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Serum Visfatin Levels in Patients with Ulcerative Colitis

Hassan Mohammed Abdelghaffar[1], Abdelmonem Mohamed Barrrak[2], Bahy Eldeen Elsayed ELbahnasawy[3], Ahmed Ali Ali Assem[4]

[1, 2, 3]Department of Internal Medicine, Faculty of Medicine, Al-Azhar University, Egypt

[4]Department of Clinical Pathology, Faculty of Medicine, Al-Azhar University, Egypt
[1]Corresponding author: Hassan Mohammed Abdelghaffar

Abstract: ***Background: Previous studies have suggested that adipokines play a role in inflammatory bowel disease by inducing proinflammatory cytokines, but it is uncertain whether visfatin is causally involved in ulcerative colitis (UC). Aim and objectives: was to evaluate serum Visfatin levels in patients with UC and its correlation with the activity of disease. Subjects and methods: This is a prospective study, was carried out on forty UC patients, attending to internal medicine department, Elsaiedgalal university hospital, and ten subjects apparently healthy volunteers as a control. Result: Visfatin, active patients group showed significantly higher levels compared to remission group (7.45 ± 0.85 Vs 5.35 ± 0.80 with p-value = 0.000). Conclusion: The visfatin level was higher in the active group than in post-treatment remission and the healthy control group. Sensitivity and specificity were similar to other inflammatory markers for assessing clinical activity, which did not improve clinical outcomes in patients with acute respiratory distress syndrome (ARDS).***

Keywords: Ulcerative colitis; Disease activity; Visfatin; adipokines

1. Introduction

Ulcerative colitis is an idiopathic inflammatory condition of the colon which results in diffuse friability and superficial erosions on the colonic wall associated with bleeding. It is the most common form of inflammatory bowel disease worldwide. It characteristically involves inflammation restricted to the mucosa and submucosa of the colon. Typically, the disease starts in the rectum and extends proximally in a continuous manner (***Gisbert and Chaparro, 2019).***

The specific cause of inflammatory bowel disease is not known. There seems to be a primary genetic component since the most important independent risk factor is a family history of the disease (8% to 14% of patients). A first-degree relative of a patient with ulcerative colitis has a four times higher risk of developing the disease. Although there is little evidence to support this, it has been postulated that alterations in the composition of the gut microbiota and defects in mucosal immunity could lead to ulcerative colitis. Autoimmunity may also play an important role in the etiology of ulcerative colitis (***Liu and Polk, 2018).***

Many types of adipokines have been shown to be derived from white adipose tissue (WAT).

Visfatin has been identified as a novel and multifaceted protein, which plays an important role in regulating a variety of physiological and pathological functions (***Carbone et al., 2017).***

Several proinflammatory and immune-regulatory cytokines are up-regulated in patients with UC, and a similar cytokine profile is induced by Visfatin, suggesting that Visfatin may play role in the emergence of UC (***Dogan et al., 2016).***

The aim of this work evaluation of serum Visfatin levels in patients with UC and its correlation with the activity of disease.

2. Patients and Methods

This a prospective study that carried on forty UC patients, attending to internal medicine department, Elsaiedgalal university hospital, and ten subjects apparently healthy volunteers as a control divided as following: Group one: forty patients with UC. The diagnosis of UC depends on standard clinical, endoscopic and histological criteria. Group two: ten apparently healthy volunteers matched for age and sex as a control.

Exclusion criteria: Patients had undergone anti-inflammatory therapies including steroid and azathioprine or combination of these treatments, patients with pregnancy, patient with previous intestinal surgery, patients suffered from diabetes mellitus (DM), patients with coronary artery disease (CAD), patient with malignancy, hypertensive patients, auto-immune connective tissue disorders, chronic kidney disease and active or chronic infections.

2.1 Methods

All patients and control groups will subject to the following: Full medical history with special emphasis on: Age, sex, viral hepatitis, chronic illness, family history of chronic inflammatory bowel diseases and history of treatment of diarrhea. Full clinical examination including: Anthropometric measures: height, weight and body mass index (BMI). Clinical examination with special emphasis on: Fever, pallor, abdominal tenderness, cramping, inflammation of iris and uvea, skin rash, inflammation of joints, aphthous ulcers and clubbing of the fingers. Laboratory investigations: Serum samples were collected

from all the subjects (Group 1 and 2) at the start of the study and from the patients group (Group 2) after remission for white blood cells (WBCs), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) Colonoscopy and biopsy for histopathological examination for patient group (Group 1). Visfatin analysis using a commercially available ELISA kit at the start of the study for all subjects and after remission for the patients group

2.2 Statistical analysis

IBM SPSS-22 program (Inc, Chicago, IL, USA) has been used to perform statistical analysis. Data have been examined for normal distribution via the Shapiro Walk testing. Qualitative data have been presented as frequency and relative percentage. Chi square testing ($\chi 2$) has been utilized to determine change among 2 or more groups of qualitative variables. Quantitative data have been presented as mean ± SD (Standard deviation). Nondependent sample t-testing has been utilized in comparing among 2 nondependent groups of normal distribution variables (parametric data) &Mann-Whitney testing. P value < 0.05 was judged significant. ROC-curve was built to permit choice of threshold values for testing findings and comparisons of various testing approaches. Areas under ROC curves and their standard errors have been calculated via the technique of Cantor, and matched via the normal distribution, with correction for association of notes resulting from the same cases. AUC of ROC shows: 0.90 – 1 = excellent, 0.80-0.90 = good, 0.70-0.80 = fair; 0.60-0.70 = poor; and 0.50-0.6 = fail. The optimal cut-off point has been recognized at point of maximum accurateness.

2.3 Ethics and patient consent

All procedures in this study had been following AL-Azhar University Ethical committee regulations, and verbal consent will be taken from all participants.

3. Results

There was no statistically significant difference between control and patients group regarding mean age (37.8 ± 11.94 Vs 40.48 ± 9.94) with p-value = 0.468, gender (40 % females Vs 45 %, 60 % males Vs 55%) with p-value = 0.776. **Table (1)**

Table 1: Comparison between control and patients group among the demographic data of the studied subjects

		Control group	Patients group	Test value	P-value	Sig.
		No. = 10	No. = 40			
Age (Year)	Mean ± SD	37.80 ± 11.94	40.48 ± 9.94	-0.731	0.468	NS
	Range	26 – 50	30 – 50			
Sex	Female	4 (40.0%)	18 (45.0%)	0.081*	0.776	NS
	Male	6 (60.0%)	22 (55.0%)			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
*: Chi-square test; •: Independent t-test

Weight was significantly lower in patients group compared to control group (73.73 ± 8.46 Vs 81.10 ± 8.18 with p-value = 0.017). Also, BMI was significantly lower in patients group compared to control group (24.39 ± 2.64 Vs 26.95 ± 2.22 with p-value = 0.007). There was no statistically significant difference between control and patients group regarding height (173.40 ± 5.38 Vs 173.95 ± 6.69) with p-value = 0.811. **Table (2)**

Table 2: Comparison between control and patients group among the anthropometric measures of the studied subjects

		Control group	Patients group	Test value•	P-value	Sig.
		No. = 10	No. = 40			
Weight (kg)	Mean ± SD	81.10 ± 8.18	73.73 ± 8.46	2.480	0.017	S
	Range	73 – 89	65 – 82			
Height (cm)	Mean ± SD	173.40 ± 5.38	173.95 ± 6.69	-0.241	0.811	NS
	Range	168 – 179	167 – 181			
BMI	Mean ± SD	26.95 ± 2.22	24.39 ± 2.64	2.825	0.007	HS
	Range	24.7 – 29	21.7 – 27			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
•: Independent t-test

ESR and CRP were significantly higher in active patients group compared to control group (ESR: 10.60 ± 2.75 Vs 7.30 ± 2.63 with p-value = 0.001), (CRP: 4.73 ± 1.45 Vs 2.90 ± 1.45 with p-value = 0.001). There was no statistically significant difference between control and active patients group regarding WBC (6582.00 ± 2085.67 Vs 6011.25 ± 1554.95) with p-value = 0.338. Colonoscopic results revealed that score 1 was found in 11 (27.5%) active patients, score 2 in 14 (35.0%) active patients, score 3 in 11 (27.5%) active patients and score 4 in 4 (10.0%) active patients. Regarding histopathology, 14 (35.0%) active patients had stage I, 22 (55.0%) active patients had stage II and 4 (10.0%) active patients had stage III. As regards Visfatin level inactive patients group showed significantly higher levels compared to control group (7.45 ± 0.85 Vs 5.42 ± 0.65 with p-value = 0.000). **Table (3)**

Table 3: Comparison between control and active patients group among the laboratory, colonoscopic, histopathology and Visfatin of the studied subjects

Active		Control group	Patients group	Test value	P-value	Sig.
		No. = 10	No. = 40			
WBC (per /mic L)	Mean ± SD	6582.00 ± 2085.67	6011.25 ± 1554.95	0.968	0.338	NS
	Range	4496 – 8667	4456 – 7566			
ESR (mm/hr)	Mean ± SD	7.30 ± 2.63	10.60 ± 2.75	-3.419	0.001	HS
	Range	4– 10	8– 13			
CRP (mg/L)	Mean ± SD	2.90 ± 1.45	4.73 ± 1.45	-3.561	0.001	HS
	Range	1 – 4	3 – 6			
Colonoscope	Score 1	--	11 (27.5%)	–	–	–

	Score 2	--	14 (35.0%)			
	Score 3	--	11 (27.5%)			
	Score 4	--	4 (10.0%)			
Histopathology	Stage 1	--	14 (35.0%)	–	–	–
	Stage 2	--	22 (55.0%)			
	Stage 3	--	4 (10.0%)			
Visfatin (ng/ml)	Mean ± SD	5.42 ± 0.65	7.45 ± 0.85	-7.000	0.000	HS
	Range	4.8 – 6.1	6.6 – 8.3			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
•: Independent t-test

There was no statistically significant difference between control and remission patients groups regarding WBC (6582.00 ± 2085.67 Vs 5983.75 ± 1396.53) with p-value = 0.280. There was no statistically significant difference between control and remission patients group regarding ESR (7.30 ± 2.63 Vs 7.10 ± 2.48) with p-value = 0.822. Also, there was no statistically significant difference between control and remission patients groups regarding CRP (2.90 ± 1.45 Vs 3.73 ± 1.30) with p-value = 0.086. Colonoscopic results revealed that all patients with remission had score 0. As regards Visfatin, there was no statistically significant difference between control and remission patients groups (5.42 ± 0.65 Vs 5.35 ± 0.80) with p-value = 0.786. **Table (4)**

Table 4: Comparison between control and remission patients group among the laboratory, colonoscopic and Visfatin of the studied subjects

Remission		Control group	Patients group	Test value	P-value	Sig.
		No. = 10	No. = 40			
WBC (per /mic L)	Mean ± SD	6582.00 ± 2085.67	5983.75 ± 1396.53	1.092	0.280	NS
	Range	4497 – 8667	4587 – 7380			
ESR (mm/hr)	Mean ± SD	7.30 ± 2.63	7.10 ± 2.48	0.226	0.822	NS
	Range	4 – 10	4 – 10			
CRP (mg/L)	Mean ± SD	2.90 ± 1.45	3.73 ± 1.30	-1.755	0.086	NS
	Range	1 – 5	2 – 5			
Colonoscope	Score 0	--	40 3.73 ± 1.30 (100.0%)	--	--	--
Visfatin (ng/ml)	Mean ± SD	5.42 ± 0.65	5.35 ± 0.80	0.273	0.786	NS
	Range	4.8 – 6.1	4.5 – 6.2			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
•: Independent t-test

ESR was significantly higher in active patients group compared to remission group (10.60 ± 2.75 Vs 77.10 ± 2.48 with p-value = 0.000). Also, CRP was significantly higher in active patients group compared to remission group (10.60 ± 2.75 Vs 77.10 ± 2.48 with p-value = 0.000) (CRP: 4.73 ± 1.45 Vs 3.73 ± 1.30 with p-value = 0.000). There was no statistically significant difference between the two groups regarding WBC (6582.00 ± 2085.67 Vs 5983.75 ± 1396.53) with p-value = 0.788. As regards Visfatin, active patients group showed significantly higher levels compared to remission group (7.45 ± 0.85 Vs 5.35 ± 0.80 with p-value = 0.000). **Table (5)**

Table 5: Comparison between active and remission patients group among the laboratory data and Visfatin of the studied subjects

Patients group		Active	Remission	Test value	P-value	Sig.
		No. = 40	No. = 40			
WBC (per /mic L)	Mean ± SD	6011.25 ± 1554.95	5983.75 ± 1396.53	-0.270	0.788	NS
	Range	4500 – 7600	4600 – 7400			
ESR (mm/hr)	Mean ± SD	10.60 ± 2.75	7.10 ± 2.48	-6.811	0.000	HS
	Range	7 – 14	4 – 10			
CRP (mg/L)	Mean ± SD	4.73 ± 1.45	3.73 ± 1.30	-3.801	0.000	HS
	Range	3 – 7	2 – 5			
Visfatin (ng/ml)	Mean ± SD	7.45 ± 0.85	5.35 ± 0.80	-21.368	0.000	HS
	Range	6.6 – 8.3	4.5 – 6.2			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
•: Paired t-test

Visfatin can determine diseased patients at cutoff point at 5.9 ng/ml with the sensitivity, specificity, PPV and NPV was 65%, 70%, 68.4% and 66.7% respectively **Figure (1), Table. (6)**

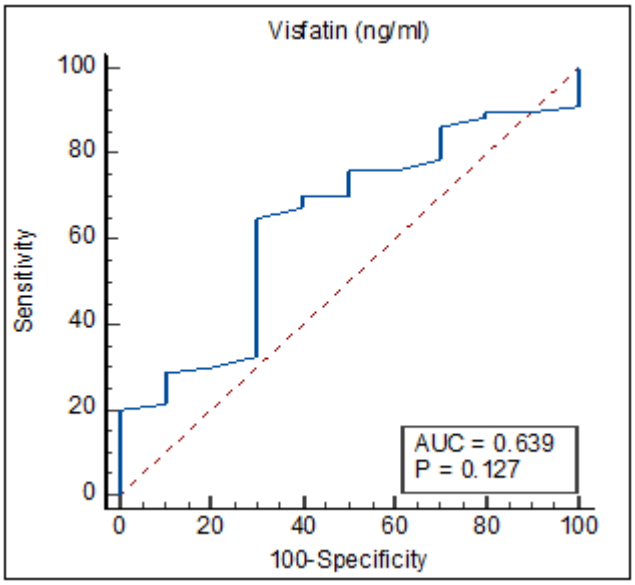

Figure 1: ROC curve for Visfatin as a predictor of patients

Table 6: Validity of Visfatin as a predictor of patients

Parameter	AUC	Cut of Point	Sensitivity	Specificity	PPV	NPV
Visfatin (ng/ml)	0.639	>5.9	65.0	70.0	68.4	66.7

Visfatin can differeniate between active patient disease and patients disease with remission at cutoff point at 6.8ng/ml with the sensitivity, specificity, PPV and NPV was 67.5%, 50%, 57.5% and 60.6% respectively. **Figure (2), Table (7).**

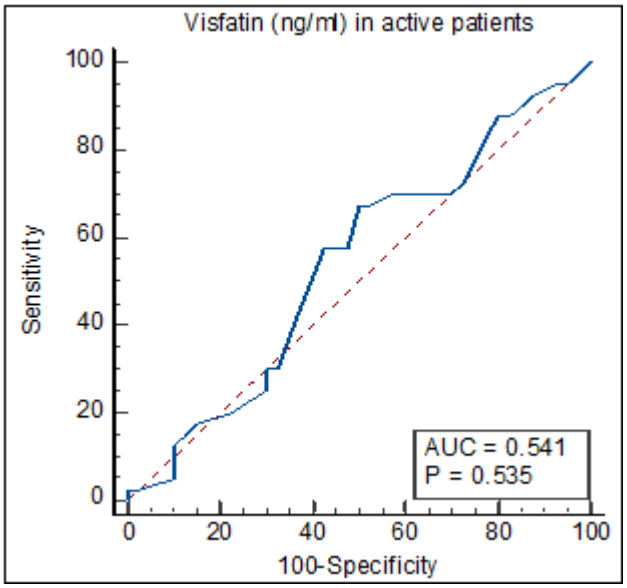

Figure 2: ROC curve for Visfatin as a predictor of disease activity.

Table 7: Validity of Visfatin as a predictor of disease activity

Parameter	AUC	Cut of Point	Sensitivity	Specificity	PPV	NPV
Visfatin (ng/ml)	0.535	>6.8	67.5	50.0	57.5	60.6

4. Discussion

Visfatin is a recently identified adipokine, secreted primarily by visceral WAT. It is also produced by various cells, and levels are elevated in the systemic circulation of patients with various diseases such as Behçet's disease, rheumatoid arthritis, chronic viral hepatitis B, nonalcoholic fatty liver disease and cardiovascular disease (**Sun et al., 2017).**

UC is an inflammatory disease of the gastrointestinal tract; its cause remains unknown, but the disease seems to be multifactorial and polygenic. Alterations in the ingredient of the gut microbiota, mucosal intolerance against microbial load, dysregulation of the mucosal immune response and autoimmunity are associated with susceptibility to UC. Research is currently focused on its immunopathogenesis. These studies have resulted in progress in understanding the process of the disease and the identification of several immunological markers that may play important roles in treatment modalities. Some of the molecules may be valuable as indicators of disease activity and severity (**Rubin et al., 2019).**

The present study showed that there were statistically significant differences between UC and the controls as regard weight. There were highly statistically significant differences between active UC and the controls as regard WBCs, ESR, CRP &Visfatin. There were no statistically significant differences between remission UC and the controls as regard WBCs, ESR, CRP &Visfatin. There were highly statistically significant differences between active UC and remission as regard ESR, CRP &Visfatin.

In accordance with our results, study of**Dogan et al., 2016** as they reported that the mean visfatin levels of the control, inactive and active UC patients were 6.54 ± 2.20, 6.18 ± 2.04 and 7.77 ± 2.41, respectively ($P < 0.05$). The serum visfatin levels of active patients were significantly higher than inactive UC patients and controls. However, there was no significant difference between the groups with active disease versus in remission, or between those in remission and controls, in WBC counts or ESR after appropriate therapy ($P = 0.65$ and 0.61, respectively).

Also, **Moschen et al., 2007** showed that visfatin induced the production of inflammatory cytokines and may be considered a new proinflammatoryadipocytokine. Plasma visfatin was found to be elevated in patients with IBD and its mRNA expression was increased significantly in the colonic tissue of IBD colitis patients versus healthy controls.

Another study held by **Waluga et al., 2014** investigated five circulating adipokines (leptin, resistin, visfatin, RBP-4 and adiponectin) and glucose homeostasis in patients with inactive and active IBD. Visfatin alone was increased in active disease versus remission. The study by **Waluga et al., 2014** investigated serum adipokine levels in IBD patients before treatment and after achieving clinical remission. Baseline serum concentrations of visfatin were significantly higher in subjects with UC than in healthy controls. None of the previously reported studies, between active and inactive groups, failed to detect a significant difference in visfatin levels (**Jia et al., 2004).** In this cohort study, involving

patients with active UC, they compared levels before treatment of the flare with anti-inflammatory and/or immunosuppressive therapy, and the post-treatment remission phase and a healthy control group. Unlike other studies, treatment decreased visfatin levels in the remission group. Although not diagnostic, elevation of CRP and ESR in IBD are well-known markers for determining and monitoring disease activity. However, surprisingly, their levels did not show a difference among the groups (P = 0.65 and 0.61, respectively) (**Jia et al., 2004).**

In the current study our results were supported by study of **Saadounet al., 2021** as they reported that the serum visfatin level was found to be significantly higher in patients with IBD than those in the control group (p<0.001).

In the study of **Hwangbo et al., 2010**, the serum levels of leptin, adiponectin, and resistin showed no significant alterations, whereas the serum visfatin level decreased significantly after induction therapy, suggesting a possible pro-inflammatory property of visfatin and a role as a marker of successful therapy of IBD. Also, **Shawky et al., 2014** demonstrated that the serum levels of resistin and visfatin decreased significantly after treatment induction for IBD so can be used as a marker for treatment success.

Furthermore, **Wenxia et al., 2017** revealed that serum level of visfatin was significantly higher in patients with active CD and UC than in healthy controls [(385.24 ± 112.64) pg/mL and (378.91 ± 118.57) pg/mL vs. (321.11 ± 96.27) pg/mL, P all < 0.05]. The current study showed that regarding ROC curve for Visfatin as a predictor of patients, the AUC was 0.639, the cutoff point was > 5.9, the sensitivity was 65%, the specificity was 70%, the PPV was 68.4% and NPV was 66.7%. Regarding ROC curve for Visfatin as a predictor of disease activity, the AUC was 0.535, the cutoff point was >6.8, the sensitivity was 67.5%, the specificity was 50%, the PPV was 57.5% and NPV was 60.6%.

Our results were supported by study of **Dogan et al., 2016** as they reported that ROC curve analysis suggested that the optimum visfatin cut-off level for active UC was 6.40, with a sensitivity, specificity, PPV and NPV of 72%, 52%, 66.7% (43.0–85.4) and 50.0% (29.1–70.9), respectively.

Whereas, **Saadounet al., 2021** demonstrated that 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%.
While, in the study of**Wenxia et al., 2017**, the area under curve (AUC) of serum visfatin for diagnosis of CD and UC were 0.654 and 0.622, respectively; the diagnostic accuracy was relatively low.

In the current study: our results showed that there was significant positive correlation between Visfatin, ESR and CRP inpatients with active disease. There was highly significant positive association between Visfatin in active colonoscopy and Histopathology. There was significant positive correlation between Visfatin in remission and CRP. There was significant positive association between Visfatin in remission and sex.

However, **Wenxia et al., 2017** revealed that significant positive correlation was found between serum visfatin level and disease activity index (Mayo score) of UC (r =0.398, P < 0.05), however, no correlations were found between serum visfatin level and disease activity index of CD, CRP and ESR, two common inflammatory indicators for IBD and location of IBD (P all> 0.05). The difference between their study and ours may be attributed to different sample size, different duration of study and different inclusion criteria.

In contrary to our results, study of **Hwangbo et al., 2010**, as they demonstrated that no significant correlation between the changes in BMI, CRP level, or the clinical indices of activity and alterations of the measured adipokines was demonstrated. The difference between their study and ours may be explained by different severity of disease.

Also, in the study of**Terzoudis et al., 2016** there were no significant correlations between chemerin, visfatin, or vaspin with C-reactive protein, BMI, and age.

5. Conclusion

We report here a connection between UC flares and visfatin levels. Visfatin levels may reflect disease activity.

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