

Comparative analysis of Bayer wide-range C-reactive protein (wr-CRP) and the Dade-Behring high sensitivity C-reactive protein (hs-CRP) in patients with inflammatory bowel disease

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OBJECTIVE: The recently introduced Bayer wide-range C-reactive protein (wr-CRP) assay might be relevant for the real-time low-cost and online determination of inflammatory bowel disease (IBD) activity. Our aim was to examine whether wr-CRP can substitute for the Dade Behring high sensitivity C-reactive protein (hs-CRP) assay in IBD patients.

METHODS: A total of 71 patients with IBD, of whom 48 had Crohn's disease CD and 23 had ulcerative colitis (UC) with various intensities of disease activity participated in the study. The CRP of patients who were under treatment at the Department of Gastroenterology

and Liver Diseases were measured using both wr-CRP and the hs-CRP.

RESULTS: A significant ($r = 0.995$; $P < 0.001$) correlation was noted between the hs-CRP and wr-CRP measurements for the whole sample as well as for the two diseases, CD ($r = 0.994$; $P < 0.001$) and UC ($r = 0.997$; $P < 0.001$), which were analyzed separately.

CONCLUSION: The Bayer wr-CRP assay might be a useful low-cost and real-time inflammation-sensitive biomarker in patients with IBD.

KEY WORDS: biomarker, C-reactive protein, inflammatory bowel disease.

INTRODUCTION

It has been repeatedly shown that C-reactive protein (CRP) is a useful inflammation-sensitive biomarker to determine the intensity of acute phase response in patients with inflammatory bowel diseases (IBD).^{1–5} In the past, less sensitive assays precluded the measurements of values below 5 mg/L. This situation has changed

following the introduction of high-sensitivity assays, of which the Dade-Behring assay is the most prevalent in clinical practice.⁶

The recently introduced Bayer wide-range C-reactive protein (wr-CRP) permits measurements of a wide range of CRP concentrations, including values below 5 mg/L. In fact, it has been shown to correlate significantly with the Dade-Behring assay in a relatively wide range of results.^{7–9} The low cost and online availability of the wr-CRP assay might be attractive for gastroenterologists, providing a real-time assessment of IBD disease activity in their daily practice.

MATERIALS AND METHODS

The patients were recruited during routine follow-up in the IBD center at the Department of Gastroenterology

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and Liver Diseases at the Tel Aviv Sourasky Medical Center, Tel Aviv, Israel. All participants gave their written informed consent according to the instructions of the local ethics committee. Individuals with 3 months' infection/inflammation and those who had a recent trauma or surgery were excluded. The disease activity was determined according to the Crohn's disease activity index^{10,11} (CDAI) in patients with Crohn's disease (CD) and according to the Mayo score¹² for patients with ulcerative colitis (UC). The patients were classified into four categories of disease activity. The Mayo and CDAI scores for each were: remission (0–2 and 0–150), mild (3–5 and 151–220), moderate (6–10 and 221–450) and severe (11–12 and 451–600)^{13,14} for the UC and CD groups, respectively.

Laboratory methods

High sensitivity C-reactive protein (hs-CRP)

High-sensitivity C-reactive protein (hs-CRP) was analyzed by an immunonephelometric assay on a BN II analyzer (Dade Behring, Marburg, Germany) using a Dade Behring kit for hs-CRP assay (Cat. No. OQIY). This assay is based on particle-enhanced immunonephelometry and permits the measurement of CRP concentrations as low as 0.16 mg/L.¹⁵ The results of the hs-CRP assay in our laboratory are routinely compared to those obtained by the College of American Pathologists, as required by ISO 9001 quality management systems requirements, and are in good agreement with them.

Wr-CRP

The Wr-CRP in the serum samples was analyzed by an immunoturbidimetric assay on the ADVIA 1650 chemistry system using Bayer Advia kit for wr-CRP (Cat. No. BO1-4800-01). It has a particularly wide sensitivity range with a lower limit of detection of 0.12 mg/L. The wr-CRP reagent is a suspension of uniform polystyrene latex particles coated with an anti-CRP antibody. When serum-containing CRP is mixed

with the latex reagent, agglutination takes place, resulting in an increase in the turbidity. This turbidity is measured at 571 nm. CRP concentration in the serum is determined from the calibration curve that is generated by the calibrators.

Statistical analysis

The data were summarized and displayed as mean \pm SD for the continuous variables (such as age and inflammatory markers). In order to compare the two methods of measuring CRP we used the Bland–Altman analysis to evaluate the mean difference between the methods, and the Deming regression to evaluate the slope and the intercept of the regression line best fitted between the methods. We further used Pearson's correlation to assess the correlation between hs-CRP to wr-CRP. Since the CRP has a non-normal distribution, we used a logarithmic transformation that converts it to a normal distribution for all statistical procedures. All the results expressed as CRP are a back-transformed geometrical mean and standard deviation. The level of significance used for all of the above analyses was two tailed, $P < 0.05$. The SPSS statistical package was used to perform all statistical evaluation (Version 13.0, SSPS Inc., Chicago, IL, USA).

RESULTS

Seventy-one IBD patients participated in this study, of whom 48 had CD and 23 had UC; their respective mean \pm SD age being 34.4 ± 10.5 and 44.6 ± 13.1 years. There were 29 CD and 12 UC patients in remission. The remainder had mild (10 CD, four UC), moderate (five CD, three UC) and severe (two CD, one UC) disease. The mean CDAI score of the CD patients was 140 ± 113 , and the mean Mayo score of the UC patients was 3.2 ± 2.95 . The average duration of the disease was 8.6 ± 7.1 and 11.9 ± 12.5 years for the CD and UC patients, respectively. Concomitant medications consumed by the patients are reported in Table 1.

Table 1. Treatment for inflammatory bowel disease

Medication	Crohn's disease Number of patients (%) [†]	Ulcerative colitis Number of patients (%) [†]
5-aminosalicylic acid (5-ASA)	32 (67)	17 (74)
Antibiotics (metronidazole/ciprofloxacin)	1 (2)	2 (9)
Steroids	9 (19)	4 (17)
Azathioprine/6MP	16 (33)	10 (44)
No treatment	5 (10.5)	3 (13)

[†]Some patients received more than one medication.

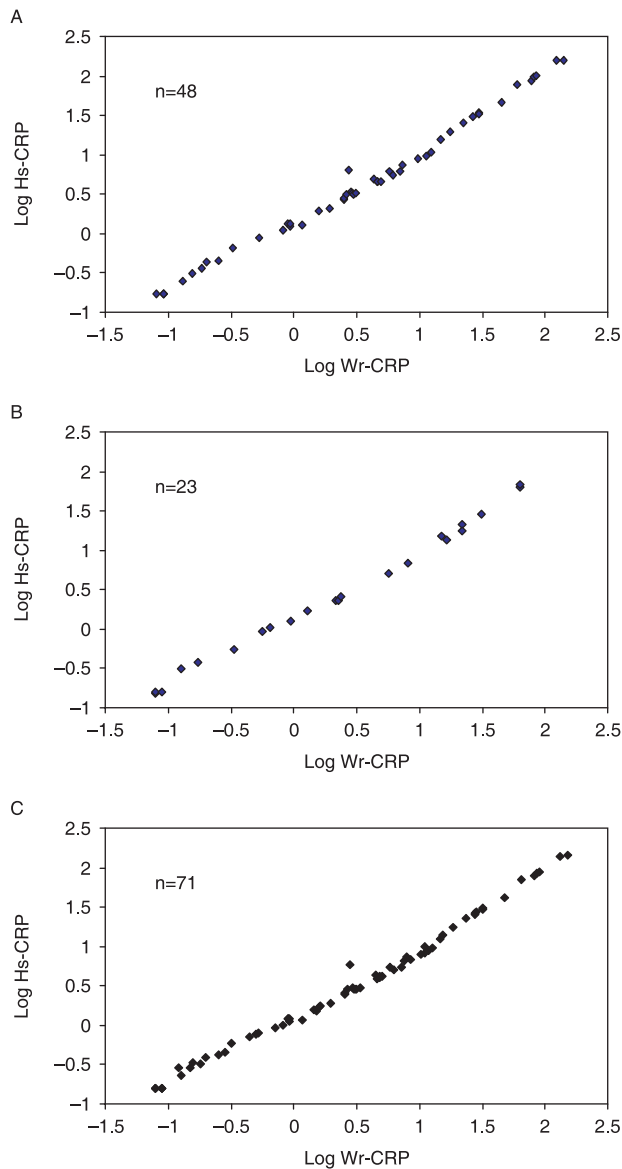


Figure 1. Correlation between hs-CRP to wr-CRP in (a) 48 Crohn's disease patients; (b) 23 ulcerative colitis patients; and (c) 71 IBD patients.

Forty-three patients had CRP values below 5 mg/L in both the hs-CRP and wr-CRP measurements. A significant correlation ($r = 0.995$; $P < 0.001$) was noted between the hs-CRP and wr-CRP measurements for the whole sample as well as for the two diseases; CD ($r = 0.994$; $P < 0.001$) and UC ($r = 0.997$; $P < 0.001$), which were analyzed separately (Fig. 1).

In order to compare the two methods, Bland–Altman statistical analysis was used. The mean difference

between the measures (wr-CRP minus hs-CRP) across all the whole range of CRP results was 0.64 with a standard deviation from the bias of 2.02 (95% confidence interval of the bias: -3.32 – 4.61). The Deming regression line between the two methods revealed a slope of 1.02, and an intercept of -0.31 . Thus the two methods had a high agreement, suggesting that they may be used as alternatives for each other.

DISCUSSION

C-reactive protein has been shown to be a useful inflammation-sensitive biomarker in patients with IBD. It is currently used in addition to the clinical score to monitor IBD activity.^{1–5,16} However, previously used assays did not permit the evaluation of CRP concentrations below 5 mg/L and in addition, they were not always available at real time and low cost. Low CRP concentration might be detected in IBD patients in remission. Importantly, a CRP concentration that is even within the normal range had been shown to have potential cardiovascular implications.¹⁷ Moreover, CRP might be an effect and not necessarily an innocent bystander in the inflammatory process,¹⁸ and may on its own account be a target for potential therapeutic manipulation.¹⁹ Thus, assays that may detect low CRP levels efficiently are required.

The recently introduced Bayer wr-CRP might be attractive for the clinician due to its low cost and real time availability. In fact, it is currently used on the Bayer Advia routine, an almost automatic system, and is performed on the same sample used for routine biochemistry. Thus, the results are available in less than an hour and at an extremely low cost, and they may be generated during the IBD patients' visit at the clinic.

In the present study we have performed a comparative analysis between the commonly used Bayer wr-CRP and the Dade-Behring hs-CRP. The good correlation is in accordance with our previously published studies in other diagnostic categories,^{7–9} suggesting the potential usefulness of this assay in IBD patients. The limitation of the present study is the relative small number of patients that precluded sub-analysis of the correlations for each disease activity category in both UC and CD. However, a sub-analysis for very low CRP concentrations was previously performed in one of our studies and showed a good correlation in individuals who have a hs-CRP concentration of below 5 mg/L. For example, in a group of 384 men in the CRP range between 1 and 3 mg/L the correlation was $r = 0.934$, $P < 0.0005$. A similar correlation was seen in women ($r = 0.926$, $P < 0.0005$, $n = 172$).⁸

We conclude that the correlation between the widely used Dade-Behring hs-CRP and the Bayer wr-CRP assay is good and is similar to our observations in other diagnostic categories. The Bayer wr-CRP might be a useful, low cost and real-time inflammation-sensitive biomarker in patients with IBD.

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