

# From Modic 1 vertebral-endplate subchondral bone signal changes detected by MRI to the concept of 'active discopathy'

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## ABSTRACT

Late-1980s MRI-detected vertebral-endplate subchondral bone signal changes associated with degenerative disc disease as well as recent studies suggest that in some patients, non-specific chronic low back pain (NS cLBP) can be defined by specific clinical, radiological and biological features, for a concept of active discopathy. This concept allows for associating a particular NS cLBP phenotype to a specific anatomical lesion, namely those with Modic 1 signal changes seen on MRI. Local inflammation is thought to play a pivotal role in these changes. Other etiopathogenic processes may include local infection and mechanical or biochemical stress combined with predisposing genetic factors; treatment strategies remain debated. Modic 1 changes detected by MRI can be considered a first biomarker in NS cLBP. Such changes are of high clinical relevance because they are associated with a specific clinical phenotype and can be targeted by specific treatments.

In 2010, chronic low back pain (cLBP) was found to be the first cause of years lived with disability.<sup>1</sup> Treatment is oriented towards non-specific physical, psychological and social actions and not towards the determination of the lesion involved in the pain process. The challenge for the physician is to try to finely phenotype the LBP in order to propose targeted treatment to a specific lesion.

Active discopathy is a concept designating a clinical, radiological and biological syndrome defining a subset of patients with non-specific cLBP (NS cLBP). Active discopathy-related spinal abnormalities were first described on MRI and histopathology. Such abnormalities include intervertebral-disc subchondral bone changes and adjacent vertebral-endplate subchondral bone (VESB) changes associated with degenerative disc disease (DDD), called Modic 1 changes.<sup>2–3</sup> Etiopathogenic mechanisms remain controversial. Current hypotheses include local infection, biological and biomechanical stresses and genetic predisposition.<sup>4</sup> Local and systemic inflammation is thought to play an important role in Modic 1 lesion genesis and related symptoms.<sup>5</sup> Differential diagnosis with other causes of inflammatory cLBP, such as spondyloarthritis (SpA), remains challenging.<sup>6</sup> Treatment strategies are not standardised. However, a recent better understanding of underlying mechanisms has led to more specific targeted treatments.

This critical narrative review briefly outlines the Modic classification system and the link to NS cLBP by specific clinical, radiological, biological and genetic features, leading to the concept of

active discopathy. Treatment is also discussed. The process of article selection was unsystematic, as available studies on the topic are too few and too heterogeneous to draw a definitive 'quantitative' conclusion. Therefore, articles included in our review were selected based on the authors' expertise, self-knowledge and reflective practice.

## MODIC CLASSIFICATION

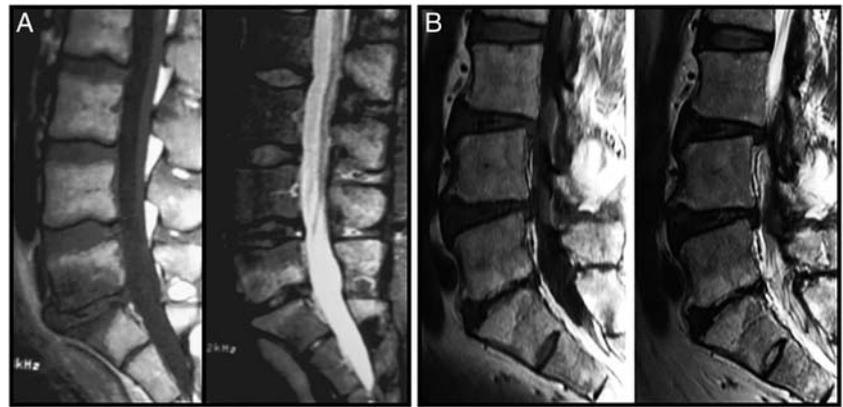
Using MRI, Modic *et al*<sup>3–7</sup> described VESB signal changes adjacent to DDD at the lumbar spine. A classification system initially included two stages. A third stage was described later. Each stage is characterised by specific VESB elementary signal changes seen on MRI. They can be asymmetrical and involve part or the whole adjacent VESB. The location and type of VESB MRI changes associated with DDD were described in 474 consecutive patients with LBP. DDD was defined as intervertebral space narrowing, *nucleus pulposus* hypointense on T2-weighted sequences and disc protrusion or herniation. DDD was detected in 323 of 474 patients, in 593 of 2370 analysed intervertebral discs. Histopathological data were also collected from intervertebral disc and adjacent VESB biopsies harvested at the time of surgery for six patients (three for each type of MRI changes). Along with MRI data, these data allowed for establishing the first two stages of the Modic classification system<sup>3</sup> (figure 1 and tables 1 and 2).

*Type 1 Modic signal changes* are characterised by a low-intensity signal on T1-weighted sequences and hyperintense signal on T2-weighted sequences with gadolinium injection enhancement, corresponding to bone marrow oedema. Histopathological analysis demonstrates a disrupted and fissured VESB associated with trabeculous bone thickening and increased number of osteoblasts and osteoclasts, supporting increased bone remodelling, as well as replacement of normal bone marrow tissue by richly vascularised granular tissue.<sup>3</sup> Ohtori *et al*<sup>8</sup> showed an increased number of cells expressing tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ) in Modic 1 VESB. Other proinflammatory, proapoptotic and procatabolic phenotypical changes in cells from Modic 1 VESB have been reported recently, showing increased expression of migration inhibitory factor and its receptor CD74,<sup>9</sup> Fas receptor<sup>10</sup> and a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS-5).<sup>11</sup>

*Type 2 Modic signal changes* are characterised by a hyperintense signal on T1-weighted and T2-weighted sequences reflecting bone marrow fatty degeneration. Histopathological analysis shows VESB

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**Figure 1** (A) Lumbar spine MRI showing Modic 1 L5/S1 vertebral-endplate subchondral bone (VESB) signal changes, with typical T1 hyposignal (left) and T2 hypersignal (right); (B) Lumbar spine MRI showing Modic 2 L5/S1 VESB changes, with typical T1 hypersignal (left) and T2 hypersignal (right).



disruption and granular tissue, with no hypervascularisation in adjacent bone marrow, which is replaced by fatty tissue.<sup>3</sup>

*Type 3 Modic signal changes* are characterised by a low-intensity signal on T1-weighted and T2-weighted sequences, assumed to reflect bone marrow sclerosis. This stage is less frequent and is associated with extensive bone condensation on radiography. Histopathology has not been addressed, but this stage is assumed to be related to poorly vascularised fibrosis with subsequent bone condensation.<sup>7</sup>

*Type 0 Modic* signal corresponds to normal VESB and bone marrow signals.

For ‘*mixed Modic*’ changes, several Modic change types are concomitantly found on the same VESB.<sup>12 13</sup>

### ETIOPATHOGENY

Modic 1 signal changes were first described in association with DDD. Similar MRI changes are observed in infectious or inflammatory diseases affecting the spine. The etiopathogenic mechanisms of Modic 1 changes remain debated<sup>4</sup> (figure 2).

### Local instability and inflammation

Crock proposed the concept of internal disc disruption. Repeated trauma to the intervertebral disc leads to the production of proinflammatory soluble mediators in the *nucleus pulposus*. Diffusion of these mediators through VESB can promote local inflammation and generate pain.<sup>14</sup> This hypothesis is supported by clinical data. In Albert and Manniche’s study,<sup>15</sup> MRI was performed at the acute phase of discal sciatica-related back pain and 14 months later in 166 patients. Modic 1 prevalence increased from 9% to 29% within 14 months, whereas Modic 2 and 3 prevalence remained unchanged. In all, 11% of patients who presented with Modic 1 or 2 changes at baseline showed new Modic 1 changes at the same spine level; patients with Modic 0 changes showed no evolution, so presence of Modic 1 and 2 changes could promote further local inflammatory

changes over time. Consistently, Kuisma *et al* described 60 patients with disc herniation. At baseline, 23% had Modic 2 changes, and at 3-year follow-up, 6% showed Modic 1 or mixed Modic 1 and 2 changes.<sup>16</sup> The association of disc herniation and Modic changes is supported by the higher prevalence in men than women of both disc herniation and Modic changes. In addition, Modic changes are often observed at L4/L5 and L5/S1,<sup>15</sup> where 95% of disc herniations occur. These clinical data indicate that disc herniation and Modic 1 changes are closely related in a spatiotemporal frame and might reflect a dynamic and active DDD.

Biomechanical changes secondary to DDD are thought to also play a role in the genesis of Modic changes. Loss of *nucleus pulposus* material leads to increased shear stress on VESB, which can promote local microfractures and accelerate bone remodelling.<sup>3</sup> Adams *et al*<sup>17</sup> described the relationship between DDD and mechanical stress. DDD-associated Modic 1 changes reflect initial bleeding, oedema and hypervascularisation secondary to microtrauma, as well as healing processes after VESB microfractures. Biomechanically induced local inflammatory changes are a source of pain. This hypothesis is supported by several clinical studies showing that surgical stabilisation can lead to suppression of Modic 1 changes, with pain relief.<sup>18 19</sup> Furthermore, targeting mechanically induced local inflammation with intradiscal glucocorticoid injections was found more effective in reducing pain in patients with Modic 1 than other Modic changes.<sup>20</sup>

Altogether, these data support the role of biomechanically and/or biochemically induced local inflammation in the pathogenesis of Modic 1 changes and related symptoms. From the clinical point of view, instability and local inflammatory changes seem to be closely related. However, it is still unclear whether in some patients, one mechanism could be predominant. Interestingly, we recently assessed Modic 1 MRI-associated structural alterations in 101 patients and were able to identify two clear clinical subsets of patients with Modic 1 changes based on their MRI features, suggesting a relationship to two distinct physiopathological mechanisms (unpublished data). Whether this finding is of therapeutic relevance remains to be determined.

### Local infection

Some authors have hypothesised that Modic changes could be secondary to local infection with anaerobic germs.<sup>21</sup> *Annulus fibrosus* disruption following disc herniation leads to neovascularisation around the extruded *nucleus pulposus* and to an inflammatory response.<sup>22</sup> This local environment promotes

**Table 1** Modic classification: MRI changes and associated pathological features

Vertebral endplates	T1-weighted sequences	T2-weighted sequences	Histopathology
Modic 1	Hyposignal	Hypersignal	Oedema, inflammation
Modic 2	Hypersignal	Isosignal or hypersignal	Fatty changes
Modic 3	Hyposignal	Hyposignal	Fibrous process

**Table 2** Prevalence of Modic VESB changes by back pain symptoms

Author	Population	No.	Modic (%)	Modic 1 (%)	Modic 2 (%)	Modic 3 (%)
Takatalo <i>et al</i> <sup>24</sup>	21-year-old, general	558	1.4	–	–	–
Kjaer <i>et al</i> <sup>36</sup>	40-year-old, general	412	22	15	7	0
Weishaupt <i>et al</i> <sup>20</sup>	Asymptomatic	60	13	3	10	0
Albert and Manniche <sup>15</sup>	Sciatica	181	25	9	14	1
Albert and Manniche <sup>15</sup>	14-month sciatica	166	49	29	13	1
Kuisma <i>et al</i> <sup>16</sup>	Radiculalgia	60	23	2	21	0
Kuisma <i>et al</i> <sup>16</sup>	3-year radiculalgia	60	28	8	20	–
Mitra <i>et al</i> <sup>41</sup>	LBP or sciatica	670	–	18	–	–
Modic <i>et al</i> <sup>3</sup>	LBP and/or sciatica	474	20	4	16	0
Toyone <i>et al</i> <sup>37</sup>	cLBP	500	19	–	–	–
Weishaupt <i>et al</i> <sup>58</sup>	LBP	50	22	14	9	0
Braithwaite <i>et al</i> <sup>12</sup>	Before arthrodesis	58	48	–	–	–
Karchevsky <i>et al</i> <sup>69</sup>	Consecutive MRI	100	58	24	33	1

cLBP, chronic low back pain; VESB, vertebral-endplate subchondral bone.

anaerobic germ growth and chronic infection. Development of new Modic changes in adjacent vertebra was found more associated with positive than negative anaerobic culture from surgically harvested disc-herniation tissue (80% vs 44% of patients).<sup>23</sup> However, the diagnosis remains challenging in the absence of symptoms of systemic infection, specific infectious spondylodiscitis features seen on MRI or easy bacterial documentation.

In a prospective study of 71 patients with Modic 1 changes followed up every 3 months for 2 years, Ohtori *et al* reported symptom worsening and MRI changes consistent with infectious spondylitis in 4 patients. Bacterial infection was confirmed in three of four patients, two with a history of diabetes.<sup>24</sup> In two open-label studies, patients with active discopathy-associated NS cLBP treated with antibiotics showed MRI (n=5)<sup>25</sup> or clinical (n=32)<sup>26</sup> improvement. However, another study failed to confirm the link between infection by anaerobic germs and active discopathy. Vertebral biopsies performed in aseptic conditions in 24 consecutive patients with Modic 1 changes did not detect anaerobic germs in any case but, rather, *Staphylococcus epidermidis* and coagulase-negative staphylococci in 2 different cases. Treatment with antibiotics did not alleviate symptoms.<sup>27</sup> Recently, Albert *et al* reported the efficacy after 1 year of treatment with antibiotics (namely, amoxicillin/clavulanic acid 500 mg/125 mg, 3 times a day, for 100 days) for active

discopathy in a randomised controlled trial. These results support the pathogenic role of local infection in some subsets of Modic changes.<sup>21</sup> However, we do not believe that active discopathies are related to low-grade bacterial infection, and future studies should determine diagnosis criteria of infection-related Modic 1 changes. The place of antibiotics in the management of active-discopathy-associated cLBP should also be better defined. In the cases of very erosive discopathies after surgery and evolution longer than expected despite conventional treatment, long-term treatment with antibiotics could be considered.

### Genetics

Studies of homozygote twins have shown a weak association of environmental factors and DDD and have suggested some role of genetics.<sup>16 28</sup> A twin study aimed at specifically addressing heritability of Modic changes using variance component analysis showed a prevalence of heritability of 30% (16%–43%).<sup>29</sup> Abnormalities in content of type IX collagen<sup>15 30</sup> and aggrecan genes<sup>31</sup> have been reported. Two recent studies addressed genetic factors associated with active discopathy. In total, 13 variations in 8 genes—collagen 9A2 (COL-9A2), COL-9A3, COL-11A2, interleukin 1A (IL-1A), IL-1B, IL-6, matrix metalloproteinase 3 (MMP-3) and vitamin D receptor (VDR)—were genotyped in a cohort of 228 individuals from North Finland, 128 with Modic changes (15% Modic 1, 32% Modic 2 and 10% mixed). IL-1A and MMP-3 polymorphisms were significantly associated with Modic 2 signals (OR 3.2, 95% CI 1.2 to 8.5; p=0.038) as were IL-1 with MMP-3 polymorphisms (OR 8.1, 1.7 to 38.4; p=0.008).<sup>32</sup> These results for IL-1A were further replicated in a cohort of 108 patients from South Finland.<sup>33</sup>

### PREVALENCE

According to the type of population studied, the prevalence of Modic signal changes varies from 1.4% to 58% (table 1). In a cross-sectional study of 558 subjects from the general population, with mean age 21.2 years, the prevalence of lumbar Modic changes was 1.4%. Modic 1 changes were more frequent than Modic 2 changes. These MRI changes were more often located in L4/L5 and L5/S1 and adjacent to grade four DDD.<sup>34</sup> A literature review by Jensen *et al*<sup>35</sup> suggested that Modic changes could be positively associated with age and negatively with the quality of the studies.



**Figure 2** Modic signal changes detected by MRI are associated with vertebral-endplate subchondral bone changes including increased vascularisation and production of soluble inflammatory mediators such as prostaglandin E2 (PGE2), nitric oxide (NO), interleukin 6 (IL-6) and tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ). Several mechanisms hypothesised to underlie these changes include vertebral instability, local and systemic inflammation, local infection and predisposing genetics.

## A CLINICAL AND BIOLOGICAL SYNDROME

Modic classification is based on MRI findings, but further studies have strongly suggested that these MRI changes may be a biomarker because they are associated with a specific clinical and biological phenotype including inflammatory-like NS cLBP and local and systemic inflammation.

### Low back pain

NS cLBP is a heterogeneous nosological group. Similar symptoms can be related to various non-specific structural changes and influenced by social and psychological factors. Identifying a causative structural lesion is difficult. On MRI, which is a more sensitive technique than radiography to detect bone changes, VESB abnormalities have been further identified as specifically associated with some NS cLBP subsets.

Modic signal changes are frequent in NS cLBP (18%–58% of patients). In an asymptomatic population, the prevalence of changes is lower, ranging from 12% to 13%.<sup>4</sup> In a cohort of 412 subjects from the general population, with mean age 40 years, NS cLBP was associated with Modic changes; NS cLBP prevalence during the previous year was 88% in subjects with Modic changes as compared with 12% in subjects without such changes.<sup>36</sup> For 166 patients (92% with disc herniation) who underwent lumbar MRI at baseline and at 14-month follow-up, 60% with Modic changes had NS cLBP; only 20% without Modic changes had cLBP (OR 6.1; 95% CI 2.9 to 13.1;  $p < 0.0001$ ). The prevalence of Modic changes increased over time, from 25% at baseline to 49% at 14-month follow-up. Furthermore, cLBP was more frequent with Modic 1 changes than with Modic 2 changes. This difference was also observed by Toyone and Kjaer *et al*,<sup>36 37</sup> which suggests that Modic 1, rather than 2, changes are specifically associated with cLBP. In a review of the literature, Jensen *et al* reported a 43% prevalence of Modic changes in patients with NS cLBP and/or sciatica versus 6% in an asymptomatic population. In 7 of the 10 studies, these changes were positively associated with NS cLBP (OR from 2.0 to 19.9).<sup>35</sup> Modic 1 changes persisting over time were associated with poor clinical outcome in a prospective cohort of patients with LBP followed up for 14 months.<sup>38</sup>

Several physiopathological hypotheses have been discussed to explain the relationship between Modic 1 signal changes and pain. Modic 1 changes could reflect early stage DDD associated with a more active and inflammatory local process leading to pain, thus sustaining the concept of active discopathy. In a study of 58 patients with cLBP associated with disc herniation, Braithwaite *et al*<sup>12</sup> found that Modic signal changes could predict pain during discography with a specificity of 97%. For 2457 intervertebral discs, Thompson *et al*<sup>39</sup> confirmed that Modic 1 changes were highly predictive of pain during discography (positive predictive value 0.81; 95% CI 0.74 to 0.87) as compared with Modic 2 or 3 changes. Pain symptoms may be related to increased levels of proinflammatory cytokines such as TNF- $\alpha$  and the number of nerve fibres expressing protein gene product 9.5 in VESB of patients with Modic changes.<sup>8</sup>

### Systemic inflammation

Active discopathy often presents as acute changes in NS cLBP symptoms.<sup>6</sup> Among 36 patients with NS cLBP (12 with Modic 1, 12 with Modic 2 and 12 with Modic 0 changes), Modic 1 changes were associated with more intense pain at night and morning and longer morning stiffness. Non-steroidal anti-inflammatory drugs were effective in this subset of NS cLBP. These inflammatory features were not observed in patients with

Modic 2 or 0 changes. Active discopathy was significantly associated with increased highly sensitive C-reactive protein level ( $4.64 \pm 3.09$ ,  $1.33 \pm 0.77$  and  $1.75 \pm 1.30$  mg/L for Modic 1, 0 and 2 changes, respectively;  $p = 0.002$  between Modic 1 and non-Modic 1 groups), which suggests the presence of low-grade systemic inflammation.<sup>5</sup>

Differential diagnosis with other aetiologies of inflammatory cLBP can be challenging. However, when addressing criteria sets for inflammatory back pain classification, namely Calin, Berlin and Assessment of SpondyloArthritis international Society criteria, the criteria for SpA (Amor criteria) and ankylosing spondylitis (AS) (New York criteria), no difference was found between patients with Modic 1 ( $n = 15$ ) and non-Modic 1 changes ( $n = 25$ ).<sup>6</sup>

## EVOLUTION

### Natural history

The three types of Modic changes could evolve over time, over a mean period of 1–3 years,<sup>3 40 41</sup> which suggests that they may be successive stages of the same dynamic process. Modic 2 and 3 signal changes correspond to clinical and biological healing stages, associated with decreased inflammation-related symptoms. In support of this hypothesis, while comparing 13 pure Modic 1 signals to 49 mixed Modic 1–2 signals, Kaapa *et al*<sup>42</sup> found higher pain scores among patients with Modic 1 than other changes. Using consecutive MRI images, Hutton *et al*<sup>43</sup> assessed 36 VESB with Modic 1 changes over time and found that Modic changes could completely reverse in some cases. In another subgroup of 44 patients with Modic 1 changes among 670 patients with LBP and/or sciatica who received conservative treatment, 37% showed conversion of Modic 1 to complete Modic 2 changes and 15% to partial Modic 2 changes; 40% showed an extension of Modic 1 changes, and for 8%, signals remained unchanged. In patients who reported improved pain, the Modic 1 signal was more often replaced with a Modic 2 signal. Conversely, among patients who reported worsening pain, Modic 1 extension was frequently reported.<sup>41</sup>

Modic *et al* also assessed the evolution of Modic signal changes in 16 patients with LBP without sciatica over 12–36 months. In 5 of 6 cases, the Modic 1 signals converted to Modic 2 signals, at least in part, whereas 10 patients with Modic 2 signals showed no changes over time.<sup>3</sup> Jensen *et al* studied 344 patients who had an MRI at 40 years of age and a second one 4 years later. They found an increase from 6% to 9% in prevalence of Modic changes. The more MRI changes were extended at baseline, being more likely to expand during follow-up, while the less extended changes disappeared.<sup>44</sup> When focusing on Modic 1 changes, 214 were detected at baseline. Over the 4-year period of follow-up, 46%, 37%, 7%, 1% and 9% of the Modic 1 changes remained stable or converted to Modic 0, 2, 3 or mixed signal, respectively.<sup>44</sup> On multivariate analysis, predictors of incident Modic changes were DDD, disc bulging and disc herniation.<sup>45</sup> In a 3-year follow-up of 60 unoperated patients with sciatica, Kuisma *et al* detected at baseline seven mixed Modic 1/2. At 3 years, two out of seven converted to Modic 2, five remained stable, and none converted to Modic 0. Unfortunately, in this study, no pure Modic 1 changes were included at baseline.<sup>16</sup>

Altogether, these clinical data suggest that the dynamic process is not exactly linear over time, as different stages of Modic changes can coexist or revert. In addition, there is no clear explanation for Modic 1 changes to remain stable in some patients. One could assume that the cause of Modic changes might persist, either instability-induced local inflammation or

local infection. One can also hypothesise that under yet unclear circumstances, some Modic lesions could become irreversible. However, experimental models of Modic changes are lacking to clearly assess how these stages do transit from one to the next and what the underlying biomechanical and biochemical mechanisms are.

### History with treatment

The natural history of Modic signal changes and associated clinical features suggests that treatments able to accelerate the course of changes to less inflammatory stages of the disease, such as Modic 0 or Modic 2 changes, could be of therapeutic interest.

Few open-label studies assessed surgery. Modic 1 changes were assessed in 17 patients with NS cLBP after posterior instrumented fusion surgery. At 6 months, all patients showed a switch from Modic 1 to non-Modic 1 changes, along with clinical improvement, which was maintained at 1-year follow-up.<sup>19</sup> Consistently, Modic changes predicted good response to surgical stabilisation in 60 cases of NS cLBP (instrumented segmental fusion (n=22) or posterolateral fusion (n=38)), and Modic 1 changes at baseline were associated with better clinical outcome after 14 months.<sup>19</sup> In another cohort of 21 patients with Modic 1-associated LBP, Ohtori *et al*<sup>46</sup> observed a conversion to Modic 0 changes in two patients and to Modic 2 changes in nine patients at 24 months after surgery. Lang *et al* evaluated lumbar fusion in 33 patients who had undergone arthrodesis. The 19 patients with solid fusion showed Modic 2 changes, whereas the 10 patients having non-union showed inflammatory Modic 1 changes.<sup>47</sup> Chataigner *et al* studied 56 patients who underwent anterior procedures with bone grafting for cLBP. A close relationship was observed between preoperative MRI Modic Type 1 changes and the result of surgery as best surgical outcomes were observed in Modic 1 changes.<sup>48</sup> These findings were consistent with Esposito results that patients with Modic 1 cLBP improved better than others after lumbar surgery.<sup>18</sup> In another surgical study, the presence of Modic changes did not have any significant influence on the overall outcome of disc replacement compared with patients without Modic changes.<sup>49</sup> To date, there are no published studies of the natural history versus surgical treatment. In addition, correlation of the vertebral subchondral changes after surgery and surgical outcomes are conflicting. Indeed, Ohtori *et al* did not find a relationship between LBP score and the type of Modic signal change before and after surgery. They included lumbar spinal canal stenosis in patients and hypothesised that the symptoms could have originated from other anatomical structures.<sup>46</sup>

Non-operative local treatments targeting inflammation, such as intradiscal corticosteroid injections, were assessed in open-label studies. Among 74 patients with cLBP, Fayad *et al*<sup>20</sup> reported better clinical response, based on pain score, in patients with Modic 1 than Modic 2 changes. Consistently, for 171 patients with LBP, clinical response was longer in patients with Modic changes than in those without.<sup>50</sup> A retrospective study comparing the efficacy of intradiscal methylprednisolone found greater self-assessed improvement in LBP in 67 patients with Modic 1 changes than in 30 patients without Modic 1 changes at 24 h after injection.<sup>51</sup> We are currently assessing efficacy and tolerance of intradiscal corticosteroid injections in disabling Modic 1-associated cLBP in a double-blind, randomised, controlled study (TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT00804531).

Other authors suggest that targeting subchondral bone using intravenous bisphosphonates, as active Modic 1-associated bone

marrow lesions are observed, could be of clinical interest. Results of an open study seem to be encouraging<sup>52</sup>; a randomised controlled trial of 5 mg zoledronic acid found a significant improvement in LBP at 1 month,<sup>53</sup> and a randomised controlled trial of 90 mg pamidronate, for 2 days consecutively, is ongoing.<sup>54</sup> Other therapeutic options targeting bone marrow oedema such as surgical decompression or the prostaglandin analogue iloprost have not been assessed yet.

Only two studies assessed the relationship between exercise therapy and Modic change-related LBP symptoms. In a prospective study of the effect of exercise therapy in patients with NS cLBP, Kleinstück *et al*<sup>55</sup> found that the presence of Modic changes did not significantly influence clinical outcomes such as pain and disability immediately after end of treatment and at 3 and 12 months. In a randomised controlled trial comparing rest versus exercise in 87 patients with cLBP and Modic changes, Jensen *et al*<sup>56</sup> found no differences between the two strategies at 10 and 52 weeks, for all the outcomes assessed. Whether patients with Modic 1 cLBP could benefit from intensive rehabilitation programme versus natural history remains to be investigated.

Finally, in a systematic literature review aiming to investigate if the presence of Modic changes at baseline was associated with a better outcome depending on the treatment provided for cLBP, Jensen *et al* raised some concerns about the heterogeneity and quality of available studies. They did not yet allow clear conclusions to be drawn whether Modic changes were of clinical relevance to guide targeted treatment in patients with cLBP.<sup>57</sup>

### CONCLUSION

Modic changes were first described on MRI and pathological examination. Further clinical studies showed that they were associated with specific and biological features, which allowed for defining a particular subset of patients with NS cLBP presenting with active DDD. Accurate phenotyping of cLBP patients has allowed for specifically relating a structural lesion to symptoms in cLBP patients. Active discopathy, defined as the specific combination of MRI, clinical and biological features, could be used as a phenotypical biomarker of a particular subset of cLBP. Being able to identify this subset in daily practice is of clinical relevance,

#### Box 1 Research agenda

- ▶ To define subsets of patients with active discopathy chronic low back pain (cLBP) according to the predominant physiopathological mechanism (instability vs inflammation vs infection) and to identify clear classification criteria.
- ▶ To determine the natural clinical and structural history of active discopathy and to identify baseline clinical and MRI determinants.
- ▶ To assess the efficacy and tolerance of targeted therapeutic strategies in larger randomised controlled trials of operative treatments (eg, stabilisation surgery) and non-operative treatments (eg, corticosteroids injections, physical therapy and other treatments), including a natural history control group, and selecting Modic 1-associated cLBP patients based on accurate phenotyping.
- ▶ To develop experimental models of degenerative disc disease and Modic changes in order to decipher underlying molecular mechanisms of structural and clinical features.

## Review

because targeted treatments could be effective. Current available therapies target processes that are thought to be involved in the pathogeny of active discopathy and its related symptoms, such as 1/instability, 2/inflammation, 3/infection, 4/bone marrow lesions. However, studies addressing finely tailored therapeutic strategies for active discopathy-associated cLBP are still lacking, and available studies are heterogeneous and show conflicting results and only a little long-term difference in outcomes. We believe that future trials should enrol better phenotyped patients, as Modic 1 subsets may exist (instability-induced inflammation vs infectious), and include a control (natural history) as well as medical therapy (intensive rehabilitation, spine corticosteroids injections) and surgery (box 1).

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# From Modic 1 vertebral-endplate subchondral bone signal changes detected by MRI to the concept of 'active discopathy'

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