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Scand J Clin Lab Invest 2003; 63: 267–272

Correlations between serum amyloid A protein and C-reactive protein in infectious diseases

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Lannergård A, Larsson A, Kragsbjerg P, Friman G. Correlations between serum amyloid A protein and C-reactive protein in infectious diseases. Scand J Clin Lab Invest 2003; 63: 267–272.

Serum amyloid A (SAA) protein is an acute phase reactant that has recently become of increasing interest as a marker for disease and treatment monitoring. We have correlated SAA levels to those of C-reactive protein (CRP) in sera from 98 patients admitted to an infectious diseases clinic because of viral and bacterial infections, including hepatitis A and B, cytomegalovirus infection, varicellae-zoster, infectious mononucleosis, influenza A, bacterial pneumonia, streptococcal pharyngitis, bacterial sepsis and severe bacterial sepsis. The study population was chosen from the clinical setting as representatives of these frequently encountered patient groups. SAA levels correlated significantly with CRP levels ($r^2 = 0.757$, $p < 0.001$) for the entire studied population. Furthermore, positive correlations were found in viral ($r^2 = 0.572$, $p < 0.001$) and bacterial ($r^2 = 0.666$, $p < 0.001$) infections. Positive correlations were also observed when the values were compared in accordance with CRP levels higher and lower than 100 mg/L ($r^2 = 0.689$, $p < 0.001$; CRP > 100; $r^2 = 0.397$, $p < 0.001$; CRP < 100). Because SAA is more sensitive than CRP for the detection of minor inflammatory stimuli, as in the viral and low CRP groups, we conclude that SAA can be of use in several viral infections, as well as in non-invasive and early invasive bacterial infections.

Key words: acute phase proteins; bacterial infections; c-reactive protein; sensitivity; serum amyloid A protein; specificity; viral infections

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INTRODUCTION

Serum amyloid A (SAA) protein is an acute phase reactant that has recently attracted considerable attention in the clinical setting. Similar to C-reactive protein (CRP), it is synthesized by hepatocytes [1]. Human SAA, which is an α-globulin belonging to the apolipoprotein family, is encoded by genes in chromosome 11 and consists of two isotypes with molecular weights of 11,685 Da [2, 3]. CRP belongs to the pentraxin superfamily; it is encoded by chromosome 1 and consists of five subunits with a total molecular weight of 118 kDa [4]. Interleukin-6

DOI 10.1080/00365510310001636

(IL-6) and interleukin-1 (IL-1) are the most potent inducers of the acute phase response in human hepatocytes. The promotor gene of SAA is more sensitive than that of CRP to the IL-1β stimuli, whereas the promotor genes for both SAA and CRP are highly sensitive to the IL-6 stimuli. Furthermore, IL-1β and IL-6 have synergistic effects on the promotor genes of SAA and CRP [1, 5, 6]. In response to similar stimuli, SAA mRNA accumulation is more pronounced than CRP mRNA accumulation, which is probably due to post-transcriptional mechanisms [7, 8]. Correlations between SAA and CRP levels in serum were found to be positive in patients with rheumatoid arthritis and osteoarthritis [9, 10].

Both SAA and CRP increase from 100- to 1000-fold in serum during infectious diseases in humans [1, 4]. Some reports conclude that SAA is of great value for supporting a diagnosis of bacterial infection, as well as monitoring treatment efficacy in bacterial infections, including urinary tract infections, bacterial infections in neutropenic patients and pulmonary infections in cystic fibrosis patients [11–15] and a few reports claim SAA may be useful even in viral infections [16, 17]. Other reports, however, are more cautious in their judgment concerning the value of SAA [18, 19]. To our knowledge, there is no published study where SAA and CRP responses in the early phase of viral and bacterial infections are compared.

Consequently, the aim of this investigation was to study the correlation between SAA and a clinically established marker of the acute phase response in patients admitted to hospital for various viral and bacterial infections. We chose to compare SAA with CRP as they have similar kinetics and the same origin.

PATIENTS AND METHODS

Patients

Ninety-eight consecutive patients admitted to an infectious disease clinic in the acute phase of various viral and bacterial infections were enrolled in the study. Blood samples for serum SAA and CRP determination were obtained on admission to hospital.

The diagnoses were established as follows: hepatitis A and B and cytomegalovirus infection (positive test for specific IgM-antibodies), varicellae-zoster and influenza A (positive immunofluorescence antigen test on blister or nasopharyngeal secretion), infectious mononucleosis (positive test for heterophilic antibodies or Epstein-Barr virus-specific IgM-antibodies), streptococcal pharyngitis (positive antigen detection test or culture), pneumonia (positive chest X-ray and positive bacterial culture from a representative sputum sample), bacterial sepsis (fulfilling criteria of Systemic Inflammatory Response Syndrome (SIRS) without signs of organ failure, and positive blood culture) and severe bacterial sepsis (fulfilling criteria of SIRS with signs of organ failure and positive blood culture).

Blood was obtained in vacutainer tubes without additive (367609, Becton Dickinson, Rutherford, NJ, USA) and centrifuged at $1300 \times g$ for 10 min. The serum samples were stored at $-20^{\circ}C$ until analysed. The study was approved by the Ethics Committee of the Faculty of Medicine, Uppsala University, Uppsala, Sweden.

CRP and SAA assays

Analysis of CRP was performed by turbidimetry on a Hitachi 717 used for routine assays (Roche Diagnostics, Mannheim, Germany). SAA was measured by an ELISA method in accordance with the manufacturer's instructions (Cytoscreen Human SAA ELISA kit, BioSource International, Camarillo, CA, USA). Minimum detectable levels were 10 mg/L for CRP and 5 mg/L for SAA.

Statistical methods

The simple linear regression model and Spearman Rank Correlation test were used for correlational analyses of the data. Differences between SAA and CRP for different diagnoses were analysed using Fisher's exact test. The statistical package used for all analyses was Statview® for Windows NT, 1999. A p-value of <0.05 was considered significant. In calculations, values below minimum detectable level were set to these levels.

RESULTS

The studied population (Table I) was divided into viral and bacterial infections. The viral

TABLE I. Median serum amyloid A (SAA) and C-reactive protein (CRP) levels (mg/L) in serum in the acute phase of different viral and bacterial infections. CRP levels below 10 mg/L are noted <10.

Diagnosis	n	SAA mg/L Median (min-max)	CRP mg/L Median (min-max)
Viral infections	*52*	*164.5 (11–1620)*	*23.5 (<10–132)*
Hepatitis A	9	95 (13–222)	<10 (<10–40)
Hepatitis B	5	73 (68–73)	<10
Cytomegalovirus infection	7	147 (87–783)	28 (<10–115)
Varicellae-zoster	12	235.5 (11–1105)	<10 (<10–78)
Infectious mononucleosis	8	264.5 (145–1001)	32 (17–73)
Influenza A	11	980 (59–1620)	85 (18–132)
Bacterial infections	*46*	*1719.5 (268—6262)*	*136.5 (10–348)*
Bacterial pneumonia	11	2600 (618–4260)	155 (75–245)
Streptococcal pharyngitis	6	1170.5 (465–5850)	88 (57–222)
Bacterial sepsis	19	1560 (557–3536)	137 (59–326)
Severe bacterial sepsis	10	1483 (268–6262)	140.5 (10–348)
Total	*98*		

infections (n = 52) included hepatitis A and B, cytomegalovirus infection, varicellae-zoster, infectious mononucleosis and influenza A; the bacterial infections (n = 46) included bacterial pneumonia, streptococcal pharyngitis, bacterial sepsis and severe bacterial sepsis.

The SAA and CRP results are summarized in Table I. SAA and CRP levels were significantly higher in the total group of bacterial infections than in the total group of viral infections ($p < 0.001$). More specifically, SAA and CRP levels were significantly higher in bacterial pneumonia than in influenza A (for both markers $p < 0.01$), a difference that is potentially helpful in clinical practice. However, a significant difference between a viral and a bacterial aetiology was not established for SAA when comparing streptococcal pharyngitis and infectious mononucleosis, whereas CRP showed significantly higher levels in the bacterial than in viral throat infections ($p < 0.05$).

The levels of SAA correlated significantly with those of CRP for the entire studied population (Fig. 1A). Furthermore, positive correlations were noted in both the viral and bacterial group when tested separately (Fig. 1B, C).

The population was also divided as a function of the CRP level: patients with a CRP level below 100 mg/L (low range) formed one group, while those with a CRP level greater than 100 mg/L (high range) formed a second group. In this setting, positive correlations between SAA and CRP levels were also revealed for both groups (Fig. 1D, E).

The sensitivities for indicating a bacterial infection were equal and high for SAA and CRP above cut-off levels of 500 mg/L and 40 mg/L, respectively. However, when the cut-off levels were set to 1000 mg/L and 100 mg/L for the SAA and CRP markers, respectively, sensitivities were lower, whereas the specificities were higher (Table II).

DISCUSSION

The present study revealed significant positive correlations between SAA and CRP in acute infectious diseases, and similar correlation coefficients were observed in viral and bacterial infections. However, the correlation coefficient was lower in the lower CRP range (<100 mg/L) than at higher CRP levels (>100 mg/L). Both SAA and CRP significantly discriminated between bacterial and viral infections though the precision varied with the infecting organism and the cut-off levels chosen.

Most viral infections elicit a weak acute phase reaction with CRP values below 100 mg/L. Thus, one study showed that CRP levels in serum in viral meningitis caused by coxsackie B, echo 30, mumps virus, cytomegalovirus and herpes simplex virus type 2 are mostly less than 10 mg/L [20]. In another study, CRP levels below 7 mg/mL were recorded in parainfluenza and respiratory syncytial virus infections [16]. Furthermore, low mean CRP levels have been reported in gastroenteritis caused by rotavirus (17 mg/L)

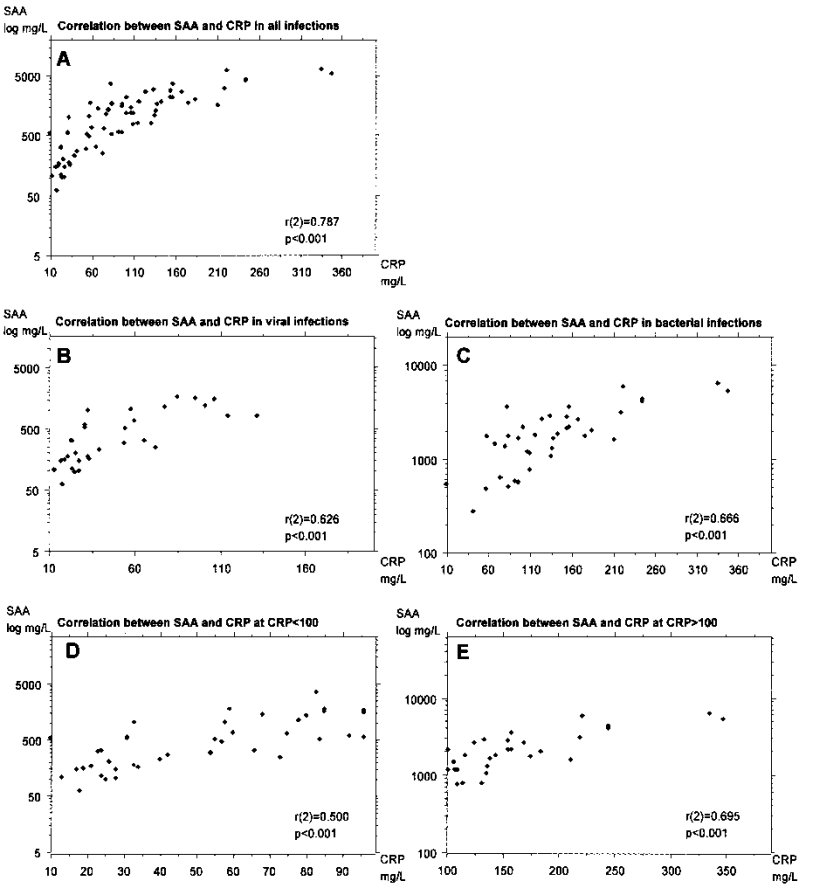

FIG. 1. Correlations between serum amyloid A (SAA) and C-reactive protein (CRP) levels (mg/L) in serum from; **A**: patients with hepatitis A and hepatitis B, cytomegalovirus infection, varicellae-zoster, infectious mononucleosis, influenza A, bacterial pneumonia, streptococcal pharyngitis, bacterial sepsis and severe bacterial sepsis; **B**: a subgroup of patients with viral infections; **C**: a subgroup of patients with bacterial infections; **D**: patients with CRP levels <100 mg/L; **E**: patients with CRP levels >100 mg/L.

[21], in uncomplicated influenza types A and B (41 mg/L) [22] and in adenovirus infection (19 mg/L) [16]. In experimental rhinovirus infection and influenza A in humans, CRP levels did not exceed 35 mg/L and 45 mg/L, respectively [19]. However, in influenza A, clinical studies have shown CRP to sometimes exceed 100 mg/L [23, 24]. In viral hepatitis, CRP levels have been found to be highest in acute hepatitis A, followed by acute hepatitis B, while the lowest levels have been observed in acute hepatitis non-A and non-B [25].

TABLE II. Sensitivity, specificity and efficiency of SAA and CRP in the discrimination between viral and bacterial infections.

Protein	Cut-off values	Sensitivity	Specificity	Efficiency
CRP mg/L	$\geq$40 mg/L	0.98	0.71	0.83
CRP mg/L	$\geq$100 mg/L	0.67	0.92	0.80
SAA mg/L	$\geq$500 mg/L	0.95	0.73	0.78
SAA mg/L	$\geq$1000 mg/L	0.79	0.87	0.78

Following experimental rhinovirus and influenza virus infections in humans, asymptomatic virus excretors showed a significant increase of SAA, whereas CRP levels were unaffected [19]. In other viral infections without complications, including measles, varicellae, mumps and echo 30 meningitis, SAA levels were increased in 56% of cases, whereas CRP levels were normal in all cases [17]. In yet another study, low mean SAA levels (31–141 mg/L) were noted in uncomplicated infections with adenovirus, measles virus, influenza virus, parainfluenza virus, respiratory syncytial virus and in aseptic meningitis [16]. Although further studies are needed, these studies suggest that SAA is a more sensitive marker than CRP in infections with low inflammatory activity, including many viral infections. In influenza A, which is often a vigorous stimulator of an acute phase response, one study showed that the mean SAA level was 503 mg/L on admission of patients to hospital [23].

SAA has been the subject of a limited number of studies on bacterial infectious diseases, where some authors have considered it to be equivalent to CRP in clinical practice. However, in cystic fibrosis patients, SAA correlated with impaired lung function associated with multiple infections and also correlated better with bacterial colonization with positive sputum cultures of *Pseudomonas aeroginosa* than did CRP [13]. SAA has also been reported to be as useful as CRP in monitoring antibiotic therapy in urinary tract infections [11].

In clinical praxis, it is difficult in the acute stages to differentiate viral from bacterial infections on the basis of SAA or CRP alone, because there is a range between 500 and 1000 mg/L for SAA, and 40 and 100 mg/L for CRP, in which the discrimination power is poor. The clinical picture and the patient's history, including the duration of illness, remain cornerstones in the making of a preliminary diagnosis. Bacterial cultures and serology tests can subsequently be used to support the initial suspicion. Further studies should elucidate critical cut-off points for SAA in relation to the duration of illness, patient history and clinical picture. In addition to viral infections, SAA is proposed to be investigated and compared to CRP in bacterial infections with low inflammatory activity, including infections related to foreign bodies, such as joint prostheses or heart valve prostheses, where low-virulent bacteria are commonly involved.

CONCLUSION

In conclusion, we found positive correlations between SAA and CRP in acute infectious diseases. The correlation is weaker at the lower CRP levels (CRP $<$ 100 mg/L) than at the higher CRP levels. We also found that the sensitivity and specificity for the two tests are comparable. Finally, our results indicated that SAA and CRP discriminate between bacterial and viral infections, depending on the infecting organism.

ACKNOWLEDGEMENTS

In memoriam, we honour the memory of Krister Hellsing, M.D., Ph.D. It was Krister who initiated this study.

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Received: 12 July 2002
Accepted: 5 May 2003