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## Fecal Calprotectin as an Activity Marker of Inflammatory Bowel Disease in Children

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article

### Abstract

**Background.** Children constitute 20% of patients with inflammatory bowel diseases (IBD). Still there is a search for a perfect marker for this group of patients which would help in the diagnosis of the disease, in determining its activity and in monitoring the treatment.

**Objectives.** Evaluate the usefulness of the application of calprotectin measurement in stool samples from children with IBD, as a marker of the severity of inflammation.

**Material and Methods.** We analysed 156 patients: 58 with ulcerative colitis (UC), 67 with Crohn's disease (CD), and 31 from the control group. In all patients the concentration of calprotectin in the sample of feces, markers of inflammation and hemoglobin were measured.

**Results.** Concentration of calprotectin in feces of patients with IBD was above the normal range in all patients with moderate and severe disease and in the majority with mild disease or in remission, but it was normal in all patients from the control group.

**Conclusions.** Elevated concentration of fecal calprotectin (FC) was observed in the majority of patients with IBD, but in none from the control group. The number of patients with elevated FC concentration increased together with the disease activity. FC concentration was higher in patients with severe and moderate disease activity. FC concentration in patients with IBD was associated with the increase of inflammatory markers and decreased haemoglobin. Percentage of laboratory abnormalities in children with Crohn's disease and perianal changes was higher. FC concentration can be a noninvasive marker of disease activity in IBD (*Adv Clin Exp Med* 2015, 24, 5, 815–822).

**Key words:** inflammatory bowel disease, children, calprotectin.

Inflammatory bowel diseases have their onset in childhood in almost 20% of the patients. These diseases usually tend to follow a chronic and progressing course and are marked by relapse periods. Their etiology is not fully recognized though it is well known that genetic, immunologic and environmental factors play a role. To the inflammatory bowel diseases belong ulcerative colitis (UC), Crohn's disease (CD) and indeterminate colitis (IC). The diagnosis of these diseases and the assessment of their course is based on a patient anamnesis, physical examination, biochemical laboratory tests, endoscopic studies, histopathologic studies, and imaging investigations. The establishment of diagnosis relies on a number of invasive studies (blood drawing, endoscopic studies). The

assessment of the activity of the disease by the use of special activity scores may be imprecise since it relies on subjective patients feelings such as well-being and pain sensation, among others. For that reason there is ongoing search for a valuable marker which would allow determining the activity of the disease accurately and precisely and, at the same time, would allow us to monitor the effects of treatment and to anticipate imminent relapses of the disease. A marker which could be obtained without the necessity of invasive or painful procedures would be an ideal solution. This is particularly important in regards to children. At the same time the marker estimation should be not expensive and should not require cumbersome laboratory procedures so that it could be used on the daily

basis. The marker should be specific enough to let us establish the diagnosis of inflammatory bowel disease (or at least help in establishing it) [1–7].

Calprotectin, one of bactericidal peptides, seems to fulfill most of those postulates. This protein is produced in inflammatory states by neutrophils, macrophages, monocytes and epithelial cells. The increase in calprotectin amount is observed in serum, cerebrospinal fluid, urine, synovial membrane and in feces, where it reaches the highest concentration, even six times higher than in serum. The concentration of calprotectin in feces depends on the migration of neutrophils to the lumen of the intestine and correlates with both the local and systemic inflammatory process and allows us to anticipate an imminent relapse of the disease in a patient in remission. However, calprotectin is not a specific marker for the inflammatory bowel disease and its concentration increases in other diseases of the alimentary tract, such as neoplasm, polyps, bacterial infections, including *H.pylori*, celiac disease and in patients taking non-steroidal anti-inflammatory drugs. Moreover, what is especially important for pediatricians is that the concentration of fecal calprotectin is higher in children (up to 5 years of age) than in adults. However, in functional diseases of the alimentary tract fecal calprotectin is so low that it can differentiate those diseases from organic diseases despite the limitations mentioned above. At the same time, since calprotectin is a protein which is resistant to intestinal proteolysis it can be stored and transported at ambient temperature even for up to 5 to 7 days without losing activity. Its determination in the sample is simple and does not generate additional costs [2, 3, 6–7, 9–16].

## Objective of the Work

Evaluation of the usefulness of calprotectin measurement in stool samples from children with inflammatory bowel diseases as a marker of the severity of inflammation.

## Material and Methods

Analysis comprised 156 patients hospitalized in the Clinic of Pediatrics, Gastroenterology and Nutrition. In 125 of them inflammatory bowel diseases were diagnosed based on the Porto criteria [1]; in 58 – ulcerative colitis (UC), in 67 – Crohn's disease (CD). As a control group, a group of 31 children without inflammatory bowel disease was recruited. In this group, functional disorders of the intestinal tract were the most common diagnosis. All patients were divided into

distinct groups taking into consideration the kind and activity of inflammatory bowel disease. The group of patients with UC was denoted as group I. Activity of the disease was determined based on PUCAI scale [5]. Group I was subdivided into 4 subgroups: IR – remission, IA – mild disease, IB – moderate disease and IC – severe disease. Patients with CD were divided similarly into groups IIR, IIA, IIB and IIC, using PCDAI scale according to Hyams [4] and group III was a control group.

In all patients fecal calprotectin was determined using CALPRO Calprotectin ELISA Test (ALP) – Calpro AS, Norway. Concentrations between 0 and 50 mg/kg of stool were treated as normal values; positive result meant that the concentration was above 50 mg/kg of feces (norm I = NI). In active inflammatory bowel disease concentration of calprotectin is usually between 200 and 20,000 mg/kg of feces, what was regarded as a norm II (NII) [2, 9, 17].

Besides, in all patients, markers of inflammation were assessed: erythrocytes sedimentation rate (ESR), C-reactive protein (CRP), white blood cells count (WBC), platelets (PLT), hemoglobin concentration (Hb) and serum seromucoid (ser).

In 42 patients fecal calprotectin concentration was measured several times during disease relapses of various activities (all together 211 measurements were analyzed, two times in 29 patients and 3 times in 13 patients). Patients in whom measurements were done 2 or 3 times were included in respective groups according to the disease activity, therefore 87 measurements were done in UC patients and 93 in CD patients.

Statistical analysis was performed using Mann-Whitney test, Spearman rank correlation and Kruskal-Wallis multiple comparison test, regarding  $p < 0.05$  as statistically significant. The descriptive data was presented as average. For statistical analysis, STATISTICA 10 PL software was used.

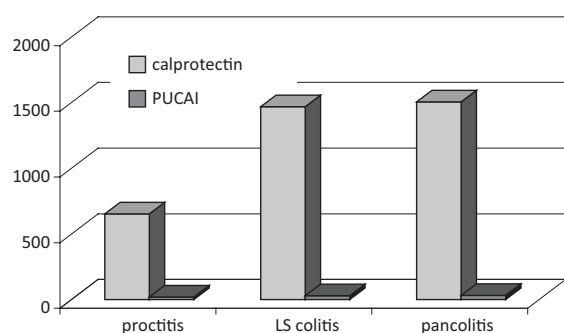
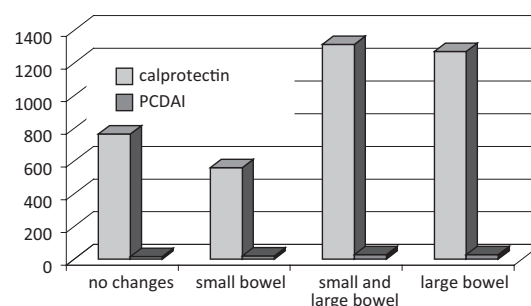
## Results

Table 1 presents the division of the patients into the groups according to the type and activity of inflammatory bowel syndrome, the number of patients, and their sex and age. Table 2 presents fecal calprotectin concentration and deviations from the normal values of laboratory tests. The normal concentration of fecal calprotectin was observed in all children from the control group.

By contrast, in all groups of inflammatory disease, including patients in remission, the average concentration of fecal calprotectin was above norm I and norm II, and was increasing proportionally to the increase in activity of the disease (Table 2).

**Table 1.** Activity of inflammatory bowel disease, age and sex of children

Diagnosis	Disease activity	Group	Number of children	Age (years)		Sex			
				min-max	average	male		female	
						number	%	number	%
Ulcerative colitis (UC)	remission	IR	23	7–18	14.0	7	30.0	16	69.6
	mild	IA	25	4.05.2018	14.01.2015	10	40.0	15	60.0
	moderate	IB	30	4.05.2018	14.02.2015	9	30.0	21	70.0
	severe	IC	9	6,6–17	12,3	1	11.01.2015	8	88.9
	total UC	I	87	4.5–18	13.9	27	31.0	60	69.0
Crohn's disease (CD)	remission	IIR	27	5–18	14.2	18	66.7	9	33.3
	mild	IIA	25	5.5–18	13.3	18	72.0	7	28.0
	moderate	IIB	30	8–18	14.9	15	50.0	15	50.0
	severe	IIC	11	8–18	15.1	4	36.4	7	63.6
	total CD	II	93	5–18	14.03.2015	55	59.1	38	40.9
Control		III	31	3.05.2017	12.05.2015	16	51.6	15	48.4

**Fig. 1.** Fecal calprotectin concentration based on the location of the disease in children with ulcerative colitis calprotectin mg/kg;  $p < 0.05$  for pancolitis vs. proctitis**Fig. 2.** Fecal calprotectin concentration based on the location of the disease in children with Crohn's disease; calprotectin mg/kg

The average concentration concentrations of calprotectin were not statistically different between UC and CD in contrast to hemoglobin, which was lower in UC than in CD in all subgroups respectively. There were significant differences between fecal calprotectin in both groups with inflammatory bowel disease (groups I and II) and the control group similarly as the differences of ESR, CRP and PLT and in the case of UC also the differences of WBC and Hb. Concentration of fecal calprotectin correlated both with the activity of the disease and also with serum inflammation markers (ESR, CRP, ser., WBC, PLT) – proportionally, and reversely with hemoglobin concentration (Table 3).

Fecal calprotectin concentration demonstrated a stronger dependence on the disease localization in the intestine in the case of UC than in the case of CD; however, in both cases the interconnection of fecal calprotectin with disease activity

determined by the punctuation scales (PUCAI and PCDAI) was clearer (Fig. 1 and 2).

In patients with CD with perianal changes, fecal calprotectin reached higher concentration than in patients without these changes. The percentage of children with the concentration of fecal calprotectin above the normal value and improper laboratory values was also bigger in patients with perianal changes than in patients without those changes, but these results were statistically significant only for PLT and PCDAI (Mann-Whitney test) (Fig. 3).

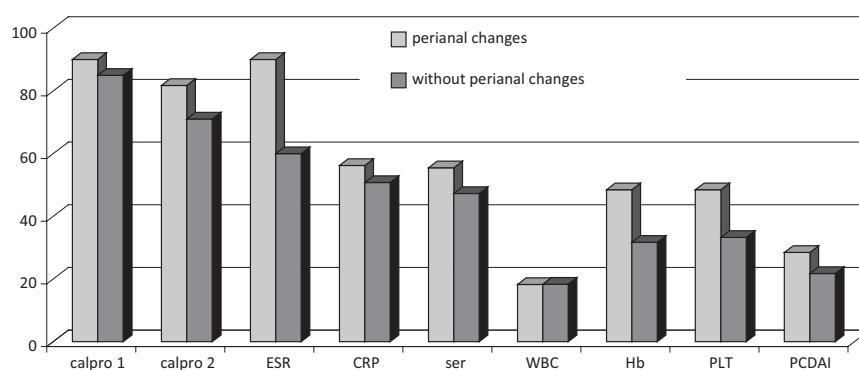
## Discussion

Calprotectin is a protein produced in inflammatory states by neutral granulocytes, macrophages, monocytes and epithelial cells. An increased

**Table 2.** Abnormalities (in %) of calprotectin concentration in stool and selected inflammatory parameters in patients with inflammatory bowel disease and in control group

Activity of inflammatory bowel disease (number of children)	Calprotectin [mg/kg]			ESR [mm/1 h]		CRP mg/L		Seromucoid [mg%]		Leukocytes [K/ $\mu$ L]		Hemoglobin [g%]		Platelets [K/ $\mu$ L]	
	average	% $\uparrow$ NI/	% $\uparrow$ NII/	av.	% $\uparrow$ N	av.	% $\uparrow$ N	av.	% $\uparrow$ N	av.	% $\uparrow$ N	av.	% $\downarrow$ N	av.	% $\uparrow$ N
IR (23)	1002.9	82.6	60.9	15.9	52.2	4.9	17.4	1.0	20.0	7.4	17.4	11.7	62.2	318.2	21.7
IA (25)	1159.1	96.0	92.0	20.6	68.0	8.2	24.0	1.2	46.7	7.8	20.0	12.1	40.0	378.7	36.0
IB (30)	1716.9	100.0	100.0	31.3	83.3	11.6	36.7	1.3	55.0	9.0	40.0	10.5	86.7	411.6	50.0
IC (9)	2187.2	100.0	88.9	36.5	100.0	48.4	66.7	1.5	80.0	13.1	77.8	9.7	100.0	456.1	66.7
<b>Total I (UC) (87)</b>	<b>1416.6<sup>a</sup></b>	<b>94.3</b>	<b>86.2</b>	<b>24.7</b>	<b>72.4</b>	<b>12.7</b>	<b>31.0</b>	<b>1.2</b>	<b>42.4</b>	<b>8.7</b>	<b>32.1</b>	<b>11.2</b>	<b>69.9</b>	<b>382.1</b>	<b>40.2</b>
IIR (27)	581.5	66.7	48.1	15.1	48.1	4.9	23.0	1.1	27.3	6.9	11.1	13.4	11.1	327.1	25.9
IIA (25)	990.0	88.0	72.0	20.5	64.0	12.5	44.0	1.2	31.6	6.9	8.0	12.7	32.0	320.0	16.0
IIB (30)	1637.9	96.7	93.3	35.4	90.0	21.6	70.0	1.8	68.4	8.6	30.0	11.8	53.3	426.1	60.0
IIC (11)	1544.0	100.0	90.1	57.6	100.0	44.6	90.1	2.1	100.0	8.3	27.3	10.2	81.8	478.8	63.6
<b>Total II (CD)(93)</b>	<b>1145.9<sup>b</sup></b>	<b>86.0</b>	<b>74.2</b>	<b>28.1</b>	<b>72.0</b>	<b>17.2</b>	<b>43.5</b>	<b>1.5</b>	<b>51.8</b>	<b>7.6</b>	<b>18.3</b>	<b>12.3</b>	<b>38.7</b>	<b>375.1</b>	<b>38.1</b>
III (31)	14.7 <sup>ab</sup>	0	0	9.0	19.3	4.4	3.2	0.8	0	5.8	6.4	13.0	12.9	283.2	6.4

<sup>a</sup> –  $p < 0.05$  for I vs. III; <sup>b</sup> –  $p < 0.05$  for II vs. III; <sup>c</sup> –  $p < 0.05$  for I vs. II.



**Fig. 3.** Percentage of laboratory abnormalities and disease activity (PCDAI) in children with Crohn's disease, depending on the prevalence of these perianal changes; percentage (%)

**Table 3.** Correlation of fecal calprotectin concentration with selectet laboratory parameters and disease activity in children with inflammatory bowel disease

Correlation	Number of valid	Rank of Spearman	t(N-2)	p
Calprotectin and ESR	222	0.485337138	8.23343277	< 0.05
Calprotectin and CRP	220	0.228518814	3.465745211	< 0.05
Calprotectin and SER	125	0.433596462	5.336565495	< 0.05
Calprotectin and WBC	223	0.314475447	4.924874306	< 0.05
Calprotectin and HB	223	-0.382893264	-6.161683559	< 0.05
Calprotectinvs and PLT	223	0.402178317	6.530212879	< 0.05
Calprotectin and PCDAI	93	0.504309833	5.57114315	< 0.05
Calprotectin and PUCAI	87	0.392180264	3.930610895	< 0.05

amount of calprotectin is observed in many body fluids; however, the highest amount is present in feces. In inflammatory bowel diseases the migration of neutrophiles to the gut is increased and thereby an increase in calprotectin amount is observed within the lumen of the intestines. Therefore, its measurement in feces may serve as an indicator of the disease activity [2, 6–8, 10–11, 13].

Fecal calprotectin concentration in our studies showed positive correlation with the activity of the disease: it was within the normal range in only small percentage (17.4%) of the patients with UC in remission and in only 4% in mild disease relapse, when in all patients with moderate and severe relapse it raised above the upper limit of the norm. Similarly in CD only in 33.3% of the patients in remission and in 12% of the patients with mild relapse the amount of fecal calprotectin was within the normal range. The concentration of fecal calprotectin was above the norm in 96.7% of the patients with moderate disease relapse and in all patients with severe activity of the disease (Table 2, 4).

In our study, 40% UC patients and in more than 50% of CD patients free of clinical symptoms in the time of the study presented elevated fecal calprotectin concentration compared to healthy individuals (but not overcome the norm II [NII]), the average fecal calprotectin concentration was

elevated (Table 2), which is also emphasized by other authors [13, 19–21] and explained by the fact that clinical remission occurs earlier than endoscopic remission or that it is a forecast of a further relapse. Correlation between fecal calprotectin concentration and mucosal pathology extension but not with the activity of the disease measured by clinical symptoms scores has also been emphasized by many authors [16, 19–26].

In our material (Fig. 1), in patients with UC, the highest fecal calprotectin concentration was observed when an extensive involvement of the large intestine was present and the smallest when only the rectum was involved (1504.9 mg/kg vs. 653.7 mg/kg). A similar correlation was described by Wagner [18] while other authors emphasized a link of fecal calprotectin content and local inflammation activity but not with its extent. In the case of CD, the highest fecal calprotectin concentration was observed when the disease involved the large intestine (1312.4 mg/kg) or both the small and large intestine (1145.9 mg/kg) and the smallest when only the small intestine was involved (559.1 mg/kg), which has also been confirmed by other authors [13, 27] (Fig. 2). But in the assessment of inflammatory indicators and fecal calprotectin in children with CD with or without perianal changes it could be seen that higher values

**Table 4.** Fecal calprotectin concentration and selected laboratory parameters value in patients with inflammatory bowel disease (ulcerative colitis and Crohn's disease) during relapses with different disease activity

Activity of inflammatory bowel disease (number of children)	Calprotectin [mg/kg]			ESR [mm/1 h]		CRP mg/L]		Seromucoid [mg%]		Leukocytes [K/ $\mu$ /L]		Hemoglobin [g%]		PLT [K/ $\mu$ L]	
	av.	% $\uparrow$ NI/	% $\uparrow$ NII/	av.	% $\uparrow$ N	av.	% $\uparrow$ N	av.	% $\uparrow$ N	av.	% $\uparrow$ N	av.	% $\downarrow$ N	av.	% $\uparrow$ N
IR (11)	1110.8	90.9	81.8	12.3	54.5	5.0	9.1	1.0	33.3	8.3	18.2	11.3	72.7	335.2	27.2
IA (14)	1158.8	92.8	92.8	23.3	71.4	8.7	21.4	1.2	36.3	9.3	28.6	11.7	42.8	425.5	50.0
IB (17)	1788.3	100.0	100.0	29.3	76.5	11.2	29.4	1.3	46.1	9.3	47.0	10.2	82.3	434.7	58.8
IC (9)	2187.2	100.0	88.9	36.5	100.0	48.4	66.7	1.5	80.0	10.0	77.8	9.7	100.0	456.1	66.7
<b>Total I (UC) (51)</b>	<b>1539.8</b>	<b>96.1</b>	<b>92.1</b>	<b>25.3</b>	<b>74.5</b>	<b>15.7</b>	<b>29.4</b>	<b>1.3</b>	<b>45.7</b>	<b>9.8</b>	<b>41.2</b>	<b>10.8</b>	<b>72.5</b>	<b>414.5</b>	<b>50.9</b>
IIR (9)	649.1	77.8	55.5	19.1	55.5	4.9	33.3	1.4	50.0	6.2	11.1	13.2	22.2	315.2	11.1
IIA (9)	1216.6	77.8	66.7	26.7	77.8	11.4	33.3	1.3	40.0	7.1	11.1	12.7	33.3	315.7	11.1
IIB (18)	1492.6	94.4	88.9	33.2	83.3	18.9	61.1	1.6	77.8	7.6	27.8	11.9	55.5	400.8	50.0
IIC (10)	1687.5	100.0	100.0	57.4	100.0	43.1	90.0	2.2	100.0	8.1	30.0	10.3	80.0	481.7	60.0
<b>Total II (CD)(46)</b>	<b>1433.6</b>	<b>89.1</b>	<b>80.4</b>	<b>29.7</b>	<b>80.4</b>	<b>17.8</b>	<b>56.5</b>	<b>1.4</b>	<b>72.7</b>	<b>8.6</b>	<b>21.7</b>	<b>11.3</b>	<b>50.0</b>	<b>400.5</b>	<b>36.9</b>

and higher percentage with elevated values were observed in patients with perianal changes (Fig. 3) but the differences were not statistically significant with the exception of PLT.

Some of the authors postulate that the correlation between fecal calprotectin concentration and the activity of the disease is stronger in the case of UC than in CD, which is linked with a rare involvement of the large intestine and with a lack of a complete mucosal healing even in remission phase [7, 23, 25]. Others have obtained similar fecal calprotectin concentration in both diseases [12, 15, 26, 28] or directed attention to the strong correlation between the activity disease in patients with CD [13, 29]. Kosiara and Komraus [14, 27] have observed lower average concentration of fecal calprotectin in patients with CD; however, other authors have noted in patients in remission higher content of fecal calprotectin in patients with CD [12, 20, 26].

In our material, concentration of fecal calprotectin in all UC patients was higher than in that in CD group, independently on the activity of the disease.

Improper values of serum laboratory elevated inflammatory indices and decreased hemoglobin and clinical activity indices (PUCAI and PCDAI) correlated with fecal calprotectin significantly ( $p < 0.05$ ). The percentage of improper values of inflammatory markers and lowered hemoglobin was higher than in the control group, also average fecal calprotectin content and values of other inflammatory markers were higher in patients with UC and CD than in control group (Table 2). Similarly in the patients in whom fecal calprotectin concentration was measured during the subsequent relapses of the disease increased from 90.9% in remission of UC and from 77.8% in remission of CD to 100% in severe relapse in both UC and CD. The percentage of improper laboratory results also increased proportionally to the increase in the activity of the disease (Table 4). All this allows us to label fecal calprotectin as a marker correlating with other serum markers of inflammation.

Fecal calprotectin is not a marker which is specific for inflammatory bowel disease since its concentration increases also in the large intestinal neoplasmas, rheumatic disorders, acute pancreatitis, liver cirrhosis, pneumonia and after a severe physical exercise and after administration of non-steroidal anti-inflammatory drugs. After intense treatment with steroids the concentration of fecal calprotectin decreases rapidly [2–3, 13, 18, 20], which was observed also in our material – in one patient with a severe relapse of UC we observed a relatively low fecal calprotectin concentration (but above the norm) after several days of glucocorticoids administration together with lasting high increase of inflammatory markers. Nevertheless, although fecal calprotectin is not specific it is exceptionally useful in assessment of inflammatory bowel disease. This examination is worth of recommendation especially in children in whom intestinal neoplasm is extremely rare and its non-invasiveness and painlessness causes that it is a promising diagnostic tool, which can supplement the standard methods [7, 15, 18, 27, 30–32].

The authors concluded that fecal calprotectin concentration above the norm was observed in the most of the patients with inflammatory bowel diseases (in 94.3% with UC and in 86% with CD) and in none in the control group. The percentage of patients with increased fecal calprotectin content increased together with the increase of the disease activity. Fecal calprotectin concentration was higher in patients with moderate and severe disease relapse than in those with mild relapse or those in remission. In patients with inflammatory diseases, the increase of fecal calprotectin concentration correlated with the increase in serum inflammatory markers and the decrease in hemoglobin. In patients with CD with perianal changes, the percentage of improper fecal calprotectin or its average concentrations were lower than these in patients without such changes. The measurement of fecal calprotectin content is uncomplicated, repeatable and noninvasive method in assessment of disease activity in inflammatory bowel disease.

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