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Original Article

The Relation between Elevated Stool Calprotectin and Inflammatory Bowel Diseases

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ABSTRACT

Purpose: Inflammatory bowel disease (IBD) is a long-life disease with remission and relapse periods. IBD arises due to an inappropriate immune response and consequently causes inflammation and intestinal ulcers. Performing colonoscopy and inflamed bowel biopsy specimens for histopathological evaluation are currently considered the gold standard for diagnosing and managing IBD. These techniques are costly and invasive. In recent decades fecal calprotectin as a biomarker has received much attention for the diagnosis and non-invasive management of IBD. The aim of this study is to assess the role of elevated fecal calprotectin as a prerequisite to suspect active and relapsed IBD.

Methods: Two hundred patients with endoscopic biopsy-proven IBD were enrolled in this study which was started in January 2021 to December 2023, all patients were negative for HBsAg, anti-HCV, HIV., negative Covid-19 PCR test, normal D-Dimer, normal CRP, normal coagulation profile (PT & INR).

Results: Thirty patients (15%) with a diagnosis of UC (ulcerative colitis) at the time of presentation have high fecal calprotectin > 200 µg/g, and 30 patients (15%) with a diagnosis of UC at relapse have also high fecal calprotectin > 200 µg/g, the remaining 50 patients (25%) with a diagnosis of UC have normal fecal calprotectin < 50 µg/g. Twenty-five patients (12.5%) with a diagnosis of CD (Crohn´s disease) at the time of presentation have high fecal calprotectin > 200 µg/g, and 45 patients (22.5%) with a diagnosis of CD at relapse also have high fecal calprotectin > 200 µg/g, the remaining 20 patients (10%) with a diagnosis of CD have normal fecal calprotectin.

Conclusions: Incorporating fecal calprotectin as a valuable noninvasive biomarker for managing IBD can significantly enhance patient care by providing timely and accurate information on disease activity and treatment response, an alternative to frequent endoscopies or imaging studies.

Keywords: Fecal, calprotectin, IBD, patient, invasive.

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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 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.[2-4]

Ulcerative colitis (UC) and Crohn´s disease (CD) are known as two main forms of IBD. These diseases cause intestinal ulcers and some 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.[5,6] Differential diagnosis is a serious challenge because CD and UC have significant similarities in terms of their clinical, endoscopic, and histological features. In addition to intestinal complications, UC and CD also have significant extra-intestinal manifestations. For example, UC is significantly associated with primary sclerosing cholangitis, and CD is also associated with cholelithiasis, especially in cases where the ileum is involved,[7] Furthermore, CD can cause fistula to the adjacent structures and leading to recurrent 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 manifestation of IBD.[9] The latest statistics show that the global prevalence of IBD currently is on the rise.[10]

According to a report published in 2018, IBD has the highest prevalence rate in Europe. Its prevalence in the newly industrialized countries of Asia, Africa, and South America also appears to have 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 counties for controlling and treating this chronic disease. Now, the gold standard method for diagnosing IBD and monitoring patient status is performing colonoscopy and histopathological evaluation, which are invasive and expensive measures.[13] Therefore, in recent years many studies have been conducted to find a suitable marker with sufficient sensitivity and specificity for non-invasive diagnosing and management of IBD. A high proportion of these studies have investigated the efficacy of fecal calprotectin in diagnosing and monitoring patients.

Calprotectin is an antimicrobial protein mainly secreted by neutrophils, this protein competes with bacteria over zinc, thus killing the bacteria.

However, this is not the only antimicrobial activity but also this protein has many clinical applications.

MATERIALS AND METHODS

A retrospective study was conducted at the Gastroenterology Department in Tripoli University Hospital from January 2021 to December 2023 where two hundred patients with endoscopic proven IBD were enrolled in this study (110 UC & 90 CD) with different presentations and from different out-patient clinics (indoor and outdoor the hospital). Eligible subjects of either gender or all ages, who agreed to participate in the study with a consent form, were included.

Detailed clinical examination of each patient was done and each patient underwent an endoscopy (gastroscopy/colonoscopy) in a standard way after getting written consent and necessary investigations like hemoglobin level, and blood group, all patients should have negative viral serology, negative COVID-19 PCR test, normal D-Dimer, normal CRP, normal coagulation profile (PT & INR). Endoscopic biopsies were taken for histopathological examinations and the decision to perform an endoscopic biopsy for each patient was made on an individual basis.

Fecal calprotectin level was sent for all patients, and serology for ASCA and ANCA also was sent. The medical records of these patients were reviewed and the relevant data for this study was obtained and the predesigned case sheet was completed.

Data was analyzed using a statistical program (SPSS) version 16. Descriptive statistics were used as mean, SD, and %, Chi-square test was used for categorical data $p< 0.05$ considered significant.

RESULTS

During the study period from January 2021 to December 2023 200 patients with histological biopsy-proven IBD (110 UC & 90 CD) were enrolled in this study.

From these 200 patients, 70 patients (35%) were asymptomatic (in remission) and 130 patients (65%) were symptomatic (Table 1) in which 60 patients (30%) were UC presented with frequent rectal bleeding, diarrhea with mucus, and occasionally abdominal pain. The other 70 patients (35%) were CD presented with frequent abdominal pain, fever, intestinal obstruction, perineal disease, and post-operative recurrence. These symptomatic patients have active disease present at the presentation or the relapse of the IBD.

Table 1: IBD patients number and percentage (types &symptoms).

Character	No. & %
IBD patients (UC & CD)	200 (100)
Asymptomatic (in remission)	70 (35%)
Symptomatic (at presentation	130(65%)
Ulcerative colitis (UC)	110 (55%)
Crohn's disease (CD)	90 (45%)

Thirty patients (15%) with a diagnosis of UC at the time of presentation have high fecal calprotectin > 200 µg/g, and 30 patients (15%) with a diagnosis of UC at relapse have also high fecal calprotectin > 200 µg/g, the remaining 50 patients (25%) with a diagnosis of UC have normal fecal calprotectin < 50 µg/g (Table 2).

Table 2: Relation between UC and fecal calprotectin.

Character	Fecal calprotectin
Thirty Patients (15%) UC at presentation	.> 200 µg/g
Asymptomatic 50 (25%)UC (in remission)	<50 µG/G
Thirty patients (15%) at relapse	> 200µg/g

Twenty-five patients (12.5%) with a diagnosis of CD at the time of presentation have high fecal calprotectin > 200 µg/g, and 45 patients (22.5%) with a diagnosis of CD at relapse have also high fecal calprotectin > 200 µg/g, the remaining 20 patients (10%) with a diagnosis of CD have normal fecal calprotectin (Table 3).

Table 3: Relation between CD and fecal calprotectin.

Character	Fecal calprotectin
Twenty-five patients (12.5%) CD at presentation	.> 200 µg/g
Asymptomatic 20 patients (10%) CD (in remission)	<50 µG/G
Forty-five patients (22.5%) CD at relapse	>200 µg/g

This study demonstrates that 130 patients out of 200 patients (65%) with a histological biopsy-proven IBD have a high fecal calprotectin >200 µg/g either at the disease presentation or its relapse, and the remaining 70 patients (35%) have a normal fecal calprotectin < 50 µg/g at the time of remission, this shows that there is a significant relation between fecal calprotectin and activity of IBD, the chi-square test was applied to test if there is any relation between fecal calprotectin and IBD activity (p=0.016). moreover, there is a significant correlation in IBD patients between active disease and fecal

DISCUSSION

During the study period from January 2021 to December 2023 at the Gastroenterology Department of Tripoli University Hospital a total of 200 patients with histologically proven biopsy of IBD (110 UC&90 CD) with different presentations and from different departments and outpatient clinics, 120 patients were males (60%), 80 patients were females (40%), and male to female ratio was 3:2, and mean age of patients was 40±25 years.

Table 4: Reported median level of fecal calprotectin of different ages.

Ages	Median level of Fecal calprotectin	Number of subjects	Used Kit
Children (1-4 years)	83.1-419 µg/g	274	ELISA
Children (4-12 years)	25-35 µg/g	159	CALPRO
Children (12-18 years)	150-200 µg/g	230	ELISA
Adults (18-60 years)	34-50 µg/g	45	Phi Cal
Adults over 60 years	27-118 µg/g	20	Phi Cal

Regarding age, one of the most serious challenges to the laboratory of fecal calprotectin is the determination of the upper limit in healthy individuals. Among healthy adults, there is a significant agreement on (50µg/g) as an upper limit, one study suggested values up to (118 µg/g) in people over 60 years old and up to (200 µg/g) in children aged 12 to 18 years old.[14] Table 4 lists the median level of fecal calprotectin in healthy individuals of different ages.

Only a small percentage of patients complaining of abdominal pain and diarrhea have IBD. In many cases, IBS (Irritable Bowel Syndrome) as a functional gastrointestinal disorder is known as the cause of such symptoms, patients with IBS have normal colonoscopy results while IBD have abnormal colonoscopy results with 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 despite fecal calprotectin not specific for IBD.

Of these 200 patients, 70 patients (35%) were asymptomatic (in remission) and 130 patients (65%) were symptomatic (active disease) either at the time of presentation or relapse.

In our study, thirty patients (15%) with a diagnosis of UC at the time of presentation have high fecal calprotectin > 200 µg/g, and 30 patients (15%) with a diagnosis of UC at relapse have also high fecal calprotectin > 200 µg/g, the remaining 50 patients (25%) with a diagnosis of UC remission have normal fecal calprotectin < 50 µg/g (Table 2).

Twenty-five patients (12.5%) with a diagnosis of CD at the time of presentation have high fecal calprotectin > 200 µg/g, and 45 patients (22.5%) with a diagnosis of CD at relapse have also high fecal calprotectin > 200 µg/g, the remaining 20 patients (10%) with a diagnosis of CD have normal fecal calprotectin (Table 3).

Our study results showed a significant correlation in IBD patients between high fecal calprotectin levels and active disease. Fecal calprotectin is a stable protein that remains stable for 4-7 days at room temperature,[15] also it seems that keeping the specimen at refrigerated temperature (4ºC) can increase the stability of fecal calprotectin,[16] the first evidence of the efficacy of fecal calprotectin in the diagnosis of IBD was obtained in the 1990s. Roseth et al.in 1992 proposed a method for measuring calprotectin in stool specimens.[17] One of the first and most interesting studies regarding fecal calprotectin utility in IBD diagnosis was the study by Roseth et al published in 1997. This study has also shown that even patients with low disease activity had higher levels of fecal calprotectin compared to healthy individuals.[18]

In a 2017 study done with 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, in another study conducted in 2018 on 76 patients with UC, a sensitivity of 98% and a specificity of 96% at a cut-off of 188 µg/g have reported in this regard.

The results of our 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.[19]

Therefore, fecal calprotectin helps rule out the possibility of IBD in patients with IBS-like symptoms as well as reducing the rate of colonoscopy, with a sensitivity and specificity above 90% for fecal calprotectin to differentiate between IBD and IBS [20], also helpful in the evaluation of the endoscopic and histological activity of the disease, and prediction of disease recurrence and response to treatment.

Pregnant patients with IBD have serious limitations for colonoscopy done only in the second trimester where there is a strong indication. [21] Therefore, non-invasive fecal calprotectin is helpful during pregnancy.

CONCLUSIONS

Incorporating fecal calprotectin as a valuable non-invasive biomarker for the management of IBD can significantly enhance patient care by providing timely and accurate information on disease activity and treatment response, and it provides a non-invasive alternative to frequent endoscopies or imaging studies, thus reducing the burden on patients.

REFERENCES

1. Abraham C. Cho J.H. Inflammatory bowel disease. N. Engl. J. Med. 2009; 361:2066-2078. Doi: 10.1056/NEMra0804647. PubMed PMID:19923578; PubMed Central PMCID: PMCPMC3491806.
2. Tamboli C. P. Neut C. Desreumaux P., Colombel J.F. Dysbiosis in inflammatory bowel disease. Gut. 2004; 53:1-4. Doi:10.1136/gut.53.1.1. PubMed PMID:14684564; PubMed Central PMCID: PMCPMC1773911.
3. Vaghari Tabari M., Moein S., Qujeq D., Kashifard M., Shokri Shirvani J., Hajian Tilaki K., et al. Evaluation of the potential antioxidant role of high-density lipoprotein-e A., cholesterol (HBL-C) in patients with ulcerative colitis. Ann Colorectal Res. 2017;5: e13699. Doi: 10.5812/acr.13699.
4. Zeng Z., Mukherje A., Zhang H. From genetics to epigenetics, roles of epigenetics in inflammatory bowel disease. Front. Genet. 2019; 10:1017. Doi: 10.3389/fgene.2019.01017. PubMed PMID:31737035; PubMed Central PMCID: PMCPMC6834788.
5. Carter M.J., Lobo A.J., Travis S .P. Guidelines for the management of inflammatory bowel disease in adults. Gut. 2004;53(Suppl 5): V1-V16. Doi: 10.1136/gut.2004.043372. PubMed PMID: 15306569; PubMed Central PMCID: PMCPMC1867788.
6. Mowat C., Cole A., Windsor A., Ahmad T., Arnott I., Driscoll R., et al. Guidelines for the management of inflammatory bowel disease in adults. Gut. 2011; 60:571-607. Doi: 10.1136/gut.2010.224154. PubMed PMID: 2146096.
7. Levine J.S., Burakoff R. Extraintestinal manifestation of inflammatory bowel disease. Gastroenterol. Hepatol. (N Y). 2011; 7:235-241. PubMed PMID: 21857821; PubMed Central PMCID: PMCPMC3127025.
8. Solem C.A., Lofus E.V., Jr., Tremaine W. J., Pemberton J.H., Wolf B.G., Sandborn W.J. Fistulas to the urinary system in Crohn´s disease: clinical features and outcomes. Am.J. Gastroenterol. 2002; 97:2300-2305. Doi: 10 .1111/j. 1572-0241.2002.05983. x. PubMed PMID: 12358248.
9. Antunes C.V., Hallack Neto A.E., Nascimento C.R. Chebli L.A., Moutinho I.L., Pinherio Bdo V., et al. Anemia in inflammatory bowel disease out-patients: prevalence, risk factors, and etiology. Biomed. Res. Int. 2015; 2015:728925.
10. Sykora J., Pomahacova R., Kreslova M., Cvalinova D. Stych P. Schwarz J. Current global trends in the incidence of pediatric-onset inflammatory bowel disease. World J. Gastroenterol. 2018; 24:2741-2763.
11. Ng S.C., Shi H.Y. Hamidi N., Underwood F.E., Tang W., Benchimol E.I., et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2018; 390:2769-2778. Doi: 10.1016/s0140-6736(17)32448-0. PubMed PMID: 29050646.
12. Johnston R.D., Logan R.F. What is the peak age for onset of IBD? Inflamm. Bowel Dis. 2008;14(Suppl 2): S4-S5. Doi: 10.1002/ibd. 20545. PubMed PMID:18816745.
13. Bharadwaj S., Narula N., Tandon P., Yaghoobi M. Role of endoscopy in inflammatory bowel disease. Gastroenterol. Rep. (oxf). 2018; 6:75-82.
14. Joshi S. Lewis S.I., CreanorS., S.J., Creanor S., Aling R, M. Age-related fecal calprotectin, lactoferrin, and tumor M2-PK concentration in healthy volunteers. Ann.Clin. Biochem. 2010; 47:259-263. Doi: 10.1258/acb.2009.009061. PubMed PMID: 19740914.
15. Naess-Andresen C.F., Egelandsdal B., Fagerhol M.K. Calcium binding and concomitant changes in the structure and heat stability of calprotectin (L1 protein) Clin Mol Pathol. 1995;48:M278-M284.
16. Haisma S.M., Van Rheenen P.F., Wagenmakers L., Muller K.A. Calprotectin instability may lead to undertreatment in children with IBD. Arch. Dis. Child. 2019 doi: 10.1136/archdischild-2018-316584. PubMed PMID: 30655264.

17. Haisma S.M., Van Rheenen P.F., Wagenmakers L., Muller K.A. Calprotectin instability may lead to undertreatment in children with IBD. Arch. Dis. Child. 2019 doi: 10.1136/archdischild-2018-316584. PubMed PMID: 30655264.

18. Roseth A.G., Fagerhol M.K., Aadland E., Schjonsby H. Assessment of the neutrophil dominating protein calprotectin in feces. A methodologic study. Scand J. Gastroenterol. 1992; 27:793-798. Doi: 10.3109/00365529209011186. PubMed PMID: 1411288.

19. Roseth A.G., Aadland E., Jahnsen J., Raknerud N. Assessment of disease activity in ulcerative colitis by fecal calprotectin, a novel granulocyte marker protein. Digestion. 1997; 58:176-180. Doi: 10.1159/000201441. PubMed PMID: 9144308.

20. Moein S., Qujeq D., Vaghari Tabari M., Kashifard M., Hajian-Tilaki K Diagnostic accuracy of fecal calprotectin in assessing the severity of inflammatory bowel disease: From laboratory to clinic. Caspian J, Int. Med. 2017;8:178-182. Doi: 10.22088/cjm.8.3.178. PubMed PMID: 28932369; PubMed Central PMCID: PMCPMC5596188.

21. Waugh N., Cummins E., Royle P., Kandala N.B., Shyangdan D., Arasaradnam R., et al. Fecal calprotectin testing for differentiating amongst inflammatory and non-inflammatory bowel disease: systemic review and economic evaluation. Health Technol. Assess. 2013:17 doi: 10.3310/hta17550. Xv-xix, 1-211. PubMed PMID: 24286461; PubMed Central PMCID: PMCPMC4781415.

22. Shergil A.K., Ben-Menachen T., Chandrasekhara V., Chathadi K., Decker G.A., Evans J.A., et al. Guidelines for endoscopy in pregnant and lactating women. Gastrointest. Endosc. 2012; 76:18-24. Doi: 10.1016/jgie. 2012.02.029. PubMed: 22579258.