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Alimentary Tract

Usefulness of fecal calprotectin as a biomarker of microscopic colitis in a cohort of patients with chronic watery diarrhoea of functional characteristics

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ABSTRACT

Background: Information on the use of fecal markers in microscopic colitis screening is limited.
Aim: To evaluate the risk variables associated with a diagnosis of microscopic colitis including fecal calprotectin.
Methods: Patients submitted for a colonoscopy due to chronic watery diarrhea fulfilling criteria of functional disease were evaluated. Colonic mucosa was normal but mild erythema and edema was allowed. Fecal calprotectin was analyzed. A logistic regression was used to evaluate variables associated with both raised fecal calprotectin and a diagnosis of microscopic colitis.
Results: 94 patients were included, 30 were diagnosed with microscopic colitis and 64 made up the control group. Median calprotectin levels were 175 (IQR, 59–325) for the microscopic colitis and 28 (IQR, 16–111) for the control group ($p < 0.001$). The optimal cut-off for fecal calprotectin was >100 μg/g (AUC, 0.73), with 67% sensitivity and 75% specificity. The number of drugs used ≥3 (OR, 3.9; CI, 1.4–10.4) and microscopic colitis diagnosis (OR, 6; CI, 2.2–16.3) were associated with raised calprotectin levels. Age >60 years (OR, 3.8; CI, 1.4–10.1) and calprotectin levels (OR, 5.3; CI, 2–14.1) were associated with a risk of microscopic colitis.
Conclusions: Elevated fecal calprotectin concentrations are often seen in microscopic colitis, and may be helpful in the diagnosis of women over 60 with chronic watery diarrhea.

1. Introduction

Microscopic colitis (MC) usually presents with symptoms that are indistinguishable from those of functional diarrhea [1,2]. MC and functional disorders share an overlap of symptoms and a normal appearance upon colonoscopy and biological markers for distinguishing between these diagnoses do not currently exist. Existing clinical guides for the management of chronic diarrhea propose that young patients with chronic watery diarrhea and normal laboratory tests (including celiac disease serology), negative stool ova and parasites and with no alarm features usually have functional diarrhea. However, an ileocolonoscopy is indicated when patients are 50 years old or older or have a familial history of colorectal cancer or inflammatory bowel disease, along with multiple biopsy sampling when the colon is macroscopically normal. Other tests, such as carbohydrate or bile acid absorption tests, are also recommended [1–3]. A diagnosis of functional diarrhea can be established when all explorations are negative and there are no alarm features. However, a specific diagnosis, including that of MC, can also be made in young adult subjects.

MC is a cause of chronic watery non-bloody diarrhea whose incidence seems to be rising, varying between 1 and 12 per 10^5 people per year [4]. Recent data reported a prevalence rate for MC of 107 per 10^5 inhabitants in the area of Terrassa, Spain, but incidence and prevalence vary between geographic areas [5]. Additionally, the prevalence of MC among patients with suspected functional diarrhea is around 9% [6]. Previous studies have evaluated a series of risk variables that can be used to identify the patients most likely to have MC and that may prove helpful when deciding

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whether to carry out multiple colonic biopsies during colonoscopy in patients with chronic non-bloody watery diarrhea [7–9]. Two of these studies derived predictive scores of MC [7,9] Several studies have examined the use of fecal markers in MC screening, the most evaluated of which is fecal calprotectin, which is a calcium-binding protein found in neutrophilic granulocytes, monocytes and macrophages. However, fecal calprotectin seems to play no role as a biomarker in MC, though results are controversial [4].

The aim of this study was to evaluate the known risk variables associated with a diagnosis of MC and whether fecal calprotectin concentration could help to differentiate between MC and chronic watery diarrhea of functional characteristics.

2. Patients and methods

The catchment area of the Hospital Universitari Mútua Terrassa (HUMT) is located in the north-east of Spain (Catalonia region) and it is of a mixed rural–urban type. The hospital offers universal coverage for primary and specialist services, with an established system for referral from primary to secondary care. In the Department of Gastroenterology of the HUMT there is a work-up clinical protocol and specific outpatient visits for chronic diarrhea. Although there are a number of private practitioners in the area, private colonoscopies and biopsies are performed at the hospital and the same diagnostic protocol is followed by all physicians in evaluating patients with chronic watery diarrhea. Colonic sample biopsies for both public and private practice are therefore processed in the Pathology Department of the HUMT. In fact, the Gastroenterology Department of the hospital is considered to be a referral center for chronic diarrheal diseases.

We evaluated all patients referred for a colonoscopy due to chronic non-bloody watery diarrhea between January 2015 and December 2016. Patients fulfilling the following criteria were included in the study: 1. Age >18 years; 2. Chronic watery diarrhea defined as the presence of ≥2 watery stools/day or at least 3 weekly episodes of ≥3 watery stools/day, Bristol scale = 6 or 7, lasting ≥4 weeks; 3. Macroscopically normal colonoscopy (mild erythema and edema was allowed); 4. Having a complete diagnostic work-up of chronic watery diarrhea and appropriate follow-up; 5. Fulfilling the Roma III criteria for either functional diarrhea or diarrhea-dominant IBS; 6. Patients living in the catchment area of the hospital. Exclusion criteria were: 1. Patients with alternating diarrhea-constipation and self-limiting diarrhea at the time of colonoscopy; 2. Drug or alcohol abuse; 3. History of cholecystectomy, vagotomy or other GI surgical interventions that may justify diarrhea; 4. Previous diagnosis with MC or other specific entities causing diarrhea; 5. An endoscopic finding justifying the diarrhea in ileocolonoscopy and/or capsule endoscopy.

We retrospectively reviewed the electronic medical records and the online-computerized system for electronic prescription of all the patients included. The consumption of medications, the presence of associated autoimmune diseases, smoking, and fecal calprotectin levels before colonoscopy were specifically recorded.

2.1. Diagnostic work-up of chronic watery diarrhea

As mentioned, all physicians in the area follow the same diagnostic work-up protocol for chronic non-bloody watery diarrhea. Medical staff at the HUMT Gastroenterology Department act as consultants for primary care physicians. All included patients showed no alarm features and normal routine blood analyses, including C-reactive protein and celiac serology. A complete colonoscopy was performed under conscious IV sedation. Multiple biopsy specimen samples were obtained from all patients when the macroscopic appearance of the colonic mucosa was normal or mildly abnormal (mild erythema or edema may be observed in MC patients). Four samples from the right colon, and two each from the transverse, descending, and sigmoid zones, were taken. MC diagnosis was based on both clinical and histological criteria, as defined in previous studies [10,11]. Histological MC diagnosis was reviewed in all cases by the same experienced pathologist (C.F.).

When the histological examination of colonic samples was normal, the following tests were performed in a stepwise routine (a) HLA-DQ2 and HLA-DQ8 haplotypes for celiac disease predisposition, (b) endoscopic biopsies from distal duodenum in all DQ2 or DQ8 positive patients to rule out gluten-sensitive enteropathy, both for histological assessment and TCR$\gamma\delta^{+}$ and $CD3^{-}$ intraepithelial lymphocytes counted by flow cytometry [12] and (c) a ^{75}SeHCAT (Se-homotaurocholate) abdominal retention test to assess bile acid malabsorption [13]. In addition, hydrogen breath tests to assess both lactose and fructose *plus* sorbitol malabsorption were performed either when all previous tests were normal or when the patient reported clinical sugar intolerance [13]. Capsule endoscopy was performed on patients with normal ileocolonoscopy and increased levels of fecal calprotectin. The use of medications was reviewed and those known to be a cause of diarrhea were in general withdrawn when possible. A definite diagnosis was established after clinical remission was achieved with the specific therapeutic strategy (either colestyramine, sugar-restricted diet, gluten-free diet, medication withdrawal or a specific drug). Finally, functional diarrhea was diagnosed when the results of all specific tests performed were normal and diarrhea persisted.

2.2. Stool analysis for fecal calprotectin

The stool analysis for fecal calprotectin was performed 1–2 weeks before colonoscopy. Fecal samples were collected by patients at home and were brought on the same day to the Biochemical Laboratory at our Hospital. They were stored in deep freeze (−80 °) and were unfrozen and used for testing two weeks after initial storage at most. The stool extraction procedure was performed using the CALEX® cap device. Fecal calprotectin concentrations (μg/g) were measured using a DSX system analyzer (Dynex technologies, Worthing, UK) and by an enzyme-linked immunosorbent assay (ELISA) (BÜHLMANN fCAL, Schönenbuch, Switzerland), according to the manufacturer's instructions. The predefined cut-off used was 50 μg/g.

2.3. Statistical analysis

Results are expressed as mean ± SEM or as median and its interquartile (IQR) range, and as percentages. We used Chi-square statistics for comparisons between categorical variables and the Student-t-test (or the non-parametric Mann–Whitney test) for quantitative variables. Wilcoxon test was used to assess changes in the fecal calprotectin levels before and after achieving clinical remission. A logistic regression analysis was performed to assess first the association of possible predictors with the presence of increased fecal calprotectin levels, and second the association of the possible predictors with MC diagnosis. Those variables with a significant association in the univariate analyses ($p < 0.05$) were introduced in the multivariate analysis. Quantitative variables were introduced as categorical. The optimal cut-off for each of them was evaluated by a receiving operator characteristics (ROC) analysis. A stepwise method of introduction was used. The odds ratio (OR) and its 95% confidence interval (CI) were calculated to assess the strength of each significant association. The diagnostic accuracy of fecal calprotectin was measured by the area under the ROC curve (AUC). The optimal cut-off was selected using the Youden index, and its sensitivity, specificity, positive and negative predictive values, and their 95% confidence intervals (CI) were calculated. All

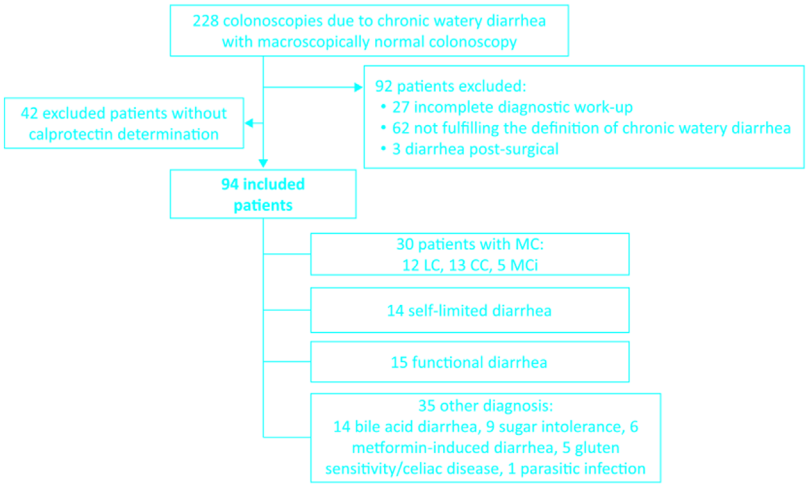

Fig. 1. Flow diagram of distribution of patients during the study.

statistical calculations were performed using the SPSS for Windows statistical package (SPSS Inc., Chicago, IL, USA), and MedCalc Statistical Software version 18.2.1 (Ostend, Belgium) for ROC curve analysis. Statistical significance was predetermined as $p < 0.05$.

3. Results

A flow diagram illustrating the distribution of patients throughout the study is presented in Fig. 1. There were 136 evaluable patients who fulfilled the inclusion criteria. The final study cohort consisted of 94 out of 136 patients, who underwent fecal calprotectin analysis prior to the colonoscopy procedure. Table S1 Suppl describes the characteristic of included compared to excluded patients. There were no differences in the clinical picture, with similar daily stool numbers and diarrhea duration, nor in the MC diagnosis rate. However, the included patients were younger and more often active smokers and NSAID users. Mean age of included patients was 56.4 ± 1.7 years and 78% were women. A specific diagnosis was achieved in 65 out of 94 (69%) patients. MC was diagnosed in 30 patients (46%) (12 lymphocytic colitis, 13 collagenous colitis, 5 incomplete MC). The remaining diagnoses were 14 (21.5%) cases of bile acid diarrhea, 9 (14%) cases of sugar (lactose and/or fructose) intolerance, 6 (9%) cases of metformin-induced diarrhea, 5 (7.8%) cases of gluten sensitivity and 1 (1.5%) case of parasitic infection. Fourteen out of the 94 patients (15%) had self-limited diarrhea after colonoscopy, all with normal multiple biopsies on a macroscopically normal colonic mucosa. Finally, all diagnostic tests were negative in 15 out of the 94 patients (16%) with persistent diarrhea, who were diagnosed as functional. All 64 non-MC patients who presented clinically with watery non-bloody chronic diarrhea with functional characteristics were assigned to the control group.

The differences between the MC and the control group are described in Table 1. There were no differences between the two groups in terms of gender, smoking habits, daily stool number, associated diseases, and the consumption of nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), statins, selective serotonin reuptake inhibitors (SSRIs) and beta-blockers. Patients with MC were older, had a shorter duration of diarrhea before colonoscopy and had higher fecal calprotectin levels (Fig. 2). There were no significant differences between CC, LC and incomplete MC (Fig. S1 Suppl). The optimal cut-off for fecal calprotectin was >100 μg/g, which was associated with an AUC of 0.73 ± 0.06 ($p < 0.0001$) and showed a sensitivity of 67% (95% CI, 47–83%), a specificity of 75% (95% CI, 63–85%), a positive predictive value of 53% (95% CI, 41–65%), and a negative predictive value of 84% (76–90%) for MC diagnosis (Fig. 3). Thus, using fecal calprotectin as a triage tool, 10 of 30 patients with microscopic colitis would not have received the colonoscopy (5 out of 10 patients <60

Table 1
Clinical and demographic characteristics of microscopic colitis and the control group.

Variables	MC (n = 30)	Control (n = 64)	p Value
Age (years)	65.3 ± 3.1	52.2 ± 1.9	<0.001
Age >60 years (%)	20 (67%)	20 (31%)	0.001
Sex (women) (%)	24 (80%)	51 (80%)	0.97
Active smoking (%)	6 (20%)	20 (32%)	0.22
Autoimmune diseases (%)	7 (23%)	10 (16%)	0.36
Celiac disease (%)	2 (6%)	1 (1.5%)	0.19
NSAID usage[a] (%)	4 (13%)	6 (9%)	0.56
PPI usage[a] (%)	15 (30%)	24 (38%)	0.25
Statin usage[a] (%)	9 (30%)	10 (15%)	0.11
SSRI usage[a] (%)	7 (23%)	9 (14%)	0.26
Beta-blockers usage[a] (%)	4 (13%)	4 (6%)	0.25
Number of drugs used	2.7 ± 0.45	1.6 ± 0.22	0.016
Number of drugs used ≥3 (%)	12 (40%)	18 (28%)	0.25
Daily stools number	4.5 ± 0.35	4.4 ± 0.24	0.86
Diarrhea duration (months)[b]	5 (3-9)	6 (5-24)	0.018
Diarrhea duration ≤9 months	24 (80%)	35 (55%)	0.018
Calprotectin (μg/g)[b]	175 (59–325)	28 (16–111)	0.0003
Calprotectin >100 μg/g (%)	20 (67%)	16 (25%)	<0.001

[a] Use of medications >3 days per week during >2 weeks.
[b] Median (IQR).

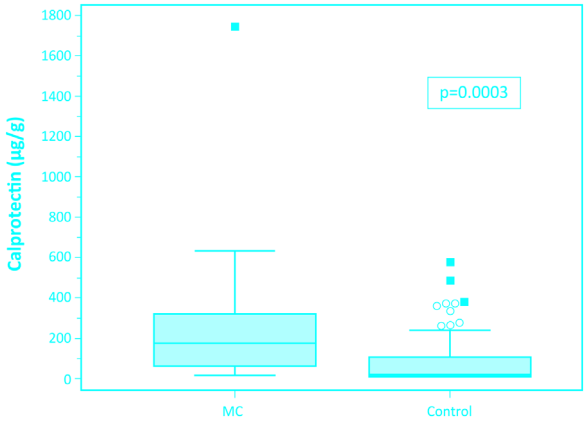

Fig. 2. Boxplot chart of the comparison of fecal calprotectin concentrations in study groups. White circles represent suspected outliers (1.5 × IQR or more above the third quartile) and dark squares represent outliers.

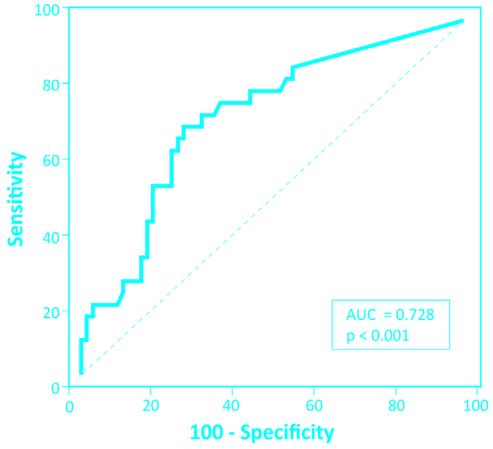

Fig. 3. Accuracy of fecal calprotectin for MC diagnosis: ROC curve.

Table 2
Factors associated with raised calprotectin levels.

Variable	Calprotectin ≤100 μg/g (n = 58)	Calprotectin >100 μg/g (n = 36)	p Value
Sex (woman) (%)	49 (84%)	26 (72%)	0.15
Age at the diagnosis >60 years (%)	38 (66%)	16 (44%)	0.045
MC diagnosis (%)	10 (17%)	20 (58%)	<0.001
Active smoking (%)	16 (28%)	10 (28%)	0.93
Autoimmune diseases (%)	9 (16%)	8 (22%)	0.412
NSAID usage (%)	4 (7%)	6 (17%)	0.135
PPI usage (%)	18 (31%)	21(58%)	0.009
SSRI usage (%)	10 (17%)	6 (16%)	0.94
Beta-blocker usage (%)	3 (5%)	5 (14%)	0.14
Number of drugs ≥3 (%)	12 (21%)	18 (50%)	0.003
Duration of diarrhea <9 months (%)	31 (53%)	28 (78%)	0.018

years, and 5 out of 20 patients ≥60 years). In fact, patients with negative fecal calprotectin (<100 μg/g) were significantly younger than those with positive fecal calprotectin (56.6 ± 5.8 *vs.* 69.7 ± 3.2 years; p = 0.042).

3.1. Multivariate-analysis

As PPI and NSAID use is a known cause of raised fecal calprotectin levels, we performed a first analysis to assess the factors associated with fecal calprotectin >100 μg/g, the results of which are provided in Table 2. Significant variables in the univariate analysis were introduced in a multivariate-adjusted logistic regression analysis. Finally, both number of drugs ≥3 (OR, 3.9; 95% CI, 1.4–10.4; p = 0.008), and Final diagnosis (MC *vs.* control) (OR, 6; 95% CI, 2.2–16.3; p < 0.001) were independently associated with the observed raised fecal calprotectin levels.

Finally, a multivariate-adjusted logistic regression analysis was performed to assess the independent factors associated with MC diagnosis. Age >60 years, duration of the diarrhea <9 months, number of drugs ≥3, and fecal calprotectin levels were introduced in the model. Both age >60 years (OR, 3.8; 95% CI, 1.4–10.1; p = 0.009) and fecal calprotectin levels (OR, 5.3; 95% CI, 2–14.1; p = 0.001) were independently associated with the risk of MC after adjusting for the other variables.

3.2. Changes of fecal calprotectin levels after clinical remission

Changes of fecal calprotectin levels after achievement of clinical remission were analyzed in 9 MC patients, not taking NSAID nor PPI drugs. Budesonide therapy was used to induce the clinical remission in 7 patients, and in the other two a spontaneous clinical remission was observed after colonoscopy. A significant reduction in fecal calprotectin levels was observed [median, 436 (IQR 189–1300) *vs.* 58 (IQR 30–167); p = 0.004] (Fig. S2 Suppl).

4. Discussion

In previous studies, the frequency of MC in patients with non-bloody watery chronic diarrhea referred for colonoscopy was around 12% [4]. In our study, 31% of the patients with chronic watery diarrhea of functional characteristics were diagnosed with MC. The reasons for this higher frequency may be our inclusion criteria, which applied a stricter definition of chronic watery diarrhea by which patients with diarrhea/constipation alternation and loose stools not fulfilling the definition of chronic watery diarrhea were excluded, while patients with incomplete MC were included.

Previous studies have evaluated the demographic and clinical variables that are predictive of MC and the derived scoring systems used to identify the patients most likely to have MC. These risk scores, which may be helpful when deciding whether to carry out multiple colonic biopsies during colonoscopy in patients with chronic non-bloody watery diarrhea, were sensitive (>90%) but not sufficiently specific (≈45–50%) [7,9]. The results of the present study confirm the predictive value of patients' age. In fact, an age of 50 or 55 years or more was a predictive variable of MC in previous studies [7–9]. In our study, a cut-off of 60 years old or more was a risk factor for MC. However, the results of the present study were not able confirm the predictive value of female gender, daily stool number, diarrhea duration, smoking, associated autoimmune diseases or the use of certain medications when comparing MC patients with those with non-MC chronic watery diarrhea. Regrettably, the retrospective nature of the present study precluded recording a number of clinical symptoms, such as the nocturnal passing of stools, changes in body weight and the presence of abdominal pain, which were predictive variables in the mentioned scoring systems.

Several factors may account for the observed discrepancies between the present and previous studies. First of all, there are differences in the definition of chronic watery diarrhea, which was not as strict in previous studies as in the present one. We did not find differences in the daily stool numbers of the two study groups, suggesting that the intensity of watery diarrhea was similar, though it was higher in the MC than in the non-MC group in previous studies [7–9]. This difference is important, since the differential diagnosis of MC must be performed with patients presenting with a similar clinical picture, and it may explain the lack of significance of the other variables. Thus, the described risk scores might only be predictive of a more severe form of diarrheal disease. Likewise, there were no differences in the female gender rate in the present study which was around 80% in both MC and control groups, whereas this difference was highly significant in previous studies [8,9].

Noteworthy, and in contrast with previous studies, is the fact that there were no differences between groups in the usage of MC-trigger drugs. However, not all PPIs, NSAIDs and SSRIs are the same in terms of both diarrhea and MC triggering and this may also have influenced the differences observed. In fact, sertraline and lansoprazole, which are considered to be more likely to trigger MC than other drugs in the same family [4,14], were used very little by patients in the present series. Finally, differences in the clinical work-up of chronic watery diarrhea with functional characteristics might also account for the differences observed. In the present study, after confirming that there were no alarm features and that the initial screening disclosed normal results, colonoscopy *plus* biopsies was indicated as the first examination.

Several studies have examined the use of fecal markers in MC screening, the most highly evaluated is fecal calprotectin, whose

levels are higher in patients with inflammatory bowel disease and can correlate with clinical disease activity [15]. Fecal calprotectin is not considered to be useful for MC diagnosis, since neutrophils are not increased in the colonic mucosa of these patients. However, although they are not the most characteristic aspect of MC, neutrophils may often be present in the lamina propria infiltrate [16]. To date, the studies evaluating fecal calprotectin in MC have included a limited number of patients with contradictory results. In fact, while several studies found 60–75% of patients with active collagenous colitis had elevated fecal calprotectin levels [17–21], another study reported no differences between MC patients and a control group with chronic watery diarrhoea [22]. However, the largest sample size included in those studies was 21 patients. Our results showed that a cut-off of >100 μg/g of fecal calprotectin had a sensitivity of 67%, a specificity of 75% and a negative predictive value of 85% for active MC diagnosis. In addition, along with patient's age, it was an independent risk variable that served to identify active MC among patients with chronic watery diarrhea. However, its diagnostic accuracy is not sufficient for it to be considered a good biomarker of MC and to justify not taking colonic biopsies when normal. In this sense, the main conclusion of the present study is that fecal calprotectin is often increased in patients with active MC, and in these cases, the performance of multiple colon biopsies is recommended in spite of macroscopically normal ileocolonic mucosa, as is not thinking only in terms of classic IBD involving the proximal intestine.

Both the number of drugs and MC diagnosis were found to be independently related with the variables associated with elevated fecal calprotectin levels. NSAID and PPI usage has been associated with an increase in fecal calprotectin levels [23]. However, in the present study only the use of 3 or more medications was independently associated with increased fecal calprotectin levels. Since there were no differences between the MC and the control group in the utilization of concomitant drugs, this variable was not associated with the risk of MC.

The limitations of the present study include its retrospective nature, precluding the recording of some clinical symptoms. However, the strengths of our study include using standardized diagnostic work-up, follow-up and diagnostic criteria, the fact that the histological diagnosis was performed by a pathologist with experience with MC, and that we used strict inclusion criteria that allowed for the selection of a control group with similar diarrhea intensity.

In conclusion, the current study showed that no clinical variable except older age was associated with MC diagnosis when the control group with chronic non-bloody watery diarrhea of functional characteristics had similar diarrhea intensity. Elevated fecal calprotectin concentrations were often seen in MC (≈70%), but do not have enough diagnostic accuracy to be considered a good fecal biomarker for MC diagnosis. However, results do reinforce the observation that increased fecal calprotectin levels may be present in MC patients, and the need to take multiple colonic biopsies when ileocolonoscopy is macroscopically normal, mainly in women aged 60 years and over.

Conference presentation

The results of this study were presented in part at the Congress of the European Crohn's and Colitis Organisation (ECCO) held in Vienna in 2018.

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Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dld.2019.07.002.

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