Associations between Acute Phase Reactant Levels and Disease Activity Score (DAS28) in Patients with Rheumatoid Arthritis

Kadir Yildirim, Saliha Karatay, Meltem Alkan Melikoglu, Gurhan Gureser, Mahir Ugur, Kazim Senel
Department of Physical Medicine and Rehabilitation, Atatürk University Medical School, Erzurum, Turkey

Abstract. Serum levels of acute phase reactants (APR) were measured in patients with rheumatoid arthritis (RA) and the correlations of these parameters with the disease activity score (DAS28) were investigated. The study included 47 patients with RA and 50 healthy controls. Laboratory tests included erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), haptoglobin (Hp), ferritin, and plasma fibrinogen. Disease activity was assessed using the DAS28 score. The means (± SD) of ESR, CRP, Hp, ferritin, and fibrinogen levels were respectively 36.0 ± 23.5 mm/hr, 2.4 ± 1.9 mg/dl, 121.3 ± 34.2 mg/dl, 67.7 ± 36.2 ng/ml, and 371.2 ± 96.0 mg/dl in the patients with RA, vs 16.4 ± 11.3 mm/hr, 0.4 ± 0.3 mg/dl, 104.0 ± 35.3 mg/dl, 50.9 ± 23 ng/ml, and 332.2 ± 58.5 mg/dl in the controls. All of the APR levels were significantly higher in patients vs controls (p <0.001 for ESR and CRP; p <0.05 for Hp, ferritin, and fibrinogen). There were significant correlations between serum APR levels and disease activity based on DAS28 score in RA patients (for CRP, r = 0.650, p <0.01; for Hp, r = 0.331, p <0.05; for ferritin, r = 0.299, p <0.05; for fibrinogen, r = 0.373, p <0.01). This study indicates that serum CRP, among the various APR tests, is the most useful biochemical marker for evaluating the disease activity of patients with RA. (received 20 August 2004; accepted 25 August 2004).

Keywords: rheumatoid arthritis, DAS28 score, acute phase reactants, C-reactive protein

Introduction

Rheumatoid arthritis (RA) is a chronic systemic disease, usually manifesting as inflammation of multiple joints. It is characterized by a number of extra-articular manifestations, including rheumatoid nodules, vasculitis, heart or lung disease, anemia, and peripheral neuropathy. Although the cause of RA is unknown, it is generally considered an autoimmune disease [1,2]. At present, no single test of disease activity in RA is effective because RA may cause various kinds of symptoms and signs.

The acute-phase response to tissue injury and inflammation is accompanied by a dramatic increase in hepatic synthesis of plasma proteins known as acute-phase reactants (APR). Therefore, characterization of APR responses in RA is essential to gain insights into the activity of this disease and to assess the degree of inflammation [3,4]. The important APR include serum C-reactive protein (CRP), amyloid A (SAA), haptoglobin (Hp), ferritin, and plasma fibrinogen.

CRP is one of the best indicators of the acute phase response to inflammation. This serum protein is synthesized by hepatocytes and is classified as an acute-phase protein on the basis of its increased serum concentration during infection and inflammation [5]. Hp is used for the detection of in vivo hemolysis and inflammation. The primary function of Hp is the irreversible binding of free oxyhemoglobin in serum. This complex is then removed within minutes by the reticuloendothelial system. Elevated values are present in chronic and acute inflammation and in neoplastic diseases [6].

Ferritin is a serum predictor of iron storage. High levels of serum ferritin have been associated with malignant disease and tissue damage [7]. Fibrinogen is a glucoprotein with a molecular weight of 340 kDa. Fibrinogen, while of primary
importance as a coagulation protein, is also an APR and its plasma concentration is increased in diseases involving tissue damage or inflammation [8].

The DAS28 score is used extensively to evaluate disease activity in patients with rheumatoid arthritis (RA). DAS28 is a composite index that provides clinicians with a simple and objective assessment of the patient’s level of disease activity and progression [9]. The aim of this study was to investigate the correlations between DAS28 score and the various APR levels in RA patients and to determine which of the acute phase reactants shows the closest relationship to the disease activity.

Material and Methods

This study involved patients with RA diagnosed according to the 1987 revised criteria of the American College of Rheumatology (formerly, the American Rheumatism Association) [10]. Clinical assessments included demographic data: age, sex, weight, and duration of disease. In the patient group (n = 47), there were 40 women and 7 men (mean age 45.7 ± 9.5 yr; range 24-66). The mean disease duration was 10.8 ± 4.4 yr (range 3-24). In the control group (n = 50), there were 45 women and 5 men (mean age 44.9 ± 8.8 yr, range, 27-63). The controls were healthy hospital personnel without any history of inflammatory diseases. No patient was receiving glucocorticoids or immunosuppressant drugs, such as cyclosporine or levamisole. At the time of the study, 27 patients were treated with a combination of methotrexate and sulfasalazine; 20 patients were receiving only methotrexate. All patients were being treated with nonsteroidal anti-inflammatory drugs. The patients were allowed to continue their drug regimens. Patients were excluded if they had signs or symptoms of severe renal, hepatic, endocrine (Paget’s disease, hyper-thyroidism, hyperparathyroidism), hematological, lymphoproliferative, and other malignant diseases. The exclusion criteria for the control group were the same as for the RA group.

The DAS28 score is the numerical sum of 4 outcome parameters: tender and swollen joint count (based on a 28-joint assessment), patient’s global assessment, visual analogue scale, and ESR value. The DAS28 score (DAS28/ESR) was calculated according to Prevoo et al [9].

Blood ESR was determined by the Westergren method and serum CRP by nephelometry using the Array Protein System (Beckman Coulter, Inc). Serum Hp level was assayed with a commercial kit by a nephelometric method (Beckman Coulter Image). Serum ferritin level was measured by an automatic analyzer system (E170 Modular System, Roche Diagnostics). Plasma fibrinogen level was determined with a commercial kit using an autoanalyzer (Dade-Behring Corp).

Statistical analyses of data were performed with the SPSS program. Laboratory results were given as mean ± SD. Differences between groups were evaluated by the Mann-Whitney U test. Correlation between variables was assessed by Spearman’s rank correlation coefficient. P values <0.05 were regarded as significant.

Results

Demographic data for the 47 RA patients and 50 control subjects are listed in Table 1. There were no significant differences between the 2 groups with respect to parameters such as age, gender, or body weight (p >0.05).

Laboratory findings in the RA patients and healthy controls are listed in Table 2. The mean levels of ESR, CRP, Hp, ferritin, and fibrinogen in RA patients were all significantly higher than in healthy controls (for ESR and CRP, p <0.001; for Hp, ferritin, and fibrinogen, p <0.05).

Strongly positive correlation was noted between the DAS28 score and serum CRP level (r = 0.650, p <0.001) in RA patients (Fig. 1). There were also significant correlations between the DAS28 score and serum Hp level (r = 0.383, p <0.01).
and other APR levels, such as Hp, ferritin, and fibrinogen (r = 0.331, p <0.05; r = 0.299, p <0.05; and r = 0.373, p <0.01, respectively).

**Discussion**

RA is a chronic disease, but the disease activity is a fluctuating process, showing great variation even during the course of one day as well as longer time periods. Elevated plasma levels of APR develop during the acute phase response following an inflammatory stimulus [11].

We performed this study to examine the correlations between several APR levels (eg, CRP, Hp, ferritin, fibrinogen) and the DAS28 score, which serves as an index of disease activity in RA patients. We observed that CRP, Hp, ferritin, and fibrinogen levels were all elevated in the RA patients, compared with control subjects. The APR levels were all significantly correlated with the DAS28 score. The strongest correlation was between serum CRP and DAS28 score. The correlation between DAS28 score and plasma fibrinogen levels was stronger than the correlations between DAS28 score and serum Hp or ferritin levels.

Elevated serum CRP, amyloid A protein (SAA), Hp, ferritin, and plasma fibrinogen levels have all been associated with inflammatory and infectious diseases [12]. Several studies have reported strong associations between these markers of the acute-phase response and disease activity in patients with inflammatory diseases [13-16]. CRP belongs to the \( \beta \)-globulin family of plasma proteins; although its physiological functions are unknown, serum levels of CRP are elevated in a wide variety of acute and chronic inflammatory conditions [17].

CRP levels are not directly affected by the commonly used anti-inflammatory drugs, including steroids; therefore change in CRP probably reflects a change in the underlying disease [17,18]. In the present study, among the various APR tests, serum CRP level was most closely correlated with the activity of the disease in RA patients. Previous investigators have also reported positive correlation between CRP levels and disease activity in RA patients [13,19]. The results of this study confirm our previous findings in patients with ankylosing spondylitis [14].

Serum Hp levels are increased in conditions with extensive tissue damage, inflammation, or necrosis. Hp may have an immunosuppressive activity [6,20]. In the present study, serum Hp and ferritin levels in patients with RA were higher than in the controls and showed weak correlations with the DAS28 score.

Serum ferritin level is a marker of body iron stores and may be an indicator of iron deficiency in patients with chronic inflammation such as RA [21]. The present findings agree with a previous report of high serum ferritin levels in RA patients compared to healthy controls [22].

Increased plasma fibrinogen levels occur with inflammation, during pregnancy, and in women taking oral contraceptives, as well as in RA patients.

### Table 2. Serum or plasma levels of some acute-phase reactants in RA patients and healthy controls and the DAS28/EAS score in RA patients (mean ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RA group (n = 47)</th>
<th>Controls (n = 50)</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>ESR (mm/h)</td>
<td>56.0 ± 23.5</td>
<td>16.4±11.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>2.4 ± 1.9</td>
<td>0.4±0.3</td>
<td>&lt;0.001</td>
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<tr>
<td>Hp (mg/dl)</td>
<td>121.3 ± 34.3</td>
<td>104.0±35.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>67.7 ± 36.2</td>
<td>50.9 ± 23.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>371.2 ± 96.0</td>
<td>332.2±58.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>DAS28/EAS score</td>
<td>5.2 ± 1.3</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; Hp: haptoglobin; DAS28/EAS: disease activity score [9].
None of our RA patients were pregnant or used oral contraceptives, so their elevated plasma fibrinogen levels are probably attributable to RA.

In conclusion, of the several APR markers that were examined in this study, serum CRP level was the best biochemical indicator of disease activity in RA patients.

References