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Evaluation of serum human galectin 3 as a marker of activity in inflammatory bowel disease in comparison to fecal calprotectin

Mohamed M. Salama[1], Moataz M. Sayed[1], Mohamed A. Saad[1], Nancy Z. Ali[1], Marwa A. Abdelwahed[2] and Hagar A. A. Elessawy[1]

[1]Departement of Internal Medicine, Gastroenterology & Hepatology Unit, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

[2]Departement of Clinical Pathology, Faculty of Medicine - Ain Shams University, Cairo, Egypt

Corresponding author: Nancy Z. Ali, Department of Internal Medicine, Gastroenterology & Hepatology Unit, Faculty of Medicine, Ain Shams University, Cairo, Egypt.
Email: cute_doctor_90@yahoo.com

Abstract

Inflammatory Bowel Disease (IBD) is a chronic and recurring inflammatory condition of the gastrointestinal system that has an unknown cause and is marked by periods of relapse and remission. Endoscopy remains the gold standard for assessing disease activity; however, noninvasive biomarkers are needed to reduce the burden of repeated invasive procedures. This study aimed to evaluate the role of serum galectin 3 as a biomarker of disease activity in IBD and compare its performance with fecal calprotectin. The study included 40 individuals who were diagnosed with active IBD ulcerative colitis (UC) or Crohn's disease, and 40 age and sex matched normal controls. Clinical assessment and laboratory investigations which included complete blood picture, C-reactive protein, fecal calprotectin, serum albumin and serum galectin 3 were measured and analyzed. Serum galectin 3 levels were higher in patients with active UC than in clinical remission patients (p<0.001) and higher in patients with Crohn's disease (p<0.001). In clinical, remission patients without full mucosal healing, serum galectin 3 was positively correlated with endoscopic disease activity represented with Mayo score, Mayo endoscopic sub-score and Ulcerative Colitis Endoscopic Index of Severity (p<0.001). The cut off value of serum galectin 3 for determining disease activity was >5.199 µg/ml with 100 % sensitivity, 92 %, specificity and accuracy of 99.6%.The combined use of Serum galectin 3, CRP and fecal calprotectin improved the performance, achieving 100% sensitivity and specificity. In conclusion, serum galectin 3 is a promising noninvasive biomarker for assessing disease activity in patients with IBD. Combined assessment with CRP and fecal calprotectin may further enhance the diagnostic accuracy

Keywords: IBD, biomarkers, fecal calprotectin, serum galectin 3.

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Introduction

Inflammatory bowel disease (IBD) is a chronic and recurrent inflammatory disorder of the gastrointestinal tract that results in persistent harm to the structure and function of the digestive system. IBD is currently believed to be caused by changes in the function of the protective layer of cells in the intestines and an inappropriate immune response in individuals who have a genetic susceptibility. The disease occurs due to a complex interaction between environmental factors, normal bacteria in the intestines, and the immune system in the colon, or a weakened protective layer of cells.[1, 2]

Crohn's disease is a type of IBD that may affect any segment of the gastrointestinal tract. At which the terminal ileum, the area most commonly affected by the illness, inflammation caused by Crohn's disease can involve different areas of the digestive tract in different people, most commonly the small intestine. This inflammation often spreads into the deeper layers of the bowel. [3]

The colonic mucosa can be affected by IBD, an inflammatory disorder that manifests as a relapsing and remitting pattern throughout time. Current therapy aims for IBD include promoting mucosal repair and anticipating dysplastic alterations, as opposed to merely obtaining and maintaining clinical remission.[4, 5]

Endoscopic evaluation is the most accurate way to assess IBD activity. The location, extent and severity can be established with this procedure, but its use is prevented by several drawbacks, as it's costly, takes a lot of time, and invasive.[6,7] Accurately detecting inflammation and monitoring disease progression in IBD patients requires the identification of new, non-invasive, and trustworthy serum biomarkers. So far, the two most extensively researched inflammatory indicators are C-reactive protein (CRP) and fecal calprotectin (FC). Although there is a link between CRP and endoscopic activity indices, the current evidence is insufficient to justify its application in IBD.[8] Although FC has shown promising outcomes, further research is needed to establish suitable cut-off levels for clinical practice-wide implementation [9, 10, 11] Therefore, novel biomarkers are still required to identify intestinal inflammation in IBD patients.

Various human cell types, including immune and epithelial cells, exhibit the expression of a group of proteins known as galectins. The galectin family comprises galectins-1, -2, -3, -4, and -8, which were observed to be present in the human intestinal epithelium.[9] Colon cancer patients have much greater serum levels of galectins compared to normal individuals.[10] These levels encourage the homogenous dispersion of tumor cells in metastasis. The etiology and progression of IBD is linked to the initiation of T cell programmed cell death and the stimulation of Nuclear Factor kappa-light-chain-enhancer of activated B cells signaling. This occurs through the interaction between galectins and galactose-terminated glycans on cell surfaces, which transmit signals.[12, 13, 14] Researchers found that IBD patients had a greater serum galectin-3 level than normal controls. This suggested that serum galectins 3 may have diagnostic utility in identifying IBD and disease progression. [(15, 16, 17, 18)] Therefore, we conducted this study to investigate the role of human serum galectin 3 as an indirect measure of activity in IBD, in comparison to FC.[19, 20]

Subjects and Methods

Study design

The IBD clinic at Ain Shams University Hospital in Cairo, Egypt, was the site of this case-control study that ran from November 2022 to November 2023. We consecutively enrolled 40 adult patients "≥18 years" diagnosed by clinical criteria and colonoscopy with biopsy as IBD. They were presented with suffering from any of the following: fever, bleeding per rectum, diarrhea, abdominal pain, or extra intestinal manifestations. A control group of 40 apparently healthy participants with matched age and sex were also recruited.

The exclusion criteria included pregnancy, indeterminate colitis, infectious colitis, urinary incontinence (to avoid contamination of fecal samples), prior colorectal surgery, in recent

times, previous use of non-steroidal anti-inflammatory drugs at a dosage of 2 tablets per week, recent use of steroids enemas or oral steroids within the past three months, initiation of azathioprine treatment within the past three months, and primary immunodeficiency.

Data collection

The research participants filled out an organized data form that inquired about their health history, physical exam results, and laboratory testing done at baseline. The ulcerative colitis (UC) endoscopic Mayo score was utilized to evaluate the level of disease activity.[20] Serum and feces samples were taken from each study participant. We measured FC, C-reactive protein, complete blood count (CBC), serum albumin, and serum galectin 3 in both groups.

The Mayo score for clinical activity of ulcerative colitis has four elements: rectal bleeding, stool frequency, physician assessment, and endoscopic appearance. The rating for each individual component spans from 0 to 3, leading to a total score ranging from 0 to 12. A score of 3 to 5 points indicated a condition with mild activity, while a score of 6 to 10 points indicated a condition with moderate activity. A score of 11 to 12 points indicated a condition with high activity.

C-reactive protein (CRP) test was done by latex agglutination kit. The test is based on agglutination of latex particles coated with antihuman CRP antibodies when mixed with serum containing CRP, producing visible agglutination within 2 minutes.

Enzyme immunoassay

Serum levels of galectin 3 were measured using a commercially available ELISA kits (provided by R&D Systems, located in Minneapolis, MN, USA), following the instructions provided by the manufacturer.

Fecal calprotectin:

A point-of-care desk-top device (the Quantum Blue Reader®, Calprotectin, Bühlmann Laboratories AG in Switzerland) was used to evaluate the amounts of calprotectin in feces samples. This is an ELISA-based lateral flow approach. We followed all of the instructions on the package to run the test. The internal standards used by the Point of Care (POC) device have a detectable range of 30-300 µg/g and 300 µg/g sensitivity. We used an extraction buffer to dilute the solution 1:10 as per the manufacturer's instructions. Achievement of FC levels up to 3000 µg/g was made possible by this method. There were 3000 µg/g and 30 µg/g recorded FC values that went outside the measurement ranges, respectively.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) program, IBM version 23, was used to examine the data. The Shapiro-Wilk test was used to determine if the numerical data followed a normal distribution. The median and interquartile ranges were used to display the numerical data that did not follow a normal distribution. Disparities between two groups were evaluated using the Wilcoxon rank sum test, while discrepancies between multiple ranked groups were evaluated using the Jonckheere-Terpstra trend test. In cases where the Jonckheere-Terpstra test showed a statistically significant difference between the groups, the Bonferroni correction was applied; post hoc comparisons were conducted using the Conover post hoc test. When comparing nominal data, we utilized the Fisher's exact test; when comparing ordinal data, we employed the chi-squared test for trend. Numeric, percentage, or ratio representations were used for the category data. The receiver-operating characteristic (ROC) curve analysis was used to assess the diagnostic effectiveness of serum Trefoil Factor 3. A $p< 0.05$ was considered significant.

Results

A total of 40 patients with IBD and 40 age- and sex-matched normal controls were included in this study. The mean age of IBD patients was 40 ± 12.7 years, and 24 patients (60%) were males. The study included 23 UC cases and 17 with Crohn’s disease. According to the Clinical Mayo Score for disease activity, 12 patients (30%) had mild activity, 26 patients (65%) with moderate activity, and 2 patients (5%) had severe disease activity, (Table 1).

Table 1. Characteristics of the inflammatory bowel disease (IBD) patients enrolled in the study.

Studied parameters	UC
Age, mean±SD	40 ± 12.7
Gender, n (%)	
Male	24 (60%)
Female	16 (40%)
Smoking habit, n (%)	
Smoker	16 (40%)
Non-smoker	24 (60%)
Family history of IBD, n (%)	
Yes	2 (5%)
No	38 (95%)
Extra-intestinal manifestations, n (%)	
Yes	3 (7.5%)
No	37 (92.5%)
Disease severity	
Mild	12 (30%)
Moderate	26 (65%)
Severe	2 (5%)

IBD: Inflammatory bowel disease. UC: ulcerative colitis ()

Patients with active IBD showed significantly higher levels of serum galectin-3 and fecal calprotectin compared with normal controls (p<0.001 for both). The mean fecal calprotectin level among UC patients was 241 ± 75.6 µg/g. Serum galectin-3 levels were significantly elevated in patients with active UC compared with controls (p< 0.001).

The mean fecal calprotectin level among Crohn's disease patients was 255 ± 66.4 µg/g. Serum galectin-3 levels were significantly elevated in patients with active Crohn's disease compared with controls (p<0.001).

Data analysis demonstrated a strong positive correlation between serum galectin-3 and fecal calprotectin levels (r=0.873, p<0.001). Serum galectin-3 showed a significant negative correlation with serum albumin levels (r=-0.428, p=0.006). In addition, serum galectin-3 was positively correlated with the Clinical Mayo Score (r=0.492, p=0.001) and Endoscopic Mayo Score (r=0.403, p=0.010).

Similarly, fecal calprotectin showed a significant negative correlation with serum albumin (r = -0.331, p = 0.037) and significant positive correlations with Clinical Mayo Score (r = 0.451, p = 0.003) and Endoscopic Mayo Score (r = 0.341, p = 0.031). No significant correlations were observed between serum galectin-3 or fecal calprotectin levels with age, hemoglobin concentration, total leukocyte count, platelet count, or Montreal classification (p>0.05), (Table 2).

Table 2. Correlation between fecal calprotectin and serum galectin-3 levels with other clinical variables in ulcerative colitis (UC) patients.

	Ulcerative colitis (UC)			
	Fecal Calprotectin		Serum Galectin-3	
	r	*p* value	r	*p* value
Fecal Calprotectin			0.873	<0.000
Age	-0.049	NS	-0.106	NS
Hemoglobin	-0.260	NS	-0.249	NS
TLC	0.165	NS	0.272	NS
Platelets	0.189	NS	0.156	NS
serum albumin	-0.331	<0.037	-0.428	<0.006
CRP	0.160	NS	0.232	NS
Clinical Mayo score / HPI	0.451	<0.003	0.492	<0.001
Endoscopic Mayo score	0.341	<0.031	0.403	<0.010
Montreal score	0.246	NS	0.220	NS

r= spearman correlation. p > 0.05 is not significant (NS).

The receiver operating characteristic (ROC) curve analysis demonstrated excellent diagnostic performance of serum galectin-3 in differentiating patients with active IBD from normal controls. The optimal cutoff value was >94.8 ng/ml, providing a sensitivity of 100% and a specificity of 97.5%, (Figure 1).

Fecal calprotectin also showed high diagnostic accuracy in detecting IBD disease activity. Furthermore, the combined use of serum Galectin-3, CRP, and fecal calprotectin achieved the highest diagnostic performance, with sensitivity and specificity reaching 100%.

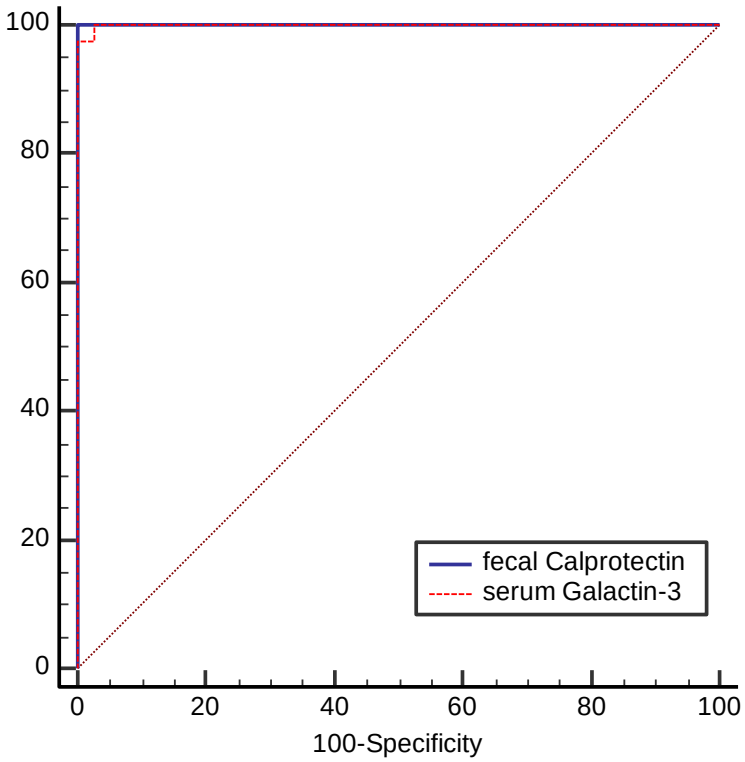

Figure 1. Receiver-operating characteristic (ROC) curve of fecal calprotectin and serum galectin to differentiate UC patients from controls

Discussion

The present study evaluated the potential role of serum galectin-3 as a biomarker of IBD disease activity in patients and compared its diagnostic performance with fecal calprotectin. Our findings demonstrated significantly higher serum galectin-3 levels in patients with active IBD compared with normal controls. Furthermore, serum galectin-3 showed a significant positive correlation with fecal calprotectin, clinical Mayo score, and endoscopic Mayo score, suggesting its potential utility as a marker of disease activity.[21-24]

The elevated serum galectin-3 levels observed in the current study may be explained by the important role of galectin-3 in inflammatory and immune-mediated pathways. galectin-3 is known to participate in leukocyte activation, macrophage recruitment, cytokine production, and regulation of apoptosis. These biological functions contribute to the persistence and amplification of intestinal inflammation in IBD.[25,26]

Our findings are consistent with previous studies that reported increased serum galectin-3 levels in patients with active inflammatory bowel disease. For instance Nakov et al., 2019

and Wang et al., 2021, demonstrated that galectin-3 levels were significantly elevated in active disease and correlated with disease severity. Similarly, Yang et al., 2020, reported that Galectin-3 may serve as a useful non-invasive biomarker reflecting intestinal inflammatory activity.[27,28]

In the present study, serum galectin-3 showed a strong positive correlation with fecal calprotectin. Fecal calprotectin is currently considered one of the most reliable non-invasive biomarkers of intestinal inflammation. Therefore, the observed association further supports the validity of galectin-3 as a marker of disease activity. This finding suggested that elevated serum galectin-3 levels reflect the underlying inflammatory burden in patients with IBD. We also found significant correlations between serum galectin-3 levels and both clinical and endoscopic disease activity scores. Since endoscopic assessment remains the gold standard for evaluating IBD disease activity, the correlation between galectin-3 and endoscopic severity, strengthens the potential clinical value of this biomarker. The ability of galectin-3 to reflect endoscopic activity may help reduce the need for repeated invasive procedures in selected patients.[29,30]

The ROC curve analysis demonstrated excellent diagnostic performance of serum galectin-3 in distinguishing active IBD from normal controls. The identified cutoff value (>94.8 ng/ml) provided high sensitivity and specificity. Moreover, combining serum galectin-3 with CRP and fecal calprotectin further improved the diagnostic accuracy, suggesting that a multi-marker approach may provide superior assessment of disease activity compared with the use of a single biomarker alone. From a clinical perspective, serum galectin-3 offers several advantages. It can be measured using a simple blood sample, which is minimally invasive, and may provide additional information regarding inflammatory activity. Therefore, it could represent a practical adjunctive tool for monitoring disease activity and treatment response in patients with IBD.

The strengths of the present study include the simultaneous assessment of serum galectin-3, fecal calprotectin, and CRP, in addition to the use of both clinical and endoscopic activity indices. However, several limitations should be acknowledged. These include that the study was conducted at a single center with a relatively small sample size. In addition, serum Galectin-3 was measured at a single time point, preventing assessment of longitudinal changes during disease progression and treatmeng. Larger multicenter prospective studies are needed to validate these findings and establish the role of galectin-3 in clinical routine.

Author Contributions

All authors certify that they participated in this work including participation in study design, collecting data, analysis and interpretation of data, practical part and writing manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

The study protocol was reviewed and approved by the Research Ethical Committee of the Faculty of Medicine, Ain Sham University..

Informed consent

Before being enrolled in the study, all participants provided a written informed consent.

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