Serum omentin-1 as a predictor of activity in Crohn's disease

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Background and aim
Crohn's disease (CD) is associated with alterations in fat mass and fat distributions, with changed productions of adipokines, including omentin-1. Omentin-1 may be involved in the pathogenesis of inflammatory bowel disease. The aim was to determine the serum and mucosal omentin-1 levels in CD patients and to evaluate its potential as a marker for disease activity.
Patients and methods
Seventy-five adult consecutive outpatients, with a confirmed diagnosis of CD, and 45 age-matched, sex-matched, and BMI-matched healthy volunteers were enrolled in this study after written conscious consent and approval by the Institutional Review Board of Mansoura University. CD was diagnosed by conventional clinical, radiological, endoscopic, and histopathological criteria. Serum levels and mucosal mRNA expression of omentin-1 were measured by commercially available kits according to the manufacturer's protocols.
Results
Serum omentin-1 and its mucosal gene expression were significantly lower in patients with CD (53.3±12.8) than in healthy controls (72.7±16.8, $P<0.0001$). Moreover, serum omentin-1 levels were significantly lower in patients with active CD (36.2±9.6) than in patients in remission (69.2±14.4, $P\leq0.0001$). No significant differences were demonstrated between patients in remission and healthy controls ($P>0.05$). In CD patients, the decrease in serum omentin-1 was associated with a significantly higher BMI, C-reactive protein, erythrocyte sedimentation rate, Crohn's disease activity index, simplified endoscopic score for CD and inflammation scores ($P\leq0.05$). Moreover, omentin-1 was much superior to C-reactive protein in predicting CD activity and severity.
Conclusion
Serum and mucosal expression of omentin-1 might be a reliable surrogate noninvasive marker of disease activity in CD with significantly high sensitivity, specificity, and diagnostic accuracy.

Keywords:
adipocytokines, Crohn', s disease, inflammatory bowel disease, omentin-1

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Introduction

Inflammatory bowel disease (IBD) is a chronic immune-mediated systemic inflammatory disorder comprised mainly of Crohn's disease (CD) and ulcerative colitis that destroy the intestinal mucosa and/or wall [1]. Despite the unknown exact etiology, IBDs may be caused by a complex interplay of immunological, infectious, and genetic factors, leading to neutrophilic activation with proinflammatory mediator production and ultimately tissue damage [2].

CD is characterized by altered fat distributions, hypertrophy of visceral fat mass, submucosal fat deposition (fat halo sign), expansion of mesenteric white adipose tissue (WAT), and intra-abdominal fat accumulations [3,4]. WAT, the major component of adipose tissue and an energy-storage site, consists of various cells such as adipocytes, which are the most abundant cells, CD31, CD14, and macrophages. WAT was demonstrated to express and secrete various bioactive multifunctional mediators, collectively the so-called adipo(cyto)kines, such as adiponectin, leptin, resistin, omentin, ghrelin, obestatin, and visfatin. These adipocytokines were evidenced to play pivotal roles in the inflammatory pathways [5].

Omentin, a 34-kDa recently discovered visceral fat-specific adipocytokine of 313 amino acids, is encoded by two genes, omentin-1 and omentin-2, and is highly expressed and exclusively secreted by stromal cells of visceral adipose tissue (VAT). There is no evidence for its secretion from subcutaneous adipose tissue. Omentin-1, also named intelectin-1, is the major circulating isoform in human serum [6]. Serum

omentin-1 level was reported to be significantly downregulated in several diseases, such as obstructive sleep apnea, colorectal cancer, pancreatitis, psoriasis, obesity, insulin resistance, diabetes mellitus, and ischemic heart disease. In some diseases, omentin-1 may be upregulated, such as liver cirrhosis, nonalcoholic steatohepatitis, and lupus nephritis [7].

The aim was to determine the serum levels and colonic mucosal mRNA expression of omentin-1 in patients with CD and to evaluate its potential as a marker for CD activity. The correlations of omentin-1 levels with clinical, endoscopic, and histological findings in participants were also studied.

Patients and methods

Patients

A total of 75 adult consecutive outpatients, older than 18 years, with a confirmed diagnosis of CD, were enrolled in this study from July 2017 to 2019. Another 45 healthy participants (volunteers, medical students, and health workers) without any signs of inflammation or intestinal symptoms matched to the cases by age, sex, and BMI were also enrolled as a control group. All patients were selected from the outpatient clinic of IBD in the Gastroenterology Department of Mansoura University Hospital. A written informed conscious consent was obtained from all participants before their participation. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and was approved by the Institutional Review Board of Mansoura Faculty of Medicine (MFM-IRB: R.18.01.22).

Exclusion criteria

Patients with incomplete ileocolonoscopy, past history of any malignant condition and major gastrointestinal surgical procedures, liver cell failure, coagulopathy, chronic renal failure, congestive heart failure, malignant hypertension or strokes, endocrinal diseases (diabetes, adrenal insufficiency, thyroid disease), cardiopulmonary diseases, advanced chronic or psychiatric illness, and pregnancy, smokers, drug or alcohol abusers, patients on NSAIDs, patients with aspirin intake and any special type of dieting or treatments for the previous 6 months were excluded from the study. Five patients and two healthy participants were excluded, and the remaining participants underwent routine laboratory and radiological investigations and gastrointestinal endoscopic evaluation at enrollment.

Methods

Initially, all participants completed a detailed questionnaire with regard to diet and habits, submitted to thorough history taking with special emphasis on abdominal pain, weight loss, rectal bleeding, diarrhea, tenesmus, passage of mucus, constipation, abdominal distension, malaise, lethargy, anorexia, nausea, vomiting and low-grade fever along with detailed physical examinations performed at fasting in the morning. At the day of study inclusion, BMI was calculated as weight in kilograms divided by height squared in meters. Venous blood samples were obtained from each participant after a minimum of 10 h of fasting. Serum tubes were centrifuged at 3500 rpm for 10 min at 4°C, aliquoted and stored at −80°C until assayed. White blood cell count, hemoglobin, hematocrit, platelet count, serum albumin, cholesterol, triglycerides, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were tested.

The diagnosis of CD was established by conventional clinical, radiological, endoscopic, and histopathological criteria. Clinical disease activity of CD patients was determined according to Crohn's disease activity index (CDAI). Active CD is defined as a CDAI score more than or equal to 150, extremely severe CD as a CDAI score more than 450, and inactive CD as a CDAI score less than 150 [8].

Endoscopy

Total colonoscopy and ileoscopy (distal ileum) (colonoscope; XQ40, Pentax Fiberoptic, Tokyo, Japan) performed after overnight fast and/or cleansing enemas between 08:00 and 10:00 am. The macroscopic endoscopic features of mucosa were evaluated, and multiple biopsies were taken from the colon or ileum (from both diseased and healthy areas) for histopathological examination and RNA isolation. The macroscopic endoscopic signs of inflammation were recorded using the simplified endoscopic score for CD (SES-CD) as follows: inactive CD (0–3), mild active CD (4–10), moderate activity (11–19), and highly active (≥20) [9].

The biopsy specimens taken were embedded in paraffin blocks, sectioned and stained with hematoxylin and eosin for conventional histopathological examination. Biopsy sections were encoded and analyzed semiquantitatively on a four-point scale (0, 1, 2, and 3; none, mild, moderate, and severe inflammation, respectively) by two independent well-trained histopathologists, who were blinded to the endoscopic diagnosis, clinical data, the treatment, and the

participant group identity. This histological inflammation score served as the reference standard to determine the inactive or active CD in this study cohort. CD was considered inactive if there were no histological signs of inflammation (inflammation score <1).

Serum omentin-1 levels

Serum omentin-1 levels were measured by commercially available human enzyme-linked immunosorbent (ELISA) assay kits performed in duplicates according to the manufacturer's guidelines (BioVendor, Laboratorni Medicina, Brno, Czech Republic). Omentin-1 Human ELISA Kit (other names: Intelectin-1, ITLN-1, Intestinal lactoferrin receptor, Endothelial lectin HL-1, Omentin): it is a sandwich ELISA, Biotin-labeled antibody; Catalog No.: RD191100200R; size: 96 wells; the kit has high sensitivity and specificity, limit of detection of 0.5 ng/ml, and calibration range of 2–64 ng/ml; sample type: serum, plasma-EDTA, plasma-heparin, and plasma-citrate; sample volume: 6 µl per well; intra-assay coefficient variation: 4.6%; interassay coefficient variation : 3.7%; and storage: 2–8°C.

The mRNA expression of omentin-1

Total RNA was extracted and purified from mucosal biopsy specimens with TRIzol Plus RNA Purification Kit (Catalog No.: 12183555; Invitrogen Life Technologies, San Francisco, California, USA) using the standard procedure. The mRNA expressions of omentin-1 were quantified and evaluated by a real-time quantitative reverse transcriptase (qRT) PCR using the isolated RNA according to the manufacturer's protocol. Real-time qRT-PCR analysis was carried out with SYBR Premix Ex Taq (Catalog No.: RR420A; Takara Bio Inc., Kusatsu, Shiga, Japan) and gene-specific primers (Catalog No: HP212467; OriGene Technologies, Inc., 9620 Medical centre Drive, Suite 200, Rockville, MD, USA). The sequences of primers were as follows: (sense):5′-ACG TGC CCA ATA AGT CCCC-3′ and (antisense):5′-CCG TTG TCA GTC CAA CAC TTTC-3′. The PCR specificity was examined by 3% Ready Agarose Precast Gel (Bio-Rad Laboratories, Inc., 2000 Alfred Nobel Drive, Hercules, California, USA). The real-time qRT-PCR results were analyzed with the SDS 7000 software. The gene mRNA levels were corrected using β-actin [10].

Statistical analyses

Statistical analyses were carried out using SPSS, version 20.0, software (SPSS Inc., Chicago, Illinois, USA). Data normality was analyzed using the Kolmogorov–Smirnov test. Data were presented as mean±SD if normally distributed or as median and interquartile range if not. Frequencies were used for categorical variables. Comparisons of the characteristics between two groups were performed by *t* test or fisher's exact test. Comparisons of the characteristics between multiple groups were performed by one-way analysis of variance. Univariate and multivariate logistic regression analyses were performed to calculate the odds ratio and 95% confidence intervals for the prediction of active CD. The correlations between serum omentin-1 and other parameters were analyzed using Spearman correlation analysis. Receiver operating characteristics Curves for omentin-1, CDAI, and CRP were analyzed for the area under the curve (AUC), sensitivity, specificity, likelihood ratios, predictive values, cut-off values, and diagnostic accuracy. Statistical significance was accepted at a level of *P* value less than or equal to 0.05.

Results

The demographic, clinical, serological, and histological data are shown in Table 1. This study included 43 healthy controls (HC) and 70 CD patients. Thirty-eight patients (58.3%; 18 female individuals and 20 male individuals) had active CD with a mean age of 40.1 years and the remaining 32 patients (41.7%; 13 females and 17 males) had inactive CD with a mean age of 41 years. The mean duration of disease was 8.1 years in active CD and 6.9 years in inactive CD. No significant differences were noticed between HC, active CD and inactive CD, as regards age, sex, visual analog scale, BMI, duration of disease, CBC, and serum albumin ($P > 0.05$). In contrast, the CRP, ESR, inflammation scores, SES-CD, and CDAI were significantly higher in patients with active disease ($P \leq 0.001$). Moreover, serum levels and mucosal mRNA expression of omentin-1 were significantly lower in patients with active CD (36.2±9.6, 25.3 ±11.7) than in patients in remission (69.2±14.4, 59.6 ±19.2) and in HC (72.7±16.8, 64.8±23) ($P < 0.001$).

The correlations between omentin-1 and different parameters in patients with active CD are presented in Table 2. It was shown that serum omentin-1 level was negatively and significantly correlated with CRP (r=–0.309), ESR (r=–0.423), inflammation scores (r=–0.349), SES-CD scores (r=–0.536), and CDAI (r=–0.346) ($P \leq 0.01$ for all). Moreover, omentin-1 had a significantly positive correlation with its mucosal mRNA expression (r=0.871, $P < 0.0001$) and with BMI (r=0.652, P=0.048). CRP was positively and

Table 1 Demographic data, and clinical, serological, and histopathological features of Crohn's disease patients and healthy controls

Group (*N*)	HC (43)	Active CD (38)	Inactive CD (32)	*P*1	*P*2	*P*3
Age (years)	47.6±11.27	45.4±10.8	46.16±11.9	0.392	0.805	0.583
Sex (53♀/♂60)	21/22	18/20	14/18	0.874	0.982	0.578
BMI (kg/m^2)	22.45±3.1	20.88±4.5	21.77±3.3	0.0001	0.164	0.182
Duration (years)	–	8.1±3.2	6.9±4.3	–	0.686	–
Hemoglobin (g/dl)	13.5±1.4	10.7±2.3	10.1±2.4	0.581	0.679	0.985
WBCs (10^3mm^3)	5.43±1.7	7.8±1.99	6.99±1.7	0.741	0.338	0.783
Platelets (10^3mm^3)	301±23.5	287.6±48.3	269±55	0.457	0.198	0.474
Serum albumin (g/dl)	4.95±0.3	3.6±0.25	3.4±0.33	0.733	0.870	0.512
CRP (mg/dl)	26.1±4.1	39.9±6.4	30.3±4.9	0.000	0.001	0.452
ESR	14.6±3.3	55.83±6.18	19.8±4.06	0.000	0.001	0.214
Inflammation score	–	2.7±0.8	0.89±0.8	–	0.000	–
SES-CD score	–	7.9±2.6	3.3±2.3	–	0.000	–
CDAI	–	178.2±12.6	125.9±16.7	–	0.000	–
Serum omentin-1 (ng/ml)	72.7±16.8	36.2±9.6	69.2±14.4	<0.001	<0.001	0.327
mRNA omentin-1	64.8±23	25.3±11.7	59.6±19.2	<0.001	<0.001	0.641

t test for equality of means was used for comparison. Data were presented as mean±SD. CD, Crohn's disease; CDAI, Crohn's disease activity index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HC, healthy controls; *P*1, compared active CD versus HC; *P*2, compared active disease versus inactive disease; *P*3, compared inactive disease versus HC; SES-CD, simplified endoscopic score for CD; WBCs, white blood cells. Significance (two-tailed) at *P* value less than 0.05.

Table 2 Spearman's rho correlations between omentin-1 and different parameters in patients with active Crohn's disease

	CRP		Omentin-1		mRNA omentin-1	
	r	*P*	*r*	*P*	*r*	*P*
BMI	–0.073-	0.502	0.652	0.048*	0.744	0.045*
CRP (mg/ml)	1.000	.	–0.309-	0.001**	–0.259-	0.008**
ESR	0.218	0.025*	–0.423-	0.000**	–0.531-	0.000**
Inflammation score	0.377	0.000**	–0.349-	0.000**	–0.277-	0.004**
SES-CD	0.357	0.000**	–0.536-	0.000**	–0.608-	0.000**
CDAI	0.421	0.000**	–0.346-	0.000**	–0.296-	0.002**
CDAI in patients with CRP< 4 mg/ml (n:13)	0.168	0.611	–0.499-**	0.001**	–0.502-**	0.001**
Omentin-1 (ng/ml)	–0.309-	0.001**	1.000	.	0.871	0.000**
mRNA Omentin-1	–0.259-	0.008**	0.871	0.000**	1.000	.

CDAI, Crohn's disease activity index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; *r*, correlation coefficient; SES, simplified endoscopic score. *P*, significant (2-tailed). Significance at *P* value less than or equal to 0.05.*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed).

significantly correlated with ESR (r=0.218), inflammation scores (r=0.377), SES-CD scores (r=0.357), and CDAI (r=0.421) ($P\leq$0.05 for all). Moreover, CRP had a significantly negative correlation with omentin-1 (r=–0.309, P=0.001) and mucosal mRNA expression of omentin-1 (r=–0.259, P=0.008). Of interest, in patients with active CD and CRP less than 4 mg/dl, the CRP was not significantly correlated with CDAI (r=0.168, P=0.611). However, in those active CD patients who were CRP negative, serum omentin-1 still had a significantly negative correlation with CDAI (r=–0.499, P=0.001). Mucosal mRNA expression of omentin-1 had a similar behavior like serum omentin-1, being negatively and significantly correlated with CRP (r=–0.259), ESR (r=–0.531), inflammation scores (r=–0.277), SES-CD scores (r=–0.608), CDAI (r=–0.296), and CDAI, with CRP being negative (r=–0.502) ($P\leq$0.01 for all).

Serum omentin-1 levels and mucosal mRNA expression of omentin-1 were demonstrated in relation to disease location in Table 3. Active CD (38 patients) was isolated ileum in 6/38 (16%) patients, isolated colon in 7/38 (18.4%) patients, isolated ileocolonic in 10/38 (26.3%) patients, isolated anal/perianal in 3/38 (8%) patients, anal/perianal with another site in 11/38 (29%) patients, and two or more sites other than anal/perianal in 1/38 (2.6%) patients. Inactive CD (32 patients) was isolated ileum in 4/32 (12.5%) patients, isolated colon in 7/32 (21.9.4%) patients, isolated ileocolonic in 9/32 (28.1%) patients, isolated anal/perianal in 2/32 (6.3%) patients, anal/perianal with another site in 7/32 (21.9%) patients, and two or more sites other than anal/perianal in 3/32 (9.4%) patients. In patients with CD, the present study did not find any significant relationship between disease location and serum omentin-1, mucosal mRNA

Table 3 Serum levels and mRNA expression of omentin-1 in relation to disease location in Crohn's disease

	Isolated ileum (10)	Isolated colon (14)	Isolated ileocolonic (19)	Isolated anal/ perianal (5)	Anal/perianal with another site (18)	Two or more sites other than anal/perianal	ANOVA
Number (38 active/32 inactive)	10 (6/4)	14 (7/7)	19 (10/9)	5 (3/2)	18 (11/7)	4 (1/3)	
Inflammation score	2.2±0.89	1.7±1.1	1.6±1.1	2.1±1.4	1.9±1.2	1.7±1.2	0.546
SES-CD score	6.44±3.5	5.66±3.7	6.4±4.9	7.2±3.8	5.8±2.9	6.3±3.6	0.934
CDAI	188±9.5	176±14.6	177±12.7	184.8±15.2	192.6±8.3	173.8±17.8	0.717
Serum omentin-1 (ng/ml)	36.5±9.5	36.1±7.15	37.4±9.3	35±9.3	37.4±7.3	388±56.4	0.912
mRNA omentin-1	59.9±11.4	60.7±15.2	54.9±9.7	44.7±15.5	74.5±7.9	54.8±115.5	0.103

Data are presented as mean±SD. ANOVA, analysis of variance; CDAI, Crohn's disease activity index; SD, standard deviation; SES-CD, simplified endoscopic score for CD. Significance at *P* value less than or equal to 0.05.

Table 4 Univariate and multivariate logistic regression analyses for the independent predictors of active Crohn's disease after adjustment for age, sex, and BMI

	Univariate regression analysis		Multivariate regression analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
ESR	1.734 (0.976–1.945)	0.039	1.517 (1.087–1.845)	0.154
CRP (mg/dl)	1.313 (0.987–1.625)	0.024	1.265 (0.987–1.645)	0.084
SES-CD score	1.032 (1.015–1.049)	0.009	0.979 (0.950–1.009)	0.161
CDAI	1.717 (1.376–2.256)	0.007	1.624 (1.296–2.278)	0.074
Serum omentin-1 (ng/ml)	1.202 (1.127–1.283)	<0.001	1.208 (1.119–1.303	<0.0001

95% CI, 95% confidence interval; CD, Crohn's disease; CDAI, Crohn's disease activity index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; OR, odds ratio; SES-CD, simplified endoscopic score for CD; WBCs, white blood cells. Significance at *P* value less than or equal to 0.05.

Table 5 Agreement of sensitivity, specificity, diagnostic accuracy, and area under the curve for serum omentin levels, C-reactive protein and Crohn's disease activity index in predicting activity in patients with Crohn's disease

	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	AUC	*P*	95% CI
Omentin-1	30.9	94.9	88.7	95.4	91.3	94.9	0.854	0.000	0.754–0.925
CDAI	150	87.67	80.72	83.87	76.47	82.35	0.722	0.000	0.617–0.827
CRP	3.6	83.71	68.75	82.78	74.47	79.67	0.658	0.009	0.548–0.767

95% CI, 95% confidence interval; AUC, area under the curve; CDAI, Crohn's disease activity index; CRP, C-reactive protein; NPV, negative predictive value; PPV, positive predictive value.

expression of omentin-1, CDAI, and SES-CD (analysis of variance; $P > 0.05$ for all).

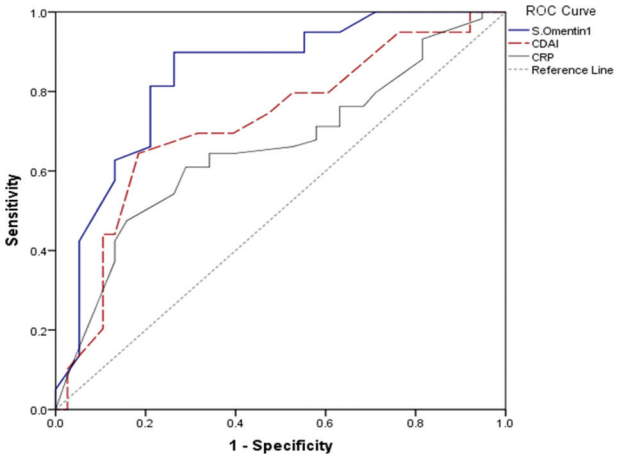
The univariate and multivariate logistic regression analyses are presented in Table 4. The univariate logistic regression analysis indicated that high ESR, high CRP, SES-CD score more than 4, CDAI more than or equal to 150, and low serum omentin-1 level showed a trend towards the significant prediction of the presence of active CD. The multivariate logistic regression model was performed using all the five parameters after adjustment for age, sex, and BMI. Of the five predictor variables, low serum omentin-1 level was demonstrated to be the only statistically significant independent predictor of the presence of active CD [odds ratio 95% confidence interval, 1.208 (1.119–1.303); $P<0.0001$].

The agreement of sensitivity, specificity, diagnostic accuracy, and AUC for serum levels of omentin-1, CDAI, and CRP in predicting patients with active CD are shown in Table 5. Serum level of omentin-1 had the best sensitivity (94.9%), specificity (88.7%), positive predictive value (95.4%), negative predictive value (91.3%), and diagnostic accuracy (94.9%). Furthermore, omentin-1 had the highest significant (AUC) and 95% confidence intervals at 0.854 (0.754–0.925). The optimal cut-off value of omentin-1 to predict active CD was 30.9 ng/ml.

Receiver operating characteristics curves for omentin-1, CDAI, and CRP are demonstrated in Fig. 1. Omentin-1 had higher and more significant AUC (95% confidence interval) than CDAI and CRP in predicting CD activity.

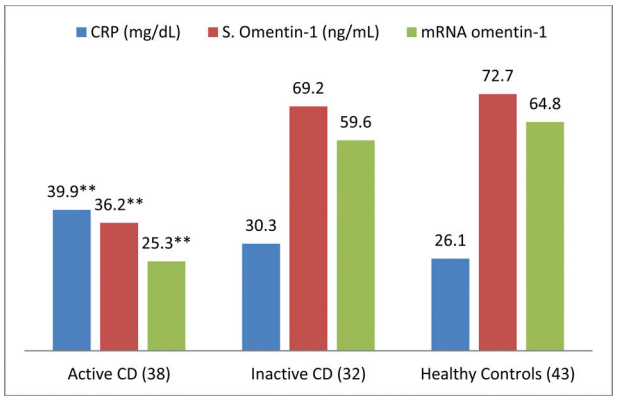
Figure 2 shows the mean values of CRP, serum omentin-1, and mRNA expression of omentin-1 in patients with CD and HC. Serum levels and mucosal

Figure 1



Receiver operating characteristics (ROC) curves for omentin-1, Crohn's disease activity index (CDAI), and C-reactive protein (CRP).

Figure 2



Mean values of C-reactive protein (CRP), serum omentin-1, and mRNA expression of omentin-1 in patients with Crohn's disease (CD) and in healthy controls (HC). **Significant when comparing active CD with inactive CD or with HC.

mRNA expression of omentin-1 were significantly lower in patients with active CD (36.2±9.6, 25.3 ±11.7) than in patients in remission (69.2±14.4, 59.6 ±19.2) and in HC (72.7±16.8, 64.8±23) ($P \leq 0.001$). On the contrary, CRP was significantly higher in patients with active CD (39.9±6.4) than in patients in remission (30.3±4.9) and in HC (26.1±4.1) ($P \leq 0.001$).

Discussion

Omentin, a recently discovered hydrophilic adipokine, is highly expressed and exclusively secreted by the stromal cells of VAT. Omentin-1, the major circulating isoform in human serum, became a hotspot of research due to its pleiotropic actions on various diseases [11]. Although CDAI is the most commonly used method to assess inflammatory activity in CD, it was reported, in some reports, that CDAI was similarly elevated in patients with CD and irritable bowel syndrome [12]. Moreover, the commonly used inflammatory markers, CRP and ESR, lack specificity for CD and are affected by concurrent factors [13]. Therefore, the present study prospectively investigated serum levels and mucosal mRNA expression of omentin-1 in patients with CD and assessed their predictive values for CD activity and severity.

In this study, it was demonstrated that serum omentin-1 levels and mucosal mRNA expression of omentin-1 were significantly lower in patients with CD than in HC. Patients with active CD had significantly lower serum levels and mucosal mRNA expression of omentin-1 than patients in remission. It was shown that serum omentin-1 level had a significantly negative correlation with CRP, ESR, inflammation scores, SES-CD scores, and CDAI. Moreover, omentin-1 had a significantly positive correlation with its mucosal mRNA expression and BMI. In patients with active CD and who were CRP negative (CRP<4 mg/ml), the CRP was not significantly correlated with CDAI. However, in those active CD patients who were CRP negative, serum omentin-1 and its mucosal mRNA expression still had a significantly negative correlation with CDAI. This observation suggested that omentin-1 was much superior to CRP in predicting CD activity and severity.

Lower serum omentin-1 level was reported to be a predictor of good coronary collateral circulation, and it was significantly downregulated in several diseases, such as heart failure and ischemic coronary heart disease [14], obstructive sleep apnea [15], colorectal cancer [16], and acute or chronic pancreatic diseases [17]. Moreover, plasma omentin-1 levels and omentin-1 mRNA expression were found to be decreased in obesity, overweight insulin-resistant women with polycystic ovary syndrome, and in diabetes mellitus. The downregulated omentin-1 in obesity may predict its metabolic consequences and comorbidities [18]. However, increased levels of plasma omentin-1 had been demonstrated in nonalcoholic steatohepatitis, an obesity-related disorder [19].

Lower plasma omentin-1 levels were also reported in patients with IBD. Consistent with the results obtained in this study, Lu *et al.* [20] demonstrated a significant decrease in serum level and mucosal mRNA expression of omentin-1. They reported that lower serum omentin-1 could be a potential marker of an active and severe CD at a cut-off value of omentin-1 at 30.34 ng/ml. The results in our study showed better

sensitivity, specificity, diagnostic accuracy, and AUC (95% confidence interval) for omentin-1 and its mucosal gene expression. Therefore, the relations between disease activity and serum omentin-1 level and colonic mucosal mRNA omentin-1 expression were better identified in the present study. Unfortunately, in the present study, patients with ulcerative colitis and functional intestinal disorders were not studied. Moreover, the relationship between omentin-1 and other adipocytokines such as leptin and adiponectin were not investigated.

The exact mechanisms underlying altered serum omentin-1 levels and its gene expression is not obvious. The attenuation of the mucosal mRNA expression for omentin-1 and the consequent reduction of omentin-1 production in the stromal cells of VAT may account for the decrease in the serum omentin-1 levels in patients with CD. Nonetheless, some studies reported increased omentin-1 expression in epicardial adipose tissue despite the decrease in its plasma level in senile patients with coronary artery disease and heart failure [21].

Although the increased fat mass and altered fat distributions during the pathogenesis of IBD were long thought to make no sense, it was recently suggested that this may lead to altered production of many adipocytokines, such as omentin-1. Hence, omentin-1 is hypothesized to be involved in the pathophysiology of CD and thereby playing striking roles in CD. The balance of immunomodulatory, anti-inflammatory, and proinflammatory factors determines the clinical course of IBD. Some reports suggested a relationship between the omentin-1 level and mucosal inflammation in the gastrointestinal tract. The mechanisms through which omentin-1 modulated various pathophysiological processes are not fully elucidated. Omentin-1 could regulate endothelial functions, apoptosis, proliferation, and cell differentiation through different molecular mechanisms. Omentin-1 may play a striking defensive role against pathogenic organisms. However, omentin-1 receptors were not identified until now.

Recently, it had been suggested that omentin-1 has anti-inflammatory roles by inhibiting p38/JNk activation, Cox-2 expression, and superoxide production in vascular endothelial smooth muscle cells, induced by the proinflammatory tumor necrosis factor-alpha (TNF-α) [22]. Moreover, omentin-1 inhibits TNF-α-induced expression of endothelial adhesion molecules, such as intercellular cell adhesion molecule-1 and vascular cell adhesion molecule-1, and suppresses vascular smooth muscle cell migration essential for the progression of vascular structure remodeling [23]. Bowel inflammation is critically dependent on the appropriate activation of nuclear factor-κB, a transcription factor that plays a pivotal role in the activation of proinflammatory cytokines (TNF-α). It was demonstrated that the activation of nuclear factor-κB and the consequent expression of interleukin-6 and TNF-α were significantly attenuated by omentin-1, thus protecting the endothelial barrier and alleviating the bowel inflammation. Besides, the inflammatory mediators released in CD may have a role in the stimulation of omentin-1 release from VAT cells [24].

This study demonstrated that omentin-1 had a significant negative correlation with CRP, suggesting that the downregulation of omentin-1 might reflect reduced anti-inflammatory activity, and hence increased inflammatory mediators and progression of CD. Thus, it could be supposed that omentin-1 exerts anti-inflammatory and protective actions in CD. This study elucidated that the greater inflammation in active CD was associated with lower omentin-1 level and decreased mucosal gene expression of omentin-1, leading to the increase of proinflammatory cytokines and progression of bowel inflammations.

Collectively, these results suggested that both serum and mucosal mRNA expression of omentin-1 could play crucial rules in pathogenesis, development, and even control of CD. Indeed, it is possible to ascertain that omentin-1 could alleviate the inflammatory process in CD. However, the exact role of omentin-1 in intestinal inflammation is not fully elucidated, and the precise mechanism of downregulated serum and mucosal omentin-1 level in active CD is not fully understood.

However, the interplay between omentin-1 and creeping fat is evident in patients with active CD. The creeping fat, submucosal fat deposition (fat halo sign), progressive expansion and hypertrophy of mesenteric WAT, and the immune cells synthesizing adipokines, such as omentin-1, modulate intestinal inflammation. There is strong evidence of intra-abdominal fat accumulations and mesenteric WAT hypertrophy in patients with CD [25]. The anatomic proximity of visceral WAT and the bowel favors the penetration of inflammatory reactions located in the bowel wall into the surrounding visceral fat with consequent activation of visceral adipocytes and secretion of many adipocytokines, such as omentin-1, adiponectin, leptin, visfatin, chemerin, resistin, ghrelin, and obestatin. These adipokines

could modulate the immune system of the gastrointestinal tract and magnify or alleviate the inflammatory reactions. As regards this assumption, measuring the local mucosal and serum adipokine levels might serve as a disease activity index. In all, the available literature on omentin-1 and colitides support the conception that this adipokine is a key component of the biological pathways aroused during the onset of such disorders.

Conclusion

Despite the unclear mechanism underlying omentin-1 downregulation, the results of this study could imply that the decreased serum and mucosal omentin-1 levels are closely related to the inflammatory pathogenesis in CD. Serum omentin-1 may be considered a reliable noninvasive predictor of disease activity in CD, with significantly high diagnostic accuracy. Moreover, omentin-1 may be approved in the future as a therapeutic tool for CD.

Recommendation

Ongoing research should explain the exact mechanisms underlying omentin-1 effects and look for its potential implications for the diagnosis and treatment of IBD.

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Conflicts of interest

There are no conflicts of interest.

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