Editorial

C-Reactive Protein: An Overview

C-reactive protein (CRP) was first identified in 1930 by William S. Tillet and Thomas Francis [1] at the Rockfeller Institute for Medical Research in the sera of patients acutely infected with pneumococcal pneumonia. It was so named because it reacted with the C-polysaccharide of Pneumococcus. It is a pentameric protein with an overall molecular weight of 118 kDa, which has five non-covalently bonded and non-glycosylated identical subunits of 206 amino acids each (Figure **1**). CRP is a member of the pentraxin family of proteins and belongs to the class of acute-phase reactants that mediates innate and adaptive immunity. It plays an important physiological role in host defense by binding to phosphocholine and related molecules expressed on the surface of dead or dying cells and microorganisms, which activates the complement system *via* the C1Q complex [2]. Therefore, it aids in the clearance of necrotic and apoptopic cells by enhancing the phagocytosis by macrophages. CRP is an early indicator of infectious or inflammatory conditions [3, 4] and is usually elevated in patients with neonatal sepsis, meningitis and occult bacteremia [5, 6]. CRP may also be elevated in urinary tract infections, pancreatitis, pneumonia and pelvic inflammatory disease. It is produced by hepatocytes in response to a variety of inflammatory cytokines, such as interleukin (IL)-6, IL-1 and tumor necrosis factor alpha (TNFα), which are released by macrophages during infection or tissue inflammation, in addition to other factors released by adipocytes.

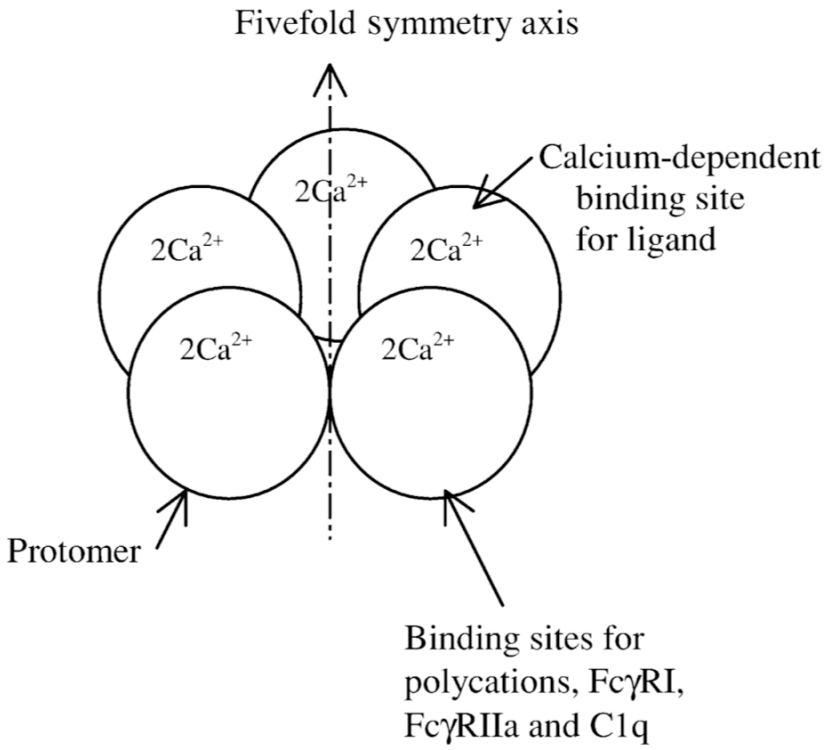

Figure 1: Structure of C-reactive protein [39]. Reproduced with permission from Elsevier Science B.V.

The American Heart Association/Center for Disease Control (AHA/CDC) identified CRP as the best inflammatory marker for use in clinical practice [7]. It has been demonstrated to be an independent strongest predictor of cardiovascular events [8-10], such as heart attacks, ischemic stroke, coronary artery disease, and acute myocardial infarction. The low, average and high risk groups, as defined by AHA/CDC, have CRP levels of <1 mg/L, 1-3 mg/L and >3 mg/mL, respectively. Recently, it has also been demonstrated to be an independent predictor for the development of diabetes in men [11]. CRP is also a marker for atherosclerotic cardiovascular risk [12]. CRP levels are important indicators of cardiac tolerance and are thus associated with cardiorespiratory fitness [13]. CRP and IL-6 play important roles in the growth and progression of malignant tumors such as esophageal cancer [14]. The reactive oxygen species in the whole blood have been shown to correlate strongly with high-sensitivity (hs) CRP

[15]. The persistently high CRP level indicates the risk for continued joint deterioration [16]. Moreover, the significantly elevated CRP levels in serum are directly associated with very high 30-day mortality rates in hospitalized medical patients [17]. The serum CRP is also a marker for wellness assessment [18].

The presence of increased adipose tissue in obesity is associated with elevated inflammatory cytokines that leads to higher hsCRP levels [19, 20]. The higher hsCRP levels correlate with the presence of insulin resistance and type 2 diabetes mellitus [21], and are further associated with many features of metabolic syndrome [22]. The hsCRP levels and other markers may predict the development of dementia, including that in the Alzheimer's disease [23]. CRP increases the clearance of apoptotic cells and binds to nuclear antigens. It may prevent autoimmunity by masking the autoantigens from the immune system or increasing their clearance [24]. It can predict long-term cardiovascular risk in individuals without any prior evidence of cardiovascular disease. The serum hsCRP levels correlates better to the metabolic syndrome [22]. The significantly elevated serum CRP levels are associated with malignant diseases, bacterial infections and very high 30-day mortality rates in hospitalized medical patients. It has been demonstrated that CRP is directly related to plasminogen activator inhibitor type 1 (PAI-1) levels in diabetics with the 4G allele at position 675 of the PAI-1 gene [25].

The serial measurements of CRP, serum amyloid A and procalcitonin (PCT) have also been proved to be accurate and reliable markers in the diagnosis of necrotizing enterocolitis in premature infants [26]. In middle-aged subjects, the CRP levels decrease continuously with increasing levels of physical fitness [27]. The repeated CRP measurements in an acute setting provide clinicians valuable information to establish the correct disease diagnosis and to refrain the unnecessary use of antibiotics. The determination of CRP is also important in renal colic patients as it is critical in deciding the placement of urinary stent [28].

The CRP levels are very important for the diagnosis of neonatal sepsis [29]. In fact, it is the best indicator of neonatal sepsis in comparison to IL-6, soluble TNF receptors (p55 and p75) and soluble adhesion molecules (Intercellular Adhesion Molecule 1 (ICAM-1) and E-selectin). Bacterial sepsis is one of the major causes of neonatal morbidity and mortality that affects 1-10 per 1000 live births. The neonatal sepsis is probably caused by bacterial exposure during intrauterine life or at delivery. The precise and early diagnosis of infected neonates, which is hindered at the moment due to unreliable clinical signs and absence of good diagnostic tests, is critical. The serial measurements on 2^{nd} and 3^{rd} days are more informative in comparison to a single CRP measurement as there are physiological changes in CRP levels in neonates during the initial days.

In case of acute inflammation, such as infection, the CRP levels rises up to 50,000-fold. It rises above the physiological level within 6 h, reaches the peak at 48 h and has a constant half-life thereafter. The CRP levels in the normal human serum are usually less than 10 mg/L. The median physiological serum concentration of CRP in humans is 0.8 mg/L. However, they can reach up to 350-400 mg/L in disease states. The CRP levels increase in the first 6-8 h with peak at ~48 h. Thereafter, it falls when the inflammatory stimulus is removed with a half-life of 18 h. The CRP levels are between 10-40 mg/L in mild inflammation and viral infections; 40-200 mg/L in active inflammation and bacterial infections; and, > 200 mg/L in severe bacterial infections and burns [30]. The CRP levels greater than the cut-off point of 3 mg/L are associated with an increased risk of occlusive arterial disease, especially acute coronary syndrome.

The two different CRP concentration ranges, normal (0.2-480 mg/L) and high sensitivity (0.08-80 mg/L), need to be detected in neonatal sepsis. The CRP levels greater than the cut-off point of 5 mg/L are indicative of neonatal sepsis. Initially, the high sensitivity CRP assay is performed. But if the CRP levels are >80 mg/L, the normal CRP assay is also performed. Although enzyme-linked immunosorbent assay (ELISA) [31], latex agglutination [32], and immunoturbidimetry [33] have been the most widely used assay formats for the precise determination of CRP, a wide range of bioanalytical techniques and assay formats [34-38] have also been devised.

REFERENCES

[1] Tillett WS, Francis T. Serological reactions in pneumonia with a nonprotein somatic fraction of pneumococcus. J Exp Med 1930; 52: 561-71.
http://dx.doi.org/10.1084/jem.52.4.561

[2] Thompson D, Pepys MB, Wood SP. The physiological structure of human C-reactive protein and its complex with phosphocholine. Structure 1999; 7: 169-77.
http://dx.doi.org/10.1016/S0969-2126(99)80023-9

[3] Ridker PM. High-sensitivity C-reactive protein, inflammation, and cardiovascular risk: from concept to clinical practice to clinical benefit. Am Heart J 2004; 148: S19-S26.
http://dx.doi.org/10.1016/j.ahj.2004.04.028

[4] Nguyen-Vermillion A, Juul SE, McPherson RJ, Ledbetter DJ. Time course of C-reactive protein and inflammatory mediators after neonatal surgery. J Pediatr 2011; 159: 121-6.
http://dx.doi.org/10.1016/j.jpeds.2010.12.048

[5] Young B, Gleeson M, Cripps AW. C-reactive protein: a critical review. Pathology 1991; 23: 118-24.
http://dx.doi.org/10.3109/00313029109060809

[6] Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest 2003; 111: 1805-12.

[7] Myers GL, Rifai N, Tracy RP, *et al*. CDC/AHA workshop on markers of inflammation and cardiovascular disease: application to clinical and public health practice: report from the laboratory science discussion group. Circulation 2004; 110: e545-9.

[8] Buckley DI, Fu R, Freeman M, Rogers K, Helfand M. C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analyses for the U.S. Preventive Services Task Force. Ann Intern Med 2009; 151: 483-95.
http://dx.doi.org/10.7326/0003-4819-151-7-200910060-00009

[9] Lewandrowski K, Chen A, Januzzi J. Cardiac markers for myocardial infarction. Am J Clin Pathol 2002; 118: S93-S99.

[10] Pepys MB, Hirschfield GM, Tennent GA, *et al*. Targeting C-reactive protein for the treatment of cardiovascular disease. Nature 2006; 440: 1217-21.
http://dx.doi.org/10.1038/nature04672

[11] Morimoto H, Sakata K, Oishi M, *et al*. Effect of high-sensitivity C-reactive protein on the development of diabetes as demonstrated by pooled logistic-regression analysis of annual health-screening information from male Japanese workers. Diabetes Metab 2012.
http://dx.doi.org/10.1016/j.diabet.2012.03.004

[12] Tomiyama H, Okazaki R, Koji Y, *et al*. Elevated C-reactive protein: a common marker for atherosclerotic cardiovascular risk and subclinical stages of pulmonary dysfunction and osteopenia in a healthy population. Atherosclerosis 2005; 178: 187-92.
http://dx.doi.org/10.1016/j.atherosclerosis.2004.08.014

[13] Kuo H-K, Yen C-J, Chen J-H, Yu Y-H, Bean JF. Association of cardiorespiratory fitness and levels of C-reactive protein: data from the National Health and Nutrition Examination Survey 1999-2002. Int J Cardiol 2007; 114: 28-33.
http://dx.doi.org/10.1016/j.ijcard.2005.11.110

[14] Groblewska M, Mroczko B, Sosnowska D, Szmitkowski M. Interleukin 6 and C-reactive protein in esophaeal cancer. Clin Chim Acta 2012.
http://dx.doi.org/10.1016/j.cca.2012.05.009

[15] Harris MT, Davis WW, Le N-A, *et al*. Free oxygen raicals in whole blood correlate strongly with high-sensitivity C-reactive protein. J Clin Pathol 2007; 1: 593-8.

[16] Jansen LMA, van der Horst-Bruinsma IE, van Schaardenburg D, Bezemer PD, Dijkmans BAC. Predictors of radiographic joint damage in patients with early rheumatoid arthritis. Ann Rheum Dis 2001; 60: 924-7.
http://dx.doi.org/10.1136/ard.60.10.924

[17] Chundadze T, Steinvil A, Finn T, *et al*. Significantly elevated C-reactive protein serum levels are associated with very high 30-day mortality rates in hospitalized medical patients. Clin Biochem 2010; 43: 1060-3.
http://dx.doi.org/10.1016/j.clinbiochem.2010.06.006

[18] Kao PC, Shiesh S-C, Wu T-J. Serum C-reactive protein as a marker for wellness assessment. Ann Clin Lab Sci 2006; 36: 163-9.

[19] Wu S, Hsu L-A, Cheng C-F, *et al*. Effect of obesity on the association between *ATF3* gene haplotypes and C-reactive protein level in Taiwanese. Clin Chim Acta 2011; 412: 1026-31.
http://dx.doi.org/10.1016/j.cca.2011.02.011

[20] Faucher G, Guenard F, Bouchard L, *et al*. Genetic contribution to C-reactive protein levels in severe obesity. Mol Genet Metab 2012; 105: 494-501.
http://dx.doi.org/10.1016/j.ymgme.2011.11.198

[21] Anan F, Masaki T, Kikuchi H, *et al*. Association between plasma high-sensitivity C-reactive protein and insulin resistance and white matter lesions in Japanese type 2 diabetic patients. Diabetes Res Clin Pract 2010; 87: 233-9.
http://dx.doi.org/10.1016/j.diabres.2009.10.017

[22] Lin M-S, Shish S-R, Li H-Y, *et al*. Serum C-reactive protein levels correlates better to metabolic syndrome defined by International Diabetes Federation than by NCEP ATP III in men. Diab Res Clin Pract 2007; 77: 286-92.
http://dx.doi.org/10.1016/j.diabres.2006.11.013

[23] O'Bryant SE, Waring SC, Hobson V, *et al*. Decreased C-reactive protein levels in Alzheimer disease. J Geriatr Psychiatry Neurol 2010; 23: 49-53.
http://dx.doi.org/10.1177/0891988709351832

[24] Clos TWD. C-reactive protein as a regulator of autoimmunity and inflammation. Arthritis Rheum 2003; 48: 1475-7.
http://dx.doi.org/10.1002/art.11025

[25] Testa R, Bonfigli AR, Sirolla C, *et al*. C-reactive protein is directly related to plasminogen activator inhibitor type 1 (PAI-1) levels in diabetic subjects with the 4G allele at position – 675 of the PAI-1 gene. Nutr Metab Cardiovasc Dis 2008; 18: 220-6.
http://dx.doi.org/10.1016/j.numecd.2006.10.001

[26] Cetinkaya M, Ozkan H, Koksal N, Akaci O, Ozgur T. Comparison of the efficiency of serum amyloid A, C-reactive protein, and procalcitonin in the diagnosis and follow-up of necrotizing enterocolitis in premature infants. J Pediatr Surg 2011; 46: 1482-9.
http://dx.doi.org/10.1016/j.jpedsurg.2011.03.069

[27] Aronson D, Sheikh-Ahmad M, Avizohar O, *et al*. C-reactive protein is inversely related to physical fitness in middle-aged subjects. Atherosclerosis 2004; 176: 173-9.
http://dx.doi.org/10.1016/j.atherosclerosis.2004.04.025

[28] Angulo JC, Gaspar MJ, Rodriguez N, Garcia-Tello A, Torres G, Nunez C. The value of C-reactive protein determination in patients with renal colic to decide to decide urgent urinary diversion. Urology 2010; 76: 301-6.
http://dx.doi.org/10.1016/j.urology.2009.12.002

[29] Dollner H, Vatten L, Austgulen R. Early diagnostic markers for neonatal sepsis: comparing C-reactive protein, interleukin-6, soluble tumour necrosis factor receptors and soluble adhesion molecules. J Clin Epidemiol 2001; 54: 1251-7.
http://dx.doi.org/10.1016/S0895-4356(01)00400-0

[30] Clyne B, Olshaker JS. The C-reactive protein. J Emerg Med 1999; 17: 1019-25.
http://dx.doi.org/10.1016/S0736-4679(99)00135-3

[31] McDade TW, Burhop J, Dohnal J. High-sensitivity enzyme immunoassay for C-reactive protein in dried blood spots. Clin Chem 2004; 50: 652-4.
http://dx.doi.org/10.1373/clinchem.2003.029488

[32] Collet-Cassart D, Van den Abbeele E, Poncelet S. A quantitative C-reactive protein assay using latex agglutination in microtiter plates. J Immunol Meth 1989; 125: 137-41.
http://dx.doi.org/10.1016/0022-1759(89)90086-0

[33] Raj V, Sreenivasan K. Selective detection and estimation of C-reactive protein in serum using surface-functionalized gold nano-particles. Anal Chim Acta 2010; 662: 186-92.
http://dx.doi.org/10.1016/j.aca.2010.01.007

[34] Bryan T, Luo X, Bueno PR, Davis JJ. An optimised electrochemical biosensor for the label-free detection of C-reactive protein in blood. Biosens Bioelectron 2013; 39: 94-8.
http://dx.doi.org/10.1016/j.bios.2012.06.051

[35] Choi HW, Sakata Y, Kurihara Y, Ooya T, Takeuchi T. Label-free detection of C-reactive protein using reflectometric interference spectroscopy-based sensing system. Anal Chim Acta 2012 ; 728: 64-8.
http://dx.doi.org/10.1016/j.aca.2012.03.030

[36] Hu WP, Hsu H-Y, Chiou A, Tseng KY, Lin H-Y, Chang GL, Chen S-J. Immunodetection of pentamer and modified C-reactive protein using surface plasmon resonance biosensing. Biosens Bioelectron 2006; 21: 1631-7.
http://dx.doi.org/10.1016/j.bios.2005.11.001

[37] Lee W-B, Chen Y-H, Lin H-I, Shiesh S-C, Lee G-B. An integrated microfluidic system for fast, automatic detection of C-reactive protein. Sens Actuators B 2011; 157: 710-21.
http://dx.doi.org/10.1016/j.snb.2011.04.087

[38] Deegan O, Walshe K, Kavanagh K, Doyle S. Quantitative detection of C-reactive protein using phosphocholine-labelled enzyme or microspheres. Anal Biochem 2003; 312: 175-81.
http://dx.doi.org/10.1016/S0003-2697(02)00439-6

[39] Ablij HC, Meinders AE. C-reactive protein: history and revival. Eur J Intern Med 2002; 13: 412-22.
http://dx.doi.org/10.1016/S0953-6205(02)00132-2

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