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ABOUT COVER

Naoki Tanaka, MD, PhD, Professor, International Relations Office, Department of Metabolic Regulation, Shinshu University School of Medicine, Matsumoto 390-8621, Nagano, Japan. naopi@shinshu-u.ac.jp

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ORIGINAL ARTICLE

Observational Study

Serum 1,3-beta-D-glucan as a noninvasive test to predict histologic activity in patients with inflammatory bowel disease

Katia Farias e Silva, Hayandra F Nanini, Cynthia Machado Cascabulho, Siane L B Rosas, Patricia T Santana, Antonio José de V Carneiro, Elias Anaissie, Marcio Nucci, Heitor Siffert Pereira de Souza

ORCID number: Katia Farias e Silva 0000-0003-2590-9053; Hayandra F Nanini 0000-0001-6866-7619; Cynthia Machado Cascabulho 0000-0001-6432-6657; Siane L B Rosas 0000-0002-4814-0868; Patricia T Santana 0000-0001-7888-5249; Antonio José de V Carneiro 0000-0002-4601-0971; Elias Anaissie 0000-0003-0880-9536; Marcio Nucci 0000-0003-4867-0014; Heitor Siffert Pereira de Souza 0000-0002-3647-7324.

Author contributions: Farias e Silva K and Carneiro AJV participated in the conception and design of the study, the acquisition, analysis, and interpretation of data, and the drafting of the manuscript; Nanini HF, Cascabulho CM, Rosas SLB, and Santana PT participated in the acquisition, analysis, and interpretation of data; Anaissie E conceptually proposed the idea of gut inflammation and high 1,3-Beta-D-glucan levels and critically revised the manuscript; Nucci M and de Souza HSP participated in the conception and design of the study, obtained funding, analyzed and interpreted the data, and critically revised the manuscript for important intellectual content; all the authors gave final approval of the submitted version of the manuscript.

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Katia Farias e Silva, Hayandra F Nanini, Siane L B Rosas, Patricia T Santana, Antonio José de V Carneiro, Marcio Nucci, Heitor Siffert Pereira de Souza, Department of Clinical Medicine, School of Medicine, Federal University of Rio de Janeiro, Rio de Janeiro 21941-913, Brazil

Cynthia Machado Cascabulho, Laboratory of Innovations in Therapies, Education and Bioproducts, Instituto Oswaldo Cruz, Rio de Janeiro 21040-360, Brazil

Elias Anaissie, Clinical Trial and Consulting Services, Cincinnati, OH 45267, United States

Heitor Siffert Pereira de Souza, Internal Medicine, D'Or Institute for Research and Education (IDOR), Rio de Janeiro 22281-100, Brazil

Corresponding author: Heitor Siffert Pereira de Souza, MD, PhD, Associate Research Scientist, Full Professor, Department of Clinical Medicine, School of Medicine, Federal University of Rio de Janeiro, Rua Prof. Rodolpho Paulo Rocco 255, Cidade Universitaria, Rio de Janeiro 21941-913, Brazil. hsouza@hucff.ufrj.br

Abstract

BACKGROUND

1,3-beta-D-glucan (BG) is a ubiquitous cell wall component of gut micro-organisms. We hypothesized that the serum levels of BG could reflect active intestinal inflammation in patients with inflammatory bowel disease.

AIM

To determine whether the serum BG concentrations correlate with intestinal inflammation.

METHODS

A prospective observational study was performed in a tertiary referral center, from 2016 to 2019, in which serum BG was determined in 115 patients with Crohn's disease (CD), 51 with ulcerative colitis (UC), and 82 controls using a photometric detection kit. Inflammatory activity was determined by ileocolonoscopy, histopathology, magnetic resonance enterography, and biomarkers, including fecal calprotectin (FC), C-reactive protein, and a panel of cytokines. The ability of BG to detect active *vs* inactive disease was assessed using the area under the receiver operating characteristic curve. In subgroup analysis, serial BG was used to assess the response to therapeutic interventions.

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RESULTS

The serum BG levels were higher in CD patients than in controls (P = 0.0001). The BG levels paralleled the endoscopic activity in CD patients and histologic activity and combined endoscopic and histologic activity in both CD and UC patients. The area under the curve (AUC) in receiver operating characteristic analysis to predict endoscopic activity was 0.694 [95% confidence interval (CI): 0.60-0.79; P = 0.001] in CD, and 0.662 (95%CI: 0.51-0.81; P = 0.066) in UC patients. The AUC in receiver operating characteristic analysis to predict histologic activity was 0.860 (95%CI: 0.77-0.95; P < 0.001) in CD, and 0.786 (95%CI: 0.57-0.99; P = 0.015) in UC patients. The cut-off values of BG for both endoscopic and histologic activity were 60 μg/mL in CD, and 40 μg/mL in UC patients. Performance analysis showed that the results based on BG of 40 and 60 μg/mL were more specific for predicting endoscopic activity (71.8% and 87.2% for CD; and 87.5% and 87.5% for UC, respectively) than FC (53.3% and 66.7% for CD; and 20% and 80% for UC, respectively); and also histologic activity (60.5% and 76.3% for CD; and 90.0% and 95.0% for UC, respectively) than FC (41.7% and 50.0% for CD; and 25% and 50% for UC, respectively). Regarding the clinical, endoscopic, and histologic activities, the BG levels were reduced following therapeutic intervention in patients with CD (P < 0.0001) and UC (P = 0.003). Compared with endoscopic (AUC: 0.693; P = 0.002) and histologic (AUC: 0.868; P < 0.001) activity, no significant correlation was found between serum BG and transmural healing based on magnetic resonance enterography (AUC: 0.576; P = 0.192). Positive correlations were detected between BG and IL-17 in the CD (r: 0.737; P = 0.001) and the UC group (r: 0.574; P = 0.005), and between BG and interferon-gamma in the CD group (r: 0.597; P = 0.015).

CONCLUSION

Serum BG may represent an important novel noninvasive approach for detecting mucosal inflammation and therapeutically monitoring inflammatory bowel diseases, particularly in CD.

Key Words: Crohn's disease; Ulcerative colitis; Inflammatory bowel disease; Beta-glucan; Histologic activity; Noninvasive test

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Core Tip: This study investigated whether serum concentrations of beta-glucan (BG), which originate from the gut microbiota, could reflect active intestinal inflammation in inflammatory bowel diseases patients. BG levels paralleled the endoscopic activity in Crohn's disease (CD) patients and histologic activity and combined endoscopic and histologic activity in both CD and ulcerative colitis patients. The BG results were better for predicting histologic inflammation than fecal calprotectin. Regarding the endoscopic and histologic activities, the BG levels were reduced following therapeutic intervention in both CD and ulcerative colitis patients. Serum BG levels may represent a novel noninvasive approach to detect mucosal inflammation and therapeutically monitor inflammatory bowel diseases.

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INTRODUCTION

In the last decade, therapeutic targets in inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), have evolved from simple clinical

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remission to more objective parameters to confirm the resolution of inflammation. Mucosal healing defined by endoscopic evaluation has been consistently associated with better disease outcomes[1,2]. Hence, the recommended goals of treatment endpoints have changed toward deep remission and include a combination of clinical remission and endoscopic healing[3-8]. However, because microscopic inflammation may persist even in patients with endoscopically normal mucosa, histologic assessment has been proposed recently as a more precise predictor of disease outcomes[9-11].

The approach for monitoring mucosal or histologic remission in IBD demands frequent endoscopic evaluations, which are costly and invasive procedures. Thus, alternative methods have been investigated, including cross-sectional imaging, such as magnetic resonance enterography (MRE)[12]. However, in addition to the high cost, MRE relies on semiquantitative analysis and experience with recommended indexes as an endpoint in clinical trials is still lacking[10]. To circumvent these issues, several biomarkers in blood and stools have been investigated. C-reactive protein (CRP), for example, has long been utilized as a systemic marker of inflammation with increased levels associated with disease activity[13]. However, it is generally accepted that CRP has both low sensitivity[14] and specificity[15]. Nevertheless, in the last decade, fecal calprotectin (FC) has become the most used biomarker in the follow-up of IBD due to practical features and the correlation with disease activity[16,17]. However, the predictive value of FC in mucosal healing is not well established, and no clear cut-off level has been defined to assess mucosal inflammation or remission[18]. Moreover, the relationship between FC and histologic inflammation, particularly in colonic CD, remains to be determined[19,20]. In this context, a reliable noninvasive biomarker that accurately identifies mucosal inflammation continues to be necessary in the follow-up of patients with IBD.

Among several factors that participate in the pathogenesis of IBD, the gut microbiota has gained increased attention in the last decade[21,22]. Although whether dysbiosis is a primary or secondary phenomenon in IBD remains to be fully elucidated, gut microbial composition and function appear to be altered in IBD[23], and a growing body of evidence supports the idea that IBD might result from a complex interaction among host, environmental, and microbial factors[24,25]. In this regard, immune reactivity to microbial antigens, such as circulating antibodies against *Saccharomyces cerevisiae*[26], *Escherichia coli* outer membrane porin C[27], bacterial flagellin[28], and antibodies against glycans, commonly present in microbial cells surface[29], has long been reported in IBD. Bacterial cell wall components, such as the endotoxin lipopolysaccharide (LPS) of Gram-negative strains, are potent inflammatory agents[30] whose levels were shown to be increased in IBD[31]. LPS may also play an important role in altering gut homeostasis, including the control of cell death processes that permit translocation among the gut, blood, and other tissues[32]. In line with this, Guo *et al*[33] detected increased levels of LPS and 1,3-beta-D-glucan (BG) in the serum of patients with CD that were positively correlated with the clinical intensity of disease[33]. BG is a ubiquitous cell wall component present in several microorganisms, including *Candida* and *Aspergillus* spp, within the gut microbiota[34]. Fungal dysbiosis was recently reported to be associated with CD patients compared with healthy controls[35]. Additionally, lamina propria mononuclear cells derived from the intestinal specimens of patients with CD showed increased release of pro-inflammatory cytokines in response to stimulation with BG *in vitro*[36], suggesting a potential contribution of BG to the pathogenesis of intestinal inflammation. Therefore, we hypothesized that high BG concentrations in the serum of patients with IBD could reflect active intestinal inflammation. Thus, this prospective study aimed to determine whether the serum BG concentrations correlate with intestinal inflammation based on other inflammatory biomarkers and endoscopic, histological, and imaging criteria and to establish an optimal cut-off level of BG to predict mucosal healing.

MATERIALS AND METHODS

Ethical considerations

The Ethical Committee of the Hospital Copa D'Or, with the co-participation of the University Hospital of the Federal University of Rio de Janeiro, approved the study protocol (CAAE: 53351116.1.0000.5249), which was implemented in agreement with the ethical standards described in the 1964 Declaration of Helsinki. All the enrolled patients provided written informed consent before participating in the study.

Study population

This prospective observational study involved patients followed up regularly at the outpatient unit for Intestinal Diseases of the Division of Gastroenterology at the University Hospital of the Federal University of Rio de Janeiro, a tertiary referral center, from March 2016 to June 2019. Eligible patients were adults (18-80 years of age) with a diagnosis of IBD (CD and UC), supported by routine clinical, imaging, endoscopic, and histologic parameters. A total of 115 patients with CD, 51 with UC, and 82 controls were included in the study. The sample size, considering a two-tailed variance analysis (fixed effects, special, main effects and interactions), including three groups, with an effect size f of 0.25, an alpha of 0.05, and power of 0.95, was estimated as 210. Patients were consecutively selected to participate, at least one week before a scheduled ileocolonoscopy. The demographics and clinical information based on the Montreal classification (including disease duration, age at diagnosis, disease extension and localization, and the predominant disease behavior[37]), presence of perianal involvement, extraintestinal manifestations, primary sclerosing cholangitis, history of surgeries due to IBD, and medical therapy at the time of enrollment, were all registered during consultation. The exclusion criteria were patients with CD with exclusive upper gastrointestinal disease (not accessible to ileocolonoscopy and/or histopathological analysis), patients with unclassified IBD, patients in the postoperative period of less than 6 mo or with total colectomy, pregnant patients, patients with evidence of abdominal abscess or colonic mucosal dysplasia, patients with cancer or acute or chronic enteric infection (*e.g.*, *Clostridioides difficile*), and individuals who had received concomitant antibiotics, nonsteroidal anti-inflammatory agents, proton-pump inhibitors, probiotics, prebiotics, and/or synbiotics in the previous 3 mo.

The control group comprised 25 men (30.5%) and 57 women (69.5%), with a median age of 51.5 years (range: 36.5-60.0 years), including 64 non-IBD patients (24 with irritable bowel syndrome, 20 with noncomplicated colonic diverticular disease, and 20 with benign polyps), and 18 healthy controls. All non-IBD patients followed up in the outpatient unit for intestinal diseases who were scheduled for ileocolonoscopy also had undergone blood and fecal sampling. In the control group, all endoscopic examinations and histological analyses were normal. None of the control individuals were taking any medication at the time of the study, and none had taken antibiotics and/or nonsteroidal anti-inflammatory agents in the previous 3 mo.

Assessment of disease activity

Clinical activity of disease was recorded at the time of ileocolonoscopy using the Harvey-Bradshaw index (HBI)[38] for CD (remission defined as HBI < 5), and the Mayo clinical score[39] for UC (remission defined as Mayo score < 2). The assessment of endoscopic activity was performed using the Simple Endoscopic Score-CD (SES-CD)[40] for CD (remission defined as SES-CD < 3) and the Mayo endoscopic subscore (MES)[41] for UC (remission defined as MES < 2). For patients who had undergone ileocolonic surgery due to CD, ileocolonoscopies were classified according to the Rutgeerts score into remission (i0-i1) and endoscopic activity (i2-i4)[42]. Endoscopic biopsies obtained during ileocolonoscopy were evaluated for histologic disease activity according to the global histologic disease activity score for CD (histologic healing defined as global histologic disease activity score < 2)[43] and the Geboes score for UC (histological healing defined as a Geboes score < 3.1)[44]. In subgroup analysis involving CD, MRE was used to obtain information on transmural inflammation whenever patients had undergone ileocolonoscopy within an interval of 30 d. MRE analysis was based on descriptive parameters, distinguishing among the predominant disease patterns (inflammatory, fibrostenosing or penetrating). The criteria for the presence of inflammatory activity included mucosal enhancement, parietal thickening, mesenteric fat infiltration, mesenteric vein engorgement, and lymphadenopathy, as previously published[45,46]. Deep healing was defined as a combination of histologic and transmural healing.

To further investigate the potential association of serum BG with disease activity in patients with IBD, subgroup analysis was performed to analyze serial alterations. Patients with IBD were selected consecutively depending on the presence of active disease based on clinical, endoscopic, and histologic evaluation. The assessment of serum BG was performed at week 0, and between weeks 12 and 16 after the medical intervention. The interval chosen was based on the practical feasibility of performing a second round of examinations and the minimum time necessary for therapeutic changes to be effective. The new therapeutic regimens included the initiation of new medications, such as biological agents, immunosuppressants (azathioprine), and

salicylates, with or without the association of a short course of steroids or the optimization of previous therapy.

Routine laboratory tests and potential new biomarkers

Peripheral blood and fecal samples were collected within 2 to 10 d before the preparation for ileocolonoscopy from all patients with IBD and controls after an overnight fast. To measure BG, serum was separated by centrifugation and processed within 10 min. The BG serum concentrations were determined at the Mycology Laboratory of the hospital using a photometric detection commercial kit (Fungitell® assay; Associates of Cape Cod, Inc., East Falmouth, MA, United States). The assay is a highly sensitive, microplate-based test that detects (1,3)-beta-D-glucan in serum at 405 nm (range: 31-500 pg/mL).

In addition to routine erythrocyte sedimentation rate and ultrasensitive C-reactive protein measurements, FC was measured using a quantitative, commercially available enzyme-linked immunosorbent assay (ELISA) kit (range: 31.2-2000 pg/mL) (Biomatik, Wilmington, DE, United States). In another subgroup analysis, blood samples were also used to assess potential circulating biomarkers. For such purpose, we analyzed a panel of cytokines, LPS-binding protein (LBP) and zonulin. The BD™ cytometric bead array human Th1/Th2/ T helper 17 (Th17) cytokine kit (BD Biosciences, San Jose, CA, United States) was used to assess interleukin (IL)-2, IL-4, IL-6, IL-10, IL-17A, tumor necrosis factor-alpha (TNF-alpha), and interferon-gamma (IFN-gamma) protein levels, whose performance has been optimized to detect physiologically relevant concentrations (pg/mL). The measurements were performed using a FACSCalibur flow cytometer (BD Biosciences, San Jose, CA, United States), and the results were analyzed with BD cytometric bead array analysis software. To measure serum LBP, we used a commercial ELISA kit and the absorbance was detected at 450 nm (range: 4.4-50 ng/mL) (Hycult Biotech Inc., Wayne, PA, United States). To assess serum zonulin, we used a commercial human zonulin ELISA kit with the absorbance read at 450 nm (range: 0.625-40 ng/mL).

Statistical analysis

Statistical analysis was performed using Statistic Package for Social Science statistical software for Windows (Version 20, Statistic Package for Social Science, Inc., Chicago, IL, United States) and Prism 8 for OS X (Version 8.4.3, GraphPad Software, LLC, San Diego, CA, United States). The distribution of individual features was determined using simple descriptive statistics. Sample size was estimated using G*Power free software for statistical analyses (University of Düsseldorf, Germany). Receiver operating characteristic analysis was used to evaluate the sensitivity and specificity of BG in reference to clinical, endoscopic, histologic and combined endoscopic and histologic remission and to determine optimal cutoff values for generating dichotomous variables. Optimal cut-off values were determined by the maximum sum of sensitivity and specificity of BG values for screening intestinal inflammatory activity. Differences among the experimental groups were assessed using the Kruskal-Wallis on ranks tests, in which multiple comparisons were performed using Dunn's test, as appropriate. Differences between the distributions of the selected variables were evaluated using chi-squared test or Fisher's exact test for categorical variables. Spearman's rank correlation was used to assess relationships between continuous variables. A pairwise Wilcoxon rank-sum test was used to compare the effect of medical intervention on the BG levels between two different time points. Preference was given to exact and nonparametric tests to avoid assumptions of normal distribution in the collected data. All the tests were two-tailed, and statistical significance was set at a P value of less than 0.05.

RESULTS

Patients' characteristics and results of serum BG

One hundred fifteen patients with CD (sixteen with ileal, thirty-nine with colonic, and sixty with ileocolonic CD), and fifty-one patients with UC (fourteen with proctitis, seventeen with left colitis, and twenty with pancolitis) were enrolled. Age; sex; disease duration; erythrocyte sedimentation rate (ESR); CRP; FC; and clinical, endoscopic, and histologic activities did not differ significantly between the CD and UC patients. Regarding clinical activity, 52.2% of patients with CD [HBI 5 (4-8; interquartile range (IQR))] and 64.7% of patients with UC [Mayo 5 (3-7; IQR)] were clinically active at the time of ileocolonoscopy. Notably, 77 (66.9%) patients with CD [SES-CD 5 (2-8; IQR)

and 35 (68.6%)] patients with UC [Mayo subscore 2 (1-3; IQR)] had endoscopic activity. Of the individuals who were regarded as endoscopically active, biopsy samples were obtained from 71/77 (92.2%) patients with CD, and from 29/35 (82.8%) patients with UC. Histological activity was detected in 33 of 71 (46.5%) patients with CD and 9 of 29 (31%) patients with UC. The median values for CRP, ESR, and FC were comparable in the CD and UC groups. The demographic and clinical characteristics of the patients and control group are provided in Table 1. A relatively weak but significant positive correlation was found between serum BG and FC concentrations (CC: 0.232; $P = 0.033$), but no correlation was detected between BG and CRP (CC: 0.106; $P = 0.221$), or between BG and ESR (CC: 0.062; $P = 0.547$). The concentrations of serum BG were significantly higher in the CD group than in the controls ($P < 0.001$). Compared with controls, a trend toward higher median serum BG was observed in the UC group, but the difference did not reach statistical significance ($P = 0.054$) (Figure 1).

Next, the levels of serum BG were evaluated among the groups of patients with IBD in relation to the clinical, endoscopic, and histologic disease activity. Although no difference was found in the BG levels regarding clinical activity, significant differences were shown for the endoscopic activity in the CD group and for histologic activity and combined endoscopic and histologic activity for both the CD and UC groups (Figure 2).

Determination of the BG cutoff and relationship with endoscopic and histologic results

Preliminary analyses were performed to estimate the optimal cutoff values to convert quantitative BG into a binary variable for the presence or absence of inflammatory activity based on standard scoring systems. The area under the curve (AUC) for the presence of clinical, endoscopic, histologic, and combined endoscopic and histologic activity and serum BG are shown in Figure 3 (CD) and Figure 4 (UC). The best cutoff value of serum BG in the CD group was 60 μg/mL for predicting endoscopic activity (AUC: 0.694; 95% confidence interval (CI): 0.60-0.79; $P = 0.001$), histologic activity (AUC: 0.860; 95%CI: 0.77-0.95; $P < 0.001$), and combined endoscopic and histologic activity (AUC: 0.847; 95%CI: 0.75-0.94; $P < 0.001$) (Figure 3). The best cutoff value of serum BG in the UC group was 40 μg/mL for predicting histologic activity (AUC: 0.786; 95%CI: 0.57-0.99; $P = 0.015$), and combined endoscopic and histologic activity (AUC: 0.741; 95%CI: 0.51-0.97; $P = 0.048$) (Figure 4). Next, the levels of serum BG were evaluated in relation to endoscopic and histologic activity compared with FC and CRP. The performance analysis of different cutoff values showed that the results with BG for predicting endoscopic activity were less sensitive, but more specific than FC, in both CD and UC groups. For predicting histologic activity, the sensitivity of BG was higher in CD and lower in UC, whereas the specificity of BG was remarkably higher in both CD and UC groups, compared with FC. In contrast to CRP, the sensitivity of BG for predicting endoscopic activity was comparable in CD and lower in UC, whereas the specificity of BG was higher in both CD and UC groups. For predicting histologic activity, the sensitivity of BG was higher in both CD and UC groups, whereas the specificity of BG was comparable in CD, but higher in the UC group, compared with CRP (Tables 2 and 3).

Comparison between serum BG and other potential serum biomarkers

In a consecutively selected subgroup of 28 patients with CD, 25 with UC and 15 controls, we performed another set of experiments to analyze the levels of BG in parallel with a series of potential serum biomarkers, including a panel of cytokines, LBP, and zonulin. Although patients with UC were more active in terms of clinical presentation, the disease activity based on endoscopic and histologic criteria were comparable. The levels of serum BG were significantly different among the groups, and pairwise comparison indicated the difference between CD and controls ($P = 0.003$). Of the other markers evaluated, only LBP showed levels significantly different among the groups, and pairwise comparisons revealed differences between the CD group and controls ($P = 0.015$), as well as between the UC group and controls (0.046) (Table 4). The assessment of potential associations between BG and the other serum markers revealed a significantly positive correlation only between BG and IL-17 (r: 0.576; $P < 0.0001$). However, analyzing the groups separately, we detected significant positive correlations between BG and IL-17 in the CD group (r: 0.737; $P = 0.001$) and the UC group (r: 0.574; $P = 0.005$) and between BG and IFN-gamma in the CD group (r: 0.597; $P = 0.015$).

Table 1 Patient demographics and medical characteristics

Parameters	Controls (*n* = 82)	Crohn's disease (*n* = 115)	Ulcerative colitis (*n* = 51)
Women	57 (69.5%)	58 (50.4%)	27 (52.9%)
Age (yr), median (IQR)	51.5 (36.5-60)	42 (28-58)	44 (37-56)
Disease duration (yr), median (IQR)		6 (3-11)	9 (3-14)
Age at diagnosis (yr)			
A1; A2; A3, *n* (%)		10 (8.7); 57 (49.6); 48 (41.7)	8 (15.7); 29 (56.9); 14 (27.5)
Disease behavior			
B1; B2; B3, *n* (%)		53 (46.1); 20 (17.4); 42 (36.5)	-
Disease location			
L1; L2; L3/E1; E2; E3, *n* (%)		16 (13.9); 39 (33.9); 60 (52.2)	14 (27.5); 17 (33.3); 20 (39.2)
Perianal disease		23 (20.0%)	-
EIM		12 (10.4%)	3 (5.9%)
PSC		6 (5.2%)	5 (9.8%)
Previous surgery		36 (31.3%)	2 (3.9%)
Medical therapy			
Biologicals		38 (33.0%)	5 (9.8%)
Immunosuppressants		66 (57.4%)	22 (43.1%)
Steroids		17 (14.8%)	3 (5.9%)
Salicylates		18 (15.7%)	26 (51.0%)
Clinically active		60 (52.2%)	33 (64.7%)
Endoscopically active		77 (66.9%)	35 (68.6%)
Histologically active		33/71 (46.5%)	9/29 (31.0%)
CRP, mg/L	1.65 (1.4-6.0)	2.8 (1.6-8.1)	4.3 (2.0-7.6)
ESR, mm/h	22 (10-30)	22 (10-42)	35 (19-67)
Fecal calprotectin, μg/g	122 (45-201)	199 (52-325)	218 (115-370)
Beta-glucan, μg/mL	17 (8-33)	35 (17-74)	23 (9-54)

The values are presented as numbers (percentages) or medians interquartile range; age at diagnosis: A1, < 17; A2, 17-40; A3, > 40; Disease behavior in Crohn's disease: B1: Inflammatory; B2: Fibrostenosing; B3: Penetrating; Disease location in Crohn's disease: L1: Ileal; L2: Colonic; L3: Ileo-colonic; Disease location in ulcerative colitis: E1: Proctitis; E2: Left sided colitis; E3: Extensive colitis; EIM: Extraintestinal manifestations; PSC: Primary sclerosing cholangitis; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.

Serial analysis of serum BG during therapeutic intervention for disease activity

To analyze potential dynamic changes of serum BG in IBD, subgroup analysis was performed and included 29 patients with CD, 12 with UC and 12 controls (Supplementary Table 1). Patients with IBD were selected consecutively depending on the presence of active disease based on both clinical and endoscopic evaluation. Nevertheless, histologically active disease was detected in 81% of patients with CD and 50% of UC at baseline (T0). Selected patients regularly followed-up in the outpatient unit were submitted to changes in their respective therapeutic regimen, including the introduction of new medications, such as biological agents (anti-TNF: infliximab or adalimumab) (9 in the CD group and 3 in the UC group), immunosuppressants (azathioprine) (5 in the CD group and 3 in the UC group), and oral salicylates (3 in the UC group), with the association of a short course of steroids (less than 8 wk) (5 in the CD group and 4 in the UC group), or optimization of previous therapy (4 in the CD group and 3 in the UC group). After 12 to 16 wk of the therapeutic intervention (T1), all the patients were again evaluated based on the same clinical, ileocolonoscopic, and histologic criteria, and sera were collected to assess BG concentrations. Significant improvements in clinical (CD group, $P < 0.001$; UC group $P = 0.002$), endoscopic (CD group, $P < 0.001$; UC group, $P = 0.014$), and histologic (CD

Table 2 Performance analysis of different cutoff values of serum beta-glucan for patients with Crohn's disease in relation to endoscopic and histological criteria

Predicted outcome		Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
Endoscopic inflammation	Beta-glucan	40	50.0 (39.0-61.0)	71.8 (56.2-83.5)	77.5 (64.1-87.0)	42.4 (31.2-54.4)	57.4 (48.3-66.0)
	(μg/mL)	60	34.2 (24.5-45.4)	87.2 (73.3-94.4)	83.9 (67.4-92.9)	40.5 (30.6-51.2)	52.2 (43.1-61.1)
	Calprotectin	100	75.0 (56.6-87.3)	53.3 (30.1-75.2)	75.0 (56.6-87.3)	53.3 (30.1-75.2)	67.4 (52.5-79.5)
	(μg/g)	200	53.6 (35.8-70.5)	66.7 (41.7-84.8)	75.0 (53.1-88.8)	43.5 (25.6-63.2)	58.1 (43.3-71.6)
	CRP	3	49.2 (37.1-61.4)	50.0 (31.4-68.6)	71.4 (56.4-82.8)	27.9 (16.7-42.7)	49.4 (39.0-59.8)
	(mg/L)	5	34.4 (23.7-46.9)	66.7 (46.7-82.0)	72.4 (54.3-85.3)	28.6 (18.4-41.5)	43.5 (33.5-54.1)
Histological inflammation	Beta-glucan	40	78.8 (62.2-89.3)	60.5 (44.7-74.4)	63.4 (48.1-76.4)	76.7 (59.1-88.2)	69.0 (57.5-78.6)
	(μg/mL)	60	57.6 (40.8-72.8)	76.3 (60.8-87.0)	67.9 (49.3-82.1)	67.5 (52.5-79.5)	67.6 (56.1-77.3)
	Calprotectin	100	69.2 (42.4-87.3)	41.7 (19.3-68.0)	56.2 (33.2-76.9)	55.6 (26.7-81.1)	56.0 (37.1-73.3)
	(μg/g)	200	46.1 (23.2-70.9)	50.0 (25.4-74.6)	50.0 (25.4-74.6)	46.1 (23.2-70.9)	48.0 (30.0-66.5)
	CRP	3	57.7 (38.9-74.5)	62.1 (44.0-77.3)	57.7 (38.9-74.5)	62.1 (44.0-77.3)	60.0 (46.8-71.9)
	(mg/L)	5	53.8 (35.5-71.2)	79.3 (61.6-90.1)	70.0 (48.1-85.4)	65.7 (49.1-79.2)	67.3 (54.1-78.2)

Endoscopic criteria based on the Simple Endoscopic Score-Crohn's disease endoscopic subscore; Histological criteria based on a modified Global Histologic disease activity score; Parentheses show lower-upper 95% confidence interval. CRP: C-reactive protein; PPV: Positive predictive value; NPV: Negative predictive value.

group, $P = 0.001$; UC group, $P = 0.023$) indexes were detected in the follow-up analysis. In parallel, the levels of serum BG decreased significantly from week 0 (T0) to week 12-16 (T1) in patients with CD ($P < 0.0001$) and UC ($P = 0.003$) but not in controls ($P = 0.407$) (Figure 5A). Considering the median values of serum BG in each group, the difference from T0 to T2 was 307% in the CD group, 141% in the UC group, and only 13% in controls.

Serum BG in relation to histologic and transmural inflammation in CD

To further investigate the potential use of BG to detect transmural inflammation in CD, we analyzed another subgroup of 62 consecutively selected patients concurrently evaluated with MRE. The levels of serum BG were significantly lower in patients with both histologic and transmural healing than in those with either histologic inflammation with transmural healing ($P = 0.047$) or combined histologic and transmural inflammation ($P = 0.041$) (Figure 5B). The AUC for the presence of transmural inflammation based on MRE findings and serum BG is shown in Supplementary Figure 1. Considering the cutoff values of 40 and 60 mg/mL, serum BG predicted deep healing (both histologic and transmural healing) in 68.4% and 84.2%, whereas no healing (both histologic and transmural inflammation) was predicted in 69.2% and 53.8% of the patients, respectively. Additionally, considering the cutoff values of 40 and 60 mg/mL serum BG detected 76.9% and 61.5% of patients in the context of histologic inflammation with transmural healing but only 41.2% and 35.3% of patients with transmural inflammation combined with histologic healing, respectively (Supplementary Table 2).

Table 3 Performance analysis of different cutoff values of serum beta-glucan for patients with ulcerative colitis in relation to endoscopic and histological criteria

Predicted outcome		Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
Endoscopic inflammation	Beta-glucan	40	40.0 (25.6-56.4)	87.5 (64.0-96.5)	87.5 (64.0-96.5)	40.0 (25.6-56.4)	54.9 (41.4-67.7)
	(μg/mL)	60	22.9 (12.1-39.0)	87.5 (64.0-96.5)	80.0 (49.0-94.3)	34.1 (21.6-49.4)	43.1 (30.5-56.7)
	Calprotectin	100	81.2 (57.0-93.4)	20.0 (3.6-62.4)	76.5 (52.7-90.4)	25.0 (4.6-69.9)	66.7 (45.4-82.8)
	(μg/g)	200	62.5 (38.6-81.5)	80.0 (37.5-96.4)	90.9 (62.3-98.4)	40.0 (16.8-68.7)	66.7 (45.4-82.8)
	CRP	3	60.9 (40.8-77.8)	20.0 (5.7-51.0)	63.7 (42.9-80.3)	18.2 (5.1-47.7)	48.5 (32.5-64.8)
	(mg/L)	5	43.5 (25.6-63.2)	60.0 (31.3-83.2)	71.4 (45.3-88.3)	31.6 (15.4-54.0)	48.5 (32.5-64.8)
Histological inflammation	Beta-glucan	40	66.7 (35.4-87.9)	90.0 (69.9-97.2)	75.0 (40.9-92.8)	85.7 (65.4-95.0)	82.8 (65.5-92.4)
	(μg/mL)	60	55.6 (26.7-81.1)	95.0 (76.4-99.1)	83.3 (43.6-97.0)	82.6 (62.9-93.0)	82.8 (65.5-92.4)
	Calprotectin	100	100.0 (64.6-100.0)	25.0 (7.1-59.1)	53.8 (29.1-76.8)	100.0 (34.2-100.0)	60.0 (35.7-80.2)
	(μg/g)	200	85.7 (48.7-97.4)	50.0 (21.5-78.5)	60.0 (31.3-83.2)	80.0 (37.5-96.4)	66.7 (41.7-84.8)
	CRP	3	57.1 (25.0-84.2)	33.3 (13.8-60.9)	33.3 (13.8-60.9)	57.1 (25.0-84.2)	42.1 (23.1-63.7)
	(mg/L)	5	42.9 (15.8-74.9)	58.3 (31.9-80.7)	37.5 (13.7-69.4)	63.6 (35.4-84.8)	52.6 (31.7-72.7)

Endoscopic criteria based on the Mayo endoscopic subscore; Histological criteria based on the Geboes score. Parentheses show lower-upper 95% confidence interval. CRP: C-reactive protein; PPV: Positive predictive value; NPV: Negative predictive value.

DISCUSSION

In this study, we performed a prospective observational investigation examining the potential role of serum BG as a biomarker to predict inflammation in patients with IBD. Overall, the results indicated a favorable performance of serum BG compared with other routinely used biomarkers and a particularly strong association with histological inflammation. Moreover, the dramatic decrease in serum BG in the context of clinical, endoscopic, and histological improvements in the responders of therapeutic interventions, indicate that the relative serum levels may be even more important than the absolute values. Therefore, the results of this study support the idea that monitoring serum BG might be an important asset in the noninvasive follow-up of patients with IBD.

The cross-sectional analysis performed in this study showed that the concentrations of serum BG were higher in IBD, but a significant difference was noted only when comparing the CD group with controls. Although discrepancies in the number of individuals constituting each group may affect the analysis, the observed differences between CD and UC remain considerably large. However, in terms of clinical activity, patients with UC tended to be more symptomatic, while the other demographic and clinical parameters were similar. Regarding routine laboratory markers, FC, ESR, and CRP were all elevated but with comparable results in the CD and UC groups. The overall endoscopic activity, considered the gold standard for mucosal healing in IBD[3,47] was similar, but the histological analysis revealed more inflammatory activity among patients with CD in our series. A potential association of serum BG with histological analysis was further reinforced after categorizing patients as active or in remission, and statistical significance emerged for both CD and UC patients. Using the same strategy, serum BG was also significantly associated with endoscopic activity in CD patients. Considering combined endoscopic and histologic evaluations, significant associations were demonstrated for both CD and UC patients. These results indicate that the levels of serum BG are associated with inflammatory activity in IBD,

Table 4 Patient demographics and medical characteristics of the subgroup for the analysis of noninvasive markers

Parameters	Control group (*n* = 15)	Crohn's disease group (*n* = 28)	Ulcerative colitis group (*n* = 25)	*P* value
Women, *n* (%)	11 (73)	12 (43)	16 (64)	0.110
Age (yr), median (IQR)	57 (37-63)	36 (26-58)	41 (33-56)	0.158
Disease duration (yr), median (IQR)		6 (2-12.5)	9 (3-10.5)	0.521
Age at diagnosis (yr)				
A1; A2; A3, *n* (%)		3 (11); 14 (50); 11 (39)	5 (20); 15 (60); 5 (20)	0.269
Disease behavior				
B1; B2; B3, *n* (%)		16 (57); 4 (14); 8 (29)	-	-
Disease location				
L1; L2; L3/E1; E2; E3, *n* (%)		5 (18); 9 (32); 14 (50)	5 (20); 12 (48); 8 (32)	-
Perianal disease, *n* (%)		5 (18)	-	-
EIM, *n* (%)		4 (14)	2 (8)	0.391
PSC, *n* (%)		1 (3.6)	3 (12)	0.263
Previous surgery, *n* (%)		9 (32)	1 (4.0)	0.010
Medical therapy, *n* (%)				
Biologicals		10 (36)	2 (8.0)	0.017
Immunosuppressants		18 (64)	5 (20)	0.001
Steroids		8 (29)	1 (4.0)	0.019
Salicylates		6 (21)	14 (56)	0.010
Clinically active, *n* (%)		13 (46)	21 (84)	0.005
Endoscopically active, *n* (%)		23 (82)	17 (68)	0.191
Histologically active, *n* (%)		14/22 (64)	4/14 (29)	0.043
Beta-glucan, μg/mL	26 (8-43)	79 (30-183)	23 (9-69)	0.0003[a]
LBP, pg/mL	19.2 (16.4-22.7)	27.3 (24.3-28.6)	21.8 (19.8-24.6)	0.002[b]
Zonulin, pg/mL	16.4 (15.3-17.1)	17.6 (16.6-19.0)	17.2 (16.6-18.7)	0.09
IL-17 (10^2), pg/mL	0.04 (0.0-1.50)	0.08 (0.0-1.75)	0.00 (0.00-0.60)	0.2479
IFN-gamma, pg/mL	0.00 (0.00-0.690)	0.021 (0.00-0.66)	0.25 (0.001-0.92)	0.5276
TNF-alpha (10^2), pg/mL	0.00 (0.00-1.00)	0.10 (0.00-7.80)	0.00 (0.00-20.01)	0.9004
IL-10, pg/mL	0.00 (0.00-0.00)	0.00 (0.00-4.56)	1.35 (0.00-3.66)	0.4801
IL-6, pg/mL	3.27 (2.38-9.05)	5.70 (0.31-35.73)	4.35 (2.28-15.91)	0.4149
IL-4, pg/mL	0.055 (0.00-6.81)	0.00 (0.00-0.087)	0.00 (0.00-1.31)	0.2597
IL-2, pg/mL	0.00 (0.00-0.052)	0.00 (0.00-0.010)	0.00 (0.00-0.04)	0.9204

In pairwise comparisons:
[a,b]Crohn's disease > Control. Values are presented as number (percentage) or median (IQR: Interquartile range); age at diagnosis: A1, < 17; A2, 17-40; A3, > 40; Disease behavior in Crohn's disease: B1: Inflammatory; B2: Fibrostenosing; B3: Penetrating; Disease location in Crohn's disease: L1: Ileal; L2: Colonic; L3: Ileo-colonic; Disease location in ulcerative colitis: E1: Proctitis; E2: Left sided colitis; E3: Extensive colitis; EIM: Extraintestinal manifestations; PSC: Primary sclerosing cholangitis; LBP: Lipopolysaccharide-binding protein.

predominantly with CD, likely related to specific aspects of the inflammatory process and differences in the pathogenic mechanisms. Similar to FC, which is considered a reliable indicator of the presence of inflammatory activity in the gastrointestinal tract[48,49], the results from this study suggest that BG measurements can also be used to screen patients with suspected IBD.

After determining the optimal cutoff values to estimate inflammatory activity, comparisons with FC and CRP showed that serum BG was slightly less sensitive,

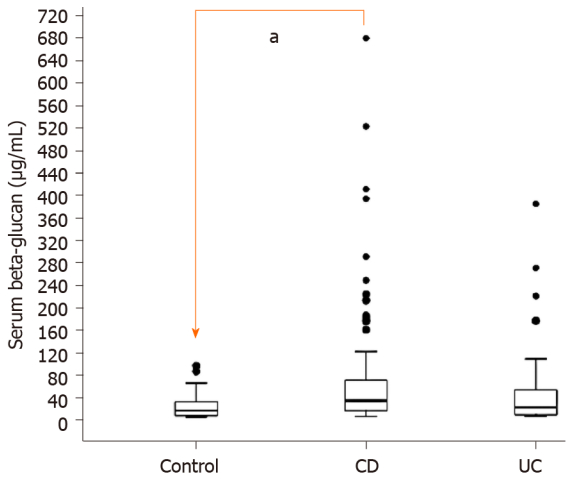

Figure 1 Serum beta-glucan concentrations in patients with Crohn's disease, ulcerative colitis, and controls. The analysis was performed by the Kruskal-Wallis on ranks test, in which multiple comparisons were performed using Dunn's test. The horizontal bars represent the medians, and the boxes represent the 25th and 75th percentiles. Significant results are depicted ($^{a}P < 0.0001$).

although more specific regarding endoscopic activity. However, the performance of serum BG in predicting histologic inflammation was remarkably better than that of FC and CRP. Comparative analysis appears to have unveiled differences regarding the nature of the proposed inflammatory markers. CRP is an acute-phase protein that often reflects systemic nonspecific inflammatory states, usually associated with the severity of underlying conditions, including IBD[50,51]. FC has been the most used noninvasive inflammatory biomarker for IBD in the last decade and indicates the presence of neutrophils in the intestinal mucosa[16,19]. However, serum BG can reflect fungal infection[52] but also may indicate the presence of ubiquitous circulating cell wall components of the gut microbiome[33]. Therefore, the presence of BG in serum may likely reflect the presence of active mucosal inflammation and an abnormal intestinal permeability, allowing the passage of components of the gut microbiome into the blood. This phenomenon may explain the stronger association of BG with histological rather than endoscopic disease activity. Therefore, we hypothesized that the levels of serum BG in patients with IBD could indicate more subtle changes, such as histological and, indirectly, epithelial permeability to luminal contents.

Currently, although histological assessment has not been recommended as a routine procedure in the follow-up of patients with IBD, persistent microscopic inflammation has been consistently associated with poor outcomes in UC[9,53]. However, the role of histological analysis is less clear in CD, and no consensus exists regarding scoring systems[54]. Nevertheless, recent data from studies with patients with CD suggest that histologic healing, more than endoscopic healing, is associated with a reduced risk of disease relapse[11,55]. Taken together, these study findings indicate that histologic assessment will become a major target in the near future for both forms of IBD; therefore, the need for invasive tests might continue and even increase.

In addition to reflecting an inflammatory state and abnormal intestinal permeability, the presence of high levels of BG per se could also promote additional inflammation. For example, BG was shown to activate macrophages through the dectin-1 receptor, increasing the production of pro-inflammatory cytokines such as IL-12 and TNF-alpha[56] and the release of arachidonic acid and eicosanoids[57], fueling inflammation. Moreover, the activation of NF-kappa B and the release of IL-6 and IL-23 by human macrophages induced by BG were shown to be enhanced by priming with LPS and interferons, suggesting a synergistic effect of an inflammatory microenvironment[58]. Nonetheless, in contrast to LPS, BG alone strongly induces the secretion of IL-1 beta from human macrophages, mediated by the NLRP3 inflammasome[59].

In subgroup analysis, we performed another set of experiments to compare serum BG with a series of other potential biomarkers. Of all candidate molecules investigated, only LBP, an endotoxin-related marker, showed significant differences among the groups. Similar to previous studies involving patients with IBD, increased serum levels of LBP correlated with disease activity[60], paralleled hs-CRP[61] and proinflammatory cytokines[62], and the recovery after treatment suggested its potential to predict clinical relapses. Although LBP demonstrated an association with the

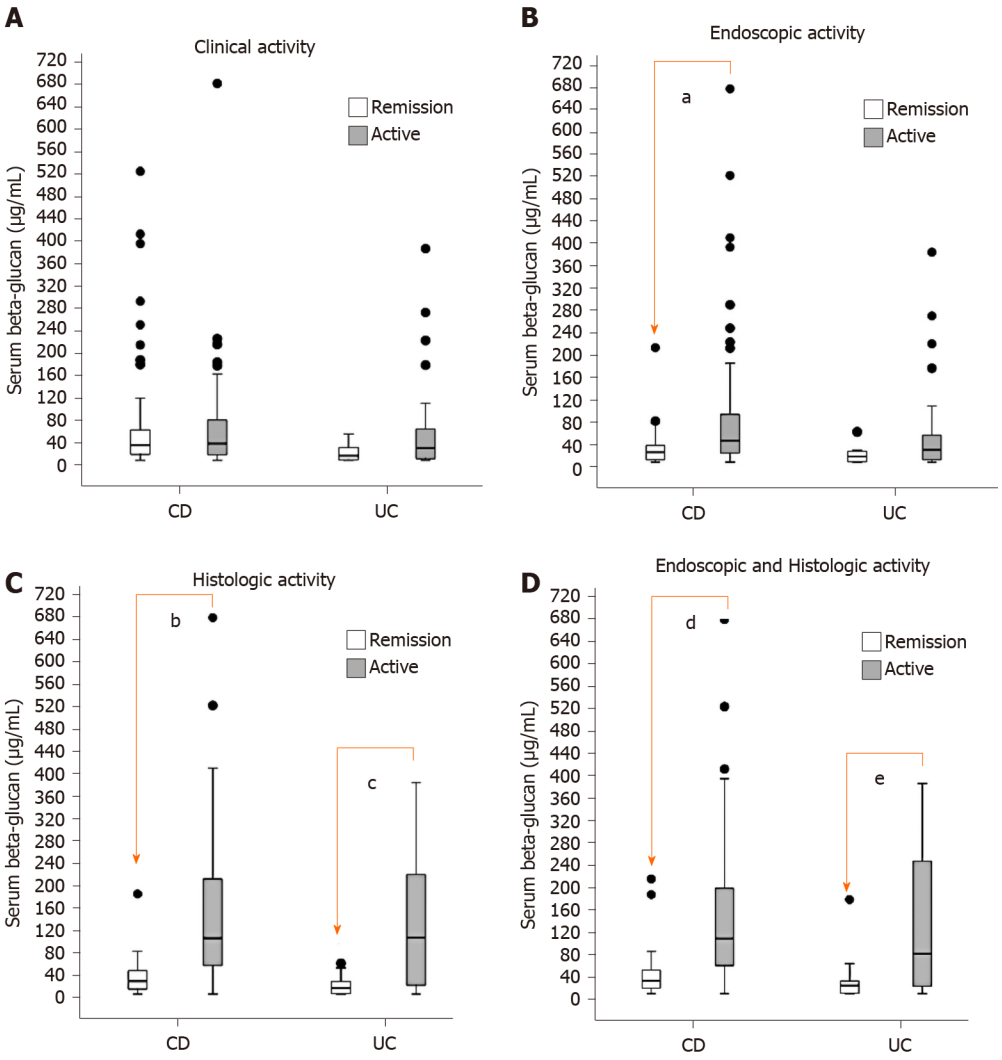

Figure 2 Although no difference was found in the beta-glucan levels regarding clinical activity, significant differences were shown for the endoscopic activity in the Crohn's disease group and for histologic activity and combined endoscopic and histologic activity for both the Crohn's disease and ulcerative colitis groups. Serum beta-glucan concentrations are stratified in Crohn's disease and ulcerative colitis according to (A) clinical; (B) endoscopic; (C) histologic; and (D) combined endoscopic and histologic indexes. The analysis was performed by the Mann-Whitney rank-sum test. The horizontal bars represent medians, and the boxes represent the 25th and 75th percentiles. Significant results are depicted ($^{a}P = 0.002$; $^{b}P < 0.001$; $^{c}P = 0.013$; $^{d}P < 0.001$; $^{e}P = 0.047$).

diagnosis of IBD in this study, no correlation was found with the levels of serum BG and inflammatory activity. Nevertheless, the finding of elevated LBP in IBD is conceptually important because it reflects the translocation of LPS into the systemic circulation, indicating intestinal barrier dysfunction[63]. Additionally, like serum BG, the increased levels of LPS/LBP support the idea of the intestinal microbiota fostering the inflammatory response. Among the cytokines investigated in this study, serum BG showed a strong positive correlation with IFN-gamma and IL-17A in CD and with IL-17A alone in UC. This finding agrees with previous studies showing that dectin-1 activates intracellular signals through CARD9, resulting in the production of pro-inflammatory cytokines and the promotion of immune responses based on Th17[64,65]. This finding may explain the stronger association of BG with CD, which typically displays marked mucosal infiltration of Th1 and Th17 cells[66,67].

In another subgroup analysis, the distinct time points analyzed aimed to determine the dynamic changes in serum BG and the potential association with the therapeutic intervention. In particular, the selection of patients with clinical and endoscopic activity allowed us to confirm that the relative levels of BG were probably more strongly correlated with disease activity than the absolute levels. Similar results were found in a previous study, showing that serum BG and LPS were increased in CD and were associated with disease activity[33]. However, in contrast to our study, the previous investigation involved a smaller number of patients, considered only the

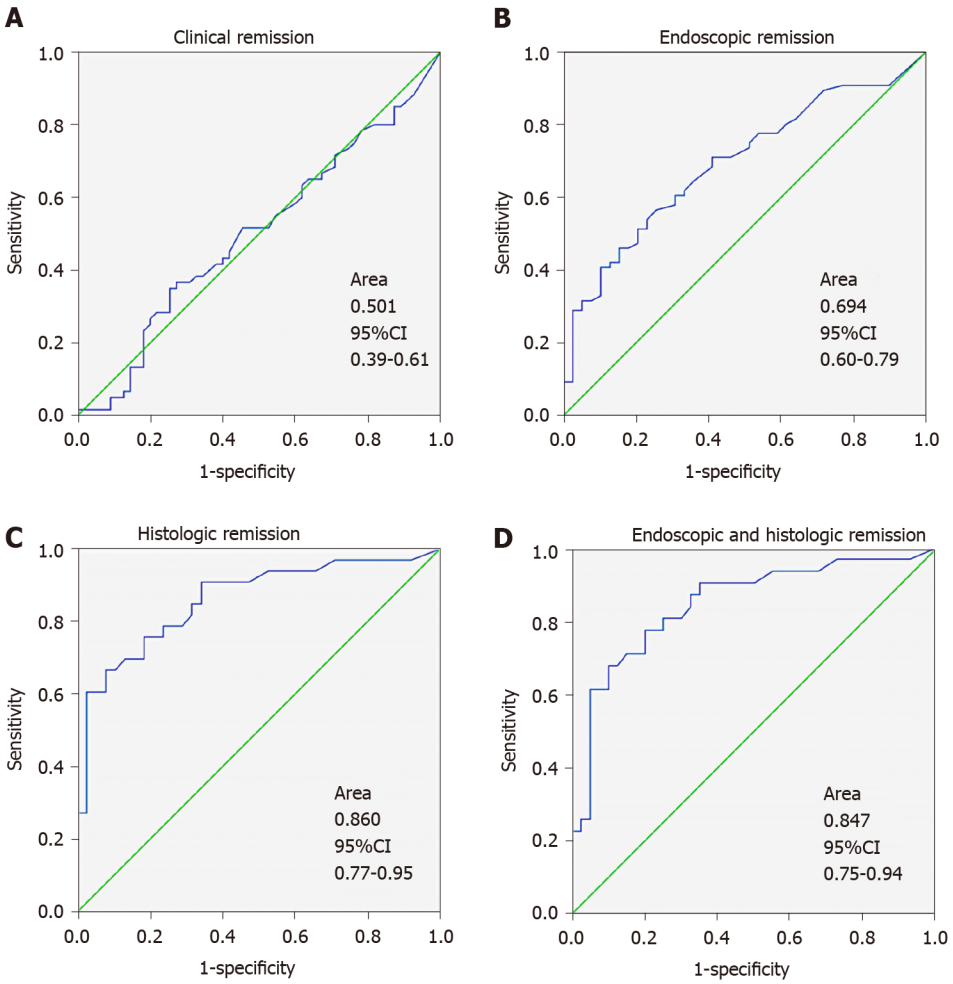

Figure 3 Receiver operating characteristic curves illustrating the diagnostic ability of serum beta-glucan for detecting disease activity in patients with Crohn's disease. Receiver operating characteristic curves are shown in relation to the (A) clinical; (B) endoscopic; (C) histologic; and (D) combined endoscopic and histologic criteria. Diagonal segments are produced by ties. The area under the curve with standard error and the 95% confidence interval (95%CI) are shown in each plot.

clinical status of the patients with CD, did not analyze patients with UC, and only healthy individuals constituted the control group. In the current study, the improvement achieved with the therapeutic intervention paralleled by the levels of serum BG strongly suggest that abnormalities in the microbiome and permeability to luminal contents probably represent crucial underlying pathogenic mechanisms in IBD, potentially modulated by the treatment.

Considering the stronger association with CD, particularly regarding histological activity, we attempted to investigate whether serum BG could also reflect the presence of transmural inflammation detected by MRE. MRE is a well-established modality for evaluating acute complications and the follow-up of patients with CD because it offers a detailed tridimensional view of the intestinal wall, can detect extraintestinal complications, and has been reported to detect mucosal inflammation, with results comparable to ileocolonoscopy[68,69]. In this subgroup analysis, the results continued to support the usefulness of serum BG for predicting histological inflammation but were relatively modest concerning transmural inflammation. Hence, we hypothesized that serum BG might serve to detect even minimal mucosal changes, probably involving permeability and dysbiosis, but probably not the transmural component of the inflammatory process underlying CD. Elevated serum BG levels may reflect preferentially acute and ongoing mucosal inflammation, but probably not damage accumulated over time due to the transmural involvement of CD. The current findings appear to corroborate previous studies suggesting that the objective assessment of lesions in CD may depend on a combination of histology and cross-sectional imaging[70].

Our study has limitations, including its predominant cross-sectional nature and the number of patients, particularly in the subgroup analyses. In view of the recognized

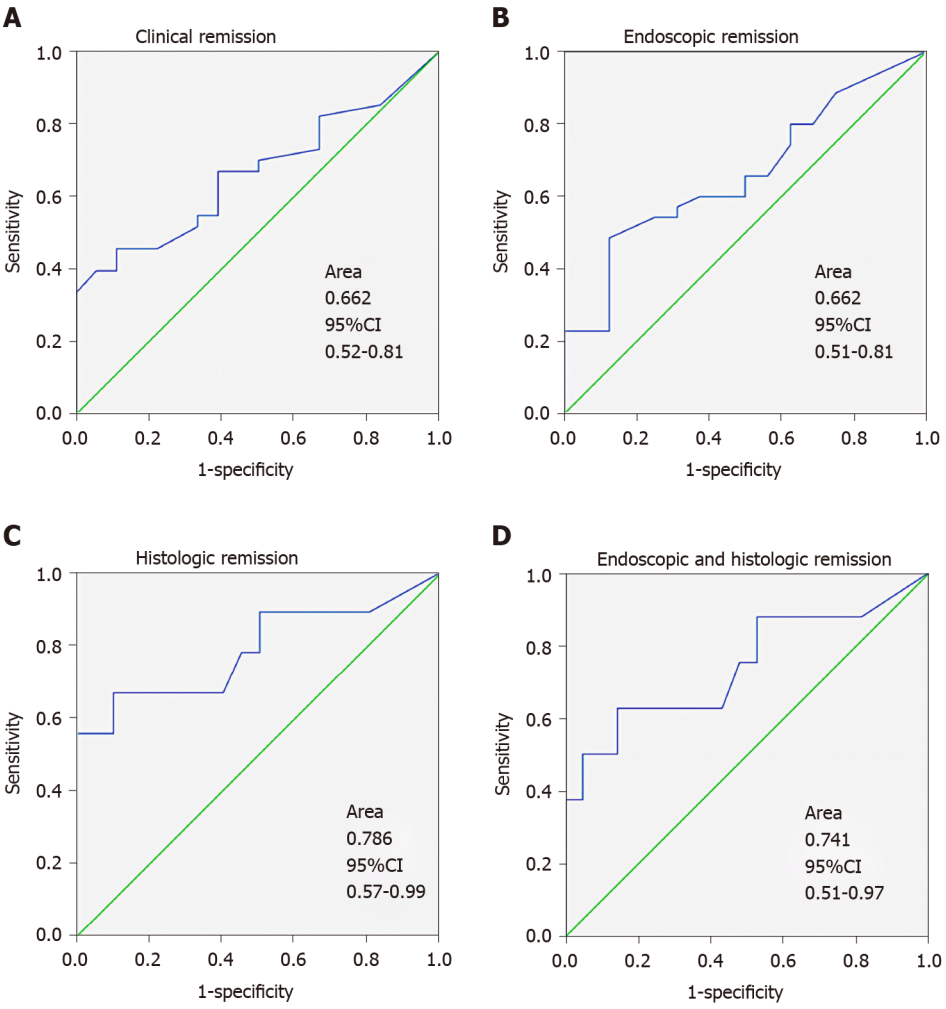

Figure 4 Receiver operating characteristic curves illustrating the diagnostic ability of serum beta-glucan for detecting disease activity in patients with ulcerative colitis. Receiver operating characteristic curves are shown in relation to the (A) clinical; (B) endoscopic; (C) histologic; and (D) combined endoscopic and histologic criteria. Diagonal segments are produced by ties. The area under the curve with standard error and the 95% confidence interval (95%CI) are shown in each plot.

disease heterogeneity in IBD, especially large in CD, including severity, age of onset, the predominant clinical aspects, localization and extent, behavior, previous surgical interventions, response to treatment, changes during the course of the disease, among other factors[71-73], it is expected that the more reliable evaluations will depend on the number of patients. In fact, a larger sample would probably allow a more precise estimation of the cut-off value for predicting disease activity. Additionally, a more detailed follow-up of the patients and more frequent serial BG measurements could have allowed an assessment of whether concentrations changes could predict early recurrence. Regarding subgroup analysis to investigate potential changes in the serial concentrations of BG, this study used a relatively small number of individuals and evaluated patients under different therapeutic regimens. However, technically, freshly collected blood for BG might result in more reliable readings than FC due to stability and conservation issues[74,75]. Moreover, the patients' acceptance of undergoing blood collection for BG would likely be greater than that of providing stool samples for FC, the compliance of which is low[76].

If elevations of serum BG detected among patients with IBD actually reflect an abnormal intestinal microbiome, it is likely that dysbiosis underlying other intestinal diseases could promote similar changes in serum BG. This could constitute a bias in this study, considering the composition of the control group. For example, several studies have shown that patients with IBS exhibit an abnormal intestinal microbiome[77-79], and treatments based on interventions in the intestinal microbiome tend to be effective, at least temporarily[80-82]. Nonetheless, the results of this study showed that the overall variability within the control group was very small compared to the dispersion seen among patients with IBD. In fact, the levels of serum BG among IBD patients in remission (both CD and UC) were not clearly distinguishable from the

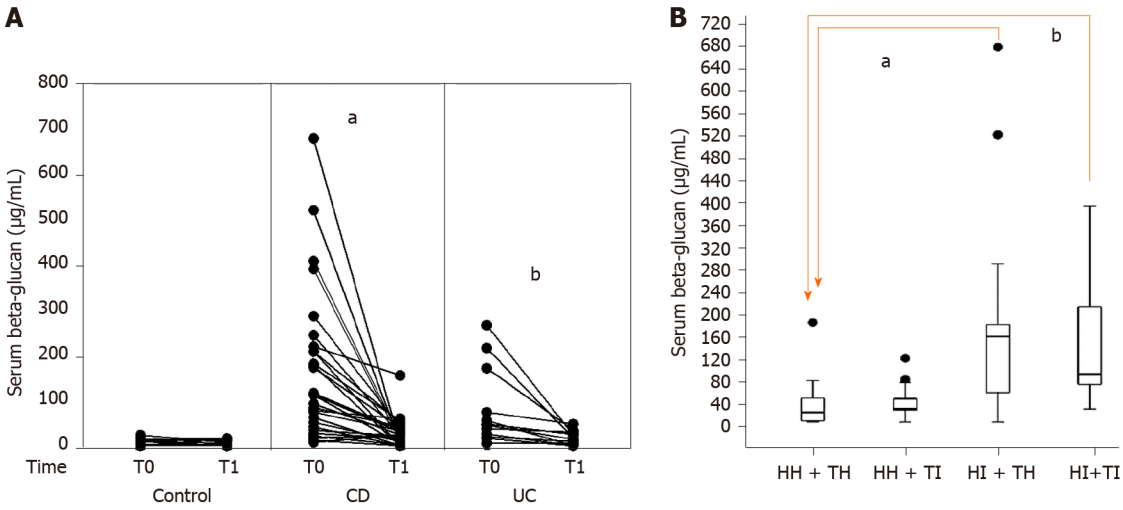

Figure 5 Analysis of serum beta-glucan in response to therapeutic intervention in inflammatory bowel diseases, and in relation to histologic and transmural inflammation in Crohn's disease. A: Serial concentrations of serum beta-glucan are shown at week 0 (T0) and between weeks 12 and 16 (T1) in controls and after therapeutic interventions in patients with Crohn's disease and ulcerative colitis. The analysis was performed by the pairwise Wilcoxon rank-sum test. Significant results are depicted ($^aP < 0.0001$; $^bP = 0.003$); B: Serum beta-glucan concentrations of patients with Crohn's disease are stratified according to histologic healing or inflammation, and transmural healing or inflammation, based on magnetic resonance enterography. The analysis was performed by the Kruskal-Wallis on ranks test, in which multiple comparisons were performed using Dunn's test. The horizontal bars represent medians, and the boxes represent the 25th and 75th percentiles. Significant results are depicted ($^aP = 0.0018$; $^bP = 0.011$).

levels detected in the control group. Therefore, although a combination of intestinal dysbiosis and abnormal permeability might be present in the context of IBD, the results of this study support the idea that the elevations of serum BG among IBD patients should be predominantly attributed to changes in the intestinal inflammatory activity.

CONCLUSION

In conclusion, serum BG concentrations are consistently associated with disease activity in IBD, particularly with histologic inflammation, the ultimate target of treatment. The stronger relationship of serum BG with CD than with UC appears to underlie differences in specific pathogenic mechanisms. The relative changes are even more tightly associated with disease activity, suggesting that repeated measurements of serum BG might become a useful resource in the follow-up of patients with IBD. Finally, serum BG might prove particularly useful in IBD because of its noninvasive nature, ease of performance and relative low cost. Further prospective studies will be necessary to determine the best time intervals for measuring serum BG routinely in patients with IBD.

ARTICLE HIGHLIGHTS

Research background

Currently, the approach for monitoring the most precise predictors of disease outcomes in inflammatory bowel diseases (IBD), mucosal or histologic remission, demands frequent endoscopic evaluations, which are costly and invasive procedures.

Research motivation

Finding novel non-invasive biomarkers to detect intestinal inflammation continues to represent a major challenge in the field of IBD research.

Research objectives

To determine whether the serum concentrations of beta-glucan (BG), a ubiquitous cell wall component of gut microorganisms, correlate with intestinal inflammation.

Research methods

A prospective observational study was performed in a tertiary referral center, from 2016 to 2019, in which serum BG was determined in patients with Crohn's disease (CD), ulcerative colitis (UC), and controls, using a photometric detection kit. The ability of BG to detect active *vs* inactive disease was assessed using the area under the receiver operating characteristic curve. Inflammatory activity was determined by ileocolonoscopy, histopathology, magnetic resonance enterography), and biomarkers, including fecal calprotectin, C-reactive protein, and a panel of cytokines. In subgroup analysis, serial BG was used to assess the response to therapeutic interventions.

Research results

The serum BG levels were higher in CD patients than in controls. The BG levels paralleled the endoscopic activity in CD patients and histologic activity and combined endoscopic and histologic activity in both CD and UC patients. Performance analysis showed that the BG results were remarkably better for predicting histologic inflammation than fecal calprotectin and C-reactive protein. Regarding the clinical, endoscopic, and histologic activities, the BG levels were reduced following therapeutic intervention in patients with CD and UC. Compared with and histologic healing, no significant correlation was found between serum BG and transmural healing based on magnetic resonance enterography, in CD patients. Positive correlations were detected between BG and interleukin-17 in the CD and the UC group, and between BG and interferon-gamma in the CD group.

Research conclusions

Serum BG concentrations are consistently associated with disease activity in IBD, particularly with histologic inflammation, the ultimate target of treatment.

Research perspectives

Serum BG emerges as an important novel noninvasive approach for detecting mucosal inflammation and therapeutically monitoring IBD.

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