The use of inflammatory laboratory tests in rheumatology

Nilton Salles Rosa Neto¹, Jozélio Freire de Carvalho²

ABSTRACT

Inflammation is the hallmark of rheumatic diseases. Tissue injury response promotes several modifications, which result in elimination of the offending agent, limitation of tissue damage, and restoration of affected structures. Such modifications depend on the increase or decrease of the serum concentration of certain proteins known as inflammatory biomarkers. Laboratory analysis of these markers assists in monitoring disease activity and treatment response. Rheumatologists have available methods that evaluate inflammatory reaction such as C-reactive protein, erythrocyte sedimentation rate, and protein electrophoresis, among others. In this paper, we review some of those biomarkers and their use in rheumatic diseases.

Keywords: acute-phase proteins, C-reactive protein, erythrocyte sedimentation rate, rheumatic diseases, inflammatory response.

INTRODUCTION

The acute-phase response is a pathophysiological defense mechanism associated with inflammatory states that, despite the already established name, occurs in both acute and chronic inflammation. It is characterized by the increase or decrease in serum concentration of certain proteins in consequence of a stimulus that causes tissue damage.¹⁻³ Currently, the term inflammatory biomarker is preferred when referring to proteins involved in this response.

Analysis of inflammation biomarkers is used in rheumatologic diseases to monitor disease activity, correlated with other clinical and laboratory data, and to differentiate between active disease and the presence of infection. This article reviews the use of inflammatory activity tests currently available in health care.

HISTORY

In 1930, investigators discovered a protein that reacted with the C-polysaccharide capsule of the S. pneumoniae from the blood of patients during the acute-phase of pneumococcal pneumonia. This protein was named C-reactive protein (CRP). Since then, studies on changes of plasma proteins in serum of patients acutely ill due to infections are performed. The proteins found in this situation were called acute-phase proteins; and the inflammatory reaction, or the organism’s response to tissue injury, called acute-phase reaction.⁴

Subsequently, the presence of these proteins was verified after other events, such as trauma, ischemia, neoplasm, and hypersensitivity reaction. Their concentration were also altered in chronic inflammatory states.¹²

ACUTE-PHASE RESPONSE

The acute-phase response is characterized by the alteration of serum concentration of certain proteins after tissue injury, some respond with increase (positive biomarkers) and others with decrease (negative biomarkers) of their concentration. These proteins have pro- and anti-inflammatory functions and can stimulate or inhibit their own production. Despite the importance of this study, in clinical practice, only some of these proteins are used as markers, either
because of the availability of the method, or the cost of its results. Tables 1 and 2 present some of the acute-phase proteins, divided according to their original biological function.

Behavioral changes and physiological, biochemical, and nutritional alterations add up to complete the acute-phase response.2,3

Neuroendocrine Changes
One of the major characteristics of this phase is the presence of fever, a response that promotes an optimal enzyme function and promotes the stabilization of cell membranes. Indisposition and drowsiness is present, which reduce the body’s energy consumption.

Modulating the inflammatory response, there is increased secretion of corticotropin releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol, antiadrenergic hormone (ADH) and catecholamines; and decrease of insulin-like growth factor (IGF-1).

Hematopoietic Changes
As a result of inflammation, leukocytosis and thrombocytosis can be found and, in prolonged cases, also anemia of chronic disease.

Metabolic Changes
These include muscle loss and negative nitrogen balance, resulting in chronic cases; there is growth limitation in children and cachexia in adults. There is a decrease of gluconeogenesis and acceleration of osteoporosis. Increased liver lipogenesis and lipolysis in adipose tissue are found, as well as a decrease in muscular and adipose lipoprotein lipases activity, with the objective, in some cases of infection, to increase the concentration of lipoproteins, promoting a larger connection to lipopolysaccharides (LPS), resulting in less toxicity to the body.

Hepatic Changes
The liver participates in the production and liberation of innumerable proteins related to the inflammatory response. Physiologically, there is an increase in metallothionein, nitric oxide synthase, heme oxygenase, superoxide dismutase, tissue inhibitor of metalloproteinase-1, and decrease in phosphoenolpyruvate carboxykinase activity.

Changes in Other Components of the Plasma
As a control of reactions in progress, there is consumption of zinc, iron and copper, and increased serum retinol and antioxidants, such as glutathione.

Table 1
Positive inflammatory biomarkers.

<table>
<thead>
<tr>
<th>Coagulation and fibrinolytic system</th>
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<tbody>
<tr>
<td>Fibrinogen</td>
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<tr>
<td>Plasminogen</td>
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<tr>
<td>Tissue plasminogen activator</td>
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<td>Urokinase</td>
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<td>Protein S</td>
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<td>Vitronectin</td>
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<td>Plasminogen-activator inhibitor 1</td>
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<th>Complement system</th>
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<tr>
<td>C3; C4; C9</td>
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<tr>
<td>Factor B</td>
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<td>C1 inhibitor (C1 INH)</td>
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<td>C4b-binding protein (C4b)</td>
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<td>Mannose-binding lectin (MBL)</td>
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<th>Transport proteins</th>
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<tr>
<td>Ceruloplasmin</td>
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<td>Haptoglobin</td>
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<td>Hemopexin</td>
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<th>Participants of inflammatory responses</th>
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<tr>
<td>Secreted phospholipase A2 (sPLA2-IIA)</td>
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<tr>
<td>Lipopolysaccharide-binding protein</td>
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<tr>
<td>Interleukin-1-receptor antagonist (IL-1 RA)</td>
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<td>Granulocyte colony-stimulating factor (G-CSF)</td>
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<th>Antiproteases</th>
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<tr>
<td>α1-Protease inhibitor</td>
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<tr>
<td>α1-Antichymotrypsin</td>
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<td>Pancreatic secretory trypsin inhibitor</td>
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<td>Inter-α-trypsin inhibitors</td>
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<th>Others</th>
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<tr>
<td>C-reactive protein</td>
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<tr>
<td>Serum amyloid A</td>
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<tr>
<td>α1-acid glycoprotein (AGP)</td>
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<tr>
<td>Fibronectin</td>
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<td>Ferritin</td>
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<tr>
<td>Angiotensinogen</td>
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<td>Retinol binding protein</td>
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CLASSIFICATION

The biomarkers of inflammation are divided into four groups: 1

Host defense proteins - they participate in the recognition
and elimination of pathogens: C-reactive protein, mannose
binding lectin, lipopolysaccharide-binding protein, complement
protein, fibrinogen;

Serum protease inhibitors - they act to limit tissue damage,
neutralizing proteolytic enzymes and oxygen metabolites:
α1-antiproteinas, α1-anti-chymotrypsin, α2-antiplasmin, C1
inhibitor;

Transport protein with antioxidant activity - responsible for
containing the inflammatory reaction and restoring the original
structure injured: ceruloplasmin, hemopexin, haptoglobin;

Others - serum amyloid A (SAA) protein, IL-1 receptor
antagonist, α1-acid glycoprotein, group IIA secretory
phospholipase A2 (sPLA2-IIA).

There is significant difference in terms of kinetics,
magnitude and response duration among the inflammatory
biomarkers. The CRP and the SAA can be detected after four
hours of injury, and they have peak concentration after 24-72
hours, which can reach a thousand times the normal value.3
Fibrinogen has peak concentration 7 to 10 days after injury,
and rises 2 to 3 times the normal (Figure 1).

Only some of these markers are available for rheumatologist’s
routine practice, and this paper addresses the origin and
biological functions of the proteins involved, and the methods
to determine their activities. In the following text the uses of
these markers in different rheumatic diseases are found in
greater detail.

C-REACTIVE PROTEIN

This is the most investigated biomarker, which promotes
the interaction between humeral and cellular immunity. It
is produced by the liver and classified as a pentraxin – a
pentamer with a binding site for phosphatidylcholine (calcium
ion dependent) and other sites in the opposite side that bind
to the complement C1q system component and to the Fe
immunoglobulin (Fcγ portion).1,3

C-reactive protein (CRP) binds to pathogens and
damaged/apoptotic cells (phosphatidylcholine), causing their
elimination by activating the complement system and the
phagocytes (C1q and Fcγ). Because of the binding and cellular
attraction function, it can be considered as an opsonin.5,6 It
also acts regulating the extension and the intensity of the
inflammatory reaction.

Although its function is similar to that of an antibody and
it participates in the innate immunity, there is no description
of CRP disabled states, which in principle is incompatible
with life.

Complement activation occurs through the classic pathway,
by the positioning of C3 and C4 fragments on CRP and
ligand, formation of C3 convertase by cleaving C3 into C3a,
an anaphilatoxin that induces the realizt of histamine from
basophiles and mast cells, and C3b, that acts as an opsonin,
attracting phagocytes (macrophages) to the inflammation
site. The activation does not convert C5; therefore, there is no
amplification of the pro-inflammatory effects or formation of
membrane attack complex (MAC) directly by the CRP. CRP
and the complement classic pathway system act together,
promoting clearance of apoptotic cells without causing cell

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<th>Table 2</th>
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<tr>
<td>Negative inflammatory biomarkers</td>
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<tr>
<td><strong>Albumin</strong></td>
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<td><strong>Transferrin</strong></td>
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<tr>
<td><strong>Transthyretin</strong></td>
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<td>α2-HS glycoprotein</td>
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<td>Alpha-fetoprotein (AFP)</td>
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<tr>
<td>Thyroxine-binding globulin</td>
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<tr>
<td>Insulin-like growth factor</td>
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<tr>
<td>Factor XII</td>
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lysis, minimizing the liberation of mediators that would increase the inflammatory reaction. It is known that, in rheumatoid arthritis (RA), the complement system is activated by the CRP, especially in those with increased disease activity, although the participation of the complement activation in the maintenance of the inflammatory reaction and joint destruction is not clear.

The interaction between CRP and Fc portion of immunoglobulins is made in phagocytes through FcγRI (CD64) and FcγRIIa (CD32) receptors, leading to the induction of phagocytosis and secretion of proinflammatory cytokines, such as interleukin (IL)-1 and tumor necrosis factor (TNF)-α. In neutrophils, the interaction promotes down-regulation of the inflammation. There is inhibition of the chemotactic response and cleavage of L-selectin, reducing the margination of leukocytes, and endocytosis of IL-6 receptors.

Therefore, it is established that CRP has pro- and anti-inflammatory function.

The determination of CRP is more sensitive, evaluating a quick response by a direct measurement. It reflects the extension of the inflammatory process or clinical activity, especially in bacterial infections (and not viral), hypersensitivity reactions, ischemia and tissue necrosis. Slightly elevated values of CRP can be found in obesity, smoking, diabetes, uremia, hypertension, physical inactivity, use of oral contraceptives, sleep disorders, among other situations. It is also a marker of artherosclerosis, used as a predictor of myocardial infarction, sudden death or stroke, and should have a role in the pathogenesis of atherogenesis.

The methodology most used is the immunonephelometric measurement, which allows the release of quantitative results, facilitating the clinical interpretation and allowing laboratorial follow up of each case.

CRP is also important as a marker of endothelial activation and inducer of vascular injury related to inflammation, especially in atheroma plaques. It can be used as a predictor of coronaropathy (angina and myocardial infarction), by accelerating the process of atherosclerosis. The designation of sensitive or oversensitive PCR concerns the methods that can detect lower values (lower then the 97,5% percentile) than the limit of usual methods (lower than the 90%); i.e., more sensitive tests, which have identified inflammatory changes in apparently healthy patients or with known risk factors, and allow to access the cardiovascular risk.

In patients with RA and Systemic Lupus Erythematous (SLE), the persistent inflammation, demonstrated by the sequential dosages of CRP, implies early cardiovascular morbidity and mortality.

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**FIBRINOGEN**

Fibrinogen is a protein abundantly found in plasma that has a fundamental role in hemostasis. It has a probable role in tissue repair and healing in the inflammatory reactions.

Its molecule is composed of two subunits linked by a disulfide bridge. The cleavage by thrombin results in two fibrinopeptides, and the resulting molecule is polymerized remaining stable through the factor XIII and inter-platelet bridges (binding of fibrinogen to glycoprotein IIb/IIIa) to form fibrin.

It interacts with endothelium due to receptors similar to glycoprotein IIb/IIIa, and interferes in the adhesion, motility and organization of the cytoskeleton. Once formed, fibrin stimulates adhesion, dispersion and proliferation of endothelial cells.

Erythrocyte sedimentation rate

The erythrocyte sedimentation rate (ESR) reflects the increase of acute-phase proteins plasmatic concentration, especially of fibrinogen. Therefore, it can determine a slow response by an indirect measurement. The sedimentation depends on hemoglobin aggregation. Due to the negative charges, they tend to repel, but the presence of other positively charged molecules can neutralize the repulsion and allow the formation of rouleaux (erythrocyte aggregation around its own axis), which, being heavier, tends to deposit on the bottom. The more macromolecules, the greater the aggregation and deposit of red blood cells, and the greater the distance between the aggregation and the top of the column, which means higher value of ESR in the time of analysis. In the plasmatic proteins, fibrinogen has the best aggregation effect, followed by globulins and albumin.

There are several factors that can interfere with the interpretation of the ESR value. Among the analytical interferences, there is the dilution error, slope of the tube, evaluation delay after collection, and room temperature. The use of medicine and oral contraceptives can also interfere. There are also the physiological differences, such as lower ESR in women and higher in the elderly and pregnant women.

Non inflammatory pathological states can also alter ESR, such as: low red blood count, macrocytosis and hypercholesterolemia tend to increase the velocity, and hypofibrinogenemia, hypogammaglobulinemia, polycythemia, microcytosis, hemolytic anemia and hemoglobinopathies tend to decrease the velocity.

Westergren ESR testing is recommended by the International Committee for Standardization in Hematology (ICSH).
SERUM AMYLOID A PROTEIN

The SAA protein is also a pentraxin, like CRP, and has three isoforms, but only two of them are acute-phase proteins (acute SAA) and the other one is a constitutive serum amyloid A protein. The major productive site is the liver.

It participates in the cholesterol metabolism by binding to a high density lipoprotein (HDL-3). During the inflammation, it takes the position of the apolipoprotein A-1, forming a link, which can be pro-atherogenic. It also has a defense role in the chemotaxis of neutrophils, monocytes and lymphocytes-T; catalysis of the secretory phospholipase A2 activity, which facilitates the action of CRP; and it has a tissue repair role, inducing the formation of metalloproteinase of matrix 2 and 3, collagenases and stromelysin. Like the CRP, it also acts in the opsonization of apoptotic cells, binding to the phosphatidylethanolamine, activating the complement system classic pathway. The binding sites of the pentraxins include lipids and microbial polysaccharide matrix component, and nuclear antigens exposed during cell death. In order to have phagocytosis, it is necessary to have interaction with FcγR.

The main cytokines involved in the inducement of acute SAA are IL-1, TNF-α and IL-6.

It is the most sensitive marker of acute inflammation, and is related to the clinical activity of RA. The chronic stimulation of its production can have a relevant role in the progression of RA, especially by the inducement of enzymes that destroy the extracellular matrix. The control of the acute-phase response and inflammation resolution, not only regarding the role of SAA function, require inhibition of transcription and transduction factors, formation of antagonist or false receptors, release of anti-inflammatory cytosines and glucocorticoid by the body, in order to maintain the homeostasis.

In chronic inflammation, the increase in SAA production associated with the decrease in degradation creates tissue deposit and can evolve to systemic AA subtype amyloidosis.

The albumin band is relatively homogeneous; however, the others are composed of a different protein mixture.

ACID α1-GLYCOPROTEIN

The α1 acid glycoprotein (AGP) is composed of a high percentage of carbohydrates and of sialic acid residues, presenting great negative charge and solubility in water. It is synthesized by the liver, granulocytes and monocytes. During the acute-phase inflammatory state, it suffers a change in the glycolisation pattern, which modifies its biological function. It has both pro- and anti-inflammatory activity. Among its functions, there is the inhibition of the quimiotaetic response and production of superoxide by neutrophils, the inhibition of platelet aggregation and induction of the release of cytosines by monocytes (IL-1β, IL-6, IL-12, TNF-α, IL-1Ra and receptor of soluble TNF-α). The used methodology to access the AGP is immunonephelometric assay.

PROTEIN ELECTROPHORESIS

The human plasma is composed of a series of proteins possible to be identified, and protein electrophoresis is a simple technique to separate them from serum. The test consists of placing the serum in a particular environment, and applying electric charge to ensure displacement of proteins from positive to negative pole, according to their molecular weight and physical properties. More specific separations can be performed with immunologically active agents that result in immunofluorescence and immunofixation. In normal conditions, five bands are found: albumin, alpha-1, alpha-2, beta (with the possible subdivision in beta-1 and beta-2), and gammaglobulins.

The albumin band is relatively homogeneous; however, the others are composed of a different protein mixture.

Albumin

It is the most abundant protein in plasma, approaching 60% of the total protein concentration. It is synthesized exclusively by the liver. Its functions include transport of various substances and maintenance of the plasma oncotic pressure. Levels of albumin are reduced in hepatic illnesses, malnutrition, nephrotic syndrome, chronic infections, hormonal therapy, pregnancy and burns, and they can be increased in dehydrated patients.

Inflammatory illnesses (acute and chronic) are the major causes of albumin concentration decline in plasma. Among the factors that predispose the decline are hemodilution; increased vascular permeability, leading to extravascular loss; increased in local cellular consumption; and lower cell synthesis, due to the inhibition by cytokines.

α1-Globulin

The α1-antitrypsin (α1-antiproteinase-1) represents about 90% of the proteins that run in this band. The deficiency of α1-antitripsina is associated with pulmonary emphysema and hepatic cirrhosis, and is only detectable by electrophoresis in its homozygous form. In the remaining 10%, the AGP and alpha-fetoprotein, among others, are found.
Levels α1-globulins are increased in the acute and chronic inflammatory illnesses, neoplasm, after traumas or surgeries, and during pregnancy. In hepatocarcinomas, its increase can happen by the increase of alpha-fetoprotein. However, hepatic illnesses can provoke overall reduction of this band.

α2-Globulin
It includes haptoglobin, α2-macroglobulin and ceruloplasmin, and is increased in adrenal insufficiency, corticotherapy, advanced diabetes mellitus, and nefrotic syndrome; and diminished in malnutrition, megaloblastic anemia, protein-losing enteropathy, serious liver diseases and Wilson’s disease.

β-Globulin
It has two peaks: beta-1, essentially composed by transferrin; and beta-2, composed by β-lipoproteins (for example, low density lipoprotein – LDL). C3 and other components of the complement system, β2-microglobulin, and antithrombin III are also found in this band. There is an increase of these globulins in the acute inflammatory process, nefrotic syndrome, hypothyroidism, iron deficiency anemia, malignant hypertension, obstructive jaundice, pregnancy, and some cases of diabetes mellitus. Diminished rates are found in cases of malnutrition.

γ-Globulin
Consisting of immunoglobulins, predominantly IgG, the immunoglobulin A, D, E, M and PCR are in the beta-gamma junction area. The absence or the reduction of the gamma band indicates congenital or acquired immunodeficiency. The increase suggests elevation of gamaglobulins, associated with chronic inflammatory illnesses, immune or not, hepatic illnesses, or even neoplasm, all of polyclonal character.

The monoclonal gammopathies produce a specific pattern (Figure 2). The monoclonal bands occur due to the proliferation of one plasmocyte clone, which liberates a certain immunoglobulin that, when found in great amount in the plasma, becomes responsible for the peak found in the assay. Lower quantities of polyclonal immunoglobulins are gradually produced as neoplastic plasmocytes replace the normal ones.

The most common diagnostic use of protein electrophoresis is for the recognition of these paraproteins, especially the M component of multiple myeloma. Monoclonal peaks can also be found in Waldenström’s macroglobulinemia, primary amyloidosis, and monoclonal gammopathy of undetermined significance, plasma cell leukemia, solitary plasmacytoma, and heavy chain disease.

The methodology used is automated agarose gel electrophoresis. Hemolysis and hyperlipemia can interfere. In rheumatology, it is used mainly in the evaluation of polyclonal gammopathies. In the differential diagnosis, different infections are found: viral (hepatitis, HIV, mononucleosis and varicela), bacterial (osteomyelitis, endocarditis and bacteremia), tuberculosis; rheumatic illnesses: LES, mixed connective tissue disease, temporal arthritis, RA, sarcoidosis; hepatic illnesses: cirrhosis, abusive use of ethanol, autoimmune hepatitis; malignant neoplasms: ovary, lung, hepatocellular, renal and stomach; hematologic illnesses: linfoma, leukemia, thalassemia, falciform anemia; and other inflammatory diseases, such as Crohn’s disease, and ulcerative proctocolitis, cystic fibrosis, bronquieactasis, among others. 19

Figure 3 shows the comparison between the result of a test in a patient with inflammatory status and another patient in normal conditions.
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**Ferritin**

Ferritin is a protein found in every cell, especially in those involved in the synthesis of ferric compounds, the metabolism and in the iron reserve. Its concentration increases in response to infections, traumas and acute inflammatory process. The increase occurs in the first 24 to 48 hours, with a peak on the third day, and is maintained for several weeks.\(^{20,21}\)

The widely used methodologies are quimioluminescense and immunonephelometric. The presence of hemolysis and hyperlipemia in the serum act as interfering factors.

Classically used in the monitoring of Still’s Disease, where it correlates with activity and remission, ferritin can be used for evaluation of macrophage activation syndrome (hemophagocytic), in which values greater than 10,000 μg/L can be found.\(^{20}\)

Currently, it has been used as a predictor of premature childbirth, severity of acute respiratory stress syndrome, cranial encephalic trauma, and as a predictor of cardiovascular disease, such as CRP.

Ferritin levels may be elevated in cases of acute and chronic leukemias, neuroblastoma, malignant melanoma, germinal tumors, acute hepatic necrosis, and hemocromatose. However, in these conditions, its levels are rarely found above 3,000 μg/L.\(^{21,25}\)

**CLINICAL APPLICATIONS**

**Rheumatoid Arthritis**

CRP levels can be used to establish diagnosis, especially to differentiate from osteoarthritis, in which, however, the levels are also higher than in the normal population.

As explained previously, the ESR reflects the activity during several weeks (slow increase and decrease) and is influenced by different factors, such as gender and anemia, while the CRP reflects short term changes, and it does not suffer the same influence from the factors previously stated, being more sensitive to changes in disease activity.\(^{26,27}\)

High initial levels of CRP correspond to a poor prognostic and progressive erosive disease. CRP has a good correlation with therapeutic and radiological progression, better than the ESR.\(^{26}\)

However, there can be great discrepancies between the results of ESR and CRP in up to 28% of the patients, being of worse clinical status those with high CRP/ high ESR. Next in classification are those with high CRP/low ESR, low CRP/ high ESR, and low CRP/low ESR, in that order, when the evaluation of affected joints, strength HAQ (Health Assessment Questionnaire), pain, and overall severity are taken into consideration.\(^{28}\)

In some cases, as in early RA, the ESR may be better for the patient initial follow-up, but with the warning that the test must be analyzed within 2 hours after collection, preferably still in the doctor’s office,\(^{29}\) which is incompatible with the routine of the rheumatologist.

It cannot be forgotten that the disease progresses independently from the CRP values normalization. Before the onset of symptoms, high levels of CRP are associated with higher levels of rheumatoid factor anti-peptide cyclic citrullinated factor (anti-CCP). However, the presence of anti-CCP was not statistically correlated to the initial values of ESR and PCR.\(^{1,29}\)

Recently, it was demonstrated that high levels of the enzyme matrix metalloproteinase (MMP)-3 are better than PCR to predict progressive erosive disease in early RA, since (MMP)-3 is more articulation specific, in addition to having less systemic influence; however, the sensitivity and the specificity have not yet been examined systematically. Transversal studies have shown conflicting results, and the cost-benefit is bad.\(^{30,31}\)

The scores and indices of disease activity include ESR or PCR in their calculations, and studies show that DAS28 (disease activity index) with ESR is as useful as DAS28 with CRP in the clinical follow-up.\(^{27}\)

Studies comparing acute-phase tests and the use of sonogram in RA evaluation showed that ESR and CRP had greater association to the Power Doppler measurements (that evaluates vascularization and reflects inflammation) than the evaluations by Modo-B (sinovial morphology).\(^{32}\)

We must remember that, besides CRP, SAA can be used to monitor these patients and that both play an important role in the pathophysiology of joint damage.\(^{33}\)

**Juvenile Idiopathic Arthritis**

High levels of CRP are associated with polyarticular or systemic onset, but not particularly. There is good correlation with remission of symptoms (except those with amyloidosis within five years of onset).\(^{1}\)

**Adult Still’s Disease**

This condition is characterized by the increase of serum ferritin, sometimes higher than 20,000 ng/mL. Ferritin increases due to hepatocyte injury or by activation of the histiocytes and macrophages. There is good correlation with disease activity, and levels above 1,000 ng/mL are considered suggestive of disease in most studies. Currently, the exam with highest sensitivity for disease follow-up is the glycated ferritin, which in healthy people has rates between 50 and 80% and, in cases of Still’s disease, the
rates are in general less than 20%. General inflammatory diseases have rates that oscillate between 20 and 50%. However, they are not part of the criteria for the disease definition.\textsuperscript{20,22,34,35}

**Ankylosing Spondylitis and Psoriatic Arthritis**

In these diseases, the correlation between CRP and ESR and clinical activity index is debatable, as well as the indices of clinical activity. Discrepancies between their values and the symptoms presented by patients were verified, especially in ankylosing spondilitis, in which about 50 to 70% of patients with active disease have elevated PCR.\textsuperscript{36-38} There was no correlation found between the severity of illness and ESR.\textsuperscript{39} The highest levels of CRP, in this group of illnesses, are seen in patients with AS that present peripheral arthritis or uveitis, questioning its utility in patients without these manifestations.\textsuperscript{1,37,38}

According to Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), which monitors the activity of AS, it was verified a greater association with the levels of CRP than with ESR, haptoglobin or β2-microglobulin.\textsuperscript{37,39}

The determination of SAA may be more sensitive in monitoring the disease activity than ESR and CRP, with good correlation with BASDAI.\textsuperscript{36,40}

In patients in treatment with infliximab, some studies showed good correlation of CRP and ESR with a clinical response just two weeks after the initial use, in contrast to others that verified low sensitivity and specificity to distinguish respondents from non-respondents.\textsuperscript{41,42} The use of both is considered more useful than one or the other separately and, although the correlation isn’t ideal, they should not be ignored.\textsuperscript{37,42}

**Rheumatic Fever**

Determination of AGP concentration has great importance in acute rheumatic fever, because it assists in the diagnosis, allows evolutive monitoring of disease activity (presents a later increase than ESR and CRP in the disease natural history), and its normalization implies clinical remission. The electrophoretic band of α2-globulins can also be used to access disease activity.

The increase of ESR demonstrates disease activity, but the levels are not correlated to the severity of the manifestations.\textsuperscript{43}

**Gout**

The levels of CRP correlate the number of joints affected with joint temperature and the value of ESR. The levels return to normal with treatment or with the end of inflammation.\textsuperscript{1}

Giant Cell Arthritis and Rheumatic Polymyalgia

Both conditions are characterized by great increases of CRP and ESR levels. It has good correlation with clinical response to prednisone. Patients with confirmed diagnosis and with low ESR levels can respond to lower doses of prednisone and enter into remission in less time. The values of ESR and CRP are not determinant for the disease diagnosis, but they present an excellent negative predictive value.\textsuperscript{44-47}

**Systemic Lupus Erythematosus**

The values of CRP are normal or discreetly increased, even in patients with disease clinically active and high levels of ESR.\textsuperscript{1} In a similar way, they also present lower levels of SAA and lesser incidence of amyloidosis. Levels of IL-6 have better correlation with clinical activity than CRP.

In patients with lupus, high levels of CRP are more associated with infections, although it can also be increased in patients with joint manifestations (synovitis), or, more importantly, serositis. Discreet increase of the CRP in lupus can also be associated with the presence of atherosclerosis, since this protein plays an important role in atherogenesis, as previously commented in this article.\textsuperscript{2,4}

**CONCLUSION**

The acute-phase inflammatory response includes changes in humoral and cellular components derived from stimuli of cytokines released after tissue injury. The analysis of markers involved in these reactions allows monitoring of the response evolution, and is very useful in the follow-up of rheumatic patients. Even simple tests, such as ESR, have a distinctive position in the rheumatologic patient care setting. However, it does not prescind the clinical data and results of other complementary exams.

The peculiar characteristics of each test and its role in rheumatic diseases are information that should be embedded in the clinical reasoning.

It is expected that in the future, other tests, already applied in clinical research, may also be used for the daily activity of the rheumatologist in the medical care of their patients.

**REFERENCES**