascular tissue in the body, and the supply of essential nutrients including oxygen, glucose, and substrates for matrix production occur through diffusion. The metabolism of cells in the NP is very sensitive to changes in pH. They are maximally active in pH ranges of 6.9–7.2, but below 6.8 their activity falls sharply and below 6.3 their activity is only approximately 15% of the maximum.

The organization of the IVD defines its response to mechanical stresses. The IVD serves three biomechanical functions. First, it sustains weight when transferring a load from one vertebra to the next. Second, it enables a rocking movement of the vertebrae by being deformable. Third, it provides the spine strength by withstanding ripping or breaking in situations of physical stress [60].

The vertebral EPs consist of a layer of cartilage and are approximately 0.6–1 mm thick. The EP cartilage is made up of hyaline cartilage and fibrocartilage. Hyaline cartilage is most prominent in the early developing stages of the disc and tends to appear on the outer portions of the IVD. Conversely, fibrocartilage is present more in older IVDs and further towards the centre of the disc. The EPs are recognisable as discrete entities at an embryonic stage in the development of the axial skeleton and remain as cartilaginous plates during the subsequent ossification of the vertebrae. In this early period, tiny blood vessels penetrating the EPs provide nutrition, not only for the cartilage itself, but also for the developing disc that eventually becomes enveloped by the AF and the vertebral body [127]. EPs function both as a mechanical barrier between the pressurized NP and the vertebral bone, and as a gateway for nutrient transport into the disc from adjacent blood vessels [169]. The creation of blood vessels in the EP is facilitated by the activation of enzymes such as matrix metalloproteinase (MMP), which are latent under normal conditions [62, 87, 127].

MMP-3 (stromelysin) in particular has been detected at high concentrations in degenerate discs.

1.3.2 Disc degeneration

Disc degeneration (DD) is a multifaceted chronic process that alters the structure and function of IVDs. DD is probably initiated by damage to the AF or vertebral EPs, or by a cell-mediated reduction in proteoglycan content [3]. Deterioration of the AF is manifested as annular tears that can extend in different directions (radial, transverse, or concentric) and that involve various depths of the AF. Radial tears or fissures progress outward from the NP, usually posteriorly or posterolaterally, and this process can be simulated in cadaveric discs by cyclic loading of bending and compression [1]. Radial fissures have been linked to ingrowth of blood vessels and nerve fibres [25] and are associated with DD. Deterioration of the AF and disc narrowing represent internal disc disruption and lead to "pathologic" discs [3]. Pathological DD is quite different from the normal aging process of the disc and often occurs in young individuals. With increasing age discs get harder and stiffer, because the mucoid matrix of the NP is progressively replaced by fibrous tissue. However, the disc height during normal aging of discs is maintained and radial tears or endplate defects are absent. Anterior osteophytes are also associated with the normal aging process of the discs.

In contrast, pathological degeneration is unrelated to aging and is characterized by mixed endplate erosions and reactive osteosclerosis, gas in the centre portion of the disc space, disc narrowing, and posterior osteophytes, where the latter is always associated with a posterior disc rupture. DD is an aberrant, cell-mediated response to progressive structural failure. A degenerate disc is one with structural failure combined with accelerated or advanced signs of aging (not normal aging) [3]. Age and degeneration are nevertheless related, but degeneration has the greater effect on intradiscal stresses. In the early stages of degeneration, the cells make collagen and proteoglycans in an attempt to repair, but as the degeneration proceeds, synthesis slows down and the disc components break down. A decrease in proteoglycan synthesis leads to a loss of water, height, and hydrostatic pressure. Age-related degenerative changes reduce the sagittal diameter of the NP by approximately 50%, and the pressure within it falls by 30%. The width of the NP increases by 80%, and compressive stress peaks within the posterior AF, which is affected more than the anterior AF, increase by 160% [2]. Over time, this can cause decreased flexibility and

strength. The degeneration process also involves an increase in the synthesis of catabolic molecules, such as MMP, which cause further degradation.

Degenerative disc disease (DDD) applies to a degenerated disc that is also painful [3]. Concentrated areas of high stress in the posterior AF and presence of inflammation and granulation tissue in the AF, may be a cause of pain, and of further structural disruption [2, 187]. DDD cases usually comprise patients with some radiological evidence (MRI) of DD and clinical symptoms, usually LBP and/or radicular pain. DDD includes lumbar DH that often leads to lumbar radicular pain and neurological signs as well as more definite radiographic evidence [77]. However, a generally accepted definition for DDD and its phenotype is lacking [45, 120]. Common structural changes visualized on MRIs include radial fissures, radial bulging of the AF, reduced disc height, osteophyte formation, reduced signal intensity (reflecting disc dehydration), and EPs defects [3, 48]. Complicating matter is the fact that the correlation of imaging findings with patient symptoms is weak and there is a high prevalence of abnormal neuroimaging findings in asymptomatic individuals [18, 42]. Factors contributing to the development of DDD include mechanical stress, nutritional factors, and genetic variables. Numerous studies have suggested that heredity is largely responsible for the development of lumbar DD [54], and that environmental factors play a much smaller role than previously believed [15, 45]. However, disc height changes seem not to be were not heritable, and disc signal changes is heritable only among those under 50 years [183].

1.3.3 Vertebral endplate (Modic) changes

Modic changes (MC) are defined as signal-intensity changes in the vertebral body marrow adjacent to the EP that are verifiable on MRI [34]. Three main forms of vertebral EP degenerative changes have been described [126]. Type I changes of the EPs are increased on T2 images and low on T1-weighted images and represent vascular fibrous tissue, bone oedema, and inflammation, which contribute to more acute changes of DD. Type II changes are increased on T1-weighted images and iso- to hyperintense on T2-weighted images. Similar to type I changes, there is EP disruption when examined histopathologically. However, in contrast to the presence of vascularized fibrous tissue seen in type I changes; there is the presence of yellow marrow accounting for the shortening of the T1 signal. Type III changes, representing dense woven bone and absence of marrow, are decreased on both

T1- and T2-weighted images and correlate with sclerotic changes seen on spine radiographs [42]. A dynamic course of these MCs was demonstrated, where type I MC evolves into type II MC; however, a reverse process of type II into type I or to total absence is not unusual [6, 74]. The incidence of new MC's was reported as 6% in patients with conservatively treated DH over a 3-year follow-up [101].

The prevalence of all types of MCs increases with age, and is lower in nonclinical populations compared with patients with chronic LBP, with prevalence rates of 6% and 46–81%, respectively [10, 80]. Moreover, earlier observations indicate that the prevalence of MC's in symptomatic DH varies between 25% in patients with acute lumbar radicular pain to 49% in patients 14 months after acute DH [7]. The prevalence of MC seems to be higher in patients with DH scheduled for surgical treatment compared with conservatively treated patients. For instance, Vredeveld et al. reported a prevalence of 32% for type I MC, 66% for type II MC, and 2% for type III MC in military men with lower lumbar DH who were scheduled for surgery (lumbar discectomy) [173]. In contrast, Albert and Manniche reported a prevalence of 9% for type I MC and 14% for type II MC in patients with present DH, who received conservative treatment [7]. There is evidence for an association between MC (particularly type I, but also type II) and LBP. Type I MCs have been shown to be both commonly observed in and associated with LBP [7, 80, 96, 102]. MCs may also play a role in the pathogenesis of lumbar radicular pain [7].

One explanation for the occurrence of MCs is that disruption of the internal architecture of the disc causes increased loading and leads to microfractures of the EPs (mechanical hypothesis). The cartilaginous EP is inclined to be damaged by mechanical injury, such as compressing forces, shear stress, and torsion [2, 3]. Histological examination of Type I MCs shows disruption, fissures, and vascular granulation tissue adjacent to the EPs [126]. EP cracks accompanied by increased vascular density and biological reactions to disc materials may lead to an inflammatory reaction during the early stages of DH and induce LBP, associated with type I MCs. Fayad et al. showed that patients with chronic LBP and predominantly Type I MCs had significant pain reduction 1month after intradiscal injection of corticosteroids (IDIC), compared to Type II MCs [47]. At 3 and 6 months, IDIC tended also to be more effective in the predominantly Type I MCs, but not significantly. This finding indicates the possible role of autoimmune reactions in type 1 MCs [116]. Ohtori et al. found significantly more protein gene product (PGP) 9.5- immunoreactive nerve fibres and

tumour necrosis factor alpha (TNFα) immunoreactive cells in vertebral EPs from patients with Type 1 or Type 2 MCs (especially in type 1) compared with LBP patients with normal EPs on MRI [131]. Bailly et al. has shown that LBP in patients with Type I MCs consists of an inflammatory pain pattern (i.e. presence of at least one of these three features: maximal pain on morning, waking at night because of pain, or morning stiffness for longer than 60 min) [14].

Infection is another possible cause of bone oedema underlying type I MCs (bacterial hypothesis). Following a severe tear in the AF as in a DH, new capilarisation and inflammation occurs around the extruded NP. This special environment enables for anaerobic bacteria to enter the anaerobic IVD and develop low virulent infection [6]. Previous studies suggest discs infected with anaerobic bacteria are more likely to develop MCs in the adjacent vertebrae compared with those in which no bacteria or aerobic bacteria are isolated. Stirling et al. found that IVD material removed during surgery for lumbar DH (microdiscectomy) was infected with low virulence anaerobic organisms, mainly Proprionibacterium acnes (*P. acnes*) in 19 out of 36 (53%) patients [163]. Distinguishing between a bacterial association with lumbar DH and contamination of the surgical wound by the normal skin microbiota is important in defining a microbial role. To eliminate possible skin contamination, Stirling et al. performed a prospective study using disc material harvested under stringent aseptic precautions from 207 microdiscectomy and 27 trauma, tumour, or scoliosis patients (controls). In the microdiscectomy group, 76/207 (37%) patients had positive cultures after seven days incubation, mainly *P. acnes*, of which 26 (34%) had positive serology. Conversely, no (0 %) bacteria were found in the extracted IVDs from the control group [162]. Theoretically, if skin contamination was the cause of bacterial presence in the IVD then the percentage of infected patients should be very similar. However, other researchers still posit that *P. acnes* found in IVDs is a skin contaminant [28, 121].

Albert et al. hypothesized that these anaerobic mouth and skin commensal organisms gain access to the disc during normal bacteremia as a result of the neovascularisation associated with DD or herniation [6]. Local inflammation in the adjacent bone may, in this case, be a secondary effect due to cytokine and propionic acid production, i.e., the infection is in the IVD and the MC is a "side effect'' manifest in the bone. *P. acnes* cannot live in the highly vascularised/aerobic bone and is not present there [180]. Albert et al. has shown that patients with LBP and type I MC due to DH, who were treated with antibiotics (amoxicillin-

clavulanate 500 mg/125 mg, 3 × daily for 100 days) showed statistically significant pain reduction compared with the placebo group [8]. Thus, treatment with certain antibiotics is significantly more effective compared with placebo against LBP due to type I MC. If these findings are replicable, they could fundamentally change the concept of type I MC associated LBP and, consequently, treatment strategies [20]. Historically, bacteria have been implicated in the pathogenesis of other conditions that do not primarily present as infectious diseases, such as gastric ulcers. Conversely, most antibiotics, including β-lactams have anti- inflammatory effects [9, 181]. Fayad et al. reported that pain relief after an intradiscal injection of corticosteroids does not support an infectious origin of the type I MC [47]. However, it is imperative to confirm these results in different settings before antibiotics are routinely prescribed for chronic LBP due to type 1 MC. Moreover, treatment with antibiotics may be relevant only for patients with type 1 MC who represent a relatively small group of LBP patients. In addition, the use of broad spectrum antibiotics over a long period may lead to the development of antibiotic resistance [159], which at the present time is a significant global concern.

Regarding operative treatment of patients with MCs, a previous study has suggested that patients with radicular pain due to DH with and without type I MCs have similar long-term recovery profiles of back pain after lumbar discectomy surgery [132]. In contrast, another study has shown that patients with type I MC had less improvement of back pain 1 year after microdiscectomy, compared with those who had no or other types of MC, but not if they smoked cigarettes [158]. In more extensive spinal surgery, better results of anterior fusion were observed for LBP patients with DDD in patients with type I MCs [29]. In addition, type I or II MCs were reported as one of the best predictors of success after disc prosthesis surgery [71].

1.4 Pathoanatomy and pathophysiology of disc herniation (DH)

Neo-angiogenesis and neurogenesis in the annular tears is associated with inflammation. This sensitizes nociceptors in the AF, which affects DRGs, and causes LBP or radicular pain [49, 187]. Both annulus tears and EP junction failure (EPJF) lead to lumbar DH. The EPJF defines radiological as vertebral corner defect, rim avulsion, frank bony avulsions, and avulsion at both upper and lower EP. Rajasekaran et al. has shown in a multimodal *in vivo* study that lumbar disc herniation (LDH) is more often the result of EPJF than AF

rupture [145]. This study confirms that EPJF by avulsion is the main cause of lumbar DH. The incidence of EPJF was 58% when only preoperative radiological assessment was considered, but increased to 65% when intraoperative findings of cartilage avulsion were added. The evidence of EPJF opens up potential opportunities for prevention of progression of lumbar DH after the initial event of EPs avulsion.

DH leads to an injury-induced inflammation mediated by biochemical and immunological factors, which determine the pathophysiology of radicular pain [22, 39, 128]. Several studies have shown an increasing role of inflammatory cells [63], immunoglobulins and pro-inflammatory agents include phospholipase A_2 [53], MMPs [87], prostaglandin E_2 [87], leukotriene B_4 and thromboxane [130], nitric oxide (NO) [68, 86], interleukin 1α (IL-1α) [155], interleukin 6 (IL-6) [87], interleukin 8 (IL-8) [27], interleukin 12 (IL-12) and interferon γ [65], TNF- α[5], and cyclooxygenases (COX) [86]. NP tissue contact with the systemic circulation in DH leads to lymphocyte activation with secretion of Interferon Gamma (IFN-gamma) and macrophage recruitment. Macrophages are specially involved in the regression of DH [76]. Further, neovascularization in herniated disc tissue may promote the formation of granulation tissue and deposits of immunoglobulins in association with blood vessels [66]. The disc material stimulates the production of IgM and IgG antibodies [160], particularly to the glycosphingolipid of nerve roots. TNF-α has been suggested to play a key role in NP mediated nerve root injury. TNF-α alone, or in combination with other cytokines, has been demonstrated to stimulate NO production. NO is also involved in the pathophysiological effects of NP in DH, through a variety of biological events including vasodilation, neurotransmission, cytotoxicity, gene regulation, vascular permeability, and blood flow alterations, and recruitment of inflammatory cells. In addition, application of NP induces a decrease in nerve-conduction velocity in spinal nerve roots after only a few days. This indicates a relatively rapid mode of action in terms of the functional effects of NP on nerve roots [26]. Taken together, the inflammatory reaction around the herniated disc material leads to an injury to the nerve root with consequent disturbance of intraradicular blood flow and breakdown of the blood-nerve barrier, resulting in intraradicular inflammatory changes such as edema and demyelination [39].

1.5 Radicular pain mechanisms

Historically, Mixter and Barr in 1934 described disc-related sciatica as a consequence of compression of the nerve root due to DH [125]. More recent research has shown that only if nerve roots have been previously inflamed does mechanical stimulation evoke radicular pain [156]. Specifically, mechanical compression of a healthy nerve root caused dysesthesia, paresthesia, or motor loss, but no pain. Compelling evidence from animal models has shown that mechanical compression of either the dorsal root ganglion (DRG) or of chronically injured roots can induce prolonged repetitive firing in sensory axons [72]. Studies in rats, using pain behaviour assessment, have indicated that the NP may well be involved in pain production. Pain behaviour in this context refers to response thresholds to thermal and mechanical stimuli. Further, Olmarker et al. provided the first evidence that the NP may induce nerve tissue injury by mechanisms other than mechanical compression [134]. Such mechanisms may be based on direct biochemical effects of the NP components on nerve fibre structure and function, and microvascular changes including inflammatory reactions in nerve roots, in the absence of mechanical compression [134]. Kawakami et al. also showed that a three-level laminectomy and an application of homologous NP or AF taken from discs in another rat, and applied at three nerve roots, produced pain behaviour [92]. Application of NP to nerve roots increases endoneurial fluid pressure (EFP) and decreases blood flow in the associated DRG, resulting in intraneural oedema in NP-treated nerve roots and DRG [185]. NP exposure and displacement at the nerve root level produced more behavioural changes compared with NP exposure and displacement of the DRG [51].

In animal studies, application of NP to nerve roots induces inflammatory changes in the form of increased vascular permeability, oedema, and intravascular coagulation [133, 185]. Inflammation damages nerve roots, blocks nerve conduction, increases nociceptive activity in the pain pathways and produces hyperalgesia and pain behaviour [41, 91, 139]. The mediators of this inflammatory response are phospholipase A_2, NO, and TNF-α [41, 75, 90]. However, both chemical and mechanical factors are needed to induce radicular pain. These factors likely exert a synergistic effect where chemical factors may play the predominant role early in the pathogenic process [128, 135]. In addition, in Olmarker et al's model, pain behaviour was present when disc incision was combined with a slight medial displacement of the nerve root or DRG. The combined action of disc incision and slight mechanical deformation induced statistically verified changes, whereas each of the two injuries by

themselves did not.

The LBP, associated with DH, may primary arise from the discs, but can also occur from facets, muscles, or vertebrae. Degenerated lumbar discs, a high intensity zone (HIZ) in the disc, facet arthropathy, and Modic changes in the vertebral bone marrow are associated with LBP [31]. Changes in paraspinal muscle morphology, smaller multifidus muscle cross-sectional area, and greater fatty infiltration are also related to LBP [52]. In spite of the fact that LBP likely arises from a physical process in the back and ensuing nociception, development of chronic LBP and disability depends more on psychological factors than on the physical condition of the back, and can be understood and managed by a biopsychosocial model [175, 176]. As pain becomes chronic (longer than 12 weeks) attitudes and beliefs, distress, and illness behaviour play an increasing role in the development of chronicity.

1.6 Pain modulation

The healthy brain maintains a dynamic balance between endogenous pain suppression and pain facilitation. This balance likely accounts, in large part, for inter-individual differences in pain response and day-to-day variation due to life circumstances [122]. Under extreme conditions such as trauma and stress, endogenous pain controls can be strongly activated; blocking the pain experience even in the presence of severe injury [122]. A shift towards facilitation (e.g. nocebo, hypervigilance, or catastrophizing) which increases pain may also occur. It is widely believed that reduced background inhibition and an enhanced "tone" of facilitation can cause chronic pain conditions [58, 103]. The pain system involves the peripheral nervous system (PNS), which generates pain-provoking signals, and the central nervous system (CNS), which integrates these signals and relays them to a conscious brain in a "*bottom-up*" process. Increased responsiveness and a reduced threshold of nociceptive neurons in the periphery to stimulation represent *peripheral sensitisation*. In response to inflammation or nerve injury, the somatosensory system may increase its sensitivity, resulting in a maladaptive response. Thus, innocuous stimuli generate an amplified response [25]. Nociceptors conduct nociceptive signals via the nociceptive Aδ- and C-fibres, which make synaptic connections with neurons in the dorsal horn of the spinal cord. However, irrespective of origin these signals are modulated. The first possible level for impulse modulation is the DRG and spinal dorsal horn [25]. Subsets of dorsal horn neurons, in turn, project axons and transmit pain messages to higher brain centres, including the reticular

formation, thalamus, and ultimately the cerebral cortex [83]. Most frequently the signals are inhibited at the spinal and/or supraspinal level. *Central sensitisation* in contrast is defined as increased responsiveness of nociceptive neurons in the CNS to their normal or subthreshold afferent input [123].

Pain is also influenced by a "*top-down*" mechanism of pain modulation. The descending modulation is controlled by supraspinal structures such as the amygdala, periaqueductal grey (PAG), and rostral ventromedial medulla (RVM). Consistent with this, several investigations have noted a relationship between abnormalities in descending modulation and clinical pain syndromes, including DH with radicular pain. Descending pain control can be experimentally assessed and is termed conditioned pain modulation (CPM); previously named diffuse noxious inhibition control (DNIC) and "pain-inhibits-pain". The DNIC system is a spinal-bulbo-spinal pathway that was first described in animals by Le Bars et al. over 30 years ago [108]. Its proposed general function is to inhibit ongoing pain in remote areas when a new pain stimulus is introduced [107]. The anatomical basis of the DNIC system is less clear in humans, suggesting the involvement of the PAG- RVM network rather than more caudal regions. Descending inhibitory effects are evoked by painful heterotopic conditioning stimuli (thermal, mechanical, electrical, or chemical) resulting in decreased pain perception induced by painful stimulation given elsewhere in the body than the heterotopic stimulus. CPM is impaired in populations with chronic pain in comparison to healthy individuals, especially in comparisons of younger populations and when only female participants are involved [111]. Stress- induced analgesia (SIA) is a second endogenous pain control paradigm where, for example, an injured soldier or accident victim transiently reports feeling much less pain than would be expected given the extent of the wounds [122, 188]. Further, the placebo/nocebo effects (and placebo/nocebo-like effects) work by engaging endogenous pain modulatory circuits in the same way that opiate drugs, CPM/DNIC, and SIA do. Activation of opioid receptor mu 1 (OPRM1) in the PAG-RVM network may activate descending inhibitory pathway. Hence, pain is moderated by endogenous CNS networks, which can be activated by a large variety of cognitive, emotional and behavioural paradigms [146]. Increased knowledge of endogenous opioid or non-opioid pain control mechanisms and how to exploit them can contribute to better pain medicine.

Approximately 25% of patients with LBP develop widespread pain over a period of 18

years [104]. The underlying mechanism and nature of the predisposing risk factors have yet to be discovered, although both neurophysiological and biosocial (psychological) explanations have been proposed [150]. There are no definitive models explaining the transition from localised pain due to tissue challenges (e.g. damage) to widespread pain conditions, although intramuscular injection of nerve growth factor causes long lasting muscle hyperalgesia with some signs of spreading sensitisation [56].

It is likely that initial excitation and sensitisation of nociceptors due to tissue damage will cause sufficient nociceptive input to the central pain systems, leading to sensitisation of dorsal horn neurones and/or higher brain centres. In various types of chronic pain, diminished inhibition in the spinal dorsal horn is believed to be a major contributor to chronic pain. Diminished activity of the descending monoaminergic pathways controlled by opioid systems in the PAG and brainstem, and decreased inhibitory interneuron activity caused by reduced synthesis of inhibitory neurotransmitters (γ- aminobutyric acid (GABA) and glycine) or loss of interneurons, may contribute to chronic pain [50, 103]. Monoamines, including serotonin, norepinephrine, and dopamine, modulate the release of neurotransmitters from nociceptive afferents and the excitability of dorsal horn neurons by binding to different receptor subtypes. Hence, alteration of serotonergic pathway induces a hyperexcitability of spinal dorsal horn neurons by activation of spinal 5-HT2 and 5-HT3 receptors. Further, decreased activity of serotonergic descending pathway exerts both antinociceptive and nociceptive effects on pain and contributes to chronic inflammatory pain [190] and postoperative pain [153]. Unlike serotonergic pathways, the descending noradrenergic pathway has only antinociceptive effects by activating α_2 receptors (presynaptic inhibition) on primary nociceptors. Activating of postsynaptic α_1 receptors may also contribute to antinociception, by causing the release of inhibitory neurotransmitters (GABA or glycine) from inhibitory interneurons [17]. Hence, alteration of noradrenergic pathway contribute to increase pain perception [103]. The role of the dopaminergic pathway in chronic pain is less studied, but thus pathway may affect spinal nociception due to the effects of dopamine and activation of D_2 and D_3 receptors on primary afferents and dorsal horn neurons [55, 103].

Neuroimaging studies have identified several brain areas that are considered to be important for the perception of pain. The primary and secondary somatosensory cortices (insular and

anterior cingulate) and the prefrontal cortices (PFCs) are commonly activated, often bilaterally, and during painful experiences [109]. Furthermore, altered activity in subcortical areas (e.g. PAG, hypothalamus, amygdala, hippocampus, and cerebellum) is also observed during pain [109]. Thus, activity within several diverse regions of the brain contributes to the multidimensional experience of pain. These regions comprise the so-called 'pain neuromatrix', in which multiple inputs are processed to produce an output (neurosignature) that is bespoke for an individual depending on context, mood and cognitive state [167]. However, none of the brain regions identified above is uniquely associated with pain; they are also involved in many other sensory, motor, cognitive, and emotional functions. Altered structure, function and neurochemistry in the frontal-limbic-brainstem regions have been revealed in neuroimaging research in patients with chronic pain compared with healthy controls. Neuroimaging can improve our understanding of pain mechanisms, analgesic action and the placebo effect [109]. Further, neuroimaging might identify functional, structural or biochemical endophenotypes for pain, linking pain conditions to genotype [61, 166]. These pain endophenotypes could 'fill the gap' between pain behavior and the genes, improving our knowledge about the etiology of pain [166].

1.7 Prognostic factors for lumbar radicular pain

The recovery from lumbar radicular pain is influenced by psychosocial, emotional, surgery-related, and clinical factors [35, 69, 117]. Psychosocial and emotional prognostic factors have been less well studied in radicular pain compared with LBP [12, 98], but they do have an impact on recovery. Comorbid subjective health complaints, emotional distress, kinesiophobia, biological factors, more LBP, longer duration of symptoms, smoking, clinical factors such as muscular weakness, and no surgical treatment are associated with non-success in lumbar radicular pain due to DH [40, 69, 158]. Lower educational level is also associated with poor recovery from LBP [93], and may influence recovery after DH. Lower education level is often associated with environmental factors such as heavy physical work and low-decision authority, which are known prognostic factors for poor recovery [30, 93]. In surgically treated patients with DH, high treatment expectancy is associated with a favorable outcome, whereas taking pain medication, a poor functional status, high leg pain and LBP at baseline are associated with poor perceived recovery and functional status at 1-year follow-up [140]. Radiological factors may predict outcome in surgically treated patients with DH. Patients with one third or more thecal sac compression had a greater surgical

treatment effect compared with patients with small DHs and type I MCs. In addition, patients with nerve root "compression" and "displacement" were shown to benefit more from surgery compared with patients with minimal nerve root impingement [115].

Occupational factors (e.g., heavy physical work, lifting heavy objects, bending over and twisting, whole-body vibration, and static operating position) can induce DD. Subsequently, the intradiscal pressure is increased and the AF strength is reduced predisposing for DH. However, the psychosocial factors at work like high professional pressure and lower job satisfaction as well as time-related stress are equally well-known risk factors for DH [192]. The biomechanical mechanisms behind this association is however unknown. It is also believed that the interaction of environmental and genetic factors influences the development of DH as well as the recovery of DH [193].

1.8 Genetic concepts and impact of genetic factors

Genes are parts of DNA molecules that contain the information used by cells to construct protein molecules. Proteins are “products” of gene transcription and translation, the two cellular processes that exploit the information encoded in the sequence of base-pairs in the DNA molecule to manufacture particular proteins. DNA in human genome is organized into 23 chromosome pairs and in most cases has nucleotide base-pair sequence of A (Adenine) - T (Thymine) - C (Cytosine) and G (Guanine). The Human Genome Project produced the first complete sequences of individual human genomes. As of 2012, thousands of human genomes have been completely sequenced, and many more have been mapped at lower levels of resolution. There are approximately 3 billion DNA base pairs containing 20.687 protein-coding genes and their variants in the human genome [142].

Variations in the DNA sequence between genomes make each human unique. The mix-and-match combination of the alleles we carry makes us genetically different from each another. Genes may therefore be polymorphic. A genetic variation with a frequency of more than 1% in the population is called a polymorphism [58]. In many cases only one base pair is changed, for example GC may be replaced with AT. This kind of variability is called a single nucleotide polymorphism (SNP). SNPs result in a substitution of a single base pair which can have important functional effects. Hence, genetic polymorphism may affect the pain signaling and modulatory system [58]. Genetic variability may also be important for

development of chronic pain conditions [58].

Genetic influence in aetiology of chronic lumbar radicular pain due to DH consists of genetic risk factors for lumbar DD, cytokine release promoting genes and pain modulating genes. During the last two decades heredity of DD has been investigated in twin studies, which have identified positive familial aggregation, suggesting some degree of genetic influence [120]. In one of the first studies, genetic component of DD was determinate in 115 pairs of male monozygotic twins [15]. Familial aggregation explained 61% and 34% of the variance in degeneration scores in the upper (Th12-L4 region) and the lower lumbar levels, respectively [15]. A more recent article by Battie et al [16] summarized the Twin Spine Study and confirms that genetic factors are a larger determinant of DD. Another twin study involving 172 monozygotic and 154 dizygotic twins found similar results [148]. In this study the summary degeneration score, which included height, signal intensity, bulging, and osteophyte formation demonstrated heritability estimates up to 74% for the lumbar spine and 73% for the cervical spine after adjusting for age, weight, height, occupation, and physical activity [148]. A "severe DDD score", which excluded minor grades, estimated heritability to be 64% at the lumbar and 79% at the cervical spine [148].

Moving on to association studies the specific risk factors for DD and LBP may be studied by two approaches: Genome wide association (GWA) and candidate gene studies. The first GWA study on lumbar DD provides evidence of association between the parkin-2 (PARK2) gene and DD [182]. PARK2 encodes a protein called parkin, which is a component of a multiprotein E3 ubiquitin ligase complex that mediates the targeting of unwanted proteins for proteasomal degradation. This complex also controls the level of proteins involved in cell division and growth. Williams et al [182] have shown that PARK2 expression is reduced with increasing DD. Furthermore, associations between lumbar DD and the several candidate genes have been reported [4, 120]. These genes are divided into five categories based on potential function of the proteins encoded by genes [120] (figure 1):

1) *Structural*: Aggrecan genes (AGc1), cartilage intermediate layer protein (CILP), collagen I (COL1A1), collagen IX (COL9A2 and COL9A3), collagen XI (COL11A2);
2) *Catabolic:* MMP1, MMP2, and MMP3;
3) *Anticatabolic*: Tissue inhibitors of metalloproteinase (TIMP);
4) *Inflammatory*: ILs, COX2;

5) *Other genes*: Vitamin D receptor (VDR) gene, apoptotic genes FAS, FAS ligand, and B-cell lymphoma 2.

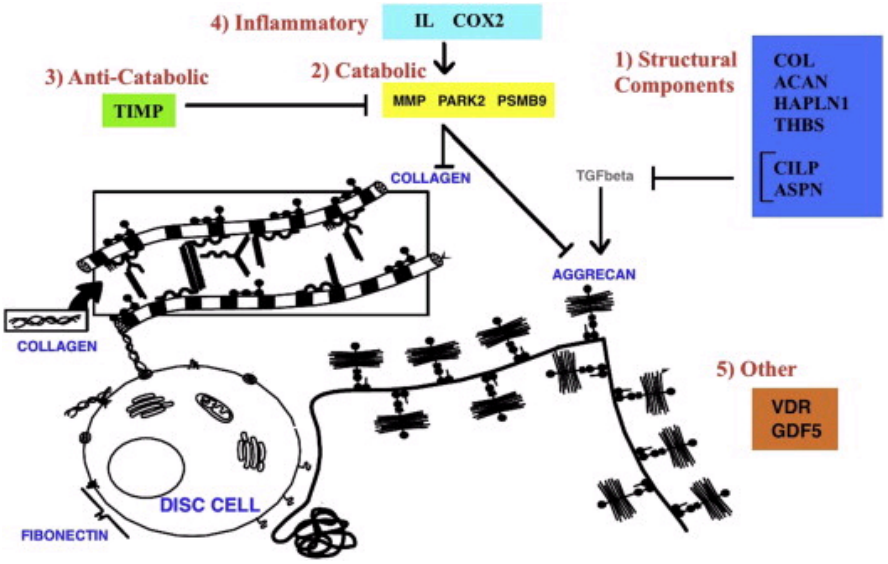

Fig. 1. Functional gene categories. This figure depicts the functional categories of the genes and the relationships between their protein products. From J.E. Mayer et al. [120]. Stimulation is indicated by → and negative impact is indicated by ⊣.

Regarding structural genes, polymorphisms of the gene encoding aggrecan have been found with varied levels of DD [89]. The expressed variable numbers of repeats occur in a highly conserved region of the gene: The glycosaminoglycan (GAG) binding domain, which binds mostly chondroitin sulphate. It is thought that aggrecan alleles with a shorter variable number of tandem repeat (VNTR) length increase the risk of DD at younger ages [89]. Further, the most obvious effect of this VNTR is variable chondroitin sulphate content in IVDs, with a 33% variation between the shortest and longest VNTR length. A diminished chondroitin sulphate content at an early age can lead to degeneration of the IVD matrix [60]. Other structural genes that have been associated with DD are genes COL9A2, COL9A3 and COL11A2 and CILP [45, 85].

Regarding catabolic genes, MMPs represent key proteins involved in the breakdown of the

extracellular matrix. MMP expression has been shown to increase with age, which correlates with an associated increase in degradation [11, 120]. The increase in MMP expression often corresponds with the severity of degeneration. Polymorphisms in MMP1, MMP2 and MMP3 have been studied as risk factors for DD. In addition, MMP3 was found to be associated with post treatment improvement in disability and pain in LBP patients [137]. From anticatabolic gene group, so far only TIMP polymorphism has been studied in association with DDD [120]. The balance between catabolic and anticatabolic enzymes is delicate and a slight increase in the catabolic or decrease in the anticatabolic enzymes could tip the balance in favor of DD [120].

Inflammatory genes, including genes encoding ILs and COX2, may be associated with predisposition for DD [105], DH and lumbar radicular pain [141]. IL1 has an important role in the degradation of matrix proteins. Increased expression of IL1 has also been observed in the degenerated discs. In normal discs, endogenous IL1 receptor antagonists exert a negative impact. In DD, this negative control is not significant because IL1 expression increases, whereas IL1 receptor antagonist does not. Further, a specific effects of the IL-1α SNP C>T (rs1800587) in early lumbar DD have been suggested [43, 44]. Patients with the IL-1α T genotype seem to have overall enhanced levels of IL-1α, resulting in an increased activation of IL-1 receptors and a more pronounced inflammatory response. Actually, the IL-1α is a very strong inducer of inflammation, and causes a broad spectrum of systemic changes in neurological, metabolic, hematological, and endocrinological systems. Another IL-1α polymorphism (rs2071375) has been found to be associated with the changes in disc signal intensity [171]. There are also many IL-β and IL6 polymorphisms that may be associated with DD [88, 120, 141].

Genes controlling pain, so-called “pain genes” have been emerged from discoveries of underlying genetic causes of distinct phenotypes. Among the best-known “pain genes” are those which cause human hereditary disease associated with extreme pain phenotypes. Such genes are carried by less than 1% of the population, which contrasts greatly with the 20% of adults in Europe suffering from chronic pain [24]. Gene polymorphism of pain modulating genes is more important for development of chronic pain conditions. Lötsch et al [114] has shown by analysing 410 genes which control the complex process of pain, that 12 clearly circumscribed functional areas of DNA are essential for pain perception. Pain modulating genes include genetic factors, affecting the endogenous pain modulatory system,

such as the OPRM1 rs1799971 gene polymorphism [136]. A decade ago Zubieta et al. [194] described the impact of the Catechol-*O*- methyltransferase (COMT) polymorphism (Val158Met) rs4680 on the relationship between pain perception and the mu-opioid neurotransmitter response, and found that volunteers with the Met/Met genotype exhibited higher sensory and affective ratings of experimental pain, and also had a higher regional density of mu-opioid receptors. Moreover, the COMT gene polymorphism contributes to treatment outcome of LBP [33, 138] and long-lasting LBP, radicular pain and disability after lumbar DH [79]. The IL-1α gene polymorphism may also possibly increase the spinal nociceptive signaling [155] and modify the cytokine profiles of patients with inflammatory diseases [70].

2. Aims of the study

The main purpose of this study was to investigate prognostic factors for recovery after lumbar radicular pain due to DH.

Specifically I aimed to:

1. Identify predictors for functional outcome, especially to investigate the influence of cytokines (IL-6 and IL-8) at 1-year recovery in patients with lumbar radicular pain.

2. Examine how variability of the IL-1α C>T rs1800587 gene affects the pain intensity and pressure pain threshold (PPT) in patients with symptomatic DH.

3. Examine whether Modic changes influence pain during one-year follow-up in patients with lumbar radicular pain.

4. Investigate the interaction between sex and the OPRM1 A118G variant rs1799971, regarding recovery from DH.

3. Methods

3.1. Study population

Participants with lumbar radicular pain were recruited from patients of the Oslo University Hospital, Ulleval (papers I and II), and from Oslo University Hospital, Ulleval, and Haukeland University Hospital (papers III and IV) between 2007 and 2009. The *inclusion criteria* were as follows: aged between 18 and 60 years, lumbar DH on MRI with corresponding distribution of pain in lower limbs, and positive straight leg raising (SLR) test results. A positive SLR test was defined as radiating pain into one or both legs when the examiner raised the straightened limb slowly until 60°. The test was performed in a supine position and supplemented with slight dorsiflexion of the foot.

The *exclusion criteria* were as follows: lumbar spinal stenosis, previous spinal surgery for a herniated disc at the same level or lumbar fusion at any level, generalised musculoskeletal pain, inflammatory rheumatic disease; diabetic polyneuropathy, cardiovascular disease (New York Heart Association class III and IV), cancer, psychiatric disease, drug misuse and alcoholism, recent surgery (within 1 month), pregnancy, poor proficiency in the Norwegian language, and non-European-Caucasian ethnicity. Patients with cauda equina syndrome were also excluded.

In papers I and II, 121 (81.8%) of the 148 patients who met the eligibility requirements were included in the intended follow-up assessment. The drop- out rate was 9%, and ultimately, 110 patients were assessed at the 1-year follow-up. In paper III, a total of 262 (87.6%) of the 299 patients assessed for eligibility were included. However, because 19 patients had missing baseline data, 243 (81%) of the 299 patients were allocated to follow-up. Only 18 (7%) of the 243 patients dropped out of the study. In paper IV, the study population consisted of 252 patients allocated to follow-up. A total of 21 (8%) patients dropped out.

3.2. Follow-up and clinical assessment

Table 1 shows follow-up times, which in paper I was 12 months, paper II 6 weeks and 12 months, and in paper III and IV three follow-ups at 6 weeks, 6 months, and 12 months. Treatment (surgery or conservative) was decided during the initial screening visit (inclusion) where surgical treatment was given to patients with persistent radicular pain lasting longer

than 8 weeks, neurological deficits (sensory changes, muscle weakness, or depressed or absent deep tendon reflexes) and corresponding MRI findings in the anticipated location. Non-surgical treatment was given to patients that did not clearly meet these criteria. Non-surgical treatment comprised brief cognitive intervention, activity guidance during the acute phase of lumbar radicular pain, and physiotherapy for most of the patients. Initiation of treatment occurred within 8 weeks after inclusion. A few patients had to wait for surgery longer than 8 weeks and were re-included with additional clinical parameters. A total of 37%, 52%, and 58% patients received surgical treatment in papers I - II; III, and IV, respectively.

Table 1. Follow-up and clinical assessment in the studies

	Pre-treatment (inclusion)	Treatment**	Follow-up		
			6 weeks	6 months	12 months
Paper I (n*=121)	✦				✦
Paper II (n*=121)	✦		✦		✦
Paper III (n*=243)	✦		✦	✦	✦
Paper IV (n*=252)	✦		✦	✦	✦

*Allocated to follow-up

**Within 8 weeks from inclusion

Data collection included clinical examination with observation of the patient's casual gait, toe- and heel-walking, assessment of reflexes, sensory, and motor function in the lower limbs. Pain-related questionnaires, such as the visual analogue scale (VAS) for present pain, pain during activity, pain at rest with separate VASs for LBP and radicular pain, and the validated Norwegian version of the McGill Pain Questionnaire (MPQ) were administered. The MPQ measures sensory, affective, and evaluative components of the pain experience [164]. The validated Norwegian version of the Oswestry disability index (ODI) (scale, 0–100%, where 0% = no disability at all, and 100% = very severe disability) was

used for measurement of function [64]. Use of analgesics and adjuvant analgesics were registered.

Sociodemographic variables and work-related factors such as marital status, duration of education, occupation, duration of sick leave, and social benefits were also registered upon inclusion in the study. Occupations were classified into three groups: mental, mixed, and physical work [78]. The demand and control subscales of the General Nordic Questionnaire for Psychological and Social Factors at Work (QPS Nordic) were administered to record quantitative job demands and the control of work pacing [177]. The Hopkins Symptom Checklist (HSCL), a 25-item questionnaire, was used to register psychological distress [36]; scores equal to or greater than 1.75 on the total scale indicated emotional distress [149]. Radiological data (lumbar MR) and blood samples were also collected.

The patients were followed-up at 6 weeks, 6 months, and 12 months after inclusion. At 6 weeks and 12 months, clinical examination, registration of pain and disability scores, work status, and collection of blood samples were repeated. At the 6-month follow-up, patients were contacted by telephone regarding changes in their spinal condition and work status, and were sent the VAS, McGill, and ODI questionnaires by mail. In cases of persistent radicular pain, MRI of the lumbar spine was repeated at 12 months. Table 2 shows when and in which papers the different measures were administered.

Table 2. **Data collected and used in papers I, II, III and IV**

	Baseline	**Follow-up after treatment**		
		6 weeks	6 months	12 months
Clinical examination	I, II, III, IV	II, III, IV		I, II, III, IV
VAS back pain	I, II, III, IV	II, III, IV	III, IV	I, II, III, IV
VAS leg pain	I, II, III, IV	II, III, IV	III, IV	I, II, III, IV
ODI	I, II, III, IV	II, III, IV	III, IV	I, II, III, IV
McGill (MPQ)	III, IV	III, IV	III, IV	III, IV
HSCL-25	I			I
QPS Nordic	I			I
Sociodemographic	I, II, III	II, III	III	I, II, III
Work-related	I, II, III	II, III	III	I, II, III
Use of analgesics	I, II, III	II, III	III	I, II, III
PPT	II	II		II
MRI	I, III			*
Genotyping	II, IV			**
ELISA measurement of cytokine in serum	I			**

*MRI of the lumbar spine was repeated at 12 months follow-up for patients with persistent radicular pain, but was not used in paper II or III.

**Blood samples were also collected at 12 months follow-up, but not analysed.

3.3. Outcome measures

Pain and disability related outcomes were selected as the most relevant primary outcome measures in the present study. In paper I, the ODI change, defined as the baseline ODI minus the ODI at the one-year follow-up, was chosen as the primary outcome measure and VAS for leg pain and LBP were chosen as secondary outcome measures. A higher value for ODI change indicated a more favourable functional outcome. In paper II, the outcome measures were the VAS leg pain and PPT for the gluteal muscles. In paper III, the outcome measures were the McGill sensory score and the VAS score for LBP. In paper IV, the outcome measures were VAS activity score, McGill sensory score, and ODI.

3.4. MRI (paper I and III)

Baseline lumbar MRI (1.5 T in 86% of the cases, 1.0 T in 12%, unknown or 3.0 T in 2%) was performed as part of clinical practice and included sagittal T2- and T1-weighted images and axial images of the L3/L4, L4/L5 and L5/S1 levels. All MRIs were de-identified and presented in random order. An experienced radiologist and a physical medicine and rehabilitation physician, independently and blinded to clinical data, graded MCs [126] and DD. DD is related to Modic changes [10] and was used as a covariate in the analyses. At each of the 10 EPs of L1–S1, we noted MCs as primary type I (hypointense signals on T1-weighted images and hyperintense signals on T2- weighted images), type II (hyperintense signals on T1-weighted images and iso/hyperintense signals on T2-weighted images), or type III (hypointense signals on both T1- and T2-weighted images). We graded the craniocaudal (CC) size of the MCs as <10%, 10%–25%, ≥ 25%–50%, or >50% of the vertebral body height [81]. In the final analyses, the first two CC size categories received a score of 0, and the subsequent categories received scores of 1, 2, and 3, respectively. A total CC size score for the 10 endplates was calculated (possible values 0-30).

DD was graded on midsagittal T2-weighted images at each of the five disc levels (L1–S1) using Schneiderman's grading system [151]: a score of 0 indicated no signal change, a score of 1 indicated a slight decrease in signal intensity in the NP, a score of 2 indicated a generalized hypointense nucleus, and a score of 3 indicated a hypointense nucleus with disc space narrowing. The total DD score (0–15) across all five discs was calculated and then grouped according to Jim [82] into severe (two or more grade 3 discs, three or more grade 2 discs, or one grade 3 and two grade 2 discs), moderate (one grade 3 disc or two grade 2

discs), mild (only one grade 2 disc and no grade 3 discs), or normal (total DD score of 0 or 1). In all cases of disagreement, a consensus score was negotiated. The independent evaluations showed mostly good interobserver agreement on type and CC size of MCs at EPs with at least 10% prevalence of MCs (L2–S1), and thus interpretable kappa values (unweighted kappa for Modic type and linearly weighted kappa for Modic CC size, paper III) [154]. At levels with at least 10% prevalence of a DD score of 2 and 3 (also L2–S1), the interobserver agreement on DD was moderate or good (linearly weighted kappa for DD) (paper III).

3.5. ELISA measurements of serum cytokine concentration (paper I)

Blood samples were drawn during the initial screening visit at the hospital. A few patients, who had to wait for surgery longer than 8 weeks, were re-included with new blood samples. The serum analysis of the blood samples was performed at the National Institute of Occupational Health, Oslo. Laboratory method: After being on ice for 45 minutes, blood samples were centrifuged for 10 minutes at 4^0C and 2000 G. Further, serum was stored in duplicate at -80^0C until use. The serum concentrations of the two pro-inflammatory cytokines IL-6 and IL-8 were determined using commercial enzyme-linked immunosorbent assays (ELISA) kits according to the manufacturer's instructions (human ultrasensitive kits for IL-6 and IL-8, Invitrogen Corporation, CA, USA). Briefly, 100 µl of serum or IL-6 or IL-8 standard was added to each well in microtitre plates pre-coated with an antibody specific for each cytokine, and then plates were incubated at room temperature. After washing the plates, 100 µl of biotinylated antibody specific for IL-6 or IL-8 was added, and then plates were incubated at room temperature. After removal of excess secondary antibody by washing, 100 µl of streptavidin-conjugated horseradish peroxidase enzyme solution was added to each well. After incubating the plates at room temperature and washing the plates to remove all unbound enzyme, a substrate solution with chromogen was added to produce colour. The reaction was stopped by adding 100 µl of stop solution. The optical density was measured at a wavelength of 450 nm using a Fusion Universal Microplate analyser (Packard Instrument Company, Meriden, CT, USA). Data were analysed using the Fusion data analysis software program (Packard Instrument Company). The amount of IL-6 and IL-8 in all samples was quantified based on a standard curve prepared for each analysed cytokine. Background absorbance was subtracted from all data points including the unknown samples and standards. Serum collected at three different time points for each patient was analysed on the same microtitre plate. Serum IL-6 was measured in pg/ml. According to the manufacturer, the

minimum detectable dose of IL-6 and IL-8 was 0.15 pg/ml and 0.4 pg/ml, respectively.

3.6. Single nucleotide polymorphism (SNP) genotyping (paper II and IV)

Blood samples were drawn and genomic DNA was extracted from whole blood cells using the FlexiGene DNA isolation kit (Qiagen, Hilsen, Germany). SNP genotyping was carried out using predesigned TaqMan SNP genotyping assays for rs1800587 (Applied Biosystems, Foster City, CA, USA). Approximately 10 ng genomic DNA was amplified in a 5-µl reaction mixture in a 384-well plate containing 1 × TaqMan genotyping master mix (Applied Biosystems) and 1 × assay mix, the latter containing the respective primers and probes. The probes were labelled with the reporter dye FAM or VIC to distinguish between the two alleles. After initial denaturation and enzyme activation at 95°C for 10 min, the reaction mixture was subjected to 60 cycles of 95°C for 15 s and 60°C for 1 min. The reactions were performed using an ABI 7900HT sequence detection system. Negative controls containing water instead of DNA were included in every run. Genotypes were determined using SDS 2.2 software (Applied Biosystems). Approximately 10% of the samples were re-genotyped and the concordance rate was 100%.

3.7. Ethics

The study was conducted in accordance with the Helsinki Declaration. The Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services approved the study protocol (REK number S-07239b), and all participants gave written informed consent.

3.8. Statistical analysis

All statistical analyses were performed using the statistical package PASW statistics 19 (paper I, II and III) and 18 (paper IV) (SPSS Inc., Chicago, IL, USA). Parametric statistical analyses based on the normally distributed data were performed. In paper I linear regression analysis was conducted; in paper II and IV repeated measures analysis of variance (rmANOVA) and one-way ANOVA were performed; and in paper III two-way and one-way ANOVAs were used to analyse the data. A p value <0.05 was chosen as the level of statistical significance in paper I, II, and IV. In paper III a Bonferroni correction was applied to adjust for multiple comparisons and a p-value of ≤ 0.013 ($p \leq 0.05/4$) was regarded as statistically

significant. Covariates (age, sex, smoking, and treatment) were used in all analyses. In addition, DD grouped by Jim [82] and duration of lumbar radicular pain were used as covariates in paper III.

4. Main results

4.1. Paper I

Less favourable ODI outcome correlated with higher serum IL-6 levels (B =-3.41, 95% CI -5.52 to -1.30, p = 0.002), non-surgical treatment (B = -7.03, 95% CI 1.21 to 12.84, p = 0.018), higher baseline back pain intensity (B =-2.28, 95% CI -3.21 to -1.35, p < 0.001), and low educational level (B = -5.57, 95% CI 0.66 to 10.47, p = 0.027). High VAS for LBP and leg pain at one year was associated with high levels of serum IL-6, higher back pain intensity, and longer duration of lumbar radicular pain at baseline.

4.2. Paper II

The IL-1α gene C>T polymorphism rs1800587 affected VAS and PPT scores in patients with symptomatic DH. Patients with the CT/TT genotype reported a higher VAS leg pain intensity (p = 0.002) and a lower PPT in the gluteal muscles (left p = 0.016; right p = 0.016) compared with patients with the CC genotype during the 1-year follow-up period.

4.3. Paper III

Pain scores had decreased significantly at 12 months follow-up. Modic type showed a significant impact on McGill sensory score at 6 weeks (p = 0.007), but not at other time points or on VAS back pain or VAS leg pain scores. At 6 weeks, the mean McGill sensory score was higher in Modic I than in Modic II-III patients (p = 0.003) and in patients without Modic changes (p =0.018). Dichotomized Modic size L1-S1 had no impact on McGill sensory, back pain, or leg pain scores.

4.4. Paper IV

The data revealed a significant interaction between sex and A118G genotype regarding the pain intensity during the 12-month follow-up (VAS, p = 0.002; McGill, p = 0.021; ODI, p = 0.205, repeated-measures ANOVA). We found that */G women had a slower recovery rate compared with */G men. Additionally, the */G women had 2.3 × as much pain as the */G men 12 months after DH (VAS, p = 0.043, one-way ANOVA; p = 0.035, Tukey HSD). In contrast, the A/A women and A/A men had mostly equivalent recovery rates.

5. Discussion

The fact that inflammation contributes to the pathogenesis of DH and radicular pain is now well established [128]. Therefore, proinflammatory cytokines, specifically ILs and TNF-α, are potential biomarkers of DD and DH [191]. The inflammatory response, initiated from the AF in case of DH [152], may lead to increased levels of pro-inflammatory cytokines close to nerve roots. This process may also be accompanied by new innervation and vascularization of discs after DH. In addition, ILs can drive inflammation through its secretion by myeloid cells [186]. However, the potential impact of cytokines in recovery after symptomatic DH is not fully understood. Our data showed an association between serum IL-6 levels and recovery of patients with lumbar radicular pain after DH. In addition to high initial back pain intensity, non-surgical treatment, lower educational level, and prolonged history of lumbar radicular pain prior to treatment, high IL-6 levels had a negative impact on the long-term recovery rate of patients with symptomatic DH. This demonstrates that intense pain and high levels of inflammatory cytokines such as IL-6 are risk factors for long-term disability in patients with lumbar radicular pain. Our findings support the concept that pro-inflammatory cytokines may promote radicular pain [39]. In addition to producing inflammation and inducing the synthesis of several nociceptor sensitizers, the pro-inflammatory cytokine IL-1 rapidly and directly activates nociceptors to generate action potentials and induce pain hypersensitivity [19]. An increased release of IL-1β can then lead to an increase in the levels of other cytokines including IL-6 [87].

An association between serum IL-6 concentration at baseline and long-term disability in lumbar radicular pain may have an impact on treatment and selection for DH surgery. However, the population in our study was too small to examine the effects of IL-6 separately in patients who received surgery compared with those managed conservatively. Regarding treatment of lumbar radicular pain, more clinical research is necessary to determine the clinical results of anti-inflammatory therapy. In the last few years, epidural steroid injections have become increasingly popular worldwide. In a recent meta-analysis, it was found high-quality evidence showing that epidural corticosteroid injections have small, short-term effects on leg pain and disability compared with placebo in patients with lumbar radicular pain, but no effect on the long-term [39, 144]. The use of TNF-α inhibitors administrated in the epidural space has also been tested in clinical trials and demonstrated controversial effects at the short-term follow-up [39]. Still, an enhanced understanding of the role of cytokines to

radicular pain due to DH, could provide new targets for the treatment of symptomatic DH and DD [147] and may be investigated in future studies.

Cytokine release may be influenced by genetics factors. According to the central dogma of molecular biology, DNA encodes RNA, which in turn encodes the amino acid sequence of proteins by translation. First, RNA is synthesized from the DNA template through a process known as transcription. The RNA, carrying the coded information in a form called messenger RNA (mRNA), is then transported from the cell nucleus to the cytoplasm, where the RNA sequence is decoded, or translated, to determine the sequence of amino acids in the protein being synthesized. The process of translation occurs on ribosomes, involving transfer RNA (tRNA). Hence, the flow of information from gene to protein involves several steps where each step is potential subject to error, leading to mutations or polymorphisms. Patients with polymorphism of inflammatory genes, for example IL-1α (rs1800587) T genotype have enhanced IL-α level, resulting in a more pronounced inflammatory response [44]. Our data show that the IL-1α CT/TT genotype may be associated with increased leg pain intensity, as well as a decreased PPT during the first year after DH. These findings may help explain more leg pain, but also a more generalized decrease in the pain threshold during the first year after DH among patients with the T allele. Thus, the present data show that genetic variation in the gene encoding IL-1α may be crucial for the PPT, often used clinically to predict clinical outcome.

IL-1α is a very strong inducer of inflammation, and causes a broad spectrum of changes in neurological, metabolic, haematological, and endocrine systems [157]. Thus, the IL-1α C>T genotype may be associated with several undesirable characteristics of the pain pathways. For example, IL-1α alters substance P and nerve growth factor expression via the IL-1 receptor [155], which could possibly increase spinal nociceptive signaling. Taken together, this emphasizes the important functional role of IL1, which may also be relevant for future treatment decisions. Recent clinical data suggest that the recombinant form of the naturally occurring IL-1 receptor antagonist (IL1RN) may be useful in the clinical management of inflammation. The polymorphism of the IL1RN suppresses inflammatory reactions and clinical symptoms caused by IL1, which would make DH patient's response to conservative treatment different [94]. An attempt to use gene therapy with IL1RN adenovirus transfection has also been performed in patients with rheumatoid arthritis or degenerative arthropathy, suggesting that genetic polymorphism of IL1RN affects clinical features of these

diseases [106]. However, whether patients carrying the IL-1α T allele may show enhanced effects of IL1RN, or other pharmacological therapies, remains to be investigated.

The inflammatory process close to the disc after DH also increase the risk for MC (especially type I) during the following year [7]. Apparently, type I MCs represents acute stages of inflammation and is strongly associated with LBP [7]. Our results also demonstrated that patients with type I MCs had a significantly higher McGill sensory pain score at 6 weeks, compared with patients with other Modic types or without MCs. This indicates slower recovery after DH among patients with type I MCs, perhaps due to inflammatory pain associated with I MCs [14, 47, 131]. Previous studies have shown an increased frequency of type I MCs in individuals with LBP [7, 102]. Here, we have extended these findings and demonstrated that type I MCs also influence the recovery in lumbar radicular pain. The increased sensory pain in patients with type I MCs is clinically important. For example, patients with Modic type I may be informed that recovery may take more than 6 weeks, but that their prognosis is still good. In addition, it may be favorable with longer follow-up of these patients.

Prevalence of MCs in our study was more that 70%, and more than 60% patients had MCs with a CC size of at least 10% of the vertebral height, which is a higher prevalence than that found among patients with lumbar DH in a previous study (range, 20%–49%) [7]. This can be partly explained by the characteristics of our study population: there is a higher prevalence of MCs among patients with chronic lumbar radicular pain versus those with acute or a combination of both types of lumbar radicular pain [7]. Similarly, the prevalence of MCs is higher among patients with chronic versus acute LBP [12, 27]. Recruitment from university hospitals may favor a high prevalence of MCs because of the higher prevalence of patients with chronic lumbar radicular pain.

A substantial pain reduction was observed during the 12-month follow-up in these pain patients with and without MCs. However, patients with type I MCs had higher sensory pain scores than other patients at 6 weeks. Moreover, at 12 months, 31% of the patients in our study reported LBP and 25% reported leg pain, based on VAS scores > 3. These data are consistent with findings in the previous study where approximately 30% of the patients with symptomatic disc herniation had LBP that restricted work and leisure after 1 year [178]. Although most patients with radicular pain due to disc herniation have spontaneous regression

of symptoms [13, 178], such pain is associated with high consumption of health resources [23, 100].

In the present work we also demonstrated an interaction between sex and the OPRM1 A118G genotype associated with recovery from LBP and sciatica. Specifically, women with the */G genotype reported more pain compared with the */G men 12 months after DH. Hence, our study supports the earlier observation that female patients with sciatica may have a slower recovery and a poorer 1-year outcome compared with male patients [143]. However, here we have extended these findings and demonstrated that pain is also related to a sex-specific genetic factor. Specifically, women carrying the 118G allele had a mean VAS activity pain score 2.3 × higher than men with the same genotype 12 months after LDH. This finding strongly support the hypothesis that the OPRM1 118G allele may influence the endogenous pain modulatory system differently depending on sex, which may be relevant for understanding the mechanisms underlying the development of persistent LBP and radicular pain due to DH. Recent study has shown that combined genotype of CYP3A4*18B and OPRM1 A118G may influence postoperative effect of fentanyl [112]. According to the another study, the OPRM1 A118G SNP is a key contributor for the inter-individual variability in opioidrequirements in cancer pain patients [59].

6. Conclusion

- High levels of serum IL-6, but not DD or MCs, were associated with less favourable recovery in patients with lumbar radicular pain. Intense initial back pain, conservative management, lower educational level, and an extended duration of radicular pain before treatment were also associated with a slower recovery at 12 months. This suggests that serum IL-6 level is a valid predictor of recovery in lumbar radicular pain.

- The IL-1α CT/TT genotype rs1800587 may be associated with increased pain intensity, and corresponding reduced PPT during the first year after DH. Thus, these data show that the IL-1α T genotype may affect clinical outcome, but may also affect the results of clinical tests of patients suffering from lumbar radicular pain.

- Most patients with lumbar radicular pain treated surgically and non- surgically can expect a substantial reduction in back and leg pain during the first year. Patients with Modic type I changes may, however, have a slower decrease in McGill sensory pain score and recovery in lumbar radicular pain than other patients. Neither the type nor the size of Modic changes seems to influence on McGill sensory pain, VAS back pain, or VAS leg pain scores at one-year follow-up.

- The OPRM1 118G allele rs1799971 is associated with increased pain intensity in women, but reduced pain intensity in men in the first 12 months after a DH. An interaction between sex and the OPRM1 A118G genotype is associated with recovery of LBP and lumbar radicular pain due to DH. This suggests that the OPRM1 118G allele may influence the endogenous pain modulatory system differently depending on sex, and contribute to the high VAS activity in women with symptomatic DH.

7. References

1. Adams MA, Burton AK, Dolan P, Bogduk N (2007) The biomechanics of back pain. Churchill Livingstone
2. Adams MA, McNally DS, Dolan P (1996) 'Stress' distributions inside intervertebral discs. The effects of age and degeneration. J Bone Joint Surg Br 78:965-972
3. Adams MA, Roughley PJ (2006) What is intervertebral disc degeneration, and what causes it? Spine (Phila Pa 1976) 31:2151-2161
4. Ahmad Omair (2013) Genetic predisposition to low back pain and lumbar disc degeneration. Doctoral Thesis. Faculty of Medicine, University of Oslo.
5. Ahn SH, Cho YW, Ahn MW, Jang SH, Sohn YK, Kim HS (2002) mRNA expression of cytokines and chemokines in herniated lumbar intervertebral discs. Spine (Phila Pa 1976) 27:911-917
6. Albert HB, Kjaer P, Jensen TS, Sorensen JS, Bendix T, Manniche C (2008) Modic changes, possible causes and relation to low back pain. Med Hypotheses 70:361-368
7. Albert HB, Manniche C (2007) Modic changes following lumbar disc herniation. Eur Spine J 16:977-982
8. Albert HB, Sorensen JS, Christensen BS, Manniche C (2013) Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy. Eur Spine J 22:697-707
9. Aminov RI (2013) Biotic acts of antibiotics. Front Microbiol 4:241
10. Arana E, Kovacs FM, Royuela A, Estremera A, Asenjo B, Sarasibar H, Amengual G, Galarraga I, Alonso A, Casillas C, Muriel A, Montoya J, Ordonez C, Martinez C, Zamora J, Campillo C, Abraira V (2011) Modic changes and associated features in Southern European chronic low back pain patients. Spine J 11:402-411
11. Arner EC, Hughes CE, Decicco CP, Caterson B, Tortorella MD (1998) Cytokine-induced cartilage proteoglycan degradation is mediated by aggrecanase. Osteoarthritis Cartilage 6:214-228
12. Ashworth J, Konstantinou K, Dunn KM (2011) Prognostic factors in non-surgically treated sciatica: a systematic review. BMC Musculoskelet Disord 12:208
13. Autio RA, Karppinen J, Niinimaki J, Ojala R, Kurunlahti M, Haapea M, Vanharanta H, Tervonen O (2006) Determinants of spontaneous resorption of intervertebral disc herniations. Spine (Phila Pa 1976)31:1247-1252

14. Bailly F, Maigne JY, Genevay S, Marty M, Gandjbakhch F, Rozenberg S, Foltz V (2013) Inflammatory pain pattern and pain with lumbar extension associated with Modic 1 changes on MRI: a prospective case-control study of 120 patients. Eur Spine J
15. Battie MC, Videman T, Gibbons LE, Fisher LD, Manninen H, Gill K (1995) 1995 Volvo Award in clinical sciences. Determinants of lumbar disc degeneration. A study relating lifetime exposures and magnetic resonance imaging findings in identical twins. Spine (Phila Pa 1976) 20:2601-2612
16. Battie MC, Videman T, Kaprio J, Gibbons LE, Gill K, Manninen H, Saarela J, Peltonen L (2009) The Twin Spine Study: contributions to a changing view of disc degeneration. Spine J 9:47-59
17. Benarroch EE (2008) Descending monoaminergic pain modulation: bidirectional control and clinical relevance. Neurology 71:217-221
18. Berg L, Hellum C, Gjertsen O, Neckelmann G, Johnsen LG, Storheim K, Brox JI, Eide GE, Espeland A (2013) Do more MRI findings imply worse disability or more intense low back pain? A cross-sectional study of candidates for lumbar disc prosthesis. Skeletal Radiol 42:1593-1602
19. Binshtok AM, Wang H, Zimmermann K, Amaya F, Vardeh D, Shi L, Brenner GJ, Ji RR, Bean BP, Woolf CJ, Samad TA (2008) Nociceptors are interleukin-1beta sensors. J Neurosci 28:14062-14073
20. Birkenmaier C (2013) Should We Start Treating Chronic Low Back Pain with Antibiotics Rather than with Pain Medications? Korean J Pain 26:327-335
21. Bogduk N (2009) On the definitions and physiology of back pain, referred pain, and radicular pain. Pain 147:17-19
22. Bogduk N (2005) Clinical anatomy of the lumbar spine and sacrum. Elsevier Churchill Livingstone, Edinburgh
23. Brage S, Ihlebaek C, Natvig B, Bruusgaard D (2010) Musculoskeletal disorders as causes of sick leave and disability benefits. Tidsskr Nor Laegeforen 130:2369-2370
24. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D (2006) Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain 10:287-333
25. Brisby H (2006) Pathology and possible mechanisms of nervous system response to disc degeneration. J Bone Joint Surg Am 88 Suppl 2:68-71
26. Brisby H, Byrod G, Olmarker K, Miller VM, Aoki Y, Rydevik B (2000) Nitric oxide as a mediator of nucleus pulposus-induced effects on spinal nerve roots. J Orthop Res 18:815-

820

27. Brisby H, Olmarker K, Larsson K, Nutu M, Rydevik B (2002) Proinflammatory cytokines in cerebrospinal fluid and serum in patients with disc herniation and sciatica. Eur Spine J 11:62-66
28. Carricajo A, Nuti C, Aubert E, Hatem O, Fonsale N, Mallaval FO, Vautrin AC, Brunon J, Aubert G (2007) Propionibacterium acnes contamination in lumbar disc surgery. J Hosp Infect 66:275-277
29. Chataigner H, Onimus M, Polette A (1998) Surgery for degenerative lumbar disc disease. Should the black disc be grafted? Rev Chir Orthop Reparatrice Appar Mot 84:583-589
30. Chibnall JT, Tait RC (2009) Long-term adjustment to work-related low back pain: associations with socio-demographics, claim processes, and post-settlement adjustment. Pain Med 10:1378-1388
31. Chou D, Samartzis D, Bellabarba C, Patel A, Luk KD, Kisser JM, Skelly AC (2011) Degenerative magnetic resonance imaging changes in patients with chronic low back pain: a systematic review. Spine (Phila Pa 1976) 36:S43-S53
32. Costello RF, Beall DP (2007) Nomenclature and standard reporting terminology of intervertebral disk herniation. Magn Reson Imaging Clin N Am 15:167-1vi
33. Dai F, Belfer I, Schwartz CE, Banco R, Martha JF, Tighioughart H, Tromanhauser SG, Jenis LG, Kim DH (2010) Association of catechol-O-methyltransferase genetic variants with outcome in patients undergoing surgical treatment for lumbar degenerative disc disease. Spine J 10:949-957
34. de Roos A, Kressel H, Spritzer C, Dalinka M (1987) MR imaging of marrow changes adjacent to end plates in degenerative lumbar disk disease. AJR Am J Roentgenol 149:531-534
35. den Boer JJ, Oostendorp RA, Beems T, Munneke M, Oerlemans M, Evers AW (2006) A systematic review of bio-psychosocial risk factors for an unfavourable outcome after lumbar disc surgery. Eur Spine J 15:527-536
36. Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L (1974) The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. Behav Sci 19:1-15
37. Deville WL, van der Windt DA, Dzaferagic A, Bezemer PD, Bouter LM (2000) The test of Lasegue: systematic review of the accuracy in diagnosing herniated discs. Spine (Phila Pa 1976) 25:1140-1147
38. Deyo RA, Tsui-Wu YJ (1987) Functional disability due to back pain. A population-based study indicating the importance of socioeconomic factors. Arthritis Rheum 30:1247-1253

39. Di Martino A, Merlini L, Faldini C (2013) Autoimmunity in intervertebral disc herniation: from bench to bedside. Expert Opin Ther Targets 17:1461-1470
40. Edwards RR, Klick B, Buenaver L, Max MB, Haythornthwaite JA, Keller RB, Atlas SJ (2007) Symptoms of distress as prospective predictors of pain-related sciatica treatment outcomes. Pain 130:47-55
41. Egeland NG, Moen A, Pedersen LM, Brisby H, Gjerstad J (2013) Spinal nociceptive hyperexcitability induced by experimental disc herniation is associated with enhanced local expression of Csf1 and FasL. Pain 154:1743-1748
42. Emch TM, Modic MT (2011) Imaging of lumbar degenerative disk disease: history and current state. Skeletal Radiol 40:1175-1189
43. Eskola PJ, Kjaer P, Daavittila IM, Solovieva S, Okuloff A, Sorensen JS, Wedderkopp N, Ala-Kokko L, Mannikko M, Karppinen JI (2010) Genetic risk factors of disc degeneration among 12-14-year-old Danish children: a population study. Int J Mol Epidemiol Genet 1:158-165
44. Eskola PJ, Kjaer P, Sorensen JS, Okuloff A, Wedderkopp N, Daavittila I, Ala-Kokko L, Mannikko M, Karppinen J (2012) Gender difference in genetic association between IL1A variant and early lumbar disc degeneration: a three-year follow-up. Int J Mol Epidemiol Genet 3:195-204
45. Eskola PJ, Lemmela S, Kjaer P, Solovieva S, Mannikko M, Tommerup N, Lind-Thomsen A, Husgafvel-Pursiainen K, Cheung KM, Chan D, Samartzis D, Karppinen J (2012) Genetic association studies in lumbar disc degeneration: a systematic review. PLoS One7:e49995
46. Fardon DF (2001) Nomenclature and classification of lumbar disc pathology. Spine (Phila Pa 1976) 26:461-462
47. Fayad F, Lefevre-Colau MM, Rannou F, Quintero N, Nys A, Mace Y, Poiraudeau S, Drape JL, Revel M (2007) Relation of inflammatory modic changes to intradiscal steroid injection outcome in chronic low back pain. Eur Spine J 16:925-931
48. Feng H, Danfelter M, Stromqvist B, Heinegard D (2006) Extracellular matrix in disc degeneration. J Bone Joint Surg Am 88 Suppl 2:25-29
49. Fields AJ, Liebenberg EC, Lotz JC (2013) Innervation of pathologies in the lumbar vertebral end plate and intervertebral disc. Spine J
50. Fields HL, Heinricher MM, Mason P (1991) Neurotransmitters in nociceptive modulatory circuits. Annu Rev Neurosci 14:219-245

51. Finskas O, Blixt A, Fujioka Y, Olmarker K (2013) New, Clinically more Relevant Model for Nerve Root Injury in the Rat. Spine (Phila Pa 1976) 38:1744-1748
52. Fortin M, Macedo LG (2013) Multifidus and paraspinal muscle group cross-sectional areas of patients with low back pain and control patients: a systematic review with a focus on blinding. Phys Ther 93:873-888
53. Franson RC, Saal JS, Saal JA (1992) Human disc phospholipase A2 is inflammatory. Spine (Phila Pa 1976) 17:S129-S132
54. Frino J, McCarthy RE, Sparks CY, McCullough FL (2006) Trends in adolescent lumbar disk herniation. J Pediatr Orthop 26:579-581
55. Gao X, Zhang Y, Wu G (2000) Effects of dopaminergic agents on carrageenan hyperalgesia in rats. Eur J Pharmacol 406:53-58
56. Gerber RK, Nie H, Arendt-Nielsen L, Curatolo M, Graven-Nielsen T (2011) Local pain and spreading hyperalgesia induced by intramuscular injection of nerve growth factor are not reduced by local anesthesia of the muscle. Clin J Pain 27:240-247
57. Gibson JN, Grant IC, Waddell G (1999) The Cochrane review of surgery for lumbar disc prolapse and degenerative lumbar spondylosis. Spine (Phila Pa 1976) 24:1820-1832
58. Gjerstad J (2007) Genetic susceptibility and development of chronic non-malignant back pain. Rev Neurosci 18:83-91
59. Gong XD, Wang JY, Liu F, Yuan HH, Zhang WY, Guo YH, Jiang B (2013) Gene Polymorphisms of OPRM1 A118G and ABCB1 C3435T May Influence Opioid Requirements in Chinese Patients with Cancer Pain. Asian Pac J Cancer Prev 14:2937-2943
60. Gopal D, Ho AL, Shah A, Chi JH (2012) Molecular basis of intervertebral disc degeneration. Adv Exp Med Biol 760:114-133
61. Gottesman II, Gould TD (2003) The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 160:636-645
62. Goupille P, Jayson MI, Valat JP, Freemont AJ (1998) Matrix metalloproteinases: the clue to intervertebral disc degeneration? Spine (Phila Pa 1976) 23:1612-1626
63. Gronblad M, Virri J, Tolonen J, Seitsalo S, Kaapa E, Kankare J, Myllynen P, Karaharju EO (1994) A controlled immunohistochemical study of inflammatory cells in disc herniation tissue. Spine (Phila Pa 1976) 19:2744-2751
64. Grotle M, Brox JI, Vollestad NK (2003) Cross-cultural adaptation of the Norwegian versions of the Roland-Morris Disability Questionnaire and the Oswestry Disability

Index. J Rehabil Med 35:241-247

65. Habtemariam A, Gronblad M, Virri J, Seitsalo S, Karaharju E (1998) A comparative immunohistochemical study of inflammatory cells in acute-stage and chronic-stage disc herniations. Spine (Phila Pa 1976)23:2159-2165
66. Habtemariam A, Gronblad M, Virri J, Seitsalo S, Ruuskanen M, Karaharju E (1996) Immunocytochemical localization of immunoglobulins in disc herniations. Spine (Phila Pa 1976)21:1864-1869
67. Harry N.Herkowitz, International Society for Study of the Lumbar Spine (2004) The Lumbar Spine. Lippincott Williams & Wilkins
68. Hashizume H, Kawakami M, Nishi H, Tamaki T (1997) Histochemical demonstration of nitric oxide in herniated lumbar discs. A clinical and animal model study. Spine (Phila Pa 1976)22:1080-1084
69. Haugen AJ, Brox JI, Grovle L, Keller A, Natvig B, Soldal DM, Grotle M (2012) Prognostic factors for non-success in patients with sciatica and disc herniation. BMC Musculoskelet Disord 13:183
70. Havemose-Poulsen A, Sorensen LK, Bendtzen K, Holmstrup P (2007) Polymorphisms within the IL-1 gene cluster: effects on cytokine profiles in peripheral blood and whole blood cell cultures of patients with aggressive periodontitis, juvenile idiopathic arthritis, and rheumatoid arthritis. J Periodontol 78:475-492
71. Hellum C, Johnsen LG, Gjertsen O, Berg L, Neckelmann G, Grundnes O, Rossvoll I, Skouen JS, Brox JI, Storheim K (2012) Predictors of outcome after surgery with disc prosthesis and rehabilitation in patients with chronic low back pain and degenerative disc: 2-year follow-up. Eur Spine J 21:681-690
72. Howe JF, Loeser JD, Calvin WH (1977) Mechanosensitivity of dorsal root ganglia and chronically injured axons: a physiological basis for the radicular pain of nerve root compression. Pain 3:25-41
73. Hsu P.S., Armon C, Levin K (2011) Lumbosacral radiculopathy: Pathophysiology, clinical features, and diagnosis. Official reprint from UpToDate
74. Hutton MJ, Bayer JH, Powell JM (2011) Modic vertebral body changes: the natural history as assessed by consecutive magnetic resonance imaging. Spine (Phila Pa 1976) 36:2304-2307
75. Igarashi T, Kikuchi S, Shubayev V, Myers RR (2000) 2000 Volvo Award winner in basic science studies: Exogenous tumor necrosis factor-alpha mimics nucleus pulposus-induced neuropathology. Molecular, histologic, and behavioral comparisons in rats. Spine (Phila

Pa 1976) 25:2975-2980

76. Ikeda T, Nakamura T, Kikuchi T, Umeda S, Senda H, Takagi K (1996) Pathomechanism of spontaneous regression of the herniated lumbar disc: histologic and immunohistochemical study. J Spinal Disord 9:136-140
77. Ikegawa S (2013) The genetics of common degenerative skeletal disorders: osteoarthritis and degenerative disc disease. Annu Rev Genomics Hum Genet 14:245-256
78. Ilmarinen J, Suurnakki T, Nygard CH, Landau K (1991) Classification of municipal occupations. Scand J Work Environ Health 17 Suppl 1:12-29
79. Jacobsen LM, Schistad EI, Storesund A, Pedersen LM, Rygh LJ, Roe C, Gjerstad J (2012) The COMT rs4680 Met allele contributes to long-lasting low back pain, sciatica and disability after lumbar disc herniation. Eur J Pain 16:1064-1069
80. Jensen TS, Karppinen J, Sorensen JS, Niinimaki J, Leboeuf-Yde C (2008) Vertebral endplate signal changes (Modic change): a systematic literature review of prevalence and association with non- specific low back pain. Eur Spine J 17:1407-1422
81. Jensen TS, Sorensen JS, Kjaer P (2007) Intra- and interobserver reproducibility of vertebral endplate signal (modic) changes in the lumbar spine: the Nordic Modic Consensus Group classification. Acta Radiol 48:748-754
82. Jim JJ, Noponen-Hietala N, Cheung KM, Ott J, Karppinen J, Sahraravand A, Luk KD, Yip SP, Sham PC, Song YQ, Leong JC, Cheah KS, Ala-Kokko L, Chan D (2005) The TRP2 allele of COL9A2 is an age-dependent risk factor for the development and severity of intervertebral disc degeneration. Spine (Phila Pa 1976)30:2735-2742
83. Julius D, Basbaum AI (2001) Molecular mechanisms of nociception. Nature 413:203-210
84. Jussila L, Paananen M, Nayha S, Taimela S, Tammelin T, Auvinen J, Karppinen J (2013) Psychosocial and lifestyle correlates of musculoskeletal pain patterns in adolescence: A 2-year follow-up study. Eur J Pain
85. Kalichman L, Hunter DJ (2008) The genetics of intervertebral disc degeneration. Associated genes. Joint Bone Spine 75:388-396
86. Kang JD, Georgescu HI, McIntyre-Larkin L, Stefanovic-Racic M, Donaldson WF, III, Evans CH (1996) Herniated lumbar intervertebral discs spontaneously produce matrix metalloproteinases, nitric oxide, interleukin-6, and prostaglandin E2. Spine (Phila Pa 1976) 21:271-277
87. Kang JD, Stefanovic-Racic M, McIntyre LA, Georgescu HI, Evans CH (1997) Toward a biochemical understanding of human intervertebral disc degeneration and herniation. Contributions of nitric oxide, interleukins, prostaglandin E2, and matrix

metalloproteinases. Spine (Phila Pa 1976) 22:1065-1073

88. Karppinen J, Daavittila I, Noponen N, Haapea M, Taimela S, Vanharanta H, Ala-Kokko L, Mannikko M (2008) Is the interleukin-6 haplotype a prognostic factor for sciatica? Eur J Pain 12:1018-1025
89. Kawaguchi Y, Osada R, Kanamori M, Ishihara H, Ohmori K, Matsui H, Kimura T (1999) Association between an aggrecan gene polymorphism and lumbar disc degeneration. Spine (Phila Pa 1976)24:2456-2460
90. Kawakami M, Matsumoto T, Kuribayashi K, Tamaki T (1999) mRNA expression of interleukins, phospholipase A2, and nitric oxide synthase in the nerve root and dorsal root ganglion induced by autologous nucleus pulposus in the rat. J Orthop Res 17:941-946
91. Kawakami M, Tamaki T, Hayashi N, Hashizume H, Nishi H (1998) Possible mechanism of painful radiculopathy in lumbar disc herniation. Clin Orthop Relat Res241-251
92. Kawakami M, Weinstein JN, Chatani K, Spratt KF, Meller ST, Gebhart GF (1994) Experimental lumbar radiculopathy. Behavioral and histologic changes in a model of radicular pain after spinal nerve root irritation with chromic gut ligatures in the rat. Spine (Phila Pa1976) 19:1795-1802
93. Keller A, Boyle E, Skog TA, Cassidy JD, Bautz-Holter E (2012) Are Modic changes prognostic for recovery in a cohort of patients with non-specific low back pain? Eur Spine J 21:418-424
94. Kim DH, Lee SH, Kim KT, Yu SD (2010) Association of interleukin-1 receptor antagonist gene polymorphism with response to conservative treatment of lumbar herniated nucleus pulposus. Spine (Phila Pa 1976) 35:1527-1531
95. Kim WH, Lee SH, Lee DY (2011) Changes in the cross-sectional area of multifidus and psoas in unilateral sciatica caused by lumbar disc herniation. J Korean Neurosurg Soc 50:201-204
96. Kjaer P, Leboeuf-Yde C, Korsholm L, Sorensen JS, Bendix T (2005) Magnetic resonance imaging and low back pain in adults: a diagnostic imaging study of 40-year-old men and women. Spine (Phila Pa 1976) 30:1173-1180
97. Koes BW, van Tulder MW, Peul WC (2007) Diagnosis and treatment of sciatica. Br Med J 334:1313-1317
98. Konstantinou K, Beardmore R, Dunn KM, Lewis M, Hider SL, Sanders T, Jowett S, Somerville S, Stynes S, van der Windt DA, Vogel S, Hay EM (2012) Clinical course, characteristics and prognostic indicators in patients presenting with back and leg pain in primary care. The ATLAS study protocol. BMC Musculoskelet Disord 13:4

99. Konstantinou K, Dunn KM (2008) Sciatica: review of epidemiological studies and prevalence estimates. Spine (Phila Pa1976) 33:2464-2472
100. Konstantinou K, Dunn KM (2008) Sciatica: review of epidemiological studies and prevalence estimates. Spine (Phila Pa1976) 33:2464-2472
101. Kuisma M, Karppinen J, Niinimaki J, Kurunlahti M, Haapea M, Vanharanta H, Tervonen O (2006) A three-year follow-up of lumbar spine endplate (Modic) changes. Spine (Phila Pa 1976) 31:1714-1718
102. Kuisma M, Karppinen J, Niinimaki J, Ojala R, Haapea M, Heliovaara M, Korpelainen R, Taimela S, Natri A, Tervonen O (2007) Modic changes in endplates of lumbar vertebral bodies: prevalence and association with low back and sciatic pain among middle-aged male workers. Spine (Phila Pa 1976) 32:1116-1122
103. Kwon M, Altin M, Duenas H, Alev L (2013) The Role of Descending Inhibitory Pathways on Chronic Pain Modulation and Clinical Implications. Pain Pract
104. Lapossy E, Maleitzke R, Hrycaj P, Mennet W, Muller W (1995) The frequency of transition of chronic low back pain to fibromyalgia. Scand J Rheumatol 24:29-33
105. Le Maitre CL, Freemont AJ, Hoyland JA (2005) The role of interleukin-1 in the pathogenesis of human intervertebral disc degeneration. Arthritis Res Ther 7:R732-R745
106. Le Maitre CL, Freemont AJ, Hoyland JA (2006) A preliminary in vitro study into the use of IL-1Ra gene therapy for the inhibition of intervertebral disc degeneration. Int J Exp Pathol 87:17-28
107. Le BD (2002) The whole body receptive field of dorsal horn multireceptive neurones. Brain Res Brain Res Rev 40:29-44
108. Le BD, Dickenson AH, Besson JM (1979) Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent neurones in the rat. Pain 6:283-304
109. Lee MC, Tracey I (2013) Imaging pain: a potent means for investigating pain mechanisms in patients. Br J Anaesth 111:64-72
110. Levin K., Hsu P.S., Armon C. (2013) Acute lumbosacral radiculopathy: Prognosis and treatment. UpToDate
111. Lewis GN, Rice DA, McNair PJ (2012) Conditioned pain modulation in populations with chronic pain: a systematic review and meta-analysis. J Pain 13:936-944
112. Liao Q, Chen DJ, Zhang F, Li L, Hu R, Tang YZ, Ou-Yang W, Huang D (2013) Effect of CYP3A4*18B polymorphisms and interactions with OPRM1 A118G on

postoperative fentanyl requirements in patients undergoing radical gastrectomy. Mol Med Rep 7:901-908

113. Loeser JD, Treede RD (2008) The Kyoto protocol of IASP Basic Pain Terminology. Pain 137:473-477
114. Lotsch J, Doehring A, Mogil JS, Arndt T, Geisslinger G, Ultsch (2013) Functional genomics of pain in analgesic drug development and therapy. Pharmacol Ther 139:60-70
115. Lurie JD, Moses RA, Tosteson AN, Tosteson TD, Carragee EJ, Carrino JA, Kaiser JA, Herzog RJ (2013) Magnetic resonance imaging predictors of surgical outcome in patients with lumbar intervertebral disc herniation. Spine (Phila Pa 1976) 38:1216-1225
116. Ma XL, Ma JX, Wang T, Tian P, Han C (2011) Possible role of autoimmune reaction in Modic Type I changes. Med Hypotheses 76:692-694
117. Mannion AF, Elfering A (2006) Predictors of surgical outcome and their assessment. Eur Spine J 15 Suppl 1:S93-108
118. Marchand S (2012) The phenomenon of Pain. IASP Press Book
119. Marchand S (2008) The physiology of pain mechanisms: from the periphery to the brain. Rheum Dis Clin North Am 34:285-309
120. Mayer JE, Iatridis JC, Chan D, Qureshi SA, Gottesman O, Hecht AC (2013) Genetic polymorphisms associated with intervertebral disc degeneration. Spine J 13:299-317
121. McLorinan GC, Glenn JV, McMullan MG, Patrick S (2005) Propionibacterium acnes wound contamination at the time of spinal surgery. Clin Orthop Relat Res67-73
122. Melzack R, Wall PD, Ty TC (1982) Acute pain in an emergency clinic: latency of onset and descriptor patterns related to different injuries. Pain 14:33-43
123. Merskey H, Bogduk N (2004) Classification of chronic pain: descriptions of chronic pain syndromes and descriptions of pain terms. IASP Press, Seattle
124. Merskey H, Bogduk N, editors (1994) Classification of chronic pain. (WA): International Association for the Study of Pain; Seattle, p.394
125. Mixter W.J., Barr J.S. (1934) Rupture of the Intervertebral Disc with Involvement of Spinal Canal. New Engl J Med 211:-215
126. Modic MT, Steinberg PM, Ross JS, Masaryk TJ, Carter JR (1988) Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. Radiology 166:193-199
127. Moore RJ (2000) The vertebral end-plate: what do we know? Eur Spine J 9:92-96

128. Mulleman D, Mammou S, Griffoul I, Watier H, Goupille P (2006) Pathophysiology of disk-related sciatica. I.--Evidence supporting a chemical component. Joint Bone Spine 73:151-158
129. Muller S, Thomas E, Dunn KM, Mallen CD (2013) A prognostic approach to defining chronic pain across a range of musculoskeletal pain sites. Clin J Pain 29:411-416
130. Nygaard OP, Mellgren SI, Osterud B (1997) The inflammatory properties of contained and noncontained lumbar disc herniation. Spine (Phila Pa 1976) 22:2484-2488
131. Ohtori S, Inoue G, Ito T, Koshi T, Ozawa T, Doya H, Saito T, Moriya H, Takahashi K (2006) Tumor necrosis factor- immunoreactive cells and PGP 9.5-immunoreactive nerve fibers in vertebral endplates of patients with discogenic low back Pain and Modic Type 1 or Type 2 changes on MRI. Spine (Phila Pa 1976)31:1026-1031
132. Ohtori S, Yamashita M, Yamauchi K, Inoue G, Koshi T, Suzuki M, Orita S, Eguchi Y, Ochiai N, Kishida S, Takaso M, Aoki Y, Ishikawa T, Arai G, Miyagi M, Kamoda H, Nakamura J, Takahashi K (2010) Low back pain after lumbar discectomy in patients showing endplate modic type 1 change. Spine (Phila Pa 1976) 35:E596-E600
133. Olmarker K, Blomquist J, Stromberg J, Nannmark U, Thomsen P, Rydevik B (1995) Inflammatogenic properties of nucleus pulposus. Spine (Phila Pa 1976) 20:665-669
134. Olmarker K, Rydevik B, Nordborg C (1993) Autologous nucleus pulposus induces neurophysiologic and histologic changes in porcine cauda equina nerve roots. Spine (Phila Pa 1976) 18:1425-1432
135. Olmarker K, Storkson R, Berge OG (2002) Pathogenesis of sciatic pain: a study of spontaneous behavior in rats exposed to experimental disc herniation. Spine (Phila Pa 1976) 27:1312-1317
136. Olsen MB, Jacobsen LM, Schistad EI, Pedersen LM, Rygh LJ, Roe C, Gjerstad J (2012) Pain intensity the first year after lumbar disc herniation is associated with the A118G polymorphism in the opioid receptor mu 1 gene: evidence of a sex and genotype interaction. J Neurosci 32:9831-9834
137. Omair A, Holden M, Lie BA, Reikeras O, Brox JI (2013) Treatment outcome of chronic low back pain and radiographic lumbar disc degeneration are associated with inflammatory and matrix degrading gene variants: a prospective genetic association study. BMC Musculoskelet Disord 14:105
138. Omair A, Lie BA, Reikeras O, Holden M, Brox JI (2012) Genetic contribution of catechol-O-methyltransferase variants in treatment outcome of low back pain: a prospective genetic association study. BMC Musculoskelet Disord 13:76

139. Omarker K, Myers RR (1998) Pathogenesis of sciatic pain: role of herniated nucleus pulposus and deformation of spinal nerve root and dorsal root ganglion. Pain 78:99-105
140. Ostelo RW, Vlaeyen JW, van den Brandt PA, de Vet HC (2005) Residual complaints following lumbar disc surgery: prognostic indicators of outcome. Pain 114:177-185
141. Paz AJ, Fernandez B, I, Lopez-Anglada FE, Montes AH, Paz AA, Pena VJ, Ramos GS, Anton GS, Lopez FP, Valle-Garay E, Asensi V (2011) The IL-1beta (+3953 T/C) gene polymorphism associates to symptomatic lumbar disc herniation. Eur Spine J 20 Suppl 3:383-389
142. Pennisi E (2012) Genomics. ENCODE project writes eulogy for junk DNA. Science 337:1159, 1161
143. Peul WC, Brand R, Thomeer RT, Koes BW (2008) Influence of gender and other prognostic factors on outcome of sciatica. Pain 138:180-191
144. Pinto RZ, Maher CG, Ferreira ML, Hancock M, Oliveira VC, McLachlan AJ, Koes B, Ferreira PH (2012) Epidural corticosteroid injections in the management of sciatica: a systematic review and meta-analysis. Ann Intern Med 157:865-877
145. Rajasekaran S, Bajaj N, Tubaki V, Kanna RM, Shetty AP (2013) ISSLS Prize winner: The anatomy of failure in lumbar disc herniation: an in vivo, multimodal, prospective study of 181 subjects. Spine (Phila Pa 1976) 38:1491-1500
146. Rhudy JL, DelVentura JL, Terry EL, Bartley EJ, Olech E, Palit S, Kerr KL (2013) Emotional modulation of pain and spinal nociception in fibromyalgia. Pain 154:1045-1056
147. Risbud MV, Shapiro IM (2013) Role of cytokines in intervertebral disc degeneration: pain and disc content. Nat Rev Rheumatol
148. Sambrook PN, MacGregor AJ, Spector TD (1999) Genetic influences on cervical and lumbar disc degeneration: a magnetic resonance imaging study in twins. Arthritis Rheum 42:366-372
149. Sandanger I, Nygard JF, Ingebrigtsen G, Sorensen T, Dalgard OS (1999) Prevalence, incidence and age at onset of psychiatric disorders in Norway. Soc Psychiatry Psychiatr Epidemiol 34:570-579
150. Sarzi-Puttini P, Atzeni F, Mease PJ (2011) Chronic widespread pain: from peripheral to central evolution. Best Pract Res Clin Rheumatol 25:133-139
151. Schneiderman G, Flannigan B, Kingston S, Thomas J, Dillin WH, Watkins RG (1987) Magnetic resonance imaging in the diagnosis of disc degeneration: correlation with

discography. Spine (Phila Pa 1976) 12:276-281

152. Schroeder M, Viezens L, Schaefer C, Friedrichs B, Algenstaedt P, Ruther W, Wiesner L, Hansen-Algenstaedt N (2013) Chemokine profile of disc degeneration with acute or chronic pain. J Neurosurg Spine
153. Silveira JW, Dias QM, Del Bel EA, Prado WA (2010) Serotonin receptors are involved in the spinal mediation of descending facilitation of surgical incision-induced increase of Fos-like immunoreactivity in rats. Mol Pain 6:17
154. Sim J, Wright CC (2005) The kappa statistic in reliability studies: use, interpretation, and sample size requirements. Phys Ther 85:257-268
155. Skoff AM, Zhao C, Adler JE (2009) Interleukin-1alpha regulates substance P expression and release in adult sensory neurons. Exp Neurol 217:395-400
156. Smyth MJ, Wright V (1958) Sciatica and the intervertebral disc; an experimental study. J Bone Joint Surg Am 40-A:1401-1418
157. Solovieva S, Kouhia S, Leino-Arjas P, Ala-Kokko L, Luoma K, Raininko R, Saarela J, Riihimaki H (2004) Interleukin 1 polymorphisms and intervertebral disc degeneration. Epidemiology15:626-633
158. Sorlie A, Moholdt V, Kvistad KA, Nygaard OP, Ingebrigtsen T, Iversen T, Kloster R, Solberg TK (2012) Modic type I changes and recovery of back pain after lumbar microdiscectomy. Eur Spine J 21:2252-2258
159. Sotto A, Dupeyron A (2013) Letter to the editor concerning: "Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized controlled trial of efficacy" by Albert HB et al. Eur Spine J (2013) 22:697-707. Eur Spine J 22:1704-1705
160. Spiliopoulou I, Korovessis P, Konstantinou D, Dimitracopoulos G (1994) IgG and IgM concentration in the prolapsed human intervertebral disc and sciatica etiology. Spine (Phila Pa 1976)19:1320-1323
161. Stafford MA, Peng P, Hill DA (2007) Sciatica: a review of history, epidemiology, pathogenesis, and the role of epidural steroid injection in management. Br J Anaesth 99:461-473
162. Stirling A, Jiggins M (2002) Association between Sciatica and Skin Commensals. International Society for the Study of the Lumbar Spine, Cleveland,
163. Stirling A, Worthington T, Rafiq M, Lambert PA, Elliott TS (2001) Association between sciatica and Propionibacterium acnes. Lancet 357:2024-2025

164. Strand LI, Wisnes AR (1991) The development of a Norwegian pain questionnaire. Pain 46:61-66
165. Tomic S, Soldo-Butkovic S, Kovac B, Faj D, Juric S, Misevic S, Knezevic L, Vukasinovic D (2009) Lumbosacral radiculopathy-- factors effects on it's severity. Coll Antropol 33:175-178
166. Tracey I (2011) Can neuroimaging studies identify pain endophenotypes in humans? Nat Rev Neurol 7:173-181
167. Tracey I, Mantyh PW (2007) The cerebral signature for pain perception and its modulation. Neuron 55:377-391
168. Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J (2008) Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology 70:1630-1635
169. Urban JP, Roberts S (2003) Degeneration of the intervertebral disc. Arthritis Res Ther 5:120-130
170. Vargas-Prada S, Martinez JM, Coggon D, Delclos G, Benavides FG, Serra C (2013) Health beliefs, low mood, and somatizing tendency: contribution to incidence and persistence of musculoskeletal pain with and without reported disability. Scand J Work Environ Health 39:589-598
171. Videman T, Saarela J, Kaprio J, Nakki A, Levalahti E, Gill K, Peltonen L, Battie MC (2009) Associations of 25 structural, degradative, and inflammatory candidate genes with lumbar disc desiccation, bulging, and height narrowing. Arthritis Rheum 60:470-481
172. Vining R, Potocki E, Seidman M, Morgenthal AP (2013) An evidence-based diagnostic classification system for low back pain. J Can Chiropr Assoc 57:189-204
173. Vredeveld T, Teitsma XM, Mert A, Van der Wurff P (2012) Prevalence of modic changes in active duty military men with lumbar disk herniation who were scheduled for surgery. J Manipulative Physiol Ther 35:622-628
174. Vroomen PC, de Krom MC, Knottnerus JA (1999) Diagnostic value of history and physical examination in patients suspected of sciatica due to disc herniation: a systematic review. J Neurol 246:899-906
175. Waddell G (1998) The epidemiology of low back pain. In: Waddell G, ed (eds) The back pain revolution. Churchill Livingstone, New York, pp 69-84
176. Waddell G, Aylward M, Sawney P (2002) Back pain, incapacity for work and social security benefits: an international literature review and analysis. The Royal Society of

Medicine Press, London

177. Wannstrom I, Peterson U, Asberg M, Nygren A, Gustavsson JP (2009) Psychometric properties of scales in the General Nordic Questionnaire for Psychological and Social Factors at Work (QPS): confirmatory factor analysis and prediction of certified long-term sickness absence. Scand J Psychol 50:231-244
178. Weber H (1994) The natural history of disc herniation and the influence of intervention. Spine (Phila Pa 1976) 19:2234-2238, discussion 2233
179. Weber H, Holme I, Amlie E (1993) The natural course of acute sciatica with nerve root symptoms in a double-blind placebo- controlled trial evaluating the effect of piroxicam. Spine (Phila Pa 1976) 18:1433-1438
180. Wedderkopp N, Thomsen K, Manniche C, Kolmos HJ, Secher JT, Leboeuf YC (2009) No evidence for presence of bacteria in modic type I changes. Acta Radiol 50:65-70
181. Wei J, Pan X, Pei Z, Wang W, Qiu W, Shi Z, Xiao G (2012) The beta-lactam antibiotic, ceftriaxone, provides neuroprotective potential via anti-excitotoxicity and anti-inflammation response in a rat model of traumatic brain injury. J Trauma Acute Care Surg 73:654-660
182. Williams FM, Bansal AT, van Meurs JB, Bell JT, Meulenbelt I, Suri P, Rivadeneira F, Sambrook PN, Hofman A, Bierma-Zeinstra S, Menni C, Kloppenburg M, Slagboom PE, Hunter DJ, MacGregor AJ, Uitterlinden AG, Spector TD (2013) Novel genetic variants associated with lumbar disc degeneration in northern Europeans: a meta-analysis of 4600 subjects. Ann Rheum Dis 72:1141-1148
183. Williams FM, Popham M, Sambrook PN, Jones AF, Spector TD, MacGregor AJ (2011) Progression of lumbar disc degeneration over a decade: a heritability study. Ann Rheum Dis 70:1203-1207
184. Woolf CJ (2004) Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med 140:441-451
185. Yabuki S, Kikuchi S, Olmarker K, Myers RR (1998) Acute effects of nucleus pulposus on blood flow and endoneurial fluid pressure in rat dorsal root ganglia. Spine (Phila Pa 1976) 23:2517-2523
186. Yazdi AS, Drexler SK (2013) Regulation of interleukin 1alpha secretion by inflammasomes. Ann Rheum Dis 72 Suppl 2:ii96-ii99
187. Yeung AT, Yeung CA (2006) In-vivo endoscopic visualization of patho-anatomy in painful degenerative conditions of the lumbar spine. Surg Technol Int 15:243-256

188. Yilmaz P, Diers M, Diener S, Rance M, Wessa M, Flor H (2010) Brain correlates of stress-induced analgesia. Pain 151:522-529
189. Younes M, Bejia I, Aguir Z, Letaief M, Hassen-Zrour S, Touzi M, Bergaoui N (2006) Prevalence and risk factors of disk-related sciatica in an urban population in Tunisia. Joint Bone Spine 73:538-542
190. Zeitz KP, Guy N, Malmberg AB, Dirajlal S, Martin WJ, Sun L, Bonhaus DW, Stucky CL, Julius D, Basbaum AI (2002) The 5-HT3 subtype of serotonin receptor contributes to nociceptive processing via a novel subset of myelinated and unmyelinated nociceptors. J Neurosci 22:1010-1019
191. Zhang Y, Chee A, Thonar EJ, An HS (2011) Intervertebral disk repair by protein, gene, or cell injection: a framework for rehabilitation-focused biologics in the spine. PM R 3:S88-S94
192. Zhang YG, Sun Z, Zhang Z, Liu J, Guo X (2009) Risk factors for lumbar intervertebral disc herniation in Chinese population: a case- control study. Spine (Phila Pa 1976) 34:E918-E922
193. Zhang YG, Zhang F, Sun Z, Guo W, Liu J, Liu M, Guo X (2013) A controlled case study of the relationship between environmental risk factors and apoptotic gene polymorphism and lumbar disc herniation. Am J Pathol 182:56-63
194. Zubieta JK, Heitzeg MM, Smith YR, Bueller JA, Xu K, Xu Y, Koeppe RA, Stohler CS, Goldman D (2003) COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. Science 299:1240-1243

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Original article:

Title: **Association between baseline IL-6 and one-year recovery in lumbar radicular pain**

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Abstract

Background: In the present study the influence of cytokines on one-year recovery in lumbar radicular pain was examined.

Methods: In total 110 patients with symptomatic lumbar disc herniation were followed for one year. Uni- and multivariate linear regression was used to assess the influence of IL-6, IL-8, disc degeneration, and endplate changes (Modic changes) on the changes in the primary outcome Oswestry disability index (ODI change) and secondary outcomes VAS for low back pain (LBP) and leg pain.

Results: Less favourable ODI outcome correlated with higher serum IL-6 levels (B =-3.41, 95% CI -5.52 to -1.30, p = 0.002), non-surgical treatment (B = -7.03, 95% CI 1.21 to 12.84, p = 0.018), higher baseline back pain intensity (B =-2.28, 95% CI -3.21 to -1.35, p < 0.001), and low educational level (B = -5.57, 95% CI 0.66 to 10.47, p = 0.027). High VAS for LBP and leg pain at one year was associated with high levels of serum IL-6, higher back pain intensity and longer duration of lumbar radicular pain at baseline.

Conclusions: High serum IL-6 levels, but not disc degeneration or Modic changes, were associated with less favourable recovery in patients with lumbar radicular pain. Intense initial back pain, non-surgical treatment, lower educational level, and longer duration of radicular pain before treatment also correlated with a slower recovery the first year after disc herniation.

Keywords: lumbar radicular pain; low back pain (LBP); ODI (Oswestry disability index); cytokines (IL-6 and IL-8); endplate changes/Modic changes; disc degeneration; magnetic resonance imaging (MRI).

Introduction

The recovery from lumbar radicular pain is influenced by psychosocial, surgery-related, clinical and biological factors. Particular, the role of biological factors predicting the recovery after symptomatic disc herniation is not fully understood.

Psychosocial and emotional prognostic factors have been less well studied in radicular pain compared with LBP, but they do have an impact on recovery (Ashworth et al 11; den Boer et al 06; Haugen et al 12). Comorbid subjective health complaints, emotional distress, kinesiophobia, more LBP, longer duration of symptoms, smoking, clinical factors such as muscular weakness, and no surgical treatment are associated with non-success in lumbar radicular pain due to DH (Edwards et al 07; Haugen et al 12). Lower education level, which is often associated with environmental and occupational factors such as heavy physical work and low-decision authority, is known prognostic factors for poor recovery (Chibnall and Tait 09; Keller et al 12).

Regarding MRI findings, the morphometric features of the herniated disc and spinal canal may be useful when predicting the outcome from surgery (Carragee and Kim 97; Sutheerayongprasert et al 12). The type of treatment (surgical or conservative) may influence the short-term time course of patients with lumbar radicular pain. In contrast disc degeneration may not be associated with disability or pain at a one-year follow-up of patients with radicular pain (Jensen et al 10). A better understanding of the benefits and limitations of MRI in evaluating patients with symptomatic disc herniation may therefore be important for future treatment (Yong and Sutherland 12).

Several lines of evidence (Burke et al 02; Kang et al 96; Kraychete et al 10) suggest that inflammation contributes to the pathogenesis of lumbar radicular pain due to disc herniation. Therefore, pro-inflammatory cytokines, specifically interleukins (ILs) and TNF-α, are potential biomarkers of disc degeneration and disc herniation. For example, previous data show that disc herniation increases the synthesis of matrix metalloproteinases, nitric oxide, prostaglandin E_2, interleukin-6 (IL-6) (Kang et al 96) and IL-8 (Burke et al 02).The inflammatory response, initiated from the annulus fibrosus in case of disc herniation, may lead to increased levels of pro-inflammatory cytokines close to nerve roots. The inflammatory reaction around the herniated disc material also affects the nerve roots with disturbance of

intraradicular blood flow and breakdown of the blood-nerve barrier, resulting in intraradicular inflammatory changes such as edema and demyelination. Moreover, there is evidence that serum levels of IL-6 may be elevated in patients suffering from persistent radicular pain 8 weeks after discectomy compared with healthy pain-free controls (Geiss et al 97). One cross-sectional study also demonstrated elevated serum IL-6 levels in patients with chronic LBP due to herniated discs (Kraychete et al 10). However, the impact of IL-6 on the recovery rate of patients with lumbar radicular pain has not been evaluated in a prospective study. The aim of this prospective study was to examine the influence of such cytokines (IL-6 and IL-8) on one-year recovery of patients with lumbar radicular pain.

Materials and Methods

Study population

Participants with lumbar radicular pain were recruited from those attending Oslo University Hospital in Ulleval between 2007 and 2009. The inclusion criteria were: age between 18 and 60 years and lumbar disc herniation on MRI with corresponding distribution of pain in lower limbs and positive straight leg raising (SLR) test results. The exclusion criteria were as follows: lumbar spinal stenosis; previous spinal surgery for a herniated disc at the same level or lumbar fusion at any level; generalised musculoskeletal pain; inflammatory rheumatic disease; diabetic polyneuropathy; cardiovascular disease (New York Heart Association class III and IV); cancer; psychiatric disease; drug misuse and alcoholism; recent surgery (within 1 month); pregnancy; poor proficiency in the Norwegian language and non-European-Caucasian ethnicity. Patients with cauda equina syndrome were also excluded. In total, 121 (81.8%) of the 148 patients who met the eligibility requirements were included in the intended follow-up assessment (Fig. 1). The drop-out rate was 9.1%, and ultimately, 110 patients were assessed at a one-year follow-up. The study was conducted in accordance with the Helsinki Declaration. The Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Service approved the study protocol, and all participants gave their written informed consent to participate.

Clinical procedures and outcome measures

At the initial screening visit and at the one-year follow-up, patients underwent a standardised clinical examination, which included an assessment of sensory and motor function and completion of standardised pain, emotional distress and function questionnaires. Demographic data and an MRI scan were obtained upon inclusion in the study. Patients were not randomised to surgery, but selected by usual clinical assessment based on the presence of neurological deficits, intense radicular pain and disability. Surgical treatment was offered to patients with persistent radicular pain lasting more than 8 weeks, neurological deficits (sensory changes, muscle weakness or depressed or absent deep tendon reflexes) and corresponding MRI findings in the anticipated location. Patients who did not fulfil these criteria were managed conservatively, a pathway that comprised a brief cognitive intervention, activity guidance during the acute phase of disc herniation and, for the majority of patients (60.3%), physiotherapy.

In general both surgical and non-surgical patients received pharmacological treatment as either monotherapy or combined therapy according to usual clinical practice. In addition, most of the patients used paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs). Opioid analgesics, antiepileptic and antipsychotic drugs were also prescribed if necessary. Regarding use of steroids, one surgical and one non-surgical patient received systemic corticosteroids in the acute phase of disc herniation and radicular pain. Finally, two conservatively managed patients received transforaminal epidural steroids injections.

Socio-demographic variables and work-related factors such as marital status, duration of education, occupation, duration of sick leave and social benefits were also registered upon inclusion in the study. Occupations were classified into three groups: Mental, Mixed and Physical work (Ilmarinen et al 91). The demand and control subscales of the General Nordic Questionnaire for Psychological and Social Factors at Work (QPS Nordic) (Wannstrom et al 09) were applied to record quantitative job demands and the control of work pacing.

Pain intensity was recorded using the visual analogue scale (VAS) with anchor values from 0 to 10 for present pain, pain during activity and pain at rest, with separate scales for LBP and leg pain. Patients were asked to report the mean pain intensity during the last week. The Hopkins Symptom Checklist (HSCL), a 25-item questionnaire, was used to register psychological distress (Derogatis et al 74); scores equal to or greater than 1.75 on the total scale indicated emotional distress (Sandanger et al 99). We used the validated Norwegian version of the Oswestry disability index (ODI, scale 0-100%, where 0% = no disability at all, and 100% = very severe disability) (Grotle et al 03). The Oswestry index was considered to be the most relevant score for the study of function and long-term outcome. Hence, the primary outcome measure in this study was ODI change, defined as the baseline ODI minus the ODI at the one-year follow-up. A higher value for ODI change indicates a more favourable functional outcome.

Image evaluation

Baseline lumbar 1.5 T or 1.0 T MRI examinations were performed as part of the clinical patient evaluation and included sagittal T2- and T1-weighted images and axial images. For the present study, all MRIs were de-identified and presented in random order. An experienced radiologist (AE) and a physical medicine and rehabilitation physician (EIS) were blinded to

the clinical data before independently grading the MRI scans for Modic changes (Modic et al 88) and disc degeneration. At each of the 10 endplates from L1 to S1, AE and ES noted Modic changes as primary type I (hypointense T1- and hyperintense T2-signal), type II (hyperintense T1- and iso/hyperintense T2-signal) or type III (hypointense T1- and T2-signal). Modic changes were classified into three groups as follows: no Modic changes, Modic type I, and Modic type II and III without type I.

Disc degeneration was graded on mid-sagittal T2-weighted images at each of the five disc levels from L1 to S1 using Schneiderman's grading system (Schneiderman et al 87): a score of 0 indicated no signal change, a score of 1 indicated a slight decrease in the signal intensity in the nucleus pulposus, a score of 2 indicated a generalised hypointense nucleus, and a score of 3 indicated a hypointense nucleus with disc space narrowing. The total disc degeneration score (0 – 15) across all five discs was calculated and then grouped according to Jim (Jim et al 05) into severe (two or more grade 3 discs, three or more grade 2 discs, or one grade 3 and two grade 2 discs), moderate (one grade 3 disc or two grade 2 discs), mild (only one grade 2 disc and no grade 3 discs), or normal (total disc degeneration score of 0 or 1). Disc degeneration was analysed as the total score and as a grouped variable. In all cases of disagreement, a consensus score was negotiated. In a sample of 275 patients with symptomatic disc herniation including the study cohort, the two observers achieved relatively consistent inter-observer agreement on the type of the Modic changes (kappa 0.59-0.77) at endplates with at least 10% prevalence of Modic changes (L2-S1), ensuring interpretable kappa values (Sim and Wright 05). In instances of at least 10% prevalence of disc degeneration with a score of 2 or 3 (also L2-S1), inter-observer agreement on disc degeneration was moderate or good (linearly weighted kappa 0.54-0.67).

ELISA measurements of cytokine concentration in serum

Blood samples were drawn during the initial screening visit at the hospital. A few patients, who had to wait for surgery longer than 8 weeks, were re-included with new blood samples. The serum analysis of the blood samples was performed at the National Institute of Occupational Health, Oslo. Laboratory method: After being on ice for 45 minutes, blood samples were centrifuged for 10 minutes at 4^0C and 2000 G. Further, serum was stored in duplicate at -80^0C until use. The serum concentrations of the two pro-inflammatory cytokines IL-6 and IL-8 were determined by the use of commercial enzyme-linked immunosorbent

assay kits according to the manufacturer's instructions (human ultrasensitive kits for IL-6 and IL-8, Invitrogen Corporation, CA, USA). Briefly, 100 µl of serum or IL-6 or IL-8 standard was added to each well in microtitre plates pre-coated with an antibody specific for each cytokine, and the plates were incubated at room temperature. After washing the plates, 100 µl of biotinylated antibody specific for IL-6 or IL-8 was added, and the plates were incubated at room temperature. After removal of excess secondary antibody by washing, 100 µl of streptavidin-conjugated horseradish peroxidase enzyme solution was added to each well. After incubating the plates at room temperature and washing the plates to remove all unbound enzyme, a substrate solution with chromogen was added to produce colour. The reaction was stopped by adding 100 µl of stop solution. The optical density was measured at a wavelength of 450 nm using a Fusion Universal Microplate analyser (Packard Instrument Company, Meriden, CT, USA). Data were analysed using the Fusion data analysis software program (Packard Instrument Company). The amount of IL-6 and IL-8 in all samples was quantified based on a standard curve prepared for each analysed cytokine. Background absorbance was subtracted from all data points including the unknown samples and the standards. Serum collected at three different time points for each patient was analysed on the same microtitre plate. Serum IL-6 was measured in pg/ml. According to the manufacturer, the minimum detectable dose of IL-6 and IL-8 was 0.15 pg/ml and 0.4 pg/ml, respectively.

Statistical analyses

Pain and function scores between the surgery and non-surgery groups were compared using t-tests at baseline and one-year follow-up. Daily use of pain medication and neurological deficits between the surgery and non-surgery groups were compared using Chi-square tests at baseline and one-year follow-up. After Bonferroni adjustment for comparison at two different time points, $p \leq 0.025$ ($p \leq 0.05/2$) was regarded as statistically significant in these comparative analyses.

The relationship between potential prognostic variables and the ODI change was determined using linear regression analysis. Analysed variables included serum cytokine concentrations, pain intensity, emotional distress and functioning, neurological deficits, daily use of analgesics and co-analgesics, Modic changes, disc degeneration and the following demographic data: age; sex; marital status; educational level; employment (full-time job or not); profession and QPS Nordic job demands and control of work pacing (Table 1).

Interleukin-6 was analysed as continuous variable. HSCL-25 data were dichotomised using the cut-off point 1.75 (Sandanger et al 99) for the purpose of the regression analysis.

In the next step, variables with a p-value <0.1 based on the univariate regression analysis were included in a stepwise multivariate regression analysis with the ODI change as the dependent variable. Each analysis was adjusted for the baseline value of the ODI. In a forward stepwise procedure, the independent variables with the largest p-value were excluded until all of the remaining variables showed a p-value below 0.05. Statistical assumptions were met as influence and leverage statistics were within a normal range. The variance inflation factors (VIFs) of the multiple regression analysis were within the acceptable range (VIF <10), suggesting acceptable co-linearity. Residual statistics revealed high Mahalanobis distance values in two patients. These patients were excluded from the analysis because these participants would otherwise have had too large an influence on the regression coefficient (Jeng and Martin 85). The residuals in the regression model showed a normal distribution. Missing pain scores (2%) were replaced with the mean value for each treatment group. Regarding other independent values there were no missing values. Multivariate regression analysis was supplied with the additional endpoint parameters VAS for LBP and VAS for leg pain separately. Each analysis with additional endpoints was adjusted for the baseline value of the VAS for LBP and leg pain, respectively. Statistical analyses were performed using the statistical package PASW statistics 19 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics of the 108 analysed patients with lumbar radicular pain are shown in Table 1. Seventy-five patients (69%) had neurological deficits, three of whom had paresis (drop-foot) during heel-toe walking. Forty patients (37%) were treated surgically, most by microdiscectomy. The mean time from baseline to surgery was 6.7 weeks (SD 6.0). Sixty-eight (63%) patients were managed conservatively. At baseline, patients treated with surgery showed poorer function than patients treated without surgery (mean ODI change of 28.0, SD 18.1 *versus* mean ODI change of 9.4, SD 15.3), and they showed a higher mean VAS for leg pain (Table 2a). Daily use of analgesics or co-analgesics and neurological deficits in patients treated with and without surgery are shown in Table 2b. At baseline, we did not observe any difference in the use of paracetamol, antiepileptic or antipsychotic drugs between surgical and non-surgical patients. Nevertheless, surgical patients used NSAIDs and opioids more frequently than the non-surgical patients (Table 2b). As expected, at the one-year follow-up, the daily use of all analgesics and co-analgesics had been reduced in both groups. At one-year follow-up, 33% in the surgery group and 15% in the non-surgery group used analgesics. However, no clear statistical difference between the groups was observed; the Chi-square test for independence (with Yates' continuity correction) indicated no significant association between use of analgesics at one-year follow-up and treatment, χ^2 (1, n = 108) = 0.21, p = 0.053, phi = 0.21. Regarding the baseline serum IL-6 levels (mean = 1.02; SD = 1.14; range 0 – 6.32), there was no significant difference in IL-6 levels between the surgery and non-surgery groups (surgery mean = 0.9, SD = 0.9, non-surgery mean = 1.1, SD = 1.3; Student's t-test t (102) = 0.8, p = 0.44).

Function improved during the one-year follow-up (mean ODI change of 16.5, SD 18.7). Results from the linear regression analysis of potential predictors of ODI change during the one-year follow-up after adjusting only for baseline ODI are shown in Table 3. The following variables had significant prognostic value (with a p-value < 0.1) for ODI change: serum IL-6 concentration, surgery, VAS for back pain, VAS for current back and leg pain, duration of lumbar radicular pain, educational level, HSCL-25, and smoking (Table 3). Modic changes, disc degeneration and daily use of pain medications were not significant prognostic factors. The results of the stepwise multivariate regression are shown in Table 4. The baseline value for ODI was included as an independent variable in the analysis. High levels of serum IL-6, non-surgical treatment, high LBP intensity, and lower educational level inversely correlated

with recovery and accounted for 58% of the variance in the ODI change together with the baseline functional level. The results of stepwise multivariate regression with the additional endpoint parameters VAS for LBP and for leg pain separately at one-year follow-up are shown in Tables 5 and Table 6, respectively. High levels of serum IL-6, high LBP intensity, and longer duration of lumbar radicular pain at baseline correlated with high VAS for LBP and accounted for 34% of the variance in the VAS for LBP at one-year follow-up. High levels of serum IL-6, high intensity of LBP, and longer duration of lumbar radicular pain at baseline correlated with high VAS for leg pain and accounted for 25% of the variance in the VAS for leg pain at one-year follow-up.

Discussion

This study is the first to show an association between serum IL-6 levels and recovery of patients with lumbar radicular pain after disc herniation when adjusted for other relevant risk factors. In addition to high initial back pain intensity, non-surgical treatment, lower educational level and longer history of lumbar radicular pain prior to treatment, high IL-6 levels had a negative impact on the long-term recovery rate of patients with symptomatic disc herniation. However, Modic changes and disc degeneration had no impact on recovery at one-year follow-up.

Patients with intense initial back pain showed less improvement in pain and function at one-year follow-up, a finding that is consistent with previous observations (Jensen et al 10). Moreover, patients with high levels of serum IL-6 also showed less improvement. This demonstrates that intense pain and high levels of inflammatory cytokines such as IL-6 are risk factors for long-term disability in patients with lumbar radicular pain. A previous study (Binshtok et al 08) has shown that in addition to producing inflammation and inducing the synthesis of several nociceptor sensitisers, the pro-inflammatory cytokine IL-1 rapidly and directly activates nociceptors to generate action potentials and induce pain hypersensitivity. An increased release of IL-1β will also probably increase the levels of other cytokines including IL-6 and vice versa (Kang et al 97). Hence, our findings support the concept that pro-inflammatory cytokines may promote pain.

Previous studies (Verri, Jr. et al 06) have shown that IL-1 and tumour necrosis factor (TNF) contribute to the activation of inflammatory immune cells, which may lead to the sensitisation of peripheral nociceptive nerve fibres. Moreover, IL-1β induces central cyclooxygenase-2 (Cox-2) upregulation, which results in an increase in the synthesis of prostaglandin E_2 (PGE_2) in spinal cord neurons or other regions of the CNS. Induction of Cox-2 expression and the production of prostanoids induce central hypersensitivity. Our study shows an association between serum IL-6 concentration at baseline and long-term disability in lumbar radicular pain. However, the population was too small to study the effects of IL-6 separately in patients who received surgery compared with those managed conservatively.

Regarding the effect of treatment, we observed that patients managed conservatively had less favourable recoveries at the one-year follow-up. These results are consistent with recent

studies (Haugen et al 12; Jacobs et al 11) indicating that surgery provides more rapid relief of pain and disability without improving the long-term course of lumbar radicular pain (Atlas et al 05). The benefits of surgical treatment become less pronounced with time. Surgery is usually considered in a minority of patients with disc herniation. In the initial course of radicular pain due to disc herniation, physicians commonly recommend conservative treatment for at least 2 months before surgical intervention unless severe neurological deterioration occurs (Orief et al 12). Notably, the group of patients in our study who received surgery was initially different from the conservatively managed group, as the former reported more intense leg pain and greater disability. Further, patients who underwent disc herniation surgery had higher consumption of pain medication at baseline, compared to the non-surgery group. Hence, these two groups of patients demonstrated differences at the baseline of the study, and thus cannot be directly compared regarding the treatment. However, differences in the use of pain medications at baseline had no impact on improvement of function at one-year follow-up.

Earlier data show that lower educational level was associated with poor recovery (Keller et al 12). Lower education is often associated with low-decision authority and heavy physical work, which are well-known prognostic factors for poor recovery (Chibnall and Tait 09;Keller et al 12). Education is also a part of the biopsychosocial model, which is important for the understanding of different contributory causes to the development of chronic pain and disability. Earlier studies have shown that emotional distress is a risk factor for reduced treatment benefit (i.e., less improvement over a 3-year follow-up) in patients with radicular pain (Edwards et al 07). Thus comorbidities should be assessed in patients with radicular pain as well (Haugen et al 12). However, since comorbid disease was adapted as an exclusion criterion, 57.4% of patients had a low HSCL-25 score; and HSCL had no significant influence on recovery from radicular pain.

As one might expect we found that patients with a longer history of lumbar radicular pain had higher VAS for LBP and leg pain at the one-year follow-up. Thus, our study suggests that patients who have suffered pain for a longer period before receiving treatment may have had a more severe pain condition, which translates to less favourable recovery relative to other patients. It is therefore likely that the longer duration of radicular pain may increase the activity in the pain pathways to the brain, which lead to central sensitisation. In fact, several

lines of evidence indicate that such central sensitisation may contribute to the development of persistent pain.

Conclusions

The present data demonstrated that high levels of serum IL-6, but not disc degeneration or Modic changes, were associated with less favourable recovery in patients with lumbar radicular pain. Intense initial back pain, conservative management, lower educational level, and an extended duration of radicular pain before treatment also correlated with a slower recovery at one-year.

Author contributions

All authors discussed the results and commented on the manuscript. J.G. and C.R. designed the study. E.I.S. contributed to patient selection, clinical evaluation of patients, and follow-up examinations. A.E. and E.I.S contributed to MRI evaluations. L.M.P performed analyses of serum cytokines. L.S., C.R. and E.I.S. contributed to analysis and interpretation of data. C.R, J.G., A.E. and E.I.S. wrote the manuscript.

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References

1. Ashworth,J., Konstantinou,K. & Dunn,K.M. (2011) Prognostic factors in non-surgically treated sciatica: a systematic review. *BMC Musculoskelet Disord.*, **12**, 208.
2. Atlas,S.J., Keller,R.B., Wu,Y.A., Deyo,R.A. & Singer,D.E. (2005) Long-term outcomes of surgical and nonsurgical management of sciatica secondary to a lumbar disc herniation: 10 year results from the maine lumbar spine study. *Spine (Phila Pa 1976)*, **30**, 927-935.
3. Binshtok,A.M., Wang,H., Zimmermann,K., Amaya,F., Vardeh,D., Shi,L., Brenner,G.J., Ji,R.R., Bean,B.P., Woolf,C.J. & Samad,T.A. (2008) Nociceptors are interleukin-1beta sensors. *J Neurosci.*, **28**, 14062-14073.
4. Burke,J.G., Watson,R.W., McCormack,D., Dowling,F.E., Walsh,M.G. & Fitzpatrick,J.M. (2002) Spontaneous production of monocyte chemoattractant protein-1 and interleukin-8 by the human lumbar intervertebral disc. *Spine (Phila Pa 1976)*, **27**, 1402-1407.
5. Carragee,E.J. & Kim,D.H. (1997) A prospective analysis of magnetic resonance imaging findings in patients with sciatica and lumbar disc herniation. *Spine*, **22**, 1650-1660.
6. Chibnall,J.T. & Tait,R.C. (2009) Long-term adjustment to work-related low back pain: associations with socio-demographics, claim processes, and post-settlement adjustment. *Pain Med*, **10**, 1378-1388.
7. den Boer,J.J., Oostendorp,R.A., Beems,T., Munneke,M. & Evers,A.W. (2006) Continued disability and pain after lumbar disc surgery: the role of cognitive-behavioral factors. *Pain*, **123**, 45-52.
8. Derogatis,L.R., Lipman,R.S., Rickels,K., Uhlenhuth,E.H. & Covi,L. (1974) The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. *Behav.Sci.*, **19**, 1-15.
9. Edwards,R.R., Klick,B., Buenaver,L., Max,M.B., Haythornthwaite,J.A., Keller,R.B. & Atlas,S.J. (2007) Symptoms of distress as prospective predictors of pain-related sciatica treatment outcomes. *Pain*, **130**, 47-55.
10. Geiss,A., Varadi,E., Steinbach,K., Bauer,H.W. & Anton,F. (1997) Psychoneuroimmunological correlates of persisting sciatic pain in patients who underwent discectomy. *Neurosci.Lett.*, **237**, 65-68.

11. Grotle,M., Brox,J.I. & Vollestad,N.K. (2003) Cross-cultural adaptation of the Norwegian versions of the Roland-Morris Disability Questionnaire and the Oswestry Disability Index. *J Rehabil.Med.*, **35**, 241-247.
12. Haugen,A.J., Brox,J.I., Grovle,L., Keller,A., Natvig,B., Soldal,D.M. & Grotle,M. (2012) Prognostic factors for non-success in patients with sciatica and disc herniation. *BMC Musculoskelet Disord.*, **13**, 183.
13. Ilmarinen,J., Suurnakki,T., Nygard,C.H. & Landau,K. (1991) Classification of municipal occupations. *Scand.J Work Environ.Health*, **17 Suppl 1**, 12-29.
14. Jacobs,W.C., van,T.M., Arts,M., Rubinstein,S.M., van,M.M., Ostelo,R., Verhagen,A., Koes,B. & Peul,W.C. (2011) Surgery versus conservative management of sciatica due to a lumbar herniated disc: a systematic review. *Eur.Spine J*, **20**, 513-522.
15. Jeng,Y.J. & Martin,A. (1985) Residuals in multiple regression analysis. *J Pharm.Sci.*, **74**, 1053-1057.
16. Jensen,O.K., Nielsen,C.V. & Stengaard-Pedersen,K. (2010) One-year prognosis in sick-listed low back pain patients with and without radiculopathy. Prognostic factors influencing pain and disability. *Spine J*, **10**, 659-675.
17. Jim,J.J., Noponen-Hietala,N., Cheung,K.M., Ott,J., Karppinen,J., Sahraravand,A., Luk,K.D., Yip,S.P., Sham,P.C., Song,Y.Q., Leong,J.C., Cheah,K.S., Ala-Kokko,L. & Chan,D. (2005) The TRP2 allele of COL9A2 is an age-dependent risk factor for the development and severity of intervertebral disc degeneration. *Spine (Phila Pa 1976)*, **30**, 2735-2742.
18. Kang,J.D., Georgescu,H.I., McIntyre-Larkin,L., Stefanovic-Racic,M., Donaldson,W.F., III & Evans,C.H. (1996) Herniated lumbar intervertebral discs spontaneously produce matrix metalloproteinases, nitric oxide, interleukin-6, and prostaglandin E2. *Spine (Phila Pa 1976)*, **21**, 271-277.
19. Kang,J.D., Stefanovic-Racic,M., McIntyre,L.A., Georgescu,H.I. & Evans,C.H. (1997) Toward a biochemical understanding of human intervertebral disc degeneration and herniation. Contributions of nitric oxide, interleukins, prostaglandin E2, and matrix metalloproteinases. *Spine (Phila Pa 1976)*, **22**, 1065-1073.
20. Keller,A., Boyle,E., Skog,T.A., Cassidy,J.D. & Bautz-Holter,E. (2012) Are Modic changes prognostic for recovery in a cohort of patients with non-specific low back pain? *Eur.Spine J*, **21**, 418-424.

21. Kraychete,D.C., Sakata,R.K., Issy,A.M., Bacellar,O., Santos-Jesus,R. & Carvalho,E.M. (2010) Serum cytokine levels in patients with chronic low back pain due to herniated disc: analytical cross-sectional study. *Sao Paulo Med J*, **128**, 259-262.
22. Modic,M.T., Steinberg,P.M., Ross,J.S., Masaryk,T.J. & Carter,J.R. (1988) Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. *Radiology*, **166**, 193-199.
23. Orief,T., Orz,Y., Attia,W. & Almusrea,K. (2012) Spontaneous resorption of sequestrated intervertebral disc herniation. *World Neurosurg.*, **77**, 146-152.
24. Sandanger,I., Nygard,J.F., Ingebrigtsen,G., Sorensen,T. & Dalgard,O.S. (1999) Prevalence, incidence and age at onset of psychiatric disorders in Norway. *Soc.Psychiatry Psychiatr.Epidemiol*, **34**, 570-579.
25. Schneiderman,G., Flannigan,B., Kingston,S., Thomas,J., Dillin,W.H. & Watkins,R.G. (1987) Magnetic resonance imaging in the diagnosis of disc degeneration: correlation with discography. *Spine (Phila Pa 1976)*, **12**, 276-281.
26. Sim,J. & Wright,C.C. (2005) The kappa statistic in reliability studies: use, interpretation, and sample size requirements. *Phys.Ther.*, **85**, 257-268.
27. Sutheerayongprasert,C., Paiboonsirijit,S., Kuansongtham,V., Anuraklekha,S., Hiranyasthiti,N. & Neti,S. (2012) Factors predicting failure of conservative treatment in lumbar-disc herniation. *J Med Assoc.Thai.*, **95**, 674-680.
28. Verri,W.A., Jr., Cunha,T.M., Parada,C.A., Poole,S., Cunha,F.Q. & Ferreira,S.H. (2006) Hypernociceptive role of cytokines and chemokines: targets for analgesic drug development? *Pharmacol.Ther.*, **112**, 116-138.
29. Wannstrom,I., Peterson,U., Asberg,M., Nygren,A. & Gustavsson,J.P. (2009) Psychometric properties of scales in the General Nordic Questionnaire for Psychological and Social Factors at Work (QPS): confirmatory factor analysis and prediction of certified long-term sickness absence. *Scand.J Psychol.*, **50**, 231-244.
30. Yong,X.Z. & Sutherland,T. (2012) Making sense of MRI of the lumbar spine. *Aust.Fam.Physician*, **41**, 887-890.

Figure legends:

Figure 1: Flow diagram of study population.

Figure 1

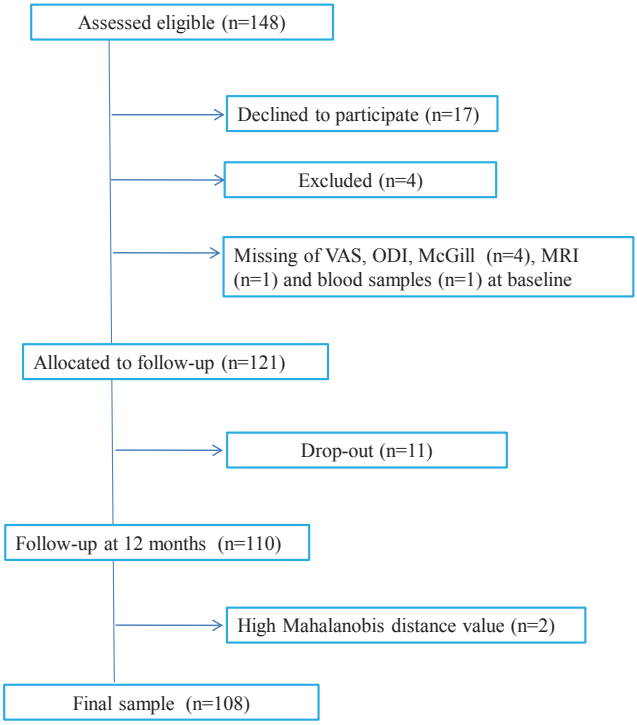
Assessed eligible (n=148)
Declined to participate (n=17)
Excluded (n=4)
Missing of VAS, ODI, McGill (n=4), MRI (n=1) and blood samples (n=1) at baseline
Allocated to follow-up (n=121)
Drop-out (n=11)
Follow-up at 12 months (n=110)
High Mahalanobis distance value (n=2)
Final sample (n=108)

Table 1. Characteristics of study population at baseline. Data presented as mean (SD) or number of patients (%).

Characteristics	All patients (n=108)
Demographics:	
Age (years)	41.3 (10.0)
Males	48 (44%)
Smokers	38 (35%)
Marital status: married, cohabitant, partner/else	59 (55%)/49 (45%)
Higher education	53 (51%)
Full-time job	84 (82%)
of whom on sick leave	56 (52%)
Profession (mental/mixed/physical)	67 (62%)/21 (19%)/15 (14%)
QPS Nordic quantitative job demands	2.9 (1.1)
QPS Nordic control of pace of work	3.0 (1.3)
Neurological deficits:	
Sensory deficit	60 (56%)
Motor deficit	32 (30%)
Reflex loss or deficit	31 (29%)
Cytokines:	
IL-6 protein in serum (pg/ml)	1.02 (1.14)
IL-8 protein in serum (pg/ml)	3.38 (3.72)
Pain, emotional distress and functioning:	
ODI	35.5 (17.3)
VAS for LBP	3.7 (2.7)
VAS for leg pain	5.9 (2.8)
VAS for pain during activity	5.7 (2.7)
VAS for pain at rest	3.8 (2.6)
Duration of sciatica (weeks)	20.3 (19.9)
HSCL-25 ($\geq$ 1.75)	46 (43%)
Pain medications:	
Daily used any type of pain medication	53 (49%)
Modic changes and disc degeneration:	
Presence of Modic type I	16 (15%)
Presence of Modic type II or III (but not I)	67 (62%)
Disc degeneration total score	5.9 (1.9)
Disc degeneration grouped according to Jim:	
mild	15 (14%)
moderate	54 (51%)
severe	38 (36%)

Table 2a. Pain intensity and functional level at baseline in patients with lumbar radicular pain, treated with and without surgery. Data presented as mean (SD).

	Surgery (n=40)	Non-surgery (n=68)	T-test p-value
VAS leg pain	7.3 (2.4)	5.0 (2.7)	$p < 0.001$
VAS back pain	4.1 (2.8)	3.5 (2.6)	$p = 0.27$
ODI	47.1 (17.4)	28.7 (13.3)	$p < 0.001$

Table 2b. Use of analgesics or co-analgesics and the presence of neurological deficits at baseline in patients with lumbar radicular pain, treated with and without surgery. Data presented as mean (SD).

	Surgery (n=40)	Non-surgery (n=68)	Pearson Chi square* *p*-value
Daily use of analgesics or co-analgesics, of whom	29 (73%)	25 (37%)	$p = 0.001$
NSAIDs	22 (55%)	16 (24%)	$p = 0.002$
opioids	18 (45%)	7 (10%)	$p < 0.001$
Sensory deficit	25 (63%)	35 (51%)	$p = 0.36$
Motor deficit	13 (33%)	18 (27%)	$p = 0.65$
Reflex loss or deficit	14 (35%)	18 (27%)	$p = 0.47$

*with Yates Continuity Correction

Table 3. Results of linear regression analyses with ODI change as dependent variable. Each independent variable was analysed separately. ODI at baseline was included as the independent variable in each analysis. Variables with a significance level p <0.1 are shown.

Independent variables at baseline	β	B	95% CI for B	*p*-value
IL-6 protein (pg/ml)	-0.22	-3.54	-5.96 to -1.12	$p = 0.005$
Surgery (yes vs. no)	0.25	9.56	3.11 to 16.02	$p = 0.004$
VAS for back pain (1 cm increase)	-0.34	-2.35	-3.35 to -1.34	$p < 0.001$
VAS for current back and leg pain (1 cm increase)	-0.18	-1.28	-2.71 to 0.16	$p = 0.080$
Duration of radicular pain (one week increase)	-0.23	-0.21	-0.35 to -0.08	$p = 0.002$
Educational level (higher education vs. else)	0.17	6.26	0.74 to 11.78	$p = 0.027$
HSCL-25 (above or equal vs. below 1.75)	-0.17	-6.53	-12.28 to -0.77	$p = 0.027$
Smoking (yes vs. no)	-0.14	-5.26	-11.06 to 0.55	$p = 0.075$

Table 4. Results of multivariate linear regression analyses with ODI change as the dependent variable. Variables with a significance level p <0.05 are shown.

Independent variables at baseline	Adjusted results			
	β	**B**	**95% CI for B**	***p*-value**
IL-6 protein (pg/ml)	-0.18	-3.41	-5.52 to -1.30	$p = 0.002$
Surgery (yes vs. no)	0.22	7.03	1.21 to 12.84	$p = 0.018$
VAS for back pain (1 cm increase)	-0.33	-2.28	-3.21 to -1.35	$p < 0.001$
High education (no vs. yes)	0.15	5.57	0.66 to 10.47	$p = 0.027$
ODI (per unit)	0.67	0.75	0.58 to 0.93	$p < 0.001$

Table 5. Results of multivariate linear regression analyses with VAS for LBP at one-year follow-up as the dependent variable. Variables with a significance level p <0.05 are shown.

Independent variables at baseline	Adjusted results			
	β	B	95% CI for B	*p*-value
IL-6 protein (pg/ml)	0.24	0.64	0.21 to 1.07	$p = 0.004$
VAS for back pain (1 cm increase)	0.46	0.52	0.34 to 0.71	$p < 0.001$
Duration of radicular pain (weeks)	0.24	0.04	0.01 to 0.61	$p = 0.005$

Table 6. Results of multivariate linear regression analyses with VAS for leg pain at one-year follow-up as the dependent variable. Variables with a significance level p <0.05 are shown.

Independent variables at baseline	Adjusted results			
	β	B	95% CI for B	*p*-value
IL-6 protein (pg/ml)	0.29	0.81	0.32 to 1.29	$p = 0.001$
VAS for LBP (1 cm increase)	0.31	0.35	0.15 to 0.55	$p = 0.001$
Duration of radicular pain (weeks)	0.25	0.04	0.01 to 0.07	$p = 0.006$

II

III

The influence of Modic changes on pain during one-year follow-up in patients with lumbar radicular pain

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Type of manuscript: Scientific article.

Abstract

Objective. To examine whether Modic changes influence pain during one-year follow-up in patients with lumbar radicular pain.

Materials and Methods. A total of 243 patients with lumbar radicular pain due to disc herniation were recruited from two hospitals in Norway and followed up at 6 weeks, 6 months, and 12 months. On baseline lumbar magnetic resonance images, two observers independently evaluated Modic changes (type I-III; craniocaudal size 0-3). Primary outcomes were sensory pain (McGill Pain Questionnaire) and back pain scores (visual analogue scale, VAS). Impact of Modic type and size on outcome at each time point was explored using two-way analyses of variance with Modic and treatment groups (surgical, n = 126; nonsurgical, n = 117) as fixed factors and disc degeneration, age, sex, smoking, and duration of lumbar radicular pain as covariates.

Results. Pain scores had decreased significantly at 12 months follow-up. Modic type showed a significant impact on McGill sensory score at 6 weeks (p = 0.007), but not at other time points or on VAS back pain or VAS leg pain scores. At 6 weeks, the mean McGill sensory score was higher in Modic I than in Modic II-III patients (p = 0.003) and in patients without Modic changes (p = 0.018). Dichotomized Modic size L1-S1 had no impact on McGill sensory, back pain, or leg pain scores.

Conclusion. Patients with lumbar radicular pain have a substantial pain reduction during one year follow-up, but Modic type I changes may imply a slower initial decrease in sensory pain.

Keywords: low back pain, lumbar radicular pain, magnetic resonance imaging, Modic changes, spine, disc degeneration.

Introduction

Lumbar radicular pain constitutes only 5%-10% of low back pain (LBP) conditions [1], but it accounts for 33% of the sick leave and 47% of the disability benefits due to such conditions in Norway [2]. It has been suggested that Modic changes may be important for lumbar radicular pain [3]. However, the potential impact of Modic changes on recovery and pain is still debated [4-6].

The essential symptom of lumbar radicular pain is radiating pain in an area of the leg typically innervated by one nerve root in the lumbar or sacral spine [1, 7]. Although the prognosis is good, a substantial proportion of affected patients (up to 30%) continue to have pain for 1 year or longer [8]. Patients with radicular leg pain due to a disc herniation often have concurrent LBP, which hampers recovery [9]. Modic changes are common in disc herniation patients [3], and assumed to be related to the LBP in these patients [10]. Modic changes are defined as signal-intensity changes in the vertebral body marrow adjacent to the endplate that are verifiable on magnetic resonance imaging (MRI) [11]. Previous research has shown that the Modic classification is reliable, reproducible, and can be applied in clinical practice [12]. The prevalence of Modic changes increases with age, and is lower in nonclinical populations than among patients with chronic LBP, with prevalence rates of 6% and 81%, respectively [10, 13]. Moreover, in an earlier study of disc herniation patients with acute and chronic lumbar radicular pain, the prevalence of Modic changes was 25% and increased to 49% at 14 months follow-up [3]. Much of the increase was due to development of type I Modic changes, which are associated with edema and inflammation [3, 14]. However, in previous studies [15, 16], Modic type I did not affect long-term recovery from back pain after surgery with discectomy. Earlier data show that surgery may provide an initial pain relief, but does not improve the long-term outcome after symptomatic disc herniation [17, 18]. The aim of the present study was to examine whether Modic changes influence pain during one-year follow-up in patients with lumbar radicular pain.

Materials and Methods

This prospective study was approved by the Regional Committee for Medical Research Ethics in Norway. All participants gave their written informed consent.

Eligibility criteria and study population

Participants with lumbar radicular pain were recruited from Oslo University Hospital, Ulleval and Haukeland University Hospital between September 2007 and October 2009.

The *inclusion criteria* were an age of 18 to 60 years, lumbar disc herniation on MRI with corresponding radicular pain, and a positive straight leg raising test result. A positive straight leg raising test was defined by radiating pain into one or both legs when the examiner raises the straightened limb slowly until 60 degrees. The test was performed in supine position and supplemented with slight dorsiflexion of the foot.

The *exclusion criteria* were symptomatic lumbar spinal stenosis, spinal surgery for a herniated disc at the same level or fusion at any level in the lumbar spine, generalized musculoskeletal pain, inflammatory rheumatic disease, diabetic polyneuropathy, cardiovascular disease (New York Heart Association functional classes III and IV), cancer, psychiatric disease, drug abuse or alcoholism, recent completion of another surgery (within 1 month), pregnancy, poor proficiency in the Norwegian language, and non-European Caucasian ethnicity.

A total of 262 (87.6%) of the 299 patients assessed for eligibility were included. However, because 19 patients had missing baseline data, 243 (81%) of the 299 patients were allocated to follow-up and included in the present analyses. Fig. 1 shows an overview of participant flow through the trial. Only 18 (7%) of the 243 patients dropped out of the study.

Clinical procedures and outcome measures

At baseline, all 243 patients underwent a standardized clinical examination including assessment of sensory and motor function. The validated Norwegian version of the McGill Pain Questionnaire (MPQ) [19] was used to measure sensory, affective and evaluative aspects of the pain experience. The sensory component of the MPQ was chosen as an essential variable for pain perception [20]. We chose to use the Norwegian version of MPQ [19] that

contained 76 descriptors of sensory pain in 12 groups, i.e. 76 pain adjectives (e.g., tingling, dull, biting, sharp). Each adjective's pre-defined attached VAS score was used to calculate a mean score for the selected adjective(s) within each of the 12 groups [19]. The McGill sensory score (a ratio between 0 and 1) was the sum of these mean scores for all 12 groups (reflecting the strength of all selected adjectives in the sensory component of the MPQ) divided by the highest possible sum score. In addition, average pain intensity during the last week was examined separately for LBP and for leg pain using a VAS with anchor values from 0 (no pain) to 10 (worst imaginable pain) [21]. For registration of function disability the validated Norwegian version of the Oswestry Disability Index (ODI) (scale, 0–100%; 0% = no experienced disability, 100% = very severe disability) was used [22]. Sociodemographic- and work-related factors such as years of education, profession, duration of sick leave, and social benefits were also registered.

At the 6-week follow-up, the same measures sampled at inclusion, with the exception of MRI, were again evaluated. At the 6-month follow-up, patients were contacted by telephone regarding changes in their spinal condition and work status and were sent the VAS, McGill, and ODI questionnaires by mail. At the 12-month follow-up, all measurements were repeated, and lumbar MRI was repeated if pain was persistent. We selected the McGill sensory score and the VAS score for LBP (i.e. back pain) as the most relevant *primary* outcome measures for assessing the back pain experience. The VAS score for leg pain was used as a *secondary* outcome.

Image evaluation

Baseline lumbar MRI (1.5 T in 86% of the cases, 1.0 T in 12%, 3.0 T or unknown in 2%) was performed as part of clinical practice using recommended sequences [23]. The images applied in this study were: 1) *sagittal T2 weighted* fast spin echo (n = 231; repetition time (TR)/echo time (TE), 2,900-4,500 ms/85-130 ms) and 3-D turbo spin echo (SPACE) images (n = 12; TR/TE, 1,500 ms/251 ms) and 2) *sagittal T1 weighted* spin echo (n = 226; TR/TE, 350-750 ms/9-15 ms) and fast fluid-attenuated inversion-recovery images (n = 17; TR/TE, 1,989 ms/20 ms). Axial images of the L3/L4, L4/L5 and L5/S1 levels were also available. Restore, Fast Recovery, or DRIVE T2 weighted images were not used, since a short TR might have affected the signal intensity. For this study, all MRIs were de-identified and presented in random order.

A radiologist with 28 years of experience and a physical medicine and rehabilitation physician with 6 years of experience, independently and blinded to clinical data, graded Modic changes [11] and disc degeneration (DD). DD is related to Modic changes [13] and was used as a covariate in the analyses. At each of the 10 endplates of L1–S1, Modic changes were noted as primary type I (hypointense T1 signal and hyperintense T2 signal), type II (hyperintense T1 signal and iso- or hyperintense T2 signal), or type III (hypointense T1- and T2 signal) (Fig. 2). The craniocaudal (CC) size of the Modic changes was graded as <10%, 10%–25%, ≥25%–50%, or >50% of the vertebral body height [24]. In the final analyses, the first two CC size categories received a score of 0, and the subsequent categories received scores of 1, 2, and 3, respectively. A total CC size score for the 10 endplates was calculated (possible values 0-30).

DD was graded on midsagittal T2 weighted images at each of the five disc levels (L1–S1) using Schneiderman's grading system [25]: a score of 0 indicated no signal change, a score of 1 indicated a slight decrease in signal intensity in the nucleus pulposus, a score of 2 indicated a generalized hypointense nucleus, and a score of 3 indicated a hypointense nucleus with disc space narrowing. The total DD score (0–15) across all five discs was calculated and then grouped according to Jim [26] into severe (two or more grade 3 discs, three or more grade 2 discs, or one grade 3 and two grade 2 discs), moderate (one grade 3 disc or two grade 2 discs), mild (only one grade 2 disc and no grade 3 discs), or normal (total DD score of 0 or 1).

The radiologist assessed all MRIs on a clinical Picture Archiving and Communication System (PACS) unit using the Agfa Impax 4.5 (Agfa HealthCare, Mortsel, Belgia) software. The other observer used a dedicated personal computer at the clinic. In all cases of disagreement, a consensus score was negotiated using the PACS unit. The independent evaluations showed mostly good interobserver agreement on type and CC size of Modic changes (kappa 0.58-0.77) at endplates with at least 10% prevalence of Modic changes and thus interpretable kappa values [27] (Table 1). Interobserver agreement on DD was moderate or good (kappa 0.54-0.67) at disc levels with at least 10% prevalence of a DD score of 2 and 3 (Table 1).

Statistical analyses

Each patient was classified as having 1) no Modic changes, 2) Modic type I changes, or 3) Modic type II and/or III, but not type I changes. The total Modic CC size score was close to

being normally distributed and was dichotomized at its mean. Paired t-tests were used to assess differences in pain scores between inclusion and 12 months. The impact of Modic type and size on each outcome (McGill sensory, VAS back pain, and VAS leg pain score) at baseline, 6 weeks, 6 months, and 12 months was evaluated by two-way analysis of variance at each time point, with the Modic and treatment groups (surgery vs. non-surgery) as fixed factors and the DD groups, age (continuous variable), sex, smoking status (current smoker, yes/no), and duration of lumbar radicular pain (< 3 months vs. ≥ 3months) as covariates. Pain scores between the Modic type groups were also compared using *post hoc* two-way analyses of variance adjusted for treatment (surgery vs. non-surgery). Missing pain scores were replaced with the mean value for each Modic group. After Bonferroni adjustment for comparison at four different time points, $p \leq 0.013$ ($p \leq 0.05/4$) was regarded as statistically significant. The analyses were conducted using SPSS version 19 (SPSS Inc., Chicago, IL).

Results

Baseline characteristics of the 243 patients with lumbar radicular pain (Table 2) showed that 111 patients (45.7%) had had pain for more than 3 months. A total of 184 (75.7%) patients had Modic changes at one or more endplates, and 163 (67.0%) patients had Modic changes with a CC size of at least 10% of the vertebral height. Moreover, 30 (12.4%) patients had Modic I changes, 147 (60.4%) had Modic II (but not Modic I) changes, and 7 (2.9%) had Modic III (but not Modic I or II) changes. Modic changes were most frequent at the L5–S1 level (57.0% of cases) and the L4–L5 level (48.3% of cases) with decreasing frequency in the upper lumbar levels. The mean total Modic CC size score was 3.2 (standard deviation = SD, 3.7; range, 0–24). All 243 patients had DD, which was mild in 45 (18.5%) patients, moderate in 115 (47.3%), and severe in 83 (34.2%).

Treatment groups

Surgery for disc herniation was performed in 126 (51.9%) patients. The type of surgery was known for 91 patients: 69.2% had microdiscectomy, 19.8% decompression, and 11% standard discectomy. A total of 117 (48.1%) patients underwent non-surgical treatment including adapted activity in the acute phase of disc herniation and physical therapy in cases of spontaneous regression of radicular pain.

Pain symptoms at 12 months follow-up

From inclusion to 12 months follow-up, a decrease ($p < 0.001$) was observed in mean McGill sensory score (from 0.53; SD, 0.23 to 0.27; SD, 0.27) (Table 3), mean VAS back pain score (from 3.97; SD, 2.68 to 2.46; SD, 2.76) (Table 3), and mean VAS leg pain score (from 6.26; SD, 2.81 to 2.01; SD, 2.65). Still, at 12 months, 71 (31%) of the 225 patients participating in this follow-up had back pain and 56 (25%) had leg pain, defined as VAS scores above 3.

Influence of Modic changes on pain symptoms

Modic type had a significant influence on the McGill sensory pain score at 6 weeks (F (2, 223) = 5.06, $p = 0.007$), but not at inclusion, at 6 months, or at 12 months (Fig. 3). The McGill sensory score at 6 weeks was higher in the Modic type I group (mean, 0.45; SD, 0.28) than in the Modic type II and III group (mean, 0.29; SD, 0.23) ($p = 0.003$) and in the no-Modic group (mean, 0.30; SD, 0.24) ($p = 0.018$). There was no significant interaction between

Modic types and treatment. Neither the VAS back pain score (Fig. 4, Table 3) nor the VAS leg pain score differed significantly between Modic type groups at any time point. There was no significant effect of total Modic CC size on McGill sensory, back pain, or leg pain scores. Regarding the covariates, treatment (surgery vs. non-surgery) affected VAS leg pain at all time points (p ranged from < 0.001 to 0.013) adjusted for Modic type/size. Smoking in contrast only influenced VAS back pain at inclusion (p = 0.006 and 0.010) and McGill sensory pain at 6 months (p = 0.008 and 0.004) adjusted for Modic type/size. In addition, the duration of lumbar radicular pain affected VAS back pain at 12 months (p = 0.003 and 0.003) adjusted for Modic type/size.

Discussion

A substantial pain reduction was observed during the 12-month follow-up in these patients with lumbar radicular pain with and without Modic changes. However, patients with Modic type I changes had higher sensory pain scores than other patients at 6 weeks. Moreover, at 12 months, 31% of the patients in our study reported LBP and 25% reported leg pain. Although most patients with lumbar radicular pain due to disc herniation have spontaneous regression of symptoms [28], such pain is associated with high consumption of health resources [2]. More than 70% of the present patients had Modic changes, and more than 60% had Modic changes with a CC size of at least 10% of the vertebral height, which is a higher prevalence than that found among patients with lumbar radicular pain due to disc herniation in a previous study (range, 25%–49%) [3]. This can be partly explained by the duration of pain before inclusion in our study population (up to 4 years, Table 2). Recruitment from university hospitals may favor a high prevalence of Modic changes because the patients may have experienced pain for a longer time. Still, the prevalence of Modic changes increases during follow-up of patients with lumbar radicular pain [3]; it is also higher in patients with chronic versus acute LBP [13, 29]. Previous data [3] obtained from patients with lumbar radicular pain show that disc herniation is a strong risk factor for developing Modic changes (especially type I) during the following year.

In our study, patients with Modic type I changes had a higher McGill sensory pain score at 6 weeks compared to patients with other Modic types or without Modic changes. This result indicates a slower recovery after symptomatic disc herniation among patients with Modic type I changes, perhaps due to inflammatory back pain associated with Modic type I [30-32]. Previous studies have shown an increased frequency of Modic type I changes in individuals with LBP [3, 29]. Here, we have extended these findings and demonstrated that Modic type I changes also influence the recovery in lumbar radicular pain. The increased sensory pain in patients with Modic type I changes is clinically important. For example, patients with Modic type I may be informed that recovery may take more than 6 weeks, but that their prognosis is still good. In addition, it may be favorable with longer follow-up of these patients.

Earlier studies showed that Modic type I changes do not predict back pain at 12 months after disc herniation surgery [16, 33]. Consistent with previous observations [34], our data showed no clear long-term association between Modic size and LBP. Importantly, our study was not

designed to assess the effect of surgery; that would require a randomized controlled trial design. Surgery is an option in the minority of patients with neurological deficits or lack of improvement. Because of the often observed favorable natural recovery of lumbar radicular pain, non-surgical treatment for at least 6 weeks is common before surgery. However, surgical treatment provides effective clinical relief for selected patients with lumbar radicular pain due to disc herniation that fails to resolve with non-surgical management [35].

Strengths and limitations

In the present study, we used strict inclusion criteria, validated questionnaires, and repeated assessments during the one-year follow-up. Modic changes and DD were rated with similar or higher reliability than that reported in some other studies [12, 36, 37]. The use of different MRI scanners and sequences, in the clinical practice, which provided the data for the present study, may have caused a slight but unwanted variation in the evaluation of the MRI findings. Modic type may differ between different MRI magnet strengths (0.2 T vs. 1.5 T) [38], but this potential problem was minimized, since 98% of the patients underwent 1.5 T (86%) or 1.0 T MRI (12%).

Notably, recruitment from hospitals represents a selection of patients; we still suggest that Modic type I changes may delay pain recovery also in other patients with symptomatic disc herniation. Our sample was large enough to explore the impact of Modic changes on recovery, but it was too small to separately study the effects of Modic type I changes in the surgical and non-surgical groups. Published data support our adjustments for treatment, age, sex, smoking, and duration of sciatica in the analyses [18, 39]. Yet, additional factors might also have been relevant to adjust for. For example, data on emotional distress were not sampled, although other observations suggest that comorbid subjective health complaints influence the prognosis of symptomatic disc herniation [18]. Therefore, further studies are needed to confirm the present results.

In conclusion, most patients with lumbar radicular pain treated surgically and non-surgically can expect a substantial reduction in back and leg pain during the first year. Patients with Modic type I changes may, however, have a slower decrease in McGill sensory pain score than other patients. Neither the type nor the size of Modic changes seems to influence on McGill sensory pain, VAS back pain, or VAS leg pain scores at one-year follow-up.

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Conflict of interest

The authors declare that they have no conflict of interest.

References

(1) Koes BW, van Tulder MW, Peul WC. Diagnosis and treatment of sciatica. Br Med J 2007 Jun 23;334(7607):1313-7.

(2) Brage S, Ihlebaek C, Natvig B, Bruusgaard D. [Musculoskeletal disorders as causes of sick leave and disability benefits]. Tidsskr Nor Laegeforen 2010 Dec 2;130(23):2369-70.

(3) Albert HB, Manniche C. Modic changes following lumbar disc herniation. Eur Spine J 2007 Jul;16(7):977-82.

(4) Berg L, Hellum C, Gjertsen O, Neckelmann G, Johnsen LG, Storheim K, et al. Do more MRI findings imply worse disability or more intense low back pain? A cross-sectional study of candidates for lumbar disc prosthesis. Skeletal Radiol 2013 Nov;42(11):1593-602.

(5) Keller A, Boyle E, Skog TA, Cassidy JD, Bautz-Holter E. Are Modic changes prognostic for recovery in a cohort of patients with non-specific low back pain? Eur Spine J 2012 Mar;21(3):418-24.

(6) Steffens D, Hancock MJ, Maher CG, Williams C, Jensen TS, Latimer J. Does magnetic resonance imaging predict future low back pain? A systematic review. Eur J Pain 2013 Nov 26.

(7) Konstantinou K, Lewis M, Dunn KM. Agreement of self-reported items and clinically assessed nerve root involvement (or sciatica) in a primary care setting. Eur Spine J 2012 Nov;21(11):2306-15.

(8) Weber H. The natural history of disc herniation and the influence of intervention. Spine (Phila Pa 1976) 1994 Oct 1;19(19):2234-8.

(9) Grovle L, Haugen AJ, Keller A, Ntvig B, Brox JI, Grotle M. Prognostic factors for return to work in patients with sciatica. Spine J 2013 Sep 21.

(10) Jensen TS, Karppinen J, Sorensen JS, Niinimaki J, Leboeuf-Yde C. Vertebral endplate signal changes (Modic change): a systematic literature review of prevalence and association with non-specific low back pain. Eur Spine J 2008 Nov;17(11):1407-22.

(11) Modic MT, Steinberg PM, Ross JS, Masaryk TJ, Carter JR. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. Radiology 1988 Jan;166(1 Pt 1):193-9.

(12) Carrino JA, Lurie JD, Tosteson AN, Tosteson TD, Carragee EJ, Kaiser J, et al. Lumbar spine: reliability of MR imaging findings. Radiology 2009 Jan;250(1):161-70.

(13) Arana E, Kovacs FM, Royuela A, Estremera A, Asenjo B, Sarasibar H, et al. Modic changes and associated features in Southern European chronic low back pain patients. Spine J 2011 May;11(5):402-11.

(14) Albert HB, Kjaer P, Jensen TS, Sorensen JS, Bendix T, Manniche C. Modic changes, possible causes and relation to low back pain. Med Hypotheses 2008;70(2):361-8.

(15) Chin KR, Tomlinson DT, Auerbach JD, Shatsky JB, Deirmengian CA. Success of lumbar microdiscectomy in patients with modic changes and low-back pain: a prospective pilot study. J Spinal Disord Tech 2008 Apr;21(2):139-44.

(16) Ohtori S, Yamashita M, Yamauchi K, Inoue G, Koshi T, Suzuki M, et al. Low back pain after lumbar discectomy in patients showing endplate modic type 1 change. Spine (Phila Pa 1976) 2010 Jun 1;35(13):E596-E600.

(17) Jacobs WC, van TM, Arts M, Rubinstein SM, van MM, Ostelo R, et al. Surgery versus conservative management of sciatica due to a lumbar herniated disc: a systematic review. Eur Spine J 2011 Apr;20(4):513-22.

(18) Haugen AJ, Brox JI, Grovle L, Keller A, Natvig B, Soldal DM, et al. Prognostic factors for non-success in patients with sciatica and disc herniation. BMC Musculoskelet Disord 2012 Sep 22;13(1):183.

(19) Strand LI, Wisnes AR. The development of a Norwegian pain questionnaire. Pain 1991 Jul;46(1):61-6.

(20) Ljunggren AE. Descriptions of pain and other sensory modalities in patients with lumbago-sciatica and herniated intervertebral discs. Interview administration of an adapted Mcgill Pain Questionnaire. Pain 1983 Jul;16(3):265-76.

(21) Price DD, Bush FM, Long S, Harkins SW. A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. Pain 1994 Feb;56(2):217-26.

(22) Grotle M, Brox JI, Vollestad NK. Cross-cultural adaptation of the Norwegian versions of the Roland-Morris Disability Questionnaire and the Oswestry Disability Index. J Rehabil Med 2003 Sep;35(5):241-7.

(23) American College of Radiology (ACR) ASoNASoCBTaMRS-M. ACR-ASNR-SCBT-MR Practice Guideline for the Performance of Magnetic Resonance imaging (MRI) of the Adult Spine. Resolution 15. 2012. 2013.

(24) Jensen TS, Sorensen JS, Kjaer P. Intra- and interobserver reproducibility of vertebral endplate signal (modic) changes in the lumbar spine: the Nordic Modic Consensus Group classification. Acta Radiol 2007 Sep;48(7):748-54.

(25) Schneiderman G, Flannigan B, Kingston S, Thomas J, Dillin WH, Watkins RG. Magnetic resonance imaging in the diagnosis of disc degeneration: correlation with discography. Spine (Phila Pa 1976) 1987 Apr;12(3):276-81.

(26) Jim JJ, Noponen-Hietala N, Cheung KM, Ott J, Karppinen J, Sahraravand A, et al. The TRP2 allele of COL9A2 is an age-dependent risk factor for the development and severity of intervertebral disc degeneration. Spine (Phila Pa 1976) 2005 Dec 15;30(24):2735-42.

(27) Sim J, Wright CC. The kappa statistic in reliability studies: use, interpretation, and sample size requirements. Phys Ther 2005 Mar;85(3):257-68.

(28) Autio RA, Karppinen J, Niinimaki J, Ojala R, Kurunlahti M, Haapea M, et al. Determinants of spontaneous resorption of intervertebral disc herniations. Spine (Phila Pa 1976) 2006 May 15;31(11):1247-52.

(29) Kuisma M, Karppinen J, Niinimaki J, Ojala R, Haapea M, Heliovaara M, et al. Modic changes in endplates of lumbar vertebral bodies: prevalence and association with low back and sciatic pain among middle-aged male workers. Spine (Phila Pa 1976) 2007 May 1;32(10):1116-22.

(30) Bailly F, Maigne JY, Genevay S, Marty M, Gandjbakhch F, Rozenberg S, et al. Inflammatory pain pattern and pain with lumbar extension associated with Modic 1 changes on MRI: a prospective case-control study of 120 patients. Eur Spine J 2013 Sep 25.

(31) Ohtori S, Inoue G, Ito T, Koshi T, Ozawa T, Doya H, et al. Tumor necrosis factor-immunoreactive cells and PGP 9.5-immunoreactive nerve fibers in vertebral endplates of patients with discogenic low back Pain and Modic Type 1 or Type 2 changes on MRI. Spine (Phila Pa 1976) 2006 Apr 20;31(9):1026-31.

(32) Fayad F, Lefevre-Colau MM, Rannou F, Quintero N, Nys A, Mace Y, et al. Relation of inflammatory modic changes to intradiscal steroid injection outcome in chronic low back pain. Eur Spine J 2007 Jul;16(7):925-31.

(33) Sorlie A, Moholdt V, Kvistad KA, Nygaard OP, Ingebrigtsen T, Iversen T, et al. Modic type I changes and recovery of back pain after lumbar microdiscectomy. Eur Spine J 2012 Nov;21(11):2252-8.

(34) Kaapa E, Luoma K, Pitkaniemi J, Kerttula L, Gronblad M. Correlation of size and type of modic types 1 and 2 lesions with clinical symptoms: a descriptive study in a subgroup of patients with chronic low back pain on the basis of a university hospital patient sample. Spine (Phila Pa 1976) 2012 Jan 15;37(2):134-9.

(35) Gibson JN, Waddell G. Surgical interventions for lumbar disc prolapse: updated Cochrane Review. Spine (Phila Pa 1976) 2007 Jul 15;32(16):1735-47.

(36) Berg L, Neckelmann G, Gjertsen O, Hellum C, Johnsen LG, Eide GE, et al. Reliability of MRI findings in candidates for lumbar disc prosthesis. Neuroradiology 2012 Jul;54(7):699-707.

(37) Nagy SA, Juhasz I, Komaromy H, Pozsar K, Zsigmond I, Perlaki G, et al. A Statistical Model for Intervertebral Disc Degeneration: Determination of the Optimal T2 Cut-Off Values. Clin Neuroradiol 2013 Nov 12.

(38) Bendix T, Sorensen JS, Henriksson GA, Bolstad JE, Narvestad EK, Jensen TS. Lumbar modic changes-a comparison between findings at low- and high-field magnetic resonance imaging. Spine (Phila Pa 1976) 2012 Sep 15;37(20):1756-62.

(39) Mannion AF, Elfering A. Predictors of surgical outcome and their assessment. Eur Spine J 2006 Jan;15 Suppl 1:S93-108.

Figure legends

Fig. 1 Overview of participant flow through the trial

Fig. 2 Modic changes. Sagittal T2 weighted (**a-c**) and sagittal T1 weighted (**d-f**) MRI images showing Modic changes (*arrows*) in three different patients with lumbar radicular pain. (**a, d**) A 43-year-old woman with Modic type I changes inferior to the L5/S1 disc. (**b, e**) A 56-year-old man with Modic type II changes superior (and inferior) to the L4/L5 disc. (**c, f**) A 45-year-old woman with Modic type III changes superior to the L4/L5 disc

Fig. 3 McGill sensory pain scores, grouped by Modic type, among patients treated surgically (A) and non-surgically (B). In both treatment groups combined, Modic type had a significant impact on McGill sensory pain score at 6 weeks ($p = 0.007$), when adjusting for treatment, age, sex, smoking status, duration of lumbar radicular pain, and disc degeneration; patients with Modic type I changes had higher McGill sensory pain scores at 6 weeks compared to patients with other Modic types ($p = 0.003$) or without Modic changes ($p = 0.018$). Data are shown by mean ± standard error of the mean

Fig. 4 VAS back pain scores, grouped by Modic type, among patients treated surgically (A) and non-surgically (B). In both treatment groups combined, Modic type had no significant impact on VAS back pain score at any time point, when adjusting for treatment, age, sex, smoking status, duration of lumbar radicular pain, and disc degeneration; VAS back pain scores did not differ significantly between Modic type groups at any time point. Data are shown by mean ± standard error of the mean

Table 1. Interobserver agreement on magnetic resonance imaging findings

Finding	Kappa*	95% confidence interval
Modic type (none, type I, type II, or type III)		
L2/L3 inf to disc	0.66	0.52 to 0.80
L3/L4 sup to disc	0.65	0.51 to 0.80
L3/L4 inf to disc	0.63	0.51 to 0.75
L4/L5 sup to disc	0.74	0.66 to 0.82
L4/L5 inf to disc	0.64	0.56 to 0.73
L5/S1 sup to disc	0.68	0.60 to 0.76
L5/S1 inf to disc	0.58	0.49 to 0.66
Modic craniocaudal (CC) size (five ordered categories)		
L2/L3 inf to disc	0.62	0.49 to 0.76
L3/L4 sup to disc	0.61	0.48 to 0.73
L3/L4 inf to disc	0.63	0.52 to 0.75
L4/L5 sup to disc	0.77	0.70 to 0.83
L4/L5 inf to disc	0.70	0.63 to 0.78
L5/S1 sup to disc	0.72	0.66 to 0.78
L5/S1 inf to disc	0.59	0.51 to 0.67
Disc degeneration (DD) (four ordered categories)		
L2/L3	0.54	0.45 to 0.63
L3/L4	0.67	0.60 to 0.73
L4/L5	0.59	0.51 to 0.66
L5/S1	0.55	0.47 to 0.63

* Unweighted Kappa for Modic type, otherwise linearly weighted kappa; kappa values concern agreement between two observers evaluating Modic changes in 275 patients and DD in 250 patients, including the 243 patients participating in the present prospective study; kappa not given for levels where the evaluated finding had prevalence below 10% (mean of both observers). Agreement beyond chance was interpreted as very good (kappa value > 0.80), good (0.61–0.80), moderate (0.41–0.60), fair (0.21–0.40), or poor (≤0.20) (Sim and Wright 2005) [27].

sup, superior; *inf,* inferior

Table 2. Baseline characteristics of total study population grouped by Modic type

	All (n = 243)	No Modic (n = 59)	Modic I (n = 30)	Modic II + III (n = 154)
Age, years, mean (SD)	41.3 (10.5)	37.2 (11.8)	39.7 (8.5)	43.2 (9.8)
Females, n (%)	114 (46.9)	31 (52.5)	19 (63.3)	64 (41.6)
Smokers, n (%)	87 (35.8)	21 (35.6)	9 (30.0)	57 (37.0)
High (i.e. university) educational level, n (%)	104 (43.3)	23 (39.7)	14 (48.3)	67 (43.8)
Duration of lumbar radicular pain, weeks, mean (SD) (range)	17.3 (22.5) (0.3-208.0)	12.4 (10.2) (0.3-44.0)	21.1 (23.5) (0.7-104.0)	18.5 (25.4) (0.3-208.0)
McGill sensory, mean (SD)	0.5 (0.2)	0.5 (0.2)	0.5 (0.2)	0.5 (0.2)
VAS back pain, mean (SD)	4.0 (2.7)	4.4 (2.8)	3.6 (2.8)	3.9 (2.7)
VAS leg pain, mean (SD)	6.3 (2.8)	6.4 (2.8)	6.8 (2.8)	6.2 (2.8)
ODI, mean (SD)	39.3 (19.4)	35.5 (18.7)	38.3 (16.0)	40.9 (20.1)

SD, standard deviation; *VAS,* visual analogue scale, 0-10; *ODI,* Oswestry Disability Index, 0-100

Table 3. McGill sensory pain scores and VAS scores for LBP in the total study population (n = 243) over time, grouped by Modic type

	McGill sensory pain score, mean (SD)				VAS score for LBP, mean (SD)			
	Inclusion	6 weeks	6 months	12 months	Inclusion	6 weeks	6 months	12 months
No Modic	0.50 (0.23)	0.30 (0.24)	0.28 (0.24)	0.26 (0.28)	4.4 (2.8)	2.5 (2.7)	2.4 (2.8)	2.4 (2.9)
Modic type I	0.55 (0.21)	0.45 (0.28)	0.31 (0.25)	0.30 (0.30)	3.6 (2.8)	3.1 (3.0)	3.1 (2.8)	2.5 (3.1)
Modic type II + III	0.54 (0.23)	0.29 (0.23)	0.26 (0.24)	0.27 (0.27)	3.9 (2.7)	2.3 (2.2)	2.3 (2.2)	2.5 (2.6)
Total	0.53 (0.23)	0.31 (0.24)	0.27 (0.24)	0.27 (0.27)	4.0 (2.7)	2.5 (2.4)	2.4 (2.5)	2.5 (2.8)

VAS, visual analogue scale, 0-10; *LBP,* low back pain; *SD,* standard deviation

Figure 1

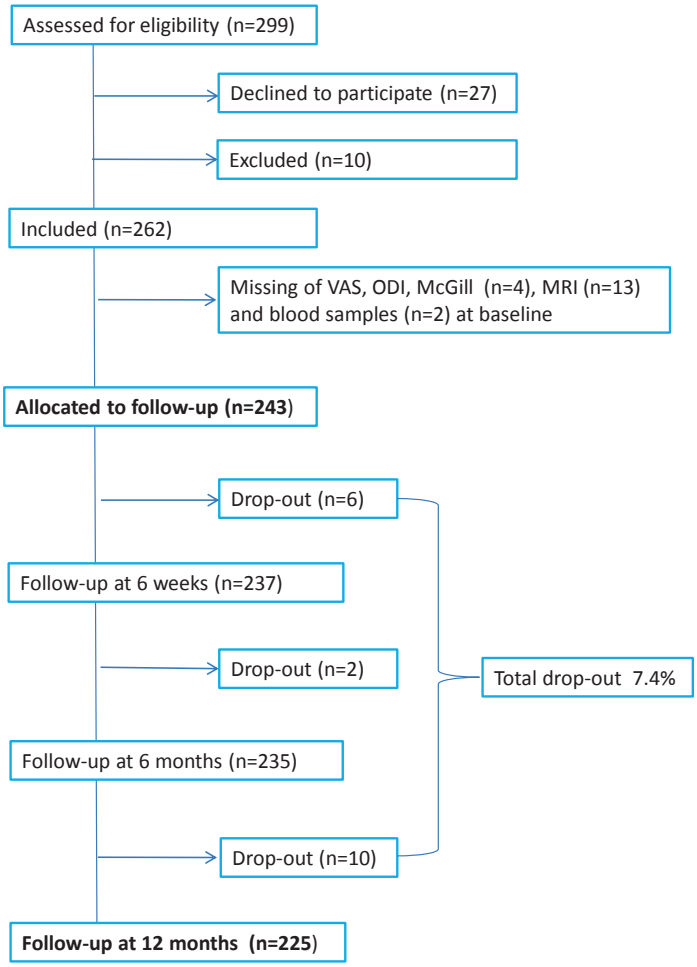

Assessed for eligibility (n=299)
Declined to participate (n=27)
Excluded (n=10)
Included (n=262)
Missing of VAS, ODI, McGill (n=4), MRI (n=13) and blood samples (n=2) at baseline
Allocated to follow-up (n=243)
Drop-out (n=6)
Follow-up at 6 weeks (n=237)
Drop-out (n=2)
Total drop-out 7.4%
Follow-up at 6 months (n=235)
Drop-out (n=10)
Follow-up at 12 months (n=225)

Fig. 2

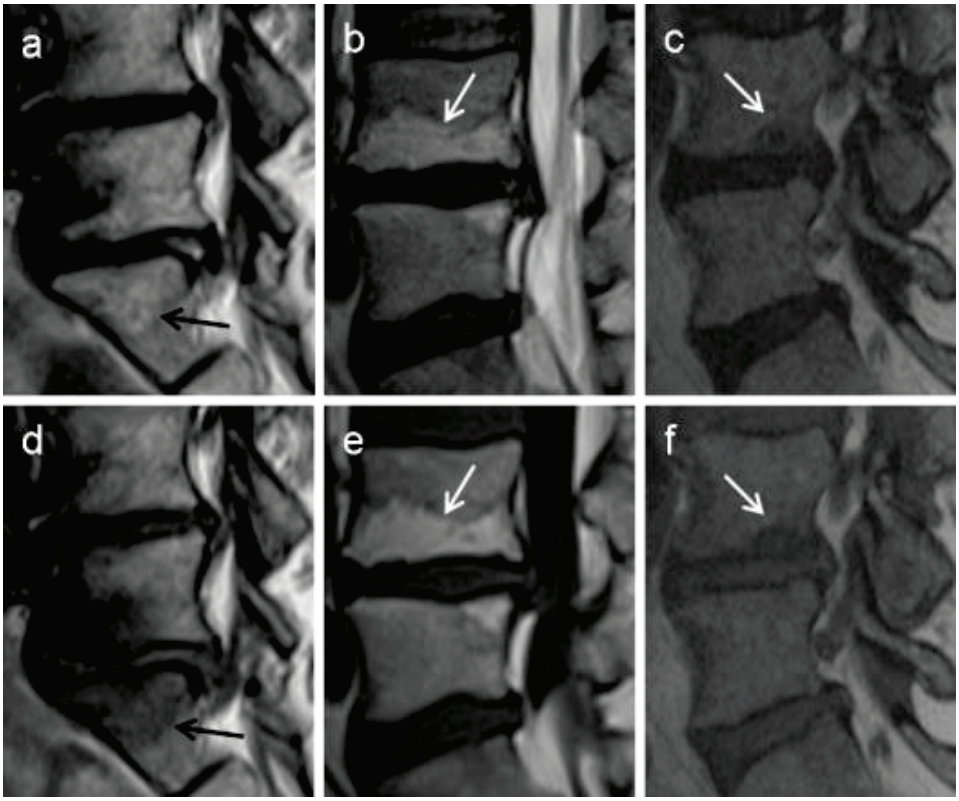


Fig. 3

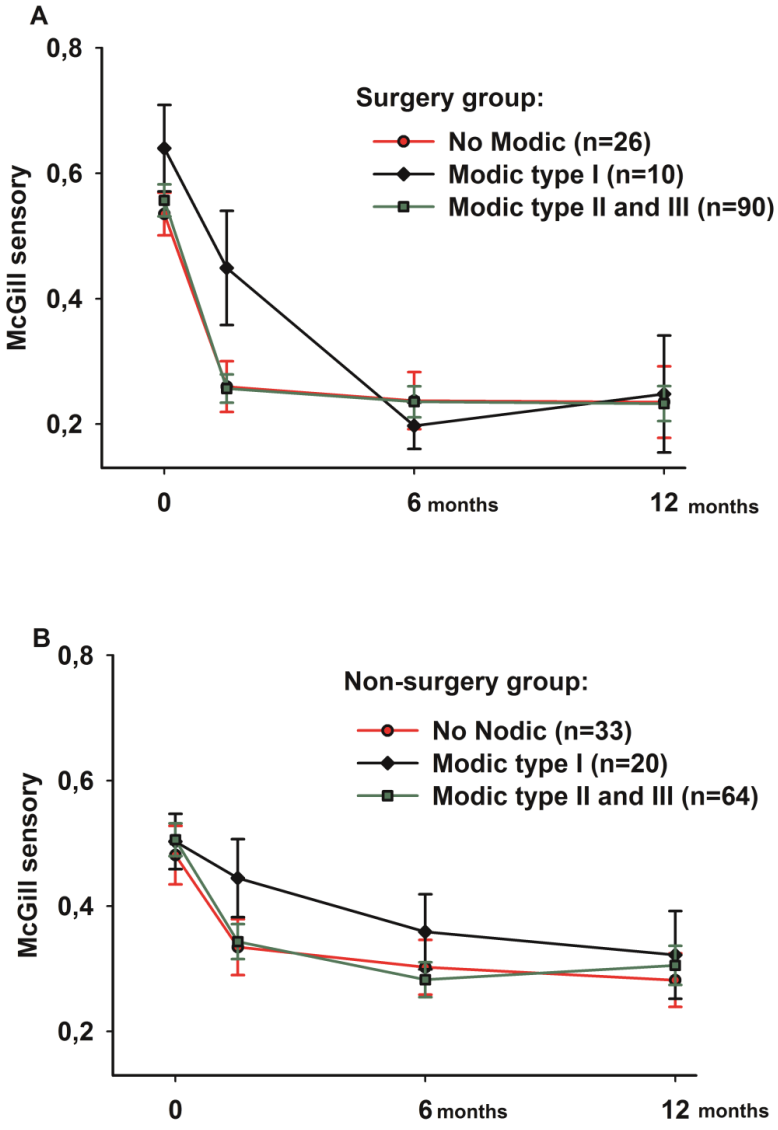
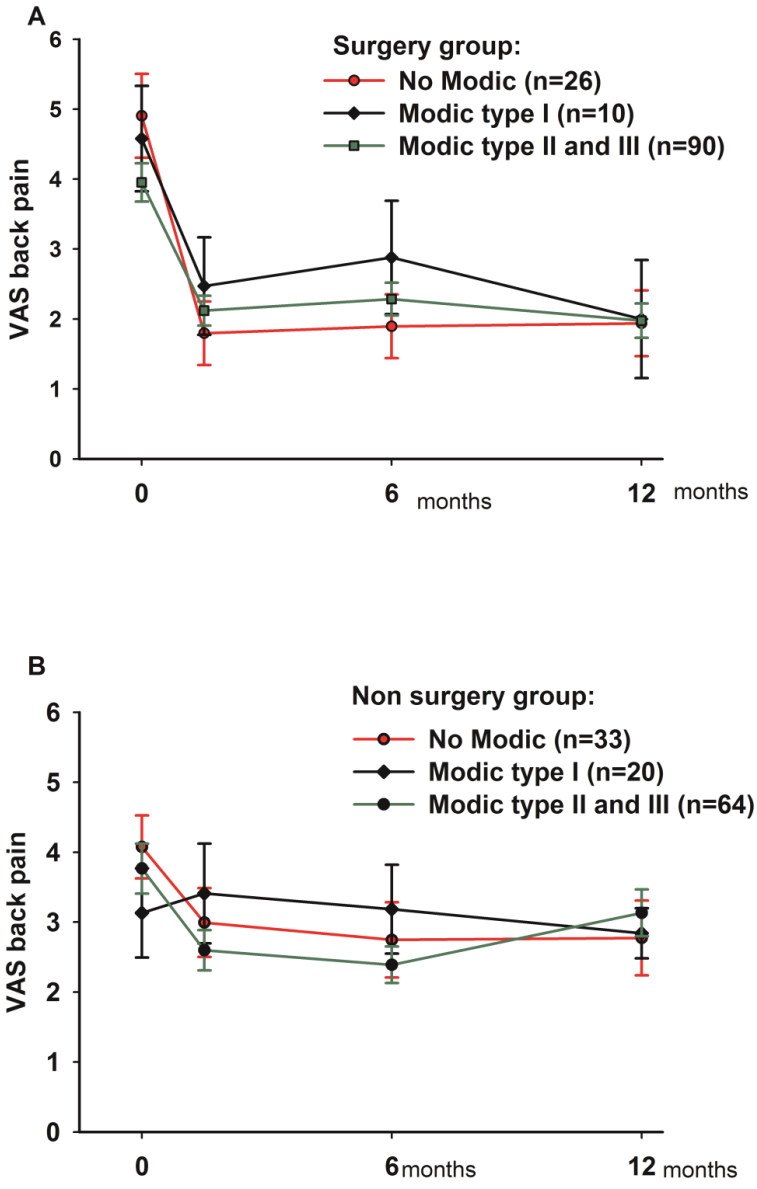

A
0,8
0,6
0,4
0,2
McGill sensory
Surgery group:
No Modic (n=26)
Modic type I (n=10)
Modic type II and III (n=90)
0
6 months
12 months
B
0,8
0,6
0,4
0,2
McGill sensory
Non-surgery group:
No Nodic (n=33)
Modic type I (n=20)
Modic type II and III (n=64)
0
6 months
12 months

Fig. 4


A
Surgery group:
No Modic (n=26)
Modic type I (n=10)
Modic type II and III (n=90)
VAS back pain
0
1
2
3
4
5
6
0
6 months
12 months
B
Non surgery group:
No Modic (n=33)
Modic type I (n=20)
Modic type II and III (n=64)
VAS back pain
0
1
2
3
4
5
6
0
6 months
12 months

IV

Brief Communications

Pain Intensity the First Year after Lumbar Disc Herniation Is Associated with the A118G Polymorphism in the Opioid Receptor Mu 1 Gene: Evidence of a Sex and Genotype Interaction

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Earlier studies have shown that the single nucleotide polymorphism (SNP) A118G (rs1799971) in the opioid receptor mu 1 (OPRM1) gene may affect pain sensitivity. In the present study we investigated whether the A118G SNP could predict clinical outcome regarding progression of pain intensity and disability in patients with low back pain and sciatica after lumbar disc herniation. Patients ($n = 258$) with lumbar disc herniation and sciatic pain, all European-Caucasian, were recruited from two hospitals in Norway. Pain and disability were rated on a visual analog scale (VAS), by McGill Sensory Questionnaire and by Oswestry Disability Index (ODI) over a 12 months period. The data revealed a significant interaction between sex and A118G genotype regarding the pain intensity during the 12 months (VAS, $p = 0.002$; McGill, $p = 0.021$; ODI, $p = 0.205$, repeated-measures ANOVA). We found that */G women had a slower recovery rate than the */G men. Actually, the */G women had 2.3 times as much pain as the */G men 12 months after the disc herniation (VAS, $p = 0.043$, one-way ANOVA; $p = 0.035$, Tukey HSD). In contrast, the A/A women and A/A men seemed to have almost exactly the same recovery rate. The present data suggest that OPRM1 G allele increases the pain intensity in women, but has a protective effect in men the first year after disc herniation.

Introduction

Many factors may contribute to the development of low back pain and sciatica. These include age related changes, body weight, smoking and occupational loading (Miranda et al., 2002; Younes et al., 2006; Samartzis et al., 2011). Moreover, psychosocial aspects as well as genetic variability may affect the risk of long-term low back pain and sciatica (Jacobsen et al., 2012).

One important genetic factor that may increase the risk of persistent low back pain and sciatica is the single nucleotide polymorphism (SNP) A118G, rs1799971, in the opioid receptor mu 1 (OPRM1) gene. This SNP leads to a substitution of asparagine (Asn) to aspartic acid (Asp) at amino acid 40 and therefore removal of a putative *N*-linked glycosylation site in the receptor (Bergen et al., 1997; Bond et al., 1998). Recent data show that the equivalent A112G SNP in the brain of mice leads to reduced OPRM1 *N*-glycosylation and similarly that the human A118G SNP causes decreased *N*-glycosylation and reduced stability of the receptor in cell cultures (Huang et al., 2012).

Among individuals free of clinical pain it has been suggested that 118G allele carriers, in particular men, have higher pressure pain thresholds than 118A carriers (Fillingim et al., 2005). Carriers of the 118G allele may also have lower cortical responses to experimental pain stimuli (Lötsch et al., 2006). However, in contrast, the women carrying the 118G allele seem to report more pain than the women homozygous for the 118A the first 24 h after a cesarean operation (Sia et al., 2008; Tan et al., 2009). In addition, evidence exist that carriers of the OPRM1 118G allele may require higher doses of morphine in the early postoperative period (Klepstad et al., 2004; Chou et al., 2006; Hayashida et al., 2008).

Consistent with these findings, the effect of the opioid agonists have also been linked to sex and strain in animal experiments (Baamonde et al., 1989; Vendruscolo et al., 2004). Moreover, in mice, the OPRM1 G allele, depending on sex, may reduce μ-opioid receptor expression in some brain regions (Wang et al., 2012). In addition, earlier data suggest that the density of the μ-opioid receptor may be different in the male and female human brain (Zubieta et al., 1999). Hence, we hypothesized that the

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Table 1. Characteristics of patients grouped by sex and OPRM1 A118G genotype

	Women */G ($n = 23$)	Men */G ($n = 41$)	Women A/A ($n = 94$)	Men A/A ($n = 94$)
Mean age (min-max)	43 (26–58)	41 (24–57)	41 (18–59)	41 (19–60)
Current smoker, yes/no (%)	9/14 (39/61)	13/28 (32/68)	31/63 (33/67)	39/55 (41/59)
Treatment, conservative/surgery (%)	9/14 (39/61)	18/23 (44/56)	44/50 (47/53)	35/59 (37/63)

Min, minimum; max, maximum.

OPRM1 A118G SNP may have different effects in men and women as well. In the present study we demonstrate that the pain after lumbar disc herniation is dependent on a sex and OPRM1 A118G genotype interaction.

Materials and Methods

Subjects. Patients with lumbar disc herniation and sciatic pain were recruited from Oslo University Hospital, Ullevaal, Norway and Haukeland University Hospital, Norway, during the period of 2007–2009 (Table 1). Inclusion criteria were: age between 18 and 60 years, confirmed lumbar disc herniation by magnetic resonance imaging (MRI) with corresponding sciatic pain and positive Straight Leg Raising (SLR) test. Further exclusion criteria were: lumbar spinal stenosis, previous surgery for herniated disc at the same level or fusion at any level in lumbar spine, generalized musculoskeletal pain, inflammatory rheumatic disease, diabetic polyneuropathy, cardiovascular disease (NYHA III and IV), cancer, psychiatric disease, neurological disease, alcohol or drug abuse, completion of another surgery within 1 month, pregnancy, nondetectable genotype, non-European-Caucasian ethnicity or poor Norwegian language. A total of 258 patients were included in the present study. However, at inclusion, 6 patients changed their mind and did not want to participate, which gave us data from 252 patients. In addition, 21 patients (8%) dropped out during the follow-up.

All participants received written information and signed an informed consent form. The study was approved by the Norwegian Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services.

Clinical procedure. After inclusion, the newly diagnosed patients had a follow-up at 6 weeks, 6 months and 12 months. Conservative treatment was received by 42% and surgical treatment received by 58%. At the time of inclusion, all patients underwent a standardized clinical examination including assessment of sensory and motor function and tendon reflexes of the lower limbs as well as an MRI scan. At 6 weeks follow-up, the clinical examination was repeated, while at 6 months follow-up, patients reported their back condition by a telephone interview and answered questionnaires by mail. At 12 months follow-up, patients underwent the same examination as by inclusion, and if their pain was persistent, an MRI scan was repeated. The sampling of the clinical data was completed before the genotyping of the patients was performed.

Clinical measures. All patients were asked to rate their pain intensity in activity during the last week on a 10 cm visual analog scale (VAS) with endpoints "no pain" and "worst possible pain." The validated Norwegian version of the McGill questionnaire was used to measure the sensory components of the pain experience (Strand and Wisnes, 1991). The validated Norwegian version of the Oswestry Disability Index (ODI) (Grotle et al., 2003) was used to assess problems with physical function related to low back pain.

Genotyping. Blood samples were drawn and genomic DNA was extracted from whole blood cells using FlexiGene DNA isolation kit (Qiagen). SNP genotyping was performed using predesigned TaqMan SNP genotyping assays (Applied Biosystems). Approximately 10 ng of genomic DNA was amplified in a 5 μl reaction mixture in a 384-well plate containing 1× TaqMan genotyping master mix (Applied Biosystems) and 1× assay mix, the latter containing the respective primers and probes. The probes were labeled with the reporter dye FAM or VIC to distinguish between the two alleles. After initial denaturation and enzyme activation at 95°C for 10 min, the reaction mixture was subjected to 60 cycles of 95°C for 15 s and 60°C for 1 min. The reactions were performed on an ABI 7900HT sequence detection system. Negative controls containing water instead of DNA were included in every run. Genotypes were determined using the SDS 2.2 software (Applied Biosystems). Approximately 10% of the samples were re-genotyped and the concordance rate was 100%.

Table 2. Significance of covariates

	Repeated-measures ANOVA			
Outcome measure	Covariates	Within-subjects effects, p values	Between-subjects effects, p values	Included in final model, yes/no
VAS	Age	0.844	0.002	Yes
	Smoking	0.697	0.924	No
	Treatment	0.000	0.250	Yes
McGill	Age	0.428	0.019	Yes
	Smoking	0.343	0.086	Yes
	Treatment	0.000	0.003	Yes
ODI	Age	0.417	0.003	Yes
	Smoking	0.070	0.150	Yes
	Treatment	0.000	0.150	Yes

The table gives an overview of the association between covariates and the three outcome measures: VAS, McGill, and ODI. Covariates with a p value ≤ 0.1 were included in the final model.

Data evaluation and statistics. The data are shown as means ± SEM. VAS activity score, McGill sensory score and ODI measurements over time were compared regarding sex and OPRM1 genotypes with the groups; women */G, men */G, women AA and men AA by repeated measures ANOVA, within-subjects effect. When sphericity assumption was not met, a Greenhouse-Geiser correction was applied. Separate analyses were performed to check for potential effects of covariates age, smoking status and treatment. Covariates with $p \leq 0.1$ were kept in the final model (Table 2). Finally, VAS activity score, McGill sensory score and ODI score at 12 months were examined regarding the four sex/genotype groups by a one-way ANOVA and Tukey honestly significant difference (HSD) *post hoc* comparison. Statistical analyses were performed using the statistical package PASW statistics 18 (SPSS). A p value <0.05 was chosen as the level of statistical significance.

Results

The present material of the 252 patients consisted of 94 homozygous A/A, 20 heterozygous A/G and 3 homozygous G/G among the females, and 94 homozygous A/A, 40 heterozygous A/G and 1 homozygous GG among the males. The allele frequency of the G allele was therefore 13%, which is in accordance with previous reports from Caucasian populations (Klepstad et al., 2004).

As expected, we observed a clear decrease in pain and disability over time the first year after the disc herniation (VAS $p = 0.000$, McGill $p = 0.000$, ODI $p = 0.000$, repeated-measures ANOVA). From inclusion to 6 weeks, a distinct reduction in pain was observed, whereas a less pronounced reduction in pain intensity was observed from 6 weeks to 6 and 12 months.

Interestingly, however, our data showed that the decrease in pain and disability, i.e., the recovery after disc herniation, may be affected by both sex and the OPRM1 A118G SNP. A significant interaction between sex and genotype regarding the pain experience over time were observed (VAS, $p = 0.002$; McGill, $p = 0.021$; ODI, $p = 0.205$, repeated-measures ANOVA, women */G, men */G, women A/A and men A/A, including covariates smoke, treatment and age with $p \leq 0.1$).

The genotype */G seemed to be associated with more pain in women, but to protect the men from pain after lumbar disc herniation (Fig. 1). Wild-type A/A women and men reported similar pain ratings. Hence, the women carrying */G alleles appeared to have a slower recovery than the */G men.

The analysis of main outcome, i.e., pain and disability at 12 months, showed a significant association between sex and genotype regarding the pain experience (VAS, $p = 0.043$; McGill, $p =$

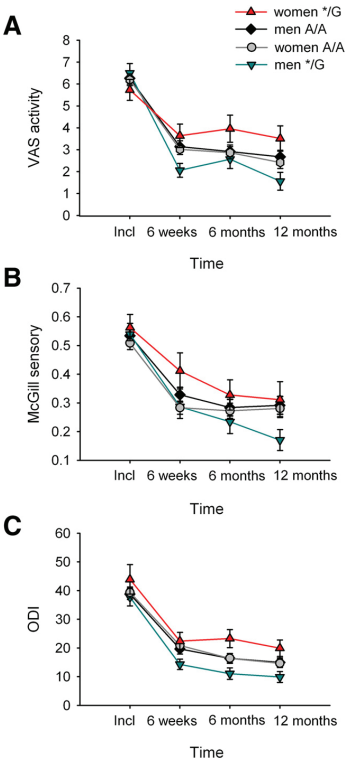

Figure 1. The time course for outcome measures grouped by sex and A118G genotypes following disc herniation. ***A***, VAS activity score ($p = 0.002$, rm ANOVA; $p = 0.043$ one-way ANOVA at 12 months). ***B***, McGill sensory score ($p = 0.021$, rm ANOVA; $p = 0.103$, one-way ANOVA at 12 months). ***C***, ODI score ($p = 0.205$, rm ANOVA; $p = 0.057$, one-way ANOVA at 12 months). Data are given as means ± SEM.

Table 3. Pain and disability ratings at 12 months

	VAS activity	McGill sensory	ODI
Women */G	3.51 ± 0.58	0.31 ± 0.06	19.92 ± 2.87
Men */G	1.56 ± 0.41	0.17 ± 0.04	9.89 ± 1.88
Women A/A	2.42 ± 0.27	0.28 ± 0.03	14.66 ± 1.47
Men A/A	2.67 ± 0.30	0.29 ± 0.03	15.00 ± 1.59

The table shows the 12 month VAS, McGill, and ODI scorings for the patients grouped by sex and A118G genotype. Mean ± SEM values are shown. *G or A allele.

0.103; ODI, $p = 0.057$, one-way ANOVA, women */G, men */G, women A/A and men AA). Mean ± SEM values at 12 months are listed in Table 3.

The *post hoc* comparison further confirmed that the */G women had more pain than the */G men (VAS, $p = 0.035$, Tukey HSD). However, the wild-type men and women seemed to have the same pain level (VAS, $p = 0.993$, Tukey HSD). The women carrying the 118G allele had, 12 months after the disc herniation, 2.3, 1.8 and 2.0 times higher VAS, McGill, and ODI scores respectively than the men with the same genotype.

Discussion

For the first time we demonstrate an interaction between sex and OPRM1 A118G genotype regarding recovery of low back pain and sciatica. Clearly, women with the */G genotype reported more pain than the */G men 12 months after the disc herniation. However, women and men with homozygote A/A alleles had almost exactly the same recovery rate regarding the pain intensity. Hence, our data indicated that the OPRM1 118G allele affected the clinical outcome after a disc herniation and that the */G women had a slower recovery than the */G men.

Our study support the earlier observation that female sciatic patients may have a slower recovery and a poorer one-year outcome than male sciatic patients (Peul et al., 2008). However, here we have extended these findings and demonstrated that the pain also is related to a sex-specific genetic factor. As presented in this study, women carrying the 118G allele had a mean VAS pain score 2.3 times higher than men with the same genotype 12 months after the lumbar disc herniation. Earlier data show that women carrying the 118G allele may have increased basal level of cortisol (Bart et al., 2006), consistent with a higher report of pain. Together these findings suggest that the high pain intensity in women compared with men in the low back pain and sciatic patients 12 months after the lumbar disc herniation may be related to the 118G substitution.

The present data are consistent with the observations of more pain in women carrying the 118G allele 24 h after a cesarean operation (Sia et al., 2008; Tan et al., 2009) and with carriers of the 118G allele, in particular males, having higher pressure pain thresholds (Fillingim et al., 2005). Interestingly, Fillingim and colleagues reported that */G women might be more sensitive to heat pain than A/A women and that the */G men might be less sensitive to heat pain than the A/A men. Moreover, sex-specific effects regarding the A118G SNP and reward effects of stimulants have been found. For example, women carrying the 118G allele have reported attenuated reward effects of nicotine (Ray et al., 2006). Also, female rats, homozygote for the 112G allele, an equivalent to the 118G allele in humans, have shown diminished reward properties of morphine (Mague et al., 2009).

At the molecular level, consistent with our observations of more pain in */G women, a 1.5–2.5-fold reduced mRNA expression of the OPRM1 has been found in human brain tissues of 118G carriers and a further tenfold reduction in protein levels has been found in cell cultures (Zhang et al., 2005). However, the molecular phenotype of the OPRM1 A118G seems to be region specific. For example, data from humans obtained by harvesting brain tissue postmortem have demonstrated that 118G allele carriers have a decreased receptor signaling efficacy in response to DAMGO in the secondary somatosensory cortex (Oertel et al., 2009). Moreover, positron emission tomography (PET) data based on the OPRM1 ligand tracer [^{11}C]carfentanil have suggested that smokers carrying the 118G allele may have lower levels of receptor binding potential in the amygdala, thalamus, and anterior cingulate cortex (Ray et al., 2011).

The Asn to Asp amino acid exchange results in reduced OPRM1 *N*-glycosylation (Huang et al., 2012). *N*-glycosylation, which has been suggested to be region-specific (Huang et al., 2008), plays a part in many cellular processes like receptor folding, sorting, expression, and ligand binding. As the level and type of *N*-glycosylation is found to differ in men and women (Knezević et al., 2009; Stanta et al., 2010; Ding et al., 2011), this mechanism has been proposed as a possible explanation for the region- and sex-specific differences observed for the OPRM1 A112G expression in the mouse brain (Wang et al., 2012). Hence, and in accordance with the data in the present study, it is tempting to speculate that lack of *N*-glycosylation, as a consequence of the amino acid exchange in the μ-opioid receptor, also may give sex-specific effects with regards to pain sensitivity in patients.

In conclusion, the present data demonstrate that the OPRM1 118G allele is associated with increased pain intensity in women, but reduced pain intensity in men the first year after a disc herniation. This finding strongly support the hypothesis that the OPRM1 118G allele may influence the endogenous pain modulatory system differently depending on sex, which also might be relevant for the understanding of the mechanisms underlying development of persistent low back pain and sciatica.

References

Baamonde AI, Hidalgo A, Andres-Trelles F (1989) Sex-related differences in the effects of morphine and stress on visceral pain. Neuropharmacology 28:967–970.

Bart G, LaForge KS, Borg L, Lilly C, Ho A, Kreek MJ (2006) Altered levels of basal cortisol in healthy subjects with a 118G allele in exon 1 of the Mu opioid receptor gene. Neuropsychopharmacology 31:2313–2317.

Bergen AW, Kokoszka J, Peterson R, Long JC, Virkkunen M, Linnoila M, Goldman D (1997) Mu opioid receptor gene variants: lack of association with alcohol dependence. Mol Psychiatry 2:490–494.

Bond C, LaForge KS, Tian M, Melia D, Zhang S, Borg L, Gong J, Schluger J, Strong JA, Leal SM, Tischfield JA, Kreek MJ, Yu L (1998) Single-nucleotide polymorphism in the human mu opioid receptor gene alters beta-endorphin binding and activity: possible implications for opiate addiction. Proc Natl Acad Sci U S A 95:9608–9613.

Chou WY, Wang CH, Liu PH, Liu CC, Tseng CC, Jawan B (2006) Human opioid receptor A118G polymorphism affects intravenous patient-controlled analgesia morphine consumption after total abdominal hysterectomy. Anesthesiology 105:334–337.

Ding N, Nie H, Sun X, Sun W, Qu Y, Liu X, Yao Y, Liang X, Chen CC, Li Y (2011) Human serum N-glycan profiles are age and sex dependent. Age Ageing 40:568–575.

Fillingim RB, Kaplan L, Staud R, Ness TJ, Glover TL, Campbell CM, Mogil JS, Wallace MR (2005) The A118G single nucleotide polymorphism of the mu-opioid receptor gene (OPRM1) is associated with pressure pain sensitivity in humans. J Pain 6:159–167.

Grotle M, Brox JI, Vollestad NK (2003) Cross-cultural adaptation of the Norwegian versions of the Roland-Morris Disability Questionnaire and the Oswestry Disability Index. J Rehabil Med 35:241–247.

Hayashida M, Nagashima M, Satoh Y, Katoh R, Tagami M, Ide S, Kasai S, Nishizawa D, Ogai Y, Hasegawa J, Komatsu H, Sora I, Fukuda K, Koga H, Hanaoka K, Ikeda K (2008) Analgesic requirements after major abdominal surgery are associated with OPRM1 gene polymorphism genotype and haplotype. Pharmacogenomics 9:1605–1616.

Huang P, Chen C, Xu W, Yoon SI, Unterwald EM, Pintar JE, Wang Y, Chong PL, Liu-Chen LY (2008) Brain region-specific N-glycosylation and lipid rafts association of the rat mu opioid receptor. Biochem Biophys Res Commun 365:82–88.

Huang P, Chen C, Mague SD, Blendy JA, Liu-Chen LY (2012) A common single nucleotide polymorphism A118G of the mu opioid receptor alters its N-glycosylation and protein stability. Biochem J 441:379–386.

Jacobsen LM, Schistad EI, Storesund A, Pedersen LM, Rygh LJ, Roe C, Gjerstad J (2012) The COMT rs4680 Met allele contributes to long-lasting low back pain, sciatica and disability after lumbar disc herniation. Eur J Pain. Advance online publication. Retrieved Mar. 1, 2012. doi: 10.1002/j.1532-2149.2011.00102.x.

Klepstad P, Rakvag TT, Kaasa S, Holthe M, Dale O, Borchgrevink PC, Baar C, Vikan T, Krokan HE, Skorpen F (2004) The 118 A > G polymorphism in the human mu-opioid receptor gene may increase morphine requirements in patients with pain caused by malignant disease. Acta Anaesthesiol Scand 48:1232–1239.

Knezević A, Polasek O, Gornik O, Rudan I, Campbell H, Hayward C, Wright A, Kolcic I, O'Donoghue N, Bones J, Rudd PM, Lauc G (2009) Variability, heritability and environmental determinants of human plasma N-glycome. J Proteome Res 8:694–701.

Lötsch J, Stuck B, Hummel T (2006) The human mu-opioid receptor gene polymorphism 118A > G decreases cortical activation in response to specific nociceptive stimulation. Behav Neurosci 120:1218–1224.

Mague SD, Isiegas C, Huang P, Liu-Chen LY, Lerman C, Blendy JA (2009) Mouse model of OPRM1 (A118G) polymorphism has sex-specific effects on drug-mediated behavior. Proc Natl Acad Sci U S A 106:10847–10852.

Miranda H, Viikari-Juntura E, Martikainen R, Takala EP, Riihimaki H (2002) Individual factors, occupational loading, and physical exercise as predictors of sciatic pain. Spine 27:1102–1109.

Oertel BG, Kettner M, Scholich K, Renne C, Roskam B, Geisslinger G, Schmidt PH, Lötsch J (2009) A common human micro-opioid receptor genetic variant diminishes the receptor signaling efficacy in brain regions processing the sensory information of pain. J Biol Chem 284:6530–6535.

Peul WC, Brand R, Thomeer RT, Koes BW (2008) Influence of gender and other prognostic factors on outcome of sciatica. Pain 138:180–191.

Ray R, Jepson C, Patterson F, Strasser A, Rukstalis M, Perkins K, Lynch KG, O'Malley S, Berrettini WH, Lerman C (2006) Association of OPRM1 A118G variant with the relative reinforcing value of nicotine. Psychopharmacology (Berl) 188:355–363.

Ray R, Ruparel K, Newberg A, Wileyto EP, Loughead JW, Divgi C, Blendy JA, Logan J, Zubieta JK, Lerman C (2011) Human Mu Opioid Receptor (OPRM1 A118G) polymorphism is associated with brain mu-opioid receptor binding potential in smokers. Proc Natl Acad Sci U S A 108:9268–9273.

Samartzis D, Karppinen J, Mok F, Fong DY, Luk KD, Cheung KM (2011) A population-based study of juvenile disc degeneration and its association with overweight and obesity, low back pain, and diminished functional status. J Bone Joint Surg Am 93:662–670.

Sia AT, Lim Y, Lim EC, Goh RW, Law HY, Landau R, Teo YY, Tan EC (2008) A118G single nucleotide polymorphism of human mu-opioid receptor gene influences pain perception and patient-controlled intravenous morphine consumption after intrathecal morphine for postcesarean analgesia. Anesthesiology 109:520–526.

Stanta JL, Saldova R, Struwe WB, Byrne JC, Leweke FM, Rothermund M, Rahmoune H, Levin Y, Guest PC, Bahn S, Rudd PM (2010) Identification of N-glycosylation changes in the CSF and serum in patients with schizophrenia. J Proteome Res 9:4476–4489.

Strand LI, Wisnes AR (1991) The development of a Norwegian pain questionnaire. Pain 46:61–66.

Tan EC, Lim EC, Teo YY, Lim Y, Law HY, Sia AT (2009) Ethnicity and OPRM variant independently predict pain perception and patient-controlled analgesia usage for post-operative pain. Mol Pain 5:32.

Vendruscolo LF, Pamplona FA, Takahashi RN (2004) Strain and sex differences in the expression of nociceptive behavior and stress-induced analgesia in rats. Brain research 1030:277–283.

Wang YJ, Huang P, Ung A, Blendy JA, Liu-Chen LY (2012) Reduced expression of the mu opioid receptor in some, but not all, brain regions in mice with Oprm1 A112G. Neuroscience 205:178–184.

Younes M, Bejia I, Aguir Z, Letaief M, Hassen-Zrour S, Touzi M, Bergaoui N (2006) Prevalence and risk factors of disk-related sciatica in an urban population in Tunisia. Joint Bone Spine 73:538–542.

Zhang Y, Wang D, Johnson AD, Papp AC, Sadee W (2005) Allelic expression imbalance of human mu opioid receptor (OPRM1) caused by variant A118G. J Biol Chem 280:32618–32624.

Zubieta JK, Dannals RF, Frost JJ (1999) Gender and age influences on human brain mu-opioid receptor binding measured by PET. Am J Psychiatry 156:842–848.