The Intercontinental Journal of
Internal Medicine

DOI: 10.51271/ICJIM-0040

Review

Acute phase reactants

İlknur Akkuş, Birgül Kaçmaz

Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkiye

Cite this article: Akkuş İ, Kaçmaz B. Acute phase reactants. *Intercont J Int Med.* 2024;2(3):74-76.

Corresponding Author: İlknur Akkuş, ilknurakks38@gmail.com

Received: 11/06/2024 ◆ **Accepted**: 24/08/2024 ◆ **Published**: 28/08/2024

ABSTRACT

The serum concentrations of certain proteins are altered in various conditions such as infection, trauma, inflammatory arthritis, malignancy, autoimmune and systemic inflammatory diseases. These proteins are known as positive or negative acute phase reactants. While albumin and transferrin belong to the negative acute phase reactants, alpha-1-acid glycoprotein, alpha-1-antitrypsin, alpha-2-macroglobulin, C-reactive protein, ceruloplasmin, haptoglobin, serum amyloid A and fibrinogen are known as positive acute phase reactants. This review discusses the clinical use of C-reactive protein, erythrocyte sedimentation rate and procalcitonin.

Keywords: Acute phase reactants, CRP, ESR, procalcitonin

INTRODUCTION

In response to infection, trauma and inflammation, changes (increases or decreases) occur in the blood levels of certain proteins in many organisms, including humans. Among these proteins, the levels of albumin and transferrin decrease under conditions such as infection, trauma and inflammation, whereas the levels of alpha-1-acid glycoprotein, alpha-1-antitrypsin, alpha-2-macroglobulin, C-reactive protein (CRP), ceruloplasmin, haptoglobin, serum amyloid A and fibrinogen increase.[1] Because of the association of these serum protein increases with inflammatory conditions, they are also referred to as acute phase reactants (APR).[2]

This review discusses the clinical use of CRP, which is the most commonly used APR in practice, erythrocyte sedimentation rate (ESR), an indirect measure of the acute phase response and in particular fibrinogen levels, and procalcitonin, which is more specific to infection.

C-REACTIVE PROTEIN (CRP)

CRP is one of the most important members of the APR family. CRP has been detected in every organism studied, including arthropods, with structural differences between species. Human CRP is a pentameric protein with a molecular weight of approximately 23 kDa, consisting of 206 amino acid residues and five non-covalently bound identical subunits.[3] Human C-reactive protein was first identified as a plasma protein that precipitates the C-polysaccharide (PnC) from the cell wall of *Streptococcus pneumoniae*.[4]

Synthesis

CRP gene expression occurs in hepatocytes in the liver in response to elevated levels of inflammatory cytokines, primarily interleukin-6 (IL-6). In addition to the liver, CRP is also synthesised by smooth muscle cells, macrophages, endothelial cells, lymphocytes and adipocytes. Many factors can alter baseline CRP levels, including age, gender, smoking, weight, blood lipid levels and blood pressure.[5] The pentameric form of native CRP (nCRP) can irreversibly dissociate into free subunits known as monomeric CRP (mCRP) under certain conditions.[6] The normal range of CRP can vary widely between laboratories. Therefore, a reported high level can sometimes be misleading. A CRP level of >1 mg/dL (10 mg/L) indicates clinically significant inflammation, while levels between 0.3 and 1 mg/dL (3 to 10 mg/L) generally indicate low-grade inflammation.[7] The half-life of CRP is approximately 19 hours under both physiological and pathological conditions.[8]

Inflammation and CRP

CRP is universally recognised as a marker of acute inflammation. However, it has also been shown that CRP is an active participant in the inflammatory process and not just a marker of inflammation. Therefore, CRP exhibits both pro-inflammatory and anti-inflammatory effects.[9] CRP assists in the recognition and elimination of pathogens and enhances the clearance of necrotic and apoptotic cells.[10] Under physiological conditions, stable nCRP gains specificity for binding to proteins such as factor H, oxidised LDL and complement C3b in the acidic environment of inflamed

tissue. Binding of circulating nCRP to membrane lipids on the surface of activated platelets and apoptotic cells leads to subunit dissociation into the mCRP form. This form of CRP induces potent pro-inflammatory activities such as secretion of IL-8 by neutrophils and human coronary endothelial cells, adhesion of neutrophils to platelets and endothelial cells, delay of neutrophil apoptosis and release of neutrophil extracellular traps.[11]

Infection and CRP

CRP has long been used as a sensitive marker to determine the presence and severity of infection and to monitor the efficacy of treatment.[1] During infection, CRP increases in response to the elevation of inflammatory cytokines, particularly IL-1 and IL-6. The interaction of CRP with the immune response to microorganisms is thought to be primarily through the classical complement pathway.[5] CRP was originally identified as a plasma protein that precipitates the C-polysaccharide from the cell wall of S. pneumoniae.[4] A study in mice showed that CRP contributes to the clearance of intravenously injected bacteria from the blood and reduces early dissemination of infection to the liver and spleen.[12] Another study reported that CRP levels are higher in systemic infections compared to local infections and colonisation, but CRP levels alone could not differentiate between different types of infection.[13]

ERYTHROCYTE SEDIMENTATION RATE (ESR)

The ESR is defined as the rate (mm/hour) at which erythrocytes settle in the plasma in a given time in anticoagulated blood.[14] Essentially, the ESR is an indirect indicator of the acute phase response and primarily acute phase proteins, particularly fibrinogen.[15] This phenomenon was first observed in 1897 by Dr Edmund Faustyn Biernacki, who noticed that red blood cells sediment more quickly in the presence of high levels of fibrinogen.[16] Many factors, including acute tissue injury, soft tissue infection, rheumatic disease, malignancy and physiological conditions such as pregnancy, can cause an increase in ESR.[17] Because the erythrocyte sedimentation rate can be influenced by several factors (inflammation, trauma, infection, morphological changes in erythrocytes, anaemia, polycythemia), it is difficult to establish a normal limit or reference range. It is generally defined as age (years)/2 for males and age (years)+10 for females.[18]

Clinical Use

Unlike other acute phase reactants, ESR does not increase very rapidly at the onset of inflammation and returns to normal levels more slowly after the inflammation subsides. This should be taken into account in clinical assessment. ESR begins to rise approximately 24-48 hours after the onset of inflammation and may take weeks to return to normal levels as inflammation resolves.[19] Although ESR has low sensitivity and specificity as an acute phase reactant, an ESR greater than 100 mm/hour indicates significant underlying inflammation.[14] In a large study of patients with an ESR greater than 100 mm/hour, 40% had infections (most commonly pneumonia), 38% had underlying rheumatic disease (most commonly rheumatoid arthritis), and 36% had malignancy.[20] In a retrospective study of 1006 patients, infections (33%) were the most common cause of ESR values above 100 mm/hour, while malignancies (17%) and inflammatory diseases (14%) were reported less frequently.[21]

PROCALCITONIN (PCT)

Procalcitonin is a prohormone composed of 116 amino acids that acts as a precursor to calcitonin and is synthesised during bacterial infections.[22]

Synthesis

Under normal conditions, PCT is synthesised in thyroid C-cells from the CALC-1 gene located on chromosome 11. This mRNA product is subsequently cleaved into three different molecules: active calcitonin (32 amino acids), katacalcin (21 amino acids) and N-terminal procalcitonin (57 amino acids).[23] In healthy individuals, all PCT synthesised by thyroid C-cells is converted to calcitonin, resulting in very low circulating levels (≤0.1 ng/ml).[22] In the presence of a pro-inflammatory stimulus, particularly of bacterial origin, PCT is secreted not only by thyroid C-cells but also by neuroendocrine cells in the gut and lungs.[24]

Infection and PCT

The relationship between procalcitonin and bacterial infections was first described in 1993, when a calcitonin-like immunoreactivity was detected at higher levels in the blood of patients with infections compared with those without signs of infection. This study showed that procalcitonin concentrations correlate with the severity of infection, increasing up to 2000-fold in patients with septic shock and decreasing rapidly with antibiotic treatment.[25] Following this study, it was suggested that procalcitonin may be more specific for infection than other acute phase reactants, prompting numerous studies.[26] According to a meta-analysis published in 2011, procalcitonin could reduce antibiotic use without increasing mortality in patients with respiratory infections and sepsis, and could be used to guide treatment.[27] Another study reported that procalcitonin is useful in diagnosing patients presenting to the emergency department with pneumonia versus heart failure and serves as an indicator of one-year mortality.[28]

Procalcitonin synthesis is activated by microbial toxins, interleukin-1, interleukin-6 and tumour necrosis factor-α, whereas it is inhibited by interferon-γ released by viruses.[29,30] An in vitro study found that procalcitonin induces human monocyte chemotaxis at concentrations present in the circulation during bacterial infections.[22] Because of its elevation during bacterial but not viral infections, the US Food and Drug Administration (FDA) has approved procalcitonin for use in initiating and determining the duration of antibiotic therapy for lower respiratory tract infections.[31] However, recommendations for the use of procalcitonin in the diagnosis of bacterial co-infections vary.[32] A study in influenza patients found that procalcitonin had a negative predictive value of 94%, making low PCT levels an effective biomarker for excluding bacterial co-infection, especially in patients without septic shock.[33] However, a study of hospitalised COVID-19 patients suggested that procalcitonin is not useful for the diagnosis of bacterial co-infection.[34] In a study of patients with Crimean-Congo haemorrhagic fever (CCHF), despite the viral nature of the infection, procalcitonin levels were higher in patients with severe clinical presentation, suggesting that procalcitonin levels in the first two days of illness may predict mortality.[35]

CONCLUSION

Acute phase reactants may increase or decrease as indicators of inflammation due to various causes such as infections, rheumatic diseases, trauma and malignancy. However, none of these alone is sufficient to diagnose a disease. In particular, acute phase reactants such as ESR and CRP, which are influenced by physiological conditions such as age, gender and race, should be evaluated in conjunction with the patient's clinical presentation.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Powanda MC, Moyer ED. A brief, highly selective history of acute phase proteins as indicators of infection, inflammation and injury. *Inflammopharmacology.* 2021;29(3):897-901.
2. Kushner I. The phenomenon of the acute phase response. *Ann N Y Acad Sci.* 1982;389:39-48.
3. Pathak A, Agrawal A. Evolution of C-reactive protein. *Front Immunol.* 2019;10:943.
4. Tillett WS, Francis T. Serological reactions in pneumonia with a non-protein somatic fraction of pneumococcus. *J Exp Med.* 1930;52(4):561-571.
5. Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. *Front Immunol.* 2018;9:754.
6. Potempa LA, Siegel JN, Fiedel BA, Potempa RT, Gewurz H. Expression, detection and assay of a neoantigen (Neo-CRP) associated with a free, human C-reactive protein subunit. *Mol Immunol.* 1987;24(5):531-541.
7. Kushner I, Antonelli MJ. What should we regard as an "elevated" C-reactive protein level?. *Ann Intern Med.* 2015;163(4):326.
8. Aziz N, Fahey JL, Detels R, Butch AW. Analytical performance of a highly sensitive C-reactive protein-based immunoassay and the effects of laboratory variables on levels of protein in blood. *Clin Diagn Lab Immunol.* 2003;10(4):652-657.
9. Marnell L, Mold C, Du Clos TW. C-reactive protein: ligands, receptors and role in inflammation. *Clin Immunol.* 2005;117(2):104-111.
10. Rhodes B, Fürnrohr BG, Vyse TJ. C-reactive protein in rheumatology: biology and genetics. *Nat Rev Rheumatol.* 2011;7(5):282-289.
11. Rizo-Téllez SA, Sekheri M, Filep JG. C-reactive protein: a target for therapy to reduce inflammation. *Front Immunol.* 2023;14:1237729.
12. Szalai AJ, VanCott JL, McGhee JR, Volanakis JE, Benjamin WH Jr. Human C-reactive protein is protective against fatal *Salmonella* enterica serovar typhimurium infection in transgenic mice. *Infect Immun.* 2000;68(10):5652-5656.
13. Kingsley A, Jones V. Diagnosing wound infection: the use of C-reactive protein. *Wounds UK.* 2008;4(4):32-46.
14. Özsoy Z, Bilgin E, Aksun MS, Eroğlu İ, Kalyoncu U. Extremely high erythrocyte sedimentation rate revisited in rheumatic diseases: a single-center experience. *Turk J Med Sci.* 2022;52(6):1889-1899.
15. Bedell SE, Bush BT. Erythrocyte sedimentation rate. From folklore to facts. *Am J Med.* 1985;78(6 Pt 1):1001-1009.
16. Grzybowski A, Sak JJ. Who discovered the erythrocyte sedimentation rate?. *J Rheumatol.* 2011;38(7):1521-1523.
17. Piva E, Sanzari MC, Servidio G, Plebani M. Length of sedimentation reaction in undiluted blood (erythrocyte sedimentation rate): variations with sex and age and reference limits. *Clin Chem Lab Med.* 2001;39(5):451-454.
18. Miller A, Green M, Robinson D. Simple rule for calculating normal erythrocyte sedimentation rate. *Br Med J (Clin Res Ed).* 1983;286(6361):266.
19. Litao MK, Kamat D. Erythrocyte sedimentation rate and C-reactive protein: how best to use them in clinical practice. *Pediatr Ann.* 2014;43(10):417-420.
20. Daniels LM, Tosh PK, Fiala JA, Schleck CD, Mandrekar JN, Beckman TJ. Extremely elevated erythrocyte sedimentation rates: associations with patients' diagnoses, demographic characteristics, and comorbidities. *Mayo Clin Proc.* 2017;92(11):1636-1643.
21. Fincher RM, Page MI. Clinical significance of extreme elevation of the erythrocyte sedimentation rate. *Arch Intern Med.* 1986;146(8):1581-1583.
22. Wiedermann FJ, Kaneider N, Egger P, et al. Migration of human monocytes in response to procalcitonin. *Crit Care Med.* 2002;30(5):1112-1117.
23. Vijayan AL, Vanimaya, Ravindran S, et al. Procalcitonin: a promising diagnostic marker for sepsis and antibiotic therapy. *J Intensive Care.* 2017;5:51.
24. Taylor R, Jones A, Kelly S, Simpson M, Mabey J. A review of the value of procalcitonin as a marker of infection. *Cureus.* 2017;9(4):1148.
25. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet.* 1993;341(8844):515-518.
26. Hoeboer SH, van der Geest PJ, Nieboer D, Groeneveld AB. The diagnostic accuracy of procalcitonin for bacteraemia: a systematic review and meta-analysis. *Clin Microbiol Infect.* 2015;21(5):474-481.
27. Schuetz P, Chiappa V, Briel M, Greenwald JL. Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. *Arch Intern Med.* 2011;171(15):1322-1331.
28. Alba GA, Truong QA, Gaggin HK, et al; Global Research on Acute Conditions Team (GREAT) Network. Diagnostic and prognostic utility of procalcitonin in patients presenting to the emergency department with dyspnea. *Am J Med.* 2016;129(1):96-104.e7.
29. Müller B, White JC, Nylén ES, Snider RH, Becker KL, Habener JF. Ubiquitous expression of the calcitonin-i gene in multiple tissues in response to sepsis. *J Clin Endocrinol Metab.* 2001;86(1):396-404.
30. Linscheid P, Seboek D, Zulewski H, Keller U, Müller B. Autocrine/paracrine role of inflammation-mediated calcitonin gene-related peptide and adrenomedullin expression in human adipose tissue. *Endocrinology.* 2005;146(6):2699-2708.
31. Kamat IS, Ramachandran V, Eswaran H, Guffey D, Musher DM. Procalcitonin to distinguish viral from bacterial pneumonia: a systematic review and meta-analysis. *Clin Infect Dis.* 2020;70(3):538-542.
32. Azijli K, Minderhoud TC, de Gans CJ, Lieveld AWE, Nanayakkara PWB. Optimal use of procalcitonin to rule out bacteremia in patients with possible viral infections. *J Am Coll Emerg Physicians Open.* 2022;3(3):e12621.
33. Rodríguez AH, Avilés-Jurado FX, Díaz E, et al. Procalcitonin (PCT) levels for ruling-out bacterial coinfection in ICU patients with influenza: a CHAID decision-tree analysis. *J Infect.* 2016;72(2):143-151.
34. Relph KA, Russell CD, Fairfield CJ, et al. Procalcitonin is not a reliable biomarker of bacterial coinfection in people with coronavirus disease 2019 undergoing microbiological investigation at the time of hospital admission. *Open Forum Infect Dis.* 2022;9(5):ofac179.
35. Gul S, Ozturk DB, Kisa U, Kacmaz B, Yesilyurt M. Procalcitonin level and its predictive effect on mortality in Crimean-Congo hemorrhagic fever patients. *Jpn J Infect Dis.* 2015;68(6):511-513.