ORIGINAL ARTICLE

Comparison of Fecal Calprotectin with Different Endoscopic Scores in the Assessment of Ulcerative Colitis (UC) Activity and Its Utility in Differentiating IBS from IBD

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Abstract

Background: Ulcerative colitis (UC), a chronic inflammatory disease of gastrointestinal tract, can have initial presentation which is clinically difficult to differentiate from functional bowel disorders [irritable bowel syndrome (IBS) and irritable bowel disease (IBD)]. Conventional laboratory tests, such as erythrocyte sedimentation rate (ESR), C-reactive protein, and albumin express systemic patient responses instead of intestinal inflammation. In the last decade, fecal calprotectin, a calcium-binding protein, has been suggested as a sensitive marker of intestinal inflammation. However, only few studies have investigated its role in relation with the extent of the disease.

Aim: To evaluate the usefulness of fecal calprotectin as a biomarker for disease activity in UC, its correlation with disease extent and its utility in differentiating IBS from IBD.

Methods: A total of 75 patients (50 cases with colonoscopic evidence of inflammation and 25 cases with normal colonoscopic examination) were included in the study. Fecal calprotectin test was done on the day of colonoscopy. Severity of the disease was assessed by modified Mayo's endoscopy score (MMES).

Results: Age and baseline parameters were comparable in both the groups (UC and IBS). Patients in the ulcerative group had tachycardia (95 vs 74), high ESR (26 vs 20), high leukocytes count (9198 vs 8852), high fecal calprotectin (594 vs 29), low albumin (3.00 vs 3.80) and low hemoglobin (11 vs 13.40). Minimum and maximum MMES were 2 and 13.2. A significant correlation was observed between fecal calprotectin and MMES (p-value < 0.001).

Conclusion: Fecal calprotectin is a simple, noninvasive, cost-effective marker that is strongly associated with colorectal inflammation; moreover, it has better role in the differentiation of IBD (UC) from IBS.

Keywords: Disease activity, Fecal calprotectin, Irritable bowel disease, Irritable bowel syndrome.

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Introduction

Ulcerative colitis (UC) is a chronic inflammatory condition characterized by relapsing and remitting episodes of inflammation limited to the mucosal layer. It usually affects the rectum and to a variable extent the colon in a continuous fashion.[1] In clinical management, assessment of disease activity is vital.[2] Determination of disease activity takes into consideration a combination of clinical features, endoscopic findings, and levels of laboratory biomarkers.[3]

To date, the most reliable and ''gold standard'' method for the assessment of the intestinal mucosa is endoscopy. Endoscopic procedures, however, are unpleasant and sometimes painful, time-consuming, and expensive. In addition, bowel-cleansing procedures are necessary in order to ensure optimal visualization. Therefore, surrogate markers that reflect the severity of mucosal inflammation and that could partially replace endoscopies are being investigated.

Conventional laboratory tests, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), platelets, blood leukocyte count, and albumin, although useful in clinical practice, express systemic patient responses instead of intestinal inflammation.[4] Fecal tests of inflammation have significant promise. One of the most attractive methods is the measurement of inflammatory proteins secreted by neutrophils in the feces. Fecal calprotectin is such a protein that can be reliably measured in stool samples and it is a measure of local gut inflammation rather than systemic inflammation. Calprotectin is a small calcium-binding protein, a member of the S100 family of zinc-binding proteins which contributes ~60% of the protein content of the cytosol in neutrophils.[5] In the presence of active intestinal inflammation, polymor-phonuclear neutrophils migrate to the intestinal mucosa from the circulation. Any disturbance to the mucosal architecture due to the inflammatory process results in leakage of neutrophils, and hence, calprotectin, into the lumen and its subsequent excretion in feces.[6]

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Table 1: Baseline characteristics of study patients

Characteristics	*IBD patients (n = 50)*	*Control group (n = 25)*	*p-value*
Age (in years)	38.46 ± 12.12	34.92 ± 8.87	0.20
Gender (M:F)	32:18	17:8	0.09
Pulse rate (/min)	95.40 ± 16.73	74 ± 10.6	<0.001
Hemoglobin (in gm/dL)	11.00 ± 2.40	13.40 ± 1.50	<0.001
ESR (in mm/hr)	26.14 ± 14.75	19.36 ± 6.36	0.03
TLC (in cells/cumm)	9198 ± 1800.50	8852.35 ± 1381.30	<0.40
Platelets (in lakhs/cumm)	3.22 ± 1.10	3.58 ± 0.90	0.16
Fecal calprotectin (µg/gm)	594.32 ± 599.66	29.46 ± 16.34	<0.001
Albumin	3.00 ± 0.70	3.80 ± 0.40	<0.001

Materials and Methods

After obtaining proper ethical clearance as per the declaration of Helsinki with ethical clearance no: RML/123/20 from institution, data were collected between November 2016 and March 2018. Patients above the age of 18 years who were willing to give informed consent were included in the study.

Study population was divided into two groups:

Group A: Included patients of UC (both newly diagnosed and patients with flare of established disease). Ulcerative colitis was diagnosed based on a combination of clinical presentation, endoscopic findings, histology, and the exclusion of alternative diagnoses.[7–9]

Group B (control group): Included a second cohort of patients with irritable bowel syndrome (IBS-D) as defined by Rome III criteria.[10]

Patients with incomplete colonoscopy, colorectal cancer, Crohn's disease (CD), indeterminate colitis, urinary incontinence (due to the risk of contamination of fecal samples), infectious colitis, pregnancy, history of colorectal surgery (hemicolectomies, colectomies, and proctocolectomies) and patients who were regularly taking aspirin and/or other nonsteroidal anti-inflammatory drugs were excluded from study.

Assessment of Disease Activity/Severity

All patients had a colonoscopy performed at inclusion. Severity of the disease was assessed by modified Mayo"s endoscopy score (MMES).[11] The colon was divided into five segments (rectum, sigmoid colon, descending colon, transverse colon, and ascending colon, and for each segment, we assessed the MES. The maximal extent of mucosal involvement at the time of colonoscopy was reported. The sum of individual MESs of all segments was calculated to obtain the modified score (MS) on a 15-point scale. Then this MS is multiplied by the disease extent in decimeters to obtain the extended modified score (EMS). Then the EMS was divided by the number of segments with active inflammation to obtain the modified Mayo's endoscopy score (MMES).

Fecal Calprotectin

Fecal calprotectin was done by using ELISA assay kit which utilizes the two-site "sandwich" technique with two selected antibody that bind to different epitopes of human calprotectin. A sample of feces was collected at the beginning of the preparation for colonoscopy in sterile container. Then the stool sample was transferred into Epitope Diagnostics Fecal Sample Collection Tube (Cat. No. 30356) which is a specially designed tube with pre-filled sample extraction buffer. The samples were preferably processed on the day of collection (within 24 hours). Samples which could not be processed within 24 hours were stored below -20°C until the day of processing. The examiner was blinded to the clinical history and colonoscopic findings of the patients.

Blood Parameters

Blood sample was collected from all the patients and the control before colonoscopy for complete blood counts, ESR, liver function test, and CRP.

Statistical Analysis

Statistical analysis was performed using the SPSS software. Parametric numerical results are presented as the mean ± standard deviation (SD), while nonparametric data are presented as the median and interquartile range (IQR). A Mann–Whitney test was used to investigate the differences between nonparametric data. Correlation analyses were performed using Spearman's rank correlation test. All *p*-values are two-sided and $p < 0.05$ was considered to be statistically significant.

Results

A total of 75 patients (50 in UC group and 25 in IBS group) fulfilling inclusion and exclusion criteria were included in the study. The group of UC patients included 32 males and 18 females and the control group included 17 males and 8 females. Age and gender distribution were comparable in both the groups (Table 1). Patients in the ulcerative group as compared with IBS patients had tachycardia (95 ± 16 vs 74 ± 10), high ESR (26 ± 14 vs 20 ± 6), high leukocytes count (9198 ± 18,000 vs 8852 ± 1381), high fecal calprotectin (594 ± 593 vs 29 ± 16), low albumin (3.00 ± 0.70 vs 3.80 ± 0.40) and low hemoglobin (11 ± 2.40 vs 13.40 ± 1.50) as given in Table 1.

Colonoscopic Findings and MMES

Twenty-one (42%) cases have mucosal involvement limited to the rectum (E1), 25 (50%) up to splenic flexure (E2) and 4 (8%) had involvement beyond splenic flexure (E3). Two cases had pancolitis. Mayo grade III was seen in 6 (12%), 2 (20%), 1 (10%) of E1, E2, and E3 disease, respectively. Both the patients with pancolitis had Mayo grade II disease. The average of the MS was 3.26 ± 1.37. The average extent of the disease (in decimeter) was 4.52 ± 1.52. The extended Mayo's score (EMS) was then calculated by multiplying the extent with the MS. The average of the EMS was 15.80 ± 10.05, maximum

Table 2: Endoscopic characteristics of the study population

Characteristics	*Maximum*	*Minimum*	*Mean*	*Std. deviation*
Modified score	8	2	3.26	1.37
Extent	9	1	4.52	1.52
Extended Mayo's score	42	6	15.80	10.05
Modified Mayo's endoscopy score	13.3	2	6.69	3.03

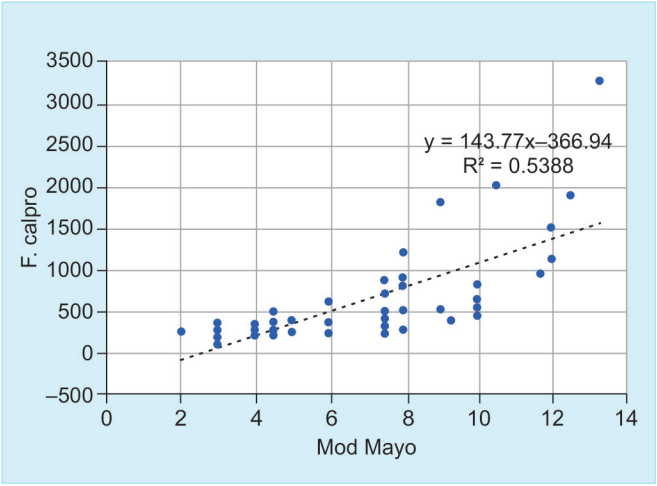

Fig. 1: Scatter plot showing correlation of fecal calprotectin with MMES

was 72 and minimum was 3. After calculation of the EMS, it was divided by the number of segments with active inflammation, that is, MES ≥1 to obtain the MMES. The average of the MMES was found to be 6.69 ± 3.03 (Table 2).

Fecal Calprotectin

In the study group of UC patients, the average of fecal calprotectin value was 594.32 ± 593.66 µg/gm minimum being 102 µg/gm and the maximum being 3343 µg/gm. In the control group, the average value of fecal calprotectin was 29.46 ± 6.0 µg/gm ranging between 11 and 85 µg/gm. The modified Mayo's endoscopic score (MMES) correlated significantly with fecal calprotectin $p < 0.001$ and with Pearson correlation coefficient of 0.734. In the control group of irritable bowel syndrome, the average value of fecal calprotectin was 29.46 ± 6.0 µg/gm ranging between 11 and 85 µg/gm. The UC patients had significantly high level of fecal calprotectin as compared with IBS patients (Figs 1 and 2).

Discussion

Irritable bowel disease and IBS are both chronic conditions affecting the gut; sometimes, distinguishing both the conditions is difficult clinically as both the conditions have somewhat similar symptoms. IBD is a chronic debilitating condition which requires lifelong treatment and monitoring whereas IBS is a functional disorder. Ulcerative colitis patients often report coinciding irritable bowel syndrome-like symptoms that might be misinterpreted as relapse or persisting disease activity.[12–14]

Colonoscopy is considered as the most accurate diagnostic modality and the standard method for estimating the inflammatory status of the intestinal mucosa.

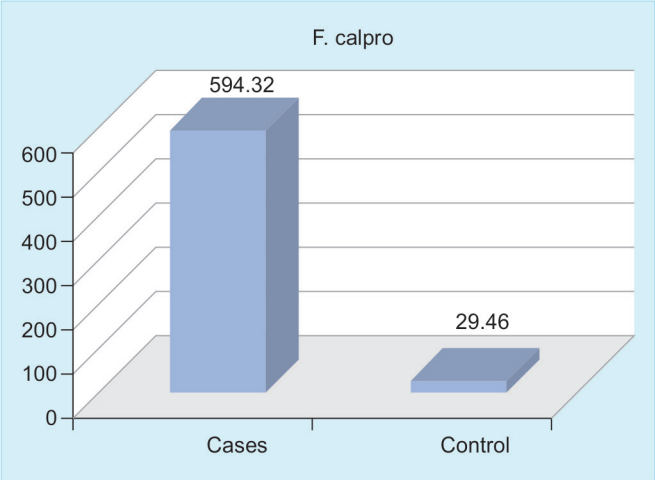

Fig. 2: Fecal calprotectin in ulcerative colitis vs irritable bowel syndrome

Fecal calprotectin is a promising marker of neutrophilic intestinal inflammation. In recent years, fecal calprotectin is being increasingly used as a noninvasive marker for the diagnosis and also treatment monitoring purposes.

In the present study, we studied whether fecal calprotectin is a useful marker in differentiating IBD and IBS and whether it can be a noninvasive marker of inflammatory activity in UC by correlating it with the endoscopic activity.

A novel thing in our study is the introduction of MMES for the assessment of endoscopic severity of UC.[11] There are very few studies and none from India (to the best of our knowledge) using MMES for assessing the endoscopy severity and correlating it with fecal calprotectin. In our study, we used this new score and we also studied its correlation with fecal calprotectin.

MMES correlates well with clinical, biological, and histological variables of disease activity. The main advantage of the MMES is the fact that it takes into account disease extent and makes it possible to assess partial mucosal healing, which may influence patient management. MMES score is calculated by assessingthe commonly used MES for five colonic segments and the total extent of mucosal inflammation.

In our study, UC patients had high average fecal calprotectin value of 594.32 ± 593.66 µg/gm compared with the average of 29.46 ± 6.0 µg/gm in patients with irritable bowel syndrome, which is consistent with the previous studies.[15–17]

There are very few indices which include disease extent as their variable, such as modified Mayo's endoscopic score by Lobatón et al.,[11] UCCIS (ulcerative colitis colonoscopic index of severity) by Lobatón et al.[11] and Pan-colonic modified Mayo score by Mari Arai et al.[18] Lobatón et al.[11] using a new endoscopic score called modified Mayo's Endoscopic score showed significant correlation with the fecal calprotectin.

Theodore Rokkas et al.[16] reported that fecal calprotectin did not correlate well with the UCAI ($p = 0.287$), whereas in our study, fecal calprotectin and MMSE correlated well with p-value < 0.001. Ahmed F Khalil et al.[19] reported that ESR did not correlate with the disease activity. However, our study showed that ESR correlated well with the fecal calprotectin and MMES. The present study also showed that CRP to be positive more among UC than compared with IBS

patients. The mean value of TLC was also found to be elevated in patients with UC compared with patients with IBS.

Conclusion

Fecal calprotectin is a simple, noninvasive, cost-effective marker that is strongly associated with colorectal inflammation; moreover, it has a better role in the differentiation of IBD from IBS.

Limitations

Since it is a cross-sectional study, lack of follow-up, which would have helped us to authenticate the serial changes in fecal calprotectin corresponding to clinical and endoscopic features of IBD.

Credits of All Authors

Kalpana Acharya was involved in the collection of data and doing all procedures. Vaishali Bhardwaj carried out in conceptualization. Imran Chauhan performed the statistical analysis. Sunil Je Bhatt has carried out manuscript writing. Syed Mushfiq Shafi was involved in data collection and re-writing.

Data Availability Statement

These data should be openly available to all and also as per the wishes of the journal policies.

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