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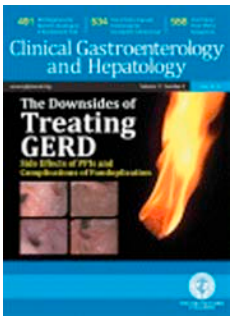

Fecal Level of Calprotectin Identifies Histologic Inflammation in Patients with Ulcerative Colitis In Clinical And Endoscopic Remission

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Title: FECAL LEVEL OF CALPROTECTIN IDENTIFIES HISTOLOGIC INFLAMMATION IN PATIENTS WITH ULCERATIVE COLITIS IN CLINICAL AND ENDOSCOPIC REMISSION

Short title: CALPROTECTIN AND HISTOLOGY IN ULCERATIVE COLITIS

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Abbreviations: UC, ulcerative colitis; FC, fecal calprotectin; IQR, interquartile range; TNF, tumor necrosis factor.

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ABSTRACT

Abstract :

BACKGROUND & AIMS: Histologic recovery of patients with ulcerative colitis (UC) is often incomplete, even among those in clinical and endoscopic remission. Persistent active microscopic inflammation is associated with an increased risk of relapse and colorectal neoplasia. A high level of fecal calprotectin (FC) is a reliable marker of endoscopic lesions in patients with UC. We evaluated the accuracy of FC in identifying patients with UC in clinical and endoscopic remission who still have histologic features of inflammation.

METHODS: We performed a prospective observational study of 59 patients with UC in clinical and endoscopic remission undergoing colonoscopy. Several biopsy specimens were collected from each colonic segment. Endoscopic remission was defined as a Mayo endoscopic subscore grades of 0 or 1. Active histologic inflammation was defined by the presence of neutrophils infiltrating crypt epithelial cells. FC was determined by ELISA analysis.

RESULTS: Eighteen patients (30.5%) showed evidence of active histologic inflammation. Patients with active histologic inflammation had a significantly higher median level of FC (278 μg/g; interquartile range, 136–696 μg/g) than those without active histologic inflammation (68 μg/g; interquartile range, 30–172 μg/g) (P=.002). In multivariate analysis, FC and Mayo endoscopic subscore (0 or 1) were each

independent predictors of histologic inflammation. Level of FC identified active histologic inflammation in patients in clinical and endoscopic remission with an area under the receiver operator characteristic curve value of 0.754.

CONCLUSIONS: Histologic inflammation is common among patients with UC in clinical and endoscopic remission. Patients with histologic features of inflammation can be reliably identified based on fecal level of calprotectin.

KEY WORDS: Mucosal healing; Deep remission; Histologic remission; IBD

INTRODUCTION

The management of inflammatory bowel disease is increasingly based on the objective assessment of mucosal integrity and tissue inflammation.[1] It has been demonstrated that macroscopic improvement of the mucosa indicates a better outcome of the disease, both in ulcerative colitis (UC) and in Crohn's disease, thus highlighting the role of endoscopy in monitoring disease activity in inflammatory bowel disease .[2, 3, 6]

However, histological recovery is often incomplete, even in UC patients achieving clinical and endoscopic remission.[6, 7, 8] There is growing evidence that persistent active microscopic inflammation is associated with an increased risk of relapse when compared to patients with a normal histology.[9, 10, 11] Furthermore, the severity of colonic inflammation is an important determinant of the risk of colorectal neoplasia.[12, 13] Therefore, histological remission may be a valuable goal of therapy.

Direct evaluation of the mucosa requires the performance of an endoscopy and biopsies, which are invasive, time consuming, expensive, and inconvenient to the patients. Surrogate markers of microscopic inflammation would be of great value to the clinician for monitoring underlying ongoing histologic inflammation in patients in clinical remission and for measuring the effects of treatment.

Fecal calprotectin (FC) represents 60% of cytosolic proteins in granulocytes. The presence of FC in feces is proportional to neutrophil migration to the gastrointestinal tract and to the degree of inflammation. Several studies indicate that FC is a reliable surrogate marker of endoscopic activity in both UC and Crohn's disease, but it is

unknown whether FC is able to predict the presence of microscopic inflammation in patients in endoscopic remission.[14, 15, 16, 17, 18]

The aim of our study is to evaluate the accuracy of FC (and to determine the optimal cutoff levels) for the prediction of underlying ongoing histologic inflammation in UC patients in clinical and endoscopic remission.

MATERIALS AND METHODS

Participants

All adult patients with previously diagnosed UC, referred for a clinically indicated colonoscopy in the Department of Gastroenterology of Bellvitge University Hospital (Hospitalet de Llobregat, Barcelona) between January 2011 and January 2012 were prospectively and consecutively screened for inclusion in the study. Indications for colonoscopy were colorectal cancer surveillance or mucosal healing monitoring. Those patients found to be in clinical and endoscopic remission were included in the study. All patients had an appropriated diagnosis for UC based on accepted endoscopic, radiologic, and histologic criteria within a minimum of 6 months previous to the study and were between 18 and 85 years of age. Clinical activity was assessed according to the clinical criteria of the Mayo score. Clinical remission was based on patient-rated Mayo subscores of stool frequency (0 points, normal number for the patient; 1 point, 1–2 stools more than normal; 2 points, 3–4 stools more than normal; and 3 points, ≥5 stools more than normal) and rectal bleeding (0 points, no blood seen; 1 point, streaks of blood with stool less than half the time; 2 points, obvious blood with stool most of the time; and 3 points, blood alone passes). Clinical remission was defined as a Mayo stool frequency subscore of 0 or 1 and a Mayo rectal bleeding subscore of 0.[4] Endoscopic activity was assessed according to the Mayo endoscopic subscore. “Endoscopic remission” was defined as a Mayo endoscopic subscore grade 0 or 1. Exclusion criteria included pregnancy, nonsteroidal anti-inflammatory drug intake, concomitant gastrointestinal infection, surgery within the past 3 months,

colorectal cancer, predominant perianal symptoms, and CD or indeterminate colitis diagnosis.

Study Design

This was a prospective observational study performed at a single tertiary referral center. Patients were visited in our IBD unit previous to their colonoscopy to invite them to participate in the study, provide them with the recipient for FC collection, perform a clinical interview, and carry out blood tests. Blood tests included leukocyte and platelet count, erythrocyte sedimentation rate, and CRP. The patients gave in previously collected fecal samples for FC on the day of the colonoscopy at the Endoscopy Department, where the samples were then stored at – 20ºC until analysis. All colonoscopies were performed blind by two experienced gastroenterologists. In surveillance colonoscopies the recommended 4-quadrant biopsies every 10 cm were taken. In colonoscopies for monitoring mucosal healing at least 2 biopsies from each colonic segment reached (rectum, left colon, transverse colon and ascending colon) were taken.

Histological evaluation

Biopsies were fixed in 10 % neutral formalin, processed, and sections were stained with hematoxylin and eosin. Microscopic examination was performed by a single gastrointestinal pathologist blinded to the endoscopic findings. The histological grade of inflammation was determined by using a simple grading system based on epithelial neutrophils: Active acute inflammation was defined by the presence of neutrophils infiltrating crypt epithelial cells (resulting or not in “crypt abscesses”); Chronic inflammation was defined by the presence of architectural changes (irregular

surface and crypt abnormalities) and an increase in lamina propria mononuclear cells; Quiescent disease meant the presence of architectural changes without alterations in the intensity and composition of the lamina propria cellular infiltrate. We dichotomized the histologic evaluation into "active histologic inflammation" or "histologic remission" according to the presence or absence of active acute inflammation. The histologic grade used for each biopsy set represented the most severely inflamed area of the available biopsies for that particular patient.

Fecal Calprotectin Determination

Stool sample collection was performed within 1 to 3 days before colonoscopy and colonic cleaning. All samples were stored at – 20ºC, thawed, and analyzed by an ELISA test (Calprotectin Bühlmann ELISA; Bühlmann, Schonenbuch, Switzerland). The range of the ELISA test is 10 to 1800 µg/g. The sample amount needed is 50 to 150 µL. Sensitivity of the test is <10 µg/g.

Statistical Analysis

The statistical analysis was carried out using the SPSS version 19.0 statistical package (SPSS, Inc., Chicago, IL). The Mann–Whitney U test and analysis of variance were used to compare continuous variables. Chi-square test and the Fisher's exact test, where deemed appropriate, were applied for dichotomous variables. Multivariate analysis consisted of multiple logistic regression. Accuracy analysis included receiver operator characteristic curve analyses with 95% confidence intervals and test characteristics such as sensitivity, specificity, positive and negative predictive values. Statistical significance was accepted for *P*-values <0.05. Power and sample size calculations were performed using the EpiTools epidemiological calculators (available

at: http://epitools.ausvet.com.au/content.php?page=home). Based on previous studies[8, 15], we projected that the ratio of patients with histologic remission and with active histologic inflammation would be 2:1. We estimated the sample size for the study assuming that mean FC levels (± standard deviation) would be 50±150 μg/g for histologic remission and 250±400 μg/g for active histologic inflammation. With these assumptions, a sample of 40 patients in histologic remission and a sample of 20 patients with active histologic inflammation would be needed for the study to detect a statistically significant difference between the two sample FC means at a significance level of 0.05 and with 80% power.

Ethical Considerations

This study was approved by the ethics committee of Bellvitge University Hospital and all patients gave their informed written consent for participation.

RESULTS

During the study period, 85 patients with UC in clinical remission were referred for colonoscopy and were potentially eligible for the study. Twenty six were excluded because of endoscopic activity (Mayo endoscopic subscore grade > 1). Among the 59 patients finally enrolled in the study, 37 patients were referred for surveillance colonoscopy and 22 patients for monitoring mucosal healing. The epidemiological, clinical, biological, and endoscopic characteristics of the patients are summarized in Table 1.

Of the 59 patients in endoscopic remission, 18 patients (30.5%) showed evidence of active histologic inflammation in at least one colonic segment. Among these 18 patients, 5 patients (28%) showed active microscopic inflammation exclusively in segments proximal to the rectum; 2 of them were undergoing topical treatment with mesalazine.

Table 2 shows median levels of FC and serum markers, as well as the Mayo endoscopic subscore corresponding to the presence of active histologic inflammation. Higher levels of FC were associated with active histologic inflammation (P=0.002). Median levels of FC according to the histologic findings are shown in figure 1. The Mayo endoscopic subscore (grade 0 or 1) also had a significant relationship with histological activity. Active histologic inflammation was present in only 2 of the 28 (7%) patients with a Mayo endoscopic subscore of grade 0, and in 16 of the 31 (52%) patients with a Mayo endoscopic subscore of grade 1 (P<0.001). None of the serum markers were significantly different between the 2 groups, but white blood cell count tended to be higher in patients with microscopic inflammation (P=0.083).

In the multivariate analysis, FC and endoscopic assessment were both independent predictors of active histologic inflammation (Table 3).

The performance of FC as a test for active histologic inflammation in patients in clinical and endoscopical remission was fair; the area under the receiver-operator characteristic curve was 0.754 (figure 2). A FC cut-off value of 155 µg/g had a sensitivity of 78%, a specificity of 71%, a negative predictive value of 89%, and a positive predictive value of 54%.

DISCUSSION

In UC, mucosal healing based on endoscopic assessment is associated with decreasing relapse rates, hospitalization rates and the need for surgery and is now becoming an endpoint of therapy.[4] Histologic remission often lags behind endoscopic improvement. Accumulating evidence suggests that the persistence of inflammatory infiltrate despite clinical and endoscopic remission may be responsible for eventual relapses and is an important determinant of the risk of colorectal neoplasia.[9, 10, 11, 12, 13] Previous studies have shown that FC is an accurate marker of endoscopic lesions in UC.[15, 18] The present study shows that FC can also predict histologic inflammation in UC patients in clinical an endoscopic remission. In our series, a value of FC < 155 µg/g is a reliable indicator of the absence of acute inflammatory infiltrate (NPV 89%). Interestingly, a similar FC cut-off value (150 µg/g) has been found to predict relapse in UC patients in clinical remission in some studies.[19, 20] It is likely that the prognostic value of FC levels lies in its ability to predict endoscopic and histologic activities.

We found that acute active inflammation was very unusual (7%) at a Mayo endoscopic subscore of grade 0. In contrast, active acute inflammation was present in about half of the Mayo grade 1 colonoscopies. These findings are in line with previous studies.[8, 21, 22] Rosenberg et al., studying the correlation between histology and endoscopy in UC, found underlying histologic evidence of inflammation in only 6 % of the colonic segments classified by endoscopy as Mayo grade 0.[8] Similarly, Lemmens et al found that a Mayo endoscopic subscore of 0 corresponded accurately to histologically normal biopsies or inactive chronic colitis.[22] However, a high level of discordance was observed with a Mayo endoscopic subscore of grade 1, with half of

the patients presenting active histologic inflammation .[22] The endoscopic definition of mucosal healing is not standardized but a Mayo endoscopic subscore of 0 or 1 is commonly accepted.[23] Our study demonstrated that FC is an independent predictor of histologic inflammation in patients with endoscopic mucosal healing. In particular, FC is able to identify patients without active inflammation that may indeed have achieved mucosal healing among those with a Mayo endoscopic subscore grade 1. Thus, FC concentrations correlate more closely to histological findings than the Mayo score.

Among the patients in our series with active histologic inflammation, one third (5/18) had rectal sparing and would have been overlooked without proximal biopsies. All of them had FC over 155 µg/g and they would therefore have been correctly classified by using a FC. It is well known that UC can become discontinuous under medical treatment.[24] Consequently, colonoscopies with multiple biopsies would be needed for an adequate microscopic evaluation. Determination of FC could results in a less costly approach than performing colonoscopies with multiple biopsies to assess histologic inflammation.

In this study we evaluated histological activity in a simple dichotomous manner on the basis of neutrofhil infiltration of the colonic epithelium with or without crypt destruction. Accordingly, our definition of active histological activity corresponds to grade ≥2 in the Modified Riley Histopathological Activity Score and to grade ≥3.1 in the Geboes score which are generally accepted as indicative of active disease (22, 25). We therefore did not take into consideration changes that are indicative of disease chronicity but not necessarily activity. Disease activity defined by the unequivocal damage of the epithelium with neutrophils can be assessed reproducibly and with high

interobserver agreement.[9, 25] Furthermore, the presence of epithelial neutrophils is a strong predictor of disease relapse.[9, 11] With this definition of histologic activity, samples showing neutrophils infiltrating the lamina propria but preserving the epithelium would have been classified as being in histologic remission. However, this is an unusual finding and when neutrophils are present they usually involve the epithelium.[22] In their study of 263 biopsy sets from patients with active and inactive disease, Lemmens et al found neutrophils infiltration of the lamina propria without affecting the epithelium in only 3% of samples.[22] In our series, all patients with active histologic inflammation showed diffuse architectural changes and increased lamina propria infiltrate in addition to neutrophils in the epithelium.

Our study has several limitations. Firstly, the small sample size. A larger sample would have allowed a more precise estimation of the cut-off value for the prediction of histologic activity. Secondly, the system employed to evaluate histologic activity is not standard. Indeed, no such standard system exists, though systems such as the Geboes or Riley scores are becoming more popular among pathologists.[9, 25] The simplicity, reproducibility and easy correlation with crucial cut-off values of these more common scores are advantageous. Thirdly, the presence of basal plasmocytosis, a finding that has been found to predict relapse, has not been evaluated.[10, 11] However, basal plasmocytosis is closely associated with the presence of epithelial neutrophils.[11] Fourthly, our results need to be validated. Finally and most importantly, given the cross-sectional nature of the study, the potential prognostic value of FC determination in patients in clinical and endoscopic remission cannot be ascertained.

In summary, our study shows that histologic inflammation is common among UC patients in clinical and endoscopic remission and can be reliably predicted by means of an FC determination. Prospective studies are needed to determine the prognostic importance of FC in such populations.

FIGURE LEGENDS

FIGURE 1: Median fecal calprotectin (FC) levels according to the histologic findings. FC concentrations in different histologic grades are illustrated by box plots. The box represents the lower and upper quartiles, and the horizontal line in the middle of the box is the median. The 95% confidence interval is represented by whiskers, and individual outliers are represented by values outside the whiskers. Median FC levels were 69.7 µg/g (IQR, 30-213) for histologically quiescent disease; 47.9 µg/g (IQR, 30-171) for chronic histologic inflammation and 278 µg/g (IQR, 136-696) for acute histologic inflammation.

FIGURE 2: Receiver operating characteristics curve for fecal calprotectin in identifying patients with active acute histologic inflammation; AUC (95% CI): 0.754 (0.607–0.902). The best cutoff was 155 µg/g, with a sensitivity of 78% and a specificity of 71%.

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Table 1. Patient Characteristics (n = 59)

	Number
Men, n (%)	38 (64)
Age, yr (IQR)	53 (44-62)
Disease duration, yr (IQR)	13 (10.2-20.5)
UC extent, n (%)	
Proctitis	8 (14)
Lef-sided colitis	27 (46)
Extensive colitis	24 (40)
Mayo Endoscopic Subscore, n (%)	
Mayo 0	28 (47)
Mayo 1	31 (53)
Histologic Activity Assessment, n (%)	
Active acute inflammation	18 (31)
Chronic inflammation	30 (51)
Quiescent disease	11 (18)
C reactive protein, mg/L (IQR)	1.7 (1-4)
Hematocrit, % (IQR)	43.2 (40.4-45.3)
Leucocytes, thousands/µL (IQR)	6.1 (5.3-8)
Medication at endoscopy, n (%)	
Mesalamine	47 (80)
Corticosteroids	4 (7)
Immunomodulators	11 (19)
TNF inhibitor	2 (3)
Fecal Calprotectin, µg/g (IQR)	98.9 (30-305.8)

NOTE. Median and interquartile range (IQR) given for continuous variables.
UC, ulcerative colitis; TNF, tumor necrosis factor. C reactive protein reference range, 0 to 5 mg/L. Hematocrit reference range, 33 to 43% for women, 37 to 50% for men. Leucocytes count reference range, 3.9 to 10 thousands/µL.

Table 2. Factors associated with Active Histologic Inflammation.

	Histologic Remission	Active Histologic Inflammation	*P* value
Number of patients	41	18	-
Fecal Calprotectin, µg/g (IQR)	68 (30-172)	278 (136-696)	0.002
C reactive protein, mg/dL (IQR)	1.7 (1-3.6)	1.6 (1-3.6)	0.764
White blood cells, thousands/µL (IQR)	5.9 (5.3-6.9)	7.5 (5.2-8.9)	0.083
Platelets, thousands/µL (IQR)	244 (211-305)	243 (188-304)	0.663
Haematocrit, % (IQR)	43 (40.3-45.7)	43.5 (41-44.7)	0.610
Mayo endoscopic subscore grade 0/1, n	26/15	2/16	<0.001

NOTE. Median and interquartile range (IQR) given for continuous variables.

Table 3. Multivariated Analysis (Logistic Regression) for the Prediction of Active Histologic inflammation.

Variable	Coefficient (β)	Standard Error	Odds ratio (95% confidence interval)	*P* value
Fecal Calprotectin > 155 µg/g	2.61	0.89	13.65 (2.36-79.08)	0.004
Mayo endoscopic subscore grade 1	3.07	1.02	21.61 (2.94-158.7)	0.003
White blood cells, thousands/µL	0.47	025	1.59 (0.98-2.58)	0.057