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# High-Sensitivity C Reactive Protein in Chronic Low Back Pain with Vertebral Endplate Modic Signal Changes

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## ABSTRACT

**Objective**.We aimed to assess high-sensitivity-C-reactive protein (hs-CRP) level as a measure of low-grade inflammation in relation to Modic vertebral endplate marrow signal change on magnetic resonance imaging (MRI) in patients with chronic low back pain (cLBP).

**Methods.**All patients hospitalized for cLBP in our institution were prospectively enrolled in this pilot study. Serum hs-CRP concentration was measured by immunoturbidimetric assay. MR images were evaluated independently by a panel of 2 spine specialists and a radiologist. Recording of clinical parameters, MRI evaluation and hs-CRP level of each patient was blinded.

**Results.**Twelve consecutive patients in each of 3 groups --Modic 0, Modic I, and Modic II signal changes on MRI-- were prospectively selected. Serum hs-CRP level was significantly different in the 3 groups ($p=0.002$) and especially high in the Modic I group ($p=0.002$ compared with Modic 0 and II groups): $1.33\pm0.77$ mg/l in the Modic 0 group, $4.64\pm3.09$ mg/l in the Modic I group, and $1.75\pm1.30$ mg/l in the Modic II group. The only difference in clinical parameters among the 3 groups ($p=0.001$) was that the worst painful moment during the previous 24 hours occurred during the late night and morning for all Modic I patients ($p=0.001$ compared with Modic 0 and $p=0.002$ compared with Modic II).

**Conclusion.**Low-grade inflammation indicated by high serum hs-CRP level in patients with cLBP could point to Modic I signal changes. This result could help physicians predict the patients with Modic I signals to more precisely prescribe the correct imaging procedure and local anti-inflammatory treatment in such patients.

## INTRODUCTION

Chronic low back pain is a major public health issue. To date, detecting lesions related to the pain of the patients is very difficult, one of the main reasons being that the morphological abnormalities detected by standard imaging is found in low back pain patients as well as in asymptomatic populations (1). However, with use of magnetic resonance imaging (MRI), de Roos and Modic have described modifications of the vertebral endplate marrow signal that are anecdotally present in the asymptomatic population but significantly present in chronic low back pain patients, which suggests the pathophysiological relevance of these signal changes (2, 3, 4, 5, 6). A Modic I signal change corresponds to vertebral body edema, whereas a Modic II signal change reflects more fatty degeneration. Biopsies of Modic I lesions show replacement of marrow by richly vascularized fibrous tissue (3). Increased level of interleukine-6 (IL-6), a proinflammatory cytokine, has been detected in the intervertebral disc in patients with chronic low back pain who show Modic I signal changes as compared to patients with Modic II signal changes (7). A significant increase in number of tumor necrosis factor (TNF) immunoreactive cells in Modic I than in Modic II and Modic 0 (absence of vertebral endplate signal changes) lesions has been shown in the vertebral endplates of patients with chronic low back pain (8). These results suggest that endplate-marrow signal changes detected by MRI in patients with chronic low back pain are related to local inflammation, which seems to be more intense in Modic I lesions.

High-sensitivity C reactive protein (hs-CRP) is a sensitive systemic marker of low-grade inflammation. IL-6 is the major up-regulator of CRP gene expression and is detected in Modic I lesions (7, 9). Thus, hs-CRP level could be increased in the subgroup of patients with chronic low back pain who show Modic I signal changes on MRI. Obesity, diabetes,

smoking, and alcohol consumption are known or supected to influence hs-CRP level. In acute lumbosciatica because of herniated disc, hs-CRP is upregulated and seems to be correlated with pain intensity (10, 11, 12, 13). However, these studies failed to show an increase in hs-CRP level in chronic low back pain, but vertebral endplate-marrow signal change was not taken into account (10, 12).

Here, we describe the results of a pilot study that aimed to assess serum hs-CRP level in patients with chronic low back pain in relation to vertebral endplate-marrow signal changes on MRI.

## PATIENTS AND METHODS

### Patient selection

For 6 months, from November 2005 to April 2006, all patients hospitalized for low back pain in the rehabilitation department of Cochin Hospital were prospectively enrolled in the study. Inclusion was based on fulfillment of all of the following criteria:

- Severe chronic low back pain, defined as low back pain persisting for longer than 3 months, with no response to 3-month conservative treatment and severe interference with lifestyle
- aged 18 years old or older
- MRI of the lumbar spine in the last 6 months

Exclusion criteria were:

- Back surgery
- Herniated disc
- Uncontrolled depression
- Low back pain related to ankylosing spondylitis, infection, tumor or fracture
- Obesity evaluated by a body mass index > 30 $kg/m^2$

- Diabetes

- Presence of sciatica



**Lumbar MRI evaluation**

MR images in patients were evaluated independently by a panel of 2 spine specialists (MR, FR) and a radiologist (HG) with at least 10 years' experience in spine MRI who were blinded to the clinical characteristics and hs-CRP level. The reviewers graded the endplate marrow signal changes of the 5 lumbar discs. The signal changes in endplate marrow of the Modic I group indicated more than 50% edema and the Modic II group more than 50% fatty deposits; the Modic 0 group showed no signal change. The final MRI evaluation was based on concordance by at least 2 of the 3 panelists. If Modic I or Modic II signals were present at more than one lumbar level, the patient was not selected.

**High-sensitivity CRP**

Serum samples were analyzed by DB, who was blinded to the MRI evaluation and clinical characteristics of each patient (11). To decrease the risk of interference with the biological analysis, the serum sample was taken with the patient abstaining from smoking, alcohol consumption, and steroid use during the previous 24 hours. hs-CRP concentration was measured by immunoturbidimetric CRP latex Tina quant assay on a Modular P instrument (Roche Diagnostics). The assay measures latex microparticles coated with monoclonal antibodies specific to human CRP that aggregate when mixed with samples containing human CRP, which results in increased turbidity. Turbidity was measured at 546 nm. The lower detection limit was 0.43 mg/L.

**Clinical characteristics**

Two authors (WO and BL), who were blinded to the MRI evaluation and the hs-CRP level of each patient, recorded age; sex; duration of symptoms; low back pain intensity on a visual analog scale (VAS; 0-100-mm); presence of a morning stiffness (yes/no) and duration; worst painful moment during the previous 24 hours (late night and morning or afternoon and early night); reproduction of pain during Valsalva maneuver (yes/no); Quebec disability score (20 items, scored from 0, no disability, to 5, impossible to do; range of final score 0-100); handicap on a VAS; lumber flexibility (modified Schöber test and finger-to-floor test); exacerbation of pain in anteflexion; hyperextension and lateral bending (yes/no), and Lasègue's sign (yes/no). The physical examination was performed in the morning as previously described (14).

**Statistical analysis**

Data were analysed with use of Systat 9 software (Chicago, IL, USA). Qualitative data were described with percentages, and quantitative data with means ± standard deviation (S.D.) and range. We compared the biological and clinical parameters between the 3 different groups (Modic 0, 1, 2). Quantitative variables were compared by nonparametric Kruskall-Wallis test. Qualitative variables were compared by Fisher's exact test. Bonferroni adjustment was used for the multiple [17] comparisons; a $p<0.003$ was considered statistically significant. When appropriate, we compared groups with Wilcoxon or Fisher's exact test.

## RESULTS

A total of 165 patients were prospectively screened. Among 80 patients excluded, the 3 main reasons for exclusion were absence of MRI or MRI older than 6 months, having undergone back surgery, and/or acute low back pain. Thus, among the 85 remaining patients, we prospectively selected the following consecutive patients: 12 with Modic 0, 12 with Modic I, and 12 with Modic II signal changes on MRI. In all cases, we selected patients after lumbar MRI and verification of the inclusion and exclusion criteria. Among the 49 patients not selected, 42 had Modic 0 and 5 Modic II signal changes, and 2 had Modic I signal changes and Modic II signal changes at 2 different levels. All patients with Modic I signal changes were included.

### Description of the patients

Table 1 describes the study population according to vertebral endplate marrow Modic signal change. The 3 groups were comparable in age, gender, pain, level of disability and handicap. Duration of symptoms, duration of morning stiffness and reproduction of pain during Valsalva maneuver tended to differ among the groups but not significantly (p=0.007, 0.009, 0.005, respectively). The only significant difference (p=0.001) was for the worst painful moment in the previous 24 hours, which occurred during the late night and morning for all Modic I patients (p=0.001 compared with Modic 0 goup and p=0.002 compared with Modic II group).

### hs-CRP value

Serum hs-CRP level was significantly different among the 3 Modic groups (p=0.002) (figure) and especially high for the Modic I group (p=0.002 compared with Modic 0 and II

groups): Modic 0, 1.33 ± 0.77 mg/l; Modic I, 4.64 ± 3.09 mg/l, and Modic II, 1.75 ± 1.30 mg/l.

**Physical characteristics**

The 3 groups were comparable in lumbar flexibility (modified Schöber test and finger-to-floor test), exacerbation of pain in anteflexion, exacerbation of pain in lateral bending, and Lasègue's sign (table 2). The only physical sign tending to a significant difference between the groups was the reproduction of pain in hyperextension (p=0.013).

## DISCUSSION

We report here, for the first time, clear differences in hs-CRP level in a pilot study of patients with chronic low back pain and Modic 0, I and II class vertebral endplate marrow signal changes on MRI. Duration of symptoms, duration of morning stiffness, and reproduction of the pain during the Valsalva maneuver tended to differ among the groups but not significantly. However, Modic I patients reported pain during the late night and the morning more frequently than Modic 0 and Modic II patients. Serum hs-CRP level was significantly higher in Modic I than 0 and II groups. Taken together, these results suggest that pain during the late night and morning and high hs-CRP level in patients with chronic low back pain might be good indicators of Modic I signal changes on MRI and could have implications for prescribing imaging and specific treatment in such patients.

Our results do not agree with those of the 2 other studies of serum concentration of hs-CRP in patients with chronic low back pain (10, 12). In the first study, the authors found a mean hs-CRP of approximately 1.3 mg/l (10). In the second, Gebhardt et al. found no difference in level of hs-CRP between chronic low back pain patients and asymptomatic

subjects (1.30 and 1.26 mg/l, respectively) (12). This discrepancy with our results probably stems from a difference in selection of patients. Even if we do not know the proportion of Modic I and Modic II patients in the 2 earlier studies, in light of other studies, the proportion is usually low in a nonselected group of patients with chronic low back pain. For example, in the initial study by Modic (3), involving 474 patients with chronic low back pain or sciatica, the authors found 4% patients (n=20) with Modic I lesions and 16% (n=77) with Modic II lesions. Toyone et al., in a retrospective study of 500 patients with chronic low back pain, found 7.40% (n=37) with Modic I lesions and 7.40% (n=37) with Modic II lesions (4). So, studies that did not specifically select patients with chronic low back pain for evidence of Modic changes found a low proportion of patients with vertebral endplate signal changes, which explains the absence of elevated hs-CRP level in the 2 studies on serum concentration of hs-CRP in patients with chronic low back pain. Another explanation for this descrepancy could be the absence of control for confounder factors. However, in our study, we excluded overweight patients (>30 $kg/m^2$), and obesity (> 28 and < 30 $kg/m^2$), smoking, alcohol consumption, NSAID intake, and physical activity did not influence hs-CRP level (data not shown).

The increased hs-CRP level we observed in the Modic I group must be considered as a strong association only. The origin of this increase can be only speculative. CRP is synthesized in hepatocytes, whose activity is stimulated by cytokines, especially IL-6 (15). Because Modic I lesions have been found to be rich in IL-6 (7), we may hypothesize that the increased hs-CRP level could be a consequence of the increased amount of IL-6 from the Modic I lesion. The origin of this local inflammation could result from repetitive endplate cracking and microfractures in subchondral bone (16).

Isolating a subgroup of Modic I patients could have therapeutic and economic interest. Recently, intradiscal injections of corticosteroids have been shown to be more effective in

patients with chronic low back pain and Modic I vertebral endplate signal changes, but the results need to be confirmed in a randomized controlled trial (17, 18). In addtion, better results of lumbar arthrodesis for such patients with degenerative disc disease have been observed for those with Modic I signal changes and accelerates the course of Modic I lesions leading more rapidly to Modic II lesions, which are less inflammatory and painful (4, 5, 7, 19, 20). These results suggest that in the very sensitive field of low back pain surgery, the subgroup of patients with chronic low back pain and Modic I lesions could be good candidates for lumbar arthrodesis after the failure of a complete medical treatment and in cases of high level of handicap. Lastly, the interest of MR imaging in patients with chronic low back pain for proposing a specific treatment is very weak. Less expensive imaging systems such as computed tomography can detect herniated disc and osteoarthritis of facet joints. Thus, our results could be a first step in physicians' decision making about MRI for patients with chronic low back pain and could lead to a significant decrease in use of the procedure for one of the most expensive diseases in developed countries.

Our study has several limitations. Our sample size was small, but our study was a pilot study, and a more extensive prospective study is needed to further define the relation between hs-CRP level and clinical parameters and test their combination to propose a predictive model of Modic I syndrome. Another limitation is that we did not record the presence of hip, knee, or hand osteoarthritis. However, in studies related to the value of hs-CRP level in hip and knee osteoarthritis, the level of microinflammtion was less important. For example, in a study of 770 patients with advanced osteoarthritis, the mean hs-CRP level was 2.7 mg/l (21). However, in a study of 67 patients with erosive osteoarthritis of the hand, the median hs-CRP level was 4.7 mg/l (22). Thus, osteoarthritis must be taken into account in a future study. Retrospectively, we checked the medical records of 36 of our patients and found no case of erosive osteoarthritis. Lastly, the existence of many known and unknown confounding factors

could affect hs-CRP level evaluation for the individual. For this concern, combining hs-CRP level and physical and clinical signs to predict the presence of a Modic I signal could be of interest. A larger study will be better able to identify this combination.

In conclusion, hs-CRP level is increased in patients with chronic low back pain and Modic I lesions, which supports a local inflammation phenomenon occuring at the vertebral endplate level. This result could be of interest to prescribe MRI and propose for the first time, in a subgroup of patients with chronic low back pain, a specific local treatment to control this local inflammation.

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## TABLES

**Table1: Patients with chronic low back pain according to vertebral endplate marrow Modic signal change on MRI**

| | All patients (N = 36) | Modic 0 (n = 12) | Modic I (n = 12) | Modic II (n = 12) | p Value |
|---|---|---|---|---|---|
| Age (year) | 52 ± 14 | 53 ± 17 | 50 ± 13 | 54 ± 14 | 0.795 |
| Sex, female, n (%) | 12 (33) | 4 (33) | 4 (33) | 4 (33) | 1 |
| Pain (VAS; 100 mm) | 57 ± 20 | 48 ± 23 | 61 ± 20 | 60 ± 13 | 0.292 |
| Quebec disability score | 48 ± 15 | 47 ± 10 | 48 ± 18 | 51 ± 16 | 0.698 |
| Handicap (VAS in mm) | 64 ± 14 | 54 ± 14 | 60 ± 16 | 71 ± 9 | 0.246 |
| Duration of symptoms (month) | 41 ± 35 | 14 ± 10 | 52 ± 32 | 54 ± 41 | 0.007 |
| Presence of morning stiffness, n (%) | 25 (69) | 5 (42) | 11 (92) | 9 (75) | 0.028 |
| Duration of morning stiffness (min) | 27 ± 37 | 9 ± 15 | 49 ± 52 | 21± 23 | 0.009 |
| Worst painful moment during late night and morning, n (%) | 17 (47) | 1 (8) | 12 (100) | 3 (25) | **0.001** |
| Reproduction of the pain during the Valsalva maneuver, n (%) | 15 (42) | 1 ± (8) | 9 (75) | 5 (42) | 0.005 |

Results are mean ± SD unless otherwise indicated.
p values from nonparametric Kruskal-Wallis test or Fisher's exact test with Bonferroni adjustments for multiple comparisons ; $p<0.003$
VAS=visual analog scale

**Table 2: Physical characteristics of patients with chronic low back pain, according to vertebral endplate marrow Modic signal change on MRI**

| | All patients (N = 36) | Modic 0 (n = 12) | Modic I (n = 12) | Modic II (n = 12) | p Value |
|---|---|---|---|---|---|
| Modified Schöber test (cm) | 20 ± 2 | 20 ± 2 | 21 ± 2 | 20 ± 1 | 0.289 |
| Finger-to-floor test (cm) | 17 ± 14 | 14 ± 9 | 15 ± 14 | 22 ± 17 | 0.498 |
| Exacerbation of pain in anteflexion, n (%) | 18 (50) | 5 (42) | 7 (58) | 6 (50) | 0.723 |
| Exacerbation of pain in hyperextension, n (%) | 21 (58) | 3 (25) | 10 (83) | 8 (67) | 0.013 |
| Exacerbation of pain in lateral bending, n (%) | 17 (47) | 4 (33) | 8 (67) | 5 (42) | 0.244 |
| Lasègue's sign, n (%) | 5 (14) | 0 (0) | 3 (25) | 2 (17) | 0.206 |

Results are mean ± SD unless otherwise indicated.
p values from nonparametric Kruskal-Wallis test or Fisher's exact test, with Bonferroni adjustments for multiple comparisons ; $p<0.003$

## FIGURE LEGEND

**Serum level of high-sensitivity C reactive protein in patients with chronic low back pain according to vertebral endplate marrow Modic signal change on MRI.** p=0.002 by nonparametric Kruskal-Wallis test. *, p<0.003 by Wilcoxon test. Bonferroni adjustment made for multiple comparisons; p<0.003.