Review Article

Acute Phase Reactants: Relevance in Dermatology

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Abstract

Acute phase reactants (APRs) are a heterogeneous group of plasma proteins whose concentration either increases or decreases by at least 25% during an inflammatory process. The conditions that commonly lead to acute phase response are infection, trauma, burns, tissue infarction, inflammatory conditions, and advanced malignancy. APRs are elevated in all infective conditions. In skin and soft tissue infection, the levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) help to predict the severity of infection. Procalcitonin can be used to differentiate between viral and bacterial infections. During active stages of systemic lupus erythematosus (SLE), ESR is elevated, but CRP either remains normal or shows only moderate elevation. In the case of superadded bacterial infection in SLE, CRP is elevated. In SLE, ferritin levels are elevated during the active stage of the disease. Serum amyloid antigen (SAA) and CRP levels are significantly higher in patients with early and late stages of diffuse systemic sclerosis. Elevated levels of serum ferritin are seen in rheumatoid arthritis and adult-onset Still's disease. CRP, SAA, and α2-macroglobulin (α_2M) are elevated in active psoriasis. In severe psoriasis, the ferritin-iron ratio is elevated. In drug-induced maculopapular rash, drug-induced hyperaemic vasculitis, and severe drug-induced cutaneous adverse reactions, CRP levels are elevated during the active stages. Neoplastic diseases in general are accompanied by increased serum ferritin. Further detailed studies are required to explore the clinical significance of APRs in dermatology and the scope of their possible application as a diagnostic tool.

Keywords: *Acute phase proteins, acute phase reactants, dermatoses*

Acute phase response is a defensive or adaptive pathophysiological phenomenon in which the body's normal homeostatic mechanisms are replaced by new set points. These are considered to be a part of the innate immune response.

Acute phase reactants (APRs) are a heterogeneous group of plasma proteins whose concentration either increases or decreases by at least 25% during an inflammatory process.[1] The APRs that rise as a result of inflammatory insult are called positive acute phase proteins, for example, C-reactive protein (CRP), serum amyloid antigen (SAA), procalcitonin, etc., whereas those which show a decreasing tendency are called negative acute phase proteins, for example, albumin, transferrin, and transthyretin.[2]

Depending on their mode of action, APRs can be classified into protease inhibitors, coagulation proteins, complement components, transport proteins, and other proteins [Table 1] .[3] Erythrocyte sedimentation rate (ESR) is a non-protein APR that changes in response to plasma fibrinogen levels and plasma viscosity and is hence called an indirect APR.[4]

APRs can be classified by the magnitude of response to a stimulus. Proteins with a 10–100-fold rise in their serum levels during acute phase reactions are considered as major APR. They start rising approximately 4 h after the initial stimulus, peak at 24–72 h, and then decline rapidly during the recovery phase, for example, CRP and SAA. A 2–10-fold elevation is considered moderate and such reactants rise after 2–4 h of initial stimulus, peak after 2–3 days, and decline 7–14 days later, for example, α-1 acid glycoproteins (AGP). Minor APRs show a gradual rise of 0.5–1-fold over the baseline during the acute phase of the reactions, for example, fibrinogen, haptoglobin, and ceruloplasmin.[2,5]

The acute phase response is not limited to acute inflammatory states alone but may accompany chronic inflammation as well. The maximal increase in APRs varies from 50% to over 1000-fold for several

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proteins.[6] These changes reflect the altered production of various APRs under different circumstances. The conditions that commonly lead to acute phase response are infection, trauma, burns, tissue infarction, inflammatory conditions, and advanced malignancy. Relatively moderate changes occur following exercise, heat stroke, and childbirth.

Most APRs are produced by hepatocytes, while some are secreted by fibroblasts, macrophages, adipocytes, endothelial cells, and parenchymal cells.[7] Although different components of acute phase response may occur together, there can be discordance between plasma concentrations of various APRs which indicate that each of them is individually regulated. Moreover, during an acute phase reaction, a single APR can play multiple roles and diverse APRs can have similar biological activities.

Inflammation-induced cytokines are the major stimuli for the induction of APRs. Other factors influencing the expression of APRs include growth factors, hormones, and other mediators. Interleukin-6 (IL-6) is the major stimulator of most APRs, whereas IL-4 and IL-10 can downregulate hepatic APR synthesis. IL-1, tumor necrosis factor-alpha (TNF-α), and glucocorticoids have positive effects on acute phase gene expression in hepatocytes.[8]

APRs generally play a beneficial role in adaptation and defence during stress events, but sometimes the acute host response may be detrimental. APRs participate in a variety of inflammation-related activities which can be either pro-inflammatory or anti-inflammatory.

Erythrocyte sedimentation rate

Normal value: ESR is calculated in men as age divided by 2 and in women as age +10 divided by 2.

It is the simple and most widely used APR. It reflects the degree of inflammation. It starts to rise within 24–48 h and falls slowly with the resolution of inflammation.[7] ESR correlates with the fibrinogen levels in the plasma. ESR can be influenced by the number, size, and shape of red blood cells (RBC), presence of other plasma proteins, age of the patient, and many other unknown factors.

C-reactive protein

Normal value: <0.3 mg/L

CRP is a pattern recognition receptor. Its production is stimulated by IL-6. CRP can be directly measured. It reflects the synthesis of a single APR. Its concentration changes rapidly in response to the changes in the inflammatory process. It is minimally influenced by age and sex. Compared to ESR, CRP is a more sensitive indicator. It starts to rise within 12–24 h and peaks within 2–3 days.[7] Its half-life is approximately 9 h.[7] High sensitive-CRP assay is used to measure very low levels of CRP. Minor elevation of CRP (0.3–1 mg/L) can be seen in obesity, pregnancy, diabetes, and periodontitis, whereas moderate elevation (1–10 mg/L) occurs in inflammatory conditions like systemic lupus erythematosus (SLE), rheumatoid arthritis, and in malignancy. Marked elevation of CRP (>10 mg/L) is seen in acute infections.[9] CRP has both pro-inflammatory and anti-inflammatory action. It initiates the elimination of targeted bacteria and necrotic cells by interaction with humoral and cellular effector systems of inflammation. It induces inflammatory cytokines and tissue factors.[3]

Procalcitonin

Normal value: <0.05 ng/mL

It is a recently identified marker of bacterial infection. Under normal conditions, procalcitonin is derived from parafollicular C-cells of the thyroid gland in response to hypercalcemia or as a part of medullary carcinoma of the thyroid, where it is converted to calcitonin. During infection, it is secreted by all parenchymal cells and differentiated cells.[10,11] Its secretion is downregulated by gamma-interferon, which is produced in response to viral infections, making it an attractive marker of bacterial infection.[11]

Procalcitonin levels rise within 2–4 h following infection, peak within 6–24 h, and also fall immediately after the infection is controlled; hence, it is superior to CRP and ESR as a marker of infection.[7,12] Its half-life is 25–30 h in plasma.[10] Procalcitonin levels are not elevated in non-infectious inflammatory conditions like polymyalgia, inflammatory bowel disease, polyarteritis nodosa, or SLE.[7,11] Procalcitonin levels are not influenced by therapy with glucocorticoids and non-steroidal anti-inflammatory agents.[13] Semi-quantitative assays of procalcitonin are less time consuming. Transient rise is seen in massive trauma like severe burns and major surgery. Any therapy that stimulates cytokines such as T-cell antibody therapy or granulocyte transfusion and graft versus host disease (GVHD) can increase procalcitonin levels. Higher levels are also seen in Addisonian crisis, malaria, fungal infection, and medullary carcinoma of the thyroid.[10,14]

Ferritin

Normal value: 15–300 µg/L

Ferritin is a major intracellular iron storage protein. Hepatocytes, proximal tubular renal cells, Kupfer cells, and macrophages secrete ferritin in various conditions. Hyperferritinemia is a marker of significant macrophage activation. During active infection, ferritin protects the host by limiting the availability of iron to the pathogen.[15] The extracellular ferritin acts as an iron delivery system and it also exhibits various immunological activities including binding to T-cells, suppression of delayed type of hypersensitivity to induce anergy, suppression of antibody production by B lymphocytes, reduction of phagocytosis by granulocytes, regulation of myelopoiesis, etc.[16]

Serum amyloid antigen

Normal value: <1 mg/L

It is a major APR and has been found to induce adhesion molecules during inflammation, and helps in opsonization. It induces cytokine production and metalloproteinase secretion. It also helps in the reverse transport of cholesterol from tissues to hepatocytes. SAA levels parallel that of CRP.[5] A persistent high expression of SAA is a prerequisite for the development of secondary amyloidosis.[17]

α-1 acid glycoproteins

AGP exhibits anti-inflammatory effect by binding to bacterial endotoxins and thus preventing endotoxin-induced septic and hypovolemic shock. It also exhibits anti-inflammatory effect in ischemia-reperfusion injury.

Others

Fibrinogen, α1-antitrypsin, haptoglobin, hemopexin, and ceruloplasmin have strong antioxidant action in addition to the anti-inflammatory effect.

APRs in Dermatoses

Infection

APRs are elevated in all infective conditions. In skin and soft tissue infections like cellulitis, ESR and CRP levels may help to predict the severity of infection.[18] To differentiate between necrotizing fasciitis and superficial skin and soft tissue infection, the laboratory risk indicator for necrotizing fasciitis score is used. This is a laboratory-based scoring method with a score of ≥6 to predict the possibility of necrotizing fasciitis, in which a score of 4 is assigned to CRP levels of more than 150 mg/L.[18] A study by Friederichs *et al*.[19] reported that a procalcitonin ratio of 1.14 or higher between postoperative day 1 and day 2 after surgery for necrotizing fasciitis indicates a successful treatment response.

In the case of viral infections, gamma-interferon response is stimulated which in turn activates many APRs, except procalcitonin making the latter a differentiating marker between viral and bacterial infections.[11] Procalcitonin is more specific than CRP for the diagnosis of sepsis and regulating antibiotic therapy.[7,13] It is also increased in fungal infection and malaria.[7,14]

The serum inhibitory factor in human serum, an unsaturated transferrin, inhibits the growth of dermatophytic fungi. High serum iron can reverse the inhibitory effect caused by unsaturated transferrin.[20]

In human immunodeficiency virus-positive (HIV^{+ve}) patients undergoing treatment, the concentrations of positive APRs are elevated, whereas the serum concentrations of negative APRs remain the same.[21] Wolf *et al*.[22] found decreased D-dimer levels in HIV^{+ve} patients after the initiation of protease inhibitors or non-nucleoside reverse transcriptase inhibitors (NNRTI) treatment. Madden *et al*.[23] reported that treatment with protease inhibitor was associated with elevated fibrinogen levels, whereas there was no increase in fibrinogen levels with NNRTI administration. HIV^{+ve} patients with an elevated D-dimer concentration are at a high risk of thrombotic thrombocytopenic purpura, cardiovascular events, and death.

ESR, CRP, α1-antitrypsin, complement C3, and circulating immune complexes are elevated in lepromatous leprosy and erythema nodosum leprosum (ENL).[24] A study by Mendes *et al*.[25] shows that Pentraxin-3 (PTX3) serum levels are higher in multibacillary leprosy patients before the onset and during acute ENL reaction. Multibacillary patients who developed reversal reaction had low levels of PTX3 before and during the reaction period; hence, PTX3 can be used to differentiate ENL from reversal reaction. Treatment with thalidomide will reduce serum PTX3 levels. Gupta *et al*.[26] found raised AGP levels in patients of ENL.

Wasunna *et al*.[27] found that serum CRP, SAA, and AGP are elevated in visceral leishmaniasis patients and the concentrations decreased with effective therapy to reach normal levels by the end of therapy (SAA and AGP) or by 3 months follow-up (CRP).

The study by Immanuel *et al*.[28] reveals a significant increase in CRP, ceruloplasmin, haptoglobin, and AGP levels in tuberculosis patients.

Autoimmune diseases

During active stages of SLE, ESR is elevated, but CRP either remains normal or shows only moderate elevation except in cases with lupus serositis, lupus synovitis, and Jaccuad's arthropathy which show a marked elevation in CRP.[29] In addition to CRP, other APRs like serum amyloid component P and mannose-binding lectin are not raised in active SLE, indicating a possible mechanism of antibody production that blocks their function.[30,31] The inhibitory effect of interferon on CRP induction is also considered as a reason for muted CRP response.[29] In the case of superadded bacterial infection in SLE, CRP levels are elevated.[29] Serum fibrinogen levels are elevated in lupus patients but do not correlate with the disease activity.[32] In SLE, ferritin levels are found to be elevated during active stages and there is a positive correlation between ferritin level and serositis and hematological manifestations.[33]

SAA and CRP levels are significantly higher in patients with early and late stages of diffuse systemic sclerosis.[34] Systemic sclerosis patients who have consistently elevated levels of CRP have more severe skin involvement and have a worse prognosis.[35] High SAA and CRP levels could be markers of pulmonary involvement in systemic sclerosis.[34] Haptoglobin, AGP, complement component C3, and α_2-macroglobulin (α_2M) are also elevated in systemic sclerosis but are usually clinically not much useful unlike in SLE and vasculitis.[36]

Elevated serum ferritin can be found in adult-onset Still's disease.[37] In addition to ferritin, CRP, ESR, SAA, haptoglobin, and fibrinogen are elevated in rheumatoid arthritis.[38] SAA is a more sensitive indicator than CRP in these patients.[39]

Psoriasis and atopic dermatitis

Serum CRP, SAA, and α_2M are elevated in active psoriasis.[40,41] SAA synthesis is stimulated by IL-17A which is over-expressed in psoriasis but not in atopic skin. This explains the higher SAA expression in psoriasis when compared to atopic dermatitis. This also explains the absence of AA amyloidosis secondary to atopic dermatitis, whereas secondary amyloidosis is reported in psoriasis.[40] In severe psoriasis, despite the diminished iron stores in many cases, the ferritin level remains high due to the inflammation-related induction of ferritin.[42]

A study by Vekaria *et al*.[43] reveals a significant elevation of CRP in atopic dermatitis. CRP can be used as a marker of disease severity in moderate to severe atopic dermatitis.

Urticaria

In chronic spontaneous urticaria, CRP is a marker of disease activity.[44] Higher SAA levels are seen in acute urticaria and moderate to severe chronic urticaria.[45] According to Czarnecka-Operacz *et al*.,[46] in patients with autoimmune urticaria, serum concentrations of CRP, AGP, α1-antichymotrypsin, ceruloplasmin, and haptoglobin are elevated significantly. Serum CRP is higher in patients suffering from autoimmune urticaria with angioedema than in those patients without angioedema. Patients with autoimmune urticaria with prolonged disease course had statistically higher serum concentration of transferrin, α_2M, and α1-antitrypsin.

Table 1: Classification of APRs based on their function

Classification	Positive APRs	Negative APRs
Protease inhibitors	α1-antitrypsin	
	Pancreatic secretory trypsin inhibitor	
Transport proteins	Hemopexin	Transferrin
	Ceruloplasmin	Transthyretin
	Haptoglobin	
Complement components	C2	
	C3	
	C4	
	C5	
	C9	
	Factor B	
	C1 inhibitor	
	C4b-binding protein	
	Mannose-binding lectin	
Coagulation and fibrinolysis	Fibrinogen	Factor XII
	Prothrombin	
	Plasminogen	
	Tissue plasminogen activator	
	Urokinase	
	Protein S	
	Plasminogen activator inhibitor-1	
Participants in inflammatory process	Secreted phospholipase A	
	Lipopolysaccharide-binding protein	
	IL-1 receptor antagonist	
	Granulocyte colony-stimulating factor	
Apolipoprotein	Serum amyloid A	
Others	CRP	Albumin
	ESR	α2-HS glycoprotein
	Ferritin	α-fetoprotein
	Fibronectin	Thyroxin binding globulin
	Angiotensinogen	Insulin-like growth factor-1

Table 2: Clinical significance of APRs in dermatology

APR	Normal value	Clinical significance
ESR	In men-age/2 In women-age +10/2	<100-autoimmune diseases, minor infections, and inflammation; >100-malignancy, severe infection, and arteritis
CRP	<0.3 mg/L	0.3-1 mg/L-osteoarthritis, coronary artery disease, smoking, uremia, and pregnancy 1-10 mg/L-autoimmune diseases and malignancy; >10 mg/L-bacterial infections
Procalcitonin	<0.05 ng/mL	>0.05 ng/mL-fungal infection; >2 ng/mL-bacterial infection and malaria
Ferritin	15-300 µg/L	<15 µg/L-severe iron deficiency anemia; >300-malignancy, hemophagocytic syndrome, and chronic inflammation
α_2M	284 mg/100 mL in men, 350 mg/100 mL in women	Autoimmune diseases and drug reaction
α1-antitrypsin	0.9-1.75 g/L	>1.75 g/L-active stages of Hansen's disease; <0.9-bronchiectasis, liver cirrhosis, pancreatitis, systemic vasculitis, psoriasis, and chronic urticaria
α1-antichymotrypsin	100-300 mg/dL	Malignancy
AGP	0.5-1 g/L	Tissue injury, infection, autoimmune diseases, and malignancy
SAA	<1 mg/L	Infections and autoimmune diseases
Complement C3	80-160 mg/dL	Autoimmune diseases and active stages of Hansen's disease
Haptoglobin	0.38-2.08 g/L	Autoimmune diseases

Acne vulgaris

A study by El-Taweel *et al*.[47] found elevated serum CRP and hepcidin in acne vulgaris and the levels of CRP correlated with disease severity. Serum ferritin levels are elevated in severe nodulocystic acne. Studies conducted by Parhizkar *et al.* and Ibrahim *et al*. revealed no significant elevation of CRP in acne vulgaris.[48,49]

Vesiculobullous diseases

A study by Handjani *et al*.[50] revealed a positive correlation between CRP and severity of pemphigus vulgaris. A study on pemphigus foliaceous by Junior *et al*.[51] found an increase in CRP in 60% of patients and an increase in ESR in all patients. There is a significant elevation of IL-6 and serum CRP in patients with bullous pemphigoid.[52] Complement deposition is related to clinical and serological disease activity in bullous pemphigoid.[53] Tissue factor, an initiator of blood coagulation, prothrombin fragments, and D-dimer levels are also elevated in bullous pemphigoid.[53]

Kawasaki disease

Procalcitonin, ESR, and CRP are elevated in the acute phase of Kawasaki disease but none of them are specific to the disease.[54] CRP levels have a significant association with disease severity and the development of coronary artery aneurysms.[54] The rise of procalcitonin levels is especially marked in children resistant to intravenous immunoglobulin (IVIG) therapy.[54] Serum calprotectin, calcium- and zinc-binding protein of the S100/calgranulin family, is markedly increased in the early stages of acute Kawasaki disease, and they rapidly decrease within 24h of IVIG administration.[55] Later, development of coronary aneurysms is observed in children with persistent elevation of calprotectin after IVIG therapy.[55]

Alopecia

According to Chisti *et al.*, decreased serum ferritin levels are associated with nonscarring alopecia in women.[56] Similar results were reported by Kantor *et al*.[57] and Rasheed *et al*.,[58] who showed that the mean ferritin levels in women with androgenetic alopecia and alopecia areata were significantly lower than those without alopecia. But a study by Bregy *et al*.[59] found no correlation between hair loss activity and serum ferritin levels.

Drug reactions

Procalcitonin and CRP are elevated in drug reaction with eosinophilia and systemic symptoms syndrome due to immune-mediated organ injury. Procalcitonin and CRP values are significantly higher among those patients with an additional cause for inflammation.[60]

In all severe drug-induced cutaneous adverse reactions, drug-induced maculopapular rash, and drug-induced hyperaemic vasculitis, CRP levels are elevated during the active stage. Though the levels fall after the clearance of the skin lesions, their values are significantly higher when compared to the healthy controls.[61,62] Similarly, the levels of α_2M show a considerable elevation in severe cutaneous adverse reactions and remain high (in comparison to healthy controls) even after the clearance of the skin lesions.[61,63]

Serum endocan, a marker of endothelial dysfunction in the systemic circulation of Stevens–Johnson syndrome-toxic epidermal necrolysis patients, is strongly associated with disease severity.[64]

In drug-induced urticaria, there is a marked elevation of CRP and α_2M during active disease. After the disappearance of the lesions, α_2M levels decline to basal levels but CRP remains significantly elevated.[65]

Sarcoidosis

Study by Ahmadzai *et al*.[66] revealed very high levels of ESR and CRP in some patients with active sarcoidosis. ESR is more likely to be elevated in sarcoidosis-associated arthritis and erythema nodosum.[66] High CRP is associated with severe fatigue in sarcoidosis, although CRP is generally lower compared to patients with tuberculosis.[67] Elevated ESR and CRP may be associated with systemic hypertension in sarcoidosis.[68] β2-microglobulin is a marker of lymphocyte activation and is elevated in ~25% of patients with sarcoidosis.[68]

Malignancy

Neoplastic diseases, in general, are accompanied by increased serum ferritin levels which could be due to increased production of ferritin by the malignant cells. Squamous cell carcinoma of the head and neck region is marked by increased plasma ferritin concentration and persistently elevated level serves as a poor prognostic indicator.[16]

Elevated serum ferritin levels are seen in advanced stages of malignant melanoma. Ferritin concentration also correlates with the degree of dissemination of the disease.[66] Adjuvant therapy with interferon can induce an increase in the serum ferritin levels in these patients.[69,70]

In mycosis fungoides (MF), an inflammatory reaction exists as reflected by the increased levels of APRs, especially AGP and α1-antichymotrypsin in all stages of MF except in stage IIA.[71] The lymphoma-associated hemophagocytic syndrome should be considered in cutaneous T-cell lymphoma (CTCL) patients with acute inflammatory symptoms, especially when cytopenia, raised triglycerides, and increased ferritin levels are present clinical significance of APRs in dermatology are summarized in [Table 2].[72]

Further detailed studies are required to explore the clinical significance of APRs in dermatology and the scope of their possible application as a diagnostic tool.

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Conflicts of interest

There are no conflicts of interest.

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