International Journal of Multidisciplinary Research and Development
Online ISSN: 2349-4182, Print ISSN: 2349-5979; Impact Factor: RJIF 5.72
Received: 05-02-2019; Accepted: 08-03-2019
www.allsubjectjournal.com
Volume 6; Issue 4; April 2019; Page No. 57-63

Calprotectin as a Fecal Marker for Diagnosis and Follow-up in Patients with Ulcerative Colitis

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Abstract
Background and study Aims: Ulcerative colitis (UC) is a lifelong intestinal inflammatory condition of unknown a etiology. Faecal calprotectin has been proposed as a non-invasive surrogate marker of intestinal inflammation in UC. This study was designed to evaluate the fecal calprotectin as a marker for diagnosis of UC and its remission and exacerbation.
Patients and Methods: 60 patients were selected. 40 patients of them had ulcerative colitis (Group I). Group I was evaluated during active UC (GIa), and after remission (G1b). Group II included 20 patients age and sex matched without ulcerative colitis as control. All patients and controls were subjected to Colonoscopy with histopathological examination of biopsy specimens, measurement of activity index and quantitative determination of Fecal calprotectin.
Results: Analysis of the data reveled: Highly significant increase in the mean value of fecal calprotectin was present in active UC (GIa) patients in comparison to the inactive UC (GIb) patients and controls (GII). Also, highly significant increase in the mean value of fecal calprotectin was present in the inactive UC (GIa) patients in comparison to the controls (GII).
Conclusion: Faecal calprotectin is a non-invasive marker in evaluating patients with UC, with high accuracy, sensitivity, specificity, PPV and NPV [positive and negative predictive value] in differentiation between active and inactive UC and could be a reliable marker for the severity of UC.

Keywords: Ulcerative Colitis, fecal calprotectin

Introduction
UC is a life-long intestinal inflammatory conditions of unknown a etiology, characterized by remissions and exacerbations [1]. Significant progress has been made in the field of UC epidemiology, pathogenesis and treatment and a number of new insights have been created. Also, there is an increasing interest in the discovery of different new aspects related to diagnosis and treatment [2]. The diagnosis and differentiation of Crohn's disease (CD) or ulcerative colitis (UC) is still based on clinical, radiographic, endoscopic, and histological findings, newer less invasive serological tests are being employed to distinguish these disorders and provide prognostic information to possibly guide therapy [3]. Calprotectin is a calcium-binding protein secreted predominantly by neutrophils and monocytes. Fecal calprotectin test is a simple, non- invasive, rapid and inexpensive diagnostic tool allowing differentiation between GIT functional disorders and inflammatory conditions and relapse prediction in non-specific inflammatory bowel disease **[4].** Parallelism between faecal calprotectin levels and IBD activity has been confirmed, although this faecal marker appears to better reflect the disease activity in ulcerative colitis than in CD [5].

Study aims: This study is designed to evaluate the role of fecal calprotectin as a marker for diagnosis of UC and its correlation with disease activity and remission.

Patients and methods
Patients
Over 2 years: (from November 2014 to November 2016), this study has been conducted on 60patients referred to the endoscopy unit or to the outpatient clinic of Internal Medicine Department in Sayad Galal Hospital complaining of abdominal pain, chronic diarrhea, dysentery and or bleeding per rectum. They were divided into:

Group I: 40 patients had clinical, laboratory, colonoscopic and histopathological findings of ulcerative colitis they were 22 (55%) males and 18 (45%) females, their age ranging from 22 – 55 years with mean age of 35.6±9.06 years. Patients in this group are studied during activity of the disease [GIa] and after remission [GIb] by medical treatment.

Group II (Control): 20 patients' age and sex matched complaining of lower GI symptoms but without clinical, laboratory, colonoscopic and histopathological findings of ulcerative colitis.

Exclusion Criteria: The following patients were excluded
1. Past history of any malignant condition especially colorectal carcinoma**.**
2. Past history of major gastrointestinal surgical procedures.
3. Liver cell failure, chronic renal failure or congestive heart failure.
4. Bleeding tendency.
5. Patients with NSAIDs use.
6. Alcoholic patients**.**
7. Patients with past or family history of IBD are excluded from group II.

Methods
After providing informed consent, all Patients were subjected to
1) **Full history and clinical examination:** with special emphasis on abdominal pain, weight loss, rectal bleeding, diarrhea, constipation, malaise, anorexia,

nausea, tenesmus, abdominal distension, passage of mucous, vomiting and low-grade fever.

2) **Laboratory investigations:** Complete stool and urine analysis, ESR and CRP titre, Complete blood count. Fasting and postprandial blood glucose, S. creatinine and blood urea nitrogen**,** S. albumin, AST, ALT, S, bilirubin, PT, PTT and INR.
3) **Abdominal Ultrasound and Abdominal Plain x- ray**
4) **Colonoscopy and biopsy:** Total colonoscopy with biopsy sampling was performed to assess the severity and extent of endoscopic findings and to confirm the diagnosis. The disease extent in UC (Montreal classification) adopted from Silverberg *et al.* [6]. Grading of colonoscopic findings adopted from Sand born [7]
5) **Histopathological examination of biopsy specimens.** *Scoring system for the* histopathological *assessment* of severity in ulcerative colitis adopted from Geboes [8]
6) **Measurement of activity index**: using Mayo scoring system for assessment of UC activity. Adopted from Sand born [7].
7) **Quantitative Determination of calprotectin in stool sample:** Fecal calprotectin was measured using the PhiCal® Calprotectin ELISA Kit For the in vitro determination of Calprotectin in stool [PhiCal®: registered German trademark of Immunodiagnostic AG]**.**

Results

Colonoscopic evidence of inflammation of various degrees and extent was illustrated in Table (1). The various degrees and extent of inflammation were present in all GIa patients while evidence of colonoscopic remission was present in all GIb patients. According to the Ulcerative Colitis Activity Index (UCAI). All GIa patients had active UC while all GIb patients had remission Table (2).

Table (3) shows the histopathological findings in the studied groups. Higher histopathological grade of mucosal inflammation were present in all GIa patients (Grade 3, 4 and 5) and lower histopathological grade of mucosal inflammation were present in all GIb patients (Grade 0, 1, 2).

The mean value of fecal calprotectin was highly significant increase in active UC (GIa) patients in comparison to the inactive UC (GIb) patients and controls (GII). Also highly significant increase in the inactive UC (GIa) patients in comparison to the controls (GII) Table (4).

There were highly significant positive correlations between fecal calprotectin and (UCAI; CRP; ESR levels and TLC; PLT count) (Figures 1, 2, 3, 4, 5)

The diagnostic validity of faecal calprotectin in differentiating UC patients from other patients with lower GI symptoms is presented in Table 5. At the cut off value of 253µg/gm faecal calprotectin has 95% accuracy, sensitivity, and specificity, Positive predictive value (PPV) and Negative Predictive Value (NPV) in differentiating active from inactive UC patients. In Receiver operating characteristic (ROC) curve The Area under curve (AUC) is 0.95 indicating 95% diagnostic accuracy in differentiating UC patient's from other patients with lower GI symptoms.

Table 1: Colonoscopic findings in the studied groups.

	GI (no=40)				**GII (no=20)** No (%)	
	Gia No (%)		**GIb** No (%)			
Degree of inflammation						
Normal	0	(0)	26	(65)	11	(55)
Mild	0	(0)	14	(35)	9	(45)
Moderate	24	(60)	0	(0)	0	(0)
Severe	16	(40)	0	(0)	0	(0)
Extent of inflammation						
No	0	(0)	26	(65)	11	(55)
Proctitis	2	(5)	12	(30)	7	(35)
Left sided colitis	30	(75)	2	(5)	2	(10)
Pancolitis	8	(20)	0	(0)	0	(0)
Piles	0	(0)	0	(0)	7	(35)

Table 2: Ulcerative Colitis Activity Index (UCAI) in GIa and GIb patients

UCAI	**GI (no=40)**			
	No	**Gia** (%)	No	**GIb** (%)
0-2 (remission)	0	(0)	36	(90)
3-5 (mild)	4	(10)	4	(10)*
6-10 (moderate)	30	(75)	0	(0)
11-12 (severe)	6	(15)	0	(0)

* These two patients have mild disease activity in GIb were having severe disease before treatment and remission.

Table 3: Histopathological findings in the studied groups.

	GI (N=40)			**GII (N=20) No (%)**
	Gia No (%)		**GIb No (%)**	
Normal	0	(0)	0(0)	11 (55)
UC grade of inflammation				
Grade 0	0	(0)	4(10)	0 (0)
Grade 1	0	(0)	32 (80)	0 (0)
Grade 2	0	(0)	4 (10)	0 (0)
Grade 3	4	(10)	0 (0)	0 (0)
Grade 4	22	(55)	0 (0)	0 (0)
Grade 5	14	(35)	0 (0)	0 (0)
Colitis other than UC	0	(0)	0 (0)	9 (45)

Table 4: Faecal Calprotectin in the studied groups.

	GI (N=40)		GII (N=20)	Paired t test P value G1a&G1b	t test P value G1a&G2	t test P value G1b&G2
	GIa	GIb				
Fecal Calprotectin µg/gm						
Mean	541.15	122.6	58.4	8.451	8.959	2.338
±SD	±222.46	±55.6	±11.3	P<0.001	P<0.001	P=0.025
Range	220-870	70-250	39-80			

(Normal fecal calprotectin level ≤ 50 µg/gm stool)

Table 5: Diagnostic validity of faecal calprotectin in differentiating UC patients from other patients with lower GI symptoms.

	Cut off Value	PPV	NPV	Specificity	Sensitivity	Accuracy
Fecal Calprotectin µg/gm	131	100%	100%	100%	100%	100%

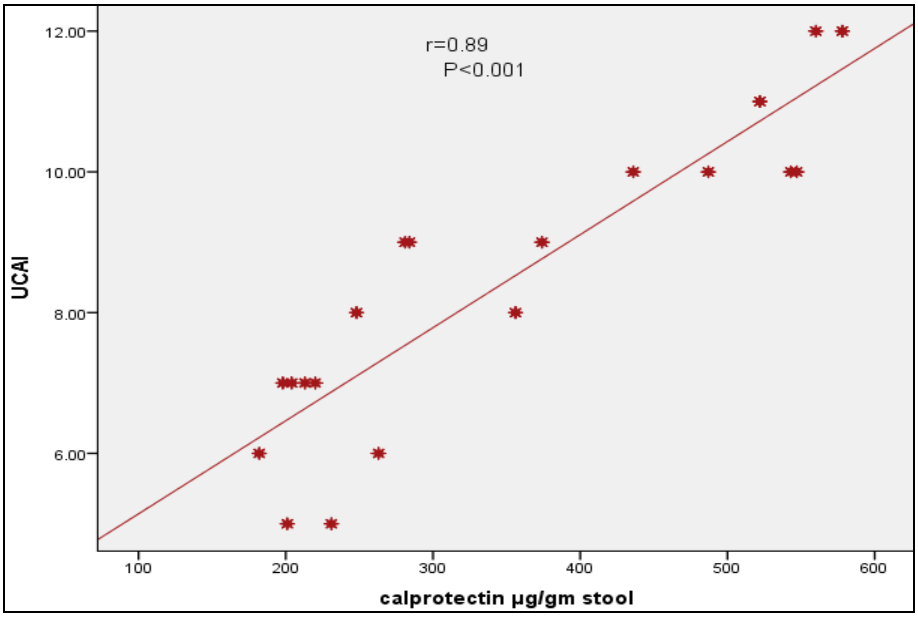

Fig 1: correlation between fecal calprotectin and UCAI (r= 0.89 and p<0.001).

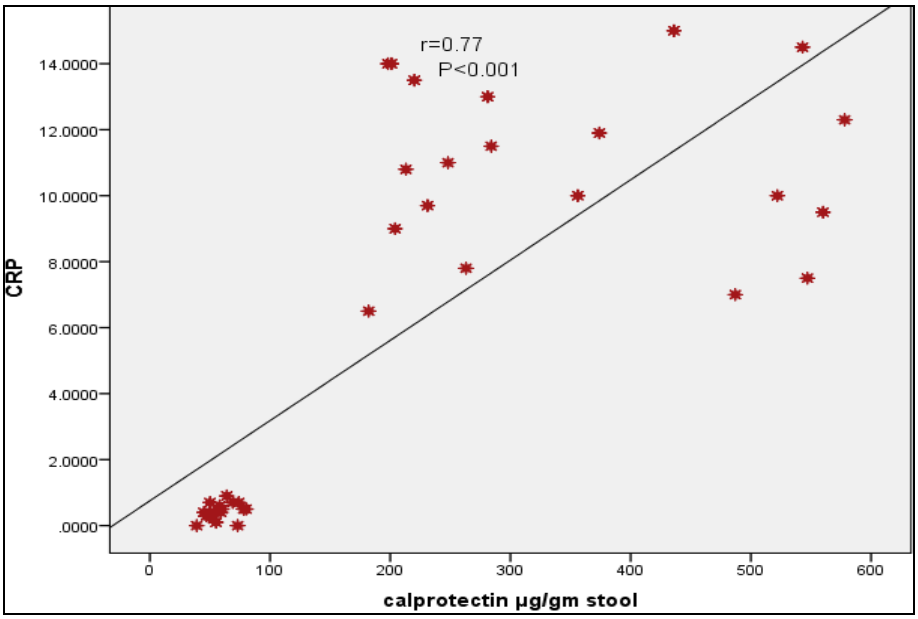

Fig 2: correlation between fecal calprotectin and CRP (r= 0.77 and p<0.001).

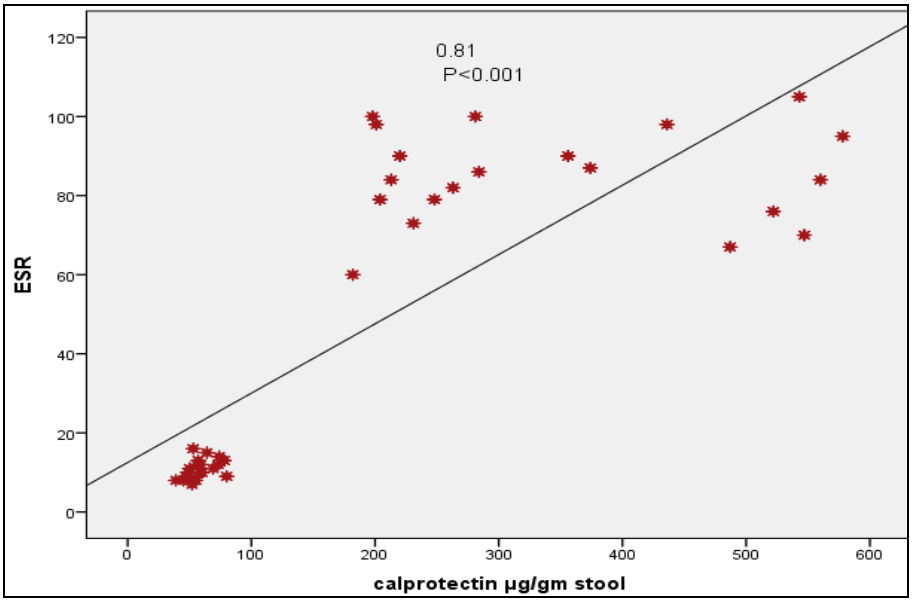

Fig 3: correlation between fecal calprotectin and ESR (r= 0.81 and p<0.001).

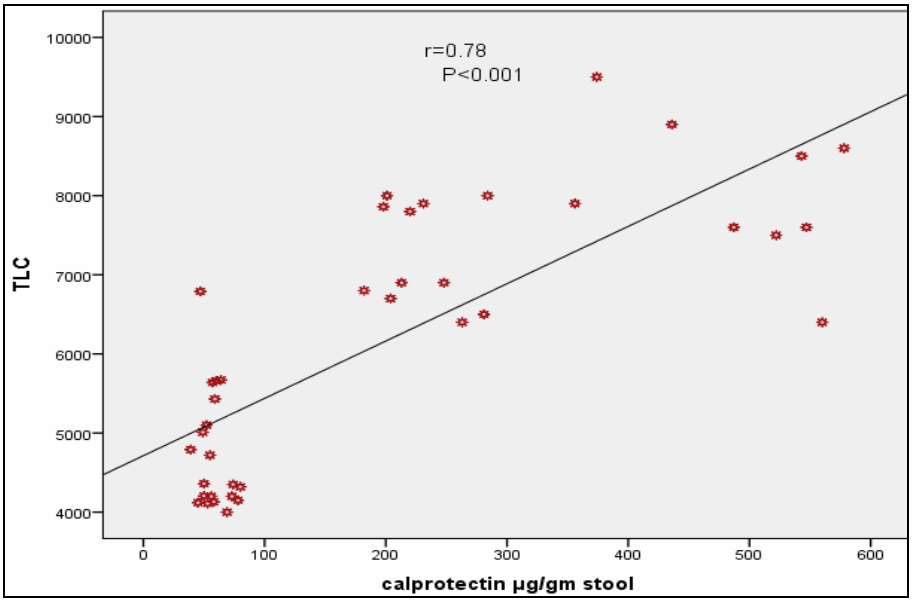

Fig 4: correlation between fecal calprotectin and TL (r= 0.78 and p<0.001)

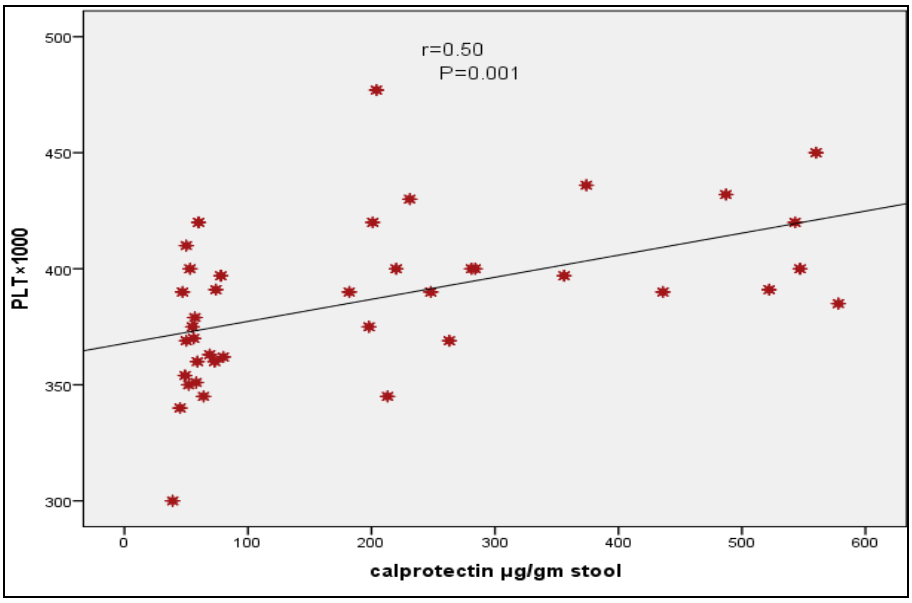

Fig 5: correlation between fecal calprotectin and PLT count (r= 0.50 and p=0.001)

Discussion

Conclusive diagnosis of IBD requires a complex combination of clinical, endoscopic and histological data [9]. The need for a diagnostic tool that would improve the conventional methods in IBD diagnosis directed the search towards other markers [10]. Neutrophil-derived markers, such as fecal calprotectin, have proven to correlate well with mucosal inflammation of UC. Fecal level of these markers reflects the mucosal influx of inflammatory cells in the gut. When the level of these markers is low, the presence of active inflammation in the colon is unlikely [11].

In the present study there was highly significant increase in the mean value of TLC and PLT count in GIa (active UC) in comparison to other groups. Several studies reported the same results as in the study done by Öztürk *et al.*, (2013) [12], they reported that, there was a statistically significant increase in platelet count in patients with active UC and CD than the other groups and conclude that platelet indices can be added to other inflammatory markers especially to monitor disease from active phase to remission phase. Also a study by Kayahan *et al*. (2007) [13], who found that the mean platelet count was increased in patients with active compared to inactive UC or healthy donors. The increase in TLC and PLT count could be explained by the fact that these parameters are increased in inflammatory conditions as acute phase reactants and play an important role in inflammation. Besides their functions in the haemostatic process and in thrombus formation after an endothelial injury, blood platelets also take part in the processes of inflammation and tissue repair that follows. For this purpose, they closely collaborate with all types of leukocytes. Activated platelets secret chemotactic substances, they facilitate the binding of leukocytes to the endothelium and their subsequent extravasation, and they may influence the inflammatory responses of leukocytes in both stimulating and inhibiting ways. **(**Klinger, 1997) [14].

In the current study, it was found that there is highly significant increase in the mean value of ESR and CRP in GIa (active UC) in comparison to other groups. Elevated ESR and CRP values in patients with active IBD were reported by several studies (Xiang *et al*., 2008) [15] and (Tibble *et al*., 2000) [16]. As the concentrations of many serum proteins vary in patients with IBD and as some have long half-lives, the ESR is not rapidly responsive to change In clinical status (the ESR may take several days to decrease even when rapid clinical improvement occurs). Hence, the ESR is a crude assessment of disease activity. In ulcerative colitis (UC), where clinical, endoscopic and histological activity is used to assess the overall disease, the correlation between ESR and disease activity is good. However, it may be normal in proctitis and proctosigmoiditis (Desai *et al.*, 2007) [17]. In our study, there was highly significant increase in the mean value of fecal calprotectin (FC) in active UC (GIa) patients in comparison to the inactive UC (GIb) patients and controls (GII). Also highly significant increase in the mean value of FC was present in the inactive UC (GIa) patients in comparison to the controls (GII). At the cut off value of 131µg/gm faecal calprotectin has 100% accuracy, sensitivity, specificity, PPV and NPV in differentiating UC patients from other patients with lower GI symptoms. At the cut off value of 253µg/gm faecal calprotectin has 95% accuracy, sensitivity, specificity, PPV and NPV in differentiating active from inactive UC patients. Erbayrak *et al*., (2009) [18], found that fecal calprotectin strongly associated with colorectal inflammation indicating organic disease. Also Langhorst *et al.* (2008) [19], assessed faecal levels of calprotectin in 139 (54 IBS, 42 UC, 43 CD) patients undergoing diagnostic ileocolonoscopy. Calprotectin had a high sensitivity and specificity in identifying IBD (81.7% and 83.5, respectively), Manz *et al.*, (2012) [20], studied Value of fecal calprotectin in the evaluation of patients with abdominal discomfort. They concluded that, In patients with abdominal discomfort, fecal calprotectin is a useful non-invasive marker to identify clinically significant findings of the gastrointestinal tract. In another study Henderson *et al.*, (2012) [21], demonstrate that FC is a highly useful biomarker and performs better than all commonly used blood parameters during the initial investigation of suspected pediatric IBD. FC level between 200 and 300 µg/g (sens 89-93%, spec 74-83%) providing an optimum sensitivity 89-93% and specificity 74-83%.In a meta-analysis, Von Roon *et al.* (2007) [22], summarised data from 30 studies that included 5983 patients. Faecal calprotectin was higher in IBD patients than in non-IBD patients (by 219 µg/g), and showed excellent pooled sensitivity and specificity rates in distinguishing between these groups (95% and 91%, respectively). Most of these studies compared IBD patients with either IBS patients or healthy volunteers, i.e. the extremes of the clinical spectrum. This could overestimate the diagnostic accuracy of the test and impair its usefulness in clinical practice (Burri & Beglinger, 2012) [23], In another meta-analysis Van Rheenen *et al.* (2010) [24], compared the diagnostic accuracy of faecal calprotectin in the evaluation of patients with suspected IBD. Thirteen studies summarising data of 1041 patients (670 adults, 371 children) were included. Pooled sensitivity and specificity rates of calprotectin testing were 93% and 96%, respectively. The specificity in children and teenagers was significantly lower (76%). In adults, using faecal calprotectin as a diagnostic test in suspected IBD for deciding upon endoscopy would result in a 67% reduction in patients requiring endoscopy, but would also result in a delayed diagnosis for 6% of patients due to false negative test results.

In the current study, highly significant positive correlation between fecal calprotectin and UCAI, ESR, CRP, TLC and PLT count. This was in agreement with Schoepfer *et al.* (2013) [25], who evaluated the correlation between endoscopic activity and fecal calprotectin, CRP, platelets, TLC, and the clinical score (Lichtiger Index). They found that endoscopic disease activity correlated best with fecal calprotectin, followed by the Lichtiger Index, CRP, TLC, and PLT count. Fecal calprotectin was the only marker that could discriminate between different grades of endoscopic activity. Fecal calprotectin with a cut off of 57µg/g had a sensitivity of 91% and a specificity of 90% to detect endoscopically active disease.Similarly Kolho&Turner. (2013) [11], made a retrospective study included all children with UC who had calprotectin measured and clinical data recorded for the assessment of the PUCAI. They found good correlation between the PUCAI and fecal calprotectin. In the clinically severe disease (PUCAI > 65), calprotectin was exceedingly high (>1000 μg/g) in all cases and did not bring any additional information to clinical assessment. It is worthwhile noting that the PUCAI is much more responsive to a rapid change than calprotectin in severe disease; that is, the PUCAI shows a sharp decrease within only a few days of starting effective medication reflecting the well-known

notion that mucosal healing lags after clinical remission. On the other hand, some of those in clinical remission according to PUCAI still had elevated calprotectin levels, but in the majority the levels were only moderately elevated. Also Rodríguez-Moranta *et al.* (2013) [26], found that fecal calprotectin shows a better correlation with the degree of inflammation than clinical indicators and serological markers. In addition, it could also be useful to predict mucosal cure and the risk of recurrence. Similarly. Lobatón *et al.*, (2013) [27], evaluate the ability of FC to predict endoscopic activity according to the Mayo score in 123 patients with UC. They found that, fecal calprotectin was an accurate marker of endoscopic remission in UC. In general, faecal calprotectin values correlate better with endoscopic findings than with clinical activity. Accordingly, this sensitive marker may detect residual inflammatory activity in patients with presumably quiescent disease (Sipponen & Kolho, 2010) [28],

Lasson *et al.* (2013) [29],evaluated the prognostic role of fecal calprotectin three months after the initial therapy. They found that Levels of fecal calprotectin three months after the initial therapy in patients with new onset of UC predict the disease course over the following years, and they are of value in the clinical management of these patients. Also Smith and Gaya. (2012) [30], Studied the Utility of faecal calprotectin analysis in adult IBD and they found that faecal calprotectin correlates well with mucosal disease activity and this in turn makes it useful in assessing activity, monitoring response to treatment, predicting relapse. Burri and Beglinger, (2012) [23], stated that measurement of faecal calprotectin is highly useful for the diagnosis and disease monitoring of patients with IBD, and might additionally predict disease outcome. Future studies should evaluate the value of faecal calprotectin testing to guide treatment decisions and assess their effect on long-term outcome.

Conclusion and Recommendations

1- Our study concluded that faecal calprotectin is a valuable, simple, easily performed and cost effective non-invasive marker with high accuracy, sensitivity and specificity in evaluating patients with ulcerative colitis. It could be a reliable surrogate marker for the severity of UC

2- Serial measurement of fecal calprotectin could be recommended for patients with UC to assess disease severity, response to treatment, induction and maintenance of remission and recurrence of activity.

3- Further studies on large number of patients are needed to determine the role of fecal calprotectin in diagnosis of other organic colonic diseases in general and colonic malignancy in particular.

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