Correlated Expression of High-Sensitivity C-Reactive Protein in Relation to Disease Activity in Inflammatory Bowel Disease: Lack of Differences between Crohn’s Disease and Ulcerative Colitis

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Abstract

Background/Aims: As opposed to regular C-reactive protein (CRP) assays, the introduction of high-sensitivity ones has enabled us to detect low grade inflammation in patients with inflammatory bowel disease (IBD). We addressed the subject of the degree of correlation between the concentration of high-sensitivity CRP (hs-CRP) and the inflammatory IBD activity score. Methods: Included were 90 patients with Crohn’s disease (CD), 70 with ulcerative colitis (UC) and 160 controls. Disease activity was determined using CD activity index (CDAI) for CD and Mayo score for UC. The Dade Boerhing BNII Nephelometer was used to determine the hs-CRP concentrations. Results: The coefficient of correlation between hs-CRP and the disease activity score was similar for both UC (0.26) and CD (0.36). Conclusions: These findings are relevant for therapeutic intervention in which a greater absolute reduction in the hs-CRP concentration in CD patients (who generally present higher CRP concentrations than those found in UC) might be interpreted as a better response compared to the same absolute reduction in UC patients. This information is needed for clinicians using the hs-CRP assay to estimate IBD disease activity in daily practice.

Introduction

Inflammatory bowel diseases (IBDs) are associated with an acute-phase response which is used by clinicians to detect and quantitate both IBD activity as well as response to treatment [1]. In this regard, C-reactive protein (CRP) is one of the most used biomarkers [2]. In fact, it became a useful tool to monitor disease activity in both Crohn’s disease (CD) [3] and ulcerative colitis (UC) [4]. Yet, it has been observed that patients with UC present lower CRP concentrations; an observation that might...
help to differentiate between UC and CD [2]. However, it has not been clarified whether the correlation between CRP and the disease activity index is the same for both conditions. This is especially true for the recently introduced high-sensitivity CRP (hs-CRP) assays.

The remarkable heterogeneity in the CRP response between CD and UC should be kept in mind when interpreting results obtained in daily practice. Although there is no good explanation for this heterogeneity, we address the question of the correlation that exists between hs-CRP concentrations and the disease activity for both UC and CD. The present study demonstrates that while patients with UC do present lower CRP concentrations, a similar degree of correlation exists between hs-CRP and the disease activity index in both diseases. These findings might contribute to the clinical utility of this biomarker in the context of patients with IBD.

**Patients and Methods**

All patients and controls agreed to participate in the study and signed written informed consent forms according to the instructions of the local ethics committee. Patients with IBD were recruited both during their routine visit to the Gastroenterology Institute and when hospitalized during an exacerbation of the disease. Disease activity was determined by using the CD activity index (CDAI) [5, 6] for CD and the Mayo Score for UC [7–9]. We divided the patients with both CD and UC into 4 categories of disease activity, namely, remission, mild, moderate and severe; the respective scores being 0–2, 3–5, 6–10 and 11–12 for the Mayo Score [7], and 0–150, 151–220, 221–450 and 451–600 for the CDAI [5].

We have used the database of the Tel Aviv Medical Center Inflammation Survey, a registered data bank, Data Banks Registry, Ministry of Justice, State of Israel [10–12] for the process of matching controls. This is a cross-sectional study to which we invited apparently healthy employees of the Tel Aviv Medical Center and the Tel Aviv Municipality (Israel) and individuals with atherothrombotic risk factors who are in follow-up at the outpatient clinics of the Medical Center. Excluded were any individuals with an underlying inflammatory disease (arthritis, IBD, etc.) as well as individuals with any infections or other inflammatory condition, including infarction, surgery or angiography during the 6 months before recruitment. Individuals with anemia (hemoglobin 13.5% for men and 11.7% for women) and those treated with steroid or non-steroidal anti-inflammatory medication, except for aspirin (at doses lower than 325 mg/day), were excluded as well.

Venous blood was drawn following an overnight fast. The blood count was performed using the Beckman STKS Coulter (Beckman Coulter, Nyon, Switzerland/Miami, Fla., USA), quantitative fibrinogen by the method of Clauss [13] and Sysmex 6000 autoanalyzer (Sysmex Corporation, Hyaga, Japan), while the erythrocyte sedimentation rate was performed by the method of Westergren [14]. The quantitative concentration of hs-CRP was determined by the Boering BN II Nephelometer (Dade Boering, Marburg, Germany) and a method according to Rifai et al. [15]. The lowest hs-CRP concentration with this method is 0.17 mg/l.

**Statistical Analysis**

All continuous variable data were summarized and are displayed as mean ± SD for each patient group, and all the categorical data were summarized and displayed as the number and percentage of participants in each group. The hs-CRP has a non-normal distribution, thus we used logarithmic transformation, and all the results expressed as hs-CRP are a back-transformed geometric means and SD. For all continuous variables, a one-way ANOVA was performed to compare the various parameters between the 2 groups of IBD and the control group. Hochberg’s multiple comparison technique was used for pair-wise comparison between those categories. For all categorical variables, the χ² test was used to determine the difference between the 3 groups. Pearson correlations for confounding variables were used to evaluate the association between the hs-CRP and the two scores of disease activity in CD and in UC. Finally, we divided each IBD group into 4 groups based on disease activity: remission, mild, moderate and severe, and then, in order to evaluate whether the means of hs-CRP were equal in the 2 groups, the Mann-Whitney U test was performed for the 2 independent samples. The SPSS statistical package was used to perform all statistical evaluation (SPSS Inc., Chicago, Ill., USA).

**Results**

We have included a total of 90 patients with CD, 70 with UC and 160 age-, sex- and body mass index-matched controls. In patients with UC, 34.3% had pancolitis, the same percentage suffered from left-sided colitis, 17% had normal histology, 8.6% had proctosigmoiditis, 3% proctitis, and 3% extensive colitis. The mean ± SD of age, body mass index and hs-CRP in both groups of IBD is reported in table 1. A significant increment in the hs-CRP concentration is seen in individuals with IBD as opposed to the controls.

The gender and cardiovascular risk factors in the 3 groups of UC, CD and controls are reported in table 2. No significant differences were noted except from a high percentage of diabetes in the UC group. Intake of anti-inflammatory medications is reported in table 3. It can be seen that the prevalence of anti-inflammatory medications is similar in both groups of IBD patients.

The mean and median of hs-CRP in the groups of disease severity in both IBD groups plus the Mann-Whitney statistical significance between the groups is reported in table 4. Although significant differences (probably due to the relatively small sample size) were not demonstrated, the absolute values of hs-CRP are higher in the CD group.
We have calculated the Pearson coefficients of correlation between log hs-CRP and the disease severity score in the 2 IBD groups and found that they were almost identical. In fact, it was 0.262 (p = 0.03) in UC and 0.365 (p = 0.001) in CD. A graphic presentation of these correlations is given in figure 1.

Finally, we performed a correlation between the disease activity score and several other acute-phase response factors.
reactants. For CD we found a significant correlation between CDAI and fibrinogen ($r = 0.29$, $p = 0.007$), erythrocyte sedimentation rate ($r = 0.32$, $p = 0.004$) as well as albumin ($r = -0.5$, $p < 0.0001$). The relevant results for the Mayo Score were $r = 0.36$ ($p = 0.003$) for platelet count, $r = 0.36$ ($p = 0.02$) for white blood cell count, $r = 0.37$ ($p = 0.002$) for the sedimentation rate, and $r = -0.45$ ($p = 0.05$) for correlation with the albumin level.

### Discussion

It has been shown that quantitative CRP measurements may help determine the degree of disease activity in patients with IBD. However, at the same time it has been noted that individuals with UC present lower CRP concentrations perhaps due to restriction of the disease solely to the intestinal mucosa [2] and that this difference might be used to differentiate both types of IBD.

The introduction of hs-CRP assays to clinical practice enabled evaluation of CRP concentrations that were previously thought to be within normal limits when studied with less sensitive assays. We therefore wished to determine the correlation between hs-CRP and IBD disease activity using the sensitive assay and to determine whether the correlation is the same for both types of IBD, namely CD and UC.

The present study shows that despite the fact that patients with CD generally present higher hs-CRP concentrations, the degree of correlation between the hs-CRP concentration and IBD disease activity is similar for both UC and CD.

CRP elevation in patients with IBD is part of a generalized acute-phase response [16]. This is a complex of events that reflects both synthetic activities as well as genetic modulation [17]. It is therefore relevant to understand the inter-relations that exist between disease activity and hs-CRP concentrations in patients with both UC and CD. The main finding of the present study is that patients with UC react to disease exacerbation with a similar hs-CRP increment although they synthesize less protein per a given score of disease activity.

CRP is not the only acute-phase reactant that was found to be lower in individuals with UC [18]. It is possible therefore that the acute-phase response in this disease is somewhat attenuated as compared with CD. Although we included several other acute-phase reactants, the focus of our study remains the use of hs-CRP in various degrees of IBD activity. The above-mentioned data are essential for clinicians who might translate this laboratory information into an erroneous impression of a less active disease.

The present findings might have special relevance for therapeutic interventions. They practically show that for a given change in CRP concentration there is a similar change in disease activity score for both patients with UC and CD. In fact, the slope of the correlation between CRP and IBD disease activity is the same for both diseases. Thus, although in terms of absolute CRP, patients with CD might show a greater CRP reduction, this might be translated to the same effect on disease activity in UC patients who show a less absolute reduction in CRP concentrations.

A limitation of our analysis in UC patients is the small number of patients with limited and distal colitis. In these individuals, CRP concentrations might be especially low.

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**Fig. 1.** Scatter plot and regression line of the log high-sensitivity C-reactive protein (hs-CRP) in relation to the disease activity scores for Crohn’s disease (a) and ulcerative colitis (b).
[19, 20]. However, due to the fact that only a few patients were included in this category, they probably did not have a major effect on the results of the whole cohort. Another limitation of the study is that several patients were under various medications with anti-inflammatory activity (table 3). Obviously one cannot exclude the possibility that this could have an effect on the results of the biomarker concentrations.

We conclude that the correlation between CRP concentrations and IBD disease activity is similar for both UC and CD. These findings might be relevant once CRP is used to monitor IBD activity.

References


C-Reactive Protein in Relation to Disease Activity in IBD

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