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Study of ectodomain of type 23 collagen as a novel marker of disease activity in patients with ulcerative colitis disease

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Abstract

Inflammatory Bowel Diseases (IBDs) are complex, multifactorial disorders characterized by chronic relapsing intestinal inflammation. This prospective cohort study aimed to assess the role of the serum ectodomain of type 23 collagen as a biomarker of disease activity in patients with ulcerative colitis (UC). The study was conducted at Ain Shams University Hospitals over one year (April 1, 2023 to April 1, 2024) and included both inpatient and outpatient cases. Serum levels of type 23 collagen ectodomain were significantly higher in UC patients (4.08 ± 1.96 ng/mL) compared to healthy controls (1.85 ± 0.6 ng/mL, $p < 0.001$). Moreover, Patients with active UC had markedly elevated levels (5.46 ± 1.85 ng/mL) compared to those with inactive disease (2.7 ± 0.66 ng/mL). These findings suggest that serum type 23 collagen ectodomain is a promising marker for evaluating UC activity and severity, correlating closely with clinical, laboratory, endoscopic, and histopathological indicators of disease activity.

Keywords: Ectodomain, Type 23 Collagen, Novel Marker, Ulcerative Colitis.

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Introduction

Inflammatory bowel disease (IBD) is a chronic idiopathic disorder resulting from a dysregulated immune response to the intestinal microbiota. It includes Crohn's disease (CD) and ulcerative colitis (UC), which, although differing in disease location and histopathology, share gastrointestinal symptoms such as diarrhea, mucus, blood in stools, and abdominal pain, as well as extraintestinal manifestations including arthritis, skin lesions, and oral ulcers.[1]

The etiology of IBD is complex, involving interactions among genetic, environmental, microbial, and immunological factors, yet remains largely unclear.[2] Accurate assessment of disease activity is crucial for patient management; however, current noninvasive biomarkers provide only indirect information, while histopathological and endoscopic evaluations, though precise, are invasive, time-consuming, and costly.[3]

The intestinal epithelium plays a central role in maintaining gut homeostasis. In IBD, impaired epithelial barrier function allows bacterial invasion, triggering immune cell infiltration and inflammation.[4] Type 23 collagen, a transmembrane protein expressed by epithelial cells, can be cleaved and released into the extracellular matrix. It has been implicated in cell adhesion and tissue remodeling.[5–7]

Given its expression in the intestinal epithelium, we hypothesized that serum levels of type 23 collagen may reflect epithelial damage in IBD and serve as a potential biomarker to monitor disease activity.[8]

This study aimed to evaluate serum type 23 collagen levels in patients with ulcerative colitis and investigate its correlation with disease activity.

Materials and Methods

This prospective cohort study was conducted at Ain Shams University Hospitals and included adult patients (≥18 years) with a confirmed diagnosis of ulcerative colitis (UC). Patients were recruited from both inpatient wards and outpatient clinics between April 2023 and April 2024.

Diagnosis of UC was based on clinical evaluation supported by laboratory investigations, endoscopic findings, and histopathological confirmation in accordance with the European Crohn's and Colitis Organization (ECCO) consensus guidelines.[9]

A total of 60 Egyptian subjects were enrolled and divided into three groups: 20 patients with active UC, 20 patients with UC in remission, and 20 apparently healthy controls. Controls were comparable to patients in terms of age and sex distribution.

UC patients were classified as active or quiescent based on clinical assessment, inflammatory markers, fecal calprotectin levels, and endoscopic findings.

Patients were excluded if they were pregnant or lactating, refused participation, or had malignancy, diabetes mellitus, hypertension, chronic liver disease, chronic kidney disease, or other inflammatory gastrointestinal disorders that may affect disease activity, including celiac disease, based on clinical evaluation and available investigations. All participants provided written informed consent, and the study was approved by the Institutional Ethics Committee.

All subjects underwent detailed history taking and full clinical examination. Laboratory workup included complete blood count, liver and kidney function tests, coagulation profile, viral hepatitis markers (HBsAg, HBcAb, HCVAb), ESR, CRP, fecal calprotectin, stool culture, and testing for Clostridium difficile toxin.

Fecal calprotectin was measured in the Clinical Pathology Laboratory at Ain Shams University Hospitals using the PETIA (particle-enhanced turbidimetric immunoassay) method with the fCAL turbo assay kit (Bühlmann Laboratories AG, Switzerland), according to the manufacturer's instructions.

Ileo-colonoscopy was performed for all UC patients at the Gastroenterology and Endoscopy Unit, Ain Shams University Hospitals, and biopsies were taken for histopathological examination with attention to cytomegalovirus infection.

Ulcerative colitis (UC) severity was assessed endoscopically using the Ulcerative Colitis Endoscopic Index of Severity (UCEIS; 0–8), based on vascular pattern, bleeding, and ulceration. UCEIS scores were stratified into remission (0–1), mild (2–4), moderate (5–6), and severe (7–8).[10] Histological severity was assessed using the Geboes scoring system (0–5.4).[11]

Sample Collection and Serum Ectodomain of Type 23 Collagen Measurement

Blood samples were collected in plain tubes and allowed to clot at room temperature, centrifuged at 3000 × g for 10 minutes, and the separated serum was aliquoted and stored at −80°C until analysis. Serum levels of ectodomain of type 23 collagen were measured using commercially available ELISA kits (Bioassay Technology Laboratory, Cat. No. E1663Hu, China) according to the manufacturer's instructions. ELISA assays were performed in duplicate, with each well receiving 50 µL of standard solution or 40 µL of serum sample,

followed by 10 µL of biotinylated anti-ectodomain type 23 collagen antibody and 50 µL of streptavidin-HRP conjugate. Plates were sealed and incubated at 37°C for 60 minutes, washed five times with wash buffer, and 50 µL of substrate solution A and 50 µL of substrate solution B were added. Plates were incubated for 10 minutes at 37°C in the dark, the reaction was stopped with 50 µL of stop solution, and optical density was measured at 450 nm using a microplate reader. Concentrations were calculated from a standard curve.

All procedures were conducted using appropriate personal protective equipment and strict infection control protocols.

Statistical Analysis

Data were coded and analyzed using IBM SPSS Statistics version 27 (IBM Corp., Armonk, NY, USA). Quantitative variables were expressed as mean ± SD or median (IQR) according to distribution, while qualitative variables were presented as numbers and percentages. Normality was assessed using the Kolmogorov-Smirnov test. Comparisons between groups were performed using Chi-square or Fisher's exact test for categorical variables, and t-test, Mann–Whitney U test, ANOVA, or Kruskal-Wallis test for continuous variables, as appropriate. Post hoc analyses (Tukey's test or Dunn's test, as appropriate) were applied for multiple comparisons. Correlations were assessed using Spearman's coefficient. Receiver operating characteristic (ROC) curve analysis was used to determine optimal cutoff values, sensitivity, specificity, positive and negative predictive values, and area under the curve (AUC) for the studied marker. A p-value < 0.05 was considered statistically significant.

Results

Regarding demographic characteristics, the study included 60 participants equally divided into three groups: active UC, inactive UC, and healthy controls (20 participants each). Patients and controls were comparable regarding age and sex (p = 0.995 and p = 1.000, respectively), and no statistically significant difference was observed in smoking status (p > 0.05).

Laboratory investigations showed significantly lower hemoglobin and higher total leukocyte count (TLC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and fecal calprotectin in active UC compared with inactive UC and healthy controls (p < 0.01 for all). Post hoc analysis confirmed significant differences between active UC and both inactive UC and healthy controls across most inflammatory parameters, while inactive UC generally showed lower inflammatory burden.

Platelet count, serum albumin, liver enzymes (AST and ALT), and serum creatinine showed no significant differences among groups (P > 0.05). However, within the active UC subgroup, serum albumin showed a significant negative correlation with serum ectodomain of type 23 collagen (r = −0.482, p = 0.031). INR showed a statistically significant difference among the studied groups (p = 0.002), with higher values observed in UC patients compared with healthy controls.

Endoscopic and histopathological scores were significantly higher in active UC compared with inactive UC. Median UCEIS was 5 (IQR 3–7) in active UC versus 1 (IQR 1–2) in inactive UC, while Geboes scores were 3.65 (2.6–4.15) versus 1.65 (1.3–1.95), respectively (p < 0.01 for both).

Serum ectodomain of type 23 collagen

Serum ectodomain of type 23 collagen levels were significantly elevated in active UC (5.46 ± 1.85 ng/mL) compared with inactive UC (2.7 ± 0.66 ng/mL) and controls (1.85 ± 0.6 ng/mL) (p < 0.01). Post hoc analysis showed significant differences between active UC and inactive UC (p< 0.001), active UC and controls (p < 0.001), and inactive UC and controls (p< 0.05) (Table 1).

Table 1. Baseline demographic, laboratory, endoscopic, and histopathological characteristics, and serum ectodomain of type 23 collagen levels among the studied groups.

		Active UC group	Inactive UC group	Healthy control group	*p*-value
		No. = 20	No. = 20	No. = 20	
Age	Mean ± SD	35.4 ± 12.13	35.75 ± 11.8**0**	35.6**0**± 9.61	NS
Gender	Male	12 (60.0%)	12 (60.0%)	12 (60.0%)	NS
	Female	8 (40.0%)	8 (40.0%)	8 (40.0%)	
Smoking	No	16 (80.0%)	14 (70.0%)	15 (75.0%)	NS
	Current	3 (15.0%)	3 (15.0%)	4 (20.0%)	
	Ex-smoker	1 (5.0%)	3 (15.0%)	1 (5.0%)	
Hb (g/dL)	Mean ± SD	10.7 ± 1.18	11.7**0** ± 0.84	11.86 ± 1.07	<0.001
TLC (×10³/µL)	Mean ± SD	8.43 ± 2.66	6.73 ± 1.85	5.91 ± 1.22	<0.001
Plts (×10³/µL)	Mean ± SD	227.45 ± 80.64	264.75 ± 74.46	290.1 ± 97.97	NS
ESR (mm/hr)	Median (IQR)	33 (24 – 51)	15.5 **0**(12.75 – 17.15)	18.5**0**(13 – 26.5)	<0.001
CRP (mg/L)	Median (IQR)	31.5 (15 – 48)	3.85 (3.1 – 8.5)	9 (6.5**0** – 16.5)	<0.001
Albumin (g/dL)	Mean ± SD	3.93 ± 0.74	4.08 ± 0.41	4.29 ± 0.48	NS
AST (U/L)	Mean ± SD	32.95 ± 15.23	36.2**0** ± 17.79	32.65 ± 12.37	NS
ALT (U/L)	Mean ± SD	32.55 ± 11.03	37.2**0** ± 13.45	42.6**0** ± 17.32	NS
INR	Mean ± SD	0.98 ± 0.14	1.04 ± 0.12	0.89 ± 0.13	0.002
Serum creatinine (mg/dL)	Mean ± SD	1 ± 0.19	0.96 ± 0.21	0.93 ± 0.19	NS
UCEIS	Median (IQR)	5 (3 – 7)	1 (1 – 2)	N/A	<0.001
Geboes score	Median (IQR)	3.65 (2.6**0** – 4.15)	1.65 (1.3 – 1.95)	N/A	<0.001
serum ectodomain of type 23 collagen (ng/mL)	Mean ± SD	5.46 ± 1.85	2.7**0** ± 0.66	1.85 ± 0.6	<0.001

TLC = Total leukocyte count; Hb = Hemoglobin; Plts = Platelets; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; ESR = Erythrocyte sedimentation rate; CRP = C-reactive protein; INR = International Normalized Ratio; UCEIS = Ulcerative Colitis Endoscopic Index of Severity**;** N/A **=** Not applicable. Data are presented as mean ± SD or median (IQR), and categorical data as n (%). One-way ANOVA was used for normally distributed variables, Kruskal–Wallis test for non-parametric variables, and Chi-square test for categorical variables. $p > 0.05$ is not significant (NS).

Association of serum ectodomain with disease extent and severity

In active UC, serum ectodomain levels increased significantly with disease severity as assessed by the Truelove and Witts index ($p = 0.008$), rising from 4.08 ± 0.87 ng/mL in mild cases to 9.32 ng/mL in the fulminant case. However, no significant differences were observed according to disease extent (left-sided: 5.61 ± 2.10, extensive: 5.68 ± 1.48, proctitis: 3.87 ± 0.16 ng/mL; $p > 0.05$).

Serum ectodomain of type 23 collagen showed strong positive correlations with fecal calprotectin, UCEIS, and GEBOES score, moderate correlations with inflammatory markers, and weak negative correlations with hemoglobin, platelets, albumin, and ALT. These associations were generally stronger in active UC compared with inactive UC.

Fecal calprotectin showed a strong positive correlation with disease severity indices. It correlated significantly with UCEIS (r = 0.897, $p < 0.001$) and GEBOES score (r = 0.859, $p < 0.001$) in all UC patients. These correlations remained significant in both active UC (UCEIS: r = 0.669, P = 0.001; GEBOES: r = 0.656, $p = 0.002$) and inactive UC subgroups (UCEIS: r = 0.665, $p = 0.001$; GEBOES: r = 0.588, $p = 0.006$) (Table 2).

Table 2. Correlation of serum ectodomain of type 23 collagen with laboratory, endoscopic, and histopathological parameters among studied patients.

	S. ectodomain of 23 collagen					
	All patients		Active UC group		Inactive UC group	
	r	*p*-value	r	*p*-value	r	*p*-value
Hb (g/dL)	-0.319	0.013	-0.368	NS	-0.011	NS
TLC (×10³/µL)	0.471	<0.001	0.564	0.010	0.435	NS
Plts (×10³/µL)	-0.272	0.036	-0.383	NS	-0.037	NS
ESR (mm/hr)	0.451	<0.001	0.453	0.045	-0.045	NS
CRP (mg/L)	0.472	<0.001	0.584	0.007	0.382	NS
Albumin (g/dL)	-0.276	0.033	-0.482	0.031	-0.096	NS
AST (U/L)	-0.111	NS	0.025	NS	-0.339	NS
ALT (U/L)	-0.272	0.035	0.035	NS	-0.349	NS
INR	0.201	NS	-0.170	NS	-0.076	NS
S. Creatinine (mg/dL)	0.082	NS	-0.162	NS	-0.019	NS
Fecal calprotectin (µg/g)	0.961	<0.001	0.965	<0.001	0.920	<0.001
UCEIS	0.853	<0.001	0.715	<0.001	0.603	0.005
GEBOES score	0.806	<0.001	0.655	0.002	0.536	0.015

TLC = Total leukocyte count; Hb = Hemoglobin; Plts = Platelets; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; ESR = Erythrocyte sedimentation rate; CRP = C-reactive protein; INR = International Normalized Ratio;
UCEIS = Ulcerative Colitis Endoscopic Index of Severity. Correlations were assessed using Spearman's rank correlation coefficient. $p > 0.05$ is not significant (NS).

Diagnostic performance of serum ectodomain

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of serum ectodomain of type 23 collagen In distinguishing patients with ulcerative colitis from healthy controls, the area under the curve (AUC) was 0.912, with a cutoff value of >2.38 ng/mL yielding a sensitivity of 85%, specificity of 85%, positive predictive value of 91.9%, and negative predictive value of 73.9% (Figure 1).

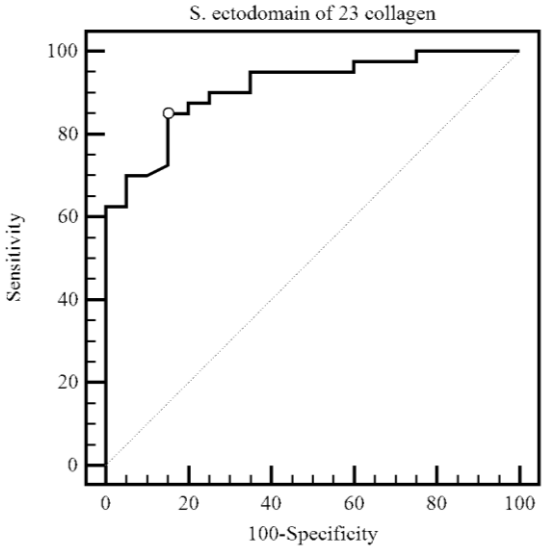

Figure 1. Receiver operating characteristics curve to assess area under the curve (AUC), sensitivity, specificity, positive predictive value and negative predictive value of S. ectodomain of 23 collagen level to differentiate between UC patients and healthy control group.

ROC curve analysis also evaluated the ability of serum ectodomain of type 23 collagen to differentiate active from inactive ulcerative colitis. The analysis yielded an area under the curve (AUC) of 0.931, with a cutoff value of >3.24 ng/mL, sensitivity of 90%, specificity of 90%, positive predictive value of 90%, and negative predictive value of 90% (Figure 2).

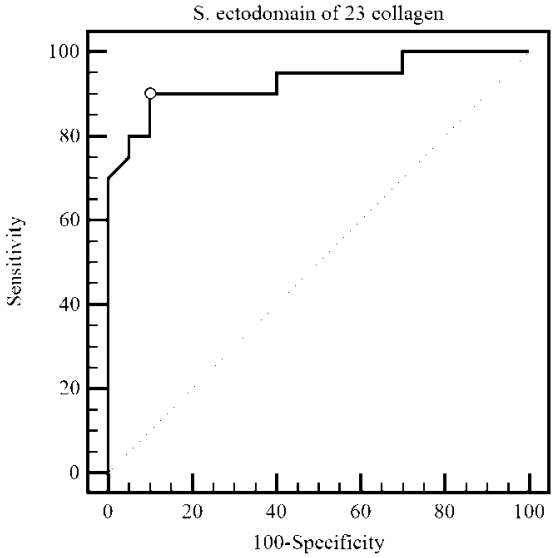

Figure 2. Receiver operating characteristics curve to assess area under the curve (AUC), sensitivity, specificity, positive predictive value and negative predictive value of S. ectodomain of 23 collagen level to differentiate between inactive UC and active UC patients.

Discussion

The present study aimed to evaluate serum ectodomain of type 23 collagen as a potential biomarker of disease activity in ulcerative colitis. Our findings demonstrated significantly elevated serum levels in UC patients compared with healthy controls, with further increase in active disease compared to inactive UC. These results suggest that this biomarker may reflect ongoing inflammatory activity and mucosal injury in UC.

In the current cohort, the demographic and baseline characteristics of UC patients were broadly comparable to previous reports, with a mean age of 35.57 ± 11.81 years, which is consistent with findings by Domislovic et al.[12] The proportion of smokers in our study was lower than that reported by Alexdottir et al.[13], which may reflect population differences and sample size variation. Variability in disease distribution and severity compared with previous studies[14–16] further highlights heterogeneity in UC cohorts and recruitment criteria across studies.

Serum ectodomain of type 23 collagen was significantly elevated in UC patients and showed a stepwise increase with disease activity, being highest in active UC. This supports its potential role as a dynamic marker of inflammatory burden. These findings are in agreement with Manon-Jensen et al.[16], who demonstrated strong associations between collagen-derived biomarkers and clinical disease activity indices including CRP, ESR, and fecal calprotectin.

Although serum albumin levels were comparable between active and inactive UC groups, albumin demonstrated a significant negative correlation with serum ectodomain of type 23 collagen within the active UC subgroup. This finding indicates that albumin may reflect individual variability in inflammatory burden rather than showing a statistically significant difference at the group level. Moreover, serum albumin is influenced by multiple factors including nutritional status, hepatic synthesis, hydration status, and protein-losing enteropathy, which may limit its ability to discriminate between disease activity categories in small cohorts.

Importantly, serum ectodomain levels showed strong correlations with endoscopic and histopathological indices of disease severity, consistent with previous reports by Manon-Jensen et al.[16] and Zhao et al.[17] These findings support the role of extracellular matrix remodeling as a marker of intestinal inflammation and tissue injury in UC, reflecting both macroscopic (endoscopic) and microscopic (histological) disease activity. This is further supported by Domislovic et al.[12], who demonstrated that collagen turnover markers can distinguish between remission and active disease.

In the present study, serum ectodomain levels were not influenced by disease extent, indicating that its elevation is more closely related to inflammatory activity rather than

anatomical distribution of disease. This is in line with findings by Manon-Jensen et al.[16], who also reported no significant association between disease extent and collagen-related biomarkers.

ROC curve analysis demonstrated good diagnostic performance of serum ectodomain of type 23 collagen, with high AUC values for distinguishing UC patients from controls and for differentiating active from inactive disease. These findings suggest potential clinical utility of this biomarker in non-invasive disease monitoring.

To the best of our knowledge, limited data are available regarding serum ectodomain of type 23 collagen in ulcerative colitis. Therefore, further studies in larger, well-characterized cohorts are warranted to validate its clinical utility and establish standardized cut-off values.

In conclusion, serum ectodomain of type 23 collagen appears to be a promising biomarker reflecting inflammatory activity, endoscopic severity, and histopathological damage in UC. It may serve as a non-invasive tool for disease monitoring and assessment, potentially reducing reliance on repeated endoscopic evaluation. However, further large-scale studies are required to validate its clinical utility and establish standardized cut-off values**.**

Author Contributions

All authors contributed to the study's conception and design. MEA and SHG; writing and preparation of the original draft. KMAR and SSAHG; writing, review, and editing. AGAD and KAHMS; conceptualization. MEA, KMAR, and AGAD; methodology. MEA and SSAHG; formal analysis and investigation. AGAD and KAHMS; resources. SSAHG and AGAD Supervision. All authors commented on previous versions of the manuscript. All authors agree with the content of the manuscript and declare that it has not been published elsewhere.

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 Shams University (Assurance FMASU MD, No.77/2023).

Informed consent

Each subject who participated in the study provided written informed consent before being enrolled in the research study.

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