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Title:
A definition and clinical grading of Modic changes

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Structured Abstract

Objective:

To provide an up-to-date description of knowledge and pitfalls related to the classification, definition and grading of Modic changes (MC) visualized on magnetic resonance imaging (MRI).

Methods:

State-of-the-art review of current knowledge regarding the definition and grading of MC on MRI.

Results:

MC on MRI have been reported to be associated with low back pain and disability. However, previous studies have shown heterogeneous results in regards to the impact of MC and its clinical relevance in patients with back pain. MC is a term used with considerable variation in the literature. No strict definition has been provided previously, this has contributed to varying diagnostic inclusion criteria, heterogeneous study populations, and discrepancy in results. A definition of MC and a proposal for grading is provided in this state-of-the-art review.

Conclusions:

MC are important, clinically relevant findings. However, issues with the nomenclature, definition and grading of these changes need to be addressed. Our current review highlights relevant issues related to MC, and provides a definition and grading score for the term MC that includes the Modic type and the extent of vertebral body involvement. Future studies should seek to validate the MC grading score in clinically relevant populations.

INTRODUCTION

Modic changes (MC) are subchondral vertebral bone marrow changes which can be identified on magnetic resonance imaging (MRI) [1–4]. MC were first described in 1987-88 by

Assheuer et al[5] and classified by de Roos and Modic et al[2–4] utilizing T1- and T2-weighted MRI and histological analysis. The classification includes MC types 1-3 and is described as follows: MC-1 hypothesized to represent reactive or inflammatory changes; MC-2 noted as lipid marrow replacement, and MC-3 noted as calcification of the endplate and subchondral vertebral marrow[1,4,6,7]. Of these, MC-1 and to a lesser extent MC-2, has been hypothesized as being a significant pain generator[8–11]. In 2006 Kjaer et al[12] found that MC in combination with disc degeneration on MRI was associated with increased likelihood of low back pain (LBP) in a population-based study of 40-year-old Danes. These findings were confirmed in studies by Teraguchi et al[13] and Kovacs et al[14], which found that disc degeneration only becomes clinically relevant on patient-reported outcome measures (PROMs) if MC is present. However, there are other papers that question the association between MC and PROMs in cross-sectional and prospective studies[11,15–17].

The three original studies describing MC have been cited more than 2000 times, and have resulted in an increased interest in degenerative marrow changes and the classification thereof.

The focus of this paper is the description of MC on MRI, MC definition and MC grading. It is not within the scope of this paper to thoroughly review the etiology of MC, treatment options for MC or associations between MC and PROMs.

The first paper by de Roos *et al* [2] from 1987 included MRI analysis of 203 disc spaces in 41 patients. Degenerative bone marrow signal changes adjacent to the endplates were identified in 50% of all interspaces with degenerative changes. No marrow changes were present adjacent to a normal disc. They concluded that these signal changes were common adjacent to degenerated discs and should not be confused with signal changes caused by infection or tumor[2].

The second paper by Modic *et al* [4] reviewed 474 MRIs of patients referred for lumbar spine imaging. The study noted two types of signal intensity change, MC-1 and MC-2, in the subchondral bone marrow adjacent to the endplates hypothesized to be related to degenerative disc changes. The study included a one- to three-year follow-up with repeat MRI in 16 patients. In addition, histopathologic analysis of the disc-endplate-vertebral junction, Figure 1-3., obtained in six patients who underwent lumbar surgery for disc disease, was performed. Marrow signal changes of MC-1 or MC-2 were found only in the presence of adjacent disc degeneration. At 14- to 36- month follow-up, five out of six patients converted from MC-1 to MC-2. Chymopapain injection was found to induce MC-1 changes and further disc degeneration within a 6-12-week period. Importantly, the study concluded that MC-1 may be interpreted as an acute to subacute reparative response to the injury that the vertebral bone marrow sustains as the disc degenerates. Whereas, MC-2 represents a more

stable state with no significant conversion over time. The study further highlighted the clinical importance of these findings as being associated with disc degeneration; distinguishable from changes secondary to malignancy or osteomyelitis[4].

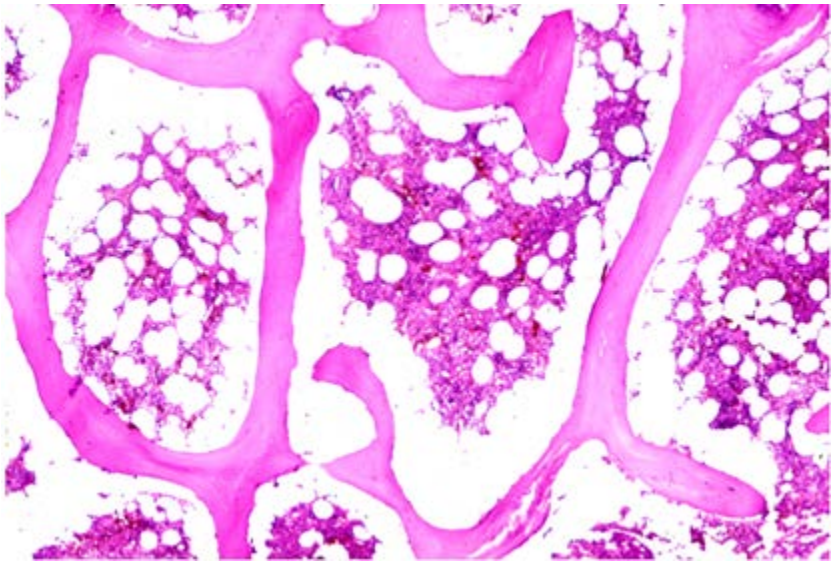


Figure 1. H&E-stain of the endplate-vertebral junction illustrating normal histologic tissue with hematopoetic elements and bone trabeculae within the vertebra.

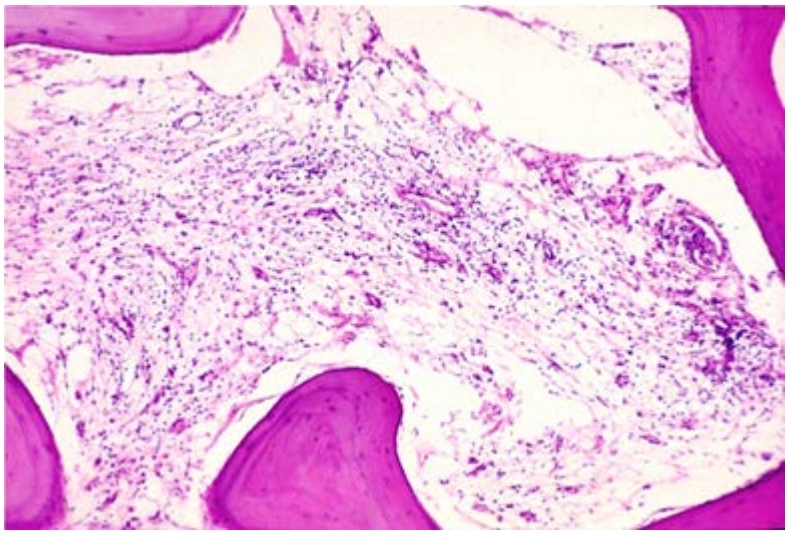


Figure 2. Histologic H&E-stain of MC-1 with fibrovascular elements and thickened bone trabeculae and fibrovascular elements

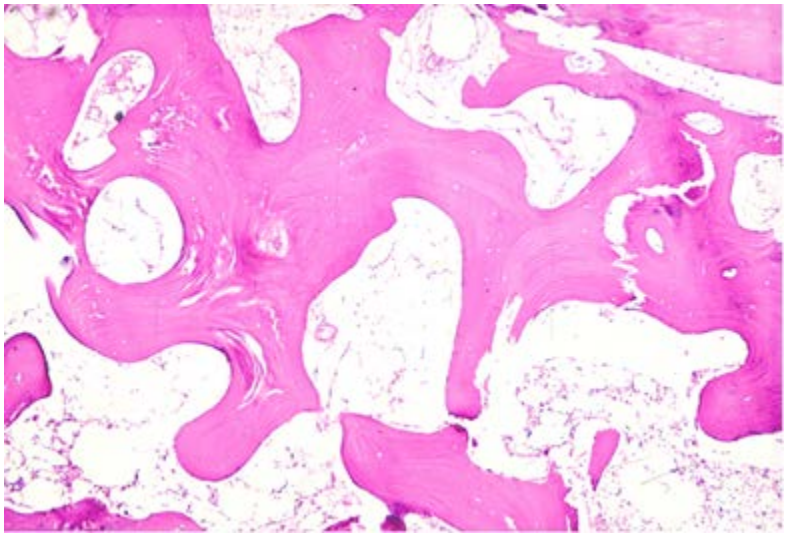


Figure 3. Histologic H&E-stain of MC-2 with fat replacement of the marrow space which gives the high signal on T1-weighted images

The third paper by Modic *et al* [3], also from 1988, reviewed the effects that improved imaging options had on the study of degenerative disc changes, including MC. The paper included a description of MC-3, a sclerotic state of dense woven bone within the vertebra visible on plain radiographs. On MRI, MC-3 is characterized by the absence of normal marrow, representing advanced sclerosis.

These three original studies describe in detail how MC is visualized and characterized on T1- and T2-weighted MRI including specifics on changes in the adjacent disc. Subsequent studies have mostly referred to the original studies for details regarding the description and classification of MC[11,18], without addressing how closely this definition was adhered to, if any modifications to the definitions were made or the consequences of using MRIs with different magnet strengths. This has led to

inconsistent conclusions on the clinical significance of MC in patients with LBP and degenerative conditions of the lumbar spine[11,18–22]. Limited methodological details regarding MC definition, classification, and grading in numerous studies highlight the need for a consistent, reproducible characterization of MC and the need to define a reliable grading score in order to ensure validity across studies[10,11,18,22]. This state-of-the-art review aims to describe the current status of the definition and characterization of MC and to propose an MC grading score.

VERTEBRAL ENDPLATES

Structure and Function

The human spine can be divided into functional spinal units (FSU) representing the segmental structures with similar properties as the entire spine[23,24]. The components of the FSU are the two adjacent vertebrae and the articulation between these, the intervertebral disc anteriorly and the two facet joints posteriorly. Components of the disc include the central nucleus pulposus (NP), the outer annulus fibrosus (AF), and the adjacent endplates. While some view the endplates as an individual anatomical structure, others consider these to be an integral part of the intervertebral disc[24–27].

The endplates are 1mm thick concave-shaped structures, with two distinct layers – the cartilage endplate (CEP) consisting of hyaline cartilage and the bony endplate (BEP) consisting of semi-porous cancellous bone[25–29]. The endplates have several physiologic properties essential to the function of the spine and are

a key regulator of nutrient transport into and out of the disc[26–28,30–32]. Until skeletal maturity, endplates have penetrating microscopic blood vessels from the vertebrae adjacent to the BEP that provide vascular supply to the disc during spinal growth[28]. The endplate also functions as a physical barrier protecting the vertebrae from disc herniation cranially and caudally.

Degenerative changes in the FSU are multifactorial and can start in different anatomical structures[26,33–35]. Endplate changes (EC) such as fissuring and tears cause depletion of proteoglycan molecules in the CEP and microfractures and sclerosis in the BEP[26–28,32]. In particular, degenerative BEP changes have been associated with reduced nutrient supply to the disc, a decline in proteoglycans and water content within the AF and NP, structural changes in the disc, and subsequent disc degeneration[27,28,32,34–36].In individuals with EC and degenerative spine changes, studies have demonstrated an increased growth of vascular vessels and nerve fibers into the endplates, a mechanism proposed as a possible cause of LBP[28,31,37].

The focus of this paper is MC, which can be described as a subgroup of EC. Other spine conditions with EC include: Schmorl's nodes (SN), trauma (fractures, epiphysiolysis), infections/spondylodiscitis, degenerative changes and iatrogenic injury[7,38–41], see Figure 4.

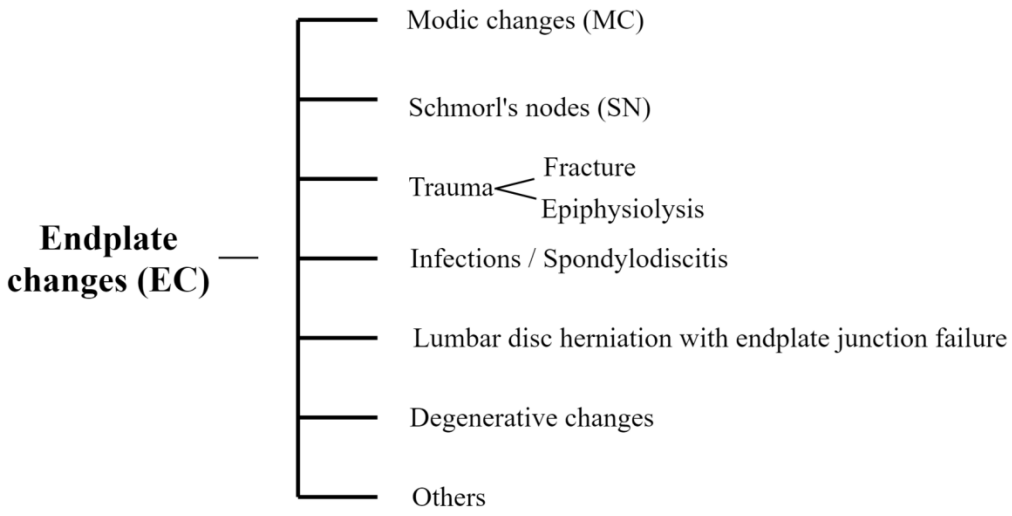


Figure 4. Overview of common causes of endplate changes, some having overlap

Lumbar disc herniation (LDH) are also closely related to EC, with BEP changes being even more common than annulus rupture in patients with disc herniation[42]. Also, the presence of endplate material in the spinal canal during LDH has been associated with increased likelihood of LBP compared to disc herniation without junctional failure of the BEP[42]. As such, BEP damage and morphological changes coincide with disc degeneration (DD, here defined by Pfirrmann grade >2)[26,43,44]. However, the association between BEP and DD varies by the type of changes – more for erosions and to a lesser extent with SN[26]. A similar relationship exists between the type of BEP change and associated LBP, suggesting variation in the etiologies with different clinical presentations[26,45,46].

Visualization of Endplate Changes

Computed tomography (CT) and MR imaging are utilized to visualize EC. MRI provides detail on the characteristics of the disc and vertebral marrow, while CT can be utilized to visualize BEP changes[47].

Although the classification of MC is primarily based on vertebral marrow changes and not EC, changes in the endplates is a feature of MC[10,11,18,20,22,38]. Studies have demonstrated substantial intra- and inter-observer variability in classifying these changes on MRI[7,10,18,20,22,48–50]. Such variability can be partly attributed to the differences in MRI machines and techniques[51]. These include differences in magnet strength (low tesla (<1.0 Tesla), high tesla (1.0-3.0 Tesla), and very high Tesla (>3.0 Tesla), the type of surface coils and signal amplification, the use of various sequences (T1, T2, STIR, fat-suppression, type of spin-echo etc.) among others[20,51].

MODIC CHANGES

Etiology of Modic Changes

MC, as described by Modic *et al* [2–4] in 1988, is a histological change that can be visualized on MRI. MC appear to be an age-related process associated with degeneration[2–4,22,52,53]. MC-1 is associated with ongoing low back symptoms and resolution of MC-1 marrow changes has been associated with an improvement in PROMs[11,54–56]. There can be a conversion between types, most commonly MC-1 to MC-2 or normal[53]. MC-2 changes appear to be more stable over time and less strongly associated

with LBP[11,55,57]. They are most common at L4/5 and L5/S1[10,15]. They may convert to MC-1 with superimposed changes, such as trauma, infection or accelerated degeneration.

MC are not isolated to the vertebra and EC solely, but can also be found in the pedicles, which might suggest an association with biomechanical instability in addition to the strong association with degenerative disc changes[38,58].

While the data is strong that there is a mechanical or reparative etiology to many of these marrow changes, there is a growing body of literature that suggests that, in some, they are a reflection of an inflammatory process or even infection facilitated partly by the degenerative changes[38,59]. The altered signal intensity detected by MR imaging is not, in and of itself, the causal pathological process, but rather a reflection of some type of mechanical stress or instability and/or a concomitant immunobiological, cellular response[38].

Definition and Classification of Modic Changes

No specific commonly-used protocol exists for the description of MC, making between-study comparisons unsound with methodological pitfalls leading to both bias and confounding. Instead, several classification systems have been utilized to describe specific patterns, degree of BEP involvement, mixed type MC (MC-1 and MC-2 at the same FSU) and extent of MC[7,18,20,22,55,60–62]. This lack of a clear definition and accepted

classification system represents the most important issue with previous and current studies on MC[7,11].

A meta-analysis on the association between MC, back pain, and activity limitation by Herlin *et al* [11] found a high risk of bias and heterogenicity in the 31 studies included from 5210 citations. Although a definition was described in the review, it did not adhere to the original description by Modic *et al*[2–4]. Among the included studies, there was considerable variation in the interpretation of the presence or absence of MC. Even more importantly, in the majority of studies, MC was not clearly defined which "made it impossible to analyze the impact of different phenotypes of MCs on outcomes"[11]. The authors from this study again highlighted the need for agreement on the definition and classification of MC across studies.

An earlier systematic review by Jensen *et al*[1] also described a wide variation in both prevalence of MC and its association with PROMs that can be explained by differences in the definition of MC. A recent evidence-based narrative review by Viswanathan *et al*[63] on MC pathology, clinical significance, and role in chronic pain describes the heterogenicity of MC nomenclature as a major issue and once again underlines the need for further research within the field.

Overall, a classification system is of use if it is clinically relevant, reliable and applicable to the majority of patients with MC. However, introducing too many variables (e.g., size, volume,

location, BEP involvement, osteophyte formation) will ultimately increase both inter- and intra-rater disagreement.

The Way Forward: Modic Changes definition and Grading

Several key issues need to be addressed to ensure a systematic and methodologically sound use of the term MC and to investigate the clinical relevance of MC grades. **First**, there needs to be consensus on the nomenclature. We suggest that the broad term EC should be used to describe structural changes in the endplates visible by histological analysis (BEP and CEP) and/or MRI/CT (BEP). BEP changes not causing vertebral marrow changes can be classified according to morphology, location or etiology, but should be distinguished from MC. For all causes of EC (e. g., trauma, infectious, degenerative, etc.), a more detailed MRI description should, as a minimum, include details regarding the grade of DD (Pfirrmann classification), and location of EC (cephal and/or caudal endplate).

For specific terms used to describe EC [vertebral endplate signal changes (VESC), endplate signal changes (ESC), MC], we suggest that EC should be used as the generic term containing all subgroups. Synonyms such as VESC and ESC should be avoided to facilitate comparisons between studies.

EC are present and is a part of MC. MC are speculated to originate from EC[38]. Change in barrier function, herniation of discus material through the endplates and into the vertebra, and upregulation of pro-inflammatory proteins are all suggested to be

part of a cascade reaction leading to the formation of MC[64]. However, the changes described on MRI as MC are the actual vertebral marrow changes on MRI and not the changes present in the 1 mm thick BEP/CEP endplates. Therefore, the term MC, should be reserved for vertebral marrow changes visualized on T1- and T2-weighted MRIs.

Such changes are associated with degeneration but can be initiated by trauma, inflammation and iatrogenic damage including chymopapain injection and discography[2,4]. The vertebral marrow changes characteristic of MC should adhere to the description and classification by de Roos and Modic et al[2–4].

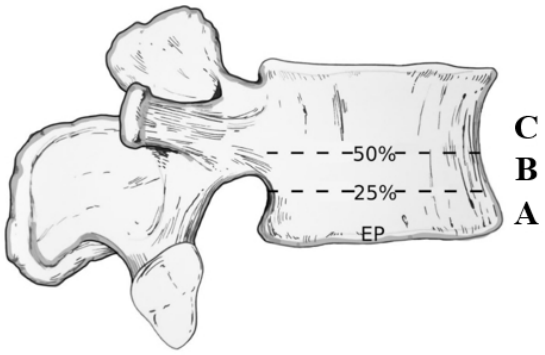
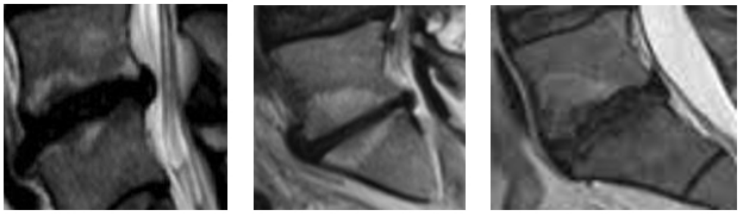
Secondly, the MRI description should at least include both the T1- and T2-weighted images of the mid-sagittal views. Technical details of the MRI unit should be provided (including Tesla strength, surface coils, and use of signal amplification) and sequences analyzed (T1, T2, STIR, and type of spin echo).

Thirdly, grading is essential for the term MC to have any clinical relevance[18,22,55]. MC simply describes the presence of marrow changes on MRI. Without any measure of the extent of involvement of the vertebral body, a clinically relevant classification is not possible. Similar to DD where the Pfirrmann classification can be used to grade its severity, a description of MC needs to take into account both the type and grading of marrow changes. Previous studies have demonstrated clinically and statistically significant relevant associations by utilizing MC

grading [10,22]. Weishaupt found that MC involving >25% of vertebral height was strongly associated with discogenic pain compared to MC involving <25% of vertebral height[22]. Määttä et al using the same grading system found that MC-1 were larger vertically compared with MC-2[55]. The intraobserver reliability ranged from 0.69-1.00 and the interobserver reliability was good to high (k>0.80) for height of MC. In the same study, subjects with MC with a minimum extent of 25% or greater of the relative height of the vertebra had a higher degree of overall degenerative disc change (p=0.001) than subjects with smaller MC involvement (<25% of vertebral height). Similarly, MC-1 component changes, in particular, were associated not only with prolonged severe and disabling LBP but also horizontally large (covering the whole AP direction or the whole endplate) and vertically largest MC was associated with severe prolonged and disabling LBP. Similarly, in a population-based birth cohort study by Saukkonen et al, severe prolonged and disabling LBP was associated not only with MC-1 but also with the vertical and horizontal extent of the MC[65].

In Table 1, the MC grading score which can be used for all types of MC is illustrated.

Table 1. The Modic changes grading score

Grade	A	B	C
Degenerative marrow changes	<25% of vertebral height	25-50% of vertebral height	>50% of vertebral height
			
Example: MC-1 Grade A, B & C on T2-weighted MRI			

The extent of the marrow changes should be measured on the sagittal T1- and T2- weighted images according to the criteria and classification described by de Roos and Modic et al[2,3]. Changes can be present on one or both adjacent vertebral bodies (with cranial or caudal extent) and the intervertebral disc should, in most cases, demonstrate signs of DD (PF≥2). If varying/mixed type MC types are present within the same FSU, the most clinically significant MC should be described (i.e., MC-1 (then MC-2, then MC-3) due to increased metabolic activity, inflammation on histologic analysis, and stronger association with PROMs compared to mixed type MC, MC-2 and MC-3). And the most severe grading, according to sagittal slice with the largest

vertical extent of the MC within the vertebra, grade C> grade B> grade A should be used, in order to plainly describe the most clinically relevant changes at the FSU (Table 1).

Further studies should seek to validate the MC grading score and ensure that the terms used are appropriate to allow for comparisons within and between studies. Also, it would be relevant to discuss the common consensus and proposed nomenclature, used to describe EC and MC, at future international spine conferences.

CONCLUSION

MC are important, clinically relevant findings. However, variation and inconsistencies exist as to how they are defined, classified, and used in clinical decision-making. Our current "state-of-the-art" review highlights relevant issues related to EC and MC, and provides a definition and grading score for the term MC that includes the Modic type and the extent of vertebral body involvement. Future studies should seek to validate the MC grading score in clinically relevant populations.

DISCLOSURES

None.

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