PhD thesis

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Long-term outcomes in degenerative spine patients - with focus on Modic changes and discectomy surgery

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Table of contents

Preface and Acknowledgement

The PhD thesis consists of three studies, which will be reviewed in the following. This includes an introduction with the background for the research questions, a method section describing the design of the studies, a presentation of the individual study results, and a discussion of the findings in the three studies in context to previous, ongoing and future international research.

The work presented in this thesis was carried out during my appointment as a PhD student from 2017 to 2019 at the Spine Research Unit, Department of Orthopedic Surgery, Zealand University Hospital, Faculty of Health and Medical Sciences, University of Southern Denmark, Denmark.

I wish to express my deepest gratitude to my supervisors, in particular, Associate Professor Mikkel Østerheden Andersen for giving me the opportunity to join the research unit at the Spine Center in Middelfart. I would also like to express my deepest thanks to Professor Tom Bendix for his patience in my academic career, his most valuable intellectual curiosity, and his guidance. Also, thank you to affiliated Professor Leah Carreon and Professor Stig Brorson for their continuous support, and guidance within the world of health research. Furthermore, I thank my family, particularly my parents for leading the way, my children Leonora, Tiabell, and Aqsa for their love and my beacon of light and love Laila - for everything. Finally, thanks to all my colleagues, and especially Dr. Zaid Issa and co-supervisor Søren Ohrt-Nissen for extensive help and support in good and bad times.

Abbreviations

ANCOVA: Analysis of covariance
BMI: Body mass index
BP: Back pain
CT: Computed tomography
DD: Disc Degeneration
DOS: Danish Orthopedic Society
DRKS: Danish Society of Spinal Surgery
EQ-5D: European Quality of Life – 5 Dimensions
ESC: Endplate sclerotic changes
FJD: Facet-Joint Degeneration
FSU: Functional spine unit
FU: Follow-up
IMAST: International Meeting on Advanced Spinal Technologies
LBP: Low back pain
LDH: Lumbar disc herniation
MC: Modic changes
MC-1: Modic changes type 1
MC-2: Modic changes type 2
MC-3: Modic changes type 3
MCs: Modic changes
+MC: Group of patients with Modic changes
-MC: Group of patients without Modic changes
MRI: Magnetic Resonance Imaging
NASS: North American Spine Society
NRS: Numeric Rating Scale
ODI: Oswestry Disability Index
PA: Weekly physical activity at leisure
PF: Pfirrmann grade
PRO: Patient-reported outcomes
RCT: Randomized controlled trial
RMDQ: Roland-Morris Disability Questionnaire
SD: Standard deviation
VAS: Visual analog score
VAS-BP: Visual analog score for back pain
VAS-LP: Visual analog score for leg pain
VESC: Vertebral endplate signal changes

Summary (English)

Back pain is a common cause of global disability. Modic changes (MCs) are commonly found on Magnetic Resonance Imaging (MRI) in adults with back pain. These characteristic changes have been classified into three different types and are visualized on MRI in the endplates and bone marrow adjacent to a degenerated intervertebral disc. MCs have been associated with low back pain (LBP) and disability in previous studies. Additionally, MCs have been associated with a less successful outcome in LBP patients treated surgically. However, previous studies have been limited by small, heterogeneous cohorts with short follow-up. In addition, limited information is available on the long-term prognosis of patients with LBP and MCs not receiving surgical treatment.

The purpose of the thesis was to evaluate the possible association between MCs, disc degeneration (DD) and facet-joint degeneration (FJD), and patient-reported outcomes (PRO) at long-term follow-up. Moreover, we aimed to evaluate if preoperative MCs are associated with outcome after discectomy.

The first two studies included patients with LBP recruited from a previous randomized controlled trial. Of the original 207 patients in the randomized cohort, 204 had a lumbar MRI performed in 2004-2005.

Study I focused on the possible association between the baseline MCs on MRI and disability 13-years later. Patients were stratified based on the presence (+MC group) or absence (-MC group) of MCs. There were 82 patients in the +MC group and 122 in the -MC group. 170 patients (83%) were available for 13-year follow-up. At baseline, demographics, PRO (including Roland-Morris Disability Questionnaire (RMDQ)) and pain scores were comparable with no statistically significant difference between the two groups. At 13-year follow-up the +MC group

had statistically significantly better RMDQ-scores and less sick-leave in the past year compared to the –MC group.

In *study II*, the same cohort was analyzed in terms of MRI parameters including DD (defined by Pfirrmann grade >3), FJD (defined by Fujiwara grade >2) and MCs. Neither DD, FJD nor MCs at baseline were found to be associated with increased 13-year disability or higher pain scores. Both weekly physical activity at leisure and MCs at baseline were associated with less long-term disability.

Study III was a registry-based cohort study on patients with lumbar disc herniation who underwent primary discectomy. We included 620 patients, all with two-year postoperative follow-up. We analyzed preoperative MRIs in all included patients and found MCs present in 290 patients (47%). Preoperative demographics and PRO were comparable between the +MC and -MC groups. An overall statistically and clinically significant improvement in PRO after discectomy was found in both groups. We found no difference in PRO between the +/-MC groups.

We conclude that MCs in LBP patients do not appear to be associated with long-term disability. Baseline degenerative MRI findings including DD and FJD are likewise not associated with long-term disability. Furthermore, MCs do not appear to be associated with outcome after primary discectomy.

Summary (Danish)

Rygsmerter er en hyppig årsag til nedsat fysisk funktion globalt. Modic forandringer (MCs) konstateres ofte på MR-skanning af voksne med rygsmerter. Disse karakteristiske ændringer er blevet klassificeret i tre forskellige typer og er på MR-skanning visualiseret i endepladerne og svarende til knoglemarv i tilstødende ryghvirvler til en degenereret intervertebral disk. MCs har været associeret med lændesmerter og nedsat fysisk funktion i tidligere undersøgelser. Derudover er MCs associeret med et mindre vellykket resultat hos lændesmerte patienter der behandles kirurgisk. Tidligere undersøgelser er imidlertid begrænset af heterogene og mindre kohorter med kort opfølgningstid. Derudover er den tilgængelig information begrænset mht. langtidsprognosen for patienter med lændesmerter og MCs som ikke gennemgår kirurgisk behandling.

Formålet med denne afhandling var at evaluere den mulige sammenhæng mellem MCs, discus degeneration (DD) og facetleds degeneration (FJD) og patientrapporterede symptomer ved langtidsopfølgning. Og i tillæg at evaluere, om præoperative MCs er associeret med resultatet efter diskektomi.

De første to studier inkluderede patienter med lændesmerter rekruteret fra et tidligere randomiseret kontrolleret forsøg. Af de 207 patienter som indgik i den oprindelige randomiserede kohorte, havde 204 gennemgået en MR-undersøgelse af lænden i 2004-2005.

Studie I fokuserede på den mulige sammenhæng mellem baseline MCs og fysisk funktion ved 13-års opfølgning. Patienter blev grupperet på basis af tilstedeværelsen (+MC-gruppe) eller fravær (-MC-gruppe) af MCs på MR-skanning ved baseline. Der var 82 patienter i +MC-gruppen og 122 patienter i -MC-gruppen. 170 patienter (83%) var tilgængelige ved opfølgning efter 13-år. Ved baseline var demografiske data, effektmål (inklusive Roland-Morris Disability

Questionnaire (RMDQ)) og smertescorer sammenlignelige uden statistisk signifikant forskel imellem de to grupper. Ved 13-års opfølgningen havde +MC-gruppen statistisk signifikant lavere RMDQ-scorer og mindre sygefravær det sidste år sammenlignet med -MC-gruppen.

I *studie II* blev den samme kohorte analyseret med hensyn til MR-fund inklusive DD (defineret ved Pfirrmann-grad> 3), FJD (defineret ved Fujiwara-grad> 2) og MCs. Hverken DD, FJD eller MCs ved baseline var associeret med nedsat fysisk funktion eller forværring af smertescorer ved 13-års opfølgning. Både ugentlig fysisk aktivitet i fritiden og MCs ved baseline var associeret med bedret fysisk funktion.

Studie III var en registerbaseret kohorte undersøgelse af patienter med discus prolaps, der gennemgik førstegangs diskektomi. Vi inkluderede 620 patienter, alle med to-års opfølgning tilgængelig. Vi analyserede de preoperative MR-skanninger hos alle inkluderede patienter og fandt MCs på 290 patienter (47%). Preoperative demografiske data og effektmål var sammenlignelige mellem +MC- og –MC-gruppen.Vi fandt en statistisk og klinisk signifikant forbedring af effektmål ved diskektomi i begge grupper. Vi fandt ingen forskel i effektmål ved sammenligning af +/-MC-grupperne.

Vi konkluderer, at MCs hos lændesmerte patienter ikke synes at være forbundet med et langvarigt nedsat fysisk funktionsniveau. Baseline degenerative MR-forandringer inklusiv DD og FJD er heller ikke forbundet med et langvarigt nedsat funktionsniveau. I tillæg synes der ikke at være en sammenhæng mellem tilstedeværelse af MCs og resultatet efter førstegangs diskektomi.

List of papers

The present thesis consists of the following three papers:

I. **Modic changes are not associated with long-term pain and disability? - a prospective cohort study with 13-year follow-up**.

Spine: September 1, 2019 – Volume 44 – Issue 17 – p.1186-1192.
The study results have been presented at IMAST 2018 and were nominated for the Whitecloud Award; Global Spine 2019, DOS 2018 and DRKS 2018.

II. **Are MRI findings associated with long-term disability in low back pain patients?**

Submitted to ***The Spine Journal***, *2019.*
The study results have been presented at NASS 2019 - where it won the Best Paper Award; IMAST 2019, DOS 2019 and DRKS 2019.

III. **Are Modic changes associated with health-related quality of life after discectomy? - a study on 620 patients with two-year follow-up.**

Submitted to ***Spine***, *2019.* Accepted for presentation at Global Spine 2020.

Introduction

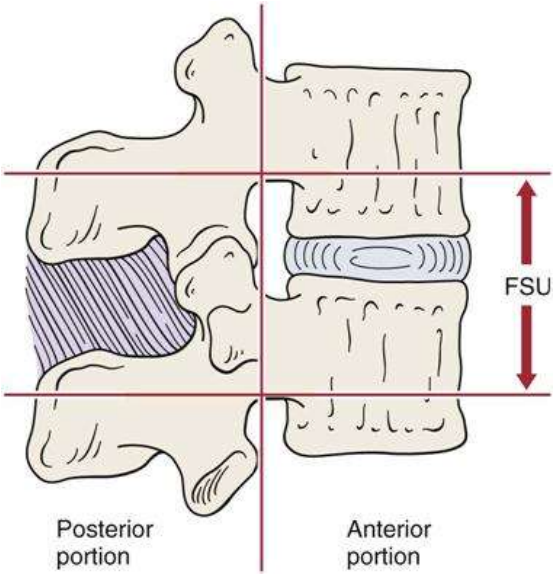
Back pain (BP) is a leading cause of global disability[1–3]. It affects 60-70 % of the population once or several times during one's life[4–8]. Within the category of BP, low back pain (LBP) is the most common presentation[1–3,6]. The high prevalence of LBP has major implications on healthcare expenses, accounting for 15% of all long-term sick leaves and 10% of all disability pensions in the United Kingdom[9,10]. In Denmark alone, the annual costs related to LBP are estimated to be more than 17 billion Danish Kroner[5,11]. In addition, the incidence and prevalence of LBP have been increasing steadily over the last 40 years[5]. Treatments including surgical procedures in the spine have increased substantially over the years[12,13]. To understand these developments, political initiatives have included the development of Health Technology Assessments on the causes, costs, and best evidence-based approach to the treatment of LBP[5,10,11,14].

Anatomy and pathophysiology

BP is multifactorial and can be traced back to a plethora of possible pain generators that can be stimulated in numerous ways[15,16]. One of the possible origins of BP is the intervertebral disc. It is composed of a central hydrated nucleus pulposus and outer collagenous annulus fibrosus with cranial and caudal endplates consisting of an osseous and cartilaginous component[16–19].

The intervertebral disc is part of the functional spine unit (FSU) which is the smallest motion segment of the spine with biomechanical properties similar to the entire spine (Figure 1)[20,21].

Figure 1: Functional spine unit



The FSU, including the soft-tissue structures of ligaments, muscles and the disc, is the anatomical foundation for the biomechanical properties of the spine[20,21]. Normal discs and facet joints ensure function and pain-free mobility. Degeneration of the disc and the FSU involves horizontal and vertical degenerative changes, compromised biomechanical properties, and often pain, and disability[20,22–24]. Disc degeneration (DD) increases with age and is predominantly controlled by genetic factors[17,22,25]. Other factors such as smoking, sex, certain type of sports, trauma and large Body mass index (BMI) and height have been associated with disc changes[17,26–30]. On the other hand, physical loads, in general, play a minor role in spine degeneration[29]. It has been demonstrated that the interplay between spinal pain mechanisms and the brain's pain perception and coping plays an even larger role than the biomechanics and physiological components in the spinal structures[31–35].

The degenerative changes within the disc and the FSU can be visualized on magnetic resonance imaging (MRI) and have been shown to be associated with PRO [36–40]. With the

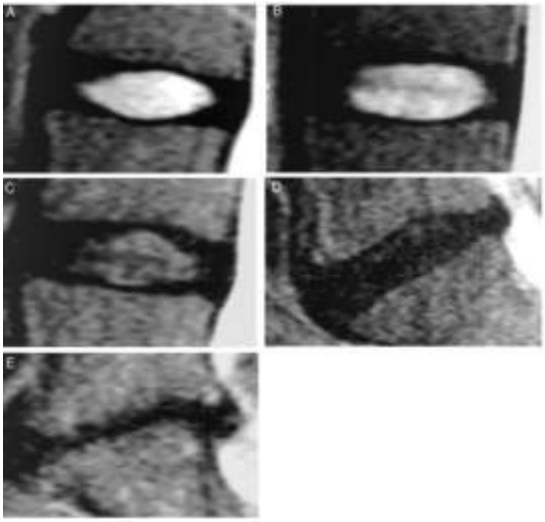
intervertebral disc having a crucial role in the normally functioning spine, much effort has been aimed at understanding, preventing, and treating DD.

Radiological imaging of the Spine

The first MRI was performed on humans in the 1970s and is now the golden standard for visualizing the soft tissue of the spine[41]. Despite technological advances and increased availability of MRIs, the correlation between radiologic pathologies and the clinical phenotype is still not fully understood, as radiologic findings are often in discordance with clinical symptoms[42–46]. Some of the most common degenerative changes found on MRI include disc, endplate, and facet joint changes[44,45,47–50]. Several different classification systems of these changes exist, based on either plain radiographs, computed tomography (CT) or MRI scans[38,51–54].

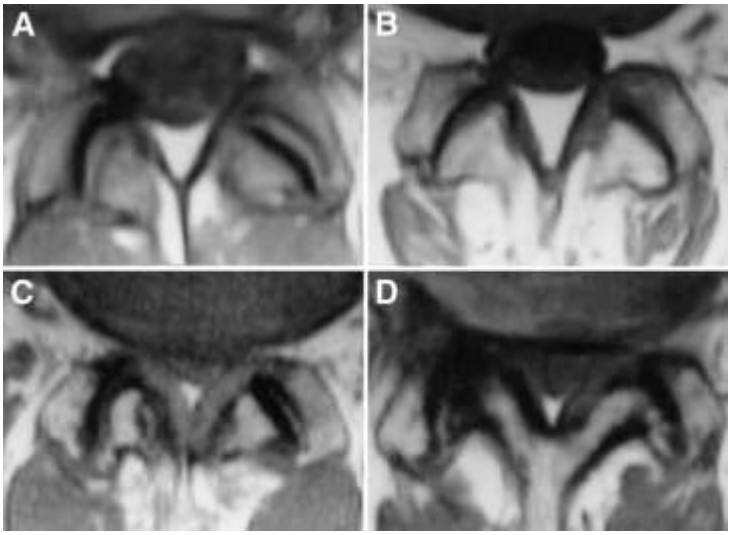
DD is a common finding in adults and has been reported on MRI in more than 90% of adults age 55 or above[45]. Several classification systems exist for evaluation DD on MRI[38,55,56]. Of these, the most commonly used are the Pfirrmann classification system, which focuses on the structure of the disc, the distinction between the nucleus and annulus, signal intensity and the height of the disc[38]. This grading system has been validated, with excellent inter- and intra-observer agreement[38,57]. In this classification, DD is graded as Pfirrmann grade (PF) I (normal disc) through V (severe degeneration), as shown in Figure 2[38]. In the literature, severe DD is commonly classified as PF>3[58,59].

Figure 2: Pfirrmann grade I (top left picture) to V (bottom left picture)



The facet joints are also part of the FSU. They add stability and are load-bearing, 20-30% of total axial weight transfer, in the posterior column of the spine[20,21,60]. Facet joint degeneration (FJD) is associated with DD and can be demonstrated in autopsies from early in life[50,54,61]. The radiographic assessment of lumbar facet joints is possible by different grading systems[54]. The reliability of these systems has been evaluated with varying inter- and intra-observer agreement[54,55]. The most commonly used MRI grading system for lumbar FJD, with an almost perfect inter-observer agreement, was developed by Fujiwara et al[54,61]. The Fujiwara based system, grade facet joint changes into grade 1 (normal) through grade 4 (severe degeneration), as shown in Figure 3[61].

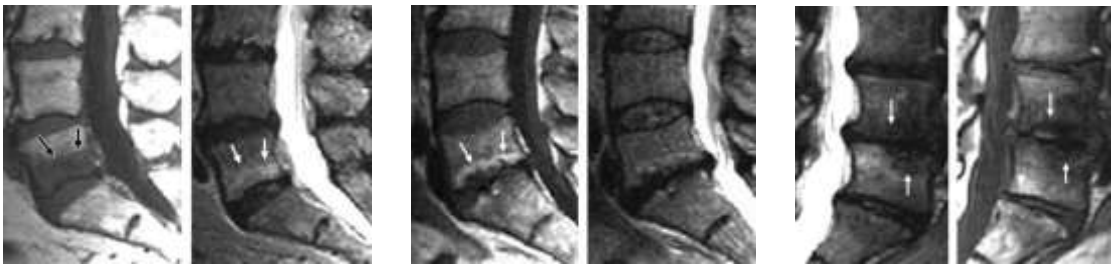
Figure 3: Fujiwara grade 1 (top left picture) to 4 (bottom right picture)



Modic changes

In the late 1980s, de Roos et al. followed by Modic et al. were the first to describe and classify specific vertebral endplate signal changes (VESC) with accompanying marrow edema also named endplate signal changes (ESC)[45,47,62,63]. They are now commonly referred to as Modic changes (MCs). MCs are MRI changes in the disc, endplates, and marrow of the vertebra and were first described on T1- and T2-weighted images. MCs are traditionally described in three different types: MCs type 1 (MC-1), MCs type 2 (MC-2) and MCs type 3 (MC-3) based on histopathological analysis of the endplate changes and visual presentation on MRI[64].

Figure 4: Modic changes – MC-1 (left), MC-2 (middle), MC-3 (right).



The pathophysiology of MCs is not fully understood. Histopathological analysis of MC-1 has shown endplate changes with disruption and fissuring. Vascularized fibrous tissue is present at the endplate-disc intersection and in the marrow; combined with an increased number of osteoblasts as a sign of rapid bone-turnover in the affected vertebra[48,53,62–66]. In MC-2 the endplates are also disrupted with similar signs of increased bone turn-over although less than in MC-1. Marrow changes in MC-2 feature a replacement of hematopoietic tissue with abundant fat (yellow marrow). MC-3 features consist of dense woven sclerotic bone changes with an absence of marrow in the affected area.

Degeneration with repetitive overloading and bacteria-induced changes has been speculated as possible causes of MCs[48,66–69]. Although the underlying etiology is controversial, there is a general agreement that endplate changes are necessary for the development of MCs. The endplates are essential for both the disc and vertebra. The diffusion of essential solutes takes place across the endplates and they support nutrition and metabolic exchange between the vertebra and the discs[17,70,71]. As such, the endplates are critical for maintaining normal disc function and injury is likely to lead to both disc and vertebra changes[17,72]. Lumbar disc herniation (LDH) diagnosed with MRI has been reported in 25% of the background population[46]. In LDH, endplate injury with junction failure has been shown to be more common and associated with greater pain than annulus fibrosus rupture alone[73,74]. Such changes could play a key role in the development of MCs and might explain the high prevalence of MCs reported in patients with LDH (40-60%)[75–77].

It is important to notice that the original description of MCs described endplate and bone marrow changes located adjacent to a degenerated intervertebral disc[62–64]. Therefore, it seems relevant to differentiate between MCs and VESC/ECS. The term VESC/ESC simply refers to

changes in the endplate visible on MRI while MCs is a term used to describe a specific finding on MRI present in endplates and marrow adjacent to a disc with signs of degeneration. The terms are often used synonymously in the literature which has led to some inconsistencies regarding both meaning, MRI interpretation, and clinical association[47,53,67,78]. Inter- and intra-observer reliability of MCs on MRI in regard to presence, size-, and location has been evaluated in previous studies as substantial to an almost perfect agreement[79,80].

The prevalence of MCs has been described with some variation but is estimated at around 5-22% of the adult population, increasing with age, and up to more than 40% in adults with LBP[47,48,78,81]. This difference in the prevalence of MCs between the background population and adults with LBP has caused much interest in MCs[67,78]. Some studies have focused on possible associations between the changes in MRI and PRO including back and leg pain, disability, and clinical presentation that could differentiate patients with MCs from those without[81,82]. Other studies have investigated known risk factors for LBP and their possible association with MCs[78,81,83,84]. The research has also been extended into the different subtypes, with some studies finding an association between MC-1 and PRO including sick-leave[47,67,78,85,86]. Overall, different study designs, variation in populations and follow-up (FU) periods, differences in the definition of MCs, combined with different outcomes has led to heterogeneous study results[47,75,78]. This only seems to have fueled the interest in the subject and annually several studies on different types of intervention aimed at treating patients with MCs, and MCs, in general, are being published[18,58,67,75,87,88].

Treatment of degenerative spine conditions

The 20th and 21st century has seen great advances in the understanding and treatment of spine-related pain[6,53]. Spine surgery has undergone tremendous development over the last 100 years

and an increasing number of patients are treated annually predominantly due to degenerative spine conditions[12,13,53]. DD, FJD, and MCs are three important components when evaluating the lumbar MRI of patients with spine-related pain and disability. Of these, both DD and FJD have been identified as possible sources of pain that can be addressed surgically, although with mixed results[16,89–95].

MCs have been associated with DD, disc herniation, pain, and disability[67,72,75,77,78,84,96]. Proposed treatment regimens for LBP associated with MCs include oral antibiotics, steroid injections, disc removal, fusion, manual therapy, exercise, and cognitive therapy[67,69,75,97–103].

In patients with DD, MCs have been associated with lumbar LDH[75,104]. In a systematic review, several studies found MCs to be associated with a less successful outcome after LDH surgery[75]. Study designs, study population, and the FU periods were heterogeneous in the included studies, but overall MCs including MC-1, are often hypothesized to negatively impact the outcome of conservative treatment and non-fusion surgery[75,97,105,106].

Perspective

The purpose of this PhD thesis was to obtain a better understanding of the long-term consequences of MCs. More specifically, we aimed to evaluate the long-term association between PRO and MCs in LBP patients more than 10 years after the diagnosis was made. Also, we wanted to investigate if other degenerative MRI changes in LBP patients are associated with long-term PRO and finally to investigate if preoperative MCs are associated with outcome after discectomy.

PhD thesis background

In 2004-2005 a randomized controlled trial (RCT) was conducted at a Danish spine center comparing the effect of cognitive therapy with physical exercise instructions on LBP and

disability in chronic LBP patients[107]. No significant difference was found at 6- and 12-months FU between the two treatment groups. All patients had a lumbar MRI performed. Positive findings on the MRI did not influence the intervention[107]. Patients included in the original study were scheduled for long-term (> 10 years) questionnaire FU. This became the basis and foundation for the collaboration that soon included three different regions – Capital Region of Denmark (Rigshospitalet / Glostrup), Region Zealand (Zealand University Hospital) and Region of Southern Denmark (Middelfart Hospital – part of Lillebælt Hospital). The framework included professors, senior consultants, and post-docs from all included institutions.

Relevance

The knowledge obtained from this thesis will provide a better understanding of LBP for both patients, doctors and health service providers. In addition, the studies will add valuable information to a healthcare area filled with uncertainties. If the hypothesis of MCs being associated with a worse long-term outcome in LBP patients is supported by the study findings, this knowledge might be used to optimize patient counseling and improve treatment algorithms. From a socio-economic perspective, improved understanding of the long-term consequences related to MCs and/or DD/FJD in LBP patients, can possibly improve treatment protocols including early intervention and thereby reduce sick-leave and healthcare-related expenses.

Objectives and hypothesis

<u>The main objective of the three studies was to answer these questions:</u>

I. Are MCs associated with increased long-term physical disability and pain?
Hypothesis: patients with MCs have increased long-term disability and pain compared to patients without MCs.

II. Are MRI findings associated with long-term disability in low back pain patients?
Hypothesis: degenerative MRI findings including DD, FJD, and MCs are associated with increased long-term disability in LBP patients.

III. Are MCs associated with outcome after discectomy?
Hypothesis: MCs are associated with a worse outcome after LDH surgery.

Methodological considerations

Design

The hypothesis described for this thesis was tested through three studies. Due to the FU needed to test hypothesis I and II, it was decided to investigate the previously mentioned cohort at long-term FU. The study design was a retrospective comparative cohort study with 13-year FU.

For hypothesis III, a two-year period was needed in order to evaluate medium-term PRO after discectomy. These data were available from the national spine database – DaneSpine. The spine unit at Middelfart hospital has 99% completeness of questionnaire submission for patients undergoing spine surgery at the institution and the preoperative MRIs are available at the institution[108]. To ensure an epidemiological quality, it was decided to carry out the investigation through a registry-based cohort study with two-year FU on patients from a single institution: Middelfart Hospital.

Populations

Study I and II

The target population consists of patients with non-specific LBP and MCs. This group is represented by BP dominating over leg pain, no identified specific cause of pain, no red flags indicating acute surgical or medical intervention, and back pain originating from the spine and not being caused by any other organ pathology. This category of patients is typically treated non-surgically and they make up the clear majority of LBP patients globally.

The study population consists of LBP patients referred from their general practitioner to a tertiary Spine Centre. The patients are typically referred due to non-specific LBP, disability and longer periods of back-related sick leave. Most have been through some form of nonsurgical treatment program including physiotherapy, chiropractic treatment, physical training or cognitive therapy with limited effect. These patients may have been evaluated, but not treated, by spine surgeons and/or rheumatologists before being referred to this tertiary unit.

Study III

The target population for this study consists of patients with clinically relevant LDH and MCs. DD is common with increasing age and LHD is an associated condition that can cause severe pain and disability[20,45,109]. MCs are present in up to 40% of patients with LBP and an even higher prevalence of MCs is found in patients with disc herniation[75,78,104].

Patients with disc herniation rarely but sometimes experience acute neurological deficits due to herniation - e.g. cauda equina syndrome, foot-drop, loss of sensory function. These patients are typically treated acutely but may have long-lasting neurological deficits. This small but important group of patients is not included in the target population.

The study population consists of patients with LDH scheduled for discectomy. All patients were surgically treated at the spine unit at Middelfart hospital, registered in DaneSpine, and had at least two-year FU data available. Due to regional guidelines, all patients had undergone a

nonsurgical treatment program, with limited effect, prior to surgery. None of the patients had acute neurological deficits.

Outcome variables

Demographics

Study I and II included relevant demographics including sex, height, weight, age, marital status, and smoking. All these factors can impact the chosen primary outcome scores and should be included to avoid possible confounding[84,110,111].

Study III included similar demographics; marital status was not included due to this information not being available within the database.

Patient-reported outcomes

Study I and II was limited by the outcomes selected at baseline for the initial RCT[107].

<u>For study I, the primary outcomes were</u>

1) Disability measured by the Roland-Morris Disability Questionnaire (RMDQ) (0 (no disability) to 23 (maximum disability))[112].
2) LBP accessed with the Numeric Rating Scale (NRS) (0 (no pain) –10 (worst possible pain)).
3) The number of sick leave days due to back pain the past year (0–200 workdays).

<u>Secondary outcomes included</u>

1) LBP Rating Scale (RS) for activity limitations survey (0 (no disability) – 30 (maximum disability))[113].
2) Leg pain accessed with NRS (0-10).
3) The physical activity level at leisure (PA) (group 1 (<60 min per week) – group 4 (>240 min per week))[107].

4) Inflammatory pain pattern (defined by at least one of three characteristics: maximal pain in the morning, waking at night because of pain, and morning stiffness for longer than 60 minutes)[82].

For study II, the primary outcome was

1) 13-year RMDQ.

Secondary outcomes were

1) 13-year RS-scores.
2) PA.

For study III, the primary outcome was

1) Oswestry Disability Index (ODI) (0 (no disability) to 100 (maximum disability))[114].

Secondary outcomes were

1) European Quality of Life – 5 Dimensions (EQ-5D) (English version).
2) Visual Analogue Scale (VAS) for back pain (VAS-BP).
3) VAS leg pain (VAS-LP).
4) Patients satisfaction (0-100%).

MRI evaluation

Study I and II

All patients underwent a low-Tesla MRI of the lumbar region (0.2 T MRI-system, Siemens Open Viva)[107]. The MRI description included DD described by PF grade, FJD described by Fujiwara, and MCs, presence, type, and location, described according to the original studies[62–64].

The use of low-field MRI was widely used in the inclusion period (MRI performed in 2004-2005). Excellent reliability between low- and high-field MRI has been demonstrated for lumbar degenerative changes[115]. MRIs were evaluated by an experienced musculoskeletal

radiologist using a standardized evaluation protocol and unaware of the clinical status of the individual patient[107]. The radiologist was blinded in terms of the patient's diagnosis and clinical symptoms. The MRI description was not available to included patients and did not influence treatment.

Study III

Patients underwent an MRI of the lumbar spine within six-months prior to their discectomy. All MRIs were performed within the Region South Denmark with 1.0-2.0 Tesla high-field scanners. The scans were evaluated by four physicians using a standardized evaluation protocol blinded to the clinical status and discectomy level. Lumbar MRI evaluation included: presence, type, and level of MCs, description of possible DD using the Pfirrmann classification, and level of disc herniation. In order to assure the correct classification of MCs, an MRI guideline was defined and followed by the physicians doing the MRI descriptions.

All MRIs were evaluated by two different physicians, and if inconsistencies existed after the second evaluation then reevaluated by a third physician.

Ethical approval

Protocol, data collection, and study ethics were approved by the National data protection agency and The Regional Committees on Health Research Ethics (reference number study I and II: S-20172000-77, reference number study III: S-20192000-112). The protocol, thesis and single studies were conducted adhering to the Helsinki protocol in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Summary of study results

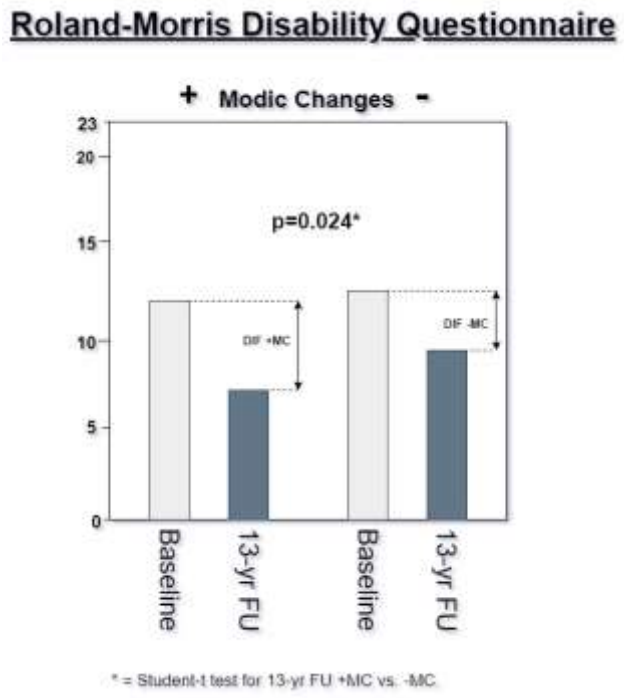
Study I – Modic changes are not associated with long-term pain and disability

A total of 204 patients with LBP and lumbar MRI were available and included in the study. Of these, 170 patients (83%) completed a questionnaire at 13-years FU. Based on the baseline MRI, the two groups consisted of 67 patients (39%) with MCs (+MC) and 103 patients (61%) without MCs (-MC). In patients with MCs, MC-1 was present in 75%, MC-2 in 24%, MC-3 in <1% of patients. Predominantly, the MCs were located at the L4-S1 level (80%). All MCs were present adjacent to a disc with signs of degeneration, PF≥2.

There were no significant differences in demographics or PRO at baseline between the +MC and –MC groups. Rates of spine surgery were equally distributed between the two groups (10% vs. 11%). The number of patients (65%), that had received any antibiotics during the 13-year period was similar for the +/- MCs groups.

At the final FU, the mean RMDQ score was statistically significantly better in the +MC group (p=0.024). Pain scores were reduced but the difference was not statistically significant. RS scores were significantly lower in the +MC group (p=0.013). There were substantially fewer sick leave days due to LBP in the +MC group (9.0 d vs. 22.9 d, p=0.003). Analysis of covariance (ANCOVA) showed MCs to be significantly associated with lower 13-year RMDQ (P=0.031). A bigger decrease in the use of pain medication was noticed in the +MC group over time but the difference was not statistically significant. Neither at baseline nor at FU was IPP significantly different between the two groups.

Figure 5: Study I – Disability measured by RMDQ for the -MC and +MC group. The improvement in RMDQ for those initially having MCs [Dif $_{+MC}$] is significantly larger than for those without MCs [Dif $_{-MC}$].



Study II – Degenerative MRI findings are not associated with disability

The study was based on the cohort described in study I, with study II primarily investigating the radiologic parameters DD, MCs, and FJD at baseline and their association with 13-year PRO. Of the 204 patients, 88 had DD (52%), 67 had MCs (39%) and 139 had FJD (82%) on baseline MRIs. In general, disability measured by RMDQ and RS, patients improved over time, resulting in less disability at 13-year FU compared to baseline. There was no change in PA over the 13-year span.

Both MCs and PA at baseline were found to be statistically significantly associated with lower 13-year RMDQ-scores, R^2=0.31 with standard β coefficients of 0.15 for MCs (p=0.031) and -0.51 for PA (p<0.001). Neither DD (β= 0.060, p=0.406) or FJD (β= -0.017, p=0.801), showed any statistically significant association with long-term disability.

Figure 6: Study II - Distribution of MRI findings incl. DD, MCs, and FJD.

Level	Worst level of DD	MCs distribution	FJD distribution
Th12-L1	2%	1%	1%
L1-L2	2%	2%	2%
L2-L3	5%	5%	4%
L3-L4	10%	12%	10%
L4-L5	35%	36%	43%
L5-S1	46%	44%	40%

Study III – Modic changes are not associated with outcome after discectomy

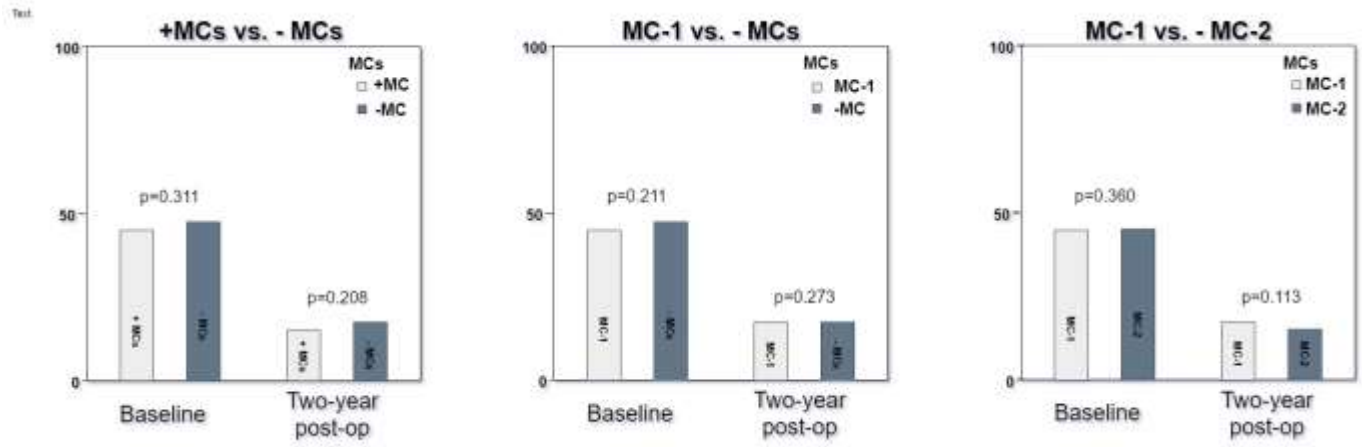
A total of 620 patients fulfilled the criteria for inclusion in the study. Of these, 290 (47%) had MCs and 330 (53%) patients had no MCs on the preoperative MRI scan. No significant differences were found between the two groups regarding preoperative demographics or PRO.

At two-year FU after primary discectomy, the improvement in disability, Health-related Quality of Life and pain scores for the entire cohort was both clinically relevant and statistically significant for ODI ($p<0.001$), EQ-5D ($p<0.001$), and pain scores (both VAS-BP and VAS-LP, $p<0.001$). Both the +MC and –MC group improved significantly over time with no difference between them at two-year FU in PRO or patients satisfaction.

In the +MC group, MC-1 was present in 73 (25%) and MC-2 in 217 (75%) of patients. No difference was found for the MC-1 vs. MC-2 group preoperatively regarding demographics or PRO-scores. Two-year postoperative FU was also without statistically significant differences except for VAS-BP between the MC-1 and MC-2 groups (33.3 vs. 24.5, $p=0.042$). Patients satisfaction was 74% for both the MC-1 and MC-2 group at FU. Gain score analysis with

ANCOVA did not find MCs type to be associated with differentiated outcomes in either ODI, EQ-5D or pain scores.

Figure 7: Study III – ODI for patients +/- MCs and for MC-1 and MC-2 before surgery and at two-year follow-up.



Discussion

MCs are not associated with long-term outcome

In the studies I and II, MCs were a frequent finding, being present on MRI in 40% of LBP patients. Contrary to our hypothesis, MCs were not associated with a worse outcome at 13-year FU. At the time of inclusion, 2004-2005, low-field MRIs were typically used whereas today high-field MRIs are used predominantly[41,47,81,116]. This can explain the difference in the ratio of MC-1 and MC-2 found compared to studies performed on high-field MRIs[47,78,81,86,116].

The results are in contrast to studies on MCs with shorter FU that have shown worse outcomes in patients with MCs[47,67,78,81,86,117]. However, a recent systematic review has questioned the previously accepted association between MCs and LBP due to conflicting results, and heterogenicity of studies[78].

The few available studies on MCs with long-term FU (>9 years) have confirmed the findings from this study, demonstrating that the presence of MCs at baseline is not associated with increased disability, back- or leg -pain or a history of back pain at long-term FU [118,119]. This suggests that the results of the current study are valid and that the association seen between MCs and PRO in cross-sectional studies becomes weaker over time. The findings could be explained by the evolution of MC-1, with histological active vascularized fibrous tissue in the marrow adjacent to the endplates, into MC-2, with yellow fat marrow replacement in the vertebra, as described in the original studies on MCs [53,62–64].

Radiologic findings are not associated with long-term outcomes

In study II, baseline MRI findings in patients with LBP were not associated with long-term disability. Degenerative MRI findings were found to be a common feature in LBP patients, with 52% having DD with PF >3, 39% having MCs, and 82% having FJD with Fujiwara grade>2, on at least one lumbar level. Low-field and high-field MRI are comparable with excellent reliability for lumbar degenerative findings except, as mentioned, for MCs subgroup ratios[115,116].

The MRI results from study II are in accordance with findings from previous studies[36,44,45,47,54,120]. Overall, the cohort improved over time. Less disability and reduced pain scores were reported at 13-year FU. Baseline MCs and PA were associated with statistically significantly improved disability in gain score analysis. The association between MRI findings and PRO in LBP patients and the general population has been investigated across studies, with an overall agreement with the results from the current study[78,118–120].

In general, there has been an increase in the treatment of patients with LBP, disability, and a positive MRI over the last 30 years[5,12,13,69,111]. Prolonged antibiotic courses >90 days,

intradiscal injections, and spinal fusion are all treatment strategies that could have been utilized in the treatment of this study cohort[69,75,97,99,100,121]. A recently published double-blinded RCT study on chronic LBP patients with MCs investigated the proposed effect of antibiotics and did not find any significant effect of 90-days antibiotic treatment compared to placebo[103]. In study I and II no invasive or pharmacological treatment was performed, and the cohort still improved on all outcomes. Studies on LBP patients not undergoing treatment are few and scarce, but relevant in order to understand the natural progression of PRO in such a cohort.

Also, it should be noted that weekly physical activity at baseline was a significant predictor of long-term outcome even in the presence of LBP and degenerative MRI changes. A systematic review of physical leisure time activity has described a similar trend[122].

MCs are not associated with outcome after discectomy

Study III results did not demonstrate an influence of MCs on outcome after primary discectomy due to LHD. MCs were found to be more prevalent (47%) in patients with herniation scheduled for discectomy compared to LBP patients in general, a finding supported by previous studies[47,75,78]. Some authors have advocated spinal fusion as an optimal early treatment strategy of patients with MCs and LBP[75,97,121]. Such a strategy has been based on the generally believed association between MCs, the progression of DD, disc herniation, and worse PRO[67,77,78,96,104,123,124]. Our study results from study II do not support an association between degenerative findings on MRI including MCs and worse long-term PRO.

For patients undergoing discectomy, a systematic review by Laustsen et al. described a trend towards less improvement in those with preoperative MCs[75]. The review included six studies on discectomy with a total cohort of 607 patients. The authors argue that even though a

trend was described they find it very questionable whether the presence of MCs led to a clinically detectable difference in outcome after discectomy.

Study III was conducted as a registry-based study of 620 patients, all of whom had two-year FU. Of patients with MCs, 25% had MC-1. The entire cohort experienced both a statistically and clinically relevant improvement postoperatively. No differences in PRO were found pre- or postoperatively between the +MC and -MC groups. Within the MCs group, preoperative PRO and demographics were similar for the MC-1 and MC-2 group. At two-year FU, VAS-BP was statistically significantly less in the MC-2 group compared to the MC-1 group. However, gain score analysis with ANCOVA found no statistically significant difference for ODI, EQ-5D or VAS-scores as respective dependent variables with MCs type (MC-1 or MC-2) as the fixed independent variable (all analysis $p>0.1$).

Findings from this study suggest that patients with clinical symptoms, LDH, and MCs can be surgically treated similar to patients without MCs.

Limitations

Study I and II

Due to the long FU, we were not able to account for a possible variation in non-surgical treatments. This is the main limitation of the studies. MCs were not associated with worse LBP in patients at baseline. Therefore, it is not likely that patients with MCs have had more treatment during the FU course than those without MCs.

In terms of spine surgery rates, no differences were found between the two groups +/- MCs. Also, no patients received a prolonged course of antibiotics aimed at eradicating possible low-grade propionibacterium acnes (also known as cutibacterium acnes)[69,103,125]. Of the 290

patients with chronic LBP who meet the inclusion criteria, only 207 patients were included in the studies. Therefore, selection bias is possible, see study 1 - Figure 1 for details.

The radiological evaluation was only performed by a single-rater senior musculoskeletal radiologist, which could lead to interpretation bias. For the studies I and II, a reliability assessment was not performed, although our radiologist had a good inter-rater reliability study in connection with other studies[80]. Also, several other studies have shown excellent inter-rater reliability in evaluating MRIs[38,54,57,79].

The MRIs were performed in 2004-2005, at that time low-field MRI scanners (low field MRI here defined by < 0.3 T) were often used and commonly cited studies on MCs from that period were performed on similar low-field MRI machines[69,80,81]. Due to relatively reduced costs of MRI imaging, mainly high-field MRI is used today[41]. It has been questioned whether the rates of MCs and the ratio of MCs subtypes are related to the MRI field strength[116]. One study found MC-1 to be more common in low-field MRIs while MC-2 findings and the total number of MCs could be increased with high-field scanners (>1.0 T)[116]. This could explain the differences in both the prevalence of MCs and MCs subtypes found in studies[47,78,80,116]. In terms of lumbar degenerative changes, not including MCs, excellent reliability between low- and high-field MRI can be expected[115].

With no FU MRI available, it is not possible to evaluate the progression and possible evolution of degenerative changes including MCs over the 13-year period. There was a discussion among the investigators of the studies on whether or not to perform an FU MRI for all three studies. This would not be possible on a low-field MRI, due to these being replaced by high-field MRIs. An additional FU MRI would most likely demonstrate an increased number of

MCs in total, in particular, MC-2 due to imagining differences in the high-field MRI and MC-1 evolution[63,64]. Overall, this would make a comparison biased.

The primary strengths of this study include a long FU period, a high responder rate of 83% at 13-years, and a low-dropout rate equally distributed between the groups. Relevant potential confounders were included in the studies e.g. BMI, smoking, etc.

Study III

The limitations of this study include the lack of a two-year FU MRI. Disc herniation has been hypothesized as the initial precursor for the development of MCs[77]. In addition, discectomy can possibly cause long-term MRI changes which can be difficult to differentiate from MCs[126–129]. Evaluation of a post-operative MRI after surgically treated disc herniation would need to take this into consideration to avoid interpretation bias.

Selection bias could be present since only patients with complete data questionnaires, pre- and post-operatively, were included in the study. Interpretation bias could also exist regarding the radiological assessment since blinding for MCs while evaluating MRI scans is not possible.

The strengths of this study include complete datasets with a two-year FU on a large cohort. Possible confounders in baseline demographics were included. Surgical treatment was carried out at one institution using the same technique. Pre-operative MRI evaluation was conducted according to a verified classification system and an MRI criterion for description was followed by all four physicians. In addition, all MRIs were evaluated by at least two physicians.

Conclusions

The presence of baseline MCs was not negatively associated with patient-reported outcomes at long-term follow-up. It is possible that patients with MCs experience less disability and sick leave at long-term follow-up compared to LBP patients without MCs.

Degenerative components within the disc, endplate, marrow, and facet joints are common findings on MRI in patients with LBP. Such findings were not negatively associated with patient-reported outcomes at long-term follow-up.

Patients with LDH and clinical symptoms had a higher prevalence of MCs on the preoperative MRI compared to LBP patients. The presence of preoperative MCs is not associated with a worse outcome after discectomy. Both patients with and without MCs can expect a statistically significant and clinically relevant improvement in self-reported pain and disability at two-year follow-up after primary discectomy.

Perspective and future research

Thirty years after their initial description, MCs continue to be the focus of academic interest[67,78]. Such interest stems from the huge impact BP has on global disability, the associated health care costs, and the vast number of patients examined by physicians daily[1,5,62,64,67,111]. A nihilistic historical perspective on MCs could be described by a bell curve adaption of Schopenhauer's three stages of truth with an added disinterest as studies show conflicting or lacking evidence of

an association between MCs and PRO[130]. Evidence on cause and association, however, can be blurred by confounders and bias in research. Multifactorial DD is key in understanding the horizontal and vertical degenerative changes that occur in the spine with increasing age. These changes are overall related to increased disability and pain.

The first studies on MCs all described these findings in the presence of DD. A citation analysis of the three original studies on MCs will provide roughly 2000 citations. Many of these are clinical studies or reviews performed on MCs. Interestingly, very few describe and even less define what MCs encompasses. Naturally, conflicting results will occur if inconsistencies exist and inclusion criteria vary between studies. This misconception has been the subject of correspondence between the author and Dr. Modic, during the writing of this thesis. Modic, a senior musculoskeletal radiologist, advocates the term *degenerative marrow changes* adjacent to a disc with signs of degeneration over MCs due to the ambiguous use in the literature. The above-mentioned description is in accordance with the criteria used to describe and categorize patients with MCs in this thesis and the three studies performed. Evidence from these three studies suggests that patients with LBP and MCs will have an about similar outcome over time compared to those patients without MCs.

Histologic and MRI evolution of MCs over time and association with PRO should be investigated in future studies. The described improvement in the long-term PRO of patients with LBP and disability not undergoing any treatment should also be validated. A systematic review with citation analysis on the use of MCs in the literature would in addition advance the understanding of conflicting results in the literature; and finally, an MRI based definition of the term MCs would be useful in order to guide future research and avoid inconsistencies in both clinical studies, systematic reviews, and meta-analysis.

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CLINICAL CASE SERIES

Modic Changes Are Not Associated With Long-term Pain and Disability

A Cohort Study With 13-year Follow-up

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Study Design. A comparative cohort study with 13-year follow-up.

Objective. To assess whether Modic changes (MCs) are associated with long-term physical disability, back pain, and sick leave.

Summary of Background Data. Previous studies have shown a conflicting association of low back pain (LBP) with MCs and disc degeneration. The long-term prognosis of patients with MCs is unclear.

Methods. In 2004 to 2005, patients aged 18 to 60 with daily LBP were enrolled in an randomized controlled trial study and lumbar magnetic resonance imaging (MRI) was performed. Patients completed numeric rating scales (0–10) for LBP and leg pain, Roland-Morris Disability Questionnaire (RMDQ), LBP Rating Scale for activity limitations (RS, 0–30), inflammatory pain pattern and sick leave days due to LBP at baseline and 13 years after the MRI. Patients were stratified based on the presence (+MC) or absence (−MC) of MCs on the MRI.

Results. Of 204 cases with baseline MRI, 170 (83%) were available for follow-up; 67 (39%) with MCs and 103 (61%) without MCs. Demographics, smoking status, BMI, use of antibiotics, LBP, leg pain, and inflammatory pain pattern scores at baseline and at 13-year follow-up were similar between the two groups. Also, baseline RMDQ was similar between the +MC and −MC groups. At 13 years, the RMDQ score was statistically significant better in the +MC group (7.4) compared with the −MC group (9.6, $P = 0.024$). Sick leave days due to LBP were similar at baseline but less in the +MC group (9.0) compared with the −MC group (22.9 d, $P = 0.003$) at 13 years.

Conclusion. MCs were not found to be negatively associated with long-term pain, disability, or sick leave. Rather, the study found that LBP patients with MCs had significantly less disability and sick-leave at long-term follow-up. We encourage further studies to elucidate these findings.

Key words: back pain, disc degeneration, LBP, long-term follow-up, Modic changes, spine.

Level of Evidence: 2

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Low back pain (LBP) is the leading cause of years lived with disability.[1] It affects 60% to 70% of the population one or several times during a lifespan. LBP is also the most frequent single diagnosis responsible for healthcare and welfare expenses, constituting 15% of all long-term sick leaves and 10% of all disability pensions and is the costliest health-entity in the UK.[2,3]

Modic changes (MCs) are magnetic resonance imaging (MRI)-signal changes seen in the vertebral endplates. They are hypothesized to represent initial inflammation (MC-1) that eventually leads to fat degeneration (MC-2) followed by calcification in the endplate and vertebral body (MC-3).[4,5] MC-1 has been hypothesized as being a significant pain generator.[6–8] In 2006, a population-based study by Kjaer *et al* found that 22% of 40-year old individuals had MCs.[9] Of the subjects with MCs, 88% reported pain in the past year, compared with 63% of those without MCs. Although back pain and disability have been associated with MC in several studies, the results are still conflicting.[10–16] The currently available studies are predominantly

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either cross-sectional or with short follow-up, and only one looked at long-term influences.[17]

The aim of the study was twofold: 1) to assess whether MCs are associated with long-term physical disability, back pain, and sick leave; and 2) to assess whether the baseline characteristics differ depending on the presence of MCs.

MATERIAL AND METHODS

This is a comparative cohort study with 13-year follow-up on patients with chronic LBP. The cohort was originally recruited for a study conducted between 2004 and 2005. In that study, patients were referred for evaluation of LBP and subsequently randomized to either cognitive training or physiotherapy.[18] Inclusion criteria were age 18 to 60 years; mean LBP score $\geq$ 4/10 for the last 14 days; pain for a minimum of four out of the past 12 months; back pain greater than leg pain (LP) and no suspicion of a herniated. Exclusion criteria were magnetic metal anywhere in the body, pregnancy, suspicion of malignancy, traditional lumbar inflammatory disease, previous spine surgery, and current psychiatric disease.

In the original randomized study, treatment with cognitive training compared with physiotherapy showed no difference at 1 year in terms of back pain, activity limitations measured, and work ability.[18] Since the cohorts were similar at both baseline and follow-up, the entire cohort, regardless of treatment arm, were pooled for the current study and analysis.

Of the original 207 cases in the randomized cohort, 204 had a lumbar MRI performed at baseline. Based on these MRIs, patients were, for the actual study, assigned into an MC group (+MC) or a no-MC group (−MC). MCs were defined in accordance with the original Modic studies and were used to describe all three types of MCs.[4,5,19]

The proportion of +MC and −MC cases were equally distributed between the two randomized groups and MRI scan findings did not influence treatment. No systematic interventions were performed during the 13-year follow-up period. Study participants completed questionnaires at baseline and at 13-year follow-up including the Roland-Morris Disability Questionnaire (RMDQ), and activity limitations survey (RS).[20,21] LBP and LP were both accessed with the Numeric Rating Scale (0–10), number of sick leave days due to back pain the past year (0–200 workdays). The presence of an inflammatory pain pattern was defined by at least one of three characteristics: maximal pain in the morning, waking at night because of pain, and morning stiffness for longer than 60 minutes.[22] Primary outcomes were RMDQ, LBP, and sick leave. Secondary outcomes were activity limitation, measured by RS, LP, and inflammatory pain pattern.

MRI EVALUATION

All patients underwent a low-Tesla MRI of the lumbar region (0.2 T MRI-system, Siemens Open Viva). MRIs were evaluated by an experienced musculoskeletal radiologist using a standardized evaluation protocol and unaware of the clinical status and the assigned treatment.[23]

STATISTICAL ANALYSES

Patients with a baseline MRI and, baseline and 13-year follow-up questionnaires were included in the analysis. Continuous data from the patients with +MC and −MC were compared using unpaired student *t* test. Ordinal data from the two groups were compared with Mann–Whitney *U* test. Categorical data was analyzed using the chi-square test. Analysis of covariance was used for 13-years RMDQ and LBP at 13-year as dependent variables with MCs as the fixed independent variable and respective baseline outcome measures as covariate. A 5% level of statistical significance was used for the analyses.

ETHICAL CONSIDERATIONS, APPROVALS, AND REGISTRATION

Protocol, data collection, and study ethics were approved by the National data protection agency and The Regional Committees on Health Research Ethics.

RESULTS

A total of 290 patients fulfilled the criteria for inclusion in the original study, 207 subjects were enrolled with 204 having lumbar MRI and being eligible for inclusion in the current study (Figure 1). Of these, 170 (83%) patients completed their questionnaire at 13 years, with 67 (39%) having +MC and 103 (61%) with −MC on their baseline MRIs. Of the 34 drop-outs, no difference was seen regarding baseline data between the groups: nine had died (four with +MC and five with −MC), five were not available (two +MC and three −MC), 20 did not respond to follow-up letters (9 +MC and 11 −MC).

In patients with +MC, MC-1 was present in 75%, MC-2 in 24%, MC-3 in <1% of patients, and Mixed (MC-1 and MC-2) in 6% of patients.

Predominantly the MCs (80%) were located at the L4-L5-S1 levels (Figure 2).

There were no significant differences in demographics, duration of LBP, or smoking status at baseline between +MC and −MC groups (Table 1).

At baseline there were no statistically significant differences in any of the patient reported outcome scores (Table 1, Figure 3).

At final follow-up, the mean RMQD score was statistically significantly better in the +MC group (7.4) compared with the −MC group (9.6, $P = 0.024$) (Table 2, Figure 3). The 13-year LBP score was lower in the +MC group (4.2) compared with the −MC group (4.8, $P = 0.104$) and LP was 2.6 *vs.* 3.4 in the +MC and −MC groups, respectively ($P = 0.097$). RS scores were statistically significant lower in the +MC group (8.32) compared with the −MC group (10.64, $P = 0.013$). There were notably fewer sick leave days due to LBP in the +MC group (9.0 d *vs.* 22.9 d, $P = 0.003$). There was no statistically significant difference in spine surgery rates between the two groups (10% for the +MC

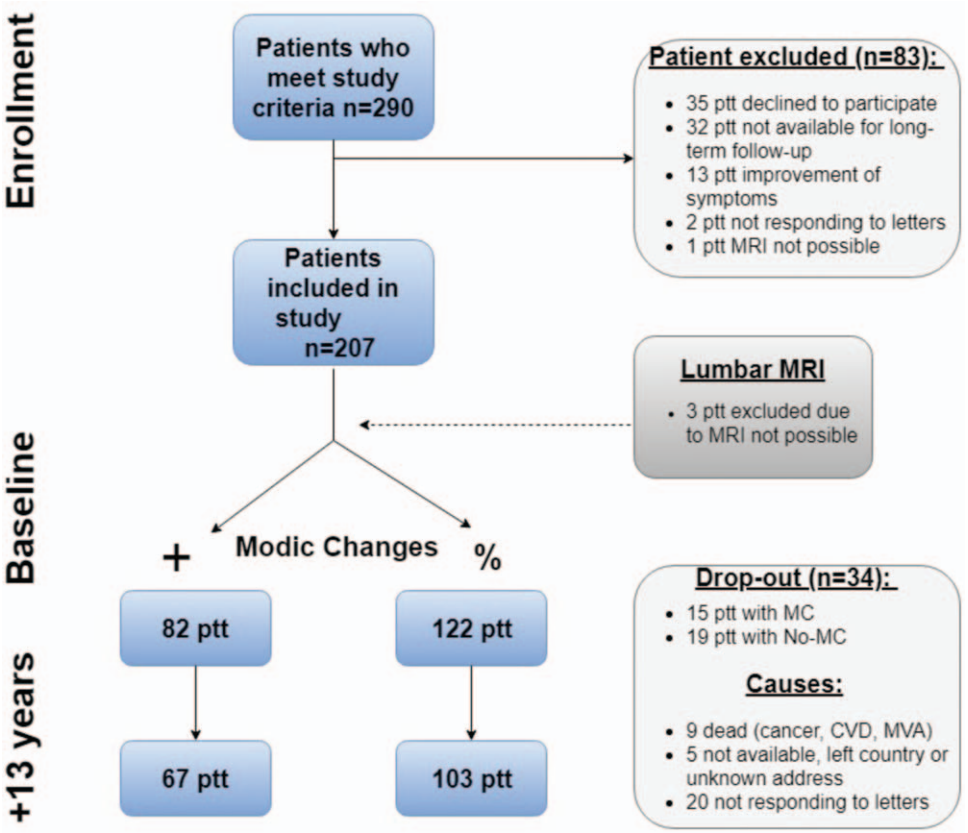

Figure 1. Study enrollment and follow-up.

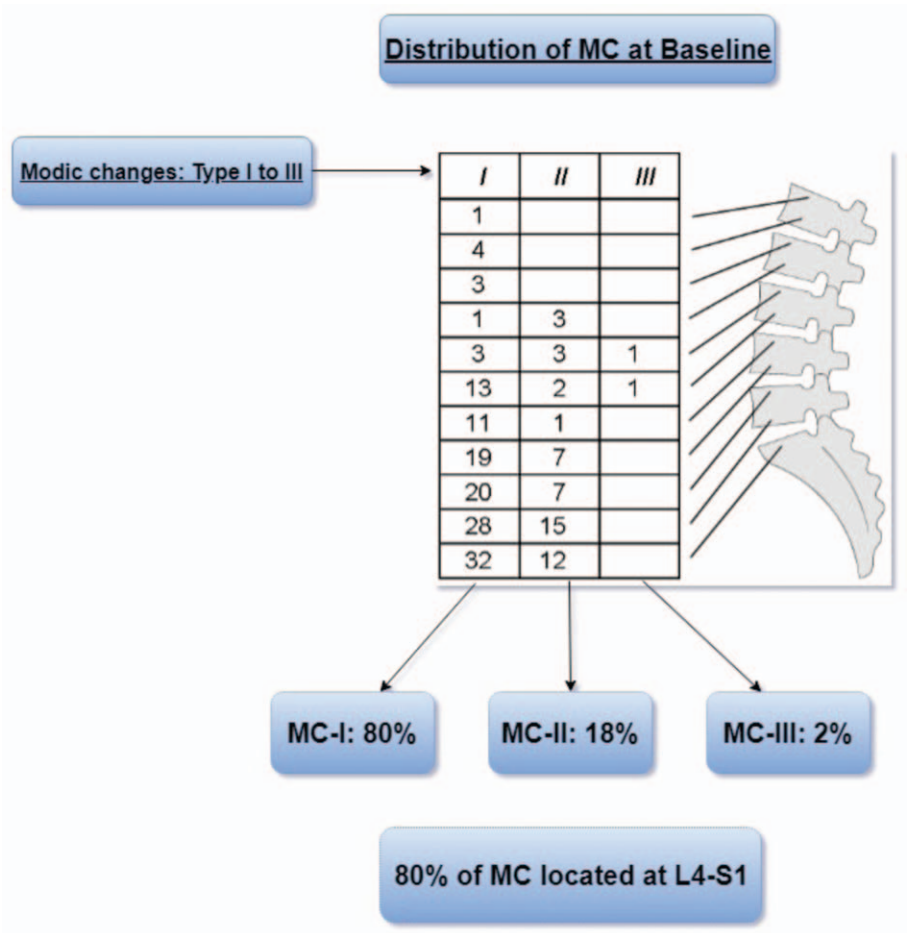

Figure 2. The distribution of Modic changes.

TABLE 1. Summary of Demographic Data of the Current Study at 13-year Follow-up

	+MC	−MC	*P* Value
n	67 (40%)	103 (60%)	
Females, N (%)	35 (52%)	57 (55%)	0.753
Weight, kg, mean (SD)	83.5 (17.1)	85.1 (19.7)	0.213
BMI, kg/m^2, mean (SD)	26.6 (4.8)	27.9 (5.2)	0.113
Age, yrs, mean (range)	54.1 (33–67)	52.4 (31–70)	0.542
Smokers, N (%)	17 (25%)	22 (22%)	0.706
Married, N (%)	42 (62%)	61 (59%)	0.749
Spine surgery after MRI, N (%)	7 (10%)	11 (11%)	0.584
Antibiotics use, N (%)	42 (63%)	68 (66%)	0.743

group and 11% in the −MC group, $P = 0.584$). Analysis of covariance showed MCs to be significantly positively associated with 13-year RMDQ ($P = 0.031$), but the R-square for the model was 0.159 indication that the presence of MCs accounts for only 16% of the variability in the 13-year RMDQ. No other significant associations were seen with the outcome measures at 13 years and the presence of MCs (Table 2).

A decrease over time in use of pain medication due to LBP was seen in +MC group, (68% at baseline and 52% at 13-yr follow-up), with no change in the −MC group (61% *vs.* 62%). Antibiotics had been prescribed in the 13-year period in; 63% and 66% of the +MC and the −MC patients, respectively ($P = 0.743$).

DISCUSSION

Several studies have highlighted the prevalence and clinical significance of MCs in patients with LBP.[9,11,15,16,24–26] Some studies have also described patients with MCs as a subgroup of LBP patients with patient-reported outcomes (PROs) and clinical features being different from LBP patients with disc degeneration (DD) and no MCs.[9,22]

Few studies, however, have examined the long-term PROs in patients with MCs.[17] In contrast to previous studies, the current study did not find any differences in PROs at initial consultation in chronic LBP patients with or without MCs.[9,16,22,27] In this aspect, we found no clinical parameters distinguishing LBP patients with MCs from those without MCs. At 13-year follow-up, however, significant changes were found between the +MC and −MC groups. Disability (measured by RMDQ and RS) and sick leave were significantly less in the +MC patients. Several studies have highlighted MCs and in particular MC-1 as a potential cause of LBP possibly due to inflammation and/or low-grade infection within the vertebral endplate.[15,16,26–28] Treatments used for LBP patients with MCs may include

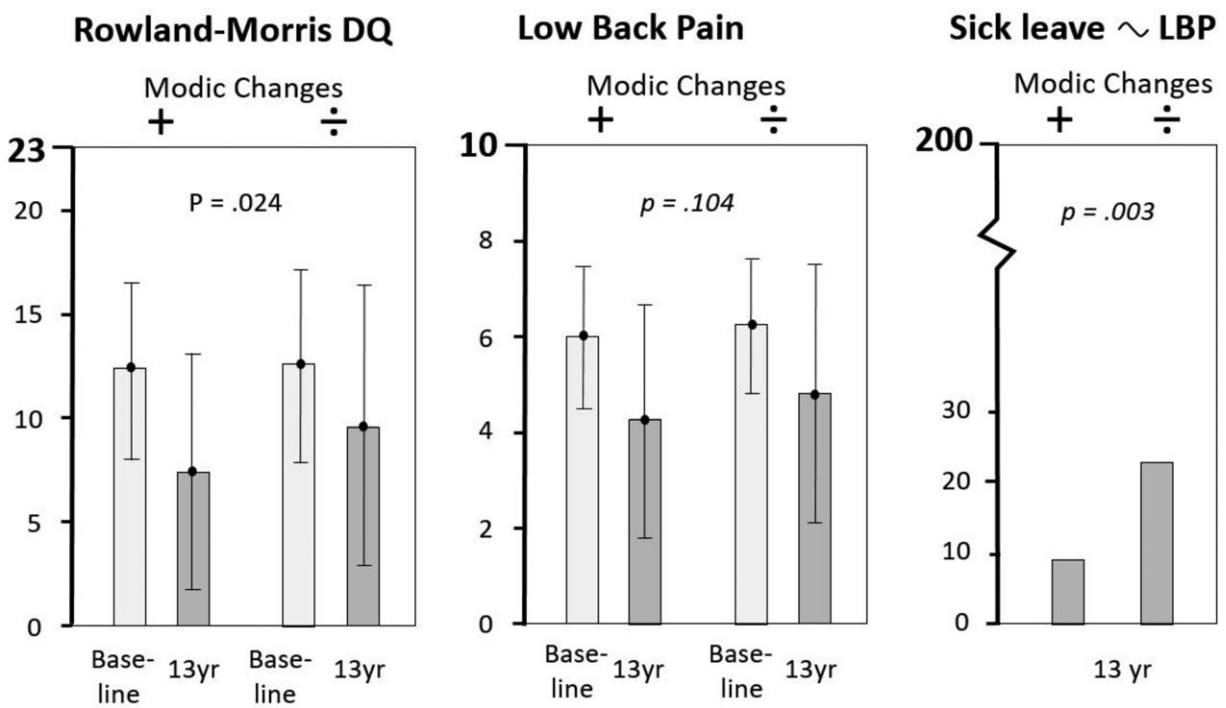

Figure 3. RMDQ, LBP, and sick leave at baseline and 13-year follow-up. *P* values represent nonpaired *t* test. Significantly less disability and fewer sick leave days was found in the +MC group at follow-up. LBP was similar both at baseline and at follow-up.

TABLE 2. Baseline and 13-year Follow-up

		+MC	−MC	*P* Value
RMDQ (disability, 0–23 score)	Baseline	12.4 [4.2]	12.6 [4.7]	0.752
	13 yr FU	7.4 [6.0]	9.6 [6.8]	0.024
RS (activity limitation, 0–30 score)	Baseline	13.0 [4.7]	14.1 [4.8]	0.161
	13 yr FU	8.32 [5.3]	10.64 [6.6]	0.013
Low back pain (NRS)	Baseline	6.0 [1.5]	6.3 [1.4]	0.254
	13 yr FU	4.2 [2.5]	4.8 [2.7]	0.104
Leg pain (NRS)	Baseline	1.9 [2.0]	2.2 [2.2]	0.638
	13 yr FU	2.6 [2.8]	3.4 [3.0]	0.097
Sick leave due to LBP (days past year)	Baseline	–	–	–
	13 yr FU	9.0 [36.6]	22.9 [59.4]	0.003
Back pain medication consumption regularly (%)	Baseline	56 (68%)	74 (61%)	0.412
	13 yr FU	35 (52%)	64 (62%)	0.252
Physical activity level at leisure (group 1–4)	Baseline	1.9 [0.7]	2.1 [0.7]	0.149
	13 yr FU	2.1 [0.7]	2.0 [0.7]	0.454
IPP	Baseline	70 (86%)	101 (83%)	0.661
	13 yr FU	43 (64%)	68 (66%)	0.945

bed rest, corticosteroids, spinal fusion, or prolonged antibiotics courses.[25,27,29,30] Eleven percent of patients had spinal surgery performed from baseline to 13-year follow-up, less than 5% had spinal fusion. Around two-thirds of all patients, (±MC), had antibiotics at some point during the 13-year period. None of the patients had prolonged courses of antibiotics aimed at eradicating Propionibacterium, a speculated associative cause of MCs, and having shown efficacy in one study.[27,31,32]

Commonly cited studies on MCs have typically been performed on low-Tesla MRI (low field MRI here defined by $\leq$ 0.3 T, high field defined by $\geq$ 1.0–3.0 T), as in this study.[9,24,27] Today, high-Tesla MRI are used in most centers which invalidates direct comparisons. Especially since MCs findings are different between low- and high-Tesla MRI scanners. MC-1 is a more common finding in low-Tesla MRIs while MC-2 findings and total number of MCs are increased with high-Tesla.[33] This may contribute to the variation of MCs prevalence reported as well as the different rates of MC-1 and -2 across studies. A follow-up MRI with a high-Tesla scanner would likely show an increased number of MCs, in particular MC-2, due to imaging differences as well as the natural progression of MC-1.[4,33,34] Combined, this would make a comparison of baseline and long-term follow-up MRI biased.

The association between MCs and LBP has previously been examined in studies with 1 to 2 year follow-up and one study with 10-year follow-up.[17] Some studies have reported a higher prevalence of LBP in patients with MCs, particularly MC-1, compared with DD alone, while other studies do not find MCs to be associated with LBP.[11–13,15,16,26] A systematic review and meta-analysis from 2018 of 31 MCs studies found the association between MCs and LBP-related outcomes to be inconsistent.[10] This may be explained by the difficulties in isolating subjects with MCs and no DD.[9] MCs are associated with DD and are part of the degenerative process.[4,5,35] Subgroup analysis of subjects with MCs only is therefore typically not feasible.[9]

It should be emphasized that the patients in our cohort were initially selected due to long-lasting LBP. Of the 290 patients who met the inclusion criteria, only 207 patients were eventually included (Figure 1). Therefore, a selection bias is possible. In contrast to the population-based studies reporting frequencies of MCs of about 20%, the rate in our cohort was twice that figure, indicating a clinical impact of MCs.

The results presented in this study might be explained by progression of active inflammatory changes with bone edema in MC-1 to fat deposits and osteosclerosis (MC-2/-3). This is the natural histopathological evolution previously hypothesized.[4,15,28,34] Evidence of this pathway is present in both laboratory studies and *in vivo* MRI studies.[15,28] Understanding the development of MCs over time and its impact on LBP is key in understanding the natural progress of disability and pain in LBP patients. This change in the patients with MCs from MC-1 to MC-2/-3 might explain the better long-term clinical status compared with the patients with isolated DD.

The value of short-term studies is limited when trying to assess the long-term consequences of relevant pain generators such as MCs. In accordance with the only other long-term follow-up study, also our study does not support the idea of MCs as a negative predictor of outcome over time.[17]

The conclusions that can be drawn from this study are strengthened by a long follow-up period, a high response rate, and a low dropout rate that was equally distributed between the groups. Factors that might influence LBP within the groups—smoking, BMI, spine surgery, antibiotics, marital status, sick leave, physical activity at leisure, alcohol consumption—were similar across the groups at baseline and at 13-year follow-up. We encourage further

studies to verify the significant and relevant findings from this study. In particular, since MCs are a common MRI finding in LBP patients and because the known treatment strategies may be both ineffective, costly, and a source of iatrogenic harm.

CONCLUSION

MCs are a common finding in LBP patients referred to a tertiary spine center due to long-lasting LBP. No clear clinical features can separate patients with MCs from those without at initial consultation. MCs were not found to be negatively associated with long-term pain, disability, or sick leave. Rather, the study found that LBP patients with MCs had significantly less disability and sick leave at long-term follow-up. We encourage further studies to elucidate these findings.

➢ Key Points

- ❑ Two hundred four LBP patients with baseline MRI were followed for 13 years with health-related quality-of-life questionnaires.
- ❑ MCs were present in 40% of chronic LBP patients.
- ❑ Patients with MCs had less disability and sick leave at 13-year follow-up compared with LBP patients without MCs.

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Are MRI findings associated with long-term disability in low back pain patients?

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Abstract

Background Context: MRI is used extensively as a diagnostic tool to evaluate and guide the treatment of patients with low back pain (LBP). Specific MRI findings have been associated with pain and disability. However, the association between these specific MRI changes and long-term disability is unclear.

Purpose: To assess whether long-term disability is associated with baseline degenerative MRI findings in patients with LBP.

Study design: A comparative cohort study with 13-year follow-up.

Patient sample: The study population consisted of 204 patients with LBP.

Outcome measures: Roland-Morris Disability Questionnaire (RMDQ) and the LBP Rating Scale for activity limitation. MRI evaluation included disc degeneration (DD), Modic changes (MC), and facet joint degeneration (FJD).

Methods: In 2004-2005, patients aged 18-60 with LBP were enrolled in a randomized controlled trial and lumbar MRI was performed. Patients completed the Roland-Morris Disability Questionnaire (RMDQ) and the LBP Rating Scale, at baseline and 13-years after the MRI. Multivariate regression analysis was performed with 13-yr RMDQ as the dependent variable and baseline DD (Pfirrmann grade), MC, FJD (Fujiwara grade), smoking status, body mass index, and self-reported weekly physical activity at leisure as independent variables.

Results: Of 204 patients with baseline MRI, 170 (83%) were available for follow-up. Of these, 88 had Pfirrmann grade >3 (52%), 67 had Modic Changes (39%) and 139 had Fujiwara >2 (82%) on at least one lumbar level. Only MC (β= -0.15, p=0.031) and weekly physical activity at leisure (β= -0.51, p<0.001) were significantly associated, both negatively, with 13-year RMDQ-score (R^2=0.31).

Conclusion: DD and FJD were not associated with long-term disability. Baseline MC and weekly physical activity at leisure were statistically significantly associated with less long-term disability.

Keywords: Modic Changes; disability; LBP; degeneration; MRI; long-term follow-up; spine.

Introduction

Since the first reports on human magnetic resonance imaging (MRI) in 1977, there has been a vast advancement in its use and functions[1]. For patients suffering from back pain and its associated disability, it has become a commonly used diagnostic imaging modality. Whereas certain imaging findings such as nerve impingement and severe canal narrowing has shown a strong association with patient-reported outcomes (PRO's), other signs of degeneration found on MRI have a more questionable clinical relevance[2–7]. Disc Degeneration (DD), Modic Changes (MC) and Facet Joint Degeneration (FJD) are all imaging findings and possible causes of LBP[5,8–10]. Several different grading systems have been utilized to classify the severity of these degenerative changes. The Pfirrmann classification system has been validated, with excellent inter- and intra-observer agreement, and is widely used to classify DD in five grades, Pfirrmann grade I (normal)-V (most severe) [11,12].

MC, also termed vertebral endplate signal changes (VESC), are endplate and adjacent vertebral body marrow changes visible on MRI. They have been histologically described, and MRI classified into three different types, MC 1-3[13,14]. Their presence, size, location, and the MRI inter- and intra-observer reliability, substantial to an almost perfect agreement, has been validated across studies[15,16].

Facet joint changes and degeneration is a common feature, which can be graded on both oblique radiographs, computed tomography scan, and MRI[9,17]. The radiographic assessment of lumbar facet joints is possible through 12 different grading systems[18]. The reliability of these systems has been evaluated with varying inter- and intra-observer agreement[18,19]. The most standard used MRI grading system for lumbar FJD, with an almost perfect inter-observer agreement, was developed by Fujiwara et al[9,18]. The Fujiwara based system, classify facet joint changes into grade 1 (normal) – grade 4 (severe degeneration)[9].

Several studies have focused on these degenerative imaging findings in the spine and their clinical relevance[3,20,21]. Few studies, however, have examined the long-term association between such findings and spine-related disability[22].

The aim of the study was to assess whether baseline MRI findings indicating degeneration are associated with long-term disability in LBP patients.

Material and methods

This is an observational cohort study with 13-year follow-up on patients with chronic LBP. The cohort was originally recruited for a randomized control trial (RCT) conducted between 2004 and 2005. The cohort and original study details have been described in previous studies[7,23].

Of the original 207 patients in the RCT, 204 had a lumbar MRI performed at baseline. Based on these MRIs, patients were, for the current study, described regarding three different radiological parameters:

- DD defined as Pfirrmann grade>3 on any lumbar level[5,24].
- MC as described by Modic et al, any type on any lumbar level[13,14,25].
- FJD defined by Fujiwara grade>2 on any lumbar level[9].

Study participants completed questionnaires with PRO's at baseline and at 13-year follow-up including the Roland-Morris Disability Questionnaire (RMDQ), and the LBP Rating Scale for activity limitations survey (RS)[26–28]. Demographic data including smoking, BMI and weekly physical activity at leisure (PA) were also recorded both at baseline and at 13-year follow-up. Information regarding antibiotic use, defined as any received course of antibiotics, and spine surgery during the 13-year period was obtained through the follow-up questionnaire.

MRI evaluation

All patients underwent a low-Tesla MRI of the lumbar region (0.2 T MRI-system, Siemens Open Viva). The use of low-field MRI was widely used in the inclusion period from 2004-2005. Excellent reliability between low- and high-field MRI has been demonstrated for lumbar

degenerative changes[29]. MRIs were evaluated by an experienced musculoskeletal radiologist using a standardized evaluation protocol and unaware of the clinical status of the individual patient[23]. The MRI description was not available to included patients and did not influence treatment.

Ethical considerations, approvals, and registration

Protocol, data collection and study ethics were approved by the National data protection agency and The Regional Committees on Health Research Ethics (reference number: S-20172000-77).

Statistical analyses

All analyses were performed using IBM SPSS® version 24. Patients with a baseline MRI, baseline and 13-year follow-up questionnaires were included in the analysis. Multivariate linear regression analysis was performed with 13-year RMDQ and RS as dependent variables and DD, MC, FJD as independent variables. Demographic data at 13-year including smoking, body mass index (BMI) and PA were included as covariates in the regression models. The association between 13-year RMDQ and the independent variables was evaluated by the standard β coefficient. The Goodness-of-Fit and explained variation were evaluated by the R^2.

Results

A total of 290 patients fulfilled the criteria for inclusion in the original study, 207 were enrolled with 204 having lumbar MRI and being eligible for inclusion in the current study (Figure 1). Of these, 170 patients (83%) completed their questionnaire at 13 years, 88 had DD (52%), 67 had MC (39%) and 139 had FJD (82%) on their baseline MRIs. Of the 34 dropouts, no difference was seen regarding baseline data on the distribution of spine degeneration on MRI. Demographics for 13-year follow-up data are described in Table 1.

Figure 1: Study enrollment and follow-up

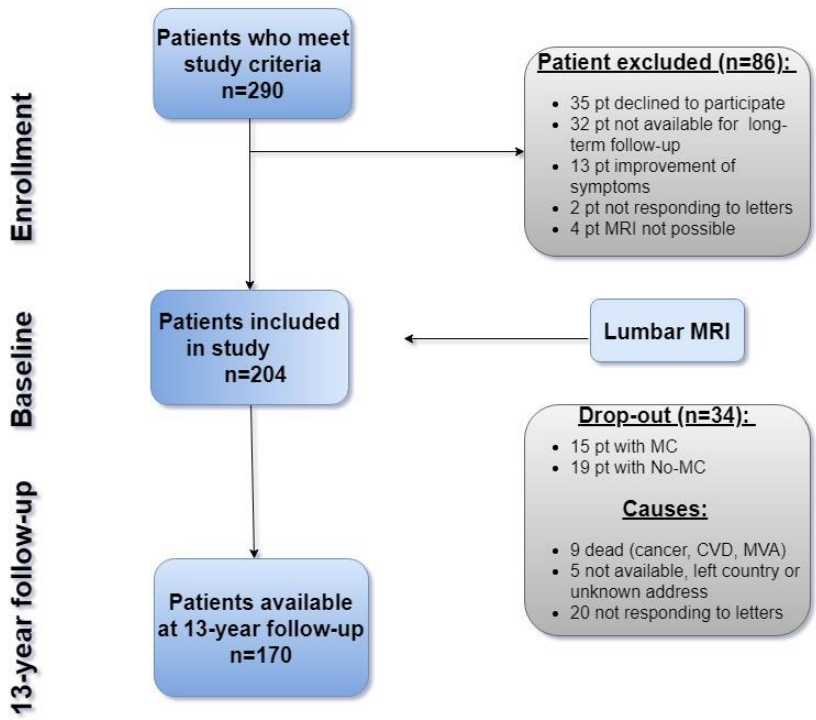

Table 1: Demographic data at 13-year follow-up

Table 1. Summary of demographic data of the current study at 13-year follow-up	
N	170
Females, N (%)	92 (54%)
Weight, kg, Mean (SD)	84.3 (18.4)
BMI, kg/m^2, Mean (SD)	27.3 (5.0)
Age, years, Mean (range)	53.3 (31-70)
Smokers, N (%)	39 (24%)
Married, N (%)	103 (61%)
Spine Surgery after MRI, N (%)	18 (11%)
Antibiotics within the last 13-years, N (%)	110 (65%)

In patients with MC, MC-1 was present in 75%, MC-2 in 24%, MC-3 in <1% of patients and Mixed (MC-1 and MC-2) in 6% of patients. Baseline and follow-up PRO's for the entire cohort are presented in table 2.

Both MC and PA at leisure were found to be statistically significantly negatively associated with 13-year RMDQ-scores, R^2=0.31 with standard β coefficients of 0.15 for MC (p=0.031) and -0.51 for PA (p<0.001). Neither DD (β= 0.060, p=0.406) or FJD (β = -0.017, p=0.801), showed any

statistically significant association with long-term disability. Smoking status (β = 0.102, p=0.127) and BMI (β = 0.092, p=0.179) also, showed no significant association with the RMDQ-scores. Similar results were found for 13-year RS with R^2=0.26 and β of -0.18 for MC (p=0.015) and -0.45 for PA (p<0.001). Neither DD, FJD, smoking status or BMI significantly affected long-term RS.

Disability measured by RMDQ and RS improved over time, resulting in less disability at 13-year follow-up compared to baseline. LBP also decreased from 6.2 (NRS) to 4.5 (NRS) over the 13-year time period. Leg pain increased slightly, from 2.1 (NRS) to 3.0 (NRS) at final follow-up. The consumption of back pain medication decreased from 65% of the group using regularly at baseline to 56% of the group using regularly at 13-year follow-up. There was no change in PA over the 13-year span.

Table 2: Baseline and 13-year follow-up

Table 2. Baseline and 13-year follow-up

Number of patients	• **Baseline** • **13y FU**	n=204 n=170
RMDQ (Disability, 0-23 score)	• **Baseline** • **13y FU**	12.5 [4.5] 8.5 [6.4]
RS (Activity limitation, 0-30 score)	• **Baseline** • **13y FU**	13.6 [4.7] 9.5 [5.9]
Low back pain (NRS)	• **Baseline** • **13y FU**	6.2 [1.4] 4.5 [2.6]
Leg pain (NRS)	• **Baseline** • **13y FU**	2.1 [2.1] 3.0 [2.9]
Sick leave due to LBP (days past year)	• **Baseline** • **13y FU**	- 16.0 [48]
Back pain medication consumption regularly (%)	• **Baseline** • **13y FU**	130 (65%) 95 (56%)
Physical activity level at leisure (group 1-4)	• **Baseline** • **13y FU**	2.0 [0.7] 2.1 [0.7]

Central tendency described as mean with SD given in braces

Discussion

Lumbar MRI scans are used to identify the possible causes of back pain, guide treatment and as a tool to provide short- and long-term prognosis. In this study, the association between long-term disability and baseline MRI findings was examined in chronic LBP patients. Degenerative changes were found to be present in the majority of patients - DD and FJD in respectively 52% and 82% of all patients. Similar results have been found in previous studies of MRI degeneration in LBP patients[3,10,30].

Neither, DD at baseline defined as Pfirrmann grade>3 on any lumbar level, or FJD, defined as Fujiwara grade>2 on any lumbar level, were associated with disability at long-term follow-up. Similar results on the prevalence and limited or lacking association with back pain and disability have been documented in cross-sectional studies and studies with shorter follow-up periods[3–5,8,31,32].

Subgroup analysis of the cohorts stratified by imaging findings was not performed in this study, as there was a substantial overlap of patients with two or all three of the possible imaging findings denoting degeneration. It would be difficult to isolate patients with DD without FJD as well as patients with MC without DD. This overlap of imaging findings has been described, in particular in relation to MC and DD, previously[7,14,25,33].

Degenerative Disc Disease (DDD) is a commonly used diagnosis and possible indication for spinal fusion in patients with chronic back pain[31,34]. However, the term DDD is used broadly across studies and should be avoided unless thoroughly defined. In this study, the Pfirrmann and Fujiwara classification systems were used to grade the degenerative MRI findings of the intervertebral discs and the facet joints, respectively.

For DD, the Pfirrmann classification is the most validated and secondly most used for LBP patients across studies[11,12,24,26]. MC was originally described based on MRI changes but also histologic examined in a few cases by Modic et al[13,14,25]. Although it is possible to add information, including size, location, distribution etc, to the MC description; it is still the original MC

classification of MC type 1-3 that is being utilized and validated across studies[8,13,15,16,35,36]. It has been questioned whether the classification of MC is related to the MRI field strength - with low field MRI scanners (defined by Tesla ≤0.3T) showing an increased number of MC type-1 compared to high field MRI (defined by Tesla ≥1.0 T) scanners showing an increased number of MC type-2[37].

In general, excellent reliability between low- and high-field MRI has been demonstrated for lumbar degenerative findings including disc herniation and lateral stenosis[29]. For FJD the classification systems suffer from certain limitations. Degeneration including osteoarthritis has been described on different imaging systems including x-rays, CT and MRI scans[18,19]. Some of the grading systems have been adapted from CT to MRI but with limited validation in inter- and intra-observer studies[9,18,19,38,39]. The Fujiwara classification has been examined and found to be reproducible in grading FJD in MRI analysis[9,18].

Limitations in this study include possible confounding in terms of different exposure, treatment, and psycho-social factors of the individual patients within the cohort. There could be a possible bias with a single-rater radiologist, however, previous studies have shown excellent inter-rater reliability and therefore a reliability assessment was not included in the present study [11,12,15,16,18].

The primary strengths of this study include a high follow-up rate of 83% at 13-years and the inclusion of relevant potential confounders in the statistical analysis, BMI, smoking etc. Also, no patients underwent long-term antibiotic courses aimed at eradicating possible bacterial agents within the disc, including propionibacterium acnes[40,41]. The findings in this study are in accordance with previous studies, showing that lumbar degenerative changes visualized by MRI are common and are to be expected to a certain degree in all mature individuals[3,5,8,38,42–46]. However, this cohort study of chronic LBP patients found more severe degeneration on MRI compared to what is found in cross-sectional population-based MRI studies[3–5,10,30,33]. The clinical relevance of these results is the prognostic value at long-term follow-up of LBP patients. Some studies with short-term follow-up and cross-sectional studies have found an association between MC in particular type-1, severe

disc degeneration, and to some degree facet joint degeneration, with LBP[31,32,47,48]. In this study, no association was found between baseline MRI findings and 13-year disability in LBP patients with severe DD or FJD. This highlights the limited prognostic value of a single baseline MRI scan on long-term disability.

MC present at baseline was predominantly MC type-1, 75%, this finding was associated with statistically significant less long-term disability in the cohort[7]. These results are in contrast to short-term studies[8,33,40,48]. Several studies have investigated the effect of both surgical and antibiotic treatment of patients with MC and LBP[40,49,50]. The relevance of such invasive treatments or prolonged antibiotic courses of patients with MC can be questioned. In particular, if the MRI findings are not associated with a worse prognosis at long-term follow-up in patients not receiving treatment[22]. It is striking that in a between-individual view, DD and MC are rather highly associated with LBP, whereas a longitudinal view within individuals does not show such an association[7,22,46,51]. One hypothesis could be that the degenerative process of the disc, including the gradually fibrotic nuclear pulposus and annulus, reduces the risk of disc penetration and thereby activation of peripheral nerve fibers within the disc.

In future studies, it would be interesting to a) verify the histologic and MRI transgression of MC over time including the timeline and clinical relevance; b) to further examine the prognostic properties of baseline degeneration found on MRI combined with clinical findings, on long-term PRO's in LBP patients; and c) to evaluate the long-term outcomes in patients with degeneration on MRI and LBP not undergoing treatment.

Conclusion

Degeneration on MRI was a frequent finding in patients with LBP.

None of the MRI changes suggesting degeneration were associated with a worse outcome at 13-year follow-up. Baseline MC was associated with statistically significant less long-term disability.

We encourage further studies to validate these findings and assess the long-term clinical consequences of abstaining from treatment in LBP patients.

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Are Modic changes associated with health-related quality of life after discectomy - a study on 620 patients with two-year follow-up

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Abstract

Study design: A registry-based comparative cohort study with two-year follow-up.

Objective: To assess whether Modic Changes (MCs) are associated with health-related quality of life, long-term physical disability, back- or leg pain after discectomy.

Summary of background data: Previous studies have failed to show a clinically significant association between MCs and patient-reported outcomes (PRO's) after discectomy.

Methods: Data from the Danish National Spine Registry on patients undergoing first-time lumbar discectomy at a single institution from 2014-17 with an accessible preoperative lumbar MRI, complete pre-operative and two-year follow-up questionnaires were obtained. PRO's including ODI, EQ-5D, VAS back and leg pain and patient satisfaction were collected. Patients were stratified based on the presence (+MC) or absence (-MC) of MCs on the preoperative MRI.

Results: Of 620 patients included, MCs were present in 290 patients (47%). Of these, MC type 1 (MC-1) was present in 73 (25%) and MC type 2 (MC-2) in 217 (75%) patients. Preoperative data for ODI, EQ-5D, VAS-BP, and VAS-LP were comparable for the +MC and -MC groups. Both groups had a statistically significant improvement in PRO's from baseline compared to two-year follow-up ($p<0.001$). At two-year follow-up, both groups had improved with no significant difference between them in regards to ODI (15.5 vs. 17.2, $p=0.208$); EQ-5D (0.75 vs. 0.72, $p=0.167$); VAS-BP (27.1 vs. 28.3, $p=0.617$); VAS-LP (26.8 vs. 25.0, $p=0.446$) and patient satisfaction (74% vs. 76%, $p=0.878$).

Conclusion: MCs were not found to be associated with health-related quality of life, disability, back- or leg pain or patient satisfaction two years after discectomy.

Keywords: Back pain; Modic changes; LBP; disc degeneration; herniated lumbar disc; spine; long-term follow-up.

Key Points:

- Of 620 patients undergoing primary discectomy due to lumbar disc herniation, 47% had Modic changes on their preoperative MRI.
- Patients with and without Modic changes experienced a statistically significant and comparable improvement in health-related quality of life, disability, and pain scores two-years after discectomy.
- Neither type-1 or type-2 Modic changes were found to be negatively associated with health-related quality of life after discectomy.

Introduction

Lumbar disc herniation (LDH) is a common pathology, that in certain cases requires surgical discectomy[1–3]. While the underlying disease mechanism is only partly understood, disc degeneration (DD) is often present although not necessarily associated with LDH[4,5]. DD is often defined by certain radiographic parameters, but the correlation between the clinical and radiographic phenotypes is not well-established[6–9]. The causes of DD and its overall association with low back pain (LBP) have been studied extensively[4,10–12]. Modic et al demonstrated an association between vertebral endplate signal changes, bone marrow edema and DD on magnetic resonance imaging (MRI)[13–15]. Based on the presentation on T1 and T2 weighted MRI imaging and the histopathologic tissue analysis these changes were described as Modic Changes (MCs) and subclassified into MC types 1 to 3 (MC-1, MC-2, and MC-3). MCs are a common finding, with a prevalence in the adult population of 5-22%, increasing with age, and being present in up to more than 40% in adults with LBP[9,16–19]. The treatment strategy for LBP patients with MCs varies greatly between healthcare professionals and includes conservative management, oral antibiotics and surgical treatment consisting of radical disc removal often combined with fusion[20–23].

Studies have demonstrated an association between both MCs and DD and MCs and LBP, in particular for MC-1[9,13,14,17,18]. In addition, studies have suggested an association between MCs and the presence of intradiscal biofilms and positive cultures of propionibacterium acnes. However, it is still uncertain whether MCs are caused by mechanical stress, as part of a degenerative process, or by a low-grade bacterial infection[20,24–27].

LDH diagnosed with MRI has been reported in 25% of the background population[9]. However, certain inconsistencies exist for the classification and description, in particular of the endplate involvement on MRI[28–30]. Endplate junction failure has been shown to be more common after LDH than annulus fibrosus rupture[30]. Such changes could play a key role in the development of MCs and might explain the high prevalence of MCs reported in patients with LDH (40-60%)[15,21,27,31].

MCs have been hypothesized to aggravate LBP in LDH patients and disc herniation has been associated with an increased incidence of MCs and worsening of patient-reported outcomes (PRO's)[21,30,31]. Additionally, as MCs may include bacteria, and end-plate damage could play a role in LDH and MC formation, it is possible that MCs could influence discectomy negatively.

The aim of this study was to evaluate if the presence of MCs on the pre-operative MRI prior to discectomy is associated with two-year PRO's after discectomy.

Material and methods

This is a comparative registry-based cohort study with two-year follow-up on patients who underwent discectomy due to LDH. The cohort consisted of patients undergoing primary discectomy at a single institution between January 2014 and July 2017.

Inclusion criteria were age 18 to 60 years; lumbar discectomy for persistent radiculopathy (duration of at least 6 weeks) with failure of nonsurgical treatment.

Exclusion criteria were incomplete questionnaire data preoperatively or at two-year follow-up and preoperative lumbar MRIs unavailable for review. Also, we excluded patients with herniation

induced motor deficits including drop-foot, cauda equina syndrome, suspicion of malignancy, fractures, disc rupture due to trauma and a history of previous spine surgery.

Based on the preoperative MRI, patients were assigned to either a group with MC present (+MC) or MC absent (-MC). MCs were described in accordance with the original studies by Ross et al. and Modic et al[13–15]. The descriptions from these studies were used to classify all three types of MCs. In order to assure relevance and radiological agreement on MRI, the following criteria were defined: MCs were only classified if present on both adjacent endplates and in the presence of DD, defined by Pfirrmann grade (PF)≥2; If mixed MCs or several types were present, only the MC type with the lowest classification, MC-1> MC-2> MC-3, was described[8]. This was done in order to avoid a type-2 error, failing to find an existing association, as previous studies have shown a strong and consistent association between MC-1 and LBP[18,32–34]. Whereas this association is less consistent for MC-2 and MC-3[17,35]. If several types of MCs were present on different levels only the MCs type at the index level was described. If not present at the index level, MCs was described as above, since adjacent segment MCs could be associated with clinical symptoms.

Study participants completed questionnaires at baseline and at 2-year follow-up including the Oswestry Disability Index (ODI), European Quality of Life – 5 Dimensions (EQ-5D), Visual Analogue Scale (VAS) 0 (no pain)-100 (maximal pain) for back pain (VAS-B) and leg pain (VAS-L) and patients satisfaction (0-100%)[36,37]. The absence or presence of MCs on MRI did not influence the choice of surgical treatment.

MRI evaluation

Patients underwent an MRI of the lumbar spine within six-months prior to their discectomy. All MRIs were performed using 1.0-2.0 Tesla high-field scanners.

The scans were evaluated by four physicians using a standardized evaluation protocol. All MRIs were evaluated twice by two different physicians, and thrice by a third physician if inconsistencies existed after the second evaluation. The evaluating physicians were blinded as to the clinical status

and discectomy level of the patients. Lumbar MRI evaluation included: Presence, type, and level of MCs, description of possible DD using the Pfirrmann classification, and level of disc herniation. In order to assure the correct classification of MCs, MRI criteria were defined and followed by the physicians doing the MRI descriptions.

Statistical analyses

Continuous data from the +MC and -MC groups were compared using the student t-test. Categorical data were analyzed using the Chi-square test. Analysis of covariance (ANCOVA) was used for two-year change in score analysis of ODI, EQ-5D, and VAS with two-year ODI, EQ-5D or VAS as dependent variables with either MCs or MCs type as the fixed independent variable and respective preoperative outcome measures as the covariates.

A 5% level of statistical significance was used for the analyses.

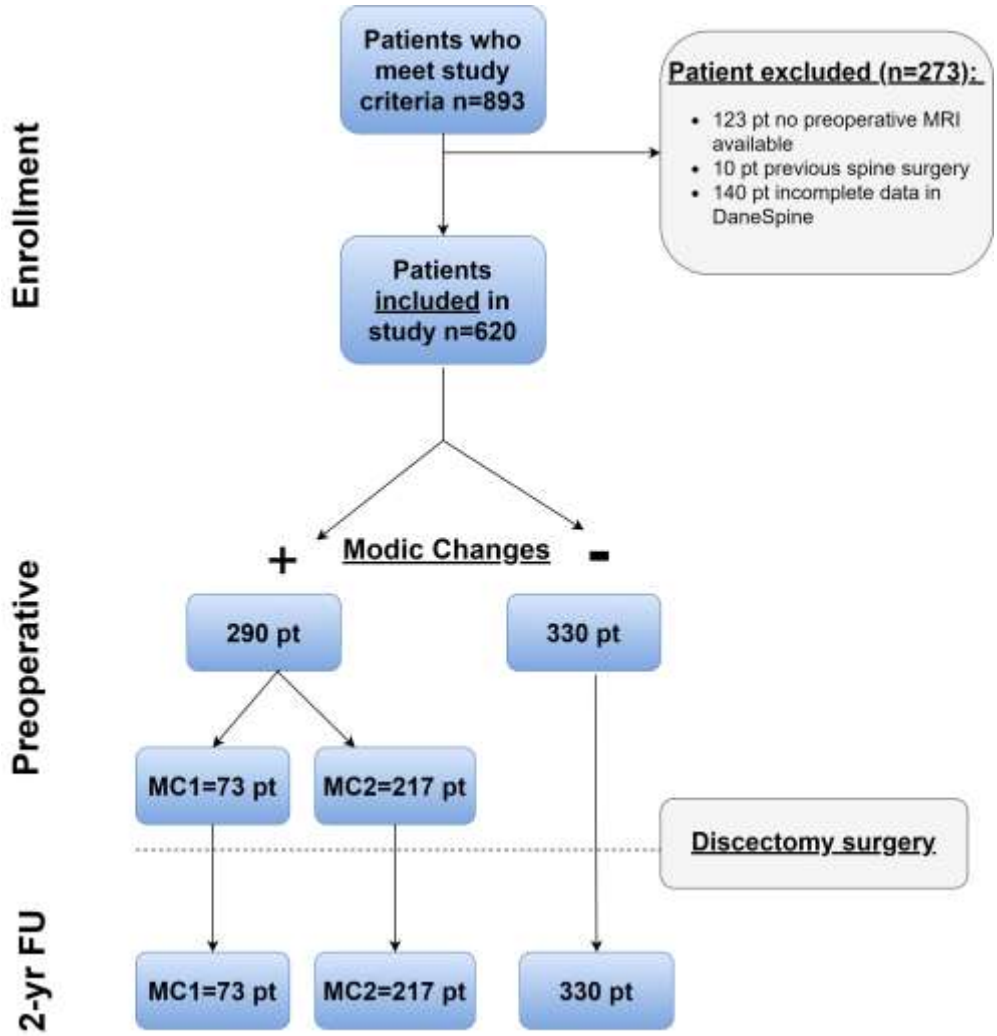
Ethical considerations, approvals, and registration

Approval for data collection was obtained from the National Data Protection Agency. The study protocol was approved by The Regional Committees on Health Research Ethics (Reference number: S-20192000-112).

Results

A total of 620 patients fulfilled the criteria for inclusion in the study. Of these, 290 (47%) had MCs and 330 (53%) had no MCs on the preoperative MRI scan, figure 1.

Figure 1: Study flowchart



Comparison of the +/- MCs groups

The preoperative demographics were similar for the +MC and -MC groups. No significant differences were found in regards to sex, age, weight, Body Mass-Index (BMI), smoking status or baseline PRO's (Table 1).

Table 1. Preoperative demographics for patients +/- MC

Table 1. Preoperative demographics for patients stratified by the presence (+MC) or absence (-MC) of Modic Change.			
	+MC	**-MC**	**p-value**
N	290 (47%)	330 (53%)	
Females, N (%)	148 (51%)	162 (49%)	0.873
Age, years, (range)	49.5 (19-73)	51.4 (20-75)	0.642
Smokers, N (%)	82 (28%)	82 (25%)	0.346
BMI, kg/m^2 *	26.3 [4.2]	26.0 [4.5]	0.333
ODI*	45.6 [19.7]	47.2 [18.5]	0.311
EQ-5D*	0.34 [0.35]	0.30 [0.33]	0.132
VAS-BP*	46.6 [29.0]	48.5 [28.8]	0.392
VAS-LP*	67.4 [24.5]	67.8 [22.7]	0.857
*=Mean with standard deviation in brackets			

Two-year postoperative follow-up showed an improvement in health-related quality of life, disability and pain scores for the entire cohort. The improvement was both clinically relevant and statistically significant for ODI (46.5 vs. 16.4, $p<0.001$) and EQ-5D (0.33 vs. 0.74, $p<0.001$). Also, the pain scores for the entire cohort improved statistically significant in terms of VAS-BP (47.1 vs. 27.9, $p<0.001$) and VAS-LP (67.6 vs. 25.9, $p<0.001$). The total number of patients overall satisfied with the outcome after surgery at two-years follow-up was 459 patients (74%) (Table 2).

The presence of preoperative MCs did not affect PRO's including patient satisfaction at two-year postoperative follow-up (Table 2).

Analysis with ANCOVA using change in score as dependent variable found no statistically significant difference for ODI, EQ-5D or VAS-scores with MCs as the fixed independent variable (all analysis $p>0.10$).

Table 2. Two-year follow-up +/-MC

Table 2. Two-year follow-up outcome scores stratified by the presence (+MC) or absence (-MC) of Modic Change.			
	+MC	**-MC**	**p-value**
N	290 (47%)	330 (53%)	
ODI*	15.5 [15.6]	17.2 [18.1]	0.208
EQ-5D*	0.75 [0.25]	0.72 [0.27]	0.167
VAS-BP*	27.1 [27.4]	28.3 [28.8]	0.617
VAS-LP*	26.8 [27.7]	25.0 [29.0]	0.446
PT satisfied with surgery (%)	74%	76%	0.878
*=Mean with standard deviation in brackets			

Comparison of the MC-1 and MC-2 groups

In the MCs group, MC-1 was present in 73 (25%) and MC-2 in 217 (75%) of patients (Figure 1). The MC-1 and MC-2 groups were similar at the preoperative stage with no statistically significant differences in demographics or PRO-scores (Table 3).

Table 3. Preoperative demographics for MC-1 and MC-2

Table 3. Preoperative demographics for MC-1 and MC-2			
	MC-1	**MC-2**	**p-value**
N	73 (25%)	217 (75%)	
Females, N (%)	38 (52%)	119 (55%)	0.741
Age, years, Mean (range)	48.4 (19-69)	50.3 (21-73)	0.542
Smokers, N (%)	21 (29%)	59 (27%)	0.131
BMI, kg/m^2 *	25.6 [3.9]	26.9 [4.1]	0.125
ODI*	43.9 [22.0]	46.3 [18.9]	0.360
EQ-5D*	0.38 [0.35]	0.33 [0.35]	0.298
VAS-BP*	51.0 [27.9]	44.6 [29.2]	0.105
VAS-LP*	68.0 [24.0]	67.2 [24.7]	0.805
*=Mean with standard deviation in brackets			

The two-year postoperative follow-up showed no difference in improvement for the MC-1 and MC-2 groups in terms of ODI (18.3 vs. 14.5, p=0.113) and EQ-5D (0.71 vs. 0.77 p=0.124). There

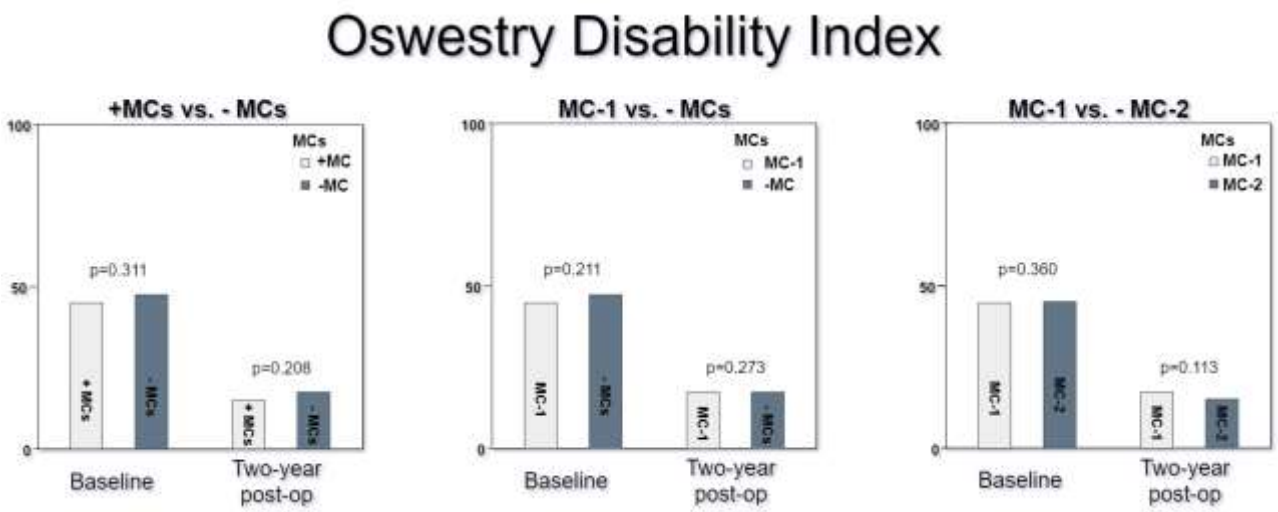
was a statistically significant difference for VAS-BP between the MC-1 and MC-2 groups (33.3 vs. 24.5, p=0.042). VAS-LP was similar in the two groups (31.3 vs. 25.4, p=0.175). No difference was found for the percentage of patients satisfied with the outcome after surgery, 74% in both groups (Table 4).

Table 4. Two-year follow-up MC-1 and MC-2

Table 4. Two-year follow-up MC-1 and MC-2			
	MC-1	**MC-2**	**p-value**
N	73 (25%)	217 (75%)	
ODI*	18.3 [18.1]	14.5 [14.7]	0.113
EQ-5D*	0.71 [0.29]	0.77 [0.23]	0.124
VAS-BP*	33.3 [30.6]	24.5 [25.6]	0.042
VAS-LP*	31.3 [30.5]	25.4 [26.7]	0.175
PT satisfied with surgery (%)	74%	74%	0.860
*=Mean with standard deviation in brackets			

Analysis with ANCOVA using change in score as dependent variable found no statistically significant difference for ODI, EQ-5D or VAS-scores with MCs type (MC-1 or MC-2) as the fixed independent variable (all analysis p>0.1).

Figure 2: Oswestry Disability Index for patients +/-MC and for MC-1 and MC-2



Discussion

This retrospective registry-based cohort study was designed to investigate the possible association between preoperative MCs and clinical outcomes after primary discectomy. The results demonstrate a high prevalence of MCs in patients with LDH scheduled for surgery. PRO's at two-year follow-up were overall similar in patients with and without MCs on pre-operative MRI. No associations were found between the presence of MCs, regardless of subtype, and PRO's after discectomy. Findings from this study suggest that patients with clinical symptoms, LDH, and MCs can be surgically treated similar to patients without MCs.

In patients with LDH, it is important for the clinicians to be able to interpret MCs on the MRI and their association with the presenting symptoms. Also, the prognostic long-term value of MCs and their possible impact on planned surgery need to be considered, in order to ensure the best possible treatment strategy. The prognostic value of MCs on postoperative outcomes has been examined in different studies[21,23,38,39]. In a systematic review, discectomy in patients with MCs was found to be associated with a less successful outcome[21]. The results from the current study do not support this conclusion. In general, the previous studies have been heterogeneous and included small cohorts[21].

The strengths of this study include a large cohort with two-year follow-up data and a high response rate. The baseline demographics included possible relevant confounders such as smoking and BMI, which were comparable between the two groups. All patients were surgically treated at the same institution within a period of three-years where the presence of MCs did not affect the surgical plan. The MRI evaluation of preoperative scans was performed using a verified classification system with excellent intra- and interobserver reliability[40,41]. MRI criteria were defined and followed by the physicians doing the MRI description. All MRIs were evaluated by two different physicians.

Weaknesses of this study include the lack of a two-year follow-up MRI. Also, potentially a selection bias could be present since only patients with complete preoperative and two-year follow-up data were included in the study. An interpretation bias could exist while describing degenerative MRI findings with or without MCs since blinding of MCs presence on the MRI is not possible.

Future studies on the presence of MCs in relation to spine surgery are needed in order to verify the findings of the current studies. Additional studies are also needed to identify factors associated with outcome after discectomy and revision rates for patients with and without MCs.

Conclusion

MCs were not found to be associated with health-related quality of life, disability, back- or leg pain or patient's satisfaction two-years after discectomy.

Both patients with and without MCs experience a statistically significant improvement in self-reported health-related quality of life, disability and pain scores at two-year follow-up after discectomy.

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