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C-reactive protein as a diagnostic and prognostic factor in inflammatory bowel diseases

Białko C-reaktywne (CRP) jako czynnik diagnostyczny i prognostyczny w nieswoistych chorobach zapalnych jelit

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Summary

Aim:	The study aimed to evaluate high-sensitivity CRP (hsCRP) as a diagnostic and predictive marker in patients with inflammatory bowel disease (IBD).
Material/Methods:	Medical history of 106 patients with IBD revealed hsCRP concentrations at diagnosis and during the follow-up period.
Results:	The study showed that the majority of investigated patients had elevated hsCRP concentrations at diagnosis, although the mean concentration was much higher in the group of patients with Crohn's disease (CD) than the group with ulcerative colitis (UC) ($P<0.001$). The overall decrease in mean hsCRP concentration observed during the follow-up period was larger in the group of CD patients. The analysis showed a correlation between hsCRP concentrations at diagnosis and risk of surgery in the group of CD patients ($r=0.408$, $P=0.002$), but not in the group of UC patients. In a logistic regression analysis, surgery in CD patients was associated with age (OR: 0.89, 95% CI: 0.8–1.0, $P=0.05$) and hsCRP concentration (OR: 1.02, 95% CI: 1.0–1.04, $P=0.03$) at diagnosis.
Discussion:	HsCRP might be a useful diagnostic marker in differentiating active IBD from other diseases. Particularly important however seems to be the predictive value of hsCRP at diagnosis in prognosing the clinical outcome of the disease in CD patients.
Keywords:	CRP • diagnostic factor • prognostic factor • inflammatory bowel diseases • Crohn's disease • ulcerative colitis

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INTRODUCTION

C-reactive protein (CRP) is one of at least 50 plasma proteins that contribute to the acute phase of the inflammatory response (an acute phase protein has been defined as one whose plasma concentration changes by at least 25% during inflammatory disorders [14]). CRP is predominantly synthesized in the hepatocytes, although extra-hepatic production has also been demonstrated [1, 20]. The exact function of CRP is largely unknown, but it has been shown that after binding to its ligand the CRP-ligand complex activates the complement cascade and induces phagocytosis, which makes it an important component of the human innate immune system. Under normal conditions, the baseline concentration of CRP in the plasma is around 0.8 mg/L and is in part genetically regulated [10, 26]. However, in the presence of acute-phase stimuli such as interleukin (IL)-6, tumor necrosis factor (TNF)- α and IL-1 β , CRP production is up-regulated within hours and may reach concentrations that are 500- to 1 000-fold higher than under basal circumstances. The relatively short half-life of CRP (approximately 19 h) also ensures that the concentrations quickly decrease once the acute-phase stimulus disappears, making it a valuable marker of inflammation [27]. It also seems that the medical therapy does not have a direct effect on CRP synthesis in the hepatocytes, and changes in CRP response during treatment are caused by the effect of the therapy on the underlying disease. In clinical practice a CRP assay can be used for different reasons, e.g.: i) to identify organic disease, ii) as a guide in differential diagnosis, iii) to monitor disease activity, iv) to select responders to treatment or v) to predict outcome. The study aimed to evaluate high-sensitivity CRP (hsCRP) as a diagnostic and predictive marker, both at diagnosis and during the follow-up, in patients with inflammatory bowel disease (IBD).

PATIENTS AND METHODS

The project was approved by the Ethics Committee at Poznan University of Medical Sciences. The group included 106 adults with CD (51.9%) and UC (48.1%). All patients were Caucasian. The disease had been diagnosed and confirmed by endoscopic and radiologic means. For UC, disease activity was estimated using the Montreal classification, and disease location was defined as proctitis (E1), left-sided colitis (E2), and pancolitis (E3)

[22]. CD patients were retrospectively classified according to the Vienna classification by age (A1-A2), localization (L1-L4) and behavior of disease (B1-B3) [11] on the basis of medical history. A relapse was defined as an aggravation of symptoms that resulted in the need for more intensive medical therapy or surgery. The surgery in turn was defined as intestinal resection. hsCRP concentrations were measured by the standard method, and the normal value was considered as ≤ 3 mg/l. At diagnosis hsCRP was measured before medical treatment was instituted, and the analysis was based on medical history.

Descriptive statistics are expressed as mean and range or as frequency counts or percentages. Normally distributed data were compared by the Student t test, while data that were not normally distributed were analyzed by the Mann-Whitney test. Categorical data were analyzed by the χ^2 test and, when appropriate, Fisher's exact test. Changes in hsCRP levels over time were analyzed by the paired-sample t test. Association between two continuous variables was measured by calculating Spearman's correlation coefficient. A multivariate logistic regression analysis was conducted to determine which variables were associated with the risk of surgery. Forward selection was used as our model for selection strategy. The categorical variables included in the analysis were gender, family history of IBD, smoking status at diagnosis, body mass index (BMI), and requirements of oral corticosteroids at diagnosis. In addition, for CD patients structuring and penetrating disease behavior at diagnosis were included. Furthermore, the following continuous variables were included in the analysis: age at diagnosis, hsCRP level, erythrocyte sedimentation rate (ESR), platelet count, albumin level, and hemoglobin level. These analyses were performed separately for patients with UC and CD and for the subgroups disease extent in UC and localization of disease in patients with CD. Results were considered statistically significant if $P \leq 0.05$. All the statistical analyses were performed with SPSS v. 15.

RESULTS

General characteristics of patients with inflammatory bowel diseases

A group of 106 adults with CD (51.9%) and UC (48.1%), comprising 65 women (61.3%) and 41 men (38.7%) with

Table 1. Clinical and demographic characteristics of patients with Crohn's disease

Characteristic	CD (n = 55)
Gender <i>n</i> (%)	
Female	32 (58.2%)
Age at diagnosis	
Mean (yrs ± SD)	31.8 ± 5.8
Median (range) yrs	33.0 (19.0-45.0)
Early onset (< 40 yrs; A1) <i>n</i> (%)	51 (92.7%)
Family history of IBD <i>n</i> (%)	17 (30.9%)
Smoking behavior at diagnosis <i>n</i> (%)	
Smoker	33 (60.0%)
Former smoker	9 (16.4%)
Non-smoker	13 (23.6%)
CD location <i>n</i> (%)	
Terminal ileum (L1)	17 (30.9%)
Colon (L2)	20 (36.4%)
Ileocolon (L3)	15 (27.3%)
Upper GI tract (L4)	3 (5.4%)
CD behavior <i>n</i> (%)	
Nonstricturing nonpenetrating (B1)	24 (43.6%)
Stricturing (B2)	11 (20.0%)
Penetrating (B3)	20 (36.4%)

Abbreviations: CD – Crohn's disease; GI tract – gastrointestinal tract; IBD – inflammatory bowel diseases; SD – standard deviation; yrs – years.

a mean age of 35.9 years (median: 36.1), was enrolled. The disease had been diagnosed and confirmed by endoscopic and radiologic means. All patients were Caucasian. Medical history revealed that 32 individuals (30.2%) had a family history of IBD. The majority of enrolled patients (43.4%) were current smokers. Medical history also revealed that 84.9% of IBD patients had elevated hsCRP concentrations (> 3 mg/L) at diagnosis. The mean serum concentration of hsCRP in the group was 37 (95% CI: 29–46) mg/L, and the median serum concentration was 18 (range: 0–196) mg/L. During the follow-up period (mean: 2.6 years, median: 2.2 years) 42 patients (39.6%) had surgery, while 34 patients (32.1%) required immunosuppressive treatment and 33 patients (31.1%) required glucocorticoid treatment. None of the patients received any biologic agents during the follow-up period.

HS-CRP IN PATIENTS WITH CROHN'S DISEASE

Clinical and demographic characteristics of CD patients participating in the study are presented in Table 1. The group included 55 adults: 32 women (58.2%) and 23 men (41.8%) of a mean age of 31.8 ± 5.8 (median: 33.0) years at diagnosis. The disease had been diagnosed and confirmed by endoscopic and radiologic means. Medical history revealed that 17 individuals (30.9%) had a family history of IBD. The majority of CD patients were current smokers (60.0%), particularly young females (50.0%). The distribution of CD extent was 27.3% ileocolonic (L3), 30.9% ileal (L1), 36.4% colonic (L2), and 5.4% upper gastrointestinal tract (L4). As for CD behavior, 24 patients (43.6%) were classified as B1 at diagnosis, 20 patients (36.4%) as B3 and 11 patients (20.0%) as B2. During the

follow-up period (mean: 2.4 years, median: 2.0 years) 26 patients (47.3%) had surgery, while 18 patients (32.7%) required immunosuppressive treatment and 10 patients (18.2%) required glucocorticoid treatment.

The majority of CD patients (91.0%) had elevated hsCRP concentrations (> 3 mg/L) at diagnosis. The mean serum concentration of hsCRP in the group was 58 (95% CI: 45–71) mg/L, and the median serum concentration was 48 (range: 0–196) mg/L. No differences in hsCRP levels were observed between subgroups of patients categorized according to the Vienna classification related to age (A1–A2), localization (L1–L4) and behavior (B1–B3) of the disease ($P > 0.05$). HsCRP levels in CD patients are presented in Table 2.

An overall decrease in mean hsCRP concentration from 58 mg/L (95% CI: 45–71) to 15 mg/L (95% CI: 9–21) was found during the follow-up period ($P < 0.001$). A significant decrease in hsCRP concentrations was observed in all investigated subgroups. The analysis also showed a correlation between hsCRP concentrations at diagnosis and risk of surgery in the group of CD patients as a whole during the follow-up period (Spearman's rho = 0.408, $P = 0.002$). No correlation was found between hsCRP concentrations and risk of surgery in CD patients categorized according to localization and behavior of the disease ($P > 0.05$). In the logistic regression analysis, surgery in CD patients was associated with age (OR: 0.89, 95% CI: 0.8–1.0, $P = 0.05$) and hsCRP concentration (OR: 1.02, 95% CI: 1.0–1.04, $P = 0.03$) at diagnosis. No association was found between surgery and other variables such as gender, family history of IBD, smoking status at diagnosis, BMI,

Table 2. Concentrations of hsCRP according to the location and behavior of Crohn's disease.

	Location of Crohn's disease			
	Ileal disease (L1) n = 17	Colonic disease (L2) n = 20	Ileocolonic disease (L3) n = 15	Upper GI disease (L4) n = 3
Mean (95% CI) [mg/L]	62 (30-94)	58 (37-79)	56 (30.6-81)	44 (0-100)
Median (range) [mg/L]	27 (4-196)	46 (3-154)	48 (0-173)	54 (18-60)
	Behavior of Crohn's disease			
	Nonstricturing nonpenetrating disease (B1) n = 24	Stricturing disease (B2) n = 11	Penetrating disease (B3) n = 20	
Mean (95% CI) [mg/L]	58 (39-78)	69 (24-115)	51 (32-71)	
Median (range) [mg/L]	51 (3-169)	57 (4-196)	34 (0-143)	
Total of patients with Crohn's disease				
Mean (95% CI) [mg/L]	58 (45-71)			
Median (range) [mg/L]	48 (0-196)			

Abbreviations: CD – Crohn's disease; GI tract – gastrointestinal tract; hsCRP – high-sensitivity C-reactive protein; SD – standard deviation; yrs – years.

requirement of oral corticosteroids, localization and behavior of the disease, erythrocyte sedimentation rate (ESR), platelet count, albumin level, or hemoglobin level ($P > 0.05$). Overall the correctly specified group percentage for this model was 76.4%. According to medical history 48% of the patients relapsed during the first year. However, no association was found between hsCRP concentrations at diagnosis and relapse in the whole group of CD patients or in investigated subgroups.

HS-CRP IN PATIENTS WITH ULCERATIVE COLITIS

Clinical and demographic characteristics of UC patients participating in the study are presented in Table 3. The group included 51 adults, 33 female (64.7%) and 18 male (35.3%), with a mean age of 40.4 ± 5.6 (median: 39.0) years at diagnosis. The disease had been diagnosed and confirmed by endoscopic and radiologic means. Medical history revealed that 15 individuals (29.4%) had a family history of IBD. The majority of UC patients were former smokers (39.2%) and non-smokers (35.3%). The distribution of UC extent was 19.6% proctitis, 29.4% left-sided, and 51.0% pancolitis. During the follow-up period (mean: 2.9 years, median: 2.5 years) 13 patients (35.8%) had surgery, while 16 patients (31.4%) required immunosuppressive treatment and 23 patients (45.1%) required glucocorticoid treatment.

The majority of UC patients (78%) had elevated hsCRP concentrations (> 3 mg/L) at diagnosis. The analysis revealed that the mean serum concentration of hsCRP at diagnosis was 15 (95% CI: 11–20) mg/L and the median serum concentration was 11 (range: 0–82) mg/L. No differences in hsCRP levels were observed between subgroups of patients categorized according to the extent (E1–E3) of disease ($P > 0.05$). HsCRP levels in UC patients are presented in Table 4.

Similarly to the group of CD patients, an overall decrease in mean hsCRP concentration from 15 mg/L (95% CI: 11–20) to 6 mg/L (95% CI: 5–7) was observed during the follow-up period ($P < 0.001$). A significant decrease in hsCRP concentrations was observed in all investigated subgroups. In contrast to the group of CD patients, however, the analysis failed to show a correlation between hsCRP concentrations at diagnosis and risk of surgery in the group of UC patients as a whole during the follow-up period or in subgroups of UC patients categorized according to the extent of disease ($P > 0.05$). In the logistic regression analysis, surgery in UC patients was associated only with age at diagnosis (OR: 0.81, 95% CI: 0.5–1.1, $P = 0.05$) and not with other investigated variables such as gender, family history of IBD, smoking status at diagnosis, BMI, requirement of oral corticosteroids, extent of the disease, hsCRP concentration, erythrocyte sedimentation rate (ESR), platelet count, albumin level, or hemoglobin level ($P > 0.05$). According to the medical history, 45% of the patients relapsed during the first year. However, no association was found between hsCRP concentrations at diagnosis and the relapse in the whole group of UC patients or in investigated subgroups ($P > 0.05$).

DISCUSSION

The study aimed to evaluate hsCRP as a diagnostic and predictive marker, both at diagnosis and during the follow-up, in patients with IBD. The study has demonstrated that hsCRP might be a useful, although non-specific diagnostic marker in IBD, particularly in CD. It showed that the majority of patients with both CD (91%) and UC (78%) had elevated hsCRP concentrations (> 3 mg/L) at diagnosis. The mean serum concentration of hsCRP was much higher in the group of patients with CD than UC (58 (95% CI: 45–71) mg/L vs. 15 (95% CI: 11–20) mg/L, $P < 0.001$). No differences in hsCRP levels at diagnosis were observed between subgroups of CD patients cate-

Table 3. Clinical and demographic characteristics of patients with ulcerative colitis (UC)

Characteristic	
Gender <i>n</i> (%)	
Female	33 (64.7%)
Age at diagnosis	
Mean (yrs ± SD)	40.4 ± 5.6
Median (range) yrs	39.0 (31.2-56.3)
Early onset (< 40 yrs) <i>n</i> (%)	
	27 (52.9%)
Duration of disease	
Mean (yrs ± SD)	2.9 ± 1.6
Median (range) yrs	2.5 (0.0-6.3)
Family history of IBD <i>n</i> (%)	
	15 (29.4%)
Smoking behavior at diagnosis <i>n</i> (%)	
Smoker	13 (25.5%)
Former smoker	20 (39.2%)
Non-smoker	18 (35.3%)
UC location <i>n</i> (%)	
Proctitis (E1)	10 (19.6%)
Left-sided (E2)	15 (29.4%)
Pancolitis (E3)	26 (51.0%)

Abbreviations: IBD – inflammatory bowel diseases; SD – standard deviation; UC – ulcerative colitis; yrs – years.

Table 4. Concentrations of hsCRP according to the extension of ulcerative colitis

	Extension of ulcerative colitis		
	Proctitis (E1) <i>n</i> = 10	Left-sided colitis (E2) <i>n</i> = 15	Pancolitis (E3) <i>n</i> = 26
Mean (95% CI) [mg/L]	17 (1-33)	15 (11-20)	15 (9-21)
Median (range) [mg/L]	8 (3-79)	13 (6-38)	12 (0-82)
Total of patients with ulcerative colitis			
Mean (95% CI) [mg/L]	15 (11-20)		
Median (range) [mg/L]	11 (0-82)		

Abbreviations: hsCRP – high-sensitivity C-reactive protein; SD – standard deviation; yrs – years.

gorized according to the Vienna classification related to age (A1–A2), localization (L1–L4) and behavior (B1–B3) of the disease or UC patients categorized according to the extent (E1–E3) of disease ($P > 0.05$), as suggested by others [13].

Previous studies have shown that CD patients generally have higher CRP production than patients with UC, and also a higher concentration of IL-6 [9, 23]. The mechanisms responsible for this phenomenon are not fully understood. One possible mechanism involves the accumulation of mesenteric fat, a major site of IL-6 and TNF- α synthesis, in CD patients [12, 18]. Also the association between the disease flare-up and the significant bacterial migration during the ongoing transmural inflammation of the intestinal wall has been proposed as a potential explanation of the phenomenon [16].

Altogether, these results are consistent with the data supporting the usefulness of CRP as a marker in differentiating active IBD from functional bowel disorders [21, 25]. They are also in line with other reports suggesting a close correlation of serum CRP concentrations with the severity and activity of IBD, particularly of CD [4, 9, 15]. It is worth mentioning however that approximately one-third of patients with active CD have normal CRP levels, while another one-third of patients in clinical remission have elevated CRP defined as > 5 mg/L [2]. Some reports suggest the CRP-negative rate among CD patients to be even higher [6, 7, 24]. This means that in many patients measuring CRP at diagnosis would not help to differentiate IBD and functional disorders or to correctly assess the disease activity and severity.

The study also demonstrated an overall decrease in mean hsCRP concentration during the follow-up period

in IBD patients. It is known that medical therapy, including anti-inflammatory and immunosuppressive agents, does not have a direct effect on CRP production in the hepatocytes, and changes in CRP response during treatment are caused by the effect of the therapy on the underlying disease. Again, the observed decrease in mean concentration of hsCRP was larger in the group of CD patients (58 mg/L to 15 mg/L, $P < 0.001$) than in the group of UC patients (15 mg/L to 6 mg/L, $P < 0.001$). Significant heterogeneity in CRP response has been observed among different inflammatory diseases, and some diseases including CD and rheumatoid arthritis are associated with a strong CRP response, while others, such as UC, systemic lupus erythematosus, dermatomyositis and Sjögren's syndrome, have only a modest to absent CRP response, despite the ongoing inflammation [27].

The analysis also showed a correlation between hsCRP concentrations at diagnosis and risk of surgery in the group of CD patients (Spearman's $\rho = 0.408$, $P = 0.002$), but not in the group of UC patients, during the follow-up period. In the logistic regression analysis, surgery

in CD patients was associated with age (OR: 0.89, 95% CI: 0.8–1.0, $P = 0.05$) and hsCRP concentration (OR: 1.02, 95% CI: 1.0–1.04, $P = 0.03$) at diagnosis. The study therefore demonstrated that hsCRP at diagnosis might be used as a predictive factor in evaluating the risk of surgery in CD. Interestingly, the study failed to prove any association between relapse and hsCRP concentrations with either CD or UC, as suggested by others [2, 8].

In summary, despite the limitations of the study such as its retrospective nature and a relatively short follow-up period that could contribute to unexpected and/or non-significant results, it seems that hsCRP might be a useful diagnostic marker in differentiating active IBD from other diseases. Particularly important however seems to be the predictive value of hsCRP in prognosing the clinical outcome of the disease in CD patients, since 70%–90% of CD patients require surgery during their lifetime [3, 19], even those who first present with a nonfistulizing, nonoperative phenotype [17], and as many as 39% require repeated surgery [5].

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