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Modic Changes are not associated with long-term pain and disability - a cohort study with 13-year follow-up

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Abstract

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 2004-2005, patients aged 18-60 with daily LBP were enrolled in an RCT study and lumbar MRI was performed. Patients completed numeric rating scales (NRS, 0-10) for LBP and leg pain (LP), Roland-Morris Disability Questionnaire (RMDQ), LBP Rating Scale for activity limitations (RS, 0-30), Inflammatory pain pattern (IPP) 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, LP and IPP 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 to 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 to the -MC group (22.9 days, 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.

Keywords: Back pain; Modic Changes; LBP; disc degeneration; spine; long-term follow-up

Level of Evidence: 2

Key Points:

- 204 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 to LBP patients without MCs.

Introduction

Low back pain (LBP) is the leading cause of years lived with disability[1]. It affects 60-70% 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 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 to 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 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 differs 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 ≥ 4/10 for the last 14 days; pain for a minimum of 4 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 to physiotherapy showed no difference at one 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 was defined in accordance with the original Modic studies and was 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 (NRS, 0-10), number of sick leave days due to back pain the past year (0-200 workdays). The presence of an Inflammatory Pain Pattern (IPP) 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 min[22]. Primary outcomes were RMDQ, LBP and sick leave. Secondary outcomes were activity limitation, measured by RS, LP and IPP.

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 (ANCOVA) 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: 9 had died (4 with

+MC and 5 with -MC), five were not available (2 +MC and 3 -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 to 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 to 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 to the -MC group (10.64, p=0.013). There were notably fewer sick leave days due to LBP in the +MC group (9.0 days vs. 22.9 days, p=0.003). There was no statistically significant difference in spine surgery rates between the two groups (10% for the +MC group and 11% in the -MC group, p=0.584). ANCOVA 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-year follow-up), with no change in the -MC group (61% versus 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 bed rest, corticosteroids, spinal fusion or prolonged antibiotics courses[25,27,29,30]. 11% of patients had spinal surgery performed from baseline to 13-year follow-up, less than 5% had spinal fusion. Around 2/3 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 ≤ 0.3 T, high field defined by ≥ 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 1-2 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 to 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 is associated with DD and is part of the degenerative process[4,5,35]. Subgroup analysis of subjects with MCs only, are 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 that 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 were 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 to 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 is 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.

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Figure 1: Study enrollment and follow-up

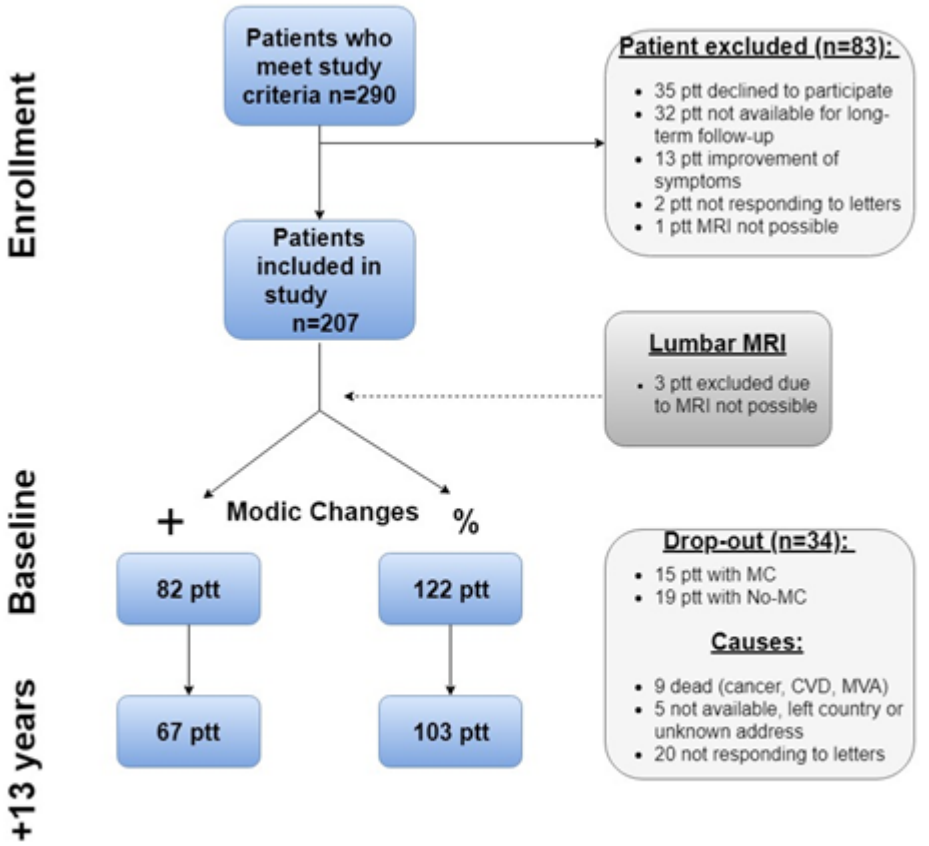

Figure 2: The distribution of Modic changes

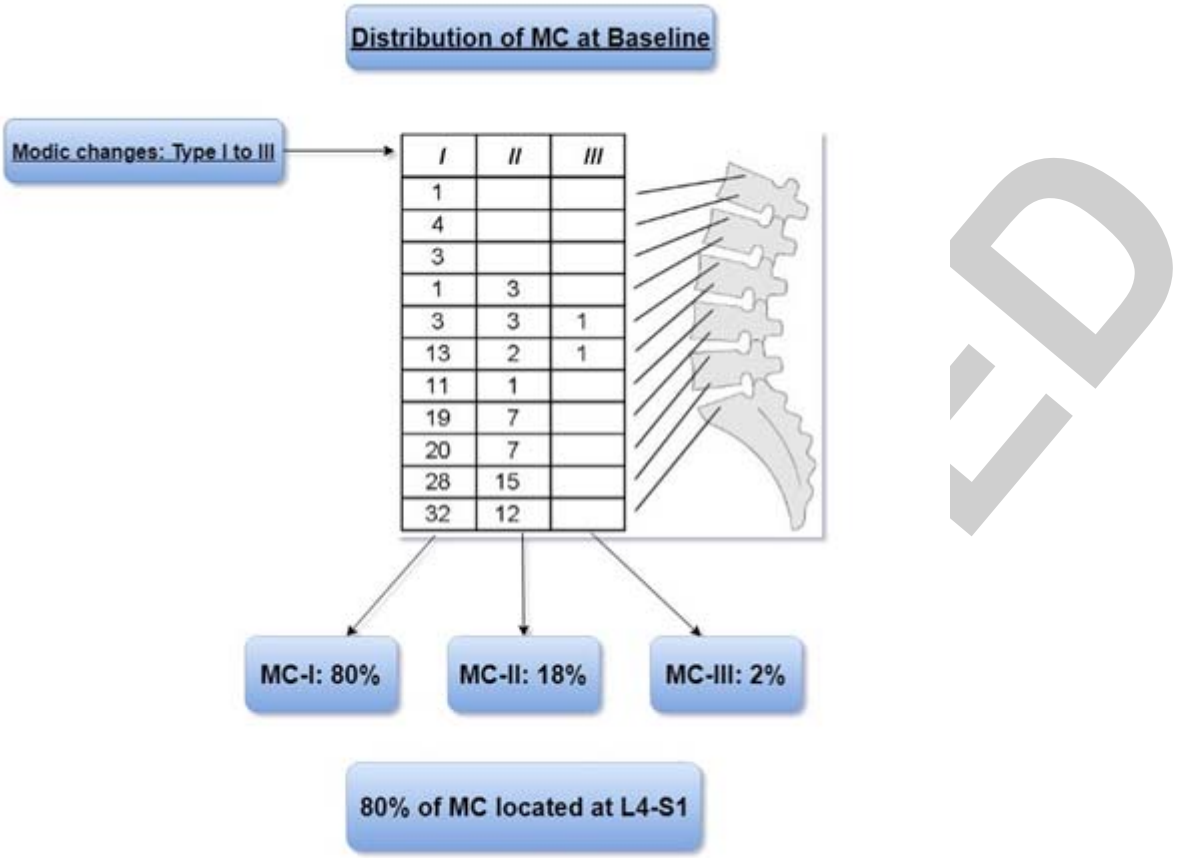

Figure 3: RMDQ, LBP and sick leave at baseline and 13-year follow-up. P-values represent non-paired t-test. Significantly less disability and fewer sick leave days was found in the +MC group at follow-up. LBP was similar both at baseline and at follow-up.

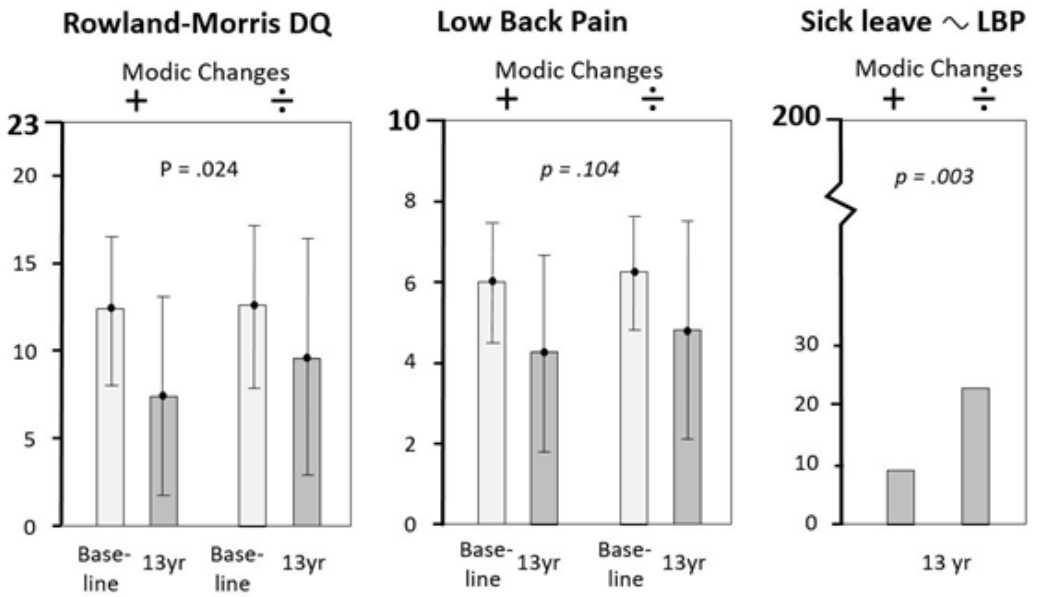

Table 1. Summary of demographic data of the current study at 13-year follow-up

	+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, years, 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

Table 2. Baseline and 13-year follow-up.

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