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Serum Visfatin as a Diagnostic Marker of Active Inflammatory Bowel Disease

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ABSTRACT

Background & Aims: Inflammatory bowel diseases (IBD) have been reported to be caused by a complex interplay of immunological, infectious, and genetic factors. Previous studies have suggested that adipokines play a role in IBD by inducing proinflammatory cytokines. We aimed to evaluate the role of visfatin in the diagnosis algorithm of active IBD.
Methods: 85 newly diagnosed IBD patients [56 diagnosed with ulcerative colitis (UC) and 29 with Crohn's disease (CD)] and 30 healthy controls were included. IBD phenotypes were described accordingly to Montreal classification. Hemoglobin, total leucocytic count (TLC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), albumin, fecal calprotectin and serum visfatin were measured.
Results: The serum visfatin level was found to be significantly higher in patients with IBD than those in the control group ($p<0.001$). It was significantly positively correlated with CRP, ESR, and FC in both IBD groups. Receiver operating characteristic curve analysis of visfatin in diagnosis of UC revealed an area under curve of 0.911. At cutoff ≥1.4 ng/ml, the sensitivity was 92.9% and the specificity was 86.7%.. In CD group, at the same cutoff, AUC was 0.974, sensitivity was 96.6% and specificity was 86.7%. There was a statistically significant elevation of serum visfatin in extensive UC (E3) as compared to the other groups. A cutoff ≥3.25 ng/ml revealed 88.9% sensitivity, and 100% specificity in detection of E3 UC. Serum visfatin was significantly increased in CD stricturing phenotype (B2) as compared to non-stricturing non-penetrating CD (B1). A cutoff ≥3.5 ng/ml revealed 83.3% sensitivity, and 100% specificity in detection of B2.
Conclusions: The serum visfatin level were significantly higher in patients with IBD than in controls. Serum visfatin might be a novel noninvasive marker to detect activity in IBD patients and can be used as predictor of disease extension in patients with UC.

Key words: calprotectin – Crohn's disease – inflammatory bowel disease – ulcerative colitis – visfatin.

Abbreviations: AUC: area under curve; BMI: body mass index; B1: non-stricturing non-penetrating Crohn's disease; B2: stricturing Crohn's disease; CD: Crohn's disease; CRP: C-reactive protein; E1: proctitis; E2: left-sided colitis; E3: extensive ulcerative colitis (beyond the splenic flexure); ESR: erythrocyte sedimentation rate; FC: fecal calprotectin; IBD: inflammatory bowel disease; IL: interleukin; ROC: receiver operating characteristic; TLC: total leucocytic count; TNF-α: tumor necrosis factor alpha; UC: ulcerative colitis**.**

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory gastrointestinal tract disease. Chronic inflammation is associated with ulcerations and with malignancy development in untreated cases [1]. The optimal target in IBD is early diagnosis and close monitoring of the disease extent and severity for improved patient outcomes [2].

Endoscopy is the standard of care in diagnosis and monitoring patients with IBD [3, 4]. However, this procedure is time-consuming, expensive, and invasive and requires bowel cleansing. Furthermore, it is uncomfortable and inconvenient for many patients. Nonspecific biomarkers, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and fecal calprotectin (FC), have been widely used as noninvasive parameters to diagnose IBD with lack of specificity or sensitivity for disease extension [5]. Thus, searching for a non-invasive marker that can diagnose IBD and predict disease extension is a valuable target.

Individuals with IBD exhibit inflammation of the mesenteric adipose tissue lying in direct proximity to the inflamed bowel as well as alterations in local or serum adipokine concentrations [6]. Visfatin, an adipokine that increases the epithelial expression of tumor necrosis factor alpha (TNF-α), interleukin (IL)-l, IL-6, and adhesion molecules would be noninvasive, easily measured, and an inexpensive marker to diagnose and monitor disease activity and severity [7, 8].

We aimed to determine the serum concentrations of visfatin in newly diagnosed IBD patients, to evaluate its role in the diagnosis of IBD and correlate it with disease activity and colonoscopic findings.

METHODS

A prospective case–control study was conducted in Egyptian patients who visited Kafrelsheikh University Hospital, Egypt and were diagnosed with IBD in the period between November 2019 and May 2020. A total of 115 participants were enrolled in the study; they were classified into 3 groups: 56 patients with UC, 29 patients with CD and 30 age, gender and body mass index (BMI) matched apparently healthy volunteer who did not have any gastrointestinal tracts symptoms, systemic disease or family history. Patients with IBD were diagnosed by clinical findings and lower gastrointestinal endoscopy with histopathological confirmation. We used the Montreal classification for IBD patients [9]. They were selected from 100 patients who attend the Outpatient Clinic of Gastrointestinal and Hepatology Department in Kafrelsheikh University Hospital, Egypt, complaining of gastrointestinal symptoms suggestive of IBD such as persistent diarrhea, abdominal pain or rectal bleeding. Ten of them were excluded (8 patients were with infectious colitis and 2 with microscopic colitis); the remaining 90 patients were proven by endoscopy and histopathological examination to have IBD, but we failed to get consent from 5 of them.

Exclusion criteria included patients previously diagnosed with IBD and already had started treatment or who had refused follow-up and evaluation. Overweight and obese participants, patients with diabetes mellitus, metabolic syndrome, pregnant women were also excluded from the study.

This study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements. A written informed consent was obtained from all patients after explanation of the research idea.

All patients were subjected to detailed medical history and complete clinical examination. Patients underwent abdominal ultrasound and ileocolonoscopic examination with biopsies from suspected lesions in the colon and terminal ileum for histopathological confirmation.

A venous blood sample was aseptically withdrawn from each subject by venipuncture, the samples were divided into K3EDTA and sodium citrate tubes for hemoglobin and ESR respectively. The remaining sample was delivered into two sterile plain vacutainer tubes, one for CRP and albumin and the other for visfatin, left to clot at 37°C for 10 minutes, then centrifuged for 10 minutes; serum samples were stored at -80°C until visfatin measurement. Stool samples were collected for measuring FC, extracted by using the BIOHIT extraction tubes and extraction buffer before measurement by enzyme-linked immunosorbent assay (ELISA) using a BIOHIT Calprotectin ELISA kit- Cat. No. 602 260 (Helsinki, Finland).

Serum visfatin level was measured by ELISA using a Human Visfatin ELISA kit from My BioSource- Cat. No. MBS723926 (San Diego, USA). Laboratory personnel were blinded from the current clinical and endoscopic disease activity of patients.

Endoscopy was performed under conscious sedation, in spontaneous breathing with oxygen mask support. Colonoscopy was conducted by a single endoscopist at the same endoscopy unit using Pentax EG3890 colonoscope with complete examination performed up to the cecum with ileal intubation and biopsy from the ileum, also, complementary upper endoscopy using a Pentax EG29-i10 endoscope was performed for patients with CD to determine the Montreal classification [9]. The endoscopist was blinded from the FC results and other laboratory measurements.

Mucosal biopsies were obtained from each affected bowel segment, targeting the area with the most significant mucosal disease activity. Two pathologists assessed all biopsies and report histology utilizing a standardized scale that includes histologically normal, quiescent, mild, moderate, or severe disease [10].

Statistical analysis was conducted using the SPSS 21 (SPSS Inc., Chicago, IL, USA). Data are expressed as median (25^{th} and 75^{th} percentiles) or mean ± standard deviation. Multiple comparisons were performed using the Kruskal–Wallis or analysis of variance tests, respectively, and Mann–Whitney U or chi-square tests were used to analyze differences between the two groups. Correlations were calculated using Spearman's rank-order correlation coefficient for non-parametric data. Receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic power of circulating visfatin as an IBD marker. Overall marker accuracy was defined as area under curve (AUC). Additionally, the optimal cut-off was established, and corresponding sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), and accuracy were calculated. All tests with p-values of<0.05 were considered statistically significant.

RESULTS

Demographic data and colonoscopic findings are illustrated in Table I. IBD patients‘ groups showed significantly lower hemoglobin, and albumin and higher total leucocytic count (TLC), ESR, CRP, and FC levels compared to the control group. ESR was higher in CD group compared to UC group. Patients‘ groups had significantly higher visfatin levels than the control group while there was no significant difference in visfatin between patients' groups (Table II, Fig. 1)

In patients with UC, serum visfatin was significantly positively correlated with the BMI, CRP, ESR, TLC, and FC and negatively correlated with serum albumin. Within the CD group, there was a significant positive correlation between serum visfatin and ESR, CRP, and FC (Table III).

According to Montreal classification, serum visfatin levels were significantly higher in UC patients with extensive UC (E3) than patients with proctitis (E1) and left-sided colitis (E2) (Fig. 2) as well as in patients with stricturing CD phenotype (B2)

Table I. Demographic data and endoscopic findings of the studied groups

Characteristics	UC	CD	Control	p
N	56	29	30	
Gender (male/female)	32/24	19/10	18/12	0.76
Age (years)*	38.3±11.7 (16 – 57)	33.8±11.8 (18 – 57)	36.2±10.6 (23 – 56)	0.22
BMI (kg/m^2)*	23.9±1.9 (18 – 27)	23.2±2.5 (19 – 28)	24.1±2.2 (19 – 28)	0.28
IBD Phenotype				
E1/E2/E3	20/18/18			
B1/B2		19/10		

UC: ulcerative colitis; CD: Crohn`s disease; BMI: body mass index; IBD: inflammatory bowel diseases; E1: proctitis; E2: left-sided colitis; E3: extensive UC (beyond the splenic flexure); B1: non-stricturing non-penetrating; B2: stricturing; *Data are presented as number or mean ± standard deviation (range)

compared to non-stricturing non-penetrating CD phenotype (B1) (Fig. 3, Table IV).

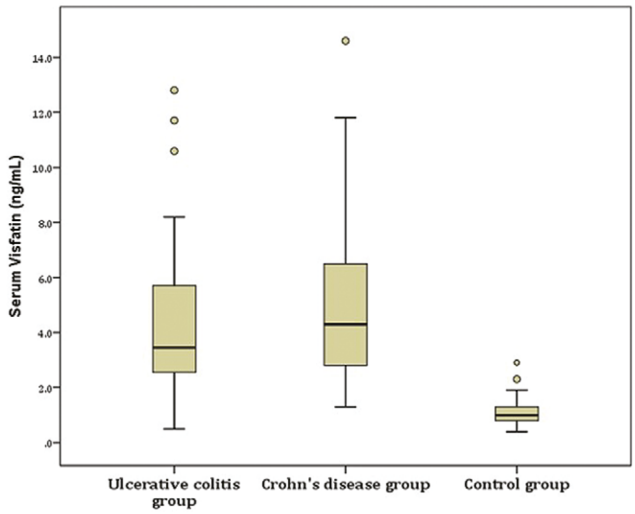

Fig. 1. Boxplot showing serum visfatin level among the studied groups

In linear stepwise regression, only FC level was significantly independently associated with serum visfatin level among patients with UC and CD (unstandardized β=0.002, $p < 0.001$).

ROC curve analysis of visfatin in diagnosis of UC revealed an AUC of 0.911. At cutoff ≥1.4 ng/ml, the sensitivity was 92.9%, the specificity was 86.7%, the positive predictive value was 92.9%, the negative predictive value was 86.7% and the accuracy was 90.7%.

For diagnosis of CD, visfatin ROC curve-AUC is 0.974. At ≥1.4 ng/ml cutoff, the sensitivity was 96.6%, the specificity was 86.7%, the PPV was 87.5%, the NPV was 96.3%, and the accuracy was 91.5% (Fig. 4, 5).

We used a ROC curve to determine the best cutoff for visfatin in the detection of E3 UC (Fig. 6). At ≥3.25 ng/ml, the sensitivity was 88.9%, the specificity was 100%, the PPV was 100%, the NPV was 93.7%, and the accuracy was 95.8%. In CD, when the cutoff of ≥3.5 ng/ml was chosen for differentiating the B2 from B1 phenotype, the sensitivity was 83.3%, the specificity was 100%, the PPV was 100%, the NPV was 90.9% and the accuracy was 93.8% (Fig. 7).

Table II. Comparison between the studied groups regarding laboratory data

Parameters	UC	CD	Control	p
Hemoglobin (g/L)*	12.1±1.6 (6.5 – 14.3)	11.1 ± 1.5 (8 – 13.9)	13.5 ± 1.2 (11.4 – 16)	<0.001**
LSD comparison	p1=1	p2=<0.001**	p3=<0.001**	
TLC (x103/mm^3)*	7.6 ± 2.1 (4.2 – 15.3)	8.5 ± 2.2 (4.6 – 13.2)	6.2 ± 1.6 (4 – 10)	<0.001**
LSD comparison	p1=1	p2=<0.001**	p3=<0.001**	
ESR (mm/hr.)†	33.5 (5 – 95)	50 (15 – 90)	12 (4 – 20)	<0.001**
Pairwise comparison	p1 =0.014*	p2=<0.001**	p3 =<0.001**	
CRP (mg/L)†	12 (0.8 – 110)	16 (1.1 – 65)	1.25 (0.8 – 4.2)	<0.001**
Pairwise comparison	p1 =0.541	p2=<0.001**	p3=<0.001**	
Albumin (g/dL)*	4.1± 0.5 (2.5 – 5.1)	3.9 ± 0.5 (2.8 – 4.6)	4.6 ± 0.4 (4 – 5.2)	<0.001**
LSD comparison	p1 =1	p2=<0.001**	p3=<0.001**	
Fecal calprotectin μg/mg)†	545 (26 – 2950)	711 (38 – 2950)	24 (13 – 56)	<0.001**
Pairwise comparison	p1=1	p2=<0.001**	p3=<0.001**	
Serum visfatin (ng/mL)†	3.5 (0.5 – 12.8)	4.3 (1.3 – 14.6)	1.0 (0.4 – 2.9)	<0.001**
Pairwise comparison	p1=0.625	p2=<0.001**	p3=<0.001**	

UC: ulcerative colitis; CD: Crohn`s disease; TLC: total leucocyte count; ESR: erythrocyte sedimentation rate; CRP: C reactive protein; *mean ± standard deviation (range); †median (range); $p < 0.05$ is statistically significant; **p≤0.001 is statistically highly significant; p1 the difference between UC and CD groups; p2 the difference between healthy control and CD groups; p3 the difference between UC and healthy control groups.

Table III. Correlation between serum visfatin and other studied parameters

Parameter	Serum visfatin (ng/mL)			
	UC group		CD group	
	r	p	r	p
Age (year)	0.11	0.42	-0.03	0.87
BMI (kg/m^2)	0.31	0.02*	0.21	0.28
Hemoglobin (g/dL)	-0.16	0.23	-0.04	0.83
TLC (x103/mm3)	0.28	0.04*	-0.21	0.29
Serum albumin (g/dL)	-0.54	<0.001**	-0.11	0.62
CRP (mg/L)	0.58	<0.001**	0.48	0.01*
ESR (mm/hr.)	0.58	<0.001**	0.44	0.02*
Fecal calprotectin (μg/mg)	0.69	<0.001**	0.64	<0.001**

BMI: body mass index; TLC: total leucocyte count; CRP: C reactive protein; ESR: erythrocyte sedimentation rate; r=Spearman rank correlation coefficient; *p<0.05 is statistically significant; **p≤0.001 is statistically highly significant.

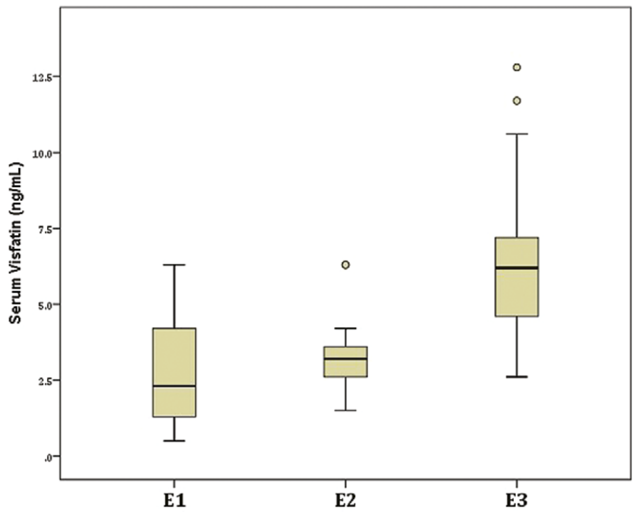

Fig. 2. Serum visfatin and phenotypes of ulcerative colitis.

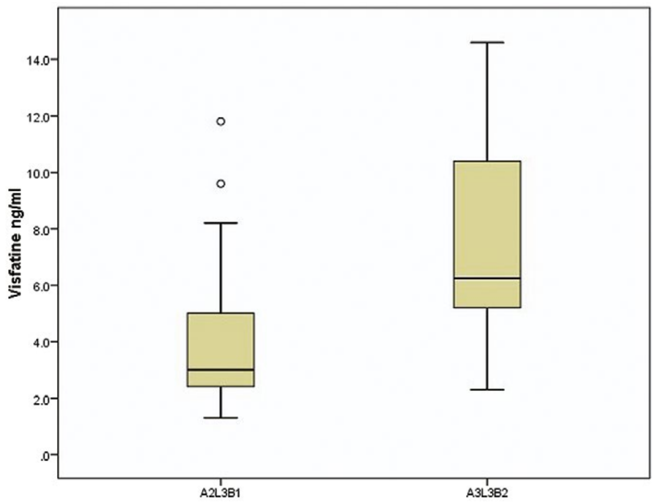

Fig. 3. Serum visfatin and phenotypes of Crohn's disease.

Table IV. Relation between serum visfatin and IBD phenotypes

Parameter	UC phenotype				CD phenotype		
	E1	E2	E3	p	B1	B2	p
Serum visfatin (ng/mL)	2.3 (0.5-6.3)	3.2 (1.5-6.3)	6.2 (2.6-12.8)		3 (1.3 – 11.8)	6.25 (2.3 – 14.6)	0.013
Pairwise comparison	p1=0.103	p2 =0.002	p3=<0.001	<0.001			

UC: ulcerative colitis; CD: Crohn's disease; E1: proctitis; E2: left-sided colitis; E3: extensive UC (beyond the splenic flexure); B1: non-stricturing non-penetrating CD; B2: stricturing CD; Data expressed as median (range); p1: the difference between E1 and E2 groups ; p2: the difference between E2 and E3 groups; p3: the difference between E1 and E3 groups.

DISCUSSION

Inflammatory bowel diseases refers to chronic, complex diseases of uncertain pathogenesis, affecting >5 million people worldwide and lacks an ideal gold standard for diagnosis and monitoring [11]. In our study, we measured FC levels as a gut inflammatory marker, and results showed highly significant elevation in patients with IBD as compared with a control group with a higher level in CD compared to UC. FC is an abundant neutrophil protein found in both plasma and stool and is markedly elevated in infectious and inflammatory conditions. Accumulation of neutrophils at the site of inflamed mucosa in the gastrointestinal tract results in the release of calprotectin into the feces where it is stable and resistant to bacterial degradation [12].

Although FC results were promising, some drawbacks exist in its use; an elevated FC is nonspecific for IBD. Any inflammatory process within the gastrointestinal tract will result in the activation of the innate immune response and release of calprotectin. Previous studies have shown that FC concentration has been elevated in many diseases' conditions, including infection, colorectal cancer, untreated coeliac disease, microscopic colitis, and diverticulitis [13]. Nonsteroidal anti-inflammatory drugs have been shown to cause significant

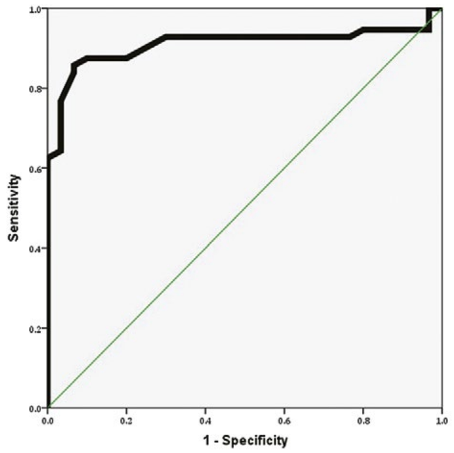

Fig. 4. Receiver operating characteristic curve showing performance of serum visfatin to detect active ulcerative colitis among studied patients (AUC 0.91).

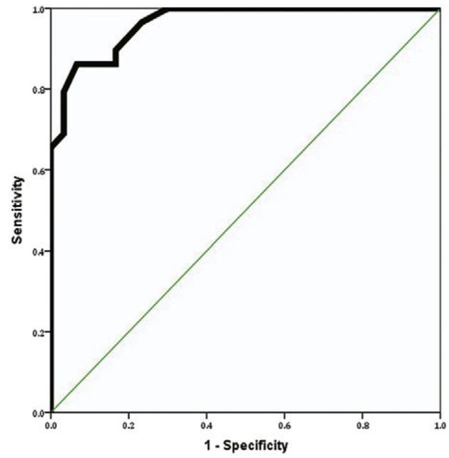

Fig. 5. Receiver operating characteristic curve showing performance of serum visfatin to detect active Crohn's disease among studied patients (AUC 0.97).

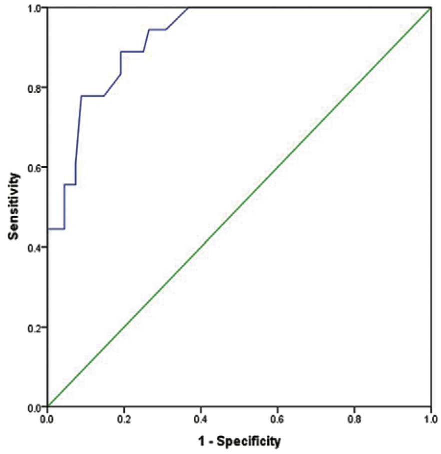

Fig. 6. Receiver operating characteristic curve showing performance of serum visfatin to detect extensive colitis (E3) among studied patients with ulcerative colitis (AUC 0.92).

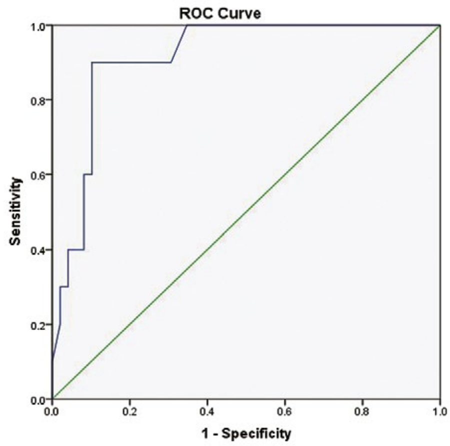

Fig. 7. Receiver operating characteristic curve showing performance of serum visfatin to diferentiate sticturing CD phenotype (B2) from non-stricturing/non-penetetring CD (AUC 0.91).

increases in FC levels within 7 days because they induced intestinal inflammation with endoscopic correlation [14].

Because of the lack of specificity of FC, another noninvasive marker should be identified to replace the invasive colonoscopic technique; one of the adipokines has been chosen, visfatin. Many adipokines with a bidirectional interaction between inflammation of the gut and visceral fat may exist in patients IBD [15]. Inflammatory reactions localized in the bowel wall may penetrate the surrounding visceral adipose tissue. Imaging methods provide evidence for hypertrophy of the mesenteric adipose tissue in patients with CD [6]. Moreover, submucosal fat deposition in the bowel is observed both in patients with CD and UC. The anatomic proximity of the bowel and visceral fat favors the activation of adipocytes [16].

This study revealed a significant increase in visfatin levels among patients with IBD compared to controls with a higher level in CD than UC although it did not reach the statistical significance. These results are in agreement with that of Waluga et al. [17] who found that baseline serum visfatin was significantly higher in subjects with CD and UC than in healthy controls which indicated that bowel inflammation was responsible for elevation of serum visfatin. They suggested that adipokines are involved in the pathogenesis of IBD. However, the lack of a direct correlation between serum levels and IBD activity implies that adipokines are modulators rather than determinants of IBD severity. Our results are also close to that of Terzoudis et al. [18] who reported that serum visfatin levels were higher in CD than in UC patients.

Visceral adipose tissue is not only an energy storage site but also an active endocrine organ. Adipokines influence the immunologic system of the gastrointestinal tract, in some cases, worsening IBD by amplifying inflammation via the secretion of proinflammatory interleukins, TNF-α, and adhesion factors. Visfatin is an example of an adipokine that increases the epithelial expression of TNF-α, IL-l, IL-6, and adhesion molecules [19, 20]. Visfatin is proposed as important pro-inflammatory mediators, which interfere with the central regulation of insulin sensitivity. It has been suggested to be a beneficial adipokine with insulin-mimicking/-sensitizing effects by activating the insulin signal transduction pathway, achieved by binding to the insulin receptor at a site different from that of insulin [21]. Other studies demonstrated that visfatin was also synthesized and released by neutrophils in response to inflammatory stimuli and that it functioned as an inhibitor of apoptosis resulting from a variety of inflammatory stimuli [22].

The results of the present study revealed a highly significant correlation between serum visfatin and ESR, CRP, and FC in both IBD groups. A better understanding of the molecular mechanism of the association between the adipose tissue function and intestinal inflammatory pathological condition development can be achieved by investigating the potential involvement of adipokines in generating these responses [23]. Additional evidence for a potential crosstalk between adipose and intestinal tissues as they were involved in the development of intestinal inflammation is provided by a biomarker of intestinal inflammation and increased risk for the development of colorectal cancer. Higher levels of FC were associated with obesity [24].

ROC curve analysis of visfatin to detect active UC revealed a high diagnostic efficacy with an AUC 0.911. At the level of ≥1.4 ng/ml, it had 92.9% sensitivity and 86.7% specificity. In CD, ROC-AUC was 0.974. At the same cutoff, sensitivity was 96.6%, while specificity was 86.7%. Our results regarding UC are better than those published by Dogan et al. [25] who reported 72% sensitivity and 52% specificity in patients with active UC achieved remission with specific anti-inflammatory therapy. The difference between our results and those reported by Dogan et al. [25] may be due to the difference in disease status of patients and the genetic difference between the two populations.

In our study, serum visfatin presented higher levels in UC E3 as compared to E1 and E2 and higher level in CD B2 phenotype compared with B1 phenotype. The significant change in the circulating visfatin levels is suggesting the suitability of serum visfatin as a non-invasive marker to predict the IBD activity as well as disease extension in UC. One recent study related leptin level, one of the adipokines, with disease activity on endoscopy. They found significantly decreased leptin in active IBD patients compared to those without disease activity on endoscopy, suggesting the involvement of a defective regulation of the leptin pathway in the pathogenesis of IBD [26].

Our results should be interpreted with caution due to some limitations. The sample size of studied groups was small, which may have affected our statistical power. The insulin resistance was not evaluated. In addition, the study was performed on Egyptian „Caucasian" population and cannot be generalized to all populations.

CONCLUSIONS

The serum visfatin level was significantly higher in newly diagnosed patients with IBD than in controls. Serum visfatin might be a novel noninvasive marker to detect activity in IBD patients and can be used as a predictor of disease extension in patients with UC. Further studies on big sample sizes and on different populations are recommended to confirm these results.

Conflicts of interest: None to declare.

Authors' contribution: M.M.S, N.A.N, H.A.A and M.H.A conceived and designed the study. M.M.S, S.M.S, H.A.A performed the analyses. M.M.S, M.H.A and S.M.S collected the data, performed the statistical analysis, interpreted the results and drafted the manuscript. M.H.A, S.M.S, H.A.A revised the manuscript. All the authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

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