Original Article

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Inflammatory Features of Low Back Pain with Modic Changes on MRI

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Abstract

Background: Recent evidence suggests a potential association between Modic Changes (MC) and inflammation in nonspecific low back pain patients. Inflammation, characterized by the activation of immune cells and the release of pro-inflammatory molecules, is known to play. This research aims to investigate the clinical and laboratory features suggestive of inflammation in patients with MC on lumbar MRI.

Methods: A retrospective analysis was conducted on 169 patients with MC identified on lumbar Magnetic Resonance Imaging (MRI). Laboratory investigations were also obtained, including Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) levels. The MC were categorized based on their MRI signal patterns. The presence of inflammatory markers and their association with clinical features was assessed using appropriate statistical methods.

Results: The majority of patients exhibited type 2 MC (n=139, 82.4%), followed by type 1 MC (n=28, 16.5%) and type 3 MC (n=2, 1.1%). Among the clinical features, patients with type 1 MC had a significantly higher prevalence of nocturnal low back pain (OR=6.76 [95%CI: 2.25-20.24], p<0.001) and morning low back stiffness (OR= 4.27 [95%CI: 1.42-12.85], p=0.006). Additionally, patients with type 1 MC were more likely to have elevated CRP levels (OR=2.61 [95%CI: 1.18-5.78]).

Conclusion: Although the majority of patients had type 2 MC (82.4%), type 1 MC was strongly associated with higher CRP levels, morning stiffness, and nocturnal pain. These associations suggest that type 1 MC may represent a more inflammatory and clinically severe form of the condition, emphasizing the importance of recognizing it in clinical practice.

Keywords: Inflammation, Low back pain, Magnetic resonance imaging, Seronegative rheumatoid arthritis

Introduction

Low Back Pain (LBP) is a prevalent condition affecting millions worldwide, causing significant disability, economic burden, and decreased quality of life (1). While several etiological factors contribute to LBP, including mechanical, degenerative, and inflammatory processes, the specific mechanisms underlying this multifaceted condition are still not entirely understood. Among the various imaging features of LBP, one manifestation that has gained attention is the presence of Modic Changes (MC) in Magnetic Resonance Imaging (MRI). MC, first described by Dr. Michael Modic in 1988, are alterations in the vertebral endplate and adjacent bone marrow detected on lumbar MRI (2). MCs refer to specific signal abnormalities observed in the vertebral bone marrow and adjacent endplates. Initially, these changes were thought to be associated with degenerative disc disease, but later studies hypothesized a correlation with infectious or inflammatory disorders (3-5).

Recent evidence suggests a potential association between MC and inflammation in nonspecific low back pain patients. Inflammation, characterized by the activation of immune cells and the release of pro-inflammatory molecules, is known to play. Serum concentration and bone marrow expression of highly-sensitive C-Reactive Protein (hs-CRP) is elevated in patients with MC type 1 (6). This research aims to investigate the association of clinical and laboratory features of inflammation in individuals with MC on their MRI presenting with nonspecific low back pain; also, correlations with different features of MC are discussed.

Materials and Methods

The Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran, had approved the study protocol IR.SSU.REC.1400.094 in July 2021.

Study population

In this retrospective study, the study population consisted of patients referred to the rheumatology clinic in Yazd, Iran, with lumbar spine MRI complaining of non-specific low back pain and having MC evident on the MRI. The patients were recruited between July 2021 and April 2023. Their anthropometric, clinical, and laboratory data were recorded. History and physical examination can strongly channel the diagnostic path through an inflammatory back pain scenario. None of the patients showed any clues addressing the alternative causes of low back or pelvic pain. It was assumed that in parallel conditions mentioned by the esteemed reviewers located in the pelvic not low back region, the back pain could be an accompanying (not main) complaint. Thus, in case of pelvic pains, clinical setting and diagnostic approach actually differs.

According to the histopathology of MC and prior investigations on this matter, plus focusing on the patterns of inflammatory low back pain in the patients, a correlation (not a causative relationship) could be addressed. However, further research may be required to confirm the idea. By the way rational ordering of MRI based on meticulous history taking and physical examination along with corresponding changes on vertebral imaging can precisely confirm the clinical diagnosis of an expert physician. It is believed that none of the cases has had pre-test clinical impression of pelvic disorders. Therefore, logically additional imaging investigations for pelvic differentials are not advised in this study. Moreover, none of the volunteers in the study on the events of any surgical procedure related to the spine.

This study has predefined inclusion and exclusion criteria, as follows:

Inclusion criteria

Patients suffering from lower back pain, with a minimum duration of symptoms of one month who have undergone an MRI scan with a minimum field strength of 1.5 Tesla in the past year showing Modic sign in the lumbar spine, were included.

Exclusion criteria

The exclusion criteria were: individuals under 18 or over 70 years of age, history of severe trauma to the lower back (accidents, falls, incidents, *etc.*), history of spinal surgery, patients with extruded disc involvement, patients with psychosis, active infection with known infectious source, febrile patient, known rheumatic or gynecologic diseases.

Clinical findings

Clinical findings including age, sex, duration of

low back pain, night-time low back pain, morning stiffness and its duration, patient's occupation [based on the modified International Standard Classification of Occupations [ISCO] (7)], finger-to-floor distance (forward lumbar range of motion), any clue to a systemic condition, not otherwise attributed was retrieved by interview and physical examination.

Laboratory findings

Venous blood samples were taken from each patient during the visit. The C-reactive protein (CRP) activity level was measured using the semi-quantitative CRP assay kit (REF CSA087027, Scalvo Diagnostics International, PCR Latex Test, Italy). Serum concentration equal to or greater than six *mg/L* of CRP was considered positive. A benchtop automated sedimentation analyzer (model DA717, Novin Gostar Medical Engineering Company, Iran) was used to measure the erythrocyte sedimentation rate (ESR) in *mm*.

Magnetic resonance imaging (MRI) findings

Type, number of lesions, number of involved lumbar levels, and craniocaudal expansion of MC were analyzed from sagittal images of MRIs (Magnetom ESSENZA 1.5T, Siemens Healthineers, Germany). MCs were classified into three types, as described in the initial study by Modic *et al*; implementing T1W and T2W images. Lesions with low signal intensity (SI) on T1W and high signal intensity on T2W are classified as type 1 MC (MC 1), type 2 MC lesions (MC 2) show high SI on both T1W and T2W and type 3 MC lesions (MC 3) demonstrate low SI on T1W and T2W, both (2). Every endplate (from the superior endplate of L1 downward to the superior endplate of S1 vertebrae) was examined. If two MC types were visible simultaneously, the dominant type was assigned to the patient.

To assess the extent to which a vertebra is involved with MC, a semi-quantitative method was implemented by the previous authors (8-10). This method classifies the vertical involvement of the vertebral body into <25%, between 25-50%, and >50%, with corresponding grades A, B, and C, respectively. In multiple lesions with different grades, we assigned the highest grading for that patient.

Data analysis

In this study, quantitative data were reported as mean (± standard deviation) or median (interquartile range [IQR]), and qualitative data as frequency (percentage) were shown. The quantitative data were analyzed using analysis of variance, and the qualitative data were compared using the chi-square test. Spearmans' correlation coefficient was used to demonstrate the relationship between the quantitative data. If the data did not follow the normal distribution, the non-parametric equivalents of the above tests were used. The significance level in this research was 0.05. Data were analyzed using Python version 3.11.3.

Ethical concerns

The identity information of the patients was not used, and only the information related to the studied variables was extracted. Before collecting the patient's data for the research, the purpose and process of this research were explained to them.

Results

A total of 169 patients and 1859 endplates were included in the study. Female patients comprised the majority of patients 116 (68.6%). Among all types of MC, 28 patients were in the MC1 group, 113 patients in MC 2 group, and two in MC 3 group. Most common MC lesions occurred on the L5-S1 level (105 lesions [62.1%]) (other levels are displayed in Figure 1). Regarding the extent (grade) of MC, 75 (44.4%) were in group A, whereas 73 (43.2%) and 21 (12.4%) were in groups B and C, respectively. Most patients had elementary occupations (63.3%) according to the ISCO classification. One hundred and eleven (65.7%) subjects had only one MC, 42 (24.9%) had two, 10 (5.9%) had three, and 6 (3.6%) patients had four or more MC lesions visible in MRI. The level at which disc herniation had happened was statistically significantly correlated with the MC lesion ($p<0.001$ for all lumbar levels) (Figure 2).

Laboratory markers

Clinical and laboratory findings between all three groups of MC is shown in table 1. The ESR and CRP levels of the patients were evaluated as markers of inflammation. The median (IQR) of ESR among all the patients was 24 (13-31) (excluding MC 3 group).

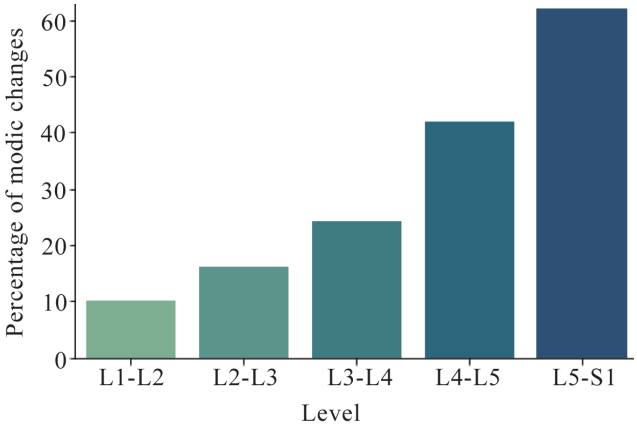

Figure 1. Distribution of Modic changes according to the vertebral levels. Percentages are calculated with the total number of Modic lesions (not cases) as the denominator.

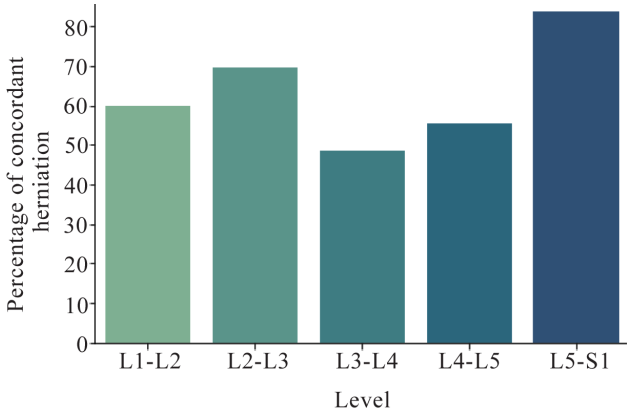

Figure 2. Distribution of disc herniations in concordance with Modic changes in each vertebral level is depicted. Modic changes evident on L5-S1 level had most concurrent disc herniation, while it was the least at the L3-L4 level.

Positive CRP was evident in 83 cases (49.1%). Of them, 67 (39.64%) 1+, ten (5.92%) 2+, four (2.37%) 3+, and one patient (0.59%) 4+, and there was 1 missed value (0.59%). There was no statistical difference between CRP and ESR levels among the gender subgroups (p=0.859 and p=0.586, respectively). CRP and ESR levels were not statistically significant between grades of involvement (p=0.108 and p=0.103, respectively) among all the groups and each group per se. The binary assessment of CRP status showed significantly higher rates of CRP positivity in MC 1 compared to MC 2 group (odds ratio [OR]=2.61, p=0.016). However, with a cutoff of 20 *mm* for ESR, there was still no statistical difference among MC 1 and MC 2 groups (p=0.378). Patients with MC 2 demonstrated a significant correlation between the number of involved levels and the ESR (Spearman's ρ=0.177, p=0.037); however, this correlation was insignificant for MC 1 patient group (Spearman's ρ=0.341, p=0.076).

Clinical findings

The median duration of low back pain (years) was 5 (3-10) among all the patients. Regardless of MC type, the patients had a median morning stiffness of 20 (10-30) *min*. One hundred sixteen (68.6%) patients had more than 30 *min* of morning stiffness. The median finger-to-floor distance was 30 *cm* (20-45). There was no statistically significant difference among the comorbid conditions between MC types (Tables 1 and 2). Having any of the ISCO items

Table 1. Clinical and laboratory findings between all three groups of Modic changes

	Type 1 modic (n=28) median (IQR)	Type 2 modic (n=139) median (IQR)	Type 3 modic (n=2) median (IQR)	p-value
Age (years)†	42±12	51.1±10.6	62±5	<0.001
Sex (Female) n (%)*	17(60.7%)	97(69.8%)	2(100%)	0.435
Height (*m*)	1.7(1.6-1.8)	1.6(1.6-1.7)	1.5(1.5-1.6)	0.605
Weight (*kg*)	77(70-83.5)	73(67-80)	68(66-70)	0.146
BMI (kg/m^2)	26.9(25-32.2)	26.4(25.4-29.1)	28.5(26.5-30.3)	0.332
Duration of symptoms (years)	7.5(3-13.5)	5(3-10)	3.5(1-6)	0.149
Morning Stiffness (*min*)	35(20-60)	25(15-30)	0(0-0)	0.003
Finger to Floor (*cm*)	40(30-60)	30(15-40)	35(20-50)	0.001
Parity	2(2-2)	3.5(2-5)	2(2-2)	0.044

Contd. table 1

Nocturnal Pain n (%)*	25(89.3%)	76(54.7%)	0(0.0%)	<0.001
Bowel symptoms n (%)*	6(21.4%)	23(16.5%)	0(0.0)	0.716
Dystrophic nail changes n (%)*	0(0.0%)	6(4.3%)	0(0.0%)	0.619
Psoriasis n (%)*	3(10.7%)	8(5.8%)	0(0.0%)	0.647
Positive CRP n (%)*	19(67.9%)	64(46.0%)	0(0.0%)	0.025
ESR (*mm*)	25(12.5-29.5)	24(13-31)	11(9-13)	0.794
Age at onset (years)†	32±10.9	43±11.7	58±1.4	<0.001

IQR: Interquartile Range, ESR: Erythrocyte Sedimentation Rate, CRP: C-reactive Protein, BMI: Body Mass Index, *m*: *Meter*, *kg*: *Kilograms*, *min*: *Minutes*, *cm*: *Centimeters*, *mm*: *Millimeters*.

*: These variables are presented in numbers (percent).

†: This variable followed a normal distribution pattern; hence values are presented in mean ± standard deviation.

Table 2. Clinical and laboratory associations with Modic changes type 1 and 2

	Type 1 modic lesion (n=28)		Type 2 modic lesion‡ (n=139)	
	OR (95%CI)	p-value*	OR (95%CI)	p-value*
Sex (Female/Male)	1.470(0.67-3.22)	0.334	0.782(0.32-1.90)	0.588
Nocturnal low back pain	6.76(2.25-20.24)	<0.001	0.23(0.78-0.729)	0.007
Morning low back stiffness	4.27(1.42-12.85)	0.006	0.652(0.24-1.74)	0.390
Positive CRP	2.61(1.18-5.78)	0.016	0.489(0.20-1.18)	0.107
ESR >=20	1.41(0.65-3.01)	0.378	1.46(0.62-3.43)	0.382
ISCO classification†	-	0.381	-	0.275

OR: Odds ratio, CI: Confidence interval, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, ISCO: International Standard Classification of Occupations.

*: p-value below 0.05 was considered significant.

†: The ISCO classification contains more than two groups, so the odds ratio could not be calculated.

‡: Due to limited sample size, the patients with type 3 Modic changes were omitted from further analysis.

(professionals, clerks, *etc.*) *per se* had no significant relationship with the type or the grade of the MC (p>0.05). For service workers and shop and market sales workers, there was an OR of having IBS equal to 11.04 (CI95% [1.91–63.53], p=0.008).

Discussion and Conclusion

Low back pain, defined as the pain perceived in the region between the inferior gluteal fold and costal margin, is the most common debilitating condition worldwide (11). The global point prevalence is 7.46%; however, it is projected to that 800 million of people will have low back pain by 2050 (12). A rough etiopathological classification of low back pain divides it into specific and non-specific categories. Specific low back pain syndromes are attributed to known causes and pathobiology, while non-specific low back pain syndromes comprising over 80% of the cases of low back pain are conditions without known etiology (13,14). Common sense on MC among clinicians and radiologists labels them as degenerative findings on the spine. This study was conducted to argue the inflammatory nature of low back pain patients with MC on MRI. Studies like this may contribute to change the proportion of non-specific low back pain in favor of specific low back pain. The clinical and laboratory indices of inflammatory low back pain were recruited to further investigate the associations with MC on MRI (Figure 3).

Symptoms and endplates

We have employed MC grading to describe how

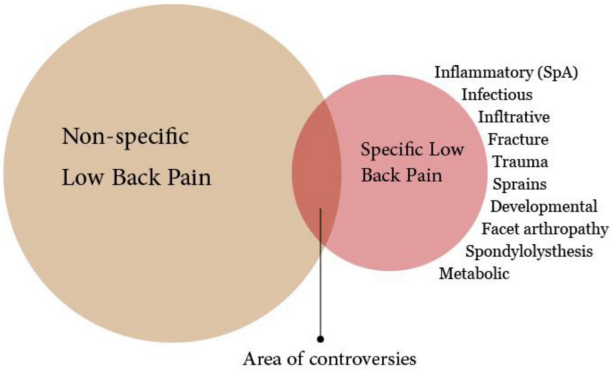

Figure 3. Diagram showing what has been known as "specific low back pain" versus "non-specific low back pain" and the area of uncertainty where the body of knowledge is growing. SpA; spondyloarthropathies.

much a vertebral body is involved with MC. Maatta *et al* found that cases with MC 1 had more extensive lesions compared to MC 2 (10). On the contrary, the results of the present study indicated no significant difference in terms of extent between MC 1 and MC 2. It is noteworthy that the cases with the highest grade (C) were significantly older than cases with grade A. In MC 1, patients with smaller lesion sizes demonstrated higher limitation in range of motion, while in MC 2 patients, larger lesions were associated with more limited range of motion. These findings may show that early stages of marrow edema (MC 1) may cause more severe pain and resultant limited range of motion. As the lesion evolves into the second phase (fat replacement, MC 2), larger lesions are associated with more severe symptoms. It can be concluded that clinical relevance of endplate pathologies in MC 1 is "type-dependent" and in MC 2 is "size-dependent".

A systematic review indicated that MC 1 is four times more prevalent in adults ≤50 years with chronic low back pain than asymptomatic individuals (15). Arnbak *et al* researched MRI findings associated with inflammatory back pain characteristics. They found that morning stiffness of over 30 *min* and nightly pain were related to vertebral endplate bone marrow edema (*i.e.* MC 1) (16). Other available data on morning stiffness in patients with MC 1 demonstrate a mean morning stiffness period of around 49 *min* (17). The results of this study show that MC 1 group has statistically significantly higher morning stiffness compared to the MC 2 patients.

The story of gut and spine

As time progresses, the spectrum of immune-mediated medical conditions expands toward boundaries of previously called non-inflammatory disorders. Instances include osteoarthritis (18,19), atherosclerosis (20-22), neurodegenerative disorders (23-27), and even developmental conditions (23-27). Increasing number of patients with so called Irritable Bowel Syndrome (IBS) has been shown to be essentially subclinical inflammatory bowel disease (IBD) (*i.e.* microscopic colitis) (28-30).

Gastrointestinal tract has shown to be involved in seronegative Spondyloarthritis (SpA) either primarily or secondarily. Typical feature of this association is famously known as IBD-associated SpA—highlighting the spine-gut interaction. Disruption of the integrity of intestinal mucosa leads to penetration of pathogenic organisms to systemic circulation cross-reacting immunologically with the axial skeleton.

Rather high number of patients (n=29) in our series demonstrated as irritable bowel syndrome, according to their history, highlights the possible relationship between subclinical bowel inflammation and subclinical inflammatory low back pain. Further well-designed studies may elucidate the hidden relationship between the two seemingly unrelated conditions, the IBS and early SpA.

We hypothesize that individuals who are suffering from IBS-like symptoms associated with extraintestinal, and more importantly axial symptoms, may actually be a new subgroup of IBDs. This subgroup of patients should be preemptively histologically examined, rather than labeling them only on clinical grounds as IBS according to the conventional criteria.

Age at onset

According to the available data, MC evolve from marrow edema (MC 1) to fatty deposition (MC 2) and finally marrow sclerosis (MC 3). Average age of the patients in each subgroup was the lowest in patients with MC 1, higher in patients with MC 2, and the highest in patients with MC 3. From our point of view of the inflammatory nature of MC 1, younger people with MC 1 and LBP should be observed closely with proper management.

One common mistake in interpreting MCs on MRI is overlooking the critical role of history of age at onset.

Degenerative phenomena emerging to be symptomatic after the age of fifty are essentially different from those had their symptoms evident earlier than forty years of age. Despite a wide age range of the patients according to the inclusion criteria, vast majority of patients in the present study reported their symptoms to be initiated before the age forty-five, regardless of the type of MC. Inflammatory LBP in a patient below age 40 almost always indicates some kinds of SpA, even it fails to meet the classification criteria of Assessment of Spondyloarthritis International Society (ASAS) for years later. This observation supports the idea of association between chronic LBP and MC with SpA spectrum.

Serum biomarkers

Results demonstrated that CRP positivity, morning lower back stiffness, and nocturnal pain were significantly related to MC 1 lesions on MRI, which aligns with recent studies investigating the role of inflammation in MC 1 patients. Highly sensitive CRP (hs-CRP) was elevated in patients with MC 1. Recent original research on cellular expression of CRP in the bone marrow of vertebrae with MC showed a relatively strong correlation with serum concentration of CRP (r=0.69) (6). They also found a threshold of 3.2 *mg/l* for serum CRP for the bone marrow to express CRP (6).

Limitations

We potentially have some limitations that can minimally influence the conclusion. Firstly, this is not a controlled study, hence we have done intergroup analysis of the patients according to the type of their lesions. However, this study could make provision for further investigations of causal relationship. Secondly, we have implemented conventional semi-quantitative CRP as a laboratory indicator of possible systemic inflammation which has a lower sensitivity than hs-CRP technique used in previous studies. Considering the nature of our study and statistically significant results using a tool with lower sensitivity may underestimate (and not overestimate) the possible role of systemic inflammation in this setting. Collectively, inflammatory pain patterns in patients with non-specific low back pain with MC on MRI may indicate a specific entity of inflammatory back pain syndromes, which conventional inflammatory back pain criteria do not include. While revisions may seem necessary, a fundamental change in the management approaches could be considered.

The sample size was limited by the number of cases available in the time limit of the project according to the exclusion or inclusion criteria aimed for the census.

Ethical considerations

We have the approval of the ethics committee of the University which is IR.SSU.REC.1400.094

Acknowledgement

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Conflict of Interest

The authors have no conflicts of interest to declare relevant to this study's content.

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