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Review

Calprotectin in inflammatory bowel disease

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ABSTRACT

The term IBD is usually used for referring to a group of inflammatory gastro-intestinal diseases (mainly Crohn's disease and ulcerative colitis). Accordingly, IBD arises as a result of inappropriate immune response to intestinal commensal organisms among genetically susceptible individuals. Performing colonoscopy and histopathologic evaluation on an inflamed bowel biopsy specimen are currently considered as gold standards for diagnosis and management of IBD. Correspondingly, these techniques are known to be invasive and costly. In recent decades, fecal calprotectin, as a biomarker, has received much attention for the diagnosis and non-invasive management of IBD. Up to now, many studies have investigated the efficacy of fecal calprotectin in the areas of IBD differentiation from IBS, prediction of endoscopic and histologic activities of IBD and prediction of disease recurrence. Although some of these studies have reported promising results, some others have shown significant limitations. Therefore, in this paper, we reviewed the most interesting ones of these studies after a brief discussion of the laboratory measurement of fecal calprotectin. Moreover, we attempted to provide an answer for the question of whether fecal-calprotectin could be considered as a potential surrogate marker for colonoscopy.

1. Introduction

Inflammatory bowel disease (IBD) is a long life disease with remission and relapse periods. IBD arises as a result of inappropriate immune response to intestinal commensal organisms in individuals with genetic predisposition and consequently causes inflammation and intestinal ulcers [1],. In addition, IBD has a complex pathogenesis and many factors such as dysbiosis, oxidative stress, and epigenetics that may also be involved in disease pathogenesis [2–4]. Ulcerative colitis (UC) and Crohn's diseases (CD) are known as two main forms of IBD. Accordingly, these diseases cause intestinal ulcers and some annoying symptoms such as diarrhea, abdominal pain, and rectal bleeding. Occasionally the severity of these symptoms is very high, which can lead patients to be hospitalized. In this regard, therapeutic approaches to treat these diseases mainly focus on prolonging remission and are almost similar; however, differential diagnosis can also help to treat the disease in a more effective way. For example, 5-ASA, which is a common drug in the treatment of IBD, is less effective on maintaining remission in CD patients. On the other hand, antibiotic therapy is not recommended for the treatment UC but it can be effective on CD patients [5],[6]. Differential diagnosis is a serious challenge because CD and UC have significant similarities in terms of their clinical, endoscopic, and histological features. However, there are some differences between UC and CD, which are summarized in Table1. In addition to intestinal complications, UC and CD also have significant extra-intestinal manifestations. For example, it was shown that UC is significantly associated with Primary sclerosing cholangitis and CD is also associated with cholelithiasis, especially in cases that the ileum is involved [7],. Furthermore, CD can cause fistulas to the urinary system, which leads intestinal bacteria to enter the urethra and recurrent urinary tract infections [8],. Both CD and UC can cause several disorders such as arthritis, Erythema nodosum, pyoderma gangrenosum, and anemia, which are known as the most important extra-intestinal manifestations of IBD [7],[9]. The latest statistics showed that the global

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Table1
Clinical, endoscopic and histological features of CD and UC.

Clinical Features		
Features	CD	UC
Rectal bleeding	Occasionally	Frequently
Abdominal pain	Frequently	Occasionally
Fever	Frequently	Not common
Mucus defection	Occasionally	Frequently
Intestinal obstruction	YES	NO
Perineal disease	YES	NO
Post-operative recurrence	YES	NO
ASCA positive	Frequently	Not common
ANCA positive	Not common	Frequently
Endoscopic Features		
Features	CD	UC
Location	Any part of GI tract	Colon and rectum
Mucosal involvement	Discontinuous	Continuous
Depth of ulceration	Deep	superficial
fistula	Yes	NO
Cobblestone appearance	YES	NO
Aphthous ulceration	Frequently	Occasionally
Mucosal friability	Not common	Frequently
Histological features		
Features	CD	UC
Granulomas	Frequently	Rare
Crypt abscesses	Not common	Frequently
Patchiness	Frequently	Not common

prevalence of IBD currently is on the rise, and it is not an exaggeration if we consider it as a global serious health problem [10],. According to a report published in 2018, IBD has the highest prevalence rate in Europe, and its prevalence in the newly industrialized countries of Asia, Africa, and South America also appears to be increased over the past three decades [11],.

Unfortunately, the peak of the disease is at the young age of 15–30 years old [12],; therefore, in addition to the suffering from inflicts on the patients, it also has many negative effects on society. Moreover, many financial burdens are annually imposed on countries for controlling and treating this chronic disease. The invasive diagnostic and therapeutic measures are currently undertaken to diagnose and manage IBD, which are unpleasant for patients as well as having the high associated costs. Now, the gold standard method for diagnosing IBD and monitoring patient status is performing colonoscopy examination and histopathologic evaluation, which are invasive measures [13],. Therefore, in recent years, many studies have been conducted to find a suitable laboratory marker with sufficient sensitivity and specificity for the purpose of diagnosing and non-invasive management of IBD. A high proportion of these studies have investigated the efficacy of fecal calprotectin in diagnosing and monitoring patients. Although some of these studies reported auspicious results, there are still some doubts on the effectiveness of fecal calprotectin on diagnosing and monitoring IBD patients. So, in this review, we addressed the advantages and limitations of fecal calprotectin for the diagnosis and management of IBD.

2. The role of fecal calprotectin in diagnosis and management of IBD

The efficacy of fecal calprotectin, as an laboratory marker, in various areas of IBD diagnosis and management have been studied including IBD differentiation from irritable bowel syndrome (IBS), evaluation of endoscopic activity of the disease, evaluation of histological activity of the disease, and prediction of disease recurrence and response to treatment. In following, after a brief introduction and mentioning the important points regarding laboratory measurement of fecal calprotectin, we reviewed the most interesting findings in all of the above-mentioned areas.

2.1. Calprotectin: A clinically valuable protein

Calprotectin is an antimicrobial protein mainly secreted by neutrophils. This protein competes with bacteria over zinc, thus kills the bacteria. However, this is not the only contribution that it has to antimicrobial activity. Moreover, this protein has many potential clinical applications, such as the elevated serum levels that have been observed under various immunological and immunopathological conditions. Serum calprotectin levels rapidly increase in response to bacterial infections in the kidney and heart or during transplant rejection. At the early stages of inflammation of the lung, serum calprotectin can also be considered as a reliable marker; besides, plasma levels of calprotectin appear to be useful in reflecting disease activity in inflammation of the joints [14],. In addition, it has been demonstrated that serum calprotectin levels are increased in patients with bacterial sepsis, so it can be considered as a reliable biomarker [15],. In Neonatal Sepsis, the serum level of calprotectin increases, as well as a sensitivity of 62.5% and a specificity of 69.7% that have been reported for serum calprotectin in diagnosis of Neonatal Sepsis [16],. It has been recently shown that serum calprotectin levels increase in patients with aneurysmal subarachnoid hemorrhage, and higher levels in the first 48 of onset are associated with a poor prognosis at the first three months [17],. Serum calprotectin levels also increase in patients with rheumatoid arthritis, and even in patients with a moderate to high disease activity who have normal or low CRP levels, so they appear to be more efficient at reflecting disease activity [18],.

Some studies have also investigated the efficacy of serum calprotectin in the diagnosis of cancers. Correspondingly, in one of these studies, it was shown that serum calprotectin levels significantly increased in patients with laryngeal carcinoma compared with healthy individuals and those with benign laryngeal pathologies. Moreover, in this study, a direct relationship was also observed between serum levels of calprotectin and stage of cancer [19],. Another study showed that the serum level of calprotectin increased in patients with papillary thyroid carcinoma, but it significantly decreased after operation [20],. Also, regarding the efficacy of serum and saliva calprotectin for the diagnosis of IBD, impressive results have been reported [21],[22]. A study on patients with IBD (both UC and CD) have shown that serum calprotectin levels were directly correlated with fecal calprotectin levels and were more potent in IBD diagnosis compared to CRP and albumin. This study also indicated that the combination of serum calprotectin with CRP or albumin can be helpful in the prediction of treatment escalation, especially in patients with CD [23],. However, no significant correlation was observed between serum calprotectin and fecal calprotectin levels in patients with CD and UC, as well as a slight correlation between serum calprotectin level and CRP that was observed only in patients with UC [24],. Another study showed that the serum level of calprotectin was significantly higher in patients with CD compared to healthy individuals. In addition, although a significant correlation was observed with the clinical activity of the disease, no significant correlation was found between the level serum calprotectin and endoscopic activity of the disease [25],. The efficacy of salivary calprotectin in the diagnosis of IBD has also been studied, which showed that salivary calprotectin significantly increased in patients with IBD compared to healthy individuals. In this study, AUC values for unstimulated saliva and stimulated saliva to distinguish IBD patients from healthy individuals were reported to be 0.927 and 0.870, respectively [22],. However, the popularity of calprotectin is mainly due to the use of fecal calprotectin in the diagnosis and management of IBD that is discussed in the following.

2.2. Laboratory measurement and reference interval

Fecal calprotectin is a stable protein that remains stable for 4–7 days at room temperature [26],. This property is an excellent advantage for a laboratory marker. Also, it seems that keeping the specimen at refrigerated temperature (4 °C) can increase the stability of fecal calprotectin [27],. However, evidence has been obtained regarding that the stability of this protein decreases after staying for three days at room temperature. On the other hand, it is not also recommended to keep samples in the refrigerator for more than 7 days [28],. It seems that fecal calprotectin remains stable up to one year at −20 °C [29],. Measurement of fecal calprotectin can be done both qualitatively and quantitatively. Accordingly, in the qualitative measurement, monoclonal antibodies are used to detect fecal calprotectin, and the positive results are characterized by the appearance of colored lines on the test cassette. However, in the qualitative one, only positive or negative results are reported, and despite 93% of sensitivity, test specificity in the evaluation of disease activity was reported to be only 50%. It seems that the main application of this test is to differentiate healthy individuals from IBD patients rapidly; however, some studies have shown that it is not accurate enough in this case, as well [30,31],[32]. Nevertheless, a significant concordance has been reported between home test results (IBDoc) and fecal calprotectin laboratory measurement results (when Quantum Blue calprotectin ELISA kit was used). Notably, the agreements between results were 80% and 92% depending on the selected cut-offs [33],. Several commercial kits are also available for fecal calprotectin qualitative test known as rapid calprotectin. These tests report positive results ranged from 3 0 to 300 μg/g. There are also several commercial kits that can be used for the quantitative measurement of fecal calprotectin. These kits are usually designed in terms of the ELISA method, and some have a measurement range between 6.5 and 2100 μg/g. Moreover, the chemiluminescence immunoassays (CLIA) method can also detect values between 5 and 8000 μg/g. Fluoro enzyme immunoassays (FEIA) and particle enhanced turbidimetric immunoassays (PETIA) can also be used for the measurement of fecal calprotectin. In this regard, one of the most serious challenges to the laboratory evaluation of fecal calprotectin is the determination of the upper limit in healthy individuals. Among healthy adults, there is a significant agreement on 50 μg/g as an upper limit. One study suggested values up to 112 μg/g in people over 60 years old and up to 186 μg/g in children aged between 2 and 9 years old, as reference ranges of fecal calprotectin in healthy individuals [34],.

Fecal calprotectin levels appear to be higher in healthy infants and children under four years old than in adults, and further studies are needed in this regard to determine the acceptable upper limit for diagnosis of pediatric IBD [35,36]. Table 2 lists the median levels of fecal calprotectin in healthy individuals with different ages reported in some studies. According to these reports, age can affect fecal calprotectin levels.

2.3. Fecal calprotectin and IBD diagnosis

Only a small percentage of patients complaining of abdominal pain and diarrhea have IBD. In many cases, IBS, as a functional gastrointestinal disorder, is known as the cause of such clinical symptoms. Patients with IBS have normal colonoscopy results, while IBD patients indicate abnormal colonoscopy results and have intestinal ulcers. Unfortunately, the significant prevalence of IBS and the overlap between clinical symptoms and IBD can increase the colonoscopy rate. Therefore, a non-invasive diagnostic marker can be very helpful in this regard. Notably, the first evidence of the efficacy of fecal calprotectin in the diagnosis of IBD was obtained in the 1990s. Røseth et al. in 1992 proposed a method for measuring Calprotectin in stool specimens [40],. One of the first and most interesting studies regarding fecal calprotectin utility in IBD diagnosis was the study by Røseth et al published in 1997. In this study, 62 patients with ulcerative colitis were studied, and according to their results, fecal calprotectin levels are higher in patients with ulcerative colitis compared to healthy controls. This study have also shown that even patients with low disease activities had higher levels of fecal calprotectin compared to healthy individuals [41],. Subsequent studies somehow confirmed and complemented the findings of this study. In another study published in 2000, AUC values of 0.89 (95% CI 0.81–0.97) were reported for fecal calprotectin in the diagnosis of colorectal inflammation [42],. Moreover, in a study on children with IBD, it was shown that the level of fecal calprotectin was higher in these patients compared to healthy children, so, it can be concluded that it is also directly correlated with ESR levels [43],. In a study published in 2014, Kolho et al. reported AUC values of 0.944 (95% CI, 0.907–0.981) for fecal calprotectin in the diagnosis of pediatric IBD [44],. In a study on patients with Crohn disease, a sensitivity of 85% and a specificity of 81% at cutoff of 150 μg/g have been reported for fecal calprotectin in diagnosis of the disease [45],. The results of our recent study along with other studies showed that fecal calprotectin is preferred over traditional inflammatory biomarkers such as CRP and ESR, in the diagnosis of IBD [46],[47]. Diamanti et al. reported a sensitivity of 100% and a specificity of 80% for fecal calprotectin at a cut-off of 160 μg/g in IBD diagnosis [48],. In our recent study, a sensitivity of 100% and a specificity of 100% at a cut-off of 78.4 μg/g were observed for fecal calprotectin in the diagnosis of IBD; however, our sample size was 30 and the majority of patients were in the active phase of the disease [47],.

In another study conducted on 76 patients with ulcerative colitis, a sensitivity of 98% and a specificity of 96% at cutoff of 188 μg/g have been reported in this regard [49],. In one study, it was shown that fecal calprotectin in cutoff of 127 μg/g is able to distinguish patients with IBD from patients without IBD (patients with diseases other than IBD, patients with IBS, and healthy persons) with 73% sensitivity and 89% specificity [50],. Caviglia et al. in their study reported a sensitivity of 87.5% and a specificity of 90.5% at a cut-off of 150 μg/g for fecal calprotectin in differentiating between IBS and IBD [51],. However, some studies have reported significantly lower values. Accordingly, in a study on 44 patients with ulcerative colitis, Kalantari et al. reported a sensitivity of 57% and a specificity of 75% at a cutoff of 164 μg/g [52],. Besides, there is a considerable agreement between fecal calprotectin and capsule endoscopy findings in patients with Crohn's disease. A sensitivity of 77% and a specificity of 73% have also been reported at a cut-off of 95 mg/kg for fecal calprotectin in predicting CE findings and diagnosis of Crohn's disease [53],. In another study, lower sensitivity and specificity rates (sensitivity: 75%, specificity: 67%) were reported for fecal calprotectin in this regard [54],. Furthermore, in one study that examined the efficacy of fecal calprotectin in predicting wireless capsule endoscopy findings, a sensitivity of 59% and a specificity of

Table 2
Reported median levels of fecal calprotectin in healthy individuals of different ages.

Ages	Median levels of fecal calprotectin (range) (μg/g)	Number of subjects	Used kit	Reference
Up to 18 month	174.3 (24–764)	288	Bühlmann ,ELISA	[37],
Children 1–4 years	83.19 (14.69–419.45)	274	Bühlmann ,ELISA	[38],
Children 4–12 years	28 (25–35)	159	CALPRO® Calprotectin ELISA Test (ALP)	[36],
Adults	18 (10–34)	43	PhiCal	[39],
Over 60 years	27 (14–118)	20	Phical	[34],

71% were reported for this biomarker at 50 μg/g in the diagnosis of small bowel inflammation in Crohn's disease [55],. Given these findings, it seems that fecal calprotectin has no ideal sensitivity and specificity for the diagnosis of IBD, where the small intestine is involved. Besides, there are some pre-analytical limitations, which are explained in the next sections. Therefore, optimistically speaking, fecal calprotectin measurement can eliminate the need for colonoscopy. However, in a meta-analysis performed to evaluate the efficacy of fecal calprotectin and some other inflammatory markers to differentiate between IBD and IBS, the probability of IBD was less than 1% at fecal calprotectin values lower than 40 μg/g or CRP values lower than 0.5 mg/dL [56],. Therefore, it seems that fecal calprotectin can be helpful, at least in ruling out the possibility of IBD in patients with IBS-like symptoms as well as reducing the rate of colonoscopy. Moreover, it should be noted that, although a systematic review has reported pooled sensitivity and specificity above 90% for fecal calprotectin to differentiate between IBD and IBS, it emphasized more on the possibility of false-positive results in low cut-off points [57],. Hence, performing extensive studies in different countries on the healthy population and the IBD patient is be needed to determine a suitable cut-off with maximum sensitivity and specificity and minimum false-positive results.

Table 3 summarizes the results of various clinical investigations regarding fecal calprotectin utility in the differential diagnosis of IBD from IBS, and Table4 summarizes some meta-analysis results in this regard. As shown in Table 3, the most important limitation of the majority of clinical studies conducted to date, is the small sample size. A large global study may be helpful in providing a more precise evaluation of fecal calprotectin clinical value in discrimination between IBD and non-IBD diseases.

2.4. Fecal calprotectin and endoscopic and histologic activity evaluation

Undoubtedly, one of the most serious challenges in the management of IBD is evaluating the endoscopic and histologic activities of the disease. Nowadays, colonoscopy and histopathologic examinations are the routine tools for the assessment of mucosal healing in patients with IBD. As noted earlier, several scoring systems have been devised to score disease activity based on the findings of colonoscopy and histopathologic examinations. In recent years, many promising results have been reported regarding the correlation between these scores and fecal calprotectin levels. In addition, many studies have been performed in the last decade, all of which cannot be reviewed in this article. The first evidence of a link between fecal calprotectin and disease endoscopic activity was obtained in the late 1990s. In one of the first studies, Roseth et al. found a significant correlation between fecal calprotectin levels and endoscopic and histologic activities in patients with ulcerative colitis [41],. Furthermore, in another study, they observed that IBD patients who were in remission clinically and had normal fecal calprotectin levels (less than 50 mg/L) had normal colonoscopy results [66],. These interesting findings indicate that fecal calprotectin can be considered as a biomarker in the evaluation of endoscopic activity and mucosal healing in IBD patients. Also, these studies were the starting point of extensive studies that have been conducted up to now. In a study conducted on 77 patients with Crohn's disease, Sipponen et al. investigated the sensitivity and specificity of fecal calprotectin in predicting endoscopic activity of Crohn's disease [67],. Correspondingly, the researchers used the Crohn's Disease Endoscopic Index of Severity (CDEIS) scoring system in their study to evaluate the endoscopic activity of Crohn's disease. As a result, they found that there was a significant correlation between the endoscopic activity of the disease and the level of fecal calprotectin. Besides, the findings of this study demonstrated that fecal calprotectin at 200 μg/g cut-off can predict the endoscopic activity of Crohn's disease with 70% sensitivity and 92% specificity. In another study, CDEIS and Mayo Disease Activity Index (MDAI) were used to evaluate the endoscopic activity of Crohn's disease and ulcerative colitis, respectively. According to the results of that study on IBD patients, there was a significant correlation between fecal calprotectin levels and disease endoscopic activity [68],. Another study showed that fecal calprotectin is more strongly correlated with the endoscopic activity of the disease in ulcerative colitis compared to the Rachmilewitz clinical activity index. In addition, in this study, the overall accuracy of fecal calprotectin for endoscopically active disease identification was obtained as 89% [69],.

Some studies have also shown the superiority of fecal calprotectin over traditional inflammatory markers like CRP. Besides, one study found that fecal calprotectin was more strongly correlated with the Simple Endoscopic Score for Crohn's disease (SES-CD) compared to the CRP and even Crohn's disease activity index (CDAI) [39],. The modified Baron Index was also used in another study to evaluate the endoscopic activity of ulcerative colitis. As a result, it was shown that calprotectin is more strongly correlated with the endoscopic activity of ulcerative colitis compared to CRP and clinical activity of the disease [70],. In this regard, similar results were also observed in our recent study, in which the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) and SES-CD were used [47],. Therefore, fecal calprotectin appears to be superior to traditional inflammatory markers in the prediction of IBD endoscopic activity. The high values of sensitivity and specificity that were mentioned earlier have raised the hope that, using fecal calprotectin can reduce colonoscopy rate for patients' monitoring. However, several recent studies have reported some significantly lower values. Accordingly, in a recent study in which Mayo Endoscopic Score [MES] was used to evaluate the endoscopic activity of ulcerative colitis, a

Table4
summarized results of some meta-analysis regarding the utility of fecal calprotectin in discrimination between patients with IBD and with-out IBD.

Sample size	Pooled Sensitivity	Pooled Specificity	References
5983	95%	91%	[61],
1041	93%	96%	[62],
853	97%	70%	[63],
5032	88%	79%	[64],
715	98%	68%	[65],

Table 3
Summary of the results of some studies regarding the utility of fecal calprotectin in discrimination between patients with IBD and with-out IBD.

Number of IBD patients	Age group	Location	Cut off	Sensitivity	Specificity	AUC	References
58 (CD and UC)	Adults	Taiwan	48(μg/g)	90%	95%	0.931	[58],
72 (CD and UC)	Adults	China	45 (μg/g)	94%	64%	0.949	[59],
24 (CD and UC and unclassified)	Adults	Italy	150(μg/g)	87.5%	90.5%	0.931	[51],
68(CD and UC)	Both adult and pediatric	Spain	150(μg/g)	78.5%	77%	0.872	SPS:refid::bib60,[60]
110 (CD and UC and unclassified)	pediatric	Finland	59.5(μg/g)	81.8%	96.3%	0.944	[44],
30 (CD and UC)	Adults	Iran	78.4(μg/g)	100%	100%	1.00	[47],
117 (CD and UC)	pediatric	Italy	160(μg/g)	100%	80%	0.991	[48],
44 (UC)	Adults	Iran	164(μg/g)	57%	75%	0.670	[52],
40 (CD)	Adults	Denmark	150(μg/g)	85%	81%	0.870	[45],
76 (UC)	Both adult and pediatric	India	188(μg/g)	98%	96%	0.999	[49],

Table 5
Summary of the results of some studies regarding the correlation of fecal calprotectin with endoscopic activity in IBD patients.

Number of IBD patients	Age group	Study location	Used endoscopic activity index	Correlation coefficient (r)	Reference
77 (CD)	Adults	Finland	CDEIS	0.729	[67],
22 (UC)	Adults	Iran	UCEIS	0.798	[47],
134 (UC)	Adults	Switzerland	Rachmilewitz	0.834	[69],
140 (CD)	Adults	Switzerland	SES-CD	0.750	[39],
228 (UC)	Adults	Switzerland	Modified Baron Score	0.821	[70],
31 (UC)	Adults	Germany	Rachmilewitz	0.510	[84],
164 (CD)	Adults	USA and Canada	SES-CD	0.450	[85],
31 (UC)	Adults	Japan	Matts	0.810	[86],
31 (CD)	Adults	Italy	SES-CD	0.480	[87],
46 (UC)	Adults	Italy	Mayo score	0.511	[87],
80 (CD)	Adults	Brazil	SES-CD	0.450	[88],
54 (CD)	Adults	France	CDEIS	0.740	[89],
32 (UC)	Adults	France	Mayo score	0.610	[89],
181 (UC)	Adults	South Korea	UCEIS	0.430	[90],

sensitivity of 69% and a specificity of 65% were reported for fecal calprotectin at 170 μg/g to differentiate active endoscopic from inactive (MES 2 or 3 from MES 0 or 1) [71],. In another study, the sensitivity and specificity of fecal calprotectin at a cutoff of 250 μg/g for differentiating MES ≤ 1 in patients with ulcerative colitis were 67% and 77%, respectively [72],. Overall, as presented in Table 5, several studies performed in different countries reported the correlation between fecal calprotectin and IBD endoscopic activity. Although some of these studies reported a strong correlation, some others reported a relatively weak correlation. As noted earlier, there are significant differences between the reports on the sensitivity and specificity of fecal calprotectin to predict the endoscopic activity of IBD. Undoubtedly, a wide range of factors, from sample size and the inclusion/exclusion criteria to pre-analysis variables and indexes used to evaluate the endoscopic activity, may also contribute to these differences. However, fecal calprotectin does not appear to be a very reliable marker for the prediction of IBD endoscopic activity, so currently it seems a bit optimistic to consider fecal calprotectin as a reliable alternative for colonoscopy. In this regard, further studies are still needed. However, under some certain circumstances such as pregnancy or pandemics, the use of fecal calprotectin to evaluate IBD endoscopic activity can be helpful.

Pregnant patients with IBD have serious limitations for colonoscopy examination, and it has been recommended that colonoscopy should be only performed in the second trimester of pregnancy and where there is a strong indication [73],. Therefore, noninvasive markers such as fecal calprotectin can be helpful during pregnancy. In one study, physician global assessment [PGA], which is a clinical symptom-based criterion, was used to evaluate IBD activity, and subsequently the association between fecal calprotectin and this criterion was investigated in pregnant women with IBD. The results of this study showed a significant correlation between fecal calprotectin and PGA levels at pre-pregnancy, during pregnancy, and postpartum stages [74],. In another study, a significant association was reported between fecal calprotectin levels and clinical activity of IBD in pregnant women. Moreover, it was shown that stool calprotectin at a cutoff of 200 mg/kg had a sensitivity between 69.7% and 80.0% as well as a specificity between 66.7% and 73.3% in the assessment of IBD clinical activity at different stages of pregnancy [75],. A recently published systematic review has also confirmed the conclusions obtained from these studies [76],. According to these results, it seems that fecal calprotectin is not affected by physiological changes during pregnancy; however, it is significantly correlated with IBD clinical activity during pregnancy. Therefore, from the viewpoint of relatively acceptable sensitivity and specificity in predicting the endoscopic activity of IBD, fecal calprotectin may be considered as a noninvasive biomarker for the evaluation of IBD endoscopic activity in pregnant women. In addition, under pandemic conditions, fecal calprotectin can be very helpful. Following the COVID-19 pandemic, which began in late 2019 and is still ongoing, healthcare systems in different countries were forced to impose significant limitations on colonoscopy. Therefore, non-invasive IBD management and fecal calprotectin, as a non-invasive laboratory marker, have become more important than before. The combination between disease clinical activity and fecal calprotectin has been recommended as a non-invasive approach that can help in making decisions on treatment during COVID-19 pandemic [77],. Therefore, it seems that, fecal calprotectin can be considered as an alternative for colonoscopy used for IBD endoscopic activity evaluation during pandemic. Fecal calprotectin appears to be associated with IBD histologic activity, as well. Given the difficulty in the evaluation of the histologic activity of Crohn's disease [78], some studies have been focused on the ulcerative colitis, and many scoring systems have been devised, so far. Correspondingly, these systems score the disease's histologic activity based on histologic observations.

Therefore, for this purpose, a biopsy of the intestinal tissue is required, which can be prepared by colonoscopy and then sent to the laboratory. In this regard, one of these histologic scoring systems is Robert's score that was used in one of our recent studies where we observed a significant correlation between the level of fecal calprotectin and the histologic activity of ulcerative colitis, which was calculated based on the Robert's scoring system [79],. Theede et al. also used the modified Harpaz Index and performed some interesting studies in this regard. In one of their studies, fecal calprotectin was found to be significantly associated with the histologic activity of the ulcerative colitis and it was shown that it could predict histological mucosal healing (AUC 0.898 CI95% 0.837–0.959, Sensitivity 75%, Specificity 90%, and Cutoff 171 mg/kg) [80],. In another study on patients with endoscopically inactive ulcerative colitis (Mayo endoscopic score = 0), the researchers showed that patients with ulcerative colitis who were in endoscopic remission, but had histologically active disease, had higher levels of fecal calprotectin compared to patients with no histologically active disease (236.5 versus 56 mg/kg, P = 0.02). Also, despite the high specificity (100%), the sensitivity of fecal calprotectin in the prediction of score = 0 of histological activity was achieved as 45% at 40.5 mg/kg [81],. In a recent study, the Geboes index has been used to evaluate histologic activity in patients with clinically quiescent ulcerative colitis. As a result, this study reported relatively low sensitivity and specificity for fecal calprotectin in the prediction of Geboes score < 3.1 (54% sensitivity, 69% specificity, and cut off 135 μg/g) [71],. In another recent study, the Nancy Index has been used to evaluate the histologic activity of ulcerative colitis, and a high sensitivity (100%) and a low specificity (48%) were finally reported for fecal calprotectin at a cut-off of 72 μg/g in the prediction of histologic activity [82],. However, some studies have reported both high sensitivity and specificity for fecal calprotectin in the prediction of histological remission. For example, one study reported a sensitivity of 100% as well as a specificity of 77% for fecal calprotectin at a cutoff of 100 μg/g in the prediction of GS < 3.1 [83],. It seems that the cause of these conflicts should be explored in the endoscopic and clinical activity of the disease, the inclusion and exclusion criteria of these studies, and possibly in the different indexes used for the evaluation of the histologic activity of the disease. Another notable issue is that all of these studies have been conducted on a relatively low number of patients with ulcerative colitis, so the need for a study with a large sample size is still strongly felt. Moreover, a large global study may be helpful in this regard.

2.5. Prediction of relapse and response to treatment

As mentioned previously, IBD has recurrence and relief periods, so predicting response to treatment and relapse is one of the significant

challenges in IBD management. The first evidence of the efficacy of fecal calprotectin to predict recurrence dates back to the early 2000s. Accordingly, a study published in 2000 by Tibble et al. is one of the first studies in this regard. In this study, 80 IBD patients in clinical remission were followed up for one year for the assessment of recurrence after preparing a stool sample to measure calprotectin. This study has also shown that fecal calprotectin levels were higher in IBD patients with recurrent disease and it was found that fecal calprotectin had a sensitivity of 90% and a specificity of 83% at a cut-off of 50 mg/L to predict IBD recurrence [91],. In a study published in 2004, Costa et al. showed that the sensitivity and specificity of fecal calprotectin to predict ulcerative colitis recurrence are more than that of Crohn's disease (a sensitivity of 89% and a specificity of 82% versus a sensitivity of 87% and a specificity 43% at a cutoff of 150 μg/g) [92],. Another study conducted on patients with ulcerative colitis has also reported appropriate sensitivity and specificity rates for fecal calprotectin in the prediction of relapse (a sensitivity of 80% and a specificity 89% at a cutoff of 341 μg/g). However, another study was conducted on 64 patients with ulcerative colitis who have been Followed-up for 1 year, and finally a lower sensitivity was reported. This study have shown that fecal calprotectin at cutoff of 250 μg/g could predict disease relapse with 41% sensitivity and 85% specificity [93],. A study on 65 patients with Crohn's disease treated with infliximab and in remission reported a sensitivity of 61% as well as a specificity of 48% for fecal calprotectin at a cutoff of 130 μg/g, to predict the recurrence of Crohn's disease [94],. Meanwhile, another study on 53 patients with Crohn's disease reported higher sensitivity and specificity rates in this regard (a sensitivity of 80% and a specificity 90.7 at a cutoff of 340 μg/g) [95],. In another study on 163 patients with IBD who were followed up for six months, a sensitivity of 69% and a specificity of 69% were reported at a cut-off of 150 μg/g. However, this study showed that only if patients with colonic CD or recurrence within the first 3 months were considered, the sensitivity of fecal calprotectin to predict recurrence would be 100% [96],. In another study on patients with IBD treated with Infliximab, the sensitivity and specificity of fecal calprotectin to predict recurrence at a cut-off of 160 μg/g were obtained as 91.7% and 82.9%, respectively [97],.

In patients treated with anti-tumor necrosis factor (TNF) drugs, sensitivity and specificity were 100% and 80% at a cut-off of 130 μg/g, respectively [98],. However, in a meta-analysis conducted on 6 prospective studies and a total of 672 IBD patients (318 UC patients and 354 CD patients), the sensitivity and specificity of fecal calprotectin to predict IBD recurrence were achieved as 87% and 73%, respectively [99],. In a recent meta-analysis that focused only on ulcerative colitis, 75% sensitivity and 77% specificity were reported for fecal calprotectin in the prediction of disease recurrence [100],. The results of these meta-analyses showed that, although fecal calprotectin measurement is an easy and non-invasive approach, its value in predicting recurrence is less than expected. In addition, it seems that fecal calprotectin has no preference for CRP in the prediction of postoperative endoscopic recurrence in Crohn's disease, and even CRP, despite having a lower sensitivity (57.1% versus 85.7%), has a higher specificity compared to fecal calprotectin in this regard (85.7% versus 45.9%) [101],. It seems that fecal calprotectin can also be effective on predicting the progression of the disease and some events such as surgery and hospitalization. In a recent study performed in the UK, 918 patients with CD were followed up (the median follow-up period was 50.6 months) and disease progression was monitored based on hospitalization, surgery, and Montreal classification system. Finally, a relationship was investigated between fecal calprotectin level and disease progression in 877 of these patients. Accordingly, in this study multivariable Cox proportional hazards analysis showed that long-term increase in disease progression was independently associated with the increased fecal calprotectin levels by passing 3 month or more from the CD diagnosis (HR: 1.49, 1.17–1.89, CI:95%, P:0.001) [102],. Another study on 90 patients with acute severe UC showed that fecal calprotectin levels after admission were higher in patients who required colectomy, compared to patients who did not require it. This study showed that fecal calprotectin in cut off of 1922.5 μg/g could predict the need for surgery with a sensitivity of 24% and a specificity of 97.4% [103],. However, the efficacy of fecal calprotectin in the prediction of some events such as hospitalization has not been adequately studied; therefore, further studies are needed in this regard. Regarding the predictive value of fecal calprotectin for the response of IBD patients to a particular type of treatment, published studies have reported many promising results. For example, one study has indicated that fecal calprotectin levels in IBD patients, after treatment with TNFα Blocking Agents, can predict the risk of clinically active disease in the next year with a sensitivity of 72% and a specificity of 80% [104],.

Given the results of this study, it seems that failure in reducing fecal calprotectin after anti- TNFα therapy may indicate a poor response to this treatment. In another study conducted on patients with acute etiologic ulcerative colitis, it was shown that fecal calprotectin (at a cutoff of 1000 μg/g) on day 3 of corticosteroid therapy could predict response to treatment with 71% and 75% sensitivity and specificity, respectively [105],. In another study, the sensitivity and specificity of fecal calprotectin for the prediction of response to corticosteroid therapy were 84.6% and 60.7% in acute severe ulcerative colitis at a cut-off of 1005 μg/g, respectively [106],. In acute severe ulcerative colitis, corticosteroid therapy is regarded as the first line of treatment, and if treatment fails, rescue therapy or surgery should be performed instead of that. Since some studies have shown that delaying surgery would have some adverse effects on these patients [107], the existence of a biomarker that can predict response to corticosteroid therapy with appropriate sensitivity and specificity, can be beneficial in saving time as well as in selecting the appropriate therapeutic approach. Therefore, the efficacy of fecal calprotectin should be further studied in this regard. Given all the above mentioned reports, fecal calprotectin seems to have relatively good sensitivity and specificity rates in predicting recurrence and response to treatment, especially in ulcerative colitis. Although fecal calprotectin may not be an ideal marker, given the ease of its measurement, it can be considered as a non-invasive predictor of relapse and response to treatment. The results of some interesting studies regarding the fecal calprotectin utility in prediction of relapse in IBD patients are summarized in Table 6.

3. Limitations

Several studies have also shown that fecal calprotectin, as a non-invasive biomarker, may have some potentially useful applications in the diagnosis and management of IBD. However, similar to any other laboratory markers, there are some limitations to be considered. As mentioned in the previous sections, although calprotectin is considered to be highly resistant to proteolysis and capable of holding the sample for up to 7 days at room temperature, it has been recently shown that after six days, fecal calprotectin concentration might decrease by about 35% [27],[115]. In one study, stability remained for three days, and a 28% decrease was also reported in mean calprotectin concentration after seven days of storage at room temperature. The sample isolated with extraction buffer seems to have a much lower stability, and a 46% decrease was also reported in the extracted calprotectin concentration after six days at room temperature [27],. These are some limitations of the pre-analysis that should be considered seriously. To overcome these limitations, it is recommended to keep the stool sample for up to 10 days at 2–8 °C or for one year at −20 °C. The extracted sample also appears to be stable for a 6-month period at −20 °C [116],. In addition, a significant intra-individual fecal calprotectin variability has been reported in IBD patients, which may lead to misdiagnosis [117],. Another limitation to be considered is the effect of certain drugs and some diseases on the concentration of fecal calprotectin. Among these drugs, NSAIDs usage appears to increase the level of fecal calprotectin, and one study has shown that Indomethacin and naproxen can increase

Table 6
Summary of the results of some studies regarding the utility of fecal calprotectin in prediction of relapse in IBD patients.

Number of patients	Age group	Study location	Cut off	Sensitivity	Specificity	Reference
62 (CD and UC)	Pediatric	Netherlands	500 (μg/g)	67%	81%	[108],
79 (CD and UC)	Adults	Italy	150 (μg/g)	89%(UC) 87%(CD)	82%(UC) 43%(CD)	[92],
163 (CD and UC)	Adults	Spain	150 (μg/g)	69%	69%	[96],
73 (CD and UC)	Pediatric	Italy	275 (μg/g)	97%	85%	[109],
53 (CD)	Adults	Tunisia	340 (μg/g)	80%	90.7%	[95],
64 (UC)	Adults	Spain	250 (μg/g)	41%	85%	[93],
80 (UC)	Adults	Japan	170 (μg/g)	76%	76%	[110],
157 (UC)	Adults	Iran	341 (μg/g)	80%	89%	[111],
62 (CD)	Adults	China	225 (μg/g)	69%	78.8%	[112],
65 (CD)	Adults	France	130(μg/g)	61%	48%	[94],
53 (CD and UC)	Adults	Spain	160 (μg/g)	91.7%	81.9%	[97],
95 (CD and UC)	Adults	Spain	130 (μg/g)	100%	80%	[98],
72 (CD and UC)	Pediatric	Finland	82 (μg/g)	38%	80%	[113],
162 (CD and UC)	Adults	Italy	130 (μg/g)	68%	67%	[114],

basal fecal calprotectin concentrations to more than twice [118],. Proton pump inhibitors also appear to be able to increase the fecal calprotectin concentration significantly [119],. The high prevalence of the above-mentioned medications can be considered as a serious limitation for fecal calprotectin. Therefore, in people who regularly consume these medications, the results of a fecal calprotectin test may not be very reliable. The elevated fecal calprotectin levels cannot be solely attributed to IBD, and fecal calprotectin levels may also increase in some other diseases. In this regard, the most important diseases are colorectal cancer, infectious diarrhea, celiac disease, diverticular disease, ankylosing spondylitis, pancreatitis, gastroesophageal reflux disease, and food allergies [120],. Therefore, in interpreting the results of fecal calprotectin test, the presence of the aforementioned diseases should be considered.

4. Conclusion and future direction

According to the results of previous studies, fecal calprotectin can be considered as a biomarker to differentiate between IBS and organic gastrointestinal disorders. However, due to the limitations of pre-analysis, a low fecal calprotectin concentration may not necessarily be considered as the reason for the absence of IBD. Nevertheless, it can be considered as a helpful test due to having relatively high sensitivity and specificity reported for this biomarker to differentiate between IBS and IBD. In the field of monitoring the IBD patients, some studies have reported a significant correlation between fecal calprotectin concentration and the endoscopic and histologic activities of IBD. Despite several promising results, recent studies have reported lower sensitivity and specificity rates for fecal calprotectin to predict endoscopic and histologic remission. Thus, despite its ease of measurement, fecal calprotectin cannot be considered as a reliable alternative for colonoscopy, with the purpose of evaluating IBD endoscopic activity. However, under some conditions such as pregnancy and COVID-19 pandemic, it may be helpful. Pre-analytical variables such as certain drugs or other diseases may have significant effects on the fecal calprotectin test results, and this issue should be considered more seriously in future studies. In recent years, some studies have reported that fecal calprotectin can be used to select treatment strategies. Altogether, given these promising results, which are particularly important regarding acute severe ulcerative colitis, future studies should focus more seriously on evaluating the predictive value of fecal calprotectin in this regard. In addition, investigating the efficacy of fecal calprotectin on some predicting events such as surgery, hospitalization, and disease-related death, can be very helpful.

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Declaration of Competing Interest

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