

Tero Korhonen

LUMBAR DISCOBLOCK
AND INTERVERTEBRAL
DISC-RELATED
DEGENERATIVE FEATURES

*INTERJACENT ASSOCIATION AND PROGNOSTIC
VALUE ON LUMBAR SPINE SURGERY OUTCOMES*

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
OULU UNIVERSITY HOSPITAL



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TERO KORHONEN

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Interjacent association and prognostic value on lumbar
spine surgery outcomes

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Abstract

Low back pain (LBP) presents a significant global health burden. Despite approximately 30–40% of chronic LBP being presumed to originate from the intervertebral disc (IVD), diagnosing painful IVD may be clinically challenging, especially noninvasively. Within invasive diagnostic methods for IVD-related LBP, discoblock is a relatively novel and less studied method. Of the magnetic resonance imaging (MRI) findings in the context of LBP, attention has focused on vertebral bone marrow (BM) alterations referred to as Modic changes (MC, types I-III [MC1-3]), which have been proposed to associate with a specific subtype of LBP.

Study I retrospectively investigated the preoperative prognostic value of discoblock on short-term disability outcomes following lumbar fusion or total disc replacement (TDR) surgery. The correlation between the degree of pain relief following discoblock ($\Delta\text{NRS}_{\text{DB}}$) and favorable short-term disability outcome was very strong and significant in the fusion subgroup. The results indicate that discoblock is a viable tool in preoperative patient selection for lumbar fusion surgery and warrants further validation studies.

Study II examined the association between $\Delta\text{NRS}_{\text{DB}}$ and the presence and type of MC. The study setting was retrospective and shared the same study population with Study I. Patients with any MC or MC1 in the lumbar segment in question exhibited significantly higher $\Delta\text{NRS}_{\text{DB}}$ values compared to those without MC. Based on the results, MC1 are associated with LBP, and the pain originates at least partly from the IVD or the adjacent endplate.

In Study III, a novel MRI-based criterion for preoperative co-occurring advanced-level IVD-related degenerative phenotypes was developed and evaluated for its efficacy in predicting short-term outcomes following lumbar single-level discectomy within a retrospective patient cohort. Meeting this criterion, termed Advanced Preoperative Degeneration (APD), was significantly correlated with worse outcomes in leg pain and disability one year postoperatively.

Keywords: discoblock, endplate damage, intervertebral disc degeneration, intervertebral disc, low back pain, lumbar discectomy, lumbar fusion, lumbar total disc replacement, magnetic resonance imaging, Modic changes

Korhonen, Tero, Lumbaalinen diskuspuudutus ja välilevyn liittyvät rappeumamuutokset. Keskinäinen yhteys ja ennustearvo alaselän leikkaustoimenpiteiden lopputuloksiin

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Tiivistelmä

Alaselkäkipu aiheuttaa merkittävän maailmanlaajuisen terveystaakan. Vaikka välilevyperäisten syiden on arvioitu aiheuttavan noin 30–40 % kroonisesta alaselkäkipusta, kipua tuottavan välilevyn diagnosoiminen voi olla kliinisesti haastavaa etenkin kajoamattomin keinoin. Kajoaviin välilevyperäisen alaselkäkipun diagnostiikkamenetelmiin lukeutuva diskuspuudutus on verrattain uusi ja vähäisesti tutkittu menetelmä. Alaselkäkipuun yhdistetyistä magneettikuvauksella (MK) todetuista löydöksistä selkänikaman luuydin- eli Modic-muutokset (MC, tyypit I-III [MC1-3]) ovat saaneet huomioita, ja niiden onkin ehdotettu liittyvän alaselkäkipuun erillisen alatyypin.

Tutkimuksessa I tarkasteltiin retrospektiivisesti diskuspuudutuksen preoperatiivista ennustearvoa alaselän luudutus- tai tekovälilevyleikkauksen lyhyen seuranta-ajan tuloksiin toimintakyvyn näkökulmasta. Diskuspuudutuksella aikaansaatu kivunlievitys ($\Delta\text{NRS}_{\text{DB}}$) korreloi erittäin vahvasti ja merkittävästi parempiin lyhyen seuranta-ajan toimintakytuloksiin luudutusleikkausryhmässä. Tulosten perusteella diskuspuudutus on käyttökelpoinen menetelmä preoperatiivisessa potilasvalinnassa alaselän luudutusleikkaukseen ansaiten validointijatkotutkimuksia.

Tutkimuksessa II arvioitiin $\Delta\text{NRS}_{\text{DB}}$:n ja MC:n esiintymisen sekä tyyppien välistä yhteyttä. Tutkimusasetelma oli retrospektiivinen ja tutkimuspopulaatio oli sama kuin tutkimuksessa I. Potilailla, jotka omasivat MC:n tai MC1:n tutkittavassa alaselän segmentissä, $\Delta\text{NRS}_{\text{DB}}$ oli merkittävästi suurempi verrattuna potilaisiin, joilla MC:tä ei ollut todettavissa. Tutkimuksen tulokset tukevat hypoteesia, että MC1:t yhdistyvät alaselkäkipuun, ja kipu on ainakin osittain peräisin välilevystä tai viereisestä päätelevystä.

Tutkimuksessa III sekä kehitettiin uusi MK-pohjainen kriteeri ennen leikkausta todettavien yhtäaikaaisesti esiintyvien edenneiden välilevyn liittyvien rappeumamuutosten arvioimiseksi että testattiin kriteerin ennustearvoa yksittäisen alaselän välilevyn diskektomian lyhyen seuranta-ajan lopputuloksiin retrospektiivisessä potilaskohortissa. APD:ksi (Advanced Preoperative Degeneration) nimetyin kriteerin täytyminen oli merkittävästi yhteydessä heikompiin leikkaustuloksiin alaraajakivun ja toimintakyvyn osalta vuoden kuluttua leikkauksesta.

Asiasanat: alaselkäkipu, diskuspuudutus, luudutusleikkaus, magneettikuvaus, Modic-muutokset, päätelevyvaurio, tekovälilevyleikkaus, välilevy, välilevypullistumaleikkaus, välilevyrappeuma

To my family

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February 9th, 2025

Tero Korhonen

Abbreviations

AF	annulus fibrosus
ALIF	anterior lumbar interbody fusion
APD	Advanced Preoperative Degeneration
BM	bone marrow
BMI	body mass index
CI	confidence interval
EP	endplate
EPD	endplate damage
EPS	endplate score
IVD	intervertebral disc
LBP	low back pain
LDH	lumbar disc herniation
MC	Modic changes
MC1	Modic changes type I
MC2	Modic changes type II
MC3	Modic changes type III
MCID	minimal clinically important difference
MD	mean difference
MEC	Modic-endplate complex
MRI	magnetic resonance imaging
NP	nucleus pulposus
NRS	Numerical Rating Scale
ODI	Oswestry Disability Index
OR	odds ratio
PABAK	prevalence-adjusted, bias-adjusted kappa
PLF	posterolateral fusion
PROMs	patient-reported outcome measures
Q1	the first quartile
Q3	the third quartile
QoL	quality of life
r	Spearman's rank correlation coefficient
RCT	randomized controlled trial
rLDH	recurrent lumbar disc herniation
SD	standard deviation
T	Tesla

T1w	T1-weighted
T2w	T2-weighted
TDR	total disc replacement
TEPS	total endplate score
TLIF	transforaminal lumbar interbody fusion
VAS	Visual Analogue Scale
$\Delta\text{NRS}_{\text{DB}}$	the degree of pain relief following discoblock
ΔODI	absolute change in ODI score
$\Delta\text{ODI}\%$	percentage change in ODI score
κ	Cohen's kappa coefficient

List of original publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:

- I Korhonen, T., Pesälä, J., Järvinen, J., Haapea, M., & Niinimäki, J. (2022). Correlation between the degree of pain relief following discoblock and short-term surgical disability outcome among patients with suspected discogenic low back pain. *Scandinavian Journal of Pain*, 22(3), 526–532. <https://doi.org/10.1515/SJPAIN-2021-0160>
- II Korhonen, T., Järvinen, J., Pesälä, J., Haapea, M., & Niinimäki, J. (2022). Modic changes associated with greater pain relief following anesthetization of the adjacent lumbar intervertebral disc: A retrospective study of chronic low back pain patients. *European Journal of Radiology*, 157, Article 110589. <https://doi.org/10.1016/j.ejrad.2022.110589>
- III Korhonen, T., Järvinen, J., Pesälä, J., Haapea, M., Kinnunen, P., & Niinimäki, J. (2024). Assessment and predictive value of preoperative co-occurring intervertebral disc-related degenerative features in lumbar discectomy: a proposal for and preliminary testing of a novel MRI-based criterion. *Manuscript*.

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1 Introduction

Low back pain (LBP) stands as a significant and economically burdensome global health concern (Hoy et al., 2012). The estimated point and 1-month prevalences of LBP are approximated at 11.9% and 23.2%, respectively. While the prognosis for an acute LBP episode is generally favorable, a small percentage of patients progress to the development of chronic LBP (Koes et al., 2006; Pengel, 2003). Consequently, LBP is recognized as the leading cause of years lived with disability on a global scale (Vos et al., 2016).

Concerning chronic LBP, it has been estimated that in 30–40% of cases, the etiology of the pain is attributed to an intervertebral disc (IVD) (DePalma et al., 2011; Manchikanti et al., 2001; Schwarzer et al., 1995). However, establishing a specific lumbar IVD noninvasively as the source of LBP can pose challenges (Hancock et al., 2007; Schwarzer et al., 1995). While certain magnetic resonance imaging (MRI) findings are linked to a painful IVD, their clinical utility is yet to be conclusively demonstrated (Han, Hancock, et al., 2023; Hancock et al., 2007). In the investigation of the painfulness of a singular IVD, invasive diagnostic methods have been developed. Among these, discoblock, a relatively novel and less studied diagnostic approach based on intradiscal anesthetic injection, has emerged. Limited evidence suggests that it may outperform its historically widely used predecessor, discography, which relies on intradiscal contrast agent injection (Manchikanti et al., 2018; McCormick et al., 2018; Ohtori et al., 2009; Putzier et al., 2013).

In the clinical context, traditionally, approximately 90% of LBP cases are considered non-specific, implying the absence of a specific demonstrable pathoanatomical cause, such as fracture or malignancy (Koes et al., 2006; Maher et al., 2017). Accordingly, the treatment options for LBP are primarily conservative. More recently, however, LBP's non-specificity has been challenged (Han, Hancock, et al., 2023). A growing body of evidence has contributed to a greater understanding of specific findings, particularly in the context of MRI. This knowledge will subsequently facilitate the development of more targeted treatments for each subtype of LBP. An epitome of such an LBP subtype-allowing feature is Modic changes (MC), which are MRI-observed alterations of vertebral bone marrow (BM) (Dudli, Fields, et al., 2016). LBP associated with MC has been proposed as a distinct clinical LBP subtype (Kjaer et al., 2006; Määttä et al., 2016; Mok et al., 2016), also contributing to the recent designation of a new ICD-

10 code “M54.51” for “vertebrogenic low back pain” (Centers for Disease Control and Prevention, 2021; Mallow et al., 2022).

Many central details of lumbar MC remain elusive. Most importantly, the precise pathogenesis (Dudli, Fields, et al., 2016; Viswanathan et al., 2020), definitive association with LBP (Czaplewski et al., 2023; Herlin et al., 2018), and their preoperative prognostic value—individually or co-occurring with other degenerative features—in lumbar spine surgery targeting IVD (Lambrechts et al., 2022) are subjects of ongoing debate. By investigating these aspects, future research has the potential to deepen our understanding of the clinical role of MC and other IVD-related degenerative features and contribute to optimizing the treatment of LBP associated with these features, thereby benefiting both patients and society.

2 Review of the literature

2.1 Anatomy and function of the lumbar spine

The human spine serves three fundamental functions: providing structural support to the body, facilitating torso movement, and protecting the integrity of the spinal cord and nerve roots (Cramer & Darby, 2014). These essential functions are enabled by a structure comprised of 24 bony vertebrae and their accompanying soft tissues. The vertebral column of the human body is anatomically organized into three distinct sections, namely the cervical spine with 7 vertebrae (C1–7), the thoracic spine with 12 vertebrae (T1–12), and the lumbar spine with 5 vertebrae (L1–5), arranged in a superior to inferior sequence.

The lumbar spine, positioned with a lordotic curvature, is situated between the last thoracic vertebra (T12) and the sacrum (Cramer & Darby, 2014). Each lumbar vertebra is composed of an anterior vertebral body with a kidney-shaped structure, as well as a posterior vertebral arch encompassing the pedicles, laminae, superior and inferior articular processes, transverse processes oriented laterally, and a spinous process oriented posteriorly. Within this structure, the vertebral foramen is surrounded by the vertebral body, pedicles, laminae, and spinous process, creating the enclosed space known as the vertebral canal, within which the spinal cord is located (Fig. 1). The bone structure of a vertebra consists of a dense outer layer of compact bone and a central region of trabecular bone, which also contains red BM.

The IVDs serve as connecting structures through endplates (EPs) between the adjacent vertebral bodies (Cramer & Darby, 2014). Adjacent vertebrae are further connected through paired synovial zygapophysial joints, also known as z-joints, facet joints, and interlaminar joints. These joints play a crucial role in stabilizing the spine by regulating the movement between two adjacent vertebrae, but they also participate in absorbing force. Positioned bilaterally between the adjacent vertebrae are laterally oriented openings known as intervertebral foramina. These foramina are bordered by the bodies and pedicles of the adjacent vertebrae and the IVD and the zygapophysial joints that lie between them (Fig. 1). The intervertebral foramen functions as a canal through which the spinal nerves exit and the recurrent meningeal (sinuvertebral) nerve enters the vertebral canal. Additionally, this canal accommodates other structures such as lymphatic vessels,

arteries, and veins, all of which are surrounded by adipose tissue during passing the foramen.

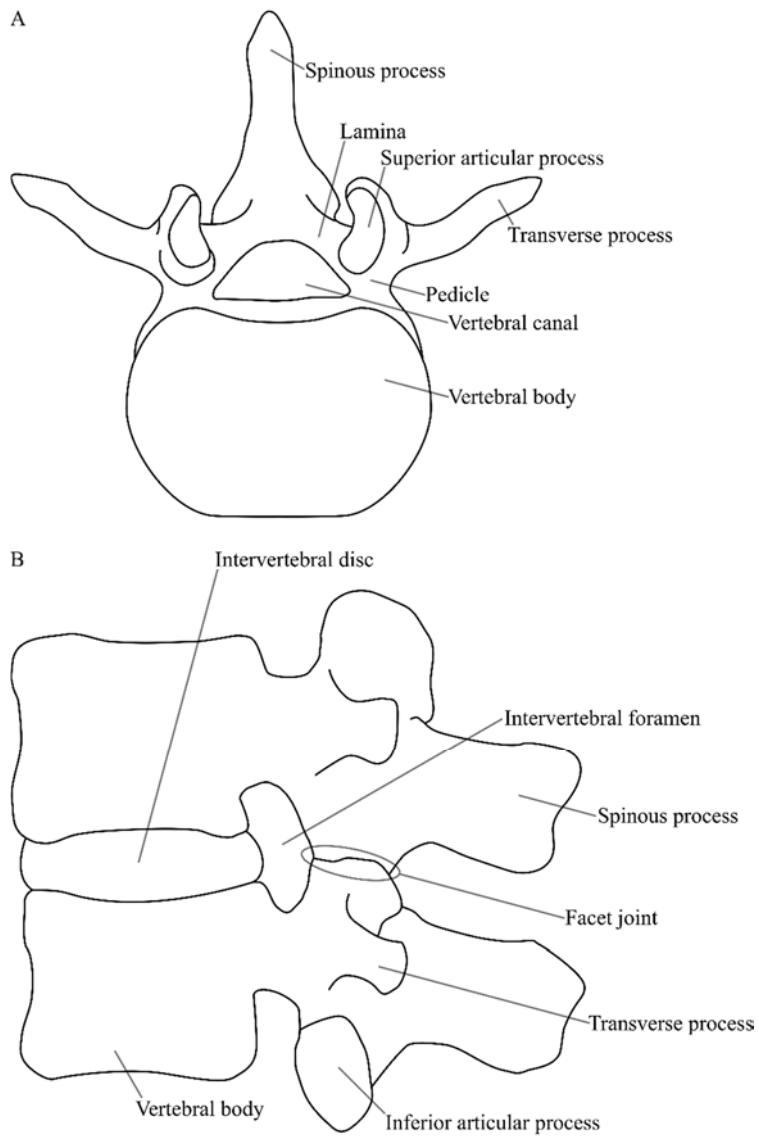


Fig. 1. Illustration of the lumbar spine anatomy, A showing a superior view and B showing a lateral view.

The anterior and posterior longitudinal ligaments attach to the anterior and posterior surfaces, respectively, of the adjacent lumbar vertebrae (Cramer & Darby, 2014). They are important in terms of connecting the vertebral body with the adjacent IVD, as well as providing stability and limiting the flexion and extension of the lumbar spine. The ligamentum flavum, found between the laminae of the adjacent vertebrae, consists of paired structures that are connected in the midline and form the anterior joint capsule of the zygapophysial joint laterally. The ligamentum flavum is composed of two layers and contributes, alongside adjacent ligaments and soft tissues, to the stabilization of the vertebral column. The interspinous ligament, which can be divided into anterior, middle, and posterior parts, extends between the spinous processes. Posterior to the spinous processes is the supraspinous ligament, which has been the subject of debate regarding its classification as a true ligament. Together with the interspinous ligament, they limit the end range of motion in lumbar flexion. Additionally, the intertransverse ligaments run bilaterally between the transverse processes, while the L5 vertebra's transverse processes gives rise to a pair of iliolumbar ligaments that extend to the sacrum and iliac crest.

The blood supply to the lumbar vertebrae is supplied by lumbar segmental arteries (Cramer & Darby, 2014). In addition to supplying periosteal arteries to nourish the vertebral body, the lumbar segmental arteries also give rise to spinal rami that traverse the intervertebral foramen. Upon passing through the foramen, each spinal ramus divides into three branches: the anterior, neural, and posterior branches. These branches supply blood to a variety of structures of the lumbar spine. However, IVDs are predominantly avascular, with the blood supply limited to their outermost regions (Raj, 2008). Consequently, they rely on diffusion from nearby blood vessels and adjacent vertebrae for their nutritional and metabolic needs. In terms of venous drainage, the lumbar spine is served by interconnected internal and external venous plexuses (Cramer & Darby, 2014; Stringer et al., 2012). The internal venous plexus is situated within the vertebral canal, while the external venous plexus surrounds the vertebrae and vertebral canal. These plexuses are responsible for draining venous blood from the lumbar region, and they also receive drainage from the basivertebral vein originating from the vertebral body.

The lumbar spine contains a pattern of overlapping innervation due to the involvement of multiple segments in innervating various structures (Bogduk, 1983; Bogduk et al., 1981; Cramer & Darby, 2014). The majority of structures in the lumbar spine receive innervation from the recurrent meningeal nerves or the

posterior rami. The former provides innervation to structures located anterior to the vertebral canal, such as the posterior aspect of the IVD and the posterior periosteum of the vertebral body. The latter, on the other hand, innervates the structures of the vertebral arch. The muscles of the lumbar spine, along with the transverse processes, receive innervation from the anterior rami. Uniting anterior rami of L1–L4 and L4–L5 segments also form nervous structures called the lumbar plexus and lumbosacral trunk, respectively. Lastly, certain nerves arise directly from the sympathetic trunk and gray ramus communicans, providing innervation to the lateral and anterior aspects of the IVD and the periosteum of the vertebral body.

2.2 Intervertebral disc and endplate

The primary role of IVDs is to facilitate the transmission of loading forces within the spinal column while allowing for multidirectional movement (Raj, 2008). Among the entire spinal column, the lumbar IVDs possess the largest surface area and are among the thickest to meet these requirements (Pooni et al., 1986). An IVD is composed of two primary components: the outer fibrous cartilage ring known as the annulus fibrosus (AF) and the gelatinous central portion called the nucleus pulposus (NP). The cartilaginous EPs separate the IVD from the adjacent vertebral bodies, both cranially and caudally (Fig. 2) (Raj, 2008).

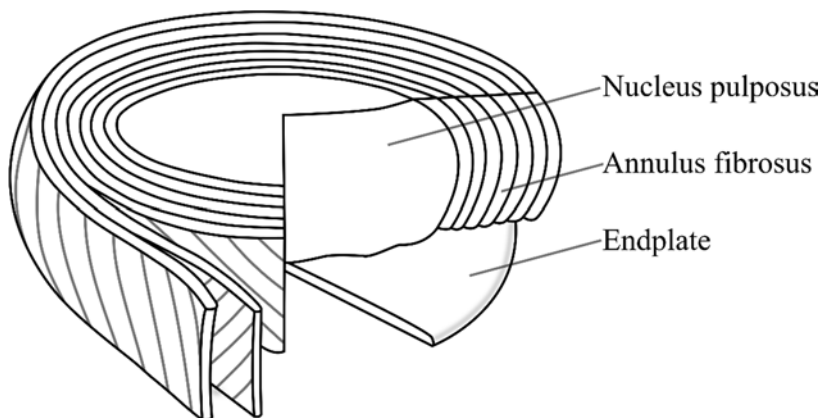


Fig. 2. Illustration of the two primary components of an intervertebral disc and the adjacent endplate. Cranial endplate removed.

2.2.1 Annulus fibrosus

The AF originates from cartilaginous EPs and encircles the NP (Humzah & Soames, 1988). It is composed of 15 to 25 sparsely interconnected fibrocartilaginous bands known as lamellae (Marchand & Ahmed, 1990; Schollum et al., 2008). Within the lamellae, the collagen fibers are parallel and have an oblique orientation of 50–60 degrees with their direction alternating between adjacent lamellae. This microstructural composition ensures resilience to both compressive and tensile loading. At a cellular level, collagen fibers are embedded in a well-hydrated proteoglycan matrix, with water forming 55–75% of its weight (Smith & Fazzalari, 2009). The main collagen types of the AF are type I and type II, with distinct distributions within the AF (Cassinelli et al., 2001; Eyre & Muir, 1976). Type I collagen is predominantly found in the outermost regions, while type II collagen is more prevalent in the inner portions of the AF. In a healthy IVD, innervation is limited into the most peripheral AF (Groh et al., 2021).

2.2.2 Nucleus pulposus

The NP is a hydrophilic structure positioned centrally within the IVD (Humzah & Soames, 1988). It exhibits an even higher level of hydration compared to the AF, with water comprising 70–90% of its weight (Inoue, 1981; Raj, 2008). The NP consists of collagen type II fibers arranged in a random orientation, as well as elastin fibers that are radially oriented. These fibers are embedded within a proteoglycan gelatinous matrix, which also contains a limited number of chondrocyte-like cells. The NP experiences swelling pressure, and its primary function is to distribute mechanical stresses generated by complex multidirectional movements to the adjacent EPs (Pattappa et al., 2012). Adams & Roughley (2006) described the NP and inner AF of a healthy IVD to function like a fluid, of which movement is restricted horizontally by the distal sections of the AF.

2.2.3 Endplate

EPs separate IVD and vertebral body, and their main functions are to prevent the adjacent NP from bulging to the vertebral body and distribute axial loading-caused hydrostatic pressure to the vertebra (Lotz et al., 2013; Moore, 2006). The

EPs are also the main route for transmission of essential molecules to the adjacent NP, and thus they balance between being strong enough to resist mechanical failure but porous enough to facilitate the molecule diffusion. EP is a bilayer structure consisting of an osseous and hyaline cartilage component, the latter of which is connected to the AF. The thickness of the bony and cartilaginous components somewhat varies; however, they have been estimated at 0.2–0.8 mm and 0.1–2.0 mm in thickness, respectively, thinning towards the central part. Along with vertebral vessels, the basivertebral nerve, which begins from the sinuvertebral nerve, extends from the central part of the vertebra terminating proximal to the cartilaginous EP (Lotz et al., 2013). The innervation density is comparable to that of the AF's (Bailey et al., 2011; Fagan et al., 2003).

2.3 Intervertebral disc degeneration

IVD degeneration, characterized by the loss of normal IVD tissue properties, can be influenced by various predisposing risk factors including age, smoking, high spinal loads, and genetic factors (Adams & Dolan, 2012; Adams & Roughley, 2006). However, it is important to note that the normal aging process itself leads to certain inevitable changes in the IVD, which include fibrotic transformation and reduced hydration of the NP due to the loss of proteoglycans, resulting in loss of IVD height (Buckwalter, 1995; Haefeli et al., 2006). Furthermore, with age, the collagen network within the IVD undergoes disruption and the cartilaginous components become stiffer and more vulnerable to injury, in addition to the EPs becoming thinner and calcified (Lotz et al., 2013; Singh et al., 2009). As a consequence, the IVD's ability to function in a fluid-like manner diminishes, and the AF may even bulge outwards as a result of abnormal force distribution (Adams & Dolan, 2012). Distinguishing these age-related changes from pathological degeneration can be challenging (Raj, 2008).

2.3.1 Pathogenesis

According to Adams & Roughley (2006), the degeneration of an IVD can be conceptualized as an accelerated aging process triggered by initial structural damage. Thus, they defined IVD degeneration as an “aberrant, cell-mediated response to progressive structural failure”. The authors stated that structural damage within the IVD creates regions of both low and high compressive stresses, which not only impede IVD cell metabolism and hinder the healing process but

also contribute to further deterioration. Consequently, a cycle of frustrated healing responses and repeated re-injury occurs, with the degenerated IVD itself synthesizing degradative enzymes and proinflammatory substances (Adams et al., 1996; Adams & Dolan, 2012; Adams & Roughley, 2006; Hughes et al., 2012). As a result, the degeneration process may cause diverse and co-occurring structural alterations in a lumbar segment, including changes in the NP, AF, EP, and vertebra (Table 1).

Table 1. The potential macro- and microscopic changes in a degenerated lumbar vertebral segment according to Vernon-Roberts & Pirie (1977) and Modic & Ross (2007).

Intervertebral disc	Vertebra	Soft tissues
Fissure, crack, and cleft formation in the NP, AF, and EP	Degenerative BM changes (Modic changes)	Loss of elastic properties, thickening, calcification, ossification of the spinal ligaments
Calcification and ossification in the NP, AF, and EP	Facet joint arthrosis and osteophytosis	
EP cartilage loss	Spondylolisthesis, instability	
IVD displacement	Vertebral osteophytosis	
Intradiscal gas	Spinal canal stenosis	
Neoinnervation	Thickening of the osseous EP	
IVD space height loss		
Signs of healing attempts: chondrocyte and granulation tissue generation and neovascularization		

NP = nucleus pulposus, AF = annulus fibrosus, EP = endplate, IVD = intervertebral disc, BM = bone marrow

Two distinct phenotypes of IVD degeneration have been proposed: endplate-driven and annulus-driven (Adams & Dolan, 2012). The endplate-driven phenotype is characterized by a damaged EP, circumferential tears in the AF, and medial bulging of the AF into the NP. According to this theory, the NP undergoes de-pressurization as a result of the damaged EP relocating into the adjacent vertebra. Consequently, the AF experiences abnormal stress forces and may collapse into the decompressed NP region. Indeed, age and degeneration of the adjacent IVD have been associated with thinning, increased porosity, and disrupted composition of the EP (Rodriguez et al., 2012). A portion of the NP may occasionally migrate vertically and calcify into the adjacent vertebrae, forming an

intravertebral IVD herniation, which is also known as a Schmorl's node (Fardon et al., 2014; Kyere et al., 2012). The endplate-driven phenotype of IVD degeneration is suggested to occur predominantly in the upper lumbar segments and at a younger age (Adams & Dolan, 2012). It is noteworthy that this cascade of events can be initiated even without any specific major traumatic incident, as it may arise from the accumulation of vertebral microdamage.

The annulus-driven phenotype is characterized by the presence of abnormal radial AF fissures that extend from the NP to the periphery of the IVD, predominantly observed in the posterior or posterolateral regions (Adams & Dolan, 2012). This phenotype is commonly observed in the lower lumbar segments, which are characterized by a relatively thin posterior AF and are subjected to high bending loads. It has been suggested that repetitive bending and lifting are associated with the initiation of this phenotype. These radial fissures, along with other differently oriented annular fissures, can be visualized in T2-weighted (T2w) MRI as areas of high intensity known as high-intensity zones (HIZs) (Aprill & Bogduk, 1992). In cases where the IVD tissue protrudes through the injured AF and exits the IVD space, a lumbar disc herniation (LDH) is formed (Fardon et al., 2014). LDHs can exhibit various shapes and reach various nearby structures. In addition to the NP tissue, herniated material may include annular, cartilaginous, and osseous components.

Nutritional factors have also been proposed to play a crucial role in IVD degeneration, as the IVD largely relies on diffusion and load-induced fluid movement through the EP for metabolite transport (Y.-J. Liu et al., 2009; Urban et al., 2004). Disruption of these processes, including events such as EP damage (EPD), EP calcification, or reduced vertebral perfusion, can potentially contribute to the progression of IVD degeneration (Fields et al., 2018). Additionally, genetic factors have been demonstrated to significantly influence IVD degeneration, with certain individuals suggested to exhibit a lower tolerance to loading and thus an increased risk for degenerative changes in the IVD (Battié et al., 2008; Roughley, 2004).

2.3.2 Clinical evaluation

The conventional methods of patient history assessment and physical examination may be inadequate in effectively determining whether a specific IVD is responsible for LBP (Hancock et al., 2007; Schwarzer et al., 1995). Among the various IVD-related MRI findings, some may increase or decrease the likelihood

of the IVD being the source of LBP. Thus, MRI, classically along with invasive discography, stands as one of the primary methods for the clinical evaluation of lumbar IVD degeneration, and the usage of these tools is discussed briefly below (Malik et al., 2013). Additionally, various other evaluation techniques have been utilized, although primarily in academic settings, including those based on gross morphology (J. P. Thompson et al., 1990) and histology (Le Maitre et al., 2021).

MRI

One of the frequently utilized macroscopic grading systems for IVD degeneration is the MRI-based scale developed by Pfirrmann et al. (2001). This scale involves assigning grades from one to five based on four key parameters evaluated within the IVD on T2w MRI sequences (Table 2). To assess the extent of EPD in MRI, the endplate score (EPS) can be employed, using a scale ranging from one to six (Rajasekaran et al., 2008). In this scoring system, grade I represents an intact EP, grade II indicates focal EP thinning, and grade III shows focal connections between IVD and BM. Grades IV and V assess EPD in relation to the width of the affected EP, with up to 25% and 50% damage, respectively. Grade VI corresponds to complete EP damage. Further, to evaluate a specific lumbar segment comprehensively, the total endplate score (TEPS) is calculated by combining the EPSs of the cranial and caudal EPs.

Table 2. The intervertebral disc degeneration grading scheme introduced by Pfirrmann et al. (2001).

Grade	Structure and color of the IVD	Distinction of NP and AF	Signal intensity of the IVD	IVD height
I	Homogenous, bright white	Clear	Hyperintense, isointense to CSF	Normal
II	Inhomogeneous with or without horizontal bands	Clear	Hyperintense, isointense to CSF	Normal
III	Inhomogeneous, gray	Unclear	Intermediate	Normal to slightly decreased
IV	Inhomogeneous, gray to black	Lost	Intermediate to hypointense	Normal to moderately decreased
V	Inhomogeneous, black	Lost	Hypointense	Collapsed

IVD = intervertebral disc, NP = nucleus pulposus, AF = annulus fibrosus, CSF = cerebrospinal fluid

Discography and discoblock

To ascertain the specific involvement of an individual IVD in LBP or to predict an IVD's responsiveness to treatment, diagnostic techniques aiming a singular IVD have been developed. Among these, provocative discography stands historically as the most extensively utilized approach (Aprill & Bogduk, 1992; Malik et al., 2013; McCormick et al., 2018). In provocative discography, the targeted IVD is subjected to contrast media injection into its central part under the guidance of fluoroscopy. The subsequent assessment involves evaluating the patient's pain response while considering parameters such as the volume and pressure of the injection and contrast distribution pattern.

Derived from discography, the discoblock technique serves a diagnostic purpose centered on the alleviation of LBP, in contrast to the provocative nature of discography (Derby et al., 2012; Ohtori et al., 2009; Putzier et al., 2013). Achieved through intradiscal administration of an anesthetic agent, discoblock may be performed alongside discography using a combination of a contrast media and local anesthetic, or it can be conducted independently by employing a pure anesthetic injectate. The test result is positive if the patient experiences a certain amount of relief to their LBP. The response to an anesthetic injection is typically assessed within a timeframe of 45 to 60 minutes, employing either a commonly used pain score or subjective measures as evaluative criteria. Given the absence of a standardized protocol for discoblock, the methodologies employed have demonstrated considerable diversity, as illustrated in Table 3. Overall, based on a very limited number of studies, discoblock may outperform discography in terms of identifying a symptomatic IVD and forecasting surgical outcomes (Manchikanti et al., 2018; Ohtori et al., 2009; Putzier et al., 2013).

Table 3. A review of the study settings and methods of discoblock in previous studies. (Reprinted [adapted] under CC BY 4.0 license from original publication II © 2022 Authors).

Authors, year	Study setting	Discoblock procedure	Positive discoblock cut-off value
Barendse et al., 2001	Patient selection	Combined discography and discoblock with a mixture of contrast medium and lidocaine	>50% LBP relief 30 minutes after the injection
Bartynski & Rothfus, 2007	Comparative	Combined discography and discoblock with a sequential lidocaine injection if positive discography	>66%, 33–66%, or <33% LBP reduction on a 0–10 VAS
DePalma et al., 2009	Comparative	Combined discography and discoblock with a sequential lidocaine injection via an intradiscal catheter if positive discography	≥50% LBP reduction on a 0–10 VAS at rest and during provocative maneuvers
Ohtori et al., 2009	Patient selection	Standalone discoblock with bupivacaine	Any pain relief
Derby et al., 2010	Comparative	Combined discography and discoblock with a mixture of contrast medium and either lidocaine or bupivacaine	≥2/10 LBP reduction on a 0–10 NRS in pain-provoking positions 15 or 45 minutes after the injection
Alamin et al., 2011	Comparative	Standalone discoblock with lidocaine via an intradiscal catheter	≥2/10 LBP reduction on a 0–10 VAS in pain-provoking position or activity 5–20 minutes after the injection
Derby et al., 2012	Comparative	Combined discography and discoblock, standalone discoblock and discoblock after discography with and without an intradiscal catheter	≥50% or ≥80% LBP relief
Fukui et al., 2013	Patient selection	Consecutive discography and discoblock with lidocaine	>70% LBP relief
Putzier et al., 2013	Comparative	Combined discography and discoblock with a mixture of contrast agent and	≥3/10 LBP reduction on a 0–10 NRS 60 minutes after the injection

Authors, year	Study setting	Discoblock procedure	Positive discoblock cut-off value
Staarfjes et al., 2018	Patient selection	bupivacaine Combined discography and discoblock with a sequential lidocaine injection if positive discography	≥50% LBP relief
J. Liu et al., 2020	Patient selection	Unspecified discoblock if positive discography	Reoccurring pain after discoblock
Nyström et al., 2023	Comparative	Consecutive discography and discoblock with lidocaine	≥30% LBP reduction on a 0–100 VAS during the 60-minute follow-up
G. Wang et al., 2023	Patient selection	Standalone discoblock with lidocaine	≥80% LBP relief

IVD = intervertebral disc, LBP = low back pain, VAS = Visual Analogue Scale, NRS = Numerical Rating Scale

2.3.3 Association with LBP

The terms “degenerative disc disease” and “discogenic LBP” are commonly used in clinical practice to describe the painful condition associated with IVD degeneration (Adams & Roughley, 2006; Fujii et al., 2019). Although lumbar IVD degeneration is a prevalent occurrence in patients without LBP (Brinjikji, Luetmer, et al., 2015; M. C. Jensen et al., 1994), it is important to highlight that lumbar IVD degeneration has been linked to LBP in a meta-analysis (Brinjikji, Diehn, et al., 2015) and various extensive studies (Cheung et al., 2009; de Schepper et al., 2010; Jamaludin et al., 2023; Teraguchi et al., 2014). Indeed, statistical estimations indicate that the IVD stands as the origin of chronic LBP in approximately 30–40% of cases (DePalma et al., 2011; Manchikanti et al., 2001; Schwarzer et al., 1995). There are several pathways through which IVD degeneration may contribute to the development of LBP. Firstly, EPD can directly stimulate the nerves within the EP, but also allow the release of physiologic metabolites and pathological substances from the adjacent IVD to irritate the nerves (Lotz et al., 2013). Secondly, the presence of neoinnervation in the deeper layers of the AF and the NP in degenerated IVDs, particularly when accompanied by radial fissures in the AF, may contribute to LBP (Bogduk et al., 2013; Freemont et al., 1997). Thirdly, the loss of IVD height associated with IVD degeneration can alter the load distribution within the segment, potentially subjecting the facet joints, ligaments, and muscles to abnormal stresses, leading to LBP (Hughes et al., 2012). Additionally, the reduction in IVD height can compress the exiting nerve root, which may already be irritated by the inflammatory molecules secreted by the IVD, resulting in pain in the buttock and lower limb region.

2.3.4 The role of operative treatments

Surgical intervention for degenerative disc disease is often regarded as a definitive treatment and may be warranted when conservative treatment modalities fail (Fujii et al., 2019; Romaniyanto et al., 2022). Among the most commonly employed surgical techniques are lumbar fusion and total disc replacement (TDR). Additionally, lumbar discectomy is frequently utilized for the surgical management of LDH (Blamoutier, 2013).

Lumbar fusion

In essence, lumbar fusion is intended to address LBP attributed to abnormal motion or mechanical instability resulting from degenerative changes (Hanley, 1995). Although the literature on the utilization of lumbar fusion for degenerative disc disease is constantly evolving, further evidence is necessary to define precise indications for the procedure and reduce variability in outcomes (Reid et al., 2019). While degenerative disc disease alone has been suggested as an indication, associated clinical conditions such as instability, spinal stenosis, and recurrent LDH (rLDH) may also justify consideration. A meta-analysis of randomized controlled trials (RCTs) on chronic LBP without spinal stenosis or spondylolisthesis indicated that fusion is marginally more effective than non-operative care in reducing disability and LBP, though it carries an increased risk of non-union, estimated at approximately 13% (Yavin et al., 2017). The weighted mean difference (MD) values were 5.1, 95% confidence intervals (CI) 0.19–10.1 for the Oswestry Disability Index (ODI) and 1.1, 95% CI 0.09–2.0 for LBP on the Visual Analogue Scale (VAS, 0–10). The strongest evidence favoring lumbar fusion over non-operative care was observed for spondylolisthesis. However, the clinical applicability of these findings is limited due to significant between-study heterogeneity, high crossover rates, and the inclusion of only primary surgeries. Furthermore, an earlier review reported moderate-level evidence suggesting that fusion is comparable to intensive rehabilitation with a cognitive component for managing chronic non-radicular LBP (Chou et al., 2009).

There is limited evidence supporting the use of preoperative tests for patient selection in lumbar fusion surgery (Reid et al., 2019). According to a systematic review by Willems et al. (2013), none of the evaluated preoperative tests—including thoracolumbar orthosis, provocative discography, or temporary external transpedicular fixation—demonstrated predictive validity for mid- to long-term lumbar fusion outcomes at a level sufficient for clinical application. However, single studies suggest that discoblock (Ohtori et al., 2009) and the pantaloon cast test (Staartjes et al., 2018) may serve as useful predictive tools for patients without prior spinal surgery. Among demographic and clinical factors, higher preoperative leg pain levels and preoperative employment status have been associated with better postoperative leg pain and disability outcomes, respectively, albeit with low certainty (Achttien et al., 2022).

Total disc replacement

TDR is a more recent surgical approach for treating degenerative disc disease, in which the IVD is replaced with an artificial disc prosthesis (Büttner-Janz et al., 2014; Jacobs et al., 2013). The proposed benefit of TDR compared to fusion is its ability to preserve motion at the operated level, potentially mitigating the risk of accelerated degeneration in adjacent segments. However, this potential benefit could come at the cost of increased facet joint loading and subsequent degeneration at the treated level. Long-term studies suggest that the efficacy of TDR is at least comparable to fusion; however, additional research is needed to determine whether TDR is clinically superior to fusion surgery (Wen et al., 2024). A review study with substantial data heterogeneity suggested no significant differences in complication or reoperation rates between TDR and fusion procedures (Formica et al., 2017).

According to a review by Büttner-Janz et al. (2014), discography may be employed to preoperatively confirm the painfulness of the targeted IVD, while facet joint anesthetic injections may help rule out pain originating from the facet joints. Furthermore, imaging is critical for excluding other potential causes of LBP. However, existing literature on the predictive value of preoperative imaging findings remains limited and inconsistent (Büttner-Janz et al., 2014).

Lumbar discectomy

Lumbar discectomy is a surgical procedure performed to address pain caused by LDH, a condition characterized by chemical and mechanical irritation of the nerve root (Deyo & Mirza, 2016). The primary symptom is typically radiating leg pain below the knee level, although LBP may also be present. Modern discectomy techniques include microdiscectomy and minimally invasive approaches, the former having largely replaced traditional open discectomy. In general, apart from emergencies, discectomy is indicated after six weeks of conservative therapy in patients with symptoms consistent with imaging findings. According to a systematic review, which provided low to very low strength of evidence, lumbar discectomy offers significant reductions in pain outcomes compared to conservative treatment for up to one year, after which the difference between operatively and conservatively treated patient groups diminishes (Clark et al., 2020). Disability outcomes show a similar trend, albeit with smaller differences between groups.

A systematic review of preoperative predictors for lumbar discectomy outcomes of at least one year revealed that certain demographic and clinical factors may influence outcomes, including age, mental health status, and the duration and severity of symptoms. Among radiological parameters, only the status of the AF was associated with poorer outcomes (Wilson et al., 2016). Specifically, high-level evidence indicated that an intact AF is a negative predictor, while low-to-moderate-level evidence suggested that a defected or ruptured AF is also a negative predictor. IVD degenerative features, evaluated in three included studies, showed no predictive value. Subsequent studies have reported inconsistent predictive values for preoperative IVD-related degenerative features on lumbar discectomy outcomes (Z. Y. Feng et al., 2021; Kumarasamy et al., 2022; Udby et al., 2020).

2.4 Modic changes

2.4.1 History and definition

Modic changes (MC) refer to alterations in the MRI signal of the vertebral BM, observed adjacent to the EP throughout the spinal column, with a predominant occurrence in the lumbar spine (Dudli, Fields, et al., 2016; Zhang et al., 2008). To differentiate MC from infectious and malignant lesions, de Roos et al. first reported abnormal BM lesions in 1987. They observed three distinct imaging patterns associated with these lesions. Subsequently, Modic, Masaryk, et al. (1988) and Modic, Steinberg, et al. (1988) classified the signal alterations into types I-III (MC1-3) based on their appearance on T1-weighted (T1w) and T2w MRI sequences, as illustrated in Table 4.

Table 4. The classification of Modic changes according to Modic, Steinberg, et al. (1988) and Modic, Masaryk, et al. (1988), and corresponding histopathology as reported by Modic, Steinberg, et al. (1988) and Perilli et al. (2015).

MC type	T1w MRI	T2w MRI	Histopathology
I	Hyposignal	Hypersignal	Oedema and inflammation in BM
II	Hypersignal	Iso- or hypersignal	Yellow fatty changes in BM
III	Hyposignal	Hyposignal	Subchondral bony sclerosis

MC = Modic changes, T1w = T1-weighted, MRI = magnetic resonance imaging, T2w = T2-weighted, BM = bone marrow

An initial histological study was conducted by Modic, Steinberg, et al. (1988) on MC1 and MC2. MC1 was correlated with EP disruption and fissuring, enhanced bone turnover and adjacent BM replacement by vascularized fibrous tissue, while MC2 showed a similar EP disruption with adjacent BM replaced by fat tissue. MC3 were assumed, without a histological analysis, to correlate with extensive bone sclerosis. This assumption was later confirmed by Perilli et al. (2015) along with reporting a consistently high bone turnover rate for MC1 and reduced bone activity for MC2.

Different MC types can co-exist in the same lesion, whereby the lesion is commonly termed MC1/2, MC2/3, or MC1/3 (Braithwaite et al., 1998; Järvinen et al., 2015; Kuisma et al., 2006). As MC have the capability to convert into different types, they are presumed to be a dynamic pathological process, in which different types represent different phases of pathology (Hutton et al., 2011; Marshman et al., 2007; Modic, Steinberg, et al., 1988). MC1 typically progress to MC2 but may also reverse from MC2 to MC1 or disappear entirely as MC1. MC1 are traditionally interpreted as the most active of the MC types, while MC2 seem to have a more stable nature (Hutton et al., 2011; T. S. Jensen et al., 2009; Modic, Steinberg, et al., 1988; Perilli et al., 2015). MC3 are rare (T. S. Jensen et al., 2008).

2.4.2 Diagnostics

Classification

There was no consensus on the reporting of MC for several years since the introduction of the lesions. Consequently, individual studies assessing MC have used diverse methodologies. For example, MC have been analyzed binarily based on their existence (Kjaer, Leboeuf-Yde, Korsholm, et al., 2005), while some have used a thorough original classification (Albert & Manniche, 2007), of which others have ignored MC3 (Peterson et al., 2014). The extensivity and location of MC have also been considered in various degrees (Arana et al., 2011; Kuisma et al., 2006; Määttä, Karppinen, et al., 2015; Weishaupt et al., 2001). Moreover, mixed MC have been analyzed separately (Saukkonen et al., 2020), combined into other groups (Määttä et al., 2016) or by estimating the relative extensivity of each MC type (Järvinen et al., 2015). The classification of borderline mixed MC has also varied (Bråten et al., 2019; Udby, Samartzis, et al., 2022). Furthermore, some have ignored small-scale signal alterations (Määttä, Karppinen, et al., 2015), while others have interpreted them as MC (T. S. Jensen et al., 2007). The strength of the MC signal intensity relative to the intensity of the adjacent cerebrospinal fluid has also been measured in the pursuit of assessing MC severity (Y. Wang et al., 2011).

To overcome the issue of radiological diagnostic inconsistency, The Nordic Modic Consensus Group aimed to distinguish clinically relevant and irrelevant BM signal changes (T. S. Jensen et al., 2007). The group developed a detailed and systematic protocol for reporting such changes, the Nordic Modic Classification. The protocol separately measures each lumbar segment, and regarding MC the scheme considers type, volume and location, height in sagittal plane, and the area of the EP's affected part. In the case of mixed MC, the most extensive type is considered the primary lesion. At the time of introduction, the consensus group proved the classification to be reproducible in assessing MC. Afterwards, independent studies have utilized the protocol with substantial to almost perfect intra- (Arana et al., 2010; Kovacs et al., 2009) and moderate to almost perfect interobserver (Arana et al., 2010; Kovacs et al., 2009; Sørliie et al., 2012) reliabilities, as per Landis & Koch (1977).

The most recent attribution to the MC classification is the introduction of the clinical grading by Udby, Samartzis, et al. (2022). The grading protocol considers the type of MC, and when mixed MC are present, the type with the lowest

classification number is searched, based on which the entire lesion is typed. That is, MC1 is preferred over MC2, MC3 being the least clinically important. Additionally, the height of the MC is measured and graded as A, B or C, per the lesion affecting less than 25%, from 25% to 50% or over 50%, respectively, of the height of the affected vertebra. Thus, each MC lesion is typed and graded. The protocol has been shown to have a clinical correlation to the population of LDH patients selected to undergo elective discectomy (Udby, Modic, et al., 2022) and has yielded substantial intra-observer (Udby, Modic, et al., 2022) and substantial to moderate inter-observer reliability (Sherwood et al., 2022; Udby, Modic, et al., 2022), as interpreted by Landis & Koch (1977).

Novel advances in MRI techniques have led to more precise and versatile explorations of MC and nearby related structures (Fields et al., 2019). For example, chemical shift encoding-based MRI may offer explicit differentiation in mixed MC (Karampinos et al., 2014), diffusion-weighted MRI (DW-MRI) may enhance differential diagnostic capabilities (Patel et al., 2014), as discussed in the following paragraph, and ultra-short echo time sequences may yield sharper visualization of the affected structures (Law et al., 2013). Recently, fat-suppressed MRI sequences have been utilized in MC diagnostics (Z. Feng et al., 2016; Kristoffersen et al., 2021). To allow comparison between studies, the MRI equipment, sequences, and parameters are encouraged to be explicitly reported, as even with conventional MRI equipment, the utilized parameters may affect the diagnostics of MC (Bendix et al., 2012; Fields et al., 2019).

Differential diagnosis

Distinguishing MC from an infection may pose a significant diagnostic challenge as MC1 can appear identical to spondylodiscitis, especially in cases lacking distinctive destructive changes of the infection (Schwarz-Nemec et al., 2020; Viswanathan et al., 2020). To aid in distinguishing these conditions, attention has been directed towards the appearance of the EP (Schwarz-Nemec et al., 2020). In T1w MRI sequences, the presence of an irregular yet intact EP has been associated with MC1, whereas the appearance of a blurred EP is indicative of either an early or advanced infection. Previous research has also highlighted the utility of DW-MRI in discerning between infections and MC1. According to Oztekin et al. (2010), both the EP and vertebral BM appear hypo- or isointense with MC1 on DW-MRI, while spondylodiscitis exhibits hyperintensity relative to normal vertebrae. Patel et al. (2014) introduced the concept of a “claw sign”,

which refers to a distinct linear region of hypersignal on DW-MRI situated within the vertebra between the normally perfused and abnormal BM, serving as a highly suggestive indicator of a non-infectious etiology. In addition to employing additional imaging modalities and contrast-enhanced MRI, repeated MRI scans at short intervals to elucidate the rapidly progressive nature of an infection may be necessary on certain occasions (Crockett et al., 2017; Viswanathan et al., 2020).

Another pertinent differential diagnosis for MC is spondyloarthritis (SpA), as these conditions may exhibit similar features in MRI (Canella et al., 2013; Viswanathan et al., 2020). To distinguish between these two entities, a comprehensive clinical approach, including laboratory tests and clinical findings, may be necessary. Supporting this notion, a study involving chronic LBP patients without a history of SpA found that widely accepted criteria for SpA diagnoses were never met, irrespective of the presence or absence of MC1 (Nguyen et al., 2010). Furthermore, similar to its utility in distinguishing spondylodiscitis from MC1, DW-MRI has been proposed as a valuable tool for discriminating between MC1 and SpA (Dallaudière et al., 2014).

2.4.3 Prevalence, incidence, and manifestation

Studies have reported a wide range of MC prevalence rates in adult non-clinical patient samples as the per-patient prevalence has ranged from 0.7% (Takatalo et al., 2012) to 87.5% (Kovacs et al., 2012). An overview of the largest population-based studies is shown in Table 5. Presumably, the variability is on account of differences in the study populations and methods across the studies (Zhang et al., 2008). MC2 has usually prevailed in population-based samples (Table 5). The majority of the lesions appear in the most caudal lumbar segments with the L5/S1 segment being the most common (T. S. Jensen et al., 2009; Mok et al., 2016; Saukkonen et al., 2020; Y. Wang et al., 2012). The extent of the lesion seems to positively correlate with its stability (R. K. Jensen, Leboeuf-Yde, Wedderkopp, Sorensen, Jensen, et al., 2012; T. S. Jensen et al., 2009).

The prevalence of MC is higher among LBP patients. A review study reported the median prevalence of MC in patients with and without non-specific LBP as 43% and 6%, respectively (T. S. Jensen et al., 2008). The same phenomenon is noted in adolescents; the prevalence rate increased from 0.5% (Kjaer, Leboeuf-Yde, Sorensen, et al., 2005) to 14.0% (Mallow et al., 2022) when observing population-based and LBP patient samples, respectively. Likewise in non-clinical samples, high variations in the MC prevalence rate are also observed among LBP

patients, from less than 10% (O'Neill et al., 2008) to over 80% (Arana et al., 2011). The prevalence of MC in selected large-scale clinical LBP patient samples is shown in Table 6. Generally, MC2 has been the most common type, the most characteristic location being the L5/S1 segment (Arana et al., 2011; O. K. Jensen et al., 2015; Modic, Steinberg, et al., 1988). Yet some studies have proved MC1 to be the most prevalent among LBP populations (Albert et al., 2011; K. J. Thompson et al., 2009; Udby et al., 2019; Weishaupt et al., 2001).

Table 5. An overview of the findings of large-scale non-clinical studies assessing Modic changes.

Authors, year	Study sample (country)	Mean age/male-%	LBP status	Overall prevalence of MC			Dominant MC type
				Of subjects	Of segments	Of EPs	
Kjaer, Leboeuf-Yde, Korsholm, et al., 2005	412 40-year-old subjects living in Funen (Denmark)	N.S./48.3%	42% having had trouble with lower back during the past month	22.3%	-	-	MC1: 70.5%
Y. Wang et al., 2012	561 subjects from the Twin Spine Study Cohort (Finland)	49.8 years/100.0%	N.S.	55.6%	-	13.5%	MC2: 64.2%
Määttä, Wadge, et al., 2015	823 subjects from the TwinsUK register (the United Kingdom)	54.0 years/4.3%	22.4% with a disabling LBP episode lasting >1 month during lifetime	32.2%	-	-	N.S.
Mok et al., 2016	2449 subjects from the Hong Kong Disc Degeneration Cohort (China)	40.4 years/N.S.	80.0% with a lifetime history of LBP period of ≥2 weeks	5.8%	1.4%	-	N.S.
Mera et al., 2021	814 subjects from the Wakayama Spine Study (Japan)	63.6 years/30.2%	31.3% with LBP on most days during the last month and during the assessment point	63.5%	-	-	MC2: 66.3%
Saukkonen et al., 2020	1512 subjects from the Northern Finland Birth Cohort 1966 (Finland)	47 years/47.0%	29.1% with >30 LBP days during the past 12 months	-	-	20.7%	MC2: 68.0%

Authors, year	Study sample (country)	Mean age/male-%	LBP status	Overall prevalence of MC		Dominant MC type
				Of subjects	Of segments	
Wu et al., 2020	644 subjects from the Hangzhou Lumbar Spine Study (China)	52.6 years/44.1%	N.S.	44.7%	-	MC2: 75.9%
Kasch et al., 2022	2415 subjects living in West Pomerania (Germany)	53.0 years/49.0%	59.5% of subjects having had LBP during the past 3 months with a mean severity of VAS 4.1 (0–10)	16.4%	-	MC2: 65.6%

N.S. = not specified, MC = Modic changes, MC1 = Modic changes type I, MC2 = Modic changes type II, MC3 = Modic changes type III, LBP = low back pain, EP = endplate

Table 6. An overview of the findings of large-scale clinical studies assessing Modic changes.

Authors, year	Study sample (country)	Mean age/male-%	LBP status	Overall prevalence of MC		Dominant MC type
				Of subjects	Of segments	
Modic, Steinberg, et al., 1988	474 subjects referred to lumbar MRI usually because of LBP or sciatica (The United States)	N.S.	N.S.	20.4%	5.8%	MC2: 85.4%
K. J. Thompson et al., 2009	736 subjects who underwent lumbar discography usually as candidates for surgical procedures (the United States)	43/N.S.	N.S.	-	12.7%	MC1: 51.3%
Albert et al., 2011	4233 subjects who seek care for LBP in a Danish secondary level spine center (Denmark)	N.S./48.9%	N.S.	27.4%	-	MC1: 60.0%
Arana et al., 2011	487 subjects with LBP lasting ≥ 3 months undergoing lumbar MRI (Spain)	43.4/46.0%	Median of VAS 5 (0–10) LBP for a median duration of 14 months	80.9%	-	MC2: 63.5%
Sheng-yun et al., 2014	Subset of a study population; 1223 subjects who sought care for LBP or sciatica (China)	45.3 years/53.1%	N.S.	21.0%	-	MC2: 81.7%

Authors, year	Study sample (country)	Mean age/male-%	LBP status	Overall prevalence of MC			Dominant MC type
				Of subjects	Of segments	Of EPs	
Hayashi et al., 2015	450 subjects with LBP (the United States)	44.6 years/59.3%	N.S.	28.7%	7.3%	-	MC2: 70.1%
Martínez-Quiriones et al., 2017	450 subjects who sought care for LBP or sciatica (Spain)	30.5 years/68.7%	N.S.	13.1%	-	-	MC1: 62.0%
Tarukado et al., 2017	585 subjects who underwent lumbar MRI due to LBP and/or sciatica (Japan)	65 years/50.4%	N.S.	36.0%	6.2%	-	MC2: 81.3%
Rajasekaran et al., 2024	1085 subjects with LBP lasting ≥3 weeks (India)	47.3 years/57.1%	N.S.	41.3%	-	12.9%	MC2: 87.1%

MRI = magnetic resonance imaging, LBP = low back pain, N.S. = not specified, MC = Modic changes, MC1 = Modic changes type I, MC2 = Modic changes type II, MC3 = Modic changes type III, EP = endplate

At a single vertebral segment, MC usually affect both the cranial and caudal EPs, whereupon both commonly express the same MC type (Kuisma et al., 2006; Luoma et al., 2008; Martínez-Quiñones et al., 2017; Y. Wang et al., 2012). In addition to MC being smaller, such a reflective pattern is not equally frequent at upper lumbar segments, however (Arana et al., 2011; L. Chen et al., 2018; O. K. Jensen et al., 2014; T. S. Jensen et al., 2009; Kuisma et al., 2006; Määttä, Karppinen, et al., 2015). The MC sizes vary, likely mirroring the differences in study populations. Some studies have reported MC to generally extend to the whole antero-posterior dimension of the affected vertebra (Kuisma et al., 2006; Y. Wang et al., 2012), while some have reported predominance for small-scale MC (Määttä, Karppinen, et al., 2015; Saukkonen et al., 2020). MC1 have been suggested to be usually larger and higher in the sagittal plane (L. Chen et al., 2018; Luoma et al., 2008; Saukkonen et al., 2020) and more extensive in the horizontal plane (Määttä, Karppinen, et al., 2015; Saukkonen et al., 2020) than other MC types.

Knowledge of the incidence of MC is scarce. Two previous studies have effectively calculated the incidence rate of MC in non-clinical study samples. The per-patient rates were 21.6% and 37.0% over a ten- and three-year periods, respectively (Määttä et al., 2014; Tamai et al., 2022). It is disputed whether new MC tend to appear in the upper (Tamai et al., 2022) or lower (Kuisma et al., 2006; Määttä et al., 2014; Teichtahl et al., 2017) lumbar spine and whether new lesions are predominantly MC1 (T. S. Jensen et al., 2010; Kuisma et al., 2006; Luoma et al., 2008) or MC2 (Tamai et al., 2022; Teichtahl et al., 2017).

2.4.4 Association with patient-related factors

Several studies have assessed patient-related factors linked with MC. Most studies agree on the association between higher age and MC prevalence, whereas the roles of sex, body mass index (BMI), smoking and physical activity are less studied or debated (Table 7). In longitudinal studies, higher age and BMI (Tamai et al., 2022) and the appearance of MC at upper lumbar levels (Määttä et al., 2014) have been suggested as factors increasing the activity of MC. On the other hand, two other studies found no predicting factors amongst lifestyle and occupational factors (Farshad-Amacker et al., 2014; Kuisma et al., 2006), and a third study reported only IVD degeneration and displacement to predict the emergence of new MC in a follow-up period of four years (T. S. Jensen et al., 2010).

Table 7. The reported positive (+) and negative (-) associations between Modic changes and patient-related factors.

Authors, year	Study population	Age	Sex	BMI	Smoking	Heavy physical demands
Kjaer et al., 2006	General				+	+
T. S. Jensen et al., 2008	General and clinical (review study)	+	-			
Albert et al., 2011	Clinical		-			
Arana et al., 2011	Clinical	-	+	+	-	-
Y. Wang et al., 2012	General	+				
Sheng-yun et al., 2014	Clinical	+				
Hayashi et al., 2015	Clinical	+				
Määttä, Wadge, et al., 2015	General	+	+/- ¹	+	-	
Mok et al., 2016	General	+	-	+	+	+
Martínez-Quiñones et al., 2017	Clinical	+	-			
Tarukado et al., 2017	Clinical	-	+			
Saukkonen et al., 2020	General		+	+	-	
Wu et al., 2020	General	+	-	+	+	+

¹ Only at the follow-up time point, BMI = body mass index

2.4.5 Pathogenesis

It is theorized that the development of MC is in conjunction with changes in the adjacent IVD (Dudli et al., 2017). However, the exact pathophysiology behind the emergence of MC is unknown, although a few leading theories exist (Dudli, Fields, et al., 2016; Viswanathan et al., 2020). These include biomechanical, inflammatory, infectious, and genetic hypotheses, which will be discussed below. In fact, it is assumed that the different etiological pathways may occur sequentially leading to a multifactorial pathogenesis (Crockett et al., 2017; Dudli, Fields, et al., 2016). The development of MC also depends on individual factors, which can be separated into three categories: structural disarrangement state of the IVD and vertebra, the capacity of the IVD to produce inflammatory stimuli and the potential of the adjacent vertebral BM to respond to these stimuli (Dudli, Fields, et al., 2016). Of note, similar BM lesions can be diagnosed in knee

osteoarthritis sharing several key characteristics with MC from shared risk factors to the dynamicity of the lesion (Dudli, Fields, et al., 2016).

Biomechanical and structural aspects

Although MC and IVD degeneration constantly co-locate, IVD degeneration alone is not capable of inducing MC (Kjaer et al., 2006; Modic, Steinberg, et al., 1988). Thus, it is postulated that further IVD damage in terms of LDH or EPD is more crucial for MC (Dudli, Fields, et al., 2016). This theory is supported by the facts that LDH and EPD co-locate with MC (Albert et al., 2011; Farshad-Amacker et al., 2017; Määttä et al., 2018) and are also significant risk factors for future MC (T. S. Jensen et al., 2010; Weiner et al., 2015). Extracted material from herniated IVDs with adjacent MC have been proven to contain significantly more cartilaginous material than from herniated segments without MC, which further emphasizes the role of EPD in MC (Z. Y. Feng et al., 2021; Shan et al., 2014). EP associated with MC also contains a higher density of nerve fibers compared to non-MC segments, possibly further indicating the importance of EPs (Ohtori et al., 2006). Ultimately, as previously described, several histological studies have connected MC to EP disruption (Heggli et al., 2023; Modic, Steinberg, et al., 1988; Perilli et al., 2015). Indeed, EP is seen as the weakest structure of a lumbar segment under loading forces, and it may be damaged either by a traumatic event or accumulating microdamage (Adams et al., 2000; Adams & Dolan, 2012; Adams & Roughley, 2006).

EPD exposes the adjacent IVD to deterioration via several pathways, including alterations in the biomechanical, nutritional, and structural properties (Rajasekaran et al., 2008). In the structural aspect, IVD and vertebra may become hydraulically coupled, allowing enhanced exchange of molecules (Ferguson et al., 2004; Rajasekaran et al., 2004). In contrast to acute EPD, whereby the BM lesion is short-lived, the chronic nature of MC is hypothesized to result from a persistent inflammatory stimulus in the vertebra (Dudli, Fields, et al., 2016; Rajasekaran, Soundararajan, et al., 2022). Such a stimulus may originate from autoimmune or infectious processes in the vertebral segment, whereby IVD-secreted substances have been suggested to be important. Due to the persistent stimulus, the healing process becomes ineffective, resulting in the phenotype seen in MC1: inflammation, fibrosis, and high bone turnover (Albert et al., 2008; Dudli et al., 2017; Dudli, Fields, et al., 2016).

Segmental instability may also induce MC as some evidence suggests that spondylolisthesis is associated with MC (Arana et al., 2011; Hayashi et al., 2015; K. J. Thompson et al., 2009). As with EPD (Adams et al., 1996, 2000), such instability may cause alterations in the load distribution patterns, and ultimately induce MC through structural deterioration. According to some evidence, MC1 disappear or transform into MC2 in 52.4–100.0% of patients undergoing lumbar fusion surgery (Ohtori et al., 2010; Vital et al., 2003). This phenomenon is hypothesized to result from the stabilization effect of the surgery.

Inflammatory and autoimmune aspects

In the 1970s and 1980s, Crock (1970, 1986) introduced the concept of “internal disc disruption”, which postulates that the NP secretes inflammatory substances in response to repeated trauma to the IVD. This secretion, when localized through the EP, could initiate a local inflammatory reaction leading to LBP. Expanding upon this theory, Braithwaite et al. (1998) suggested that in specific instances, MC could be attributed to the presence of these inflammatory substances in the vertebral BM. Consequently, MC may be considered a secondary MRI-detected manifestation of internal disc disruption.

NP, surrounded by AF and EPs, is isolated from the immune system (Sun et al., 2020). If NP comes into contact with the immune system, it can trigger an autoimmune response. This phenomenon has been proposed as an important mechanism in the formation of MC (Ma et al., 2011). It is hypothesized that the NP tissue may migrate into the adjacent BM through disrupted EP, leading to an inflammatory autoimmune reaction in the BM. Dudli et al. (2018) conducted in vitro and in vivo experiments using a rat tail model to test this hypothesis. They demonstrated that an inflammatory response between IVD and BM cells could only be triggered in a proinflammatory environment created by interleukin supplementation. Similarly, in vivo MRI changes resembling MC1 were observed in rat tail vertebrae after intra-vertebral implantation of an IVD surrogate, but only when the surrogate was pretreated with proinflammatory lipopolysaccharide. The authors reached the conclusion that, alongside EP defects, the existence of a proinflammatory “MC disc” is a prerequisite for MC development via the autoimmune pathway. It was postulated that the “MC disc” might be attributed to the secretion of proinflammatory substances by a degenerated IVD.

Infectious aspect

Albert et al. (2008) suggested that MC are caused by low-virulent anaerobic bacteria, for which avascular IVD could provide an ideal environment to grow (Urquhart et al., 2015). A subsequent, slowly developing infection may be caused, resulting in local inflammation and the expression of cytokines and bacterial toxins, which induce edematous changes in the BM seen as MC1 in MRI (Albert et al., 2008). The exact mechanism for the possible bacterial invasion into the IVD is unknown, although LDH has been proposed to be a precondition. Firstly, the bacteria may invade the circulatory system through damaged skin or mucosa, or a distant septic focus may be already present. Following LDH, neovascularization occurs at the site of damaged AF, through which the bacteria may proceed to the NP (Albert et al., 2008; Arndt et al., 2012; Z. Chen, Cao, et al., 2016). An alternative route for bacterial relocation into the NP is inside macrophages; hypothetically, macrophages could capture these bacteria in the circulatory system, transport them into the NP and following the death of the macrophage, operational bacteria are released (Z. Chen, Cao, et al., 2016). Additionally, impaired defense and elimination mechanisms of bacteria due to IVD degeneration and bacterial colonization during invasive spinal procedures have been suggested (Z. Chen, Cao, et al., 2016; Fritzell et al., 2004).

Propionibacterium acnes (*P. acnes*), an important opportunistic anaerobic human normal flora bacterium, has been proven to be one of the most common bacteria present in the IVD (Perry & Lambert, 2011; Urquhart et al., 2015). In favor of the suggested bacterial etiology of MC, a study reported that 80.0% and 41.7% of the patients with and without anaerobic bacteria in the extracted LDH material, respectively, developed new MC in the lumbar segment in question (Albert, Lambert, et al., 2013). Moreover, findings resembling MC1 have been observed in rats and rabbits after intradiscal injection of *P. acnes* harvested from symptomatic patients with MC (Z. Chen, Zheng, et al., 2016; Dudli, Liebenberg, et al., 2016). Interestingly, previous studies have reported elevated C-reactive protein (CRP) levels in blood and in the MC-harboring BM of patients with MC1 (Dudli et al., 2023; Rannou et al., 2007).

Without confirming the presence of an actual infection, two RCTs explored the effect of amoxicillin (one with and the other without clavulanic acid) versus a placebo on LBP and the related disability of chronic LBP patients with MC on a lumbar segment with a previous LDH (Albert, Sorensen, et al., 2013; Bråten et al., 2019). Although the studies yielded some evidence on the superiority of

antibiotics compared to the placebo in patients with MC1, the results were inconclusive; for example, the possibility of bacterial contamination during previous spinal interventions has been questioned (Dean, 2013; Gilligan et al., 2021).

Rigal et al. (2016) assessed 385 IVD biopsies taken from 313 patients during video-assisted anteriorly approached lumbar IVD surgery. Although 361 (93.8%) of the biopsy sites were accompanied by MC, only six (1.6%) samples showed bacterial growth after culturing. A previous study reported a similar unrelatedness between MC and the presence of bacteria in anteriorly obtained IVD biopsies, albeit nearly half of the 83 IVD samples contained bacteria (Arndt et al., 2012). Similarly, Wedderkopp et al. (2009) showed no evidence for bacterial infection in relation to MC as they obtained osseous biopsies from MC1 lesions from 24 consecutive patients and reported only two positive cultures, both of which were deemed to be due to contamination.

In a recent Swedish multicenter study, bacterial samples were collected from the skin, subcutaneous tissue, vertebra and IVD from surgically operated LDH patients, and young scoliosis patients serving as a control (Fritzell et al., 2019). They reported that, in both groups, bacterial growth in the vertebra or IVD was nearly always accompanied by bacterial growth in the adjacent skin or subcutaneous tissue, indicating contamination. The MC and bacterial findings did not correlate. Conclusively, a recent meta-analysis indicated no correlation between the bacterial status of IVD and the presence of MC1 or MC2 (X. Chen et al., 2023).

A recent study assessed the changes seen in MRI and computed tomography (CT)-imaging of a mild-grade spondylodiscitis and low-grade spinal fracture (Rajasekaran, Pushpa, et al., 2022). Based on these findings, the authors developed and validated the Endplate Infection Probability Score (EIPS, scale from -6 to 6), whereby higher values are indicative of an infectious etiology. The EIPS was adapted to a set of patients with non-specific LBP. Patients with MC showed significantly higher EIPS compared to patients without MC (4.85 vs. -0.66, respectively), but also more severe pain patterns and higher inflammatory parameters. It was concluded that MC are of an infectious etiology and the infection may primarily originate from the EP, as opposed to the more echoed theory of an IVD-based infection. Thus, “primary endplatitis” was introduced as a pathway for MC development.

Genetical aspect

MC are assumed to have a heritable component; the heritability has been approximated at 30% (Määttä et al., 2014). However, knowledge on the associated genetic variants is largely lacking (Freidin et al., 2019). Alterations in PTPRD (Freidin et al., 2019), HSPG2 (Kraatari et al., 2017) and MAML1 (Kraatari et al., 2017) genes have been connected to MC, all of which are involved in musculoskeletal tissue homeostasis by encoding PTP receptor type D—a protein controlling various cellular processes, perlecan—a structural protein and MAML1—a signaling protein, respectively. Additionally, MC were associated with vitamin-D receptor and matrix-metalloproteinase-20 gene single-nucleotide polymorphisms (Rajasekaran et al., 2016).

2.4.6 Association with other lumbar degenerative changes

Intervertebral disc degeneration

Already in the most original studies MC were connected to degenerative changes of the adjacent IVD (de Roos et al., 1987; Modic, Masaryk, et al., 1988; Modic, Steinberg, et al., 1988). Thereafter, large-scale studies have corroborated the association between MC and MRI-seen IVD degeneration in both clinical (Albert et al., 2011; Arana et al., 2011; Martínez-Quiñones et al., 2017; Sheng-yun et al., 2014) and non-clinical (L. Chen et al., 2018; Määttä, Wadge, et al., 2015; Mok et al., 2016; Saukkonen et al., 2020; Teraguchi et al., 2015) patient samples. It has been shown that IVD degeneration serves as a risk factor for the emergence of MC from the perspective of a singular lumbar segment (Albert et al., 2011; T. S. Jensen et al., 2010) and the lumbar spine as a whole (Mok et al., 2016). Further, the progression of MC (i.e., growth or conversion to MC1 of an existing lesion or emergence of a new lesion) was correlated with the progression of degeneration of the adjacent IVD (Farshad-Amacker et al., 2017). In a population-based patient cohort, a unit rise in the lumbar IVD degeneration sum score within the range of 0 to 15 was associated with a 37% increase in the likelihood of MC (Mok et al., 2016).

Of the MC types, MC1 have been connected to particularly fast progressing (Kerttula et al., 2012; Luoma et al., 2009) and overall advanced (Määttä, Karppinen, et al., 2015) degeneration of the adjacent IVD. On the contrary, some studies have not found differences in the degenerative status of the IVD adjacent

to different MC types (L. Chen et al., 2018; T. S. Jensen et al., 2009), and a recent study contradictorily connected MC2 to late-stage degeneration of the adjacent IVD (Y. Chen, Bao, et al., 2019). The extensivity of the MC may correlate positively to advanced degeneration of the adjacent IVD (Arana et al., 2011; L. Chen et al., 2018; Farshad-Amacker et al., 2017). Moreover, more extensive MC were correlated with a finding of severe IVD degeneration anywhere in the lumbar spine (Udby, Modic, et al., 2022).

Endplate damage

Agreeing with the most original histological findings of disrupted EP adjacent to MC by Modic, Steinberg, et al. (1988), the presence of MC have been associated with MRI-seen defects of the neighboring EP, in particular with local and erosive defects (Farshad-Amacker et al., 2017; Z. Feng et al., 2018; Määttä et al., 2018). EP defects are larger when adjacent MC are present (Zehra et al., 2019). Two previous studies, both of which assessed EP defects according to the EPS and TEPS schemes, reported parallel threshold values in the context of adjacent MC. Farshad-Amacker et al. (2017) assessed merely the single EP adjacent to which MC extended and showed that $EPS \geq 4$ served as a risk factor for the progression of MC. Määttä et al. (2018) instead observed TEPS 6 as a cut-off point above which the probability of MC was significantly higher in the perspective of a singular lumbar segment.

IVD displacement

Lumbar IVD displacements co-locate with adjacent MC (Albert et al., 2011; Määttä, Karppinen, et al., 2015). Mok et al. (2016) demonstrated that among non-clinical subjects, the existence of an IVD bulge or extrusion significantly elevated the likelihood of MC by more than fourfold. Määttä, Karppinen, et al. (2015) noted segments with MC1 had significantly more IVD bulges and protrusions than segments with MC2. The authors also assessed the cumulative IVD displacement score of the lumbar spine and found that patients with any MC had significantly higher scores compared to patients without MC. Lumbar IVD bulges (T. S. Jensen et al., 2010) and LDHs (Albert & Manniche, 2007; T. S. Jensen et al., 2010; Kuisma et al., 2006) have also been identified as segment-specific risk factors for new MC. Additionally, some studies have shown a correlation between MC and Schmorl's node at the levels of a singular segment (Ekşi et al., 2022;

Määttä, Karppinen, et al., 2015) and whole lumbar spine (el Barzouhi et al., 2014; Määttä, Karppinen, et al., 2015).

MC are also associated with the composition of herniated IVD tissue (Kawaguchi et al., 2018; Rajasekaran et al., 2013; Schmid et al., 2004). LDH frequently occurs by damaging the adjacent EP, and, accordingly, extracted LDH material commonly contains cartilaginous fragments. When adjacent MC are observed prior to discectomy, the extracted LDH material contains cartilaginous material significantly more often and in greater quantities compared to non-MC segments (Z. Y. Feng et al., 2021; Joe et al., 2015; Kawaguchi et al., 2018; Schmid et al., 2004; Shan et al., 2014).

2.4.7 Association with pain and disability

Low back pain

The association between MC and LBP is under debate, although several studies from various study populations have proved such an association (Kjaer, Leboeuf-Yde, Korsholm, et al., 2005; Määttä, Wadge, et al., 2015; Mok et al., 2016; O'Neill et al., 2008). Consequently, MC-associated LBP is suggested as a specific clinical LBP subtype (Kjaer et al., 2006; Määttä et al., 2016; Mok et al., 2016). A pooled analysis of longitudinal studies revealed marginally poorer short-term LBP outcomes for both any MC and MC1 (Han, Maher, et al., 2023). Indeed, MC1 have been more strongly connected with LBP, and to longer-lasting and more severe LBP (Kjaer, Leboeuf-Yde, Korsholm, et al., 2005; Kuisma et al., 2007; Mera et al., 2021; Saukkonen et al., 2020; K. J. Thompson et al., 2009). Accordingly, the resolution of MC1 may be associated with the relief of LBP symptoms (Järvinen et al., 2015; Luoma et al., 2016). More extensive MC lesions have shown a more robust correlation with LBP (Määttä et al., 2016; Saukkonen et al., 2020; Weishaupt et al., 2001). The correlation between MC and LBP seems to be strongest at the two most caudal lumbar segments (Kuisma et al., 2007; Mok et al., 2016).

Regarding the nature of the LBP, Määttä, Wadge, et al. (2015), in their twin study, reported that individuals diagnosed with MC have a higher likelihood of recalling at least one episode of severe and incapacitating LBP that persisted for a minimum of one month, in comparison to individuals without MC. Other studies reported that LBP patients with MC1 more often clinically present inflammatory

pain patterns, i.e., at least one of the following characteristics: worst LBP in the morning, waking at night because of LBP and morning stiffness for over 60 minutes (Arnbak et al., 2018; Bailly et al., 2014). Bailly et al. (2014) also found a co-linearity between the side of LBP and the presence of MC1 on the same side.

The association between MC and LBP has been questioned, however. Some studies have not found any such association (el Barzouhi et al., 2014; Jarvik et al., 2001; Kovacs et al., 2012), and longitudinal studies have contested a significant negative short- to long-term effect of MC on LBP (Carragee, Alamin, et al., 2006; Carragee et al., 2005; Keller et al., 2012; Kleinstück et al., 2006; Udby et al., 2019; Wilkens et al., 2013). In concordance, a recent meta-analysis (Lambrechts et al., 2023) and a systematic review (Hopayian et al., 2023) indicated a clinically non-significant association between MC and LBP, although earlier meta-analysis (Brinjikji, Diehn, et al., 2015) and review articles (T. S. Jensen et al., 2008; Zhang et al., 2008) were able to connect MC1 and any MC with LBP. Table 8 presents the outcomes from prior review studies.

In their recent meta-analysis, Herlin et al. (2018) classified only one study of the 31 included studies to have a low risk of overall bias. Moreover, due to the divergent methods of the included studies, the authors were unable to conduct a pooled analysis of the included 22 clinical studies using other than discography as a diagnostic method for LBP. A meta-analysis was conducted for the discography studies, and the authors reported a statistically significant association for positive discography results and the presence of MC. Thereafter, Czaplewski et al. (2023) aimed to reduce the heterogeneity of Herlin et al.'s (2018) meta-analysis by re-assessing the included discography studies. Considering specifically MC types, an aggregated analysis of five homogenous discography studies yielded slightly higher odds ratios (OR) between MC and a positive discography result: OR 8.34, 95% CI 5.86–11.87; OR 4.46, 95% CI 3.22–6.18; OR 3.39, 95% CI 1.50–7.64; and OR 1.97, 95% CI 1.22–3.16 for MC1 vs. MC0, MC2 vs. MC0, MC3 vs. MC0 and MC1 vs. MC2, respectively.

Table 8. An overview of the findings of review studies assessing the association between Modic changes and low back pain.

Authors, year	Purpose	Number of included studies/N	Meta-analysis performed?	Results	Conclusion
T. S. Jensen et al., 2008	To assess the prevalence of MC and their association with LBP	77 studies/N.S.	No	The median prevalence of MC is 43% among non-specific LBP patients and 6% among non-clinical subjects, while 7 out of 10 studies noted a positive association between MC and LBP with ORs ranging from 2.0 to 19.9	MC are common among LBP patients and are reported to associate with LBP in various study populations
Brinjikji, Diehn, et al., 2015	To compare the prevalence of lumbar degenerative MRI findings in 15–50 years old subjects with and without LBP	MC: 5 studies, MC1: 2 studies/N.S.	Yes	MC1 have a higher prevalence among subjects with LBP compared to those without LBP (OR 4.01, 95% CI 1.10–14.55), while any MC showed no difference (OR 1.62, 95% CI 0.48–5.41)	MC1 are more prevalent in subjects with LBP compared to subjects without LBP
Herlin et al., 2018	To assess whether the presence of MC is	31 studies/12 238 subjects	Yes for discography studies, no for non-	Concordant pain in discography is	The correlation between MC and LBP-related

Authors, year	Purpose	Number of included studies/N	Meta-analysis performed?	Results	Conclusion
	associated with LBP-related outcomes		discography studies	associated with any MC (OR 4.01, 95% CI 1.52–10.61), MC1 (OR 6.14, 95% CI 2.47–15.27) and MC2 (OR 3.15, 95% CI 1.00–9.93)	outcomes is inconsistent
Lambrechts et al., 2023	To assess whether MC associates with worse baseline LBP or disability in patients undergoing any treatment intervention in lumbar spine	17 studies/3889 subjects	Yes	The presence of MC correlates to slightly worse LBP (MD -0.38, 95% CI -0.61–-0.16 on a 0–10 VAS) and disability (MD -2.52, 95% CI -3.93–-1.12 ODI points) without difference between MC types	MC associates with worse LBP and disability, although the differences fail to surpass MCID
Czaplewski et al., 2023	To independently re-evaluate studies included in the meta-analysis by Herlin et al. (2018) to reduce heterogeneity	5 studies/1023 subjects	Yes	Concordant pain in discography is associated with MC1 (OR 8.34, 95% CI 5.86–11.87), MC2 (OR 4.46, 95% CI 3.22–6.18) and MC3 (OR 3.39, 95% CI 1.50–7.64) with a significant difference between MC1 and MC2 (OR 1.97, 95% CI 1.22–	MC1 and MC2 can be painful

Authors, year	Purpose	Number of included studies/N	Meta-analysis performed?	Results	Conclusion
Hopyayan et al., 2023	To examine the presence and strength of the possible association between MC and LBP	15 studies/9082 subjects	No	<p>3.16)</p> <p>Ten out of twelve studies that had applicable ORs reported an association between MC and LBP with most ORs being in the range of from 1.47, 95% CI 1.13–1.87 to 13.32, 95% CI 1.83–96.9</p>	The current inconsistent evidence remains inconclusive on the association between MC and LBP

MC = Modic changes, MC1 = Modic changes type I, MC2 = Modic changes type II, MC3 = Modic changes type III, LBP = low back pain, MRI = magnetic resonance imaging, N.S. = not specified, OR = odds ratio, CI = confidence intervals, MD = mean difference, VAS= Visual Analogue Scale, ODI = Oswestry Disability Index, MCID = minimal clinically important difference

Leg pain

Knowledge on the correlation between MC and leg pain is scarce. In concordance with the etiological considerations, patients with MC report a significantly more prominent history of sciatica (Kjaer et al., 2006). However, this correlation has been found only for the most caudal lumbar spine segments (Mok et al., 2016), with some evidence of more severe sciatica symptoms in MC1 and extensive MC (Kuisma et al., 2007).

Disability

A discrepancy exists in the reported associations between MC and disability. The two largest cross-sectional investigations, based on the same Chinese population-based study cohort, showed divergent results with only one study reporting a significant association (Määttä et al., 2016; Mok et al., 2016). Similarly, longitudinal studies have produced varying outcomes (Carragee et al., 2005; Y. Chen, Yang, et al., 2019; Järvinen et al., 2015; Keller et al., 2012; Udby et al., 2019). There is a suggestion that MC1 may have a more pronounced negative impact on short-term improvement in LBP-related disability (O. K. Jensen et al., 2014). Additionally, MC2 may be more strongly associated with disability (Määttä et al., 2016). The extensivity of MC1 has also been positively correlated with the degree of LBP-related disability in several studies (Hanımoğlu et al., 2019; Järvinen et al., 2015; Kääpä et al., 2012; Mitra et al., 2004).

2.4.8 Clinical prognostic value of MC

Despite the lack of consensus regarding the optimal treatment for LBP associated with lumbar MC, the possibility that MC may have prognostic implications for various treatment modalities has been discussed (R. K. Jensen & Leboeuf-Yde, 2011). As a result, numerous studies have explored the efficacy of various treatment modalities for MC-associated LBP, including operative interventions and pharmacological and non-pharmacological treatments (Issa et al., 2023; Lambrechts et al., 2022).

Lumbar fusion

The existing body of evidence regarding the effectiveness of fusion surgery for MC-associated LBP primarily relies on a limited number of studies that have examined the impact of preoperative MC on surgical outcomes. These studies have demonstrated some degree of variation in surgical indications, which may contribute to the inconsistent findings.

In the context of chronic LBP patients undergoing single-level fusion, the presence of MC1 or MC1/2 was associated with improved postoperative outcomes in terms of LBP and disability measures at a mean final follow-up of 14 months (Esposito et al., 2006). Similarly, a study investigating patients undergoing single-level fusion for LDH, lumbar spinal stenosis, or lumbar spondylolisthesis found a significant correlation between preoperative MC1 and lower levels of LBP at a final follow-up period of 22–24 months (Jiao et al., 2021). However, disability scores did not exhibit significant differences across the various MC groups. Moreover, Buttermann et al. (1997) reported preoperative MC1 as a significant risk factor for continuing LBP after single- or multi-level posterolateral fusion.

Negative findings have also been reported regarding this matter. A study examining patients who underwent single-level fusion for LDH and associated instability revealed comparable one-year outcomes in terms of LBP, disability, and general health status among groups categorized by the absence of MC or the presence of MC1 or MC2 (MacLean et al., 2021). Similarly, in patients with a primary IVD pathology requiring stabilization, the presence of preoperative MC did not serve as a predictor for LBP, leg pain, or disability outcomes at the two- to three-year follow-ups in another two studies (Djurasovic et al., 2012; Staartjes et al., 2018). Furthermore, the presence of preoperative MC was not found to be predictive of surgical outcomes in patients undergoing fusion for various diagnoses such as LDH, lumbar spinal stenosis, or degenerative disc disease, regardless of the presence of instability (Gautschi et al., 2017).

Vital et al. (2003) conducted a study to evaluate the impact of stabilization on MC1 of chronic LBP patients with IVD pathology. Six months postoperatively, all 17 patients demonstrated satisfactory outcomes, with their preoperative MC1 lesions exhibiting notable changes: 13 patients showed conversion to MC2, while the remaining four patients displayed a restoration of normal signal intensity on MRI. Ohtori et al. (2010) demonstrated a similar trend following posterolateral fusion in patients with lumbar spinal stenosis. In a more recent investigation by

Mu et al. (2022), the incidence of new MC following lumbar stabilization was examined in patients with chronic LBP due to degenerative IVD disease. Out of the 43 patients studied, 13 (30.2%) developed new MC, primarily at the level operated on, with some cases also manifesting in adjacent segments. Notably, 61.5% of the newly formed MC were classified as MC2. The authors also included other common lumbar surgeries in their analysis, and interestingly, fusion surgery, in contrast to microdiscectomy, -sequestrectomy, and -decompression, did not exacerbate pre-existing MC. Moreover, fusion surgery demonstrated a trend towards a lower incidence of new MC compared to the other three surgical procedures. According to the authors, it appears that the first postoperative year is the period characterized by the highest MC activity.

Total disc replacement

The available literature concerning the impact of preoperative MC on the outcome of TDR surgery remains inconclusive. Two studies, Siepe et al. (2006) and Hellum et al. (2012), presented divergent findings at 2–3 years of follow-up. Siepe et al. (2006) found no predictive value for MC, while Hellum et al. (2012) reported better disability outcomes in the presence of preoperative MC. Notably, the study conducted by Hellum et al. (2012) underwent an extension to include an 8-year follow-up period and consistently observed the same results (Furunes et al., 2018). Furthermore, the extent of MC, specifically when it covered over 50% of the affected vertebra's height, emerged as a significant prognostic factor for clinically significant improvement in disability. Moreover, investigations focusing on the specific types of MC have yielded inconsistent results. Studies with follow-up periods ranging between 2–6 years reported superior disability outcomes for both preoperative MC1 (Blondel et al., 2011) and MC2 (Gornet et al., 2014).

Lumbar discectomy

A recent systematic review of 11 studies reported mixed findings regarding the preoperative prognostic value of MC for lumbar discectomy outcomes (Lambrechts et al., 2022). Of these, five and four studies were included in meta-analyses for improvements in ODI and LBP, respectively, comparing outcomes based on the presence or absence of MC. Neither analysis identified statistically significant differences. However, the limited number of studies and substantial

heterogeneity among the included studies precluded definitive conclusions. The authors emphasized the need for future research, particularly focusing on the preoperative value of MC1.

Basivertebral nerve ablation

The significance of the basivertebral nerve in chronic discogenic LBP has been proposed, leading to the exploration of basivertebral nerve ablation as a minimally invasive treatment for selected chronic LBP patients (Becker et al., 2017). Two recent RCTs evaluated the effectiveness of basivertebral nerve ablation in patients with non-radicular chronic LBP and either MC1 or MC2 in the treatment area. The RCTs included segments ranging from L3 to S1 and compared basivertebral nerve ablation to sham treatment (Fischgrund et al., 2018) and to standard care involving pain medication and physical therapy (Khalil et al., 2019). Both studies demonstrated statistically significant superiority of the active treatment based on the primary outcome measure of the ODI score at a 3-month follow-up. Specifically, the treatment group in Fischgrund et al.'s (2018) study exhibited an ODI score change of -20.5 , compared to -15.2 in the sham-treatment group, while in Khalil et al.'s (2019) study, the treatment groups showed an ODI score change of -25.3 , compared to -4.4 in the standard care group.

Long-term efficacy was further confirmed through a mean follow-up period of 6.4 years for the Fischgrund et al.'s study, although the RCT design was discontinued after one year due to a high crossover rate of the sham-treated patients to active treatment (Fischgrund et al., 2020). Similarly, the study by Khalil et al. demonstrated sustained treatment results over a 24-month follow-up period (Koreckij et al., 2021).

According to a subsequent meta-analysis including additional single-arm studies also comprising patients with MC1 or MC2, the percentage of patients experiencing a clinically significant decrease in LBP ($\geq 50\%$) at 6 and 12 months was 65% and 64%, respectively (Conger et al., 2022). Similarly, the rates for disability reduction (≥ 15 ODI points) were 75% at both time points. It was concluded that these data provide moderate-quality evidence supporting the effectiveness of basivertebral nerve ablation as a treatment option for chronic LBP patients with MC1 or MC2. Furthermore, another review study emphasized the need for large-scale, high-quality, non-industry-funded research involving

representative clinical patient populations to validate these findings (Nwosu et al., 2023).

Pharmacological treatments

Building on a pilot study (Albert et al., 2007), Albert, Sorensen, et al. (2013) conducted a pioneering study to assess the efficacy of oral antibiotics for the treatment of chronic LDH- and MC-associated LBP. Chronic LBP patients aged 18–65 with MC1 adjacent to a segment with LDH 6–24 months prior were randomized to receive a 100-day course of amoxicillin-clavulanate or placebo. At the one-year follow-up, the antibiotic group showed statistically significant and clinically meaningful improvements in the primary outcomes of LBP and disability. However, the study has faced substantial criticism, primarily regarding its methodology and clinical applicability, leaving this issue highly controversial (Lings, 2014). Bråten et al. (2019) conducted an RCT to replicate these findings, expanding inclusion to MC2 alongside MC1. Participants were randomized to receive daily oral amoxicillin or placebo for three months. At the final 12-month follow-up, no clinically significant differences were observed in the primary outcome of disability.

In a recent RCT, Tavares et al. (2021) found that intradiscal prednisolone acetate reduced mean LBP by 2.7 on a 0–10 scale after one month, compared to a 0.1 increase with lidocaine among chronic LBP patients with MC1. Similarly, Nguyen et al. (2017) reported a greater short-term effect of intradiscal prednisolone during discography versus plain discography, with 55.4% and 33.3% achieving LBP intensity less than 40 on a 0–100 scale at one month, respectively. However, the glucocorticoid group's mean LBP worsened at three months and surpassed that of the non-glucocorticoid group. These results align with prior studies and a meta-analysis confirming the short-term effectiveness of glucocorticoids (Beaudreuil et al., 2012; Buttermann, 2004; Fayad et al., 2007; Riegger et al., 2023).

In an RCT involving chronic LBP patients with MC, Koivisto et al. (2014) found that a single dose of intravenous zoledronic acid reduced LBP by a MD of 1.4 points (on a 0–10 scale) compared to placebo after one month. At one year, the treatment group used significantly fewer non-steroidal anti-inflammatory drugs than those in the placebo group, which could also have contributed to the non-significance of other outcome measures at that time point. Zoledronic acid

also showed greater efficacy in converting MC1 to MC2 than placebo (Koivisto et al., 2017).

Non-pharmacological treatments

Previous studies have produced conflicting findings regarding the response of MC-associated LBP to physical therapy interventions. Studies with up to one year of follow-up have reported no effect of MC (Kleinstück et al., 2006), a slight negative effect of MC2 (Y. Chen, Yang, et al., 2019), and a significant negative effect of MC1 (O. K. Jensen et al., 2014) on the outcome. In an RCT of chronic LBP patients with at least one MC, R. K. Jensen, Leboeuf-Yde, Wedderkopp, Sorensen, & Manniche (2012) compared a ten-week lumbar support belt intervention to exercise. One year after treatment, no significant differences in LBP, disability, or general health were observed between the 76 evaluated patients. In contrast, a French retrospective study found that 79% of chronic LBP patients with MC1 experienced at least a 30% reduction in LBP after three months of daytime use of a custom-made lumbar brace (Boutevillain et al., 2019).

3 Aims of the thesis

The primary objectives of this thesis were threefold. First, the study sought to determine whether the response to preoperative lumbar discoblock holds predictive value for the short-term outcomes of lumbar fusion or TDR surgery. Second, it aimed to evaluate the painfulness of different MC types by analyzing the discoblock responses of lumbar segments with MC. Third, the study aimed to establish a reliable and clinically useful criterion for identifying the preoperative co-occurrence of common IVD-related degenerative features. The clinical relevance of this criterion was then assessed by examining its association with differing lumbar discectomy outcomes compared to cases with either singular or no degenerative features. The specific research questions and hypotheses were as follows:

1. *Does the degree of pain relief achieved through preoperative discoblock for the lumbar segment scheduled for surgery serve as a predictive indicator for short-term disability outcomes following lumbar fusion or TDR surgeries?*

The hypothesis was that the response to lumbar discoblock could serve as a predictor for surgical disability outcomes.

2. *Does the presence or type of MC in the lumbar segment modify the response to lumbar discoblock in chronic LBP patients?*

The hypothesis was that patients with lumbar MC, particularly MC1, in the lumbar segment in question experience greater pain relief from discoblock compared to patients without MC.

3. *Can a novel MRI-based criterion reliably evaluate the preoperative co-occurrence of IVD-related degenerative features in the operated segment, and does it demonstrate clinical value by distinguishing short-term outcomes of single-level lumbar discectomy from those with singular or absent degenerative features?*

The hypothesis was that a reliable criterion for identifying the co-occurrence of advanced-level IVD-related degenerative phenotypes could be established and that its presence would correlate with inferior short-term outcomes after lumbar discectomy.

4 Materials and methods

4.1 Study populations

The study population for this thesis was extracted from two separate retrospective patient cohorts from the Oulu University Hospital (OUH), whereby Studies I and II shared the same base population.

The participants for Studies I and II were patients with chronic LBP who had undergone a lumbar discoblock at the OUH between 2011 and 2018 (N=78). These patients were initially referred to OUH from primary or secondary care, or from private healthcare facilities as potential candidates for surgery due to their persistent LBP. The decision to perform a discoblock was made after a clinical evaluation by a spine surgeon, which included a review of the patient's MRI results and was based on the suspicion that the chronic LBP was originating from a specific lumbar IVD.

From this cohort, individuals were chosen for inclusion in Study I if they met the following criteria: their LBP had persisted for a minimum of six months with unsatisfactory responses to conservative treatment, they underwent a single-level lumbar discoblock, they had undergone subsequent fusion or TDR surgery targeting the lumbar segment that had been examined by discoblock, and comprehensive clinical data pertaining to both the discoblock and surgery were retrospectively accessible. Exclusion criteria encompassed the suspicion of an alternative cause of chronic LBP, such as facet joint pathology, malignancy, fracture, infection or rheumatic spine disease, a history of prior fusion or TDR surgery at the lumbar segment in question, and age below 18 years.

For Study II, patients were selected from the base population based on the following inclusion criteria: the presence of chronic LBP persisting for a minimum duration of six months with unsatisfactory responses to conservative treatment, lumbar MRI performed within a timeframe of one year prior to the discoblock, lumbar discoblock at a single-level, and retrospective access to adequate clinical parameters pertaining the discoblock. Excluded were patients with any other alternative suspected cause for their LBP, such as an alternate IVD more likely to be responsible for their LBP, facet joint pathology, fracture, malignancy, infection, rheumatic spine disease, or significant anatomical variance. Additionally, patients who had undergone previous fusion or TDR surgery

involving the segment of interest and patients below 18 years of age were ineligible for participation.

The participants for Study III were derived from FinSpine, a Finnish electronic national spine register (Marjamaa et al., 2023). This register has undergone internal validation against a national hospital discharge register in terms of spine procedure codes. It encompasses data from over 90% of the spinal procedures performed in Finnish public hospitals. In the clinical context, a patient file is automatically generated when the register software detects the scheduling of a procedure associated with a spine-specific procedure code. This data is then enriched through contributions from the operating room data system. Furthermore, the operating surgeon provides specific details regarding the procedure and the related hospitalization.

Using the integrated reporting tool in the register software, prospectively collected clinical data from patients who underwent single-level lumbar discectomy for LDH at OUH between October 2017 and September 2022 were retrospectively collected. Exclusion criteria included prior lumbar surgery, preoperative MRI more than six months before discectomy, the absence of pre- or one-year postoperative patient-reported outcome measures (PROMs) data, and a re-operation during the follow-up period. All patients were included, irrespective of the urgency of the surgery.

4.2 Clinical characteristics

In addition to age and sex distribution measures, key descriptive variables were collected in all the studies. These encompassed the percentage of current smokers and the duration of the postoperative follow-up period in Study I. In Study II, the intervals between MRI and discoblock were collected. For Study III, the collected descriptive data consisted of the BMI, smoking status, duration of symptoms, preoperative mental health status, presence of preoperative cauda equina syndrome, preoperative motor deficit impairing walking (defined as leg strength of 3 or lower on a 0–5 scale), and the lumbar level of surgery.

4.3 Magnetic resonance imaging

In Study II, patients had undergone lumbar MRI within a year prior to the discoblock. The mean interval between the MRI and discoblock was 5.0 months. The imaging was conducted at various healthcare facilities, including secondary

and tertiary-level hospitals and the private sector. The imaging parameters adhered to the standards commonly employed in routine spinal MRI examinations. If performed outside the OUH, the MR images were transferred into the picture archiving and communication system (PACS) of the OUH for image analysis. All MRIs were obtained using either 1.5 or 3.0 T units. All of the MRI procedures included the acquisition of sagittal T1w fast-spin echo (FSE) (N=29; 64.4%) or T1w fluid-attenuated inversion recovery (FLAIR) (N=16; 35.6%), sagittal T2w FSE, and axial T2w FSE. For 37 (82.2%) patients, an additional sagittal short tau inversion recovery (STIR) sequence was available for analysis.

All the patients included in Study III underwent a preoperative MRI using 1.5 or 3.0 T equipment within the six-month period preceding their discectomy. The majority of these patients had their MRI scans conducted at the OUH. In instances where the MRI scans were performed at external facilities, the images were transferred to the PACS of the OUH for image analysis. All of the MRI protocols comprised sagittal T1w FSE or FLAIR, sagittal T2w FSE, and axial T2w FSE sequences. While some variations in MRI parameters were noted due to the use of different MRI equipment, these parameters remained consistent with those conventionally employed in spinal imaging.

4.4 Image analysis

In Study II, two experienced musculoskeletal radiologists independently analyzed the MRIs, with each radiologist reviewing half of the study sample. The analyses were conducted using clinical workstations (Neaview Radiology, v. 2.23, Neagen Corp., Helsinki, Finland) at the OUH. The MRIs were examined for the presence and type of MC in the specific lumbar segment that had undergone discoblock. MC were categorized into MC1, MC2, and MC3, following the classification scheme introduced by Modic, Masaryk, et al. (1988). In instances where a mixed MC was observed, it was classified as either MC1-dominant, MC2-dominant, or MC3-dominant based on the type with the greatest extent on the sagittal plane. These mixed cases were then grouped together with pure MCs of the corresponding type for the purpose of statistical analyses. Thus, patients with pure or dominant MC1 and MC2 constituted the MC1 and MC2 groups, respectively. Pure or dominant MC3 were absent. To assess interobserver reliability, 15 patients' MRIs selected by random were analyzed by both radiologists.

In Study III, the analysis of MRIs was conducted by the same experienced musculoskeletal radiologists as in Study II utilizing identical clinical workstations.

The radiologists had no access to clinical information, except for the operated lumbar segment. The workload was unequally distributed, with one radiologist (JN) responsible for 63.6% of the MRI evaluations within this study. The evaluation process involved the assessment of EPD, MC, and IVD degeneration from the operated lumbar segment. EPD and MC were individually assessed from the cranial and caudal section of the lumbar segment. EPD assessments were conducted employing a modified version of the TEPS scale (Rajasekaran et al., 2008), while the evaluation of MC encompassed categorization by type, sagittal plane height measurement, and horizontal extent determination. IVD degeneration was categorized using the Pfirrmann classification (Pfirrmann et al., 2001). A comprehensive classification scheme for EPD, MC and IVD degeneration is provided in Table 9.

Table 9. The classification scheme for the included MRI features in Study III.

Variable	Classification/grading	Definition		
EPD	No damage or focal EP thinning (EPS 1–2)	Of the EPD's maximum area in relation to the affected EP, EPS classification according to		
	Damaged, area of damage less than 25% (EPS 3–4)	Rajasekaran et al. (2008)		
	Damaged, area of damage over 25% (EPS 5–6)			
MC	Type	Pure MC1 or MC1 predominancy in mixed MC	As per the MRI SI-based classification introduced by Modic, Masaryk, et al. (1988), predominance for the type with the greatest volume in mixed MC	
		Other MC		
		MC absent		
	Height	Less than 50%		Highest MC section in relation to the affected vertebra on the sagittal plane
		Over 50%		
	Extent	Less than 50%		MC's area in relation to the affected vertebra in axial plane estimated from the slice with the largest MC area
Over 50%				
IVD degeneration	Grade 1–3	T2w-SI-based IVD degeneration classification according to Pfirrmann et al. (2001)		
	Grade 4–5			

EPD = endplate damage, EP = endplate, EPS = endplate score, MC = Modic changes, MC1 = Modic changes type I, MRI = magnetic resonance imaging, SI = signal intensity, IVD = intervertebral disc, T2w = T2-weighted

4.5 Discoblock

Lumbar discoblocks were performed in Studies I and II, employing a standardized technique. The procedures were conducted by an experienced radiologist in a sterile environment at the OUH. Imaging guidance was facilitated through a combination of a C-arm fluoroscopy and a cone-beam CT (CBCT) machine (Philips Allura 20C, Amsterdam, the Netherlands). Patients were positioned in a prone manner, and a local anesthetic, typically around 5 ml of 10 mg/ml lidocaine, was administered into the superficial soft tissues.

Access to the IVD was established using a single 21-gauge Chiba needle through the posterolateral route. Prior to the injection of 20 mg/ml of lidocaine with a normal hand-operated syringe with a target volume of 2 ml into the IVD to perform the discoblock, the accurate needle placement in the inner third of the IVD was confirmed through fluoroscopy from two perpendicular angles, and in cases where there was uncertainty, additional confirmation was obtained through CBCT. The injection process was halted in the event that the patient reported significant pain or a substantial increase in injection pressure was observed. A pressure-controlled syringe was not employed in this procedure.

The pre- and postprocedural LBP degrees were retrospectively obtained from the OUH's radiology information system (RIS). The Numerical Rating Scale (NRS), which employs a scale from 0 to 10 with lower scores indicating less pain (Haefeli & Elfering, 2006), was utilized during the discoblock to evaluate the LBP. The preprocedural NRS pain score was recorded just before the injection at rest while the postprocedural NRS pain score was assessed 45 minutes after the injection. Provocative movements were not employed during the postprocedural NRS assessment; however, patients were permitted slight movements to gauge their level of LBP. Subsequently, the degree of pain relief following discoblock ($\Delta\text{NRS}_{\text{DB}}$) was calculated for each patient as follows:

$$\Delta\text{NRS}_{\text{DB}} = \text{postprocedural NRS} - \text{preprocedural NRS} \quad (1)$$

In Study II, patients were also included if their $\Delta\text{NRS}_{\text{DB}}$ was documented non-numerically, provided that their preprocedural NRS pain score was accessible, and they did not experience any relief from LBP. Additionally, in the same study, aside from calculating $\Delta\text{NRS}_{\text{DB}}$, we evaluated positive discoblock results using predefined thresholds of a ≥ 3 or $\geq 80\%$ NRS decrease to compare our findings with previous discoblock studies. Direct procedural complications were recorded.

4.6 Development of the criteria for co-occurring preoperative degenerative features

To assess the co-occurrence of advanced-level IVD-related degenerative phenotypes in Study III, the study group, including senior musculoskeletal radiologists and spine surgeons, collaboratively developed a criterion termed “Advanced Preoperative Degeneration” (APD). This criterion was based on a review of existing literature and included common degenerative MRI findings (Table 9) to enhance its clinical and academic relevance. In addition to the APD criterion, two additional criteria were included in a sensitivity analysis.

4.6.1 Advanced Preoperative Degeneration (APD)

The APD criterion was considered fulfilled when at least two advanced-level phenotypes of EPD, MC, or IVD degeneration were preoperatively present in the operated segment. Since late-stage IVD degeneration may have a protective effect against LDH (Brooks et al., 2021), requiring the presence of all three advanced-level phenotypes was rejected, as it could reduce the clinical utility of the APD criterion. The rationales for the thresholds defining advanced-level phenotypes of the included degenerative features are detailed below, while Table 10 provides an overview of the APD criterion.

Table 10. An overview of the APD criterion in Study III.

Variable	Criterion
APD (criterion met if ≥2 of the following positive) ¹	
EPD	Damaged, area of damage ≥25% (EPS 5-6)
MC	Pure MC1 or MC1 predominancy in mixed MC
IVD degeneration (Pfirrmann)	Grade ≥4

¹ If met based on MC and EPD, the findings had to be on the same side of the lumbar segment. APD = Advanced Preoperative Degeneration, EPD = endplate damage, MC = Modic changes, MC1 = Modic changes type I, IVD = intervertebral disc, EPS = endplate score

For EPD, the criterion was defined as an area of damage $\geq 25\%$ in relation to the EP in question, corresponding to grade ≥ 5 in the EPS classification introduced by Rajasekaran et al. (2008). Farshad-Amacker et al. (2017) conducted a longitudinal study on LBP patients and observed that with rising EPS, more MC and higher grades of IVD degeneration are noted. Importantly, the authors were able to associate EPS ≥ 4 as a threshold value for the progression of both IVD

degeneration and MC. Moreover, Zehra et al. (2019) illustrated among their population-based study sample that a width-based EPD-EP ratio of 0.20–0.32 serves as a distinctive threshold for the presence of various degenerative features, including IVD degeneration and MC. Moreover, among clinical and population-based samples, a cumulative score of ≥ 6 for the EPSs of the cranial and caudal EPs has been established as a cut-off value, beyond which the likelihood of MC presence and advanced IVD degeneration is significantly higher (Määttä et al., 2018; Rajasekaran et al., 2008). Thus, the highest level, i.e. a relative damaged EP area $\geq 25\%$, of the utilized 3-graded classification scheme for EPD was considered an advanced-level in the present study.

Considering its traditional classification as the most active MC type, MC1 was integrated into the APD criterion (Modic, Steinberg, et al., 1988; Perilli et al., 2015). Moreover, over other types, MC1 have been correlated more strongly with LBP (Kjaer, Leboeuf-Yde, Korsholm, et al., 2005; Mera et al., 2021; Saukkonen et al., 2020), and as is intuitive, the MC1 regression has been connected to relieving LBP (Järvinen et al., 2015; Luoma et al., 2016). MC1 have also been suggested to associate with particularly rapid progression and overall advanced degeneration of the adjacent IVD (Kerttula et al., 2012; Luoma et al., 2009; Määttä, Karppinen, et al., 2015).

The threshold of Pfirrmann grade ≥ 4 was adopted from prior studies (Farshad-Amacker et al., 2017; Rade et al., 2018; Rajasekaran et al., 2008), and was considered suitable for an advanced-level phenotype as grades 4–5 indicate degenerative changes resulting in at least moderate collapse of the IVD height (Pfirrmann et al., 2001). Furthermore, Jamaludin et al. (2023) demonstrated the strongest association between Pfirrmann grade ≥ 4 and LBP for the two most caudal lumbar segments among patients under 50 years old—demographic characteristics typical of the lumbar discectomy patient population (Weinstein et al., 2006).

4.6.2 Criteria for sensitivity analysis

Two additional MRI-based criteria were included in the sensitivity analysis (Table 11). The first analysis assessed the size of the MC instead of their type, as the extent of MC may hold clinical significance, demonstrating a positive correlation with both advanced degeneration of the adjacent IVD and LBP (L. Chen et al., 2018; Farshad-Amacker et al., 2017; Määttä et al., 2016; Saukkonen et al., 2020). The second criterion included in the sensitivity analysis was adapted from a

previous cervical spine study by Baker et al. (2022), who introduced the Modic-endplate complex (MEC) criterion, wherein the degenerative features of MC and EPD are not strictly categorized. The inclusion of this criterion was supported by Baker et al.'s (2022) findings, which highlighted its clinical value for cervical stabilization surgery patients, and by a large-scale register study suggesting that the segment-wise co-occurrence of IVD degeneration and MC is more strongly associated with LBP than individual features, even without definitive categorization of the included degenerative features (Teraguchi et al., 2015).

Table 11. An overview of the two criteria included in sensitivity analysis in Study III.

Variable	Criterion
Sensitivity analysis 1: MC size-based criterion (criterion met if ≥ 2 of the following positive) ¹	
EPD	Damaged, area of damage $\geq 25\%$ (EPS 5–6)
MC	Height $\geq 50\%$ or extent $\geq 50\%$
IVD	Grade ≥ 4
Sensitivity analysis 2: criterion according to Baker et al. (2022) termed “MEC” (criterion met if 2 of the following positive) ²	
EPD	Any EPD
MC	Any MC

¹ If met based on MC and EPD, the findings had to be on the same side of the lumbar segment. ² The findings had not to be on the same side of the lumbar segment. MC = Modic changes, EPD = endplate damage, EPS = endplate score, IVD = intervertebral disc, MEC = Modic-endplate complex

4.7 Surgical procedures and outcome assessment

The included patients in Study I had subsequently undergone lumbar fusion or TDR surgery in the lumbar segment that had been assessed with discoblock. Various fusion techniques were employed, with the choice of technique made by the attending spine surgeon on a patient-by-patient basis. The fusion techniques utilized included posterolateral fusion with pedicle screw fixation (PLF), transforaminal lumbar interbody fusion (TLIF) involving PLF, and anterior lumbar interbody fusion (ALIF). These procedures, as well as TDR operations, adhered to the well-established technique standards (Mobbs et al., 2015; Tajima et al., 2004; Tropiano et al., 2006). Operative complications were retrospectively recorded.

Surgical outcomes were evaluated using ODI version 2.0, which has a score range of 0 to 100, with lower scores indicating less disability (Fairbank & Pynsent, 2000). The ODI scores were retrospectively retrieved from the OUH’s medical records. The last ODI score assessed by a spine surgeon served as the preoperative value, typically obtained during a preoperative meeting with the surgeon. The most recent ODI score evaluated by a spine surgeon during a postoperative follow-up meeting was used as the postoperative value. From these pre- and postoperative ODI scores, both absolute (Δ ODI) and percentage (Δ ODI%) changes were calculated as follows:

$$\Delta\text{ODI} = \text{postoperative ODI} - \text{preoperative ODI} \quad (2)$$

and

$$\Delta\text{ODI}\% = (\text{preoperative ODI} - \text{postoperative ODI}) / \text{preoperative ODI} \quad (3)$$

A minimum clinically important difference (MCID) in the ODI score was defined as a 30% decrease, in accordance with previously published data (Ostelo et al., 2008).

In Study III, the patients underwent either a standard microdiscectomy or an endoscopic discectomy (Blamoutier, 2013). Included patients provided electronic preoperative and 12-month postoperative data on their LBP and leg pain using VAS, which ranged from 0 to 100, with higher values denoting greater pain. They also reported their disability using the ODI score version 2.0 (Fairbank & Pynsent, 2000) and their health-related quality of life (QoL) via the EQ-5D-3L questionnaire. This questionnaire comprises two parts (Rabin & Charro, 2001). The first section serves as a descriptive system, evaluating QoL aspects of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, assigning values of 1 to 3 for each dimension, where higher scores signify a lower QoL in the specific sector. The second part of the questionnaire assesses the patient’s overall health with a visual scale (EQ-VAS), where a score of 0 is minimum and indicates “the worst health imaginable” and a score of 100 is maximum, signifying “the best health imaginable”. Using the Finnish value set established by Ohinmaa & Sintonen (1999), a summary index score was computed from the first section of the questionnaire for each patient. The index score ranged between 1.000 (optimal health state) and -0.011 . It is noteworthy that the EQ-VAS was oriented horizontally in the register software, in contrast to the vertical orientation recommended by the EuroQoL office.

4.8 Statistical analyses

Descriptive statistics were employed to present the data in each study, with frequencies and percentages for categorical variables, and means with standard deviations (SD) or medians with 1st (Q1) and 3rd (Q3) quartiles for continuous variables, depending on their distribution. A p-value less than 0.05 was considered statistically significant for all studies. All data analyses were conducted using IBM SPSS v. 29 (IBM Corp., Armonk, NY, USA).

In Study I, the Wilcoxon signed-rank test was utilized to assess $\Delta\text{NRS}_{\text{DB}}$ and ΔODI concerning discoblock and surgery, respectively. The Spearman's rank correlation coefficient (r) was calculated to examine the relationship between postoperative ODI scores and both preprocedural NRS pain scores and preoperative ODI scores. Moreover, r was computed to determine the correlation between $\Delta\text{NRS}_{\text{DB}}$ and $\Delta\text{ODI}\%$ for the fusion and TDR subgroups, both combined and separately. The indicative strength of the linear relationship was interpreted according to Chan (2003): 1–0.8 as very strong, 0.79–0.6 as moderate, 0.59–0.3 as fair, and 0.29–0 as poor.

In Study II, a Mann-Whitney U test was employed to identify variations in $\Delta\text{NRS}_{\text{DB}}$ between the two groups: those with MC and those without MC (referred to as the MC0 group) in the relevant lumbar segment. To investigate differences in $\Delta\text{NRS}_{\text{DB}}$ among the MC0, MC1 and MC2 groups, a Kruskal-Wallis test was conducted for a comprehensive analysis, while Mann-Whitney U tests were employed for individual pairwise comparisons. To reduce the potential for false discoveries, pairwise analyses utilized the Benjamini-Hochberg method with a false discovery rate of 5% (Benjamini & Hochberg, 1995).

In Study III, the study population was categorized into three groups: APD-positive (having two or more of the required phenotypes), APD1/3 (having one of the required phenotypes), and APD0 (having none of the required phenotypes). Descriptive statistics were expressed as means \pm SD or as frequencies with percentages. Continuous variables were compared using a one-way analysis of variance (ANOVA), and dichotomous variables were analyzed with chi-square tests. When a segment contained two different APD grades, the patient was classified according to the higher grade for reporting descriptive statistics. For statistically significant differences between groups, post hoc comparisons were performed using Tukey's test for ANOVA and Holm-Bonferroni-corrected pairwise comparisons for chi-square tests.

A linear mixed-effects model was utilized to estimate the prognostic value of the APD criterion on one-year lumbar discectomy outcomes. The PROMs parameter in question was the dependent variable, with the patient as the subject factor and the side of the segment as a within-subject factor. The models incorporated the interaction term “group * surgery” and adjusted for demographic and clinical covariates. This approach was also applied to evaluate the two additional criteria in the sensitivity analysis.

Due to low incidence rates, certain variables were combined for statistical feasibility: symptom duration was grouped into <12 weeks, 3–12 months, or >12 months, and preoperative mental health status was categorized as either present (question 5 in EQ-5D-3L: 2–3) or absent (question 5 in EQ-5D-3L: 1) for anxiety or depression. Due to its exceedingly rare occurrence, cauda equina syndrome was excluded from the analysis.

To evaluate interobserver reliability when identifying the presence and type of MC in the relevant lumbar segment in Study II, Cohen’s kappa (κ) with 95% CIs was calculated using 15 MRIs analyzed by both radiologists. To assess intra- and interobserver reliability when detecting the phenotypes included in the APD criterion and APD-positivity in Study III, both κ and prevalence-adjusted bias-adjusted kappa (PABAK) (Byrt et al., 1993) with 95% CIs, were computed. In Study III, both radiologists re-evaluated 15 randomly selected MRIs, and an additional set of 19 MRIs were analyzed by both radiologists, all blinded to the previous results. These analyses included the entire lumbar spine to increase the prevalence of the required phenotypes. The κ and PABAK values were interpreted following Landis & Koch (1977): <0 indicates poor agreement, 0.00–0.20 slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, and 0.81–1.00 almost perfect agreement. These analyses were conducted using R v. 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria) with the “EpiR” and “vcs” packages.

4.9 Ethical considerations

All studies were conducted in accordance with the tenets of the World Medical Association’s Helsinki Declaration (Holstila et al., 2013). Additionally, all studies were approved by the Ethics Committee of the OUH (record number 174/2019 for Studies I and II, and 175/2022 for Study III).

5 Results

5.1 The preoperative predictive value of lumbar discoblock (I)

Of the initial cohort of 78 patients who underwent discoblock within the specified timeframe, 44 patients (56.4%) subsequently underwent lumbar fusion or TDR surgery. A total of 29 patients were excluded from the study; this included 4 patients who had previously undergone fusion or TDR surgery at the segment of interest, and 25 patients with insufficient discoblock and/or operative parameter data available for retrospective analysis. Consequently, the final study sample comprised 15 patients, constituting 19.2% of the base population. Among these, nine patients underwent subsequent fusion surgery (comprising 3 patients for PLF, 2 patients for TLIF, and 4 patients for ALIF), while six patients underwent TDR surgery. The demographic characteristics of the study sample are presented in Table 12.

Table 12. Demographic characteristics of the study sample in Study I. (Reprinted [adapted], with permission, from original publication I © 2022 De Gruyter).

Feature	Total	Fusion	TDR
N (%)	15 (100.0%)	9 (60.0%)	6 (40.0%)
Number of males (%)	8 (53.3%)	6 (66.7%)	2 (33.3%)
Age range (mean ± SD), years	21.2-59.0 (44.9 ± 11.3)	21.2-59.0 (47.3 ± 13.0)	31.2-53.1 (41.5 ± 7.7)
Number of non-smokers (%)	9 (60.0%)	5 (55.6%)	4 (66.7%)
Follow-up time range (mean ± SD), months	3.0-18.5 (10.8 ± 5.3)	3.0-18.5 (9.2 ± 6.2)	12.0-16.0 (13.3 ± 2.1)

TDR = total disc replacement, SD = standard deviation

5.1.1 Discoblock results

The median $\Delta\text{NRS}_{\text{DB}}$ was -5.0 (Q1 -7.0 , Q3 -2.5), while the median pre-procedural and post-procedural NRS pain scores were 7.0 (Q1 5.0 , Q3 8.0) and 1.0 (Q1 0.0 , Q3 3.0), respectively, for the entire study population. $\Delta\text{NRS}_{\text{DB}}$ was statistically significant in the overall study population ($p < 0.001$) and in the fusion and TDR subgroups ($p = 0.004$ and $p = 0.031$, respectively). Further details of the discoblock parameters for each subgroup are presented in Table 13.

5.1.2 Surgical results

Twelve patients' ODI scores decreased and three patients' scores increased following surgery. Δ ODI was statistically significant in the total study cohort (median -8.0 , $p=0.021$) and in the fusion subgroup (median -18.0 , $p=0.043$), whereas it was statistically insignificant in the TDR subgroup (median -7.0 , $p=0.313$). The operative parameters by subgroup are shown in Table 13. For the entire study population, the mean interval between preoperative ODI score assessment and surgery was 133 days (range 9–228 days, median 151 days). The mean follow-up time was 10.8 ± 5.3 months. Follow-up periods for the subgroups are shown in Table 12.

Three out of the fifteen (20.0%) patients included in the study experienced postoperative complications following their respective surgeries. These complications comprised one instance of nonunion following PLF surgery, one case of prosthesis misalignment following TDR surgery, and one occurrence of neuropathic pain after TDR surgery. Two of these cases necessitated re-operation.

Table 13. Discoblock and operative parameters of the study sample in Study I. (Reprinted [adapted], with permission, from original publication I © 2022 De Gruyter).

Parameter	Total			Fusion			TDR		
	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3
Discoblock (NRS)									
Pre-procedural	7.0	5.0	8.0	7.0	3.3	7.8	7.5	5.8	8.3
Post-procedural	1.0	0	3.0	1.5	0	3.3	1.0	0.8	3.4
Δ NRS _{DB}	-5.0	-7.0	-2.5	-4.0	-6.0	-2.3	-5.5	-7.0	-4.4
p	<0.001			0.004			0.031		
Surgery (ODI)									
Preoperative	50.0	42.0	54.0	44.0	38.0	58.0	52.0	49.0	55.0
Postoperative	36.0	14.0	52.0	27.0	14.0	48.0	48.0	29.5	59.0
Δ ODI	-8.0	-28.0	-2.0	-18.0	-30.0	0	-7.0	-18.0	6.0
p	0.021			0.043			0.313		
Δ ODI%	-13.8%	-66.7%	-3.7%	-40.9%	-74.1%	-0.8%	-12.7%	-36.5%	12.2%

TDR = total disc replacement, Q1 = first quartile, Q3 = third quartile, NRS = Numerical Rating Scale, Δ NRS_{DB} = the degree of pain relief following discoblock, ODI = Oswestry Disability Index, Δ ODI = absolute change in ODI score, Δ ODI% = percentual change in ODI score

5.1.3 Correlation analysis

The postoperative ODI score exhibited no statistically significant correlation with either the preprocedural NRS pain score or the preoperative ODI score ($r=-0.30$, $p=0.276$ and $r=0.31$, $p=0.257$ for the overall cohort; $r=-0.52$, $p=0.156$ and $r=0.19$, $p=0.620$ for the fusion group; $r=0.058$, $p=0.913$ and $r=0.20$, $p=0.700$ for the TDR group).

The correlation analyses between $\Delta\text{NRS}_{\text{DB}}$ and $\Delta\text{ODI}\%$ revealed a r of 0.57 ($p=0.026$) for the overall study cohort, and 0.85 ($p=0.004$) and 0.62 ($p=0.191$) for the fusion and TDR groups, respectively. Figure 3 presents a graphical representation.

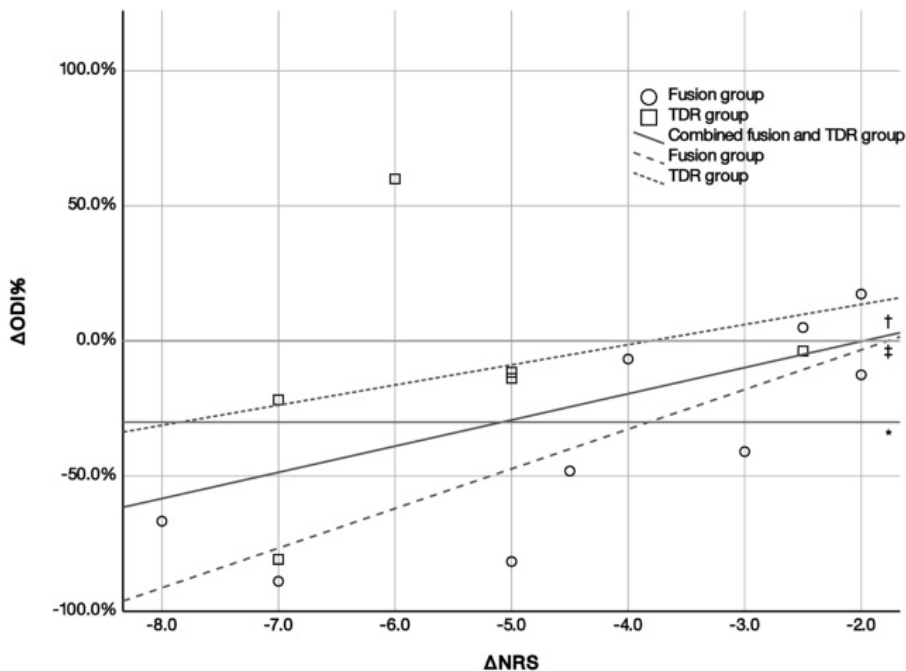


Fig. 3. A scatter plot illustrating the correlations between the degree of pain relief following discoblock (ΔNRS) and the percentage change in the Oswestry Disability Index score ($\Delta\text{ODI}\%$) for the overall study cohort († indicating $p=0.026$), and for the fusion (‡ indicating $p=0.004$) and total disc replacement (TDR) subgroups in Study I. The line marked by an asterisk (*) denotes a minimal clinically important difference (MCID) of -30% in the Oswestry Disability Index score. (Reprinted, with permission, from original publication I © 2022 De Gruyter).

5.2 The association between discoblock results and MC (II)

From the initial population of 78 patients, a total of 45 (57.7%) patients were included in the study. Exclusion criteria and their respective frequencies were as follows: an interval of more than 1 year between an MRI and discoblock (N=9), unavailability of adequate discoblock parameters in retrospect (N=9), multi-level discoblock (N=7), undergoing a procedure other than a stand-alone diagnostic discoblock (N=4), identification of an alternative cause for chronic LBP (N=3), and prior fusion or TDR surgery at the relevant level (N=1). Comprehensive demographic characteristics of the study sample can be found in Table 14.

Table 14. Demographic characteristics of the study sample in Study II. (Reprinted [adapted] under CC BY 4.0 license from original publication II © 2022 Authors).

Feature	Total	MC present	MC absent	MC1 or MC1-dominant	MC2 or MC2-dominant
N (%)	45 (100.0%)	35 (77.8%)	10 (22.2%)	16 (35.6%)	19 (42.2%)
Number of males (%)	23 (51.1%)	17 (48.6%)	6 (60.0%)	8 (50.0%)	9 (47.4%)
Age range (mean ± SD), years	31.2–72.6 (46.7 ± 9.9)	31.2–72.6 (47.7 ± 10.3)	31.2–56.8 (43.5 ± 8.1)	34.3–72.6 (46.8 ± 11.0)	31.2–64.7 (48.4 ± 9.9)
Number of non-mixed lesions (%)	-	5 (14.3%)	-	2 (12.5%)	3 (15.8%)

MC = Modic changes, MC1 = Modic changes type I, MC2 = Modic changes type II, SD = standard deviation

5.2.1 Prevalence of MC

Out of the 45 IVDs that underwent discoblock examination, 35 (77.8%) displayed adjacent MC. Among these, two (5.7%) were pure MC1, 14 (40.0%) were MC1-dominant, three (8.6%) were pure MC2, and 16 (45.7%) were MC2-dominant lesions. A comprehensive breakdown of MC locations can be found in Table 15. Consequently, the MC0 group comprised 10 (22.2%) patients, the MC1 group included 16 (35.6%) patients, while the MC2 group encompassed 19 (42.2%) patients.

The interobserver reliability for the identification of MC presence and type exhibited substantial degrees of agreement, with κ values of 0.727, 95% CI 0.389–1.000 and 0.610, 95% CI 0.301–0.919, respectively.

5.2.2 Discoblock results

Thirty-six patients (80.0%) reported relief from their LBP following discoblock, while seven patients (15.6%) experienced no change in their LBP symptoms, and LBP exacerbation was observed in two patients (4.4%). Comprehensive NRS pain scores were accessible for 41 patients (91.1%), while the remaining four patients (11.1%) had non-numerical $\Delta\text{NRS}_{\text{DB}}$ data available for analysis. Applying a threshold of ≥ 3 NRS points reduction to denote a positive discoblock, 32 patients (71.1%) were categorized as positive, whereas 14 patients (31.1%) met the positive criterion with a $\geq 80\%$ NRS decrease. No immediate complications were identified in any case.

The median pre-procedural NRS pain score was 7.0 (Q1 6.0, Q3 8.0), while the median post-procedural NRS pain score was 2.0 (Q1 1.0, Q3 3.5) for the entire patient cohort. The median $\Delta\text{NRS}_{\text{DB}}$ was -4.0 (Q1 -5.5 , Q3 -2.0) across the study population. Further details regarding discoblock parameters specific to each subgroup are presented in Table 15.

Table 15. Intervals from imaging to discoblock and discoblock parameters in Study II. (Reprinted [adapted] under CC BY 4.0 license from original publication II © 2022 Authors).

Feature	Total	MC present	MC absent	MC1 or MC1-dominant	MC2 or MC2-dominant
Interval between MRI and discoblock (mean \pm SD), months	5.0 \pm 3.5	4.9 \pm 3.4	5.4 \pm 4.0	5.5 \pm 4.2	4.3 \pm 2.7
Intervention level/MC location					
L1-L2 (%)	-	-	-	-	-
L2-L3 (%)	1 (2.2%)	1 (2.9%)	-	1 (6.3%)	-
L3-L4 (%)	3 (6.7%)	3 (8.6%)	-	1 (6.3%)	2 (10.5%)
L4-L5 (%)	18 (40.0%)	11 (31.4%)	7 (70.0%)	4 (25.0%)	7 (36.8%)
L5-S1 (%)	23 (51.1%)	20 (57.1%)	3 (30.0%)	10 (62.5%)	10 (52.6%)
Pre-procedural NRS median (Q1; Q3)	7.0 (6.0; 8.0)	7.0 (6.0; 8.0)	7.5 (5.4; 9.8)	7.0 (5.3; 7.0)	7.0 (6.0; 8.0)
Post-procedural NRS median (Q1; Q3)	2.0 (1.0; 3.5)	1.5 (0.5; 3.0)	4.0 (2.1; 6.8)	1.8 (0.0; 2.0)	1.0 (1.0; 4.5)
Δ NRS _{DB} median (Q1; Q3)	-4.0 (-5.5; -2.0)	-5.0 (-6.0; -3.0)	-2.5 (-4.0; 0.0)	-5.0 (-5.9; -3.3)	-4.0 (-6.0; 0.0)

MC = Modic changes, MC1 = Modic changes type I, MC2 = Modic changes type II, MRI = magnetic resonance imaging, SD = standard deviation, NRS = Numerical Rating Scale, Q1 = the first quartile, Q3 = the third quartile, Δ NRS_{DB} = the degree of pain relief following discoblock

5.2.3 Comparative analysis

A statistically significant difference in $\Delta\text{NRS}_{\text{DB}}$ was found between the group with MC and the MC0 group (median $\Delta\text{NRS}_{\text{DB}}$ -5.0 vs. -2.5 , respectively, $p=0.043$). While a multiple group analysis within subgroups did not reveal any significant differences in $\Delta\text{NRS}_{\text{DB}}$ ($p=0.079$), pairwise analyses demonstrated a significant difference in $\Delta\text{NRS}_{\text{DB}}$ between the MC1 and MC0 groups (median $\Delta\text{NRS}_{\text{DB}}$ -5.0 vs. -2.5 , respectively, $p=0.012$). A visual representation of these findings is given in Figure 4.

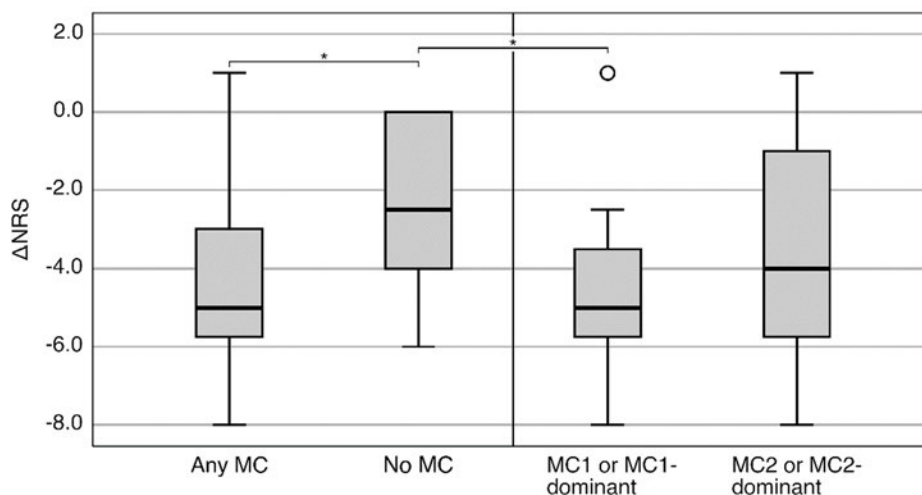


Fig. 4. Boxplot illustrating the degrees of pain relief following discoblock (ΔNRS) among subgroups categorized by the presence of any Modic changes (MC), Modic changes type I (MC1), or Modic changes type II (MC2) in Study II. The asterisks (*) indicate a statistical significance at $p < 0.05$. (Reprinted under CC BY 4.0 license from original publication II © 2022 Authors).

5.3 The prognostic value of individual and co-occurring IVD-related degenerative features on lumbar discectomy outcomes (III)

In Study III, 593 patients were identified from the register, of which 140 (23.6%) with a mean age of 45.3 ± 14.0 years were included after exclusion for unanswered pre- or postoperative PROMs ($N=429$), previous lumbar surgery

(N=14), an MRI older than six months from the surgery (N=5), and a re-operation during the follow-up period (N=5). The majority of the patients underwent a microdiscectomy (N=136; 97.1%), while four (2.9%) patients underwent an endoscopic discectomy. At the baseline, significant differences were found in the symptom duration ($p=0.007$), with that of the APD-positive group's being significantly longer than those of the APD1/3 and APD0 groups ($p=0.011$ and $p=0.020$, respectively) and in leg pain levels ($p=0.050$), where the APD1/3 exhibited significantly higher values compared to the APD-positive group ($p=0.040$). The demographic and clinical characteristics are summarized in Tables 16 and 17.

Table 16. Demographic characteristics of the study sample in Study III.

Feature	Total	APD0	APD1/3	APD-positive	p
N (%)	140 (100.0%)	29 (20.7%)	66 (47.1%)	45 (32.1%)	
Age, mean (SD)	45.3 (14.0)	43.6 (13.5)	44.6 (13.9)	47.5 (14.6)	0.431
Sex					0.081
Male, N (%)	81 (57.9%)	22 (75.9%)	36 (54.5%)	23 (51.1%)	
Female, N (%)	59 (42.1%)	7 (24.1%)	30 (45.5%)	22 (48.9%)	
BMI, mean (SD)	28.0 (5.5)	28.1 (4.8)	27.9 (5.7)	28.2 (5.8)	0.968
Active smoking					0.567
Yes, N (%)	27 (19.3%)	4 (13.8%)	15 (22.7%)	8 (17.8%)	
No, N (%)	110 (78.6%)	25 (86.2%)	49 (74.2%)	36 (80.0%)	
Missing data, N (%)	3 (2.1%)	-	2 (3.0%)	1 (2.2%)	
Preoperative anxiety					0.098
Yes, N (%)	39 (27.9%)	4 (13.8%)	23 (34.8%)	12 (26.7%)	
No, N (%)	99 (70.7%)	25 (86.2%)	41 (62.1%)	33 (73.3%)	
Missing data, N (%)	2 (1.4%)	-	2 (3.0%)	-	
Duration of symptoms					0.007
<6 weeks, N (%)	22 (15.7%)	6 (20.7%)	7 (10.6%)	9 (20.0%)	
6–12 weeks, N (%)	28 (20.0%)	10 (34.5%)	14 (21.2%)	4 (8.9%)	
3–12 months, N (%)	58 (41.4%)	9 (31.0%)	34 (51.5%)	15 (33.3%)	
>12 months, N (%)	32 (22.9%)	4 (13.8%)	11 (16.7%)	17 (37.8%)	
Level of herniation					0.427
L1-L2, N (%)	-	-	-	-	
L2-L3, N (%)	5 (3.6%)	1 (4.5%)	2 (3.0%)	2 (4.4%)	
L3-L4, N (%)	14 (10.0%)	4 (10.0%)	5 (7.6%)	5 (11.1%)	
L4-L5, N (%)	66 (47.1%)	18 (62.1%)	29 (43.9%)	19 (42.2%)	
L5-S1, N (%)	55 (39.3%)	6 (20.7%)	30 (45.5%)	19 (42.2%)	

Feature	Total	APD0	APD1/3	APD-positive	p
Preoperative motor deficit of leg impairing walking					0.414
Yes, N (%)	44 (31.4%)	12 (41.4%)	20 (30.3%)	12 (26.7%)	
No, N (%)	96 (68.6%)	17 (58.6%)	46 (69.7%)	33 (73.3%)	
Preoperative cauda equina syndrome					>0.99
Yes, N (%)	3 (2.1%)	1 (3.4%)	1 (1.5%)	1 (2.2%)	
No, N (%)	137 (97.9%)	28 (96.6%)	65 (98.5%)	44 (97.8%)	
Preoperative PROMs assessment-surgery interval, mean (SD), days	8.8 (8.4)	9.5 (8.4)	8.6 (8.8)	8.8 (7.8)	0.897
Preoperative MRI-surgery interval, mean (SD), days	44.7 (45.4)	45.2 (46.1)	44.3 (44.5)	44.8 (47.3)	0.996

APD = Advanced Preoperative Degeneration, SD = standard deviation, BMI = body mass index, PROMs = patient-reported outcome measures, MRI = magnetic resonance imaging

Table 17. Unadjusted pre- and postoperative patient-reported outcomes measures (PROMs) of the study sample in Study III.

Parameter	Total	APD0	APD1/3	APD-positive	p ¹
LBP, mean (SD)					
Baseline	52.3 (29.2)	46.0 (28.2)	57.5 (29.7)	48.0 (28.5)	0.146
Follow-up	26.1 (26.2)	24.2 (22.9)	23.6 (23.7)	30.8 (31.1)	0.468
Leg pain, mean (SD)					
Baseline	67.2 (26.7)	66.0 (31.6)	72.8 (24.5)	59.3 (25.4)	0.050
Follow-up	27.5 (29.1)	19.6 (23.3)	28.2 (29.0)	31.4 (32.2)	0.389
ODI, mean (SD)					
Baseline	45.4 (16.4)	43.8 (15.1)	47.2 (17.2)	44.0 (16.2)	0.522
Follow-up	16.1 (16.7)	12.0 (11.0)	14.7 (15.6)	20.6 (20.1)	0.127
EQ-index, mean (SD)					
Baseline	0.50 (0.15)	0.54 (0.10)	0.47 (0.17)	0.50 (0.15)	0.090
Follow-up	0.73 (0.20)	0.72 (0.17)	0.74 (0.19)	0.71 (0.23)	0.789
EQ-VAS, mean (SD)					
Baseline	45.8 (22.7)	48.4 (19.5)	42.7 (24.0)	48.6 (22.5)	0.331
Follow-up	72.7 (23.2)	67.7 (23.1)	74.0 (23.4)	73.9 (23.4)	0.561

¹ for between-group differences in baseline and follow-up values, PROMs = patient-reported outcome measures, APD = Advanced Preoperative Degeneration, LBP = low back pain, SD = standard deviation, ODI = Oswestry Disability Index

5.3.1 Magnetic resonance imaging

The mean MRI-operation interval was 44.7 ± 24.4 days. Forty-five (32.1%) patients were APD-positive, 66 (47.1%) were in the APD1/3 group, and 29 (20.7%) belonged to the APD0 group. Inter- and intra-rater reliabilities for detecting the required phenotypes for APD and for detecting APD-positivity were substantial to almost perfect, except for moderate interrater reliability for the MC phenotype (Table 18).

Table 18. Intra- and interrater reliabilities for the detection of the required phenotypes in the APD criterion and the detection of APD-positivity in Study III.

Degenerative feature	Intra (reader 1)		Intra (reader 2)		Inter (reader 1&2)	
	κ	PABAK	κ	PABAK	κ	PABAK
	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
EPD	0.66 (0.45–0.86)	0.88 (0.78–0.94)	0.72 (0.48–0.95)	0.93 (0.85–0.98)	0.71 (0.53–0.90)	0.92 (0.83–0.96)
MC	0.94 (0.83–1.00)	0.99 (0.93–1.00)	0.61 (0.35–0.87)	0.91 (0.81–0.96)	0.42 (0.12–0.71)	0.89 (0.81–0.95)
IVD degeneration	1.00 (1.00–1.00)	1.00 (0.90–1.00)	0.94 (0.56–1.00)	0.95 (0.81–0.99)	0.91 (0.82–1.00)	0.92 (0.79–0.98)
APD criterion	0.75 (0.59–0.90)	0.88 (0.78–0.94)	0.66 (0.45–0.86)	0.88 (0.78–0.94)	0.69 (0.51–0.86)	0.88 (0.80–0.94)

κ = Cohen's kappa, PABAK = prevalence-adjusted, bias-adjusted kappa, EPD = endplate damage, MC = Modic changes, IVD = intervertebral disc, APD = Advanced Preoperative Degeneration

5.3.2 Primary outcome analysis

Significant differences were noted in estimated mean baseline values for leg pain ($p=0.012$) and EQ-VAS ($p=0.007$), but not for LBP ($p=0.267$), ODI ($p=0.639$) or the EQ-index ($p=0.588$). Meanwhile all groups displayed significant improvements in all PROMs, significant between-group differences in improvement rates were noted in LBP ($p=0.038$), leg pain ($p=0.002$) and ODI ($p=0.034$), but not in QoL measures ($p=0.129$ for EQ-index, and $p=0.199$ for EQ-VAS). Table 19 and Figure 5 display the estimated mean baseline and follow-up values for each of the PROMs.

The regression coefficients (compared to the APD0 group) for the APD-positive group were statistically significant for leg pain ($+26.5$, $p=0.001$) and ODI

(+10.7, $p=0.016$), while those of the APD1/3 group were not significant for any of the PROMs (Table 19).

Table 19. Estimated means of the group's patient-reported outcome measures (PROMs) and regression coefficients in Study III.

Parameter	PROMs			Regression coefficients					
	APD0, est. mean (s.e.)	APD1/3, est. mean (s.e.)	APD-positive, est. mean (s.e.)	Surgery		Interaction: surgery * APD1/3		Interaction: surgery * APD- positive	
				B ¹ (s.e.)	p ¹	B ² (s.e.)	p ²	B ² (s.e.)	p ²
LBP									
Baseline	53.2 (4.7)	60.0 (2.9)	46.9 (3.4)						
Follow-up	29.7 (4.8)	29.2 (3.0)	32.1 (4.1)	-23.5 (6.0)	<0.001	-7.3 (7.1)	0.301	8.8 (7.9)	0.269
p ³		0.038							
Leg pain									
Baseline	69.6 (4.4)	74.5 (2.8)	57.0 (3.7)						
Follow-up	19.8 (5.1)	32.5 (3.2)	33.8 (4.5)	-49.7 (6.1)	<0.001	7.8 (7.1)	0.276	26.5 (8.1)	0.001
p ³		0.002							
ODI									
Baseline	47.6 (2.3)	47.9 (1.5)	43.7 (2.0)						
Follow-up	13.6 (2.8)	17.1 (1.7)	20.4 (2.5)	-33.9 (3.3)	<0.001	3.2 (3.9)	0.416	10.7 (4.4)	0.016
p ³		0.034							
EQ-index									
Baseline	0.47 (0.02)	0.44 (0.01)	0.45 (0.02)						
Follow-up	0.64 (0.03)	0.70 (0.02)	0.65 (0.03)	0.18 (0.04)	<0.001	0.08 (0.04)	0.073	0.02 (0.05)	0.666
p ³		0.129							
EQ-VAS									
Baseline	40.2 (3.3)	40.3 (2.2)	48.3 (2.9)						
Follow-up	60.6 (4.0)	70.3 (2.5)	73.2 (3.6)	20.4 (4.7)	<0.001	9.6 (5.6)	0.085	4.5 (6.3)	0.477
p ³		0.199							

¹ for the overall effect of the surgery, ² for group-specific interaction (compared to the APD0 group), ³ for between-group differences in improvement rates, PROMs = patient-reported outcome measures, APD = Advanced Preoperative Degeneration, est. mean = estimated mean, s.e. = standard error, B = regression coefficient, LBP = low back pain, ODI = Oswestry Disability Index

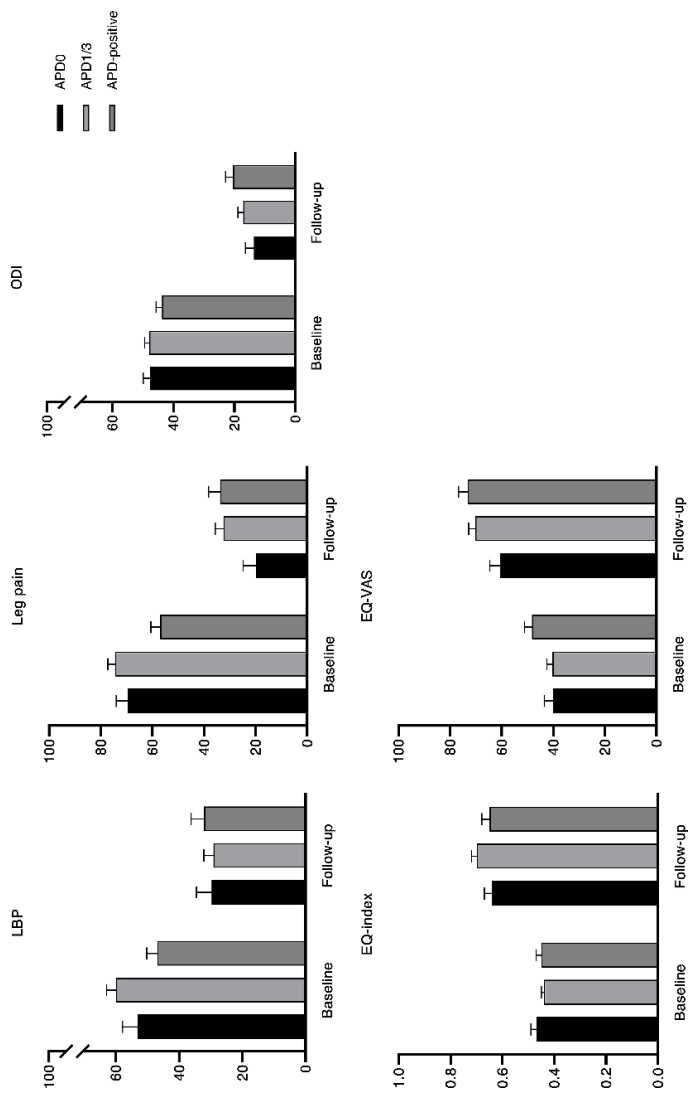


Fig. 5. A bar chart with standard errors showing the estimated means of patient-reported outcome measures (PROMs) for each group in Study III.

5.3.3 Sensitivity analysis

The MC-size-based criterion revealed significant between-group differences in leg pain improvement rates ($p=0.028$). The regression coefficients for the 1/3 group were statistically significant for leg pain (+18.5, $p=0.008$) and ODI (+8.3, $p=0.026$), while those for the positive group were not significant for any of the PROMs. The MEC criterion was associated with significant between-group differences in EQ-index improvement rates ($p=0.032$), for which the regression coefficient was statistically significant for the MEC-positive group (-0.069 , $p=0.032$). Data are presented in Tables 20 and 21.

Table 20. Estimated means of the group's patient-reported outcome measures (PROMs) and regression coefficients using the MC-size-based criterion in Study III.

Parameter	PROMs			Regression coefficients					
	0/3, est. mean (s.e.)	1/3, est. mean (s.e.)	Positive, est. mean (s.e.)	Surgery		Interaction: surgery * 1/3		Interaction: surgery * positive	
				B ¹ (s.e.)	p ¹	B ² (s.e.)	p ²	B ² (s.e.)	p ²
LBP									
Baseline	54.4 (4.5)	56.6 (2.9)	52.7 (4.3)						
Follow-up	28.7 (4.7)	30.3 (2.9)	32.2 (4.7)	-25.7 (5.7)	<0.001	-0.64 (6.8)	0.925	5.2 (8.3)	0.531
p ³		0.696							
Leg pain									
Baseline	70.8 (4.4)	67.5 (2.8)	69.0 (4.3)						
Follow-up	19.2 (5.0)	34.5 (3.1)	29.9 (5.1)	-51.6 (5.9)	<0.001	18.5 (6.9)	0.008	12.5 (8.6)	0.147
p ³		0.028							
ODI									
Baseline	49.3 (2.2)	45.4 (1.4)	47.5 (2.2)						
Follow-up	14.1 (2.7)	18.4 (1.7)	18.2 (2.7)	-35.3 (3.1)	<0.001	8.3 (3.7)	0.026	6.0 (4.5)	0.183
p ³		0.085							
EQ-index									
Baseline	0.44 (0.02)	0.46 (0.01)	0.44 (0.02)						
Follow-up	0.67 (0.03)	0.66 (0.02)	0.70 (0.03)	0.23 (0.03)	<0.001	-0.02 (0.04)	0.609	0.04 (0.05)	0.438
p ³		0.360							
EQ-VAS									
Baseline	40.4 (3.2)	41.6 (2.1)	46.9 (3.2)						
Follow-up	60.8 (3.8)	69.4 (2.4)	75.8 (3.8)	20.5 (4.5)	<0.001	7.4 (5.4)	0.170	8.4 (6.4)	0.193
p ³		0.324							

¹ for the overall effect of the surgery, ² for group-specific interaction (compared to the APD0 group), ³ for between-group differences in improvement rates, PROMs = patient-reported outcome measures, APD = Advanced Preoperative Degeneration, est. mean = estimated mean, s.e. = standard error, B = regression coefficient, LBP = low back pain, ODI = Oswestry Disability Index

Table 21. Estimated means of the group's patient-reported outcome measures (PROMs) and regression coefficients using the MEC criterion in Study III.

Parameter	PROMs		Regression coefficients			
	MEC-negative, est. mean (s.e.)	MEC-positive, est. mean (s.e.)	Surgery	Interaction: surgery * MEC-positive	p^1	p^2
			B ¹ (s.e.)	B ² (s.e.)		
LBP						
Baseline	58.4 (3.2)	52.8 (3.0)				
Follow-up	30.8 (3.3)	30.3 (3.1)	-22.5 (3.7)	-5.1 (5.4)	<0.001	0.344
p^3		0.344				
Leg pain						
Baseline	70.8 (3.1)	67.4 (3.0)				
Follow-up	30.8 (3.5)	30.5 (3.4)	-36.9 (3.9)	-3.0 (5.6)	<0.001	0.587
p^3		0.587				
ODI						
Baseline	47.9 (1.6)	45.8 (1.5)				
Follow-up	17.7 (1.9)	17.0 (1.8)	-28.7 (2.1)	-1.5 (3.0)	<0.001	0.625
p^3		0.625				
EQ-index						
Baseline	0.47 (0.01)	0.43 (0.01)				
Follow-up	0.65 (0.02)	0.69 (0.02)	0.26 (0.02)	-0.07 (0.03)	<0.001	0.032
p^3		0.032				
EQ-VAS						
Baseline	40.0 (2.3)	44.7 (2.2)				
Follow-up	65.4 (2.7)	40.0 (2.3)	27.6 (3.0)	-2.2 (4.3)	<0.001	0.611
p^3		0.611				

¹ for the overall effect of the surgery, ² for group-specific interaction (compared to the MEC-negative group), ³ for between-group differences in improvement rates, PROMs = patient-reported outcome measures, MEC = Modic-endplate complex, est. mean = estimated mean, s.e. = standard error, B = regression coefficient, LBP = low back pain, ODI = Oswestry Disability Index

6 Discussion

The objective of this research was to evaluate the preoperative predictive values of discoblock and common degenerative MRI features on lumbar spine surgery. This research also sought to study the relationship between discoblock results and the presence of MC. The results of Study I contribute insights to the limited body of knowledge concerning the usability of discoblock as a preoperative patient selection tool for lumbar fusion and TDR surgeries. Furthermore, Study II provides a deeper understanding of the pain characteristics associated with lumbar MC. Lastly, Study III clarifies the previous conflicting research regarding whether preoperative degenerative features in the operated lumbar segment influence the treatment outcomes of lumbar discectomy. Single degenerative features were also combined into a novel multi-dimensional criterion named APD to assess the preoperative predictive value of co-occurring advanced-level degenerative phenotypes.

6.1 The preoperative predictive value of lumbar discoblock (I)

Study I demonstrated a statistically significant association between the discoblock result and the short-term disability outcome of lumbar fusion or TDR surgery. Across the entire study cohort, this correlation was classified as moderate in strength and held statistical significance ($r=0.57$, $p=0.026$). In subgroup analyses based on the treatment modality, the correlation was found to be non-significant in the TDR group ($r=0.62$, $p=0.191$), but very strong and statistically significant in the fusion group ($r=0.85$, $p=0.004$). Previous research, which has reported consistent findings for up to one- and three-year follow-up periods, has indicated the preoperative value of discoblock in the context of oblique lumbar interbody fusion (OLIF) and ALIF, aligning with the findings of this study (J. Liu et al., 2020; Ohtori et al., 2009).

The protocol of discoblock in the current study somewhat differed compared to previous research on the preoperative screening value of discoblock. A novel approach was introduced, as the discoblock result was assessed as a continuous variable ($\Delta\text{NRS}_{\text{DB}}$) derived from the difference between pre- and post-procedural LBP scores. In contrast, Ohtori et al. (2009) employed a standalone discoblock, considering any decrease in LBP sufficient for a positive result in their RCT comparing discography with discoblock for diagnosing LBP before ALIF. Similarly, J. Liu et al. (2020) employed a standalone discoblock in their study,

focusing on its utility as a preoperative selection tool for OLIF surgery. According to their protocol, however, patients underwent discoblock only if a prior discography yielded positive results, and a recurrence of LBP after discoblock was used as the criterion for a positive discoblock outcome.

Overall, there is an absence of a universally recognized cut-off value for defining a positive discoblock. Consequently, individual studies have employed a range of criteria to define a positive result, as delineated in Table 3 on pages 29–30. In the present research, alongside the correlation analysis, the calculation of $\Delta\text{NRS}_{\text{DB}}$ allowed for a more comprehensive examination of the efficacy of discoblock in preoperative settings. This approach facilitated an investigation into whether a specific threshold for $\Delta\text{NRS}_{\text{DB}}$ could be identified, beyond which the likelihood of achieving the commonly accepted MCID of a 30% reduction in ODI is heightened (Ostelo et al., 2008). Our analysis suggested that a $\Delta\text{NRS}_{\text{DB}}$ value of 4 could serve as a potential cut-off point for a positive result, as only one out of six patients (16.7%) with a mild discoblock response (i.e., $\Delta\text{NRS}_{\text{DB}}$ score of -2.0 to -4.0) managed to surpass the MCID of the ODI score in the overall cohort. Consequently, we propose that a $\Delta\text{NRS}_{\text{DB}}$ exceeding four be considered a criterion for a positive discoblock. However, it is essential to validate this finding in future studies. Additionally, the range for a positive discoblock, from -4.5 to -10.0 , remains broad. Further research may help establish a more precise range for a positive result, reducing potential heterogeneity within the positive result group.

While the pre-procedural NRS pain scores appeared to be similar across fusion and TDR groups, suggesting no impact on the outcomes, a statistical analysis was not conducted to confirm this observation. In interpreting the results, it is important to acknowledge that patient-specific $\Delta\text{NRS}_{\text{DB}}$ values may be influenced by the initial level of pre-procedural LBP as this factor determines the potential magnitude of LBP reduction. Therefore, when employing a specific numerical threshold for LBP reduction as a criterion for a positive discoblock result, as proposed in this study, this issue should be considered. An alternative perspective suggested in previous research involves assessing the percentual change in $\Delta\text{NRS}_{\text{DB}}$ when judging a result to be positive or negative (Barendse et al., 2001; Bartynski & Rothfus, 2007; Derby et al., 2012; Nyström et al., 2023). However, this approach is not without its limitations, as achieving for example a 50% reduction in LBP requires markedly different absolute reductions in patients with low and high preprocedural LBP scores. Thus, in the clinical context, it may

be most advantageous to report the preprocedural LBP score in addition to the absolute pain relief value that is suggested by the present research.

A limited number of studies have assessed the discoblock results in comparison to discography, which was historically more widely used and considered one of the main tests for the diagnosis of discogenic LBP (Carragee, 2001; Malik et al., 2013). Putzier et al. (2013) investigated a combined discography-discoblock procedure in degenerated lumbar segments of chronic LBP patients. They found that the positive discoblock criterion was met in ten out of eleven patients (90.9%) with a concordant pain response in discography, and in approximately half (7 out of 13 patients, 53.9%) with discordant responses. A significant correlation was found between discoblock results and binarily (concordant or any other response) categorized discography results. These results allowed the authors to conclude that discoblock may serve as a suitable alternative to discography or could at least be considered as a discriminative tool for those with a debatable discography result, that is a disconcordant pain response.

Ohtori et al. (2009) similarly reported results supporting the utilization of preoperative discoblock. They randomized chronic LBP patients into two groups, one receiving preoperative lumbar discoblock and the other preoperative discography, with patients with positive results undergoing ALIF surgery. At the final follow-up of three years, the discoblock group exhibited significantly better outcomes in pain reduction and reduced disability compared to the discography group. Nonetheless, also concerning the present research, the utilization of surgical outcomes as the definitive benchmark for assessing the efficacy of preoperative discoblock can pose challenges (Buenaventura et al., 2007; Carragee, Lincoln, et al., 2006). This is because a multitude of factors, including the severity of the preoperative symptoms, occupational status, and demographic characteristics, can influence the results of lumbar spine surgery (Khor et al., 2018; McGirt et al., 2017). In other words, even if the preoperative diagnostic test was impeccable, surgical results might still prove to be unsatisfactory. On a broader scale, the absence of a universally accepted reference standard for diagnosing discogenic LBP and the lack of comparative studies between discoblock and other diagnostic methods in a preoperative setting further complicate the critical evaluation of discoblock (Hancock et al., 2007; Hartvigsen et al., 2018).

From another viewpoint, some studies have explored the extent of agreement between consecutive stand-alone discoblock and discography procedures

conducted on the same lumbar segment. DePalma et al. (2009) conducted an analysis on a highly selected cohort of patients with major structural changes in the IVDs that were subjected to discography. Among the IVDs with either completely or partially concordant pain in response to discography, a notable portion of 80.0% exhibited a positive response to discoblock, that is a reduction of more than 50% in LBP. In contrast, findings from two other study samples indicate that discoblock aligns with the positive outcomes of discography in approximately 30–50% of cases, with variations based on the chosen criteria for a positive discoblock result (Alamin et al., 2011; Derby et al., 2012). In these studies, it remains debatable whether primarily discography is associated with low specificity or discoblock with low sensitivity.

It is also unclear whether discoblock is a safer invasive method for diagnostics of discogenic LBP. Discography was linked to adverse clinical outcomes in a series of studies with ten-year follow-ups on subjects without major LBP (Carragee et al., 2009; Cuellar et al., 2016). The studies compared lumbar degenerative MRI changes in those undergoing discography to matched controls. The discography group exhibited significantly greater degenerative progression and associated clinical deterioration, including increased LBP episodes, work loss, medical visits, imaging, and surgeries. The authors assumed that these effects resulted from the puncture and pressurization of the IVD. The injection fluid was not reported, and, importantly, the injection pressures possibly rose above the recommended limits in guidelines, as criticized elsewhere (McCormick et al., 2018). In contrast, such a progression of degenerative MRI changes was not seen in two other five-to-seven-year follow-up studies of subjects who had undergone discography (McCormick et al., 2019) or discoblock (Ohtori et al., 2013).

Due to the unavoidable AF puncture during both discography and discoblock procedures, such variability in the results might be attributed to the composition of the injected substance. However, consensus regarding the toxicity of the injectate remains inconclusive. In vitro studies on bovine and human IVD cells have demonstrated the short-term toxicity of local anesthetics (Cai et al., 2014; Iwasaki, Sudo, Yamada, Higashi, et al., 2014; Lee et al., 2010; Quero et al., 2011) and contrast medium (Gruber et al., 2012). It is in fact suggested that the toxicity of local anesthetics may exceed that of contrast medium (Chee et al., 2014; Iwasaki, Sudo, Yamada, Ito, et al., 2014). Nevertheless, findings from an in vivo rabbit model showed no marked difference in the IVD cell count or histological scores between groups injected with local anesthetic or saline after six or twelve

months (Iwasaki, Sudo, Yamada, Higashi, et al., 2014). Yet human IVD cells harvested during surgery four weeks after preoperative discoblock revealed significantly greater injury compared to the discography group injected with gadobutrol (Strube et al., 2017).

6.2 The correlation between discoblock result and MC (II)

Study II revealed significant associations between $\Delta\text{NRS}_{\text{DB}}$ and both the presence and type of adjacent MC. Patients with adjacent MC exhibited significantly higher $\Delta\text{NRS}_{\text{DB}}$ compared to those without (median $\Delta\text{NRS}_{\text{DB}}$ -5.0 vs. -2.5 , respectively, $p=0.043$). Moreover, those with MC1 experienced significantly greater pain relief in contrast to those without adjacent MC (median $\Delta\text{NRS}_{\text{DB}}$ -5.0 vs. -2.5 , respectively, $p=0.012$). Previous studies have similarly explored the relationship between discoblock outcomes and the presence of MC, aligning with the findings of the present research. One study reported a non-significant trend toward a higher occurrence of adjacent MC1 in chronic LBP patients with a positive discoblock versus those with a negative response (Alamin et al., 2011). Subsequently, Putzier et al. (2013) found a statistically significant correlation between the presence of MC1 or MC2 and a positive discoblock. The criterion for a positive discoblock varied across these studies, and, importantly, their injection methodologies either predominantly required a preceding positive discography or combined discoblock with discography, in contrast to the present study.

It is plausible that patients with adjacent MC1 formed the distinctive group within this study sample, thereby contributing to the significant difference in the analysis based on the presence of MC. This assumption is supported by previous understandings of MC1 characteristics. MC1 are not only suggested to exhibit the strongest association with LBP compared to other MC types (Mera et al., 2021; Saukkonen et al., 2020; K. J. Thompson et al., 2009) but are also recognized for their increased lability (Hutton et al., 2011; T. S. Jensen et al., 2009) and metabolic activity (Järvinen et al., 2020; Perilli et al., 2015). Järvinen et al. (2020) explored MC characteristics through bone scintigraphy, where the tracer uptake intensity is correlated with the bone blood flow. Their findings indicated a significantly increased likelihood of tracer uptake in regions containing an MC1-component (74.1% vs. 4.6% in segments with and without an MC1-component within the lesion, respectively). Pure MC1 exhibited the most intense tracer uptake. These results were concluded to support the theory of increased blood flow and bone turnover in lesions containing MC1 components. Additionally,

Perilli et al. (2015) conducted a micro-CT assessment of biopsies of MC-harboring BM, demonstrating that MC1 displayed high a bone formation and erosion ratio, further implying the heightened activity of these lesions.

Although no statistical tests were employed, the data implies no clinically significant differences in preprocedural NRS pain scores between the groups. Consequently, the initial levels of LBP are unlikely to account for the outcomes, thereby leaving three primary theories for the observed results based on previous research. Firstly, nerve penetration in healthy IVDs is typically confined to superficial layers (Groh et al., 2021), while degenerated IVDs may display deeper innervation aligned with damaged areas, sometimes reaching even the NP (Coppes et al., 1997; Freemont et al., 1997; W. E. B. Johnson et al., 2001; Peng et al., 2005). This neoinnervation is often considered one of the primary factors contributing to discogenic LBP (Fujii et al., 2019). Concurrently, MC are strongly linked with IVD degeneration, particularly MC1, which correlate with advanced degeneration of the adjacent IVD compared to other MC types (Määttä, Karppinen, et al., 2015; Mok et al., 2016). Therefore, the stronger response to discoblock in IVDs featuring adjacent MC1 may result from the local anesthetic's more effective interaction with the internal innervation of the IVD. This could occur either through the penetration of nerves to the injection site or the ability of the local anesthetic to reach the site of innervation through IVD tears. The role of IVD tears on the result of discoblock was highlighted by Bartynski & Rothfus (2007): after discoblock executed following discography, only 20.7% of the non-leaking IVDs demonstrated complete or near-complete pain relief, whereas the same proportion was 74.0% for the IVDs that were noted to leak contrast medium.

Secondly, the changes in the EP might have relevance to the current study's outcomes. Typically, innervation ends in the BM just proximal to the cartilaginous EP (Lotz et al., 2013). However, immunohistochemical analyses revealed that EPs related to MC1 or MC2 display significantly higher nerve density compared to EPs without adjacent MC (Ohtori et al., 2006). Although no difference in nerve density was observed between MC1 and MC2 groups, the expression of TNF, a mediator of the inflammatory response, was significantly elevated in EPs associated with MC1. This increased TNF expression and subsequent inflammation were suggested by the authors to provoke irritation in the EP nerves, potentially contributing to LBP. Research on cadaver spines further supported this notion, indicating notably higher EP innervation in the presence of MC1

compared to EPs not connected to MC (Fields et al., 2014). These notions might clarify the highlighting of the MC1 group in the present study.

The potential influence of co-localizing EPD in the present study remains open to discussion. Fields et al. (2014) demonstrated a greater prevalence of nerves in EPs associated with EPD compared to those linked to MC1. Moreover, MC and EPD commonly co-exist, and the severity of the EPD corresponds to the presence of MC (Farshad-Amacker et al., 2014; Z. Feng et al., 2018; Määttä et al., 2018; Zehra et al., 2019). Hence, it remains a matter of debate whether the primary pathology contributing to the heightened pain relief rates in patients with MC1 could be more related to EPD than to MC.

Concerning the third theory, it is plausible that the enhanced pain relief observed in patients with MC1 may be attributed to the relocation and effect of the anesthetic in the adjacent BM. The presence of MC1 has been associated with more advanced degeneration of the adjacent EP, leading to increased communication between the IVD and BM through the EP region (Määttä, Karppinen, et al., 2015; Rajasekaran et al., 2004). This interaction can facilitate the transfer of IVD cells or their secreted substances into the BM, initiating an inflammatory response and as previously hypothesized, subsequent formation of MC (Braithwaite et al., 1998; Ma et al., 2011). Indeed, previous research has illustrated an ongoing crosstalk between the IVD and adjacent MC-harboring BM (Dudli et al., 2017). Thus, considering that the vertebral body itself contains nerves and can also be a source of pain (Bailey et al., 2011), the greater pain relief observed in patients with MC1 might be attributed to the anesthetics' ability to anesthetize the inflammatorily irritated nerves within the BM.

6.3 The prognostic value of individual and co-occurring IVD-related degenerative features on lumbar discectomy outcomes (III)

The primary aim of the Study III was to establish a reliable criterion for evaluating the preoperative co-occurrence of advanced-level IVD-related degenerative phenotypes and to assess its clinical utility in predicting short-term outcomes following single-level lumbar discectomy. Initially, EPD, MC, and IVD degeneration were examined independently, categorizing them into non-advanced and advanced phenotypes. Subsequently, drawing upon existing literature, a novel MRI-based criterion termed "Advanced Preoperative Degeneration" (APD) was established and evaluated for its reliability. While single advanced-level degenerative phenotypes did not demonstrate preoperative predictive value for the

outcome measures, meeting the APD criterion preoperatively was significantly associated with poorer outcomes in terms of leg pain and disability. In other words, patients with at least two of the three included advanced-level MRI-detected degenerative phenotypes in the operated lumbar segment preoperatively suffered from higher levels of leg pain and disability one year postoperatively. Thus, our findings may contribute to understanding the relatively common persistence of low-grade leg pain, along with LBP and disability, following lumbar discectomy (Rushton et al., 2020).

The selection of the APD criterion components—EPD \geq 25%, MC1, and IVD degeneration of Pfirrmann grade \geq 4—was based on prior literature on lumbar spine degeneration. These degenerative features were chosen because they are common in clinical lumbar spine imaging and, to enhance the validity of the criterion, their suggested association with LBP (Jamaludin et al., 2023; Määttä et al., 2018; Mera et al., 2021). Furthermore, simplicity in the categorization of the included features was prioritized, avoiding complex classification systems like the Nordic Modic Classification (T. S. Jensen et al., 2007), due to the exploratory nature and limited sample size of the study.

The cohort of lumbar single-level primary discectomy patients was selected to preliminarily test the APD criterion's clinical predictive value for inferior surgical outcomes, given the notable prevalence of post-discectomy pain (Parker et al., 2015; Suri et al., 2017) and the suggested influence of degenerative features of the operated segment on such pain (Lurie et al., 2013; Papanastasiou et al., 2020; Takahashi et al., 2021). By restricting the sample to discectomy patients and applying deliberate inclusion and exclusion criteria, we aimed to enhance the homogeneity of the study population, which is crucial for such a preliminary study. Naturally, further validation studies are essential, and future studies may demonstrate the APD criterion's clinical relevance also in different and possibly more complex spine surgery populations, such as patients with chronic discogenic LBP. In addition, future research may be able to refine the co-occurrence combinations to enhance clinical utility.

The threshold for a positive APD criterion was defined as the presence of at least two advanced phenotypes, inherently leading to diverse combinations of advanced phenotypes and heterogeneity among the 45 patients classified as APD-positive. However, the degenerative processes involving EPD, MC and IVD degeneration are highly correlated (Farshad-Amacker et al., 2017), suggesting that the APD-positive group represents an analogous pathological degenerative

entity, thereby supporting the validity of the APD criterion. Notably, the APD-positive group exhibited significantly longer symptom durations, and also the baseline leg pain estimate was markedly lower than those reported in general discectomy patient populations in previous studies (Clark et al., 2020). As hypothesized, these patients exhibited poorer short-term surgical outcomes. These findings may reflect that their symptoms are not solely attributable to the LDH or that their clinical pathway leading to LDH, as well as their post-discectomy progression, differs from that of the other groups. Two primary mechanisms that may explain the potentially differing postoperative progression are discussed below.

Firstly, surgical excision of the LDH may induce biomechanical changes within the operated segment, potentially resulting in reduced IVD space height, which likely was already somewhat decreased in the APD-positive group. With such changes and potential subsequent instability, residual mechanical compression of the affected nerve root may follow explaining the higher levels of leg pain and disability. Such mechanical compression of the nerve root has been termed as vertical stenosis in previous literature (C. Chan & Peng, 2011; Kotilainen et al., 2001; Schaller, 2004).

Secondly, patients in the APD-positive group may have been more susceptible to residual nerve root irritation due to rLDH. In their meta-analysis, Brooks et al. (2021) demonstrated that preoperative MC1 represents a significant risk factor for rLDH. Additionally, the authors identified an increased disc height index, i.e. preserved IVD space height, as a significant risk factor for rLDH, while Pfirrmann classification grades 1–3 vs. 4–5 showed no predictive value. Conversely, in the present study, MC1 or any other individual advanced phenotype did not appear to influence PROMs, as evidenced by the outcomes of the APD1/3 group. Taken together, these findings may suggest that a composite phenotype of MC1 and advanced EPD presents a greater risk factor for rLDH compared to MC1 alone, potentially explaining the results observed in the APD-positive group. However, radiological postoperative data is needed to validate this hypothesis.

Hypothetically, biochemical factors may also explain the findings. It is known that degenerated IVDs secrete increased levels of pain-related inflammatory molecules (Lyu et al., 2021). Due to the implicated higher degrees of postoperative degeneration, the APD-positive group may have secreted higher levels of these molecules. Given the suggested theory on the chemical irritation component in LDH and non-LDH sciatica (Mulleman et al., 2006; Peng et al.,

2007), perhaps such elevated levels of IVD-secreted substances caused the increased leg pain through sustained nerve irritation. However, it is important to note that certain cytokines are also suggested as important factors in the resolution process of LDH (Z. Johnson et al., 2015).

Radiological data indicate that segmental degeneration progresses in the years following lumbar discectomy, with some studies linking it to post-discectomy LBP (Barth et al., 2008; Gelalis et al., 2019; Rahme et al., 2010; Takahashi et al., 2021; Weiner et al., 2015). These post-discectomy degenerative changes include progressive damage to EPs, the formation of MC, IVD desiccation, a decrease in IVD height, and facet joint osteoarthritis. However, our findings suggest that the short-term risk of post-discectomy LBP does not increase in the presence of preoperative single or co-occurring advanced degenerative phenotypes. It is important to note that the potential longer-term effects of the APD criterion cannot be ruled out, as demonstrated in the study by Yorimitsu et al. (2001), where a combination of age ≤ 35 years and advanced preoperative IVD degeneration was identified as a significant risk factor for severe LBP ten years after discectomy. Furthermore, a meta-analysis linked preoperative MC1 with significantly poorer disability outcomes at two years, but not at the one-year postoperative time point following lumbar discectomy (Nian et al., 2023). Thus, the one-year postoperative follow-up in the current study may not be adequate for detecting significant differences in post-discectomy LBP across the groups. Nonetheless, the APD-group exhibited significantly poorer disability outcomes at one year, suggesting that significant differences in LBP may emerge later, or that the VAS for LBP, as a unidimensional tool, may be inadequate in this context (Haefeli & Elfering, 2006).

In addition to the APD0 group, which included patients with no advanced phenotypes, the APD1/3 group—comprising patients with one of the included advanced phenotypes—was utilized as a comparison group. This group, consisting of 66 patients (47.1% of the study sample), was the largest and likely the most heterogeneous; by definition, this group included patients with three distinct advanced degenerative phenotypes. This heterogeneity may compromise its validity, as some included phenotypes might have lower clinical relevance. For instance, in the case of MC, the relationship with clinically significant LBP and associated disability remains inconclusive (Lambrechts et al., 2023). However, evaluating the predictive value of individual advanced phenotypes was beyond the scope of this study, and rigorous subgroup analyses were therefore not

conducted. Consequently, although no predictive value was demonstrated for the APD1/3 group, definitive conclusions regarding the role of singular advanced degenerative phenotypes cannot be drawn. The significantly higher leg pain estimate of 74.5 in this group, compared to 57.0 in the APD-positive group, aligns more closely with values reported in previous lumbar discectomy studies (Clark et al., 2020). Thus, the APD1/3 group, along with the APD0 group, may more accurately represent typical lumbar discectomy patients.

The sensitivity analysis on the co-occurrence of advanced degenerative phenotypes revealed that findings significant for the APD-positive group became insignificant when the threshold for MC was based on lesion size rather than type. This suggests that, in this context, MC1 may be a critical component in the co-occurrence of the included IVD-related degenerative features. This notion is supported by evidence indicating that MC1 may be more clinically significant, as that specific MC type potentially correlates with markedly faster degeneration of the affected segment (Kerttula et al., 2012; Luoma et al., 2009). Meanwhile, MC2, traditionally regarded as more stable lesions (Modic, Steinberg, et al., 1988; Perilli et al., 2015), may be less clinically significant even when extensive, as supported in the present study. Notably, the sensitivity analysis identified a statistically significant and clinically meaningful regression coefficient for leg pain in the 1/3 group (+18.5, $p=0.008$), highlighting the need for further research to refine the role of specific degenerative phenotypes in this subgroup.

The sensitivity analysis demonstrated no predictive value for the MEC criterion, suggesting that the mere co-occurrence of MC and EPD lacks clinical relevance in this context unless they exhibit specific characteristics, such as being of a particular type or extensive. The original study on the MEC criterion by Baker et al. (2022) reported its association with inferior disability outcomes when identified preoperatively within the surgical segment in a cohort of cervical fusion surgery patients. However, comparing the results of the present study with those of Baker et al. (2022) is not straightforward. Importantly, their methodology included stabilization in their surgical procedures, potentially preventing similar biomechanical changes as those following standalone discectomy. Additionally, MC are less common in the cervical spine, and clinically more significant MC lesions, for example MC1, may have been relatively rare (Lambrechts et al., 2023). Finally, the different biomechanical environments in the cervical and lumbar spines may signify differing clinical values for MC and other degenerative features, as suggested by previous literature (Cramer & Darby, 2014; Lambrechts et al., 2022, 2023).

6.4 Strengths and limitations

6.4.1 *The preoperative predictive value of lumbar discoblock (I)*

Study I contains some limitations. The study setting was retrospective, the study population was small, and the exclusion rate was high. Regarding demographic characteristics, some smokers were included. Smoking is a known risk factor for inferior outcomes in lumbar surgery (Khor et al., 2018; McGirt et al., 2017), and predisposes patients undergoing lumbar fusion to non-union (Li et al., 2021). In our study cohort, smokers were strongly advised to quit preoperatively by the operating surgeon. However, cessation of smoking was not included in the inclusion criteria, and as it was not considered as a confounder in statistical testing, we are unable to totally rule out its effect on the study outcomes.

A control group consisting of patients who underwent lumbar fusion or TDR surgery without preoperative discoblock or alternative screening measures was not included in the study. In fact, we were unable to control the number of patients who underwent the operations without a preoperative discoblock. Consequently, the potential for selection bias arises, as certain patients included in the study may have presented with distinct symptomatology or imaging characteristics compared to those who did not undergo a preoperative discoblock assessment.

The use of $\Delta\text{NRS}_{\text{DB}}$ as the assessment criterion for discoblock is subject to inherent limitations. Firstly, although the pre-procedural NRS values were roughly comparable within each subgroup, statistical confirmation of this equivalence was not conducted. At the individual patient level, the pre-procedural value potentially exerts a significant influence on the outcome of discoblock, as it may constrain the extent of achievable pain relief, particularly when the pre-procedural NRS value falls towards the lower end of the spectrum. Importantly, the pre-procedural NRS was not accounted for as a confounding factor in the analyses.

Study I exclusively employed the ODI as its sole outcome measure, lacking additional assessments, for example pain outcome measures. Furthermore, for certain patients, there was a considerable duration of up to 228 days between the assessment of preoperative ODI scores and the surgical procedure. This discrepancy may have resulted in inaccuracies in capturing true preoperative disability levels, as these patients might have still been receiving conservative

treatment earlier in their care pathway, which has demonstrated the potential to improve disability levels (Chou et al., 2009). However, in clinical practice, symptoms were reaffirmed as unchanged immediately before surgery, thereby mitigating the likelihood of major erroneous preoperative ODI scores. Some potential for recall bias still remains, as the recollection of disability levels at the time of the past assessment may have changed during the relatively long interval.

It is important to note that the follow-up periods varied, particularly in the fusion group, ranging from 3.0 to 18.5 months. Patients with shorter follow-up durations fell below the generally recommended 12-month minimum for lumbar degenerative spine surgery (Staartjes et al., 2019). As a result, these patients may still have experienced further postoperative improvement or deterioration, adding a level of uncertainty to the final outcome assessments.

The primary strength of the Study I lies in its novelty. While stand-alone discoblock has been previously utilized in preoperative patient selection settings (J. Liu et al., 2020; Ohtori et al., 2009; G. Wang et al., 2023), our study introduced a novel and potentially more informative approach to preoperative discoblock evaluation by analyzing the result as a continuous variable ($\Delta\text{NRS}_{\text{DB}}$), calculated as the difference between pre- and post-procedural LBP scores. Additionally, the study population consisted entirely of clinical patients, thereby enhancing the direct clinical applicability of our findings.

6.4.2 The correlation between discoblock result and MC (II)

Due to methodological similarities, Study II shares certain limitations with Study I. The study was retrospective and involved a relatively small patient cohort, resulting in the need to combine some of the MC type groups. The impact of pre-procedural NRS values on $\Delta\text{NRS}_{\text{DB}}$ remained uncontrolled, despite efforts to ensure approximately equal pre-procedural NRS values through descriptive statistics. Similarly, Study II may exhibit some degree of selection bias, as we were unable to regulate whether patients were referred for discoblock based on specific symptoms or MRI findings. Indeed, it remains uncertain whether the relatively high prevalence of MC was inherent to the study population or if patients with MC were more readily referred for discoblock to evaluate the impact of such lesions on the patients' LBP.

While competing structures that could potentially cause LBP, such as alternative IVDs, were excluded through clinical and radiological assessments, the complete elimination of other painful structures was not feasible. Indeed,

demonstrating a singular IVD as the source of pain using non-invasive methods can be challenging (Hancock et al., 2007; Schwarzer et al., 1995). This may also partially account for the fact that two patients experienced worsening LBP following the procedure, and these cases could potentially influence the results. Moreover, it is possible that some patients had minor potentially significant findings in neighboring lumbar structures; however, these were not included in the analysis.

Due to the study's design, we were unable to standardize the MRI equipment used to diagnose MC. Images were obtained using both 1.5 and 3 T equipment, resulting in slight variations in imaging parameters. While the parameters used were typical for spinal imaging, they might have contributed to some variability in the diagnosis of MC (Fields et al., 2019). It has been proven that high-field MRI (1.5 T) tends to detect more MC and categorize them more readily as MC2 compared to low-field MRI (0.3 T) (Bendix et al., 2012). Although it remains uncertain whether a similar effect exists between 1.5 and 3 T scanners, this effect is likely less significant (Graves, 2022). Additionally, 17.8% of the study population lacked a fat suppression MRI sequence.

The main strength of the study is its originality. We established the painful nature of MC using a discoblock method that has not been previously employed, which we believe to be more precise compared to methodologies utilized in other studies. These findings not only contribute to the existing body of evidence on the pain linked to MC but also aid in discerning the source of pain associated with such lesions. Secondly, experienced musculoskeletal radiologists conducted the MRI analyses, demonstrating satisfactory reliability in detecting the presence and type of MC. Lastly, the homogeneity of the study sample was aimed to be maximized by including only single-level discoblock patients and excluding those with any other suspected causes of their LBP, such as alternative IVDs or nearby structures more likely responsible for their LBP.

6.4.3 The prognostic value of individual and co-occurring IVD-related degenerative features on lumbar discectomy outcomes (III)

Study III also contains inherent limitations. The study setting was retrospective and had an observational design. As the register was relatively novel and was under clinical development especially during the first years during which patients were included in the study, many PROMs queries were left unanswered, resulting

in considerable exclusion rates in the present study (Marjamaa et al., 2023). Previous studies on various spine registers, with up to 59% one-year loss to follow-up, have found no clinically significant differences in preoperative or postoperative PROMs among patients undergoing lumbar spine surgery for different indications (Endler et al., 2020; Højmark et al., 2016; Kaur et al., 2023; Schröder et al., 2019). However, the potential for selection bias and the unrepresentativeness of the study cohort compared to the entire register patient population cannot be definitively excluded in the present study. For instance, active smoking has been identified as a significant independent predictor of loss to follow-up, which, in turn, may have indirectly influenced both preoperative and postoperative PROMs (Schröder et al., 2019).

Despite utilizing imaging parameters commonly used in spinal imaging, the included variation between 1.5 T and 3 T equipment might have brought variation in the diagnostics of the degenerative features, especially in the context of MC (Bendix et al., 2012; Fields et al., 2019). Moreover, only IVD-related degenerative features were included in the analysis. Thus, some clinically important findings may still have affected the results, for example facet joint pathology. It is important to notice also that the findings of adjacent segments were not analyzed, and their health might also have an effect on the outcomes.

Regarding implicated degenerative changes following discectomy, the one-year postoperative follow-up period may fall short, as some symptoms may still be evolving and become significant only with longer follow-ups. Lastly, some potentially significant confounding demographic factors were not included in the study and therefore remained uncontrolled. These include somatic comorbidities, educational level, and economic factors.

The strengths of the Study III are the comprehensive classification of the MRI findings and careful controlling of the inter- and intra-observer reliability. Moreover, the categorization of each of the single MRI features into non-advanced and advanced phenotypes was strongly based on previous literature, and therefore the testing of the APD criterion can be considered clinically meaningful. The data were collected prospectively and reflect the typical clinical discectomy patient population (Weinstein et al., 2006). Lastly, multidimensional outcome measures were employed to better understand the results of surgery.

6.5 Clinical implications and future prospects

The findings of this thesis contribute to the existing body of literature on preoperative discoblock and MC, potentially assisting clinicians in their decision-making processes by elucidating the roles of discoblock and IVD-related degenerative features in the clinical context. In Study I, we demonstrated that the evaluation of discoblock's $\Delta\text{NRS}_{\text{DB}}$ may be a feasible method for selecting patients for lumbar IVD surgery, particularly for stabilization procedures. We were able to propose a cutoff value for positive discoblock in this context, providing a new perspective for interpreting discoblock results in hospitals where the procedure is already employed. If further large-scale studies can validate our findings, discoblock may become a widely adopted confirmatory method for positive discography results, thereby enhancing diagnostic accuracy and surgical outcomes. Additionally, discoblock may have the potential to serve as a standalone method in preoperative patient selection. From an academic viewpoint, a comparative study investigating different discoblock methodologies and evaluating surgical outcomes in patient groups with positive and negative discoblock responses, as well as an RCT comparing discoblock against other patient selection methods for IVD surgery, could offer further insights into the utility of preoperative discoblock.

Demonstrating the pain associated with MC using a novel discoblock method, Study II also holds clinical significance. Our findings suggest the painful nature of MC1, emphasizing their relevance in evaluating LBP clinically. Furthermore, our results suggest that the pain attributed to MC likely arises, at least partially, from the IVD or EP, indicating that treatment strategies potentially should target these structures. Consequently, our findings may contribute to more effective management of MC-associated LBP. Nevertheless, numerous critical details about MC remain unresolved, including their pathogenesis and definitive association with LBP. Addressing these aspects necessitates cross-sectional and longitudinal population-based and clinical studies from diverse perspectives, employing homogeneous patient samples. Furthermore, research utilizing novel imaging techniques will provide more accurate insights, for example, into the structural changes associated with MC.

In Study III, by integrating individual advanced-level degenerative phenotypes into a composite APD criterion, we suggest that co-occurring degenerative features in the operated segment have a more negative impact on

short-term lumbar discectomy outcomes than individual or absent features. In the future, the APD criterion should be tested in different discectomy patient populations to further assess its predictive value. After additional validation, it may be useful in clinical practice for informing patients preoperatively about expected outcomes. Moreover, our findings indicate that particular academic and clinical attention should be given to treatment methods for APD-positive patients. For instance, operative techniques and postoperative rehabilitation could be optimized for this group to improve discectomy outcomes.

7 Conclusions

In conclusion, the main findings in relation to the study questions are:

1. *Does the degree of pain relief achieved through preoperative discoblock for the lumbar segment scheduled for surgery serve as a predictive indicator for short-term disability outcomes following lumbar fusion or TDR surgeries?*

The degree of pain relief following preoperative discoblock correlated significantly with short-term disability outcomes, particularly after lumbar fusion surgery, suggesting that discoblock may serve as a valuable preoperative patient selection tool.

2. *Does the presence or type of MC in the lumbar segment modify the response to lumbar discoblock in chronic LBP patients?*

The presence of any MC and specifically MC1 in the lumbar segment in question was significantly associated with greater degrees of pain relief following discoblock.

3. *Can a novel MRI-based criterion reliably evaluate the preoperative co-occurrence of IVD-related degenerative features in the operated segment, and does it demonstrate clinical value by distinguishing short-term outcomes of single-level lumbar discectomy from those with singular or absent degenerative features?*

The novel APD criterion reliably assessed the co-occurrence of advanced phenotypes of the included IVD-related degenerative features and showed potential clinical relevance by its association with poorer leg pain and disability outcomes in lumbar single-level discectomy compared to those with singular or no advanced degenerative phenotypes.

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Original publications

- I Korhonen, T., Pesälä, J., Järvinen, J., Haapea, M., & Niinimäki, J. (2022). Correlation between the degree of pain relief following discoblock and short-term surgical disability outcome among patients with suspected discogenic low back pain. *Scandinavian Journal of Pain*, 22(3), 526–532. <https://doi.org/10.1515/SJPAIN-2021-0160>
- II Korhonen, T., Järvinen, J., Pesälä, J., Haapea, M., & Niinimäki, J. (2022). Modic changes associated with greater pain relief following anesthetization of the adjacent lumbar intervertebral disc: A retrospective study of chronic low back pain patients. *European Journal of Radiology*, 157, Article 110589. <https://doi.org/10.1016/j.ejrad.2022.110589>
- III Korhonen, T., Järvinen, J., Pesälä, J., Haapea, M., Kinnunen, P., & Niinimäki, J. (2024). Assessment and predictive value of preoperative co-occurring intervertebral disc-related degenerative features in lumbar discectomy: a proposal for and preliminary testing of a novel MRI-based criterion. *Manuscript*.

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