Serum C-reactive protein level does not correlate with Crohn's Disease Activity Index

Stężenie białka C-reaktywnego nie koreluje ze wskaźnikiem aktywności choroby Leśniowskiego-Crohna

Maciej Kohut, Katarzyna Kozioł*, Emilia Olek*, Anna Koclęga*, Marek Hartleb

Department of Gastroenterology and Hepatology, Medical University of Silesia, Katowice, Poland
*Students organized in scientific Students Circle at the Department of Gastroenterology and Hepatology, Medical University of Silesia, Katowice, Poland

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Słowa kluczowe: choroba Leśniowskiego-Crohna, białko C-reaktywne, aktywność choroby.

Address for correspondence: Maciej Kohut, MD, PhD, Department of Gastroenterology and Hepatology, Medical University of Silesia, ul. Medyków 14, 40-752 Katowice, Poland, phone +48 32 789 44 01, e-mail: kohutm66@wp.pl

Abstract

Introduction: Crohn's Disease Activity Index (CDAI) is a conventional, but poorly validated estimate of severity of Crohn's disease (CD). Similarly, the clinical significance of elevated levels of C-reactive protein (CRP) in CD patients is not well recognized. It is also unknown whether these two indices have similar informative value.

Aim: To investigate the correlation between serum CRP level and CDAI.

Material and methods: One hundred and forty-six patients (66 men and 80 women, mean age 37 ±12 years) with well established diagnosis of CD were included in the study. According to the admittance protocol in all patients the serum CRP was measured and all data necessary to calculate CDAI were collected.

Results: There was no significant correlation between CRP and CDAI either in the entire population or in subgroups selected on the basis of CD severity, site of bowel involvement, kind of ongoing pharmacological therapy, past surgery or body mass.

Conclusions: There is no correlation between serum CRP level and CDAI. These two indices reflect different aspects of CD severity.

Streszczenie

Wstęp: Wskaźnik aktywności choroby Leśniowskiego-Crohna (*Crohn's Disease Activity Index* – CDAI) to typowy, ale niedostatecznie standaryzowany sposób szacowania ciężkości tej choroby. Również kliniczne znaczenie zwiększonego stężenia osoczowego białka C-reaktywnego (CRP) nie zostało ostatecznie ustalone w tej chorobie. Nie jest pewne, czy dwa wymienione wskaźniki niosą podobną informację kliniczną.

Cel: Zbadanie korelacji między stężeniem osoczowego CRP i wartością CDAI.

Materiał i metody: Stu czterdziestu sześciu kolejnych chorych (66 mężczyzn i 80 kobiet, średni wiek 37 ±12 lat) z pewnie ustalonym rozpoznaniem choroby Leśniowskiego-Crohna zostało włączonych do badania. Posługując się wcześniej ustalonym prokołem badania, u wszystkich chorych oznaczno przy przyjęciu stężenie osoczowe CRP i zebrano wszystkie niezbędne dane do obliczenia wskaźnika CDAI.

Wyniki: Nie stwierdzono istotnej statystycznie korelacji między stężeniem CRP i CDAI zarówno w całej badanej kohorcie, jak i w podgrupach wydzielonych na podstawie ciężkości choroby, lokalizacji choroby, stosowanego obecnie leczenia farmakologicznego, uprzedniego leczenia chirurgicznego oraz masy ciała.

Wnioski: Nie stwierdzono korelacji między osoczowym stężeniem CRP a wartością CDAI. Badane wskaźniki odzwierciedlają różne aspekty ciężkości choroby Leśniowskiego-Crohna.

Introduction

The natural course of Crohn's disease (CD) is characterized by periods of exacerbations and remissions. The exacerbations are life-threatening events which usually come unpredictably and could be prevented if early stages of flares were discovered by a non-invasive test. Therefore, it is of great importance to find a reliable indicator of existing mucosal inflammatory activity [1].

Crohn's disease is associated with impairment of the bowel mucosal barrier and profound dysfunction of the

immunological system reflected by increased activity of T lymphocytes (mostly the Th1 subpopulation). Activated Th1 cells are the source of pro-inflammatory cytokines, such as IL-6, that stimulate hepatic synthesis of C-reactive protein (CRP) [2, 3]. CRP was first described in 1930 by Tillet and Francis [4], who identified this substance in the serum of a patient infected with *pneumococcal pneumonia* CRP was subsequently considered an "acute phase protein" playing an important diagnostic role in infectious and inflammatory conditions. Moreover, it has been shown that CRP is unaffected by most medications [5].

Many studies have demonstrated elevated CRP levels in patients with active CD [6-9]. It was suggested that CRP may better reflect the surface of active mucosal inflammation in CD than in ulcerative colitis [7-11]. However, a recently published study denied any correlation between CRP level and endoscopically assessed mucosal status in CD patients [12]. There is also no consensus on the role of CRP measurement in prediction of exacerbations in inflammatory bowel disease (IBD) [13].

Crohn's Disease Activity Index (CDAI) is a numerical calculation of 8 clinical variables selected empirically and multiplied by weighting factors derived from multivariate analysis (tab. I). CDAI was developed for the National Cooperative Crohn's Disease Study to objectively assess response to therapy among patients managed at many participating centres [14]. CDAI score below 150 indicates disease remission, of 150-219 denotes mild active disease, of 220-450 means moderately active disease, and above 450 signifies a severe flare [14, 15]. The CDAI has been criticized as a measure of illness rather than disease activity. Generally, the variables entered into CDAI lack specificity and their assessment may be easily influenced by subjective interpretation of both the patient and the gastroenterologist [14, 15]. Though imperfect, the CDAI remains the most commonly used index of severity of CD.

Taken together, the clinical significance of CDAI or CRP for estimation of the extent and activity of mucosal involvement in different stages of CD is not well established. This issue is becoming especially important in view of newly emerging tests, such as faecal measurements of calprotectin or lactoferrin [16, 17]. It is also unknown whether CDAI and CRP carry similar information on activity of CD. The aim of this study was to investigate in a large group of patients with CD the relationship between serum CRP level and disease activity measured by CDAI, taking into account clinical characteristics of these patients.

Table I. Crohn's Disease Activity Index (Best 1976)
Tabela I. *Wskaźnik aktywności choroby Leśniowskiego-Crohna (wg Best 1976)*

No.	Factor	Multiplication
1	Number of liquid or very soft stools in the last week	× 2
2	Abdominal pain score in the last week	× 5
3	General well-being in the last week	× 7
4	6 extra-intestinal symptoms or findings presumably related to Crohn's disease	× 20
5	Treatment with anti-diarrhoeal drugs	× 30
6	Abdominal mass on physical exam	× 10
7	Haematocrit (ideal – actual)	× 6
8	100 × (1-[body weight/standard weight])	× 1
	Total CDAI	...

Material and methods

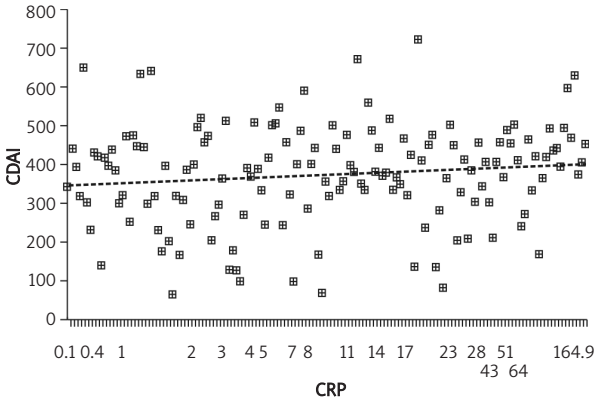
One hundred and forty-six consecutive patients (66 men, 80 women) in whom a diagnosis of CD was unequivocally established on the basis of clinical, radiological, endoscopic and histological criteria were prospectively included in the study, irrespective of disease activity. All patients were hospitalized in the Department of Gastroenterology and Hepatology of the Silesian Medical University in Katowice between February, 2005 and November, 2007. Demographic characteristics of patients are shown in table II.

In all patients the disease activity was determined by CDAI. The CDAI and CRP were determined at the same time according to the admittance protocol. The CRP levels were measured using a turbidimetric immunoassay.

The correlation between CRP and CDAI was calculated by Pearson's correlation test (Excel Microsoft, 2003).

Table II. Demographic and clinical characteristics of 146 patients
Tabela II. *Charakterystyka demograficzna i kliniczna 146 chorych*

Variable	Result
Men : women	66 : 80 (45% : 55%)
Age [years]	37 (range 19-80)
Duration of disease [years]	6.23 (range 0.25-50)
CD limited to the small bowel, *n* (%)	12 (8.22)
Ileo-colonic disease, *n* (%)	120 (82.19)
Crohn's colitis, *n* (%)	14 (9.59)
External fistulas, *n* (%)	55 (38)
Past resective surgery, *n* (%)	60 (41)
Appendectomy, *n* (%)	27 (18.5)



Pearson's correlation coefficient r = 0.184

Fig. 1. Overall correlation between CRP and CDAI
Ryc. 1. *Ogólna korelacja między CRP i CDAI*

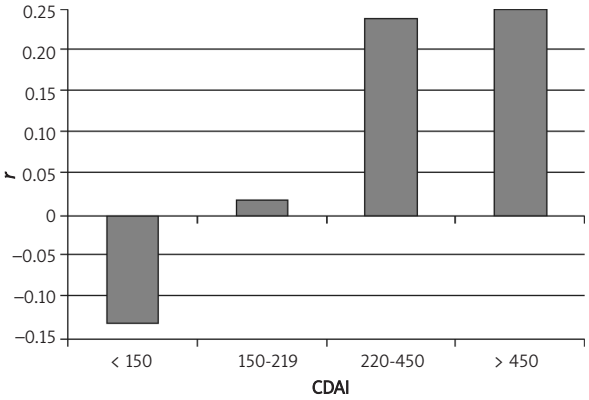
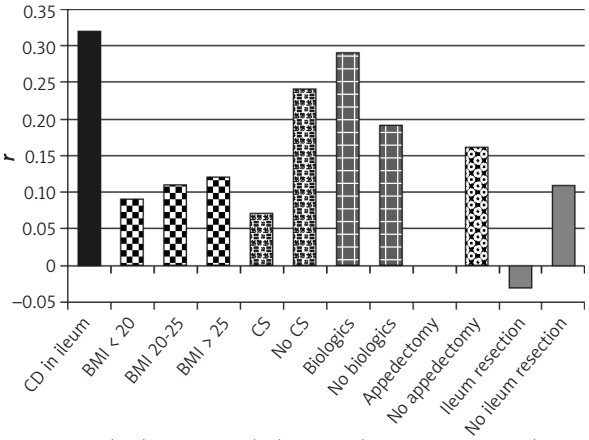


Fig. 2. Correlation coefficients (*r*) between CRP and different CDAI score ranges
Ryc. 2. *Współczynnik korelacji (r) między CRP i CDAI w różnych przedziałach wartości CDAI*



CD – Crohn disease, BMI – body mass index, CS – corticosteroids

Fig. 3. Correlation coefficients (*r*) between CRP and CDAI in different clinical subgroups
Ryc. 3. *Współczynnik korelacji (r) pomiędzy CRP i CDAI w różnych podgrupach chorych*

A *p* value of < 0.05 was considered as significant. We also calculated correlations between CDAI and CRP in the following subgroups of CD patients with:

- CDAI < 150, 150-219, 220-450, > 450 points,
- disease involving exclusively the ileocaecal region vs. other locations,
- body mass index (BMI) < 20, 20-25 and > 25 kg/m^2,
- ongoing treatment with corticosteroids,
- ongoing biological treatment (infliximab or adalimumab),
- previous appendectomy,
- previous bowel resective surgery.

Results

The median CDAI score of all patients was 388 points (range 65-621). Non-active or mild form of CD was diagnosed in 20 patients (CDAI ≤ 220) and moderately or highly active disease in 126 patients (CDAI > 220). Serum CRP level above the upper limit of the normal range (5 mg/l) was found in 91 patients. The median CRP level was 8.7 mg/l (range 0.1-220 mg/l). Overall CRP and CDAI Pearson's correlation factor was 0.184. Detailed results of correlations between CRP and CDAI in subgroups of CD patients are summarised in figures 1-3.

Discussion

The measurement of inflammatory activity in CD is important not only in clinical trials but also in the setting of everyday practice to predict the course of the disease and to monitor effects of treatment [10, 18, 19]. An ideal biomarker should be disease specific, easy to perform, non- or minimally invasive, and providing rapid and reproducible results. Endoscopic or radiological methods fulfil only in part the above targets.

Measurement of serum CRP level was proposed to differentiate between intestine inflammation and functional disorders [16, 17]. An increased interest in CRP as a marker of inflammation in CD is derived from clinical trials evaluating effects of biological agents. In patients treated with infliximab, a pre-therapeutic CRP level more than 5 mg/l was associated with 76% positive therapy response compared with only 46% found in patients with baseline CRP level lower than 5 mg/l. Similar results have been demonstrated with the use of adalimumab and anti-adhesion molecules [20-22].

Recent studies have suggested that polymorphisms in the CRP gene, located on the long arm of chromosome 1 (1q23-24), account for inter-individual differences in CRP synthesis in humans [23-25]. However, data on the effect of CRP gene polymorphisms on the level of this peptide in IBD patients provide no clear

message. A recent study investigating CRP polymorphisms in IBD patients showed no apparent association with serum CRP levels [26].

In the study of Karoui *et al.* the correlation coefficient between CRP and CDAI, although statistically significant, was only 0.3 [6]. Our study shows an even less significant correlation between serum CRP levels and CDAI. This finding holds true not only for the whole investigated population of patients with CD, but also for subpopulations selected on the basis of disease activity, intestinal location of inflammation, administered medications, past surgery and body mass index. A weak correlation was found in CD patients showing exclusive involvement of the terminal ileum.

Mucosal healing is the best prognostic factor with respect to such outcomes as need for hospitalisation (including costly ICU treatment) and for surgery [27]. In common opinion CRP may be a more appropriate indicator of mucosal status than CDAI [2, 28-30].

Conclusions

There is no correlation between serum CRP level and CDAI. The clinical significance of both indices should be further investigated as they seem to reflect different aspects of CD-related pathology.

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