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Original article

Fecal Calprotectin: A Marker of Crohn's Disease Activity

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SUMMARY

Introduction. Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) with periods of remission and exacerbation. Numerous studies have been conducted in order to identify the ideal marker when it comes to the inflammatory bowel diseases. In the literature, fecal calprotectin is mentioned as a marker of inflammation. Elevated levels of calprotectin can be detected in stool and they indicate the migration of neutrophils to the intestinal mucosa that occurs with intestinal inflammation.
The aim. The main goal of this study was to examine the concentration of fecal calprotectin and CRP depending on the clinical, endoscopic and histological characteristics of patients with Crohn's disease and whether there is a correlation of these markers with disease activity.
Methods. The research was conducted in the period from January 2015 to January 2016. The study included subjects who had been diagnosed with Crohn's disease. The study involved 45 respondents, aged 20 - 58 years. All subjects included in the study underwent a colonoscopic examination with biopsy and pathohistological analysis. Fecal calprotectin was determined in one stool sample in all subjects, and that was done quantitatively by a commercial ELISA assay. Determination of serum CRP concentrations was performed in the Central Biochemical Laboratory by standard methods.
Results. Fecal concentrations of calprotectin are elevated in all three forms of the disease, while they are significantly higher in moderately severe (545 vs. 218, $p < 0.001$) and severe forms of the disease (1000 vs. 218, $p < 0.001$) compared to the mild form. Fecal concentrations of calprotectin are significantly higher at endoscopic grade 3 compared to the other three endoscopic grades (765.3 vs. 314, $p < 0.001$), (765.3 vs. 392.8, $p < 0.001$), (765.3 vs. 448.2, $p < 0.001$). Fecal concentrations of calprotectin are significantly higher in extensive pathological findings compared to normal epithelial surface (1000 vs. 21, $p < 0.001$) as well as in extensive pathological findings compared to focal pathological findings (1000 vs. 309, $p < 0.001$).
Conclusion. The more severe form of clinical disease activity is accompanied by higher fecal values of calprotectin and higher endoscopic grade, and a more severe histological grade of disease is accompanied by higher fecal values of calprotectin.

Keywords: **Crohn's disease, fecal calprotectin, C-reactive protein, disease activity**

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) with periods of remission and exacerbation. One of the most common presentations of the disease is the appearance of abdominal pain with frequent bloody stools, accompanied by fever and significant disturbance of body mass index (1, 2). It can affect any part of the digestive tract, from the mouth to the anus, and the most common localizations are: terminal ileum, quantitative form of CD, ileolic form and upper parts of the digestive tract, but there are also extraintestinal manifestations of the disease (3, 4). The gold standard for diagnosing CD is colonoscopy with a biopsy of the terminal ileum for pathohistological verification of the disease (5). In addition, the mentioned method is used to monitor the effect of therapy i.e. whether there is a recovery of the intestinal mucosa or further progression of the disease (6). However, there are a number of limiting factors for its implementation from the economic moment, through the discomfort of the procedure itself for the patient, to the possibility of bleeding and the occurrence of intestinal perforation. From the above, we conclude that it is necessary to have markers that will help us assess the activity of Crohn's disease (7). The marker must be highly specific with minimal false-positive and negative results and able to clearly reflect the early stage of the disease; it must be easy to detect and the screening method should be economically viable (8, 9). Most research relates to fecal calprotectin. It is a small calcium-binding protein consisting of two heavy and one light polypeptide chain. It is abundant in neutrophilic granulocytes, in which it makes up 60% of the cytoplasmic fraction, as in monocytes and macrophages (10).

Of the serum markers, the greatest importance is given to C-reactive protein (CRP) where patients may have a 1000-fold increase in CRP depending on the intensity and extent of the disease, but it is also a reliable marker in differentiating inflammatory diseases (11, 12).

The main goal of this study is to examine the concentration of fecal calprotectin and CRP depending on the clinical, endoscopic and histological characteristics of patients with Crohn's disease and whether there is a correlation of these markers with disease activity.

MATERIAL AND METHODS

The research was conducted at the Clinic for Gastroenterology and Hepatology, University Clinical Center Kragujevac in the period from January 2015 to January 2016. The study included subjects who had been diagnosed with Crohn's disease and who met all inclusion criteria and did not have any exclusion criteria. The study involved 45 respondents, aged 20 - 58 years. All subjects included in the study underwent a colonoscopic examination. During the endoscopic examination of subjects with Crohn's disease, the extent of the disease was determined according to the length of the gastrointestinal tract involvement. The subjects with Crohn's disease were classified according to the Simple Endoscopic Scorefor Crohn's Disease (SES-CD).

During the colonoscopy, tissue sections were taken at the sites of the altered colonic mucosa. These tissue sections were used for pathohistological analysis (5 tissue sections, size 4 - 5 mm) and were taken from each subject. Fecal calprotectin was determined in one stool sample in all subjects, and that was done quantitatively by a commercial ELISA assay (199). Determination of serum CRP concentrations was performed in the Central Biochemical Laboratory of the University Medical Center Kragujevac by standard methods, using the Beckman Coulter AU 400 Unicel DXC 800 Synchron Clinical System. To determine the serum CRP concentration, 5 ml of blood was taken from all subjects by vein puncture. The data were analyzed using the IMBS PSS Statistics 20 software package and are presented in tables and graphs.

RESULTS

The analysis included 45 subjects with Crohn's disease, who were classified into three groups: mild

(n = 27), moderate (n = 16) and severe (n = 2) according to the Crohn's disease activity index (CDAI). Fecal concentrations of calprotectin and CRP were analyzed and compared between these groups of subjects.

Fecal concentrations of calprotectin are elevated in all three forms of the disease, while they are significantly higher in moderately severe (545 vs. 218, $p < 0.001$) and severe forms of the disease (1000 vs. 218, $p < 0.001$) compared to the mild form. There was no statistically significant difference in fecal calprotectin concentrations between moderately severe and severe disease (1000 vs. 545) which is shown in Figure 1, while CRP values were elevated in all three forms of the disease but no statistically

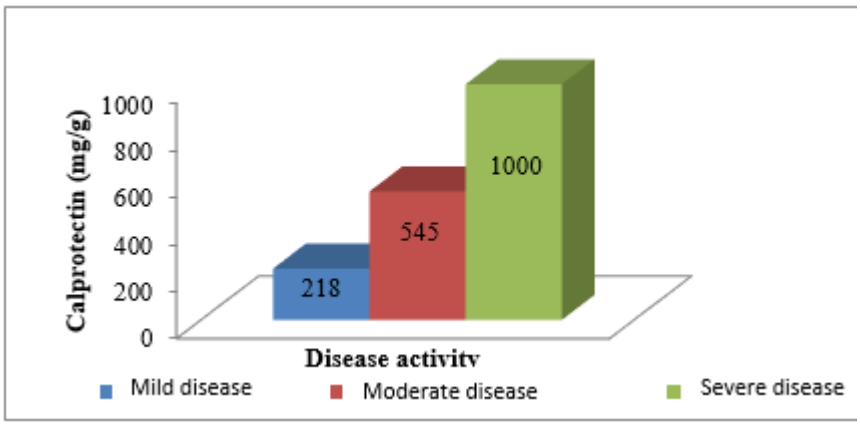

Figure 1. *Concentrations of fecal calprotectin depending on the clinical activity of the disease*

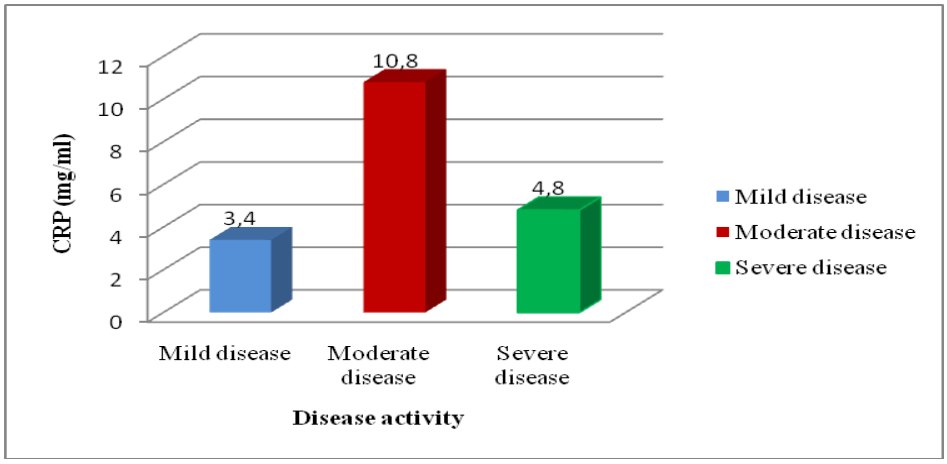

Figure 2. *Serum CRP values depending on the clinical activity of the disease*

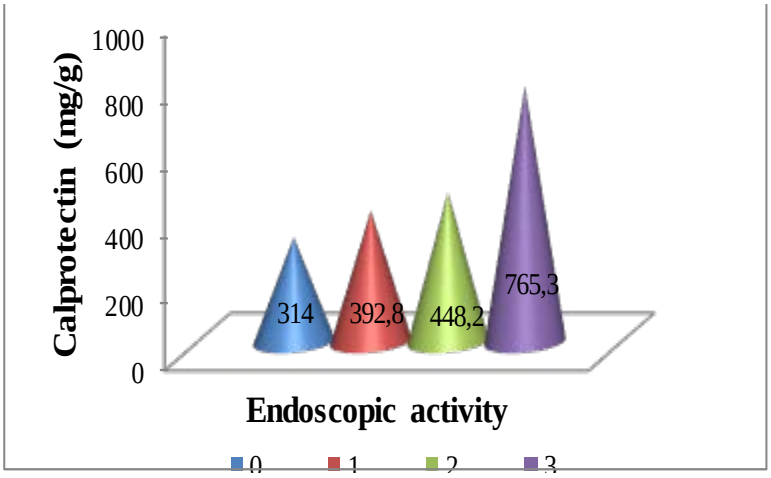

Figure 3. *Concentrations of fecal calprotectin depending on the endoscopic activity of the disease*

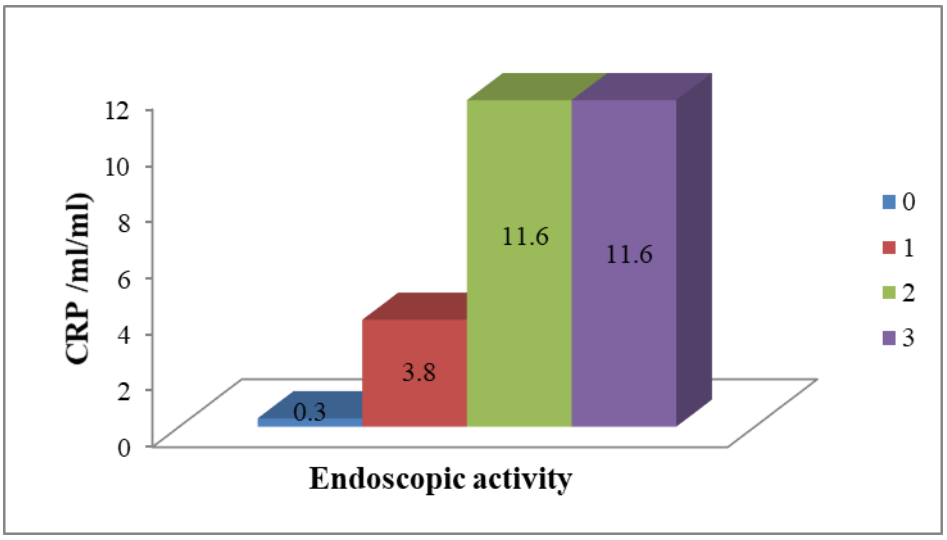

Figure 4. *Serum values of CRP depending on the endoscopic activity of the disease*

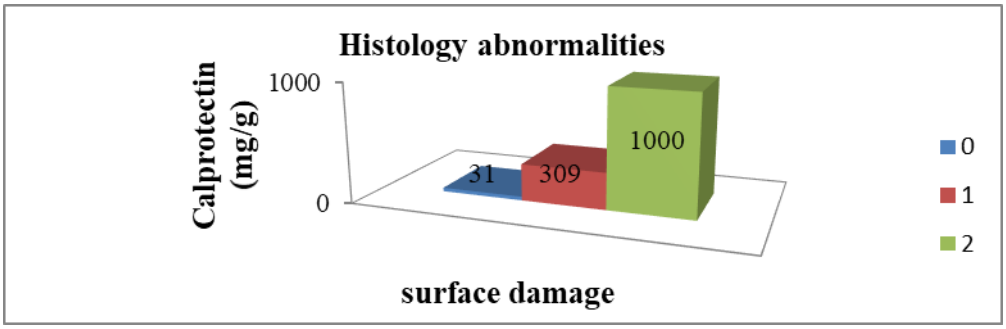

Figure 5. *Concentrations of fecal calprotectin depending on damage to the epithelial surface*

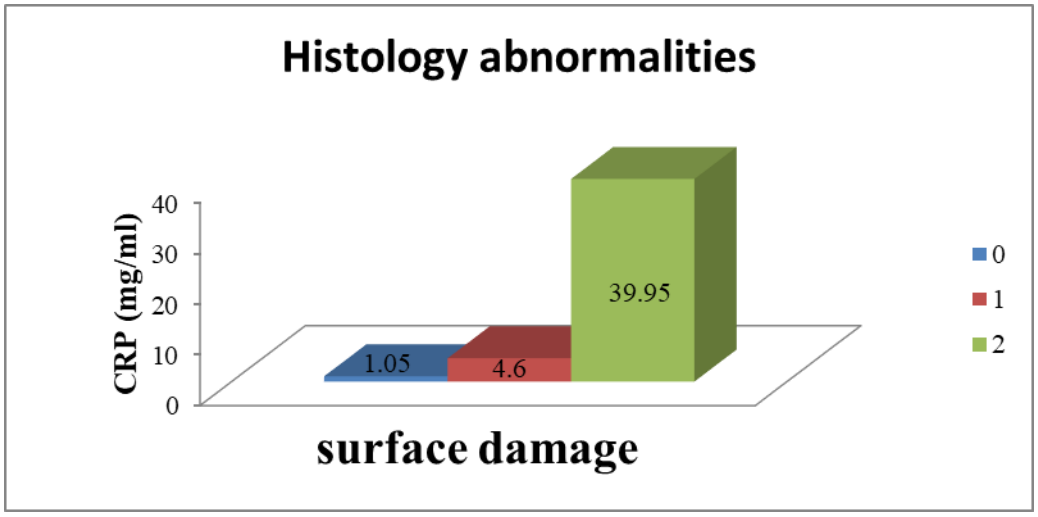

Figure 6. *Serum CRP values depending on epithelial surface damage*

significant difference was shown between the groups compared to serum CRP values (3 , 4 vs. 10.5 vs. 4.8), which is shown in Figure 2.

The analysis included 45 subjects with Crohn's disease who were classified into four groups according to the degree of endoscopic changes: 1) endoscopic grade 0 (n = 5), 2) endoscopic grade 1 (n = 19), 3) endoscopic grade 2 (n = 6) and 4) endoscopic grade 3 (n = 15). According to endoscopic disease activity, subjects with Crohn's disease were classified according to the Simple Endoscopic Score for Crohn's Disease (SES-CD).

Fecal concentrations of calprotectin are significantly higher at endoscopic grade 3, compared to the other three endoscopic grades (765.3 vs. 314, $p < 0.001$), (765.3 vs. 392.8, $p < 0.001$), (765.3 vs. 448.2, $p < 0.001$). There is no statistically significant difference in stool calprotectin values between endoscopic grade 0, 1, and 2, which is shown in Figure 3. The concentrations of fecal calprotectin and CRP were analyzed and compared between the four groups of subjects. There was no statistically significant difference in serum CRP levels relative to endoscopic activity (0.3 vs. 3.8 vs. 11.6 vs. 11.6), which is shown in Figure 4.

The analysis included 45 subjects with Crohn's disease, who were classified into three groups: 0) without damage to the epithelial surface, (n = 10), 1) with focal pathological findings, (n = 24) and 2) with extensive pathological findings, (n) = 11), according to the scoring system for monitoring histological abnormalities in Crohn's disease mucosal biopsy specimens.

Fecal concentrations of calprotectin are significantly higher in extensive pathological findings compared to normal epithelial surface (1000 vs. 21, $p < 0.001$), as well as in extensive pathological findings compared to focal pathological findings (1000 vs. 309, $p < 0.001$), which is shown in Figure 5. A statistically significant difference was also shown in the values of fecal calprotectin between normal and focal pathological findings (31 vs. 309, $p < 0.001$). Serum concentrations of CRP and fecal calprotectin were analyzed and compared between the three groups of subjects. Serum CRP values were statistically significantly higher in the extensive pathological finding compared to the focal pathological finding (39.95 vs. 4.06, $p < 0.001$) and normal epithelium (39.95 vs. 1.05, $p < 0.001$), which is shown in Figure 6.

Analysis of logistic regression of fecal levels of calprotectin and serum markers in patients with Crohn's disease

A ROC curve in Figure 7 shows the relationship between specificity and sensitivity of serum fecal markers and suggests potential markers for differentiating clinical disease activity. Binary logistic regression indicates that increased levels of fecal calprotectin correlate with severe disease. Fecal calprotectin is observed to be the most sensitive and specific marker of severe disease (area = 0.681, p =

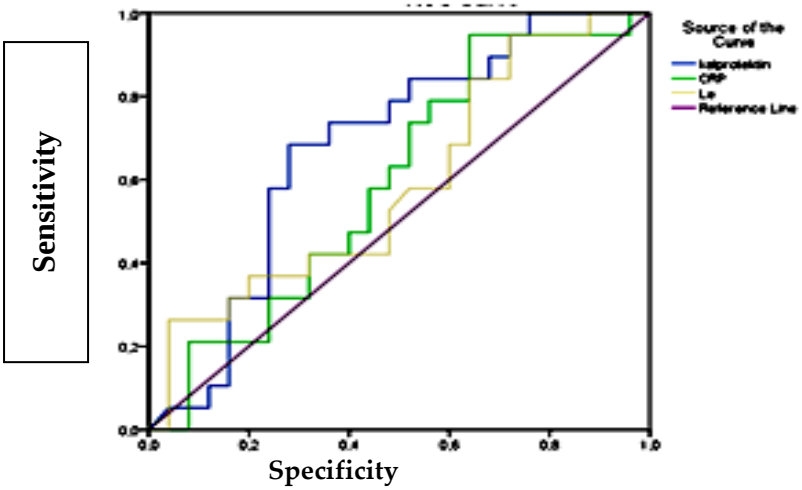

Figure 7. *Receiver operating characteristic curve (ROC) analysis of biomarkers in differentiating the clinical activity of Crohn disease. The ROC curve shows the sensitivity specificity of fecal calprotectin levels, serum CRP levels and leukocyte count*

AUC (FKP) = 0.682, p = 0.001, sensitivity 86.0%, specificity 87.1%, cut-off point 852.50 mg/g;
AUC (CRP) = 0.596, p = 0.003, sensitivity 73.7%, specificity 62.0%, cut-off point 7.36 mg/ml;
AUC (Le) = 0.591, p = 0.004, sensitivity 84.2%, specificity 64.0%, cut-off point 5.76 x 10 9/l;
AUC (area under the curve)

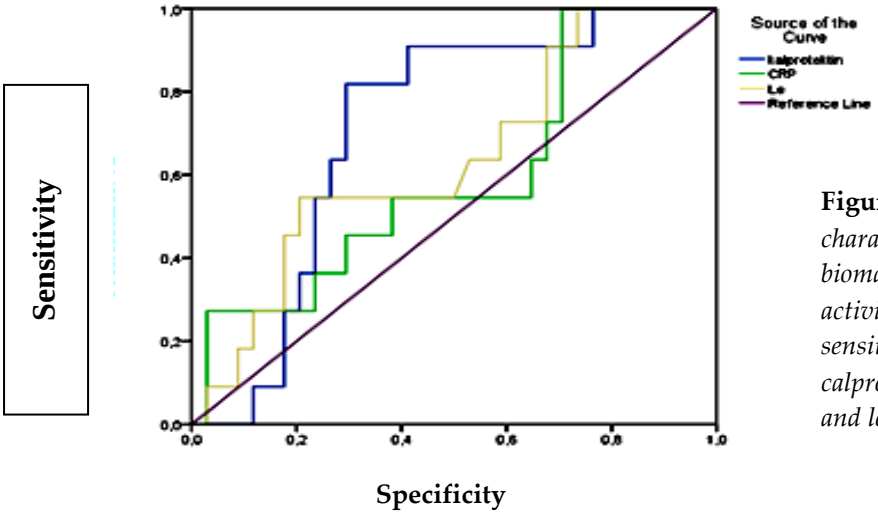

Figure 8. *ROC (Receiver operating characteristic curve) analysis of biomarkers in distinguishing endoscopic activity. The ROC curve shows the sensitivity specificity of fecal calprotectin levels, serum CRP levels and leukocyte count*

AUC (FKP) = 0.711, p = 0.001, sensitivity 81.8%, specificity 85.7%, cut-off point 922.50 mg/g;
AUC (CRP) = 0.596, p = 0.06, sensitivity 54.5%, specificity 38.2%, cut-off point 13.99 mg/ml;
AUC (Le) = 0.638, p = 0.04, sensitivity 54.5%, specificity 20.6%, cut-off point 8.49 x 10 9/l;
AUC (area under the curve)

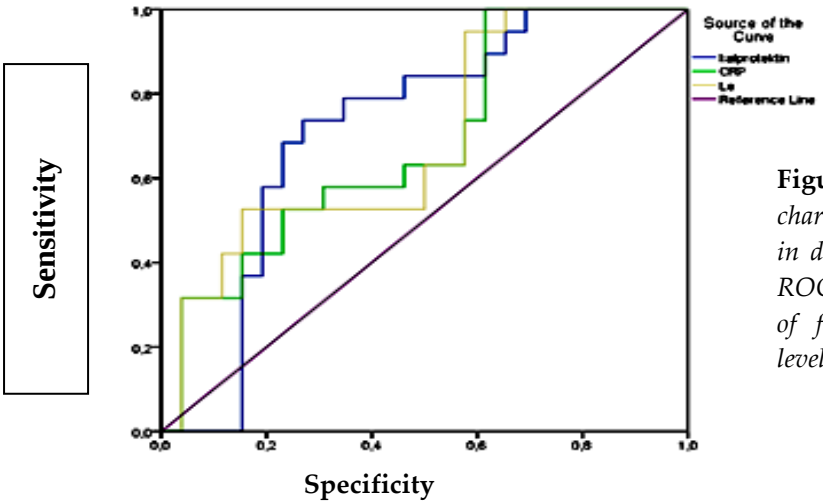

Figure 9. *ROC (Receiver operating characteristic curve) analysis of biomarkers in distinguishing histological activity. The ROC curve shows the sensitivity specificity of fecal calprotectin levels, serum CRP levels and leukocyte count*

AUC (FKP) = 0.719, p = 0.002, sensitivity 90.7%, specificity 85.7%, cut-off point 852.50 mg/g;
AUC (CRP) = 0.684, p = 0.06, sensitivity 52.6%, specificity 23.1%, cut-off point 19.10 mg/ml;
AUC (Le) = 0.690, p = 0.04, sensitivity 52.6%, specificity 20.6%, cut-off point 8.26 x 10 9 l;
AUC (area under the curve)

0.001). The results of this study suggest that the optimal limit in fecal concentration of this marker is 852.50 mg/g and that this limit value of calprotectin may serve to discriminate patients with severe form (sensitivity 86.0%, specificity 87.1%).

We then analyzed the ROC curve showing the relationship between the specificity and sensitivity of serum and fecal markers and suggesting potential markers for distinguishing endoscopic disease activity. Binary logistic regression indicates that increased levels of all analyzed markers correlate with the most severe degree of endoscopic changes. It is observed that fecal calprotectin is the most sensitive and most specific non-invasive marker for distinguishing the activity of Crohn's disease (area = 0.711, p = 0.001). The results of this study suggest that the optimal limit fecal concentration of this marker is 922.50 mg/g and that this limit value of calprotectin may serve to discriminate patients with endoscopically severe disease in relation to other degrees of endoscopic changes (sensitivity 81.8%, specificity 85.7%), which is shown in Figure 8.

We then analyzed the specificity and sensitivity of markers in serum and stool to distinguish histological changes of inflamed mucosa. Figure 9 shows a ROC curve that presents the relationship between the specificity and sensitivity of serum and fecal markers and suggests potential markers for distinguishing the histological activity of the disease. Binary logistic regression indicates that increased levels of all analyzed markers correlate with the most severe degree of mucosal histological changes.

It is observed that fecal calprotectin is the most sensitive and the most specific marker of histological changes of the colonic mucosa (area = 0.719, p = 0.002). The results of this study suggest that the optimal limit fecal concentration of this marker is 852.50 mg/g and that this limit value of calprotectin can serve to discriminate patients with histologically severe degree in relation to other degrees of histological changes (sensitivity 90.7%, specificity 85, 7%).

DISCUSSION

Numerous studies have been conducted in order to identify the ideal marker when it comes to the inflammatory bowel diseases. In the literature, in addition to fecal calprotectin, neopterin, lactoferrin or S100A12 are mentioned as markers of inflammation. There are currently insufficient data on their significant role in relation to fecal calprotectin as well as the justification for using more than one fecal test at the same time (13). As early as 2000, Fagerhol et al. showed that fecal calprotectin could be used as a screening test to select patients for further examination (14). Elevated levels of calprotectin can be detected in the stool and indicate the migration of neutrophils to the intestinal mucosa, that occurs with intestinal inflammation (15). In patients with active inflammatory bowel diseases such as ulcerative

colitis and Crohn's disease, there is a 10-fold increase in fecal calprotectin. It is also useful for making a differential diagnosis of patients with IBS (irritable bowel syndrome, IBS) from patients with IBD (16, 17). Elevated values were also registered in patients with colorectal cancer, celiac disease, pancreatitis, infectious diseases, nutritional allergies, which shows their sensitivity to diseases but not specificity to only one disease. At the same time, these values can be falsely elevated in patients who used proton pump inhibitors as well as antirheumatics before sampling (18).

Numerous clinical studies have examined the correlation between calprotectin concentration and clinical indicators. Gay and colleagues in their study did not show a correlation between calprotectin values and the index of clinical activity of the disease in patients with Crohn's disease (19). Similar results were shown in studies by Jones (20) and Sipponen (21) on the same population of subjects. In general, most studies have shown a weak correlation between calprotectin values and the clinical activity index of the disease (22).

In the study we conducted, we obtained the results that do not correspond to the previously mentioned publications which showed a significant correlation between the values of markers and clinical disease activity. Solem et al. registered a positive correlation of CRP with clinical disease activity (23). Another study has also shown a significant correlation of serum CRP values with disease activity, while some other studies did not confirm this correlation (24, 25), as well as our study that demonstrated elevated CRP values, however, those were not correlated with the degree of clinical disease activity. Previous studies have confirmed a strong correlation between fecal calprotectin values and endoscopic and histological activity of the disease. A correlation was documented in both ulcerative colitis and Crohn's disease patients (26, 27). In addition, based on calprotectin values, endoscopically, it was possible to clearly distinguish inactive disease from mild, moderate, and severe Crohn's disease. Our study showed similar results as most studies regarding the value of fecal calprotectin and CRP in relation to endoscopic and histological activity of the disease, which confirms that fecal calprotectin is a quality marker in monitored disease activity, while being non-invasive and more accessible and comfortable to use than other methods. The results of this study indicate a possible role of fecal calprotectin as a biomarker for differentiating the clinical activity of the disease and that elevated levels of calprotectin in the stool increase the risk of developing a severe form of the disease. According to our results from all analyzed serum markers, fecal calprotectin showed the highest sensitivity and specificity, which enables discrimination of subjects with the most severe degree of endoscopic changes. Measurement of fecal calprotectin may be useful in assessing the histological activity. According to our results from all analyzed serum markers, calprotectin in stool showed the highest sensitivity and specificity, which enables discrimination of subjects with the most severe degree of inflamed colonic mucosa, in relation to milder histological changes.

CONCLUSION

The results presented in this paper indicate a potentially significant role of fecal calprotectin and CRP that can be used as surrogate markers of inflammation in the intestinal tract and may improve the prediction of active Crohn’s disease or remission in these patients.

The conclusion is based on the following results:

1. The more severe form of clinical disease activity is accompanied by higher fecal values of calprotectin, while CRP values do not correlate with the form of clinical activity.

2. Higher endoscopic grade of disease is accompanied by higher fecal values of calprotectin, while CRP values do not correlate with endoscopic grade of disease.

3. Higher values of calprotectin in the stool of subjects with severe histological grade indicate more severe intestinal destruction, while CRP values are higher with more severe histological grade.

Competing interests

There are no conflicts of interest.

Funding

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Fekalni kalprotektin kao marker aktivnosti Kronove bolesti

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SAŽETAK

Uvod. Kronova bolest (CD) je hronična inflamatorna bolest creva (IBD) sa periodima remisije i egzacerbacije. Sprovedene su brojne studije sa ciljem identifikacije idealnog markera kada su u pitanju inflamatorne bolesti creva. U literaturi se fekalni kalprotektin pominje kao marker upale. Povišeni nivoi kalprotektina mogu se otkriti u stolici i ukazuju na migraciju neutrofila u crevnu sluzokožu, koja se javlja kod upale creva.
Cilj. Osnovni cilj ove studije je da se ispita koncentracija fekalnog kalprotektina i CRP-a u zavisnosti od kliničko-endoskopsko-histoloških karakteristika pacijenata sa Kronovom bolešću i postojanje korelacije ovih markera sa aktivnošću bolesti.
Metode. Istraživanje je sprovedeno u periodu od januara 2015. do januara 2016. godine. Istraživanjem su obuhvaćeni ispitanici kojima je dijagnostikovana Kronova bolest. U istraživanju je učestvovalo 45 ispitanika, starosti 20–58 godina. Svi ispitanici uključeni u studiju podvrgnuti su kolonoskopskom pregledu sa biopsijom i patohistološkom analizom. Fekalni kalprotektin je određen u jednom uzorku stolice kod svih ispitanika, što je urađeno kvantitativno-komercijalnim ELISA testom. Određivanje serumskih koncentracija CRP-a vršeno je u Centralnoj biohemijskoj laboratoriji standardnim metodama.
Rezultati. Fekalne koncentracije kalprotektina su povišene kod sva tri oblika bolesti. Značajno su veće kod umereno teških (545 naspram 218, p < 0,001) i teških oblika bolesti (1000 naspram 218, p < 0,001) nego kod blagog oblika. Fekalne koncentracije kalprotektina su značajno veće i na endoskopskom gradusu 3 u poređenju sa ostala tri endoskopska stepena: 765,3 naspram 314, p < 0,001; 765,3 naspram 392,8, p < 0,001; 765,3 naspram 41 < 00, p < 0,001; 765,3 vs. 41 < 0, p. Fekalne koncentracije kalprotektina značajno su veće u ekstenzivnim patološkim nalazima u poređenju sa normalnom površinom epitela (1000 vs. 21, p < 0,001), kao i u ekstenzivnim patološkim nalazima u poređenju sa fokalnim patološkim nalazima (1000 vs. 309, p < 0,001).
Zaključak. Teži oblik kliničke aktivnosti bolesti praćen je većim fekalnim vrednostima kalprotektina i višim endoskopskim stepenom, a teži histološki stepen bolesti većim fekalnim vrednostima kalprotektina.

Ključne reči: **Kronova bolest, fekalni kalprotektin, C-reaktivni protein, aktivnost bolesti**