CORRELATIONS OF FECAL CALPROTECTIN WITH CLINICAL AND ENDOSCOPIC SCORES IN INFLAMMATORY BOWEL DISEASES IN CHILDREN

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Abstract

Background: An accurate monitoring of mucosal inflammation is important for an effective management of children with inflammatory bowel disease (IBD). The aim of the study was to evaluate the efficacy of the fecal calprotectin as indicator of inflammatory activity in children with Crohn's disease (CD) and ulcerative colitis (UC) by correlating it with biological, clinical and endoscopic indices. Methods: A total of 22 children presenting IBD were evaluated (16CD/6UC). Fecal calprotectin, blood tests, Pediatric CD Activity Index (PCDAI), Pediatric UC Activity Index (PUCAI), CD Endoscopic Index of Severity (CDEIS) and Mayo Disease Activity Index (MDAI) were used for children evaluation at diagnosis and after 6 months of treatment. Results: In CD children, calprotectin showed a high correlation ($r = 0.775$) with the histologic grade of mucosal inflammation, showed by CDEIS and a medium correlation with CRP($r = 0.623$). lt didn't correlated with PCDAI ($r = 0.325$). In UC children, calprotectin correlated moderate (r=0.581) with CRP and it was strongly correlated with PUCAI (r = 0.752) and MDAI (r = 0.796). Calprotectin levels decreased significantly after 6 months of treatment in all IBD patients (p = 0.038). Conclusions: In CD children fecal calprotectin was more accurate in detection of active mucosal inflammation when compared to clinical score and serum marker CRP. The relatively poor correlation between calprotectin levels and PCDAI might not be due to a calprotectin low sensitivity in CD children, but to the fact that PCDAI is mostly a clinical score and is not sensitive enough to detect subclinical activity of the disease. Fecal calprotectin correlated well with endoscopic indices both in CD and UC children. So, it can provide a reliable noninvasive marker for monitoring IBD activity.

Key words: Crohn's disease, ulcerative colitis, calprotectin, children

Introduction

Inflammatory Bowel Disease (IBD) includes Crohn's Disease (CD), Ulcerative Colitis (UC) and Indeterminate Colitis (IC), which is considered to be an intermediary condition that will progress to one of those two entities above, according to some authors. *(1)* These are chronic idiopathic disorders, characterized by recurrent episodes of inflammation of the gastrointestinal tract, interspersed with periods of remission*)*.

In order to monitor patient's clinical evolution and adjust the therapy, it is very important to determine the degree of inflammatory activity at the moment of diagnosis and in evolution. *(2*An accurate monitoring of mucosal inflammation is important for an effective management of patients with IBD. *(3)* Beside clinical and biological remission, the mucosal healing represents an important goal to be achieved by treatment. Several indexes are proposed for evaluation of disease activity, which differ from each other in terms of being more subjective (clinical), more objective (endoscopic-histological) or a combination of the two. *(4)* However, despite the different scores available, there is not any consensus in the literature as which is the most valid. *(5)* Laboratory parameters such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum fibrinogen level and haematocrit, among others, are not specific for active IBD, so those can not be used routinely as markers of inflammatory activity in clinical practice. *(6)*

Many authors consider that colonoscopy with biopsy represents the best method for evaluating inflammation location, extent, and severity. *(7)* Beside from being an invasive method especially in children, this approach carries risks of complications. Various studies have described fecal markers as powerful biomarkers of inflammation of the intestinal mucosa in patients with IBD. Fecal markers selected and studied by different recent authors as indicators of inflammation include neutrophil granule proteins, lactoferrin and calprotectin. *(8)*

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Objectives of the study

Several studies have compared fecal calprotectin with activity indexes and/or endoscopic/histological evaluation to confirm intestinal inflammation in IBD adult patients. The results of these studies are promising, demonstrating that these markers are useful in detecting inflammation and differentiating it from other diseases as well as in predicting recurrence for periods of up to one year. *(9)* The objectives of this paper were to assess calprotectin in children as indicator of IBD activity and to determine if this marker correlates with other indexes of inflammatory activity including laboratory measures (CRP), two diseases activity scores (Paediatric Crohn's Disease Activity Index – PCDAI, Pediatric Ulcerative Colitis Activity Index – PUCAI) and endoscopic evaluation, at the moment of diagnosis and after 6 months of treatment.

Material and methods

We conducted a retrospective, descriptive study on a lot of 22 children diagnosed with IBD between February 2005 and December 2010. The lot of study included 16 children with CD and 6 children with UC. The patients were aged between 4 and 18 years.

The work-up diagnosis included at all children detailed clinical examination followed by biological assessment (blood cells count, CRP, ESR, fibrinogen, serum iron, glicemia, liver and renal function tests). Fecal calprotectin was measured in all cases and IBD diagnosis was certified by endoscopic assessment (colonoscopy± upper digestive endoscopy) and histological interpretation of the biopsy samples (from colon and/or ileum).

Fecal calprotectin was measured using a quantitative ELISA tests.

Calprotectin, also known as MRP-8/MRP-14 or S100A8/A9 heterocomplex, is formed out of the calcium-binding, migration inhibitory factor-related proteins MRP-8 (S100A8) and MRP-14 (S100A9). The expression of these proteins is largely confined to the cytosol of neutrophils and monocytes. The complex formation of these proteins is calcium-dependent. Calprotectin comprises 60% of the cytoplasmic protein fraction of circulating polymorphonuclear granulocytes and is also found in monocytes, macrophages and ileal tissue eosinophils. *(10)* It was suggested that measurement of faecal calprotectin would represent a surrogate marker of neutrophil influx into the bowel lumen and in turn act as a marker of intestinal inflammation. *(11)*

In our study, results interpretation for fecal calprotectin values is described in table I, according to manufacturing recommendations:

For all children with IBD, we calculated clinical and endoscopic indices of disease activity.

In 16 cases of children with CD we calculated the activity index PCDAI (table II) and in 6 cases of children with UC we calculated the activity index PUCAI (table III).

Conform to some authors, no single clinical or biochemical parameter consistently reflects activity of intestinal inflammation. Therefore, multi-attribute measures of disease activity have been developed for use in the clinical trial setting. Although other CD activity indices have been used, the Crohn's Disease Activity Index (CDAI) is generally accepted as the standard clinical outcome measure in adult CD trials. The Pediatric Crohn's Disease Activity Index has became the accepted disease activity measure in childhood CD. PCDAI, in contrast to the adult-derived CDAI, includes linear growth, recognizing that height velocity is an important marker of disease activity among children with CD. *(12)*

PCDAI values were considered negative for disease activity between 6.8 ± 6.6, mild inflammatory activity between18.7 ± 7.3, moderate between 38.5 ± 12.9 and severe between 54.2 ± 14.0 points *(13)*

In the context of a Pediatric IBD Clinical trials workshop, sponsored by the Crohn's and Colitis Foundation of America (CCFA) in 2004, a group of pediatric IBD experts was assembled to reach consensus concerning outcome assessment in pediatric IBD. Although recommendations for outcome assessment in CD made use of existing measures, the panel concluded that for UC, a novel instrument measuring disease activity in pediatric patients should be developed. *(14)* Clinical trials in adult patients with UC most commonly include post-treatment endoscopic examination as an endpoint, with or without clinical criteria, but follow-up colonoscopy is not routinely performed and would not be well accepted at pediatric institutions. The result was the development of the Pediatric UC Activity Index (PUCAI).

Table I

Fecal calprotectin values (µg/g)	Results interpretation
< 50	There is no inflammation of the gastrointestinal tract
50-150	Mild inflammation of the gastrointestinal tract; the inflammatory response can be due to an enteral infection, alimentary allergy or previous treatment with non-steroidian anti-inflammatory drugs.
>150	Important inflammation of the gastrointestinal tract, associated to IBD, infections, non-steroidian anti-inflammatory drugs, polyps, colonic cancer. Further investigations are needed for establishing the cause of inflammation.
> 250	Besides the previous comment, in case of known IBD patients, this result indicates an active period of disease. In case of IBD patients in remissions, this result confers a high risk of relapse within an year.

Table II: The PCDAI score

Abdominal pain	No abdominal pain	0
	Mild; no interference with Activities of Daily Living (ADL)	5
	Moderate/severe; daily, nocturnal, interferes with ADL	10
Stools/day	0-1 liquid, no blood	0
	≤ 2 Semi-formed + small blood or 2-5 liquid	5
	≥ 6 liquid stools, gross blood or nocturnal diarrhoea	10
General function	Well, no limitation of activities	0
	Occasional difficulty with activities	5
	Very poor, frequent limitation of activities	10
Weight	Weight gain (or voluntary stable, reduction)	0
	Weight loss < 10% (or involuntary stable)	5
	Weight los ≥ 10%	10
Height (at diagnosis)	< 1 channel decrease from previous percentile	0
	1 to < 2 channel decrease from previous percentile	5
	≥ 2 channel decrease from previous percentile	10
OR		
Height velocity	≤ -1 standard deviation from normal	0
	-1 to < -2 standard deviation from normal	5
	≥ -2 standard deviation from normal	10
Abdomen	No tenderness or mass	0
	Tenderness, or mass without tenderness	5
	Tenderness, involuntary guarding, definite mass	10
Peri-rectal disease	None, asymptomatic tags	0
	1-2 indolent fistula, scant drainage, non-tender	5
	Active fistula, drainage, tenderness, or abscess	10
Extra-intestinal	None	0
	1 manifestation	5
	≥ 2 manifestations	10
Haematocrit (%) M = male F = female	M/F 6-10 years ≥ 33	0
	M 11-14 years ≥ 35	
	F 11-19 years ≥ 34	
	M 15-19 years ≥ 37	
	M/F 6-10 years 28-32	2,5
	M 11-14 years 30-34	
	F 11-19 years 29-33	
	M 15-19 years 32-36	
	M/F 6-10 years < 28	5
	M 11-14 years < 30	
	F 11-19 years < 29	
	M 15-19 years < 32	
ESR (mm/hr)	< 20	0
	20-50	2,5
	> 50	5
Albumin (g/L)	≥ 35	0
	31-34	5
	≤ 30	10

Table III: The PUCAI score

ITEM	POINTS
1. Abdominal pain	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
2. Rectal bleeding	
None	0
Small amount only, in less than 50% of stools	10
Small amount with most stools	20
Large amount (> 50% of the stool content)	30
3. Stool consistency of most stools	
Formed	0
Partially formed	5
Completely unformed	10
4. Number of stools per 24 hours	
0-2	0
3-5	5
6-8	10
>8	15
5. Nocturnal stools (any episode causing wakening)	
No	0
Yes	10
6. Activity level	
No limitation of activity	0
Occasional limitation of cativity	5
Severe restricted activity	10

The PUCAI is able to detect change also in a short period of a few weeks and can perform well in both in and outpatient setup including patients with mild to severe disease activity. *(14)* The rigorously developed PUCAI is a non-invasive, valid, highly reliable and responsive index with which to assess disease activity in pediatric ulcerative colitis.

The values of PUCAI score varies between 0 and 85 points, reflecting absence or presence of disease activity of various degrees as following: 0-10 inactive disease, 10-34 mild disease activity, 35-64 moderate disease activity, 65-85 severe disease activity. *(14)*

Assessment of disease severity and extension of the lesions at children with CD was made by computing Crohn's Disease Endoscopic Index of Severity (CDEIS) and at children with UC we used the sub-endoscopic score Mayo Disease Activity Index (MDAI) (table IV).

CDEIS reflects endoscopists' global appraisals of lesions'severity. For calculating this index, the presence of nine preselected lesions was recorded in the following segments: (1) rectum, (2) sigmoid and left colon, (3) transverse colon, (4) right colon, and (5) ileum. The nine mucosal lesions recorded were: pseudopolyps, healed ulcerations, frank erythema, frankly swollen mucosa, aphthoid ulcerations, superficial or shallow ulcerations, deep ulcerations, non ulcerated stenosis, ulcerated stenosis. In addition the extent of the diseased and ulcerated areas were estimated in each segment. The percentage of the segmental surfaces involved by the disease (SSD) - taking into account these nine lesions – and the percentage of the segmental surfaces involved by ulcerations only (SSU) were recorded. For colonic segments only partially explored and for ileum, the 10 cm scale represented the area actually seen. *(15)*

The following calculations were carried out: (1) The average segmental surfaces involved by the disease (ASSD) was calculated by dividing the sum of SSD by the number of segments explored at endoscopy. An identical calculation was performed with SSU to obtain the average segmental surfaces involved by ulcerations only (ASSU). (2) For each mucosal lesion, two variables were derived: (a) the first (PRES) was either 0 if the lesion was not seen at all or 1 if it was seen at least once at a given endoscopy; (b) the second - the individual segmental recto-colonic frequency (ISRCF) - was calculated by dividing the number of segments in which a lesion was seen by the number of segments examined. Thus ISRCF could take a series of values from 0 (lesion not seen in any of the segments explored) to 1 (lesion seen in all segments explored). *(16)*

Table IV Components of Mayo Disease Activity Index

Stool Frequency
0 = Normal
1 = 1–2 stools/day more than normal
2 = 3–4 stools/day more than normal
3 = >4 stools/day more than normal
Rectal bleeding
0 = None
1 = Visible blood with stool less than half the time
2 = Visible blood with stool half of the time or more
3 = Passing blood alone
Mucosal appearance at endoscopy
0 = Normal or inactive disease
1 = Mild disease (erythema, decreased vascular pattern, mild friability
2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3 = Severe disease (spontaneous bleeding, ulceration)
Physician rating of disease activity
0 = Normal
1 = Mild
2 = Moderate
3 = Severe

The final formula for CDEIS calculation is as follows:

CDEIS = 12 x ISRCF (deep ulcerations)
+ 6 x ISRCF (superficial ulcerations)
+ ASSD
+ ASSU
+ 3 x PRES (non ulcerated stenosis)
+ 3 x PRES (ulcerated stenosis)

*ISRCF: number of segments exhibiting the lesion divided by the number of explored segments.

PRES is taken to be 1 if the lesion is seen at least once at a given endoscopy and 0 otherwise.

ASSD: Average surface involved by the disease.

ASSU: Average surface involved by ulcerations only.

CDEIS varies from 0 to 30 points, reflecting the severity of mucosal injury. *(16)*

The Mayo Score and the nearly identical Disease Activity Index (DAI) described by Sutherland are two of the most commonly used activity indices in placebo-controlled clinical trials for ulcerative colitis. Each is composed of four categories (bleeding, stool frequency, physician assessment, and endoscopic appearance) rated from 0–3 that are summed to give a total score that ranges from 0–12. *(17)*

Statistic analyze was made using SPSS 16 soft (Statistical Package For Social Sciences for Windows, version 16).

Results and discussions

IBD is a lifelong disease with significant morbidity and requires endoscopy for diagnosis and disease monitoring. Identifying markers of IBD that allow noninvasive diagnosis and disease monitoring would be of great advantage, especially in children. This study examined if fecal calprotectin correlates with CRP serum level, clinical activity indexes and endoscopic indices in CD and UC paediatric patients.

Clinical parameters of patients are presented in Table V.

We tried to correlate the values of fecal calprotectin quantitative assessed with serum CRP, clinical activity scores: PCDAI, PUCAI and endoscopic score CDEIS for Crohn's disease and sub-endoscopic score MDAI in ulcerative colitis. We studied if there are significant differences between the inflammatory markers values and clinical/endoscopic indices before and after 6 months of treatment.

We studied among the 16 CD children if fecal calprotectin correlates with CRP level and disease activity showed by clinical score PUCAI and endoscopic score CDEIS.

Table V Summary of IBD patients' clinical data

Illness	**CD**	**UC**
Number of patients	16	6
Sex (male/female)	9/7	3/3
Median age (minimum-maximum years)	7,5 (4-18)	15,5 (14-17)
Family history of IBD (yes/no)	3/13	0/6
Extent of disease		
Terminal ileum	0	
Ileum and colon	13	
Pancolitis	1	5
Rectal + sigmoid + descending colon	2	1
Rectal	0	0
Surgery intended (Yes/no)	1/15	0/6
Treatment		
Aminosalicylate	2	4
Immunosuppressant	9	2
Anti-TNF	5	0

Fecal calprotectin values correlated positive with clinical indices of disease activity PUCAI at UC children (r=0,752). We obtained also a high direct correlation, statistically significant between calprotectin and sub-endoscopic index MDAI (r = 0,796) and a medium direct correlation between calprotectin and seric CRP (r =0,623) in UC lot.

An important tool to assess inflammation is the analysis of the infiltration of neutrophils in the intestinal mucosa and their transmigration to the lumen. When intestinal inflammation occurs, fecal calprotectin rises rapidly and correlates with endoscopic and histological alterations in patients with IBD, supporting the idea that it is a sensitive and specific means to identity inflammatory activity in these patients. *(17)*

Many authors have claimed that calprotectin levels correlate closely with histological evaluation than macroscopic findings, suggesting that this biological marker is more sensible than endoscopy in evaluating IBDs activity. Furthermore fecal calprotectin concentrations predicted the severity of colorectal inflammation, with advanced histological grades of colorectal inflammation. *(18)*

This study showed that more intense levels of inflammation are associated with elevated calprotectin values, demonstrating a significant correlation between calprotectin and the severity of inflammation.

Calprotectin determination appears to better reflect disease activity in UC than CD. The relatively poor correlation between calprotectin levels and PCDAI might not be due to a calprotectin low sensitivity in CD children, but to the fact that PCDAI is mostly a clinical score and is not sensitive enough to detect subclinical activity of the disease, which is known to occur rather frequently in CD.

It has been suggested that CD patients' stratification based on phenotypical pattern (inflammatory, stricturing or fistulizing) could improve calprotectin's predictive capacity for this disease. As calprotectin is an inflammation marker, its predictive role will probably produce best results in the inflammatory pattern of the disease. In summary, the exact strength of any correlation of fecal calprotectin levels with disease activity clinical indicators is therefore not well established at present. *(19)*

In our study, calprotectine correlated very well with endoscopic index CDEIS in children. Similar resuls were reported in literature. Sipponen found that both fecal calprotectin and lactoferrin correlated significantly with CDEIS but in adults patients (Spearman's r 0,729, $p < 0,001$). With a cut-off level of 200 microg/g for a raised fecal calprotectin concentration, sensitivity was 70%, specificity 92% in predicting endoscopically active disease. *(16)*

In children with ulcerative colitis, it was observed that all patients with clinical and endoscopic signs of inflammation (as determined by the PUCAI and MDAI) had high values of calprotectin presents in their stool and these parameters were significantly correlated.

High values of calprotectin were present in the majority of samples from children with elevated CRP, these two inflammatory markers correlated moderate in both groups of children, with CD and UC.

We compared the medium values calculated separately in CD group and UC group respectively, for fecal calprotectin, CRP, clinical scores PCDAI/PUCAI and endoscopic indices CDEIS/MDAI at diagnosis and after 6 months of treatment. The results are presented in table VI. There were no significant differences between calprotectin medium values at CD and UC lot before treatment ($p>0,05$). We found a higher medium value of CRP at CD group compared to UC lot before treatment ($p=0.05$). After 6 months of treatment, we obtained a significant decreasing of calprotectin and CRP medim values in both lots with CD and UC ($p<0.05$). We found a direct significant correlation between calprotectin levels and endoscopic indices CDEI and MDAI after 6 months of treatment.

Table VI: Medium values for calprotectin, CRP, clinical and endoscopic sores in both CD and UC groups before and after 6 months of treatment

	Parameter	Medium value before treatment	Medium value after 6 months of treatment
Crohn's disease lot	Calprotectin (μg/g)	266.5±12.5	50.2±9.5 *p<0.05*
	CRP (g/l)	107.9±10.3 *p=0.05*	6.5±1.3
	PCDAI	39.5±6.5	11.5±3.5
	CDEIS	23.3±6.4	8.6±2.4 *r=0.75*
Ulcerative colitis lot	Calprotectin(μg/g)	236.4±13.6 *p>0.05*	48.2±9.3 *p<0.05*
	CRP (g/l)	86.5±7.2	6.2±1.5
	PUCAI	62.5±8.3	17.2±6.5
	MDAI	8.6±2.4	4.3±1.5 *r=0.78*

Conclusions

Fecal calprotectin represents a sensitive and specific marker for the detection of intestinal inflammation in IBD children. Calprotectin levels are directly proportional to the degree of inflammation in the intestinal mucosa, but did not correlated with clinical activity score in Crohn's disease children, only in the group with ulcerative colitis. The relatively poor correlation between calprotectin levels and PCDAI might not be due to a calprotectin low sensitivity in CD children, but to the fact that PCDAI is mostly a clinical score and is not sensitive enough to detect subclinical activity of the disease. Instead, it strongly correlated with both endoscopic indices, CDEIS and MDAI in CD and respectively UC children. These results suggest that fecal calprotectin may be valuable not only for screening children suspected of having IBD but also for monitoring disease activity and reducing the need for colonoscopy in disease follow-up.

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