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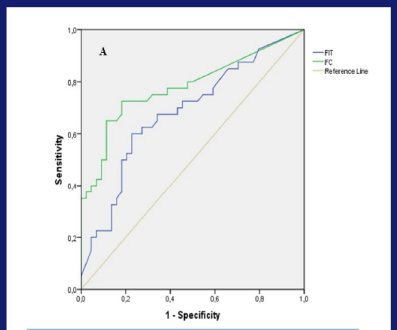
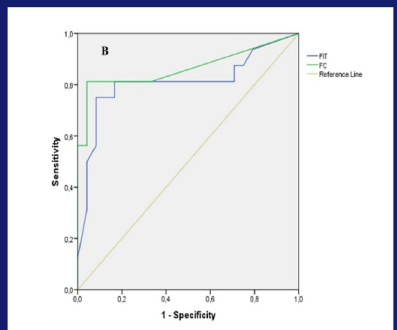
FECAL IMMUNOCHEMICAL TEST FOR HAEMOGLOBIN VERSUS FECAL CALPROTECTIN TO MONITORING ENDOSCOPIC ACTIVITY IN INFLAMMATORY BOWEL DISEASE

In IBD, fecal tests show a significant correlation when it comes to discriminating the presence of endoscopic activity



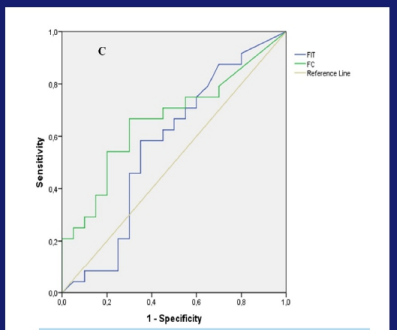
AUC FIT: 0.68; AUC FC: 0.78; p = 0.08

In the case of UC, FIT is a clear alternative to monitoring endoscopic inflammatory activity



AUC FIT: 0.81; AUC FC: 0.86; p = 0.4

In CD, more studies are needed to determine the role of fecal biomarkers



AUC FIT: 0.56; AUC FC: 0.66; p = 0.36

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Fecal immunochemical test for hemoglobin versus fecal calprotectin to monitor endoscopic activity in inflammatory bowel disease

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Conflict of interest: the authors declare no conflict of interest.

ABSTRACT

Aim: endoscopy identifies inflammatory activity, however, it is an unpleasant test and is not always accessible. The aim of the study was to compare the usefulness of quantitative fecal immunochemical test (FIT) *versus* fecal calprotectin (FC) to determine endoscopic activity in patients with inflammatory bowel disease (IBD).

Methods: cross-sectional prospective observational study. The stool samples were collected within three days before starting the preparation for the colonoscopy. We used the Mayo index for ulcerative colitis (UC) and the simplified endoscopic index for Crohn's disease (CD). Mucosal healing (MH) was defined as the score 0 points in each of the endoscopic indices.

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Results: eighty-four patients were included, 40 (47.6 %) with UC. In patients with IBD, FIT and FC showed a significant correlation with the presence of inflammatory activity/MH on endoscopy, with no statistically significant differences between the two receiver-operating characteristic (ROC) curves. Both tests improved their diagnostic performance when assessing patients with UC; the Spearman correlations between FIT and FC and endoscopic inflammatory activity were r = 0.6 (p = 0.0001) and r = 0.7 (p = 0.0001), respectively. In Crohn's disease, the diagnostic utility of both tests was lower.

Conclusions: FIT is an alternative to monitor endoscopic activity among ulcerative colitis patients. In Crohn's disease, more studies are needed to determine the role of fecal biomarkers.

Keywords: Fecal immunochemical test. Haemoglobin. Fecal calprotectin. Inflammatory bowel disease.

INTRODUCTION

Repeated monitoring of objective inflammatory activity followed by treatment adjustment is a current strategy in patients with inflammatory bowel disease (IBD) (1). Endoscopy monitoring, although it has shown important clinical benefits, is not practical. Therefore, there is an incessant search for non-invasive markers that can reflect inflammatory activity and could be used frequently (2). Fecal calprotectin (FC) is a sensitive marker of endoscopic activity in IBD (3) and has been correlated with the risk of relapse (4). However, there are problems related to variation in cut-off values of FC (5), no standardized measurement methods and its high cost (6).

Quantitative fecal immunochemical test (FIT) for hemoglobin has attracted interest as a non-invasive marker in IBD (7). FIT measures fecal hemoglobin concentrations using an antibody specific for human hemoglobin (8). The OC-sensor is the most popular FIT system; sample collection and analysis results are internationally standardized (8). The universal nature of the FIT is a great advantage; in addition, its stability, clearly established cut-off points, ease of handling and, fundamentally, the cost, make this technique a very attractive biomarker in IBD (5). The application of

FIT in IBD has shown its usefulness in detecting mucosal healing (MH) (9,10) and patients with ulcerative colitis (UC) showed high values one or two months before presenting clinical relapse (11). However, as shown in a recent meta-analysis, most of the studies are conducted in an Asian population (only one study is from Canada) and information on the usefulness of FIT in Crohn's disease (CD) is scarce (12,13).

For this reason, this study aimed to compare the usefulness of FIT *versus* FC to determine endoscopic activity in patients with IBD.

METHOD

Patient selection criteria

This was a cross-sectional prospective observational study. Between January 2019 and December 2019, all patients with a suspected or confirmed diagnosis of IBD, in whom a lower gastrointestinal endoscopy was requested, were consecutively included.

Exclusion criteria: patients under 18 years old, patients who decided not to participate, pregnancy, patients with incomplete colonoscopy, and hospitalized patients.

Endoscopic assessment

All the examinations were performed by two endoscopy specialists (LP and L-SA) who were unaware of the results of the others examinations. To determine endoscopic activity, Mayo index (14) for patients with UC and the simplified endoscopic score for patients with CD (SES-CD) (15) were used. The presence of inflammatory activity was considered when a score ≥ 1 point and MH was defined as a score 0 points in each of the endoscopic indices.

Fecal tests analysis

The stool samples should be collected within three days before preparation for the colonoscopy and kept in the refrigerator at 4 °C until the day of processing. The samples should not contain visible blood, and no specific diet or medication restrictions were necessary.

The concentration of hemoglobin (Hb) in fecal samples was assessed using an OC-SENSOR® automatic quantitative analyzer (Biogen Diagnostica), being considered as positive if values were above 100 ng/ml. These units were converted to µg Hb/g feces using a multiplication coefficient of 0.2 (16). Thus, the cut-off point was 20 µg Hb/g feces.

For the correct collection of the stool sample for FC determination, patients were instructed to collect the first stool sample of the day, avoiding highly liquid or too solid stools, and keep samples frozen (17). FC was determined by immunoassay technique that is time-resolved fluorimetry using a lanthanide chelate (europium). The autoanalyzer used was the AQT90 (Radiometer, Copenhagen, Denmark) and the results (quantitative) are expressed in micrograms per gram of stool, considering the values < 50 µg/g as negative; 50-100 µg/g as indeterminate; and > 100 µg/g as positive.

Statistical analysis

Basic descriptive statistics were used, which included the median and range for continuous variables, and absolute frequency and percentages for discrete variables. Mann-Whitney U test (MWU) was used to compare the medians between groups. Using the receiver operating characteristic (ROC) curve, the FC and FIT values that had the best accuracy to reflect endoscopy activity were determined. Subsequently, the correlation between fecal tests and endoscopic activity was evaluated using the Spearman test. The ability of fecal tests to assess endoscopic activity was determined by calculating sensitivity, specificity, positive and negative predictive values (PPV and NPV), accuracy and odds ratio (OR); and the 95 % confidence interval (95 % CI). The IBM Statistical Package for the Social Sciences version 22.0; 2013 (IBM Corp., Armonk, NY, USA) was used, considering p-values < 0.05 as significant. To compare the ROC curves, the Epidat 3.1 program was used.

Ethical considerations

The approval of the Ethics Committee of Hospital Universitario Doctor Peset was obtained (protocol code TSOH-I/CF-2018). Patients were informed of the nature of

the study and gave their written consent prior to their inclusion.

RESULTS

Study population

The sample size calculation was 105 patients. During the inclusion period, 103 patients with confirmed or suspected IBD underwent colonoscopy; of these, 84 patients were included (Fig. 1). The main characteristics of the patients included in the study are shown in table 1. Colonoscopy was requested in 13 (15.5 %) patients due to clinical suspicion of IBD and only 15 (21.1 %) patients with known IBD reported symptoms attributable to the disease at the time of inclusion. The indications for colonoscopy in the 71 (84.5 %) patients with known IBD were: screening for colon cancer in 48 (67.6 %) patients; post-surgical recurrence study in 11 (15.5 %) patients and assessment of activity in 12 (16.9 %) patients.

Endoscopic findings

In the 84 patients, the colonoscopies were complete and no complications occurred in any patient. In 40 (47.6 %) patients, some degree of inflammatory activity was evidenced at endoscopy *versus* 44 (52.4 %) patients who showed MH.

Among the patients with UC, 24 (60.0 %) patients had MH (Mayo index = 0 points); among the remaining 16 (40.0 %) patients with UC who showed endoscopic activity, 12 (30.0 %) patients had a Mayo index of 1 point, three (7.5 %) patients of 2 points, and only one patient (2.5 %) had a Mayo index of 3 points. The mean of Mayo index was 0.54 (± 0.75 standard deviation).

Of the patients with CD, 20 (45.5 %) showed MH; among the remaining 24 (54.5 %) patients, the median of SES-CD was 2 points (range: 0-25 points). Isolated ileal involvement was present in 16 (36.4 %) patients, including 13 (81.3 %) with previous surgery; among the patients with isolated ileal involvement, ten (62.5 %) patients had endoscopic activity.

Fecal tests results

The median of FIT and FC was 4.5 µg Hb/g feces (range: 0-551) and 32 µg/g (range: 0-3014), respectively. The median of FIT among UC patients was no different from that of CD patients: 5.3 µg/g (range: 0-551) *versus* 4.1 µg/g (range: 0-200) (p = 0.76, MWU test), respectively. The median of FC did not present differences between both diseases: UC 18.5 µg/g (range: 0-1,613) *versus* CD 37.5 µg/g (range: 0-3,014) (p = 0.29, MWU test), respectively.

Correlations between fecal test and endoscopy findings

All patients

The FIT and FC values that showed the best sensitivity and specificity to detect the presence of inflammatory activity on endoscopy according to the ROC curve were 20 µg/g (sensitivity 50.2 %; specificity 80.0 %) and 50 µg/g (sensitivity 57.5 %; specificity 88.6 %), respectively. Both tests showed a significant correlation with the presence of inflammatory activity on endoscopy: Spearman's coefficient r = 0.3 (p = 0.04) for FIT and r = 0.5 (p = 0.0001) for FC. The areas under the curve (AUC) and the rest of the values that reflect the utility of both tests for the detection of presence of endoscopic activity are shown in figure 2 and table 2, respectively. The comparison between the AUC did not show statistically significant differences.

Ulcerative colitis

When assessing patients with UC, both tests improved their diagnostic performance. The correlation between FIT and FC to determine the presence of inflammatory activity on endoscopy was: Spearman's coefficient r = 0.6 (p = 0.0001) and r = 0.7 (p = 0.0001), respectively. Both tests also showed greater accuracy and a greater AUC (Table 2 and Fig. 2). The comparison between the AUC did not show statistically significant differences.

Crohn's disease

In these patients, the diagnostic utility of both tests was clearly lower. The correlation between FIT and the presence of endoscopic activity did not reach statistical significance: Spearman's coefficient r = 0.04 (p = 0.8). The correlation

between FC and endoscopic activity was Spearman's coefficient r = 0.31 (p = 0.04). For both tests, the accuracy and the AUC were clearly lower than in the UC (Table 2 and Fig. 2). The comparison between the AUC did not reveal statistically significant differences.

The worst results were obtained among patients with isolated ileal disease. In these patients, the correlation between endoscopic activity and fecal tests was: Spearman's coefficient r = -0.2 (p = 0.4) for FIT and r = 0.1 (p = 0.7) for FC; with ten and nine false negatives, respectively. Among patients with colonic or ileocolonic CD, correlations between FIT and FC with endoscopic activity were: Spearman's coefficient r = 0.2 (p = 0.4) and r = 0.4 (p = 0.05), respectively.

DISCUSSION

In this study, both fecal tests show a significant correlation (although in low to moderate prediction range) to discriminate the presence of endoscopic activity in patients with IBD, without showing significant differences between the diagnostic capacities of both tests according to the areas under the ROC curve.

In the case of UC, FIT is a clear alternative to monitoring endoscopic inflammatory activity. The AUC of both tests is elevated (0.81 for FIT and 0.86 for FC), with no statistically significant differences between them (p = 0.4). Our results among patients with UC are consistent with those published in the literature, whose information about FIT was collected in a systematic review and meta-analysis (12), which included six studies with 625 patients with UC, where the ranges of sensitivity, specificity, PPV and NPV to assess MH were: 58-94 %, 66-95 %, 93-79 %, and 52-93 %, respectively. In this study, FIT was more sensitive and had a slightly higher negative predictive value than FC (75 *versus* 68.8 and 84 % *versus* 82.1 %, respectively) to discriminate between endoscopic activity and MH. Mooiweer et al. also showed a negative predictive value of 84 % for FIT and highlight the importance of the test in monitoring MH among patients undergoing treatment due to this high value (13). In this study, the usefulness of the two fecal biomarkers, FIT and FC, was assessed in 164 patients with IBD. The correlation between both tests and endoscopic activity was excellent in patients with UC and in patients with CD;

however, this last group did not include patients with disease located exclusively in the small intestine.

Our results among CD patients are worse; the correlation between FIT and endoscopy does not reach statistical significance. These poor results are mainly evident among patients with disease located in the small intestine. These results are like those obtained in 71 patients with CD by Inokuchi et al., where FIT did not correlate with endoscopic activity in patients with small bowel involvement. In this paper, balloon-assisted enteroscopy was used to correctly evaluate endoscopic lesions in the small intestine. These authors attribute the poor results of the FIT to the fact that it is designed to detect bleeding in the colon, and propose the use of capsule endoscopy or imaging techniques as an alternative in this location of the CD (10). Our results support this hypothesis, given the low capacity of FIT to detect endoscopic activity among patients with disease located exclusively in the ileum with ten false negatives. Our results with FC to determine endoscopic activity in patients with CD reach statistical significance and are among the values published in the literature (18). However, when we analyze the subgroup of disease located exclusively in the ileum, the degree of correlation decreases and does not reach statistical significance. In this sense, several studies have shown lower FC performance when CD affects the small intestine (19,20).

In our center, as commented by other authors (10), the price of FC determination is up to six times more expensive than performing FIT. This means that we must bear in mind the use of this test in patients with UC who require exhaustive monitoring. Inokuchi et al. (10) propose that, based on its low cost and its high negative predictive value for MH, FIT could be used in active patients with positive FIT until its conversion to negative.

Several aspects may have influenced the results obtained. First, the small sample size, which makes it difficult to compare the different locations of the CD; second, the scant inflammatory activity found in the examinations (90 % of patients with UC have a Mayo index of 0-1 points; and the median of the SES-CD is 2 points), because the most frequent indication for endoscopy was the surveillance of dysplasia, which may have influenced the difficulty of establishing stronger correlations; and finally,

the strict criteria to establish MH with scores of 0 in both indices.

CONCLUSION

FIT is an alternative to monitor endoscopic activity among UC patients. In CD, more studies are needed to determine the role of fecal biomarkers and the monitoring of endoscopic inflammatory activity according to the location of the disease.

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Table 1. Demographic and clinical characteristics of the 84 patients included in the study

Variable	n (%)
Females sex	36 (42.9)
Age (years), median (range)	50.0 (18-18)
Disease	
Ulcerative colitis	40 (47.6)
Crohn's disease	44 (52.4)
Years since diagnosis, median (range)	12.5 (0-40)
Extent of ulcerative colitis	
Proctitis	8 (20.0)
Left colitis	10 (25.0)
Extensive colitis	22 (55.0)
Age at diagnosis*	
< 16 years	5 (11.4)
17-40 years	30 (68.2)
> 40 years	9 (20.5)
Behavior at the time of the study*	
Inflammatory	36 (81.8)
Stenosis	2 (4.5)
Fistulizing	6 (13.6)
Location*	
Ileum	16 (36.4)
Colon	11 (25.0)
Ileum and colon	17 (38.6)
Perianal involvement	14 (16.7)
Previous surgery*	13 (29.5)
Treatment	
No treatment	16 (19)
Mesalamine	26 (31)
Immunosuppressor in monotherapy	22 (26.2)

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Biologic in monotherapy	18 (21.4)
Combined treatment	2 (2.4)

*Crohn's disease.

Table 2. Results of endoscopic activity assessment using FIT and FC in the 84 patients included in the study

	Inflammatory bowel disease		**Ulcerative colitis**		**Crohn's disease**	
	FIT	**FC**	**FIT**	**FC**	**FIT**	**FC**
Sensitivity	50.0 (35.2-64.18)	57.5 (42.2-71.5)	75.0 (50.5-89.8)	68.8 (44.4-85.8)	33.3 (18.0-53.3)	50 (31.4-68.6)
Specificity	79.5 (65.5-88.8)	88.6 (76.0-95.0)	87.5 (69.0-95.7)	95.8 (79.8-99.3)	70.0 (48.1-85.5)	80.0 (58.4-91.9)
PPV	69.0 (50.8-82.7)	82.1 (64.4-91.1)	80.0 (54.8-93.0)	91.7 (64.6-98.5)	57.1 (32.6-78.6)	75.0 (50.5-89.8)
NPV	63.6 (50.4-75.1)	69.6 (56.7-80.1)	84.0 (65.3-93.6)	82.1 (64.4-92.1)	46.7 (30.2-63.9)	57.1 (39.1-73.5)
Accuracy	65.5 (54.8-74.8)	73.8 (63.5-82.0)	82.5 (68.0-91.3)	85.0 (70.9-92.9)	50.0 (35.8-64.2)	63.6 (48.9-76.2)
Positive likelihood ratio	2.4 (1.3-4.7)	5.1 (2.1-12.0)	6.0 (2.0-17.6)	16.5 (2.3-115.6)	1.1 (0.7-2.7)	2.5 (0.9-6.5)
Negative likelihood ratio	0.6 (0.4-0.9)	0.5 (0.3-0.7)	0.3 (0.1-0.7)	0.3 (0.2-0.7)	0.9 (0.6-1.5)	0.6 (0.4-1.0)
OR	3.89 (1.5-10.1)	10.5 (3.4-32.4)	21.0 (4.0-110.0)	50.6 (5.3-486.9)	1.2 (0.3-4.2)	4.0 (1.0-15.6)

All results expressed as % and CI 95 %. FIT: fecal immunochemical test; FC: fecal calprotectin; PPV: positive predictive value; NPV: negative predictive value; OR: odds ratio.

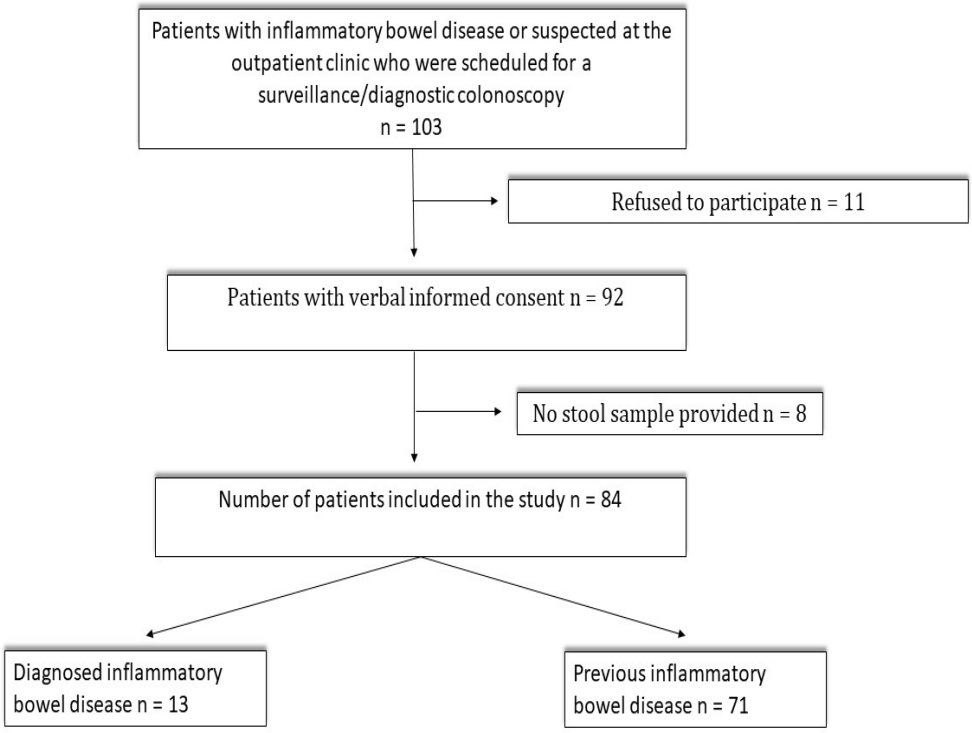
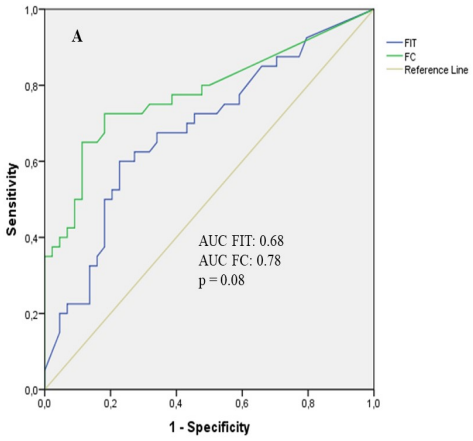


Fig. 1. Flow chart showing the recruitment process.


A
FIT
FC
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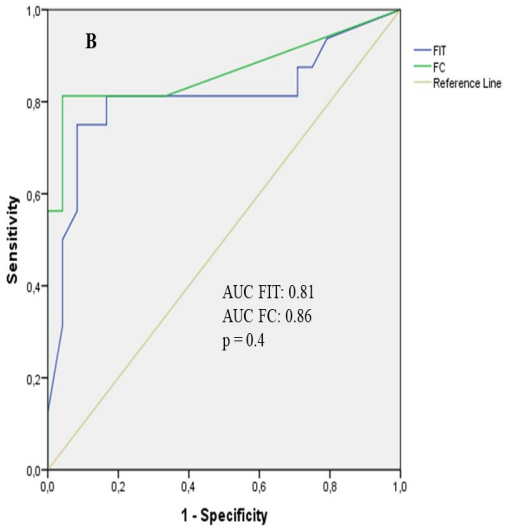
AUC FC: 0.78
p = 0.08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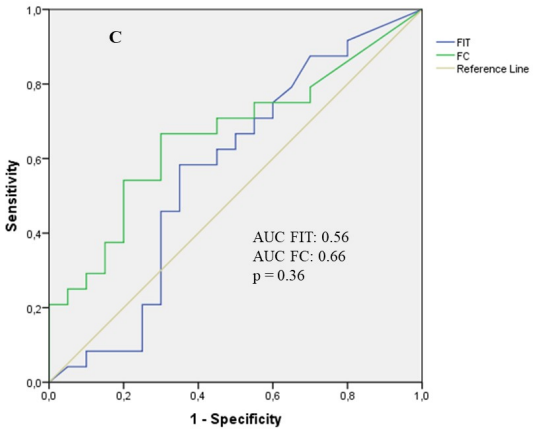

Fig. 2. Fecal immunochemical test (FIT) and fecal calprotectin (FC) receiver operating characteristic curve to assess endoscopic inflammatory activity in patients with inflammatory bowel disease (A), patients with ulcerative colitis (B) and patients with Crohn's disease (C). AUC: area under the curve.