

High-Sensitivity C-Reactive Protein in Chronic Low Back Pain With Vertebral End-Plate Modic Signal Changes

FRANÇOIS RANNOU,¹ WALID OUANES,¹ ISABELLE BOUTRON,² BIANCA LOVISI,¹ FOUAD FAYAD,¹ YANN MACÉ,¹ DIDIER BORDERIE,¹ HENRI GUERINI,¹ SERGE POIRAUDEAU,¹ AND MICHEL REVEL¹

Objective. To assess high-sensitivity C-reactive protein (hsCRP) level as a measure of low-grade inflammation in relation to Modic vertebral end-plate marrow signal change on magnetic resonance imaging (MRI) in patients with chronic low back pain.

Methods. All patients hospitalized for chronic low back pain in our institution were prospectively enrolled in this pilot study. Serum hsCRP 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 hsCRP level of each patient was blinded.

Results. Three groups of 12 consecutive patients (Modic 0, Modic I, and Modic II signal changes on MRI) were prospectively selected. Serum hsCRP 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): mean \pm SD 1.33 ± 0.77 mg/liter in the Modic 0 group, 4.64 ± 3.09 mg/liter in the Modic I group, and 1.75 ± 1.30 mg/liter 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 hsCRP level in patients with chronic low back pain 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 antiinflammatory treatment in such patients.

KEY WORDS. Chronic low back pain; High-sensitivity CRP; Microinflammation; Modic; Vertebral end-plate signal; Magnetic resonance image.

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 morphologic abnormalities detected by standard imaging are

found both in patients with low back pain and in asymptomatic populations (1). However, using magnetic resonance imaging (MRI), de Roos et al (2) and Modic et al (3) have described modifications of the vertebral end-plate marrow signal that are anecdotally present in the asymptomatic population but significantly present in patients with chronic low back pain, which suggests the pathophysiologic relevance of these signal changes (4–6). A Modic I signal change corresponds to vertebral body edema, whereas a Modic II signal change reflects more fatty degeneration. Biopsy samples of Modic I lesions show replacement of marrow by richly vascularized fibrous tissue (3). Increased levels of interleukin-6 (IL-6), a proinflammatory cytokine, have been detected in the intervertebral disc in patients with chronic low back pain who show Modic I signal changes as compared with patients with Modic II signal changes (7). A significant increase in the number of tumor necrosis factor immunoreactive cells in Modic I lesions compared with Modic II and

¹François Rannou, MD, PhD, Walid Ouanes, MD, Bianca Lovisi, MD, Fouad Fayad, MD, Yann Macé, MD, Didier Borderie, MD, Henri Guerini, MD, Serge Poiraudreau, MD, PhD, Michel Revel, MD: Assistance Publique–Hôpitaux de Paris, Université René Descartes, Groupe Hospitalier Cochin, Paris, France; ²Isabelle Boutron, MD, PhD: Assistance Publique–Hôpitaux de Paris, Université Paris VII, Groupe Hospitalier Bichat-Claude Bernard, Paris, France.

Address correspondence to François Rannou, MD, PhD, Service de rééducation, Hôpital Cochin, 27 rue du faubourg Saint-Jacques, 75014 Paris, France. E-mail: francois.rannou@cch.aphp.fr.

Submitted for publication August 30, 2006; accepted in revised form March 6, 2007.

Modic 0 (absence of vertebral end-plate signal changes) lesions has been found in the vertebral end plates of patients with chronic low back pain (8). These results suggest that end-plate 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 (hsCRP) 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, hsCRP level could be increased in a 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 suspected to influence hsCRP level. In acute lumbosciatica due to herniated disc, hsCRP is up-regulated and seems to be correlated with pain intensity (10–13). However, these studies failed to demonstrate an increase in hsCRP level in chronic low back pain, but vertebral end-plate marrow signal change was not taken into account (10,12). Here, we describe the results of a pilot study that aimed to assess serum hsCRP level in patients with chronic low back pain in relation to vertebral end-plate 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 >3 months, with no response to 3-month conservative treatment and severe interference with lifestyle; age ≥ 18 years; and 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/m²; diabetes; and presence of sciatica.

Lumbar MRI evaluation. MR images in patients were evaluated independently by a panel of 2 spine specialists (MR and FR) and a radiologist (HG) with at least 10 years of experience in spine MRI who were blinded to the clinical characteristics and hsCRP level. The reviewers graded the end-plate marrow signal changes of the 5 lumbar discs. The signal changes in end-plate marrow indicated >50% edema in the Modic I group and >50% fatty deposits in the Modic II group; 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 1 lumbar level, the patient was not selected.

High-sensitivity CRP. Serum samples were analyzed by one researcher (DB) who was blinded to the MRI evaluation and clinical characteristics of each patient (11). To

decrease the risk of interference with the biologic analysis, the serum sample was obtained with the patient abstaining from smoking, alcohol consumption, and steroid use during the previous 24 hours. The hsCRP concentration was measured by immunoturbidimetric CRP latex Tina quant assay on a Modular P instrument (Roche Diagnostics, Mannheim, Germany). 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/liter.

Clinical characteristics. Two authors (WO and BL), who were blinded to the MRI evaluation and the hsCRP 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 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 the 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, lumbar flexibility (modified Schober 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 analyzed using Systat 9 software (Systat, Chicago, IL). Qualitative data were described with percentages, and quantitative data with mean \pm SD and range. We compared the biologic and clinical parameters between the 3 groups (Modic 0, I, and II). Quantitative variables were compared by nonparametric Kruskal-Wallis test. Qualitative variables were compared by Fisher's exact test. Bonferroni adjustment was used for the multiple comparisons (17 comparisons); a *P* value less than 0.003 was considered statistically significant. When appropriate, we compared groups with Wilcoxon's signed rank test 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. Therefore, 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 signal changes and 5 had 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.

Table 1. Patients with chronic low back pain according to vertebral end-plate marrow Modic signal change on magnetic resonance imaging*

	All patients (n = 36)	Modic 0 (n = 12)	Modic I (n = 12)	Modic II (n = 12)	P†
Age, years	52 ± 14	53 ± 17	50 ± 13	54 ± 14	0.795
Female sex, no. (%)	12 (33)	4 (33)	4 (33)	4 (33)	1
Pain (100-mm VAS)	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, months	41 ± 35	14 ± 10	52 ± 32	54 ± 41	0.007
Presence of morning stiffness, no. (%)	25 (69)	5 (42)	11 (92)	9 (75)	0.028
Duration of morning stiffness, minutes	27 ± 37	9 ± 15	49 ± 52	21 ± 23	0.009
Worst painful moment during late night and morning, no. (%)	17 (47)	1 (8)	12 (100)	3 (25)	0.001‡
Reproduction of the pain during the Valsalva maneuver, no. (%)	15 (42)	1 (8)	9 (75)	5 (42)	0.005

* Values are the mean ± SD unless otherwise indicated. VAS = visual analog scale.

† Nonparametric Kruskal-Wallis test or Fisher's exact test with Bonferroni adjustments for multiple comparisons; $P < 0.003$.

‡ Difference is significant.

Description of the patients. The study population according to vertebral end-plate marrow Modic signal change is described in Table 1. The 3 groups were comparable in age, sex, pain, level of disability, and handicap. Duration of symptoms, duration of morning stiffness, and reproduction of pain during the Valsalva maneuver tended to differ among the groups, but not significantly ($P = 0.007$, 0.009 , and 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 the Modic 0 group and $P = 0.002$ compared with the Modic II group).

Serum hsCRP value. Serum hsCRP level was significantly different among the 3 Modic groups ($P = 0.002$) (Figure 1) and was especially high for the Modic I group ($P = 0.002$ compared with Modic 0 and II groups): mean ± SD 1.33 ± 0.77 mg/liter in the Modic 0 group, 4.64 ± 3.09 mg/liter in the Modic I group, and 1.75 ± 1.30 mg/liter in the Modic II group.

Physical characteristics. The 3 groups were comparable in lumbar flexibility (modified Schober 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

This is the first report to describe clear differences in hsCRP level in a pilot study of patients with chronic low back pain and Modic 0, I, and II class vertebral end-plate 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 hsCRP level was significantly higher in the Modic I group than in the Modic 0 and II groups. Taken together, these results suggest that pain during the late night and morning

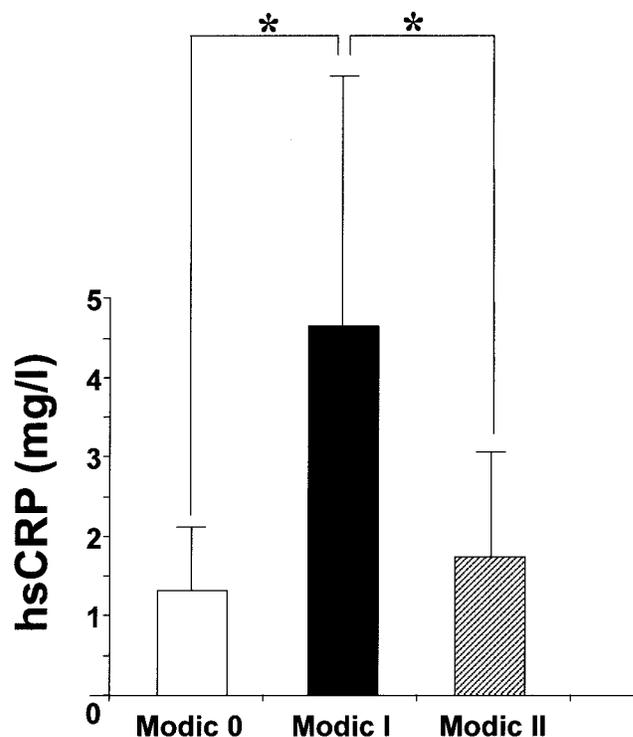


Figure 1. Serum level of high-sensitivity C-reactive protein (hsCRP) in patients with chronic low back pain according to vertebral end-plate marrow Modic signal change on magnetic resonance imaging. $P = 0.002$ by nonparametric Kruskal-Wallis test. * $P < 0.003$ by Wilcoxon's signed rank test. Bonferroni adjustment made for multiple comparisons; $P < 0.003$.

Table 2. Physical characteristics of patients with chronic low back pain, according to vertebral end-plate marrow Modic signal change on magnetic resonance imaging*

	All patients (n = 36)	Modic 0 (n = 12)	Modic I (n = 12)	Modic II (n = 12)	P†
Modified Schober 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, no. (%)	18 (50)	5 (42)	7 (58)	6 (50)	0.723
Exacerbation of pain in hyperextension, no. (%)	21 (58)	3 (25)	10 (83)	8 (67)	0.013
Exacerbation of pain in lateral bending, no. (%)	17 (47)	4 (33)	8 (67)	5 (42)	0.244
Lasègue's sign, no. (%)	5 (14)	0 (0)	3 (25)	2 (17)	0.206

* Values are the mean ± SD unless otherwise indicated.
† Nonparametric Kruskal-Wallis test or Fisher's exact test, with Bonferroni adjustments for multiple comparisons; *P* < 0.003.

and high hsCRP 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 hsCRP concentration in patients with chronic low back pain (10,12). In the first study, the authors found a mean hsCRP of ~1.3 mg/liter (10). In the second study, Gebhardt et al found no difference in hsCRP level between patients with chronic low back pain and asymptomatic subjects (1.30 mg/liter and 1.26 mg/liter, 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 et al (3), involving 474 patients with chronic low back pain or sciatica, the authors found 20 patients (4%) with Modic I lesions and 77 patients (16%) with Modic II lesions. Toyone et al, in a retrospective study of 500 patients with chronic low back pain, found 37 patients (7.40%) with Modic I lesions and 37 patients (7.40%) with Modic II lesions (4). Therefore, 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 end-plate signal changes, which explains the absence of elevated hsCRP level in the 2 studies on serum hsCRP concentration in patients with chronic low back pain. Another explanation for this discrepancy could be the absence of control for confounder factors. However, in our study, we excluded overweight patients (>30 kg/m²), and obesity (>28 kg/m² and <30 kg/m²), smoking, alcohol consumption, nonsteroidal antiinflammatory drug intake, and physical activity did not influence hsCRP level (data not shown).

The increased hsCRP level observed in the Modic I group must be considered a strong association only. The origin of this increase can only be speculated. 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 hsCRP 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 end-plate 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 end-plate signal changes, but the results need to be confirmed in a randomized controlled trial (17,18). In addition, better results of lumbar arthrodesis for such patients with degenerative disc disease have been observed for those with Modic I signal changes, and lumbar arthrodesis 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 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 discs and osteoarthritis of facet joints. Therefore, our results could be a first step in physicians' decisions concerning 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 relationship between hsCRP level and clinical parameters and to 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 hsCRP level in hip and knee osteoarthritis, the level of microinflammation was less important. For example, in a study of 770 patients with advanced osteoarthritis, the mean hsCRP level was 2.7 mg/liter (21). However, in a study of 67 patients with erosive osteoarthritis of the hand, the me-

dian hsCRP level was 4.7 mg/liter (22). Therefore, 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 symptoms related to currently activated hand erosive osteoarthritis. Lastly, the existence of many known and unknown confounding factors could affect hsCRP level evaluation for the individual. For this concern, combining hsCRP 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, hsCRP level is increased in patients with chronic low back pain and Modic I lesions, which supports a local inflammation phenomenon occurring at the vertebral end-plate level. This result could be of interest to prescribe MRI and indicates for the first time, in a subgroup of patients with chronic low back pain, a specific local treatment to control this local inflammation.

AUTHOR CONTRIBUTIONS

Dr. Rannou had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Rannou, Boutron, Lovisi, Guerini, Poiraudou, Revel.

Acquisition of data. Rannou, Ouanes, Lovisi, Macé, Borderie, Guerini.

Analysis and interpretation of data. Rannou, Ouanes, Boutron, Fayad, Revel.

Manuscript preparation. Rannou, Ouanes, Fayad, Borderie, Revel.

Statistical analysis. Rannou, Ouanes, Boutron, Poiraudou.

REFERENCES

- Jensen MC, Brant-Zawadzki MN, Obuchowski N, Modic MT, Malkasian D, Ross JS. Magnetic resonance imaging of the lumbar spine in people without back pain. *N Engl J Med* 1994;331:69–73.
- De Roos A, Kressel H, Spritzer C, Dalinka M. MR imaging of marrow changes adjacent to end plates in degenerative lumbar disk disease. *ARJ Am J Roentgenol* 1987;149:531–4.
- Modic MT, Steinberg PM, Ross JS, Masaryk TJ, Carter JR. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. *Radiology* 1988;166:193–9.
- Toyone T, Takahashi K, Kitahara H, Yamagata M, Murakami M, Moriya H. Vertebral bone-marrow changes in degenerative lumbar disc disease: an MRI study of 74 patients with low back pain. *J Bone Joint Surg Br* 1994;76:757–64.
- Kjaer P, Leboeuf-Yde C, Korsholm L, Sorensen JS, Bendix T. Magnetic resonance imaging and low back pain in adults: a diagnostic imaging study of 40-year-old men and women. *Spine* 2005;30:1173–80.
- Weishaupt D, Zanetti M, Hodler J, Boos N. MR imaging of the lumbar spine: prevalence of intervertebral disk extrusion and sequestration, nerve root compression, end plate abnormalities, and osteoarthritis of the facet joints in asymptomatic volunteers. *Radiology* 1998;209:661–6.
- Burke JG, Watson RW, McCormack D, Dowling FE, Walsh MG, Fitzpatrick JM. Intervertebral discs which cause low back pain secrete high levels of proinflammatory mediators. *J Bone Joint Surg Br* 2002;84:196–201.
- Ohtori S, Inoue G, Ito T, Koshi T, Ozawa T, Doya H, et al. Tumor necrosis factor-immunoreactive cells and PGP 9.5-immunoreactive nerve fibers in vertebral endplates of patients with discogenic low back pain and modic type 1 or type 2 changes on MRI. *Spine* 2006;31:1026–31.
- Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, et al. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor- α , in vivo. *J Clin Endocrinol Metab* 1997;82:4196–200.
- Sturmer T, Raum E, Buchner M, Gebhardt K, Schiltenswolf M, Richter W, et al. Pain and high sensitivity C-reactive protein in patients with chronic low back pain and acute sciatic pain. *Ann Rheum Dis* 2005;64:921–5.
- Le Gars L, Borderie D, Kaplan G, Berenbaum F. Systemic inflammatory response with plasma C-reactive protein elevation in disk-related lumbosciatic syndrome. *Joint Bone Spine* 2000;67:452–5.
- Gebhardt K, Brenner H, Sturmer T, Buchner M. The course of high-sensitive C-reactive protein in correlation with pain and clinical function in patients with acute lumbosciatic pain and chronic low back pain: a 6 months prospective longitudinal study. *Eur J Pain* 2006;10:711–9. E-pub ahead of print 5 Jan 2006.
- Sugimori K, Kawaguchi Y, Morita M, Kitajima I, Kimura T. High-sensitivity analysis of serum C-reactive protein in young patients with lumbar disc herniation. *J Bone Joint Surg Br* 2003;85:1151–4.
- Poiraudou S, Foltz V, Drape JL, Fermanian J, Lefevre-Colau MM, Mayoux-Benhamou MA, et al. Value of the bell test and the hyperextension test for diagnosis in sciatica associated with disc herniation: comparison with Lasegue's sign and the crossed Lasegue's sign. *Rheumatology (Oxford)* 2001;40:460–6.
- Castell JV, Gomez-Lechon MJ, David M, Fabra R, Trullenque R, Heinrich PC. Acute-phase response of human hepatocytes: regulation of acute-phase protein synthesis by interleukin-6. *Hepatology* 1990;12:1179–86.
- Hansson T, Roos B. Microcalluses of the trabeculae in lumbar vertebrae and their relation to the bone mineral content. *Spine* 1981;6:375–80.
- Buttermann GR. The effect of spinal steroid injections for degenerative disc disease. *Spine J* 2004;4:495–505.
- Benyahya R, Lefevre-Colau MM, Fayad F, Rannou F, Demaille-Wlodyka S, Mayoux-Benhamou MA, et al. Intradiscal injection of acetate of prednisolone in severe low back pain: complications and patients' assessment of effectiveness. *Ann Readapt Med Phys* 2004;47:621–6. In French.
- Vital JM, Gille O, Pointillart V, Pedram M, Bacon P, Razanabola F, et al. Course of Modic 1 six months after lumbar posterior osteosynthesis. *Spine* 2003;28:715–21.
- Chataigner H, Onimus M, Polette A. Surgery for degenerative lumbar disc disease: should the black disc be grafted? *Rev Chir Orthop Reparatrice Appar Mot* 1998;84:583–9. In French.
- Sturmer T, Brenner H, Koenig W, Gunther KP. Severity and extent of osteoarthritis and low grade systemic inflammation as assessed by high sensitivity C-reactive protein. *Ann Rheum Dis* 2004;63:200–5.
- Punzi L, Ramonda R, Oliviero F, Sfriso P, Mussap M, Plebani M, et al. Value of C-reactive protein in the assessment of erosive osteoarthritis of the hand. *Ann Rheum Dis* 2005;64:955–7.