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ORIGINAL RESEARCH

Omentin-1, a Protective Adipokine for Irritable Bowel Syndrome

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Introduction: Irritable bowel syndrome (IBS) is characterized by patients' high level of suffering. There is increasing evidence for involvement of the immune system in this disease. Adipokines have been reported to be critical immunoregulators in many clinical conditions, including gastrointestinal (GI) inflammatory diseases. Our study aimed to investigate associations of omentin-1 (a newly discovered adipokine) with IBS.

Methods: In the current study, serum levels of omentin-1 were measured in 209 patients with IBS (including three subtypes) and 188 healthy controls by enzyme-linked immunosorbent assay (ELISA). The somatic symptoms of IBS were determined by the 5-item IBS symptoms severity score (IBS-SSS), quality of life (QOL) by 34-item IBS-QOL questionnaire, and psychological disorders by Patient Health Questionnaire (PHQ-9), Hospital Anxiety and Depression Scale (HADS), Visceral Sensitivity Index (VSI). Therapeutic effect of omentin-1 for IBS was investigated in a 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced IBS mouse model.

Results: We found that serum levels of omentin-1 were significantly decreased in patients with the diarrhea-predominant IBS (IBS-D) subtype (not the constipation or alternating subtype) compared to those in healthy subjects. Patients with lower serum omentin-1 levels suffered from higher severity of somatic symptoms (abdominal pain and distention, flatulence, rumbling), lower QOL, and worse psychological status. In a one-year follow-up, serum omentin-1 levels showed potential to reflect the disease progression. Additionally, lower omentin-1 levels were found to be accompanied with higher levels of serum pro-inflammatory cytokine concentrations in patients with IBS-D. Supplement of omentin-1 was protective against visceral hypersensitivity and mucosal inflammation in an IBS mouse model.

Discussion: Our findings highlight the potential value of serum omentin-1 levels as an innovative biomarker in IBS, emphasizing its significance in improving clinical treatment and management of the disease.

Keywords: irritable bowel syndrome, adipokine, omentin-1, clinical symptoms, quality of life, psychological symptoms

Introduction

Irritable bowel syndrome (IBS) stands as a frequently diagnosed gastrointestinal (GI) disorder, making it imperative to deepen our understanding of its pathogenesis. In China, the prevalence of IBS reaches a noteworthy 12.9%, positioning this disease among the most prevalent digestive tract conditions.[1,2] However, the diagnosis of IBS currently relies primarily on clinical symptoms and the exclusion of other organic diseases, lacking specific biological markers or clinical indicators as a definitive diagnostic standard.[3]

The management of IBS remains a significant clinical challenge due to the multitude of unexplained complaints experienced by patients, leading to substantial suffering. Nearly half of these patients seek medical assistance, often repeatedly, resulting in substantial direct and indirect costs.[1,2] The primary reason behind this phenomenon lies in our insufficient understanding of IBS pathogenesis. Previous studies have primarily focused on the fact that IBS belongs to functional GI diseases, with treatments predominantly involving psychological counseling and symptomatic drugs.

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However, recent in-depth exploration has shed light on the role of low-grade inflammation in the development of IBS,[4–7] although the exact mechanisms linking inflammation and immune dysregulation to the pathogenesis of this disease remain largely unknown.

Over the past few decades, adipose tissue has transcended its traditional role as a mere fat repository, and is now acknowledged as an essential and intricate endocrine organ. Extensive evidence has demonstrated that adipose tissue secretes numerous adipokines that exert specific effects on various biological processes.[8,9] These peptides are implicated in the onset of inflammation and possess both pro-inflammatory and anti-inflammatory properties. Consequently, adipokines have been implicated in the pathophysiology of various diseases. Notably, recent evidence suggests that adipokines may have regulatory roles in GI inflammation.[10,11] While studies have indicated altered levels of adiponectin, apelin, and chemerin in patients with IBS compared to healthy controls,[12] the exact role of adipokines in IBS remains limited.

Among these adipokines, omentin has garnered attention as a newly discovered adipokine primarily produced in visceral fat, as well as the small and large intestine. In humans, the most prevalent form of serum omentin is omentin-1, also known as Intelectin-1 (ITLN1). Omentin-1 has been recognized for its anti-inflammatory properties. The initial reports by Yamawaki and Kazama highlighted its ability to counteract TNF-α-induced expression of cyclooxygenase-2 (COX-2) in vascular endothelial cells[13] and vascular cell adhesion molecule (VCAM-1) in smooth muscle cells,[14] respectively. In clinical settings, reduced levels of omentin-1 have been associated with inflammatory diseases such as IBD, obesity, atherosclerosis, and metabolic syndrome.[15] However, the relationship between serum omentin-1 levels and IBS remains largely unexplored.

Here, we demonstrated the clinical importance of serum omentin-1 levels as a biomarker in IBS and investigated the effect of omentin-1 on IBS. Its links to clinical symptoms and inflammation status, indicative of its potential in guiding treatment strategies and improving patient outcomes. Through investigating its relationship with the disease, we look forward to the utilization of omentin-1 to enhance disease management strategies and improve outcomes for individuals with IBS. Furthermore, we unveiled a previously unrecognized therapeutic effect of omentin-1 for IBS in a mouse model, suggesting a novel approach for future drug development targeting IBS treatment.

Materials and Methods

Participants

The present investigation received approval from the Institutional Review Board for Clinical Research of Sichuan Provincial People's Hospital, in accordance with the principles in the Declaration of Helsinki. Written informed consent was obtained from all participants prior to their inclusion in the study. To determine the association between serum omentin-1 and IBS, patients with IBS were recruited from the clinics of our hospital. Our sample consisted of 209 individuals (88 female and 121 male) diagnosed with IBS, including 146 diarrhea subtype (IBS-D), 48 constipation (IBS-C), and 15 alternating subtype (IBS-A). These participants with a median age of 39 years and interquartile range (IQR) of 30–48 years, were selected based on their adherence to the Rome III Diagnostic Criteria for IBS.[3] For comparison, we included a control group consisting of 188 healthy controls who underwent routine physical examinations at our hospital during the study from the same time period. The control group was matched in terms of sex, with 96 females and 92 males, as well as age, with a median age of 37 years and IQR of 28–45 years. Exclusion criteria encompassed evidence of infections, celiac disease, other gastrointestinal disorders such as inflammatory bowel disease (IBD), previous abdominal surgery, chronic diseases including diabetes, smoking, excessive alcohol consumption, and use of steroidal and non-steroidal anti-inflammatory drugs. In the control group, individuals were screened through medical interviews to ensure the absence of IBS or any other functional bowel disorders. Moreover, none of the participants were currently taking medications known to impact the gastrointestinal tract or immune system.

Evaluation of Somatic Symptoms in IBS

The severity of clinical symptoms in patients with IBS was evaluated using the IBS symptoms severity score (IBS-SSS) questionnaire as reported previously.[16] This questionnaire evaluated five clinically applicable items over a 10-day period, including dissatisfaction with bowel habits, abdominal pain and distention, frequency of abdominal pain, and how much

IBS interferes with one's life in general. Each item was graded on a visual analog scale ranging from 0 to 100, and the total score of IBSSS was calculated as the sum of these scores. The distribution of IBS-SSS was categorized into 3 levels: IBSSS scores between 75 and 175, 175 and 300, and > 300 were considered as mild, moderate, and severe IBS, respectively.[12] In our follow-up study, a decline in IBS-SSS distribution levels was considered as improvement in somatic symptoms. Furthermore, a self-reporting 100-mm visual analog scale was utilized for assessment of other GI symptoms such as flatulence, rumbling, and overall GI symptoms, where 0 represented no symptom and 100 represented the worst symptom.

Assessment of the Quality of Life (QOL) and Psychological Status

The QOL and psychological symptoms were assessed as reported previously.[16] In order to evaluate the QOL of patients with IBS, a 34-item questionnaire known as the IBS-QOL questionnaire was utilized. The responses of the participants to all 34 items were aggregated and then converted to a 0-to-100 scale. For the assessment of psychological symptoms, the 9-item Patient Health Questionnaire (PHQ-9) was employed for participants' perceived stress levels. The distribution of PHQ-9 scores was categorized into 5 levels: Minimal (0–4), Mild (5–9), Moderate (10–14), Moderately severe (15–19), Severe (20–27). In our follow-up study, a decline in PHQ-9 distribution levels was considered as "improvement in PHQ-9". The Hospital Anxiety and Depression Scale (HADS) questionnaire was employed for anxiety and depression in individuals. Moreover, the GI symptom-related anxiety was assessed by the Visceral Sensitivity Index (VSI, a 15-item questionnaire). The overall score varies from 0 to 75, with 0 and 75 indicating the absence and representing intense of gastrointestinal-specific anxiety, respectively.[17]

Measurement of Serum Cytokine Levels

Venous blood samples were collected from the patients and transported to the laboratory for serum collection within 2 hours. Following a previously reported protocol,[18] the serum was separated from the blood cells through centrifugation at 3000 × g for 10 minutes, and subsequently stored at a temperature of –80°C until analysis. The measurement of serum omentin-1 levels was conducted using a commercially available enzyme-linked immunosorbent assay (ELISA) kit from BlueGene Biotech Co. (Shanghai, China). ELISA kits for IL-1β, IL-8, IL-6, and TNF-α were purchased from BioLegend (San Diego, CA, USA). These measurements were carried out in accordance with the manufacturer's instructions.

The Establishment and Evaluation of the IBS Mouse Model

Wild type (WT) mice were purchased from the Shanghai Model Organisms (Shanghai, China). All mice enrolled in the current study were male and on a C57BL/B6J background and used at their age of 8–10 weeks. All mice were maintained in our facility under specific pathogen-free (SPF) conditions. The establishment and evaluation of the IBS mouse model were performed as described in our previous work.[19] Briefly, mice were received with a single enema of 2,4,6-trinitrobenzenesulfonic acid (TNBS) to induce colonic inflammation. Five weeks after TNBS insults, visceral hypersensitivity was determined using the abdominal withdrawal reflex (AWR) test was used to evaluate the visceral hypersensitivity. The intestinal motility was assessed using the colon transportation test (CTT). In addition, the stool consistency was evaluated by the Bristol stool grade. Human Omentin-1 recombinant protein (BioVendor, Europe) was administered intraperitoneally at the dosage of 25μg/kg/day beginning from 10 days post TNBS insults to the end of the experiment.

Quantitative Real-Time PCR (qRT-PCR)

As reported previously,[19] Trizol (TransGen Biotech, Beijing, China) was used to extracted total RNA from cells or tissues. Reversible transcription PCR was performed to transcribe the total RNA into cDNA by a reverse transcription kit (TransGen Biotech). A SYBR Green PCR kit (TaKaRa, Japan) was used to carried out qRT-PCR in a fluorescence thermocycler (Roche Diagnostics, Germany). An Epoch 2 reader (BioTek, Winooski, VT) was used to acquire the data from qRT-PCR assays.

Statistical Analysis

All statistical analyses were performed using Prism software Version 8.4 (GraphPad Software, San Diego, California, USA). Prior to conducting further statistical tests, a thorough examination of the data was conducted to assess its

adherence to normality assumptions. The Kolmogorov–Smirnov test was employed to ascertain if any significant deviations from a normal distribution were present. For presenting parametric data, the mean ± standard deviation (SD) was utilized, while nonparametric data was presented as median with interquartile range (IQR), denoting the 25th and 75th percentiles. To compare variables between groups, appropriate statistical tests were employed. Two-sample unpaired t-tests were used for quantitative variables that adhered to parametric assumptions, whereas the Mann–Whitney *U*-test was applied for nonparametric quantitative variables. Categorical variables were compared using the chi-squared test. To explore the associations between serum omentin-1 levels and the severity of GI symptoms, IBS-SSS, IBS-QOL, PHQ-9, HADS, VSI, as well as circulating cytokine concentrations in patients with IBS, Pearson correlation analysis was employed. Multiple linear regression analysis was performed to eliminate the interference of confounders where needed. A significance threshold of $p < 0.05$ was deemed appropriate for all statistical tests.

Results

Characteristics of the Participants

In the current study, a total of 234 individuals diagnosed with IBS underwent evaluation for eligibility. As depicted in Figure 1, 25 participants were excluded from the study due to their excessive alcohol consumption (n = 2) or the presence of other diseases (n = 9), as per our predefined exclusion criteria. Additionally, 6 individuals withdrew their consent, while 8 were excluded for infection or use of anti-inflammatory drugs/antibiotics. Consequently, a final cohort of 209 patients was included for analysis. For the selection of healthy controls, a group of 198 subjects was assessed for eligibility. Among them, 10 individuals were excluded due to withdrawal of consent or use of anti-inflammatory drugs/antibiotics. The demographic and clinical characteristics of both the IBS and control groups are presented in Table 1. No significant differences were observed in terms of gender, age, body mass index (BMI), education level between the two groups. To evaluate serum omentin-1 levels, we employed ELISA measurements, comparing the levels between the IBS and control groups. Notably, multiple comparisons showed patients with IBS-D, not those with IBS-C or IBS-A, exhibited significantly lower serum omentin-1 levels when compared to the control group (Figure 2).

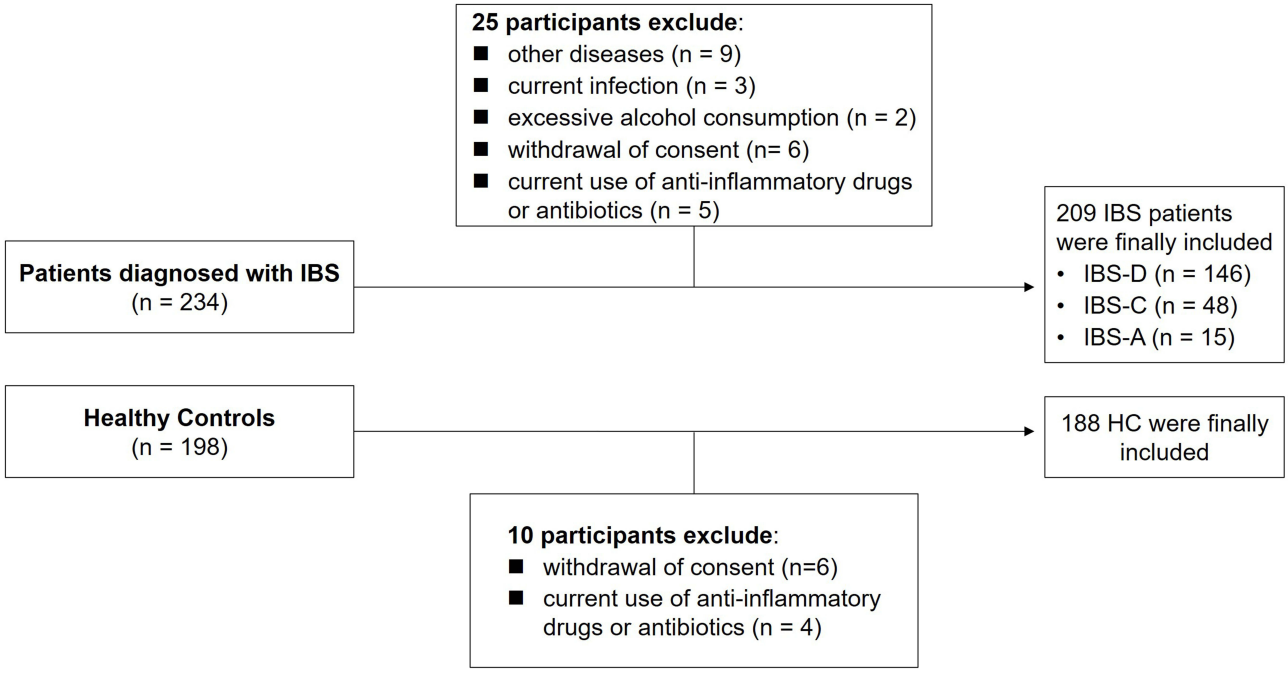

Figure 1 Flow chart of participant recruitment.
Abbreviations: IBS, irritable bowel syndrome; IBS-D, diarrhea-predominant IBS; IBS-C, constipation-predominant IBS; IBS-A, alternating IBS; HC, healthy controls.

Table 1 Clinical Characteristics and Serum Concentrations of Omentin-1

	IBS	HC	p value
Subjects (n)	209	188	
Age (year)	39 (30, 48)	37 (28, 45)	0.09[a]
Gender (n)			
Female	88	96	0.06[b]
Male	121	92	
IBS subtypes			
IBS-D	146		
IBS-C	48		
IBS-A	15		
BMI (kg/m^2)	21.7 (19.5, 24.2)	22.2 (20.8, 23.1)	0.67[b]
Education level			
None/primary	31	32	0.25[b]
Middle/high school	84	87	
University or higher	94	69	
Work status			
Employees	108	113	< 0.01[b]
Unemployed	59	23	
Student	42	52	
Marriage			
Single	42	64	< 0.01[b]
Married	132	101	
Other	35	23	

Notes: Data are presented as median (IQR) when applicable. [a]Mann–Whitney test, $p < 0.05$ was considered statistically significant; [b]Chi-square test, $p < 0.05$ was considered statistically significant.

Abbreviations: HC, healthy controls; IBS, irritable bowel syndrome; IBS-D, diarrhea-predominant IBS; IBS-C, constipation-predominant IBS; IBS-A, alternating IBS; IQR, interquartile range; BMI, body mass index.

Associations Between Omentin-1 and GI Somatic Symptoms in Patients With IBS-D

Subsequently, our investigation aimed to explore potential correlations between the diminished levels of omentin-1 and the GI somatic symptoms experienced by patients with IBS-D. We observed an inverse association between serum omentin-1 levels and various symptoms (Table 2). Notably, there was a significant negative correlation between omentin-1 levels and abdominal pain

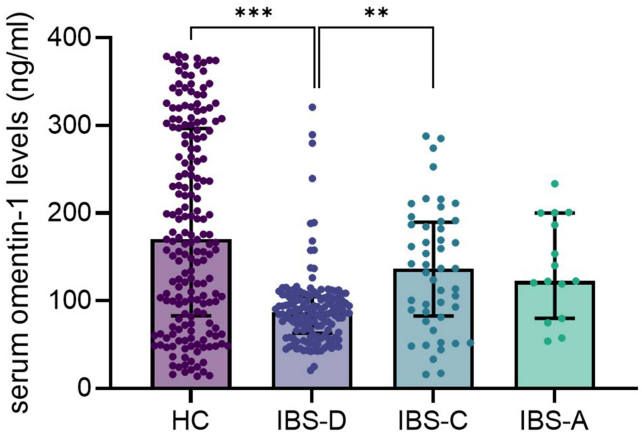

Figure 2 Serum levels of omentin-1 in IBS subtypes and HC. Serum omentin-1 levels were compared among HC, IBS-D, IBS-C, and IBS-A. Kruskal–Wallis test followed by Dunn's multiple comparisons test, **$p < 0.01$, ***$p < 0.001$.

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Table 2 Associations of Serum Omentin-1 Levels With the Gastrointestinal (GI) Symptoms of IBS

	Serum omentin-1 levels	
	r	p[a]
Abdominal pain	–0.617	< 0.001
Abdominal distention	–0.635	< 0.001
Flatulence	–0.629	< 0.001
Rumbling	–0.609	0.027
Overall GI symptoms	–0.594	0.045
IBS-SSS	–0.612	< 0.001

Notes: [a]Pearson's correlation analysis, $p < 0.05$ was considered statistically significant.
Abbreviation: IBS-SSS, IBS symptoms severity score.

(Pearson r = –0.617, $p < 0.001$), abdominal distention (Pearson r = –0.635, $p < 0.001$), flatulence (Pearson r = –0.629, $p < 0.001$), rumbling (Pearson r = –0.609, $p = 0.027$), and overall GI symptoms (Pearson r = –0.594, $p = 0.045$), respectively. Additionally, a significant inverse association between serum omentin-1 levels and IBS-SSS was revealed (Pearson r = –0.612, $p < 0.001$). These data suggest that patients with IBS-D, who have lower serum levels of omentin-1, might suffer from severer GI somatic symptoms.

Associations of Omentin-1 With IBS QOL and Psychological Symptoms

In addition to considering somatic symptoms, it is crucial to acknowledge the role of sociocultural, environmental, and behavioral factors in comprehending the etiology and outcomes of IBS. Thus, it becomes imperative to assess their overall impact from the patient's perspective. There is an emerging consensus that the assessment of health-related QOL should be a fundamental component of clinical studies and treatment trials.[20,21] In line with this notion, we employed a comprehensive, self-administered, 34-item condition-specific questionnaire to evaluate the QOL of individuals with IBS (Table 3). Remarkably, our results revealed a negative correlation between serum omentin-1 levels and IBS-related QOL (Pearson r = 0.646, $p < 0.001$). To delve deeper into the psychological status in IBS-D patients (Table 3), PHQ-9 was used to analyze depression symptoms, which revealed a significant association between lower serum omentin-1 levels and severer depression among individuals with IBS (r = –0.445, $p = 0.002$). HADS questionnaire were also utilized to comprehensively evaluate the mental status of IBS-D patients, showing a negative association between serum omentin-1 levels and both anxiety (r = –0.454, $p < 0.001$) and depression (r = –0.557, $p < 0.001$) scores. Additionally, the VSI suggested that IBS-D patients with lower serum omentin-1 levels suffered from severer GI symptom-related

Table 3 Associations of Serum Omentin-1 Levels With the QOL and Psychological Symptoms of Patients With IBS

	Serum omentin-1 levels	
	r	p[a]
IBS-QOL	0.646	< 0.001
PHQ-9	–0.445	0.002
HADS-anxiety	–0.454	< 0.001
HADS-depression	–0.557	< 0.001
VSI	–0.586	< 0.001

Note: [a]Pearson's correlation analysis, $p < 0.05$ was considered statistically significant.
Abbreviations: QOL, quality of life; PHQ-9, 9-item Patient Health Questionnaire; HADS, Hospital Anxiety and Depression Scale; VSI, Visceral Sensitivity Index.

Table 4 Multiple Linear Regression Analysis of Serum Omentin-1 With the QOL and Psychological Symptoms in IBS Patients

Variable	Estimate	Standard error	|t|	*p* value
IBS-QOL	–2.444	0.756	3.233	0.002
HADS-depression	–3.965	1.803	2.199	0.029
HADS-anxiety	–2.952	4.738	0.623	0.534
PHQ-9	6.297	4.766	1.321	0.189
VSI	–0.4689	0.1543	3.040	0.003

Notes: Multivariate models were adjusted for the variables as relevant confounders, including age, BMI, sex, work, marriage, education, and IBS-SSS. $p < 0.05$ was considered statistically significant.

anxiety ($r = –0.586$, $p < 0.001$). Furthermore, we also performed multiple linear regression analysis, showing that after accounting for age, BMI, sex, work, marriage, education, and IBS-SSS, serum omentin-1 levels remained significantly correlated with IBS-QOL and psychological symptoms (Table 4). These findings indicate that IBS-D patients with lower serum levels of omentin-1 are more likely to experience heightened psychological distress and diminished QOL.

Serum Omentin-1 Levels Reflect the Clinical Outcome of IBS-D

To further reveal the relationship between omentin-1 and IBS, we conducted a one-year follow-up study on a cohort of 72 patients with IBS-D. The detailed grouping scheme is shown in Figure 3A. Patients who exhibited an increase of 30% or more in serum omentin-1 levels were categorized as Group 1, whereas the remaining constituents were aptly assigned to

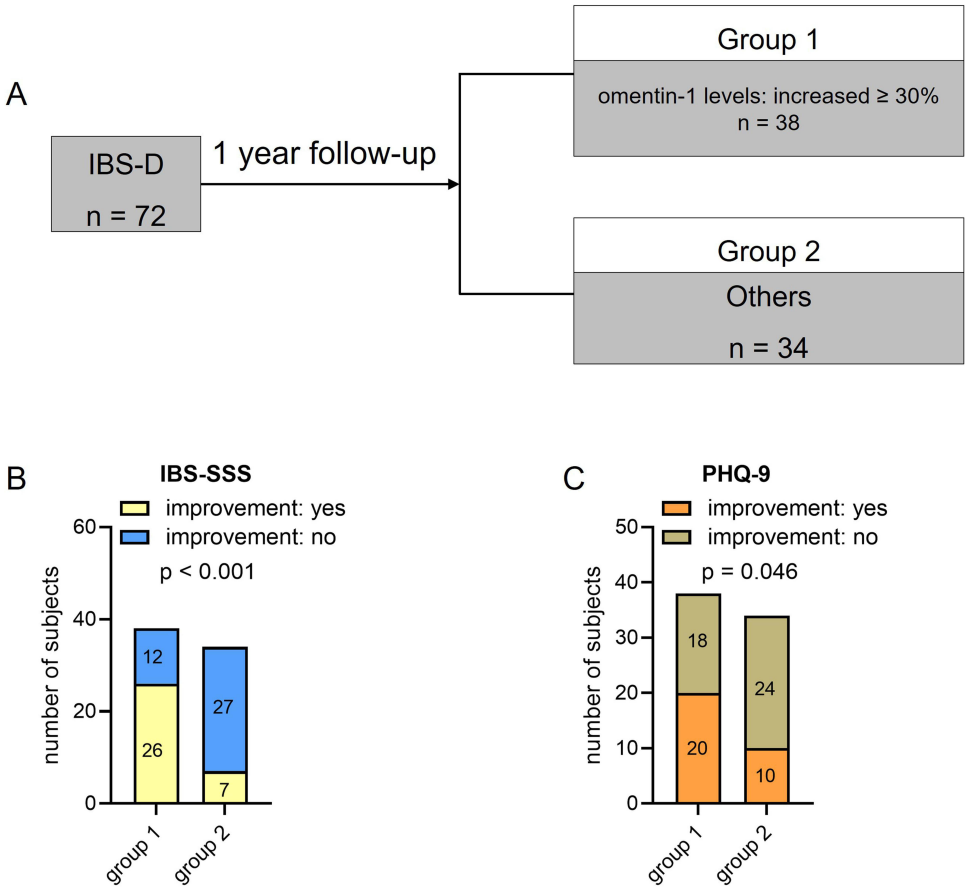

Figure 3 Serum omentin-1 levels reflect the clinical outcome of IBS-D. (**A**) Study design. The number of patients with indicated outcome in (**B**) IBS-SSS and (**C**) PHQ-9. The p value < 0.05 (Chi-square test) was considered statistically significant.

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Group 2. To determine the association of serum omentin-1 changes and IBS somatic/psychological symptom outcome, we employed IBS-SSS and PHQ-9: a decline of IBS-SSS and PHQ-9 distribution was considered as "improvement in somatic symptoms" and "improvement in psychological symptoms", respectively. Subsequent statistical analyses showed that Group 1 had significantly higher number of patients acquired improvement in somatic (26 out of 38, accounting for 68.4%, versus Group 2, 7 out of 34, 20.6%, $p < 0.001$) (Figure 3B) and psychological symptoms (20 out of 38, accounting for 52.6%, versus Group 2, 10 out of 34, 29.4%, $p = 0.046$) (Figure 3C). This evidence strongly suggests that serum omentin-1 levels hold potential for discerning clinical IBS progression, which could facilitate the evaluation of patient improvement.

Associations of Omentin-1 With Inflammatory Responses in IBS-D Patients

Growing evidence has demonstrated the signs of persisting low grade inflammation in IBS patients, which are also thought to play a role in the development of symptoms.[7,22] Since omentin-1 has been considered as an anti-inflammatory regulator in GI diseases, we assumed that decreased levels of omentin-1 might contribute to the development of inflammation in IBS. To better understand the role of omentin-1, we measured the serum levels of pro-inflammatory cytokines, and found that serum omentin-1 levels were inversely correlated with serum IL-1β (Figure 4A), TNF-α (Figure 4B), IL-6 (Figure 4C), and IL-8 (Figure 4D), and levels. These observations indicate that serum omentin-1 might able to reflect the systemic inflammatory burden in IBS patients. Additionally, after accounting for inflammatory cytokines (IL-1β, IL-8, IL-6, and TNF-α) as well as other confounders (age, BMI, sex, work, marriage, education), serum omentin-1 levels were significantly correlated with psychological symptoms (Supplementary Table 1).

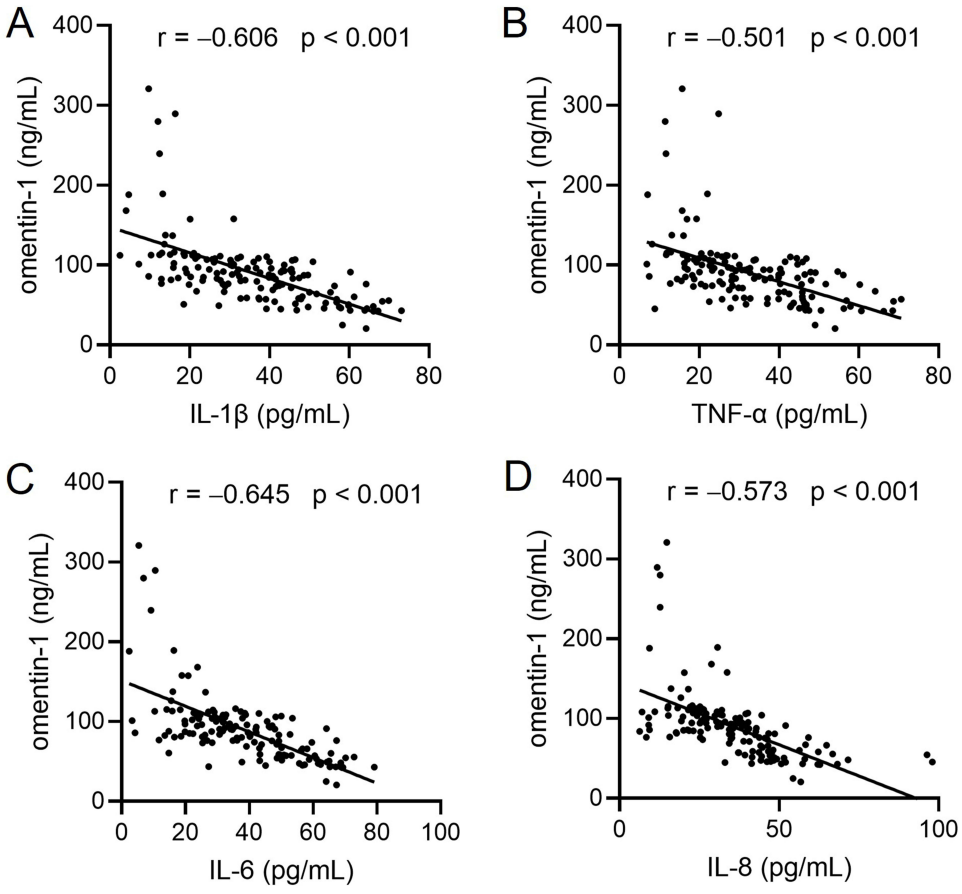

Figure 4 Associations of omentin-1 with inflammatory burden in IBS patients. Correlation of serum omentin-1 levels with (**A**) IL-1β, (**B**) TNF-α, (**C**) IL-6 and (**D**) IL-8 was examined by Pearson's correlation analysis. $p < 0.05$ was considered significant.

Supplement of Omentin-1 Alleviates Visceral Hypersensitivity and Mucosal Inflammatory Responses in Mice With IBS

To investigate whether omentin-1 was therapeutic for IBS, we established a TNBS-induced IBS mouse model. As shown in Figure 5A, IBS mice exhibited decreased serum levels of omentin-1, which was consistent with observations in our human study. Significantly higher AWR scores was found in IBS mice compared with TNBS-unexposed control mice,

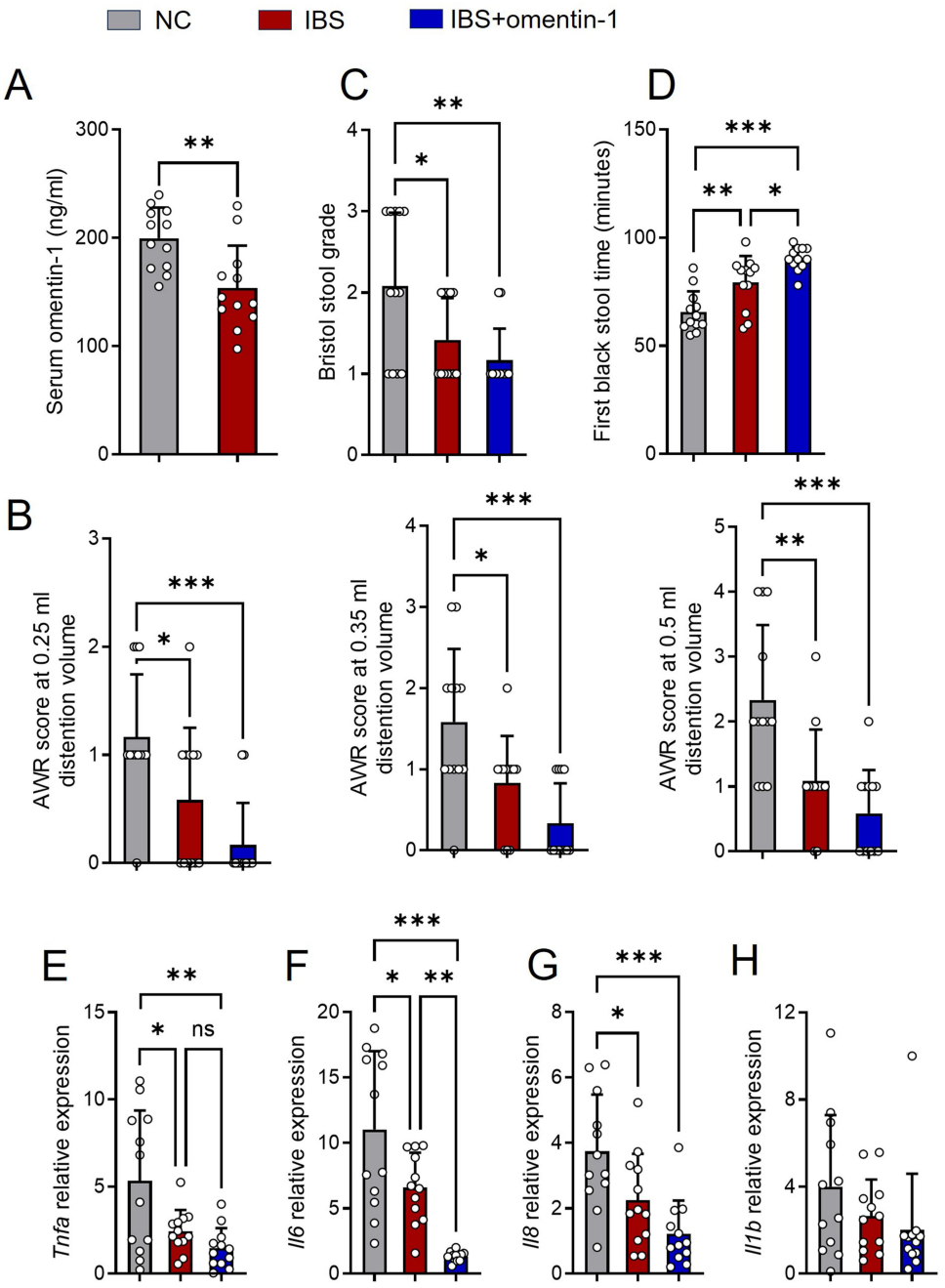

Figure 5 Omentin-1 alleviates visceral hypersensitivity and inflammatory responses in mice with IBS. An IBS mouse model was established and omentin-1 treatment was administered as indicated. Age- and gender-matched wild type (WT) mice that were not exposed to 2,4,6-trinitrobenzenesulfonic acid (TNBS) served as the naïve control group (NC). (**A**) Serum levels of omentin-1 were measured using ELISA. **p < 0.01, unpaired Student's *t* test (two-tailed) (**B**) The abdominal withdrawal reflex (AWR) test was performed to evaluate the visceral hypersensitivity in response to colorectal distention (CRD) in mice at distending volume of 0.25 (left panel), 0.35 (middle panel), or 0.5 mL (right panel). (**C**) Bristol stool grade. (**D**) The first black stool time. (**E-H**) The transcript expression levels of colonic TNF-α (**E**), IL-6 (**F**), IL-8 (**G**), and IL-1β (**H**) were measured by qRT-PCR. (**B-H**) *p < 0.05, **p < 0.01, ***p < 0.001, one-way analysis of variance (ANOVA). n = 12 mice in each group. Representative results from one of three independent experiments were shown.

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indicative of increased visceral hypersensitivity (Figure 5B). Next, we found that omentin-1 treatment potently reduced the AWR scores at all distention volumes (Figure 5B). In addition, the colon transportation test (CTT) and Bristol stool grade was used to evaluate the intestinal motility alteration and stool consistency, respectively. Both the first black stool time and stool consistency suggested that the intestinal motility was obviously increased in IBS mice compared with TNBS-unexposed control mice, which was largely reversed by omentin-1 treatment (Figure 5C and D). These data suggest that omentin-1 could effectively relief the clinical presentations in IBS mice. Furthermore, we examined levels of several inflammatory cytokines in the colon, and showed that omentin-1 remarkably decreased the expression of TNF-α, IL-6, and IL-8 in IBS mice (Figure 5E–H). These data suggest that omentin-1 might exert a therapeutic effect on IBS via inhibiting mucosal inflammation and enhancing anti-inflammatory responses.

Discussion

The present study unveiled a noteworthy revelation regarding the considerable reduction in serum omentin-1 levels among patients with IBS-D, when compared to those of healthy individuals. Moreover, these omentin-1 levels exhibited a negative correlation with both the severity of somatic and psychological symptoms and IBS-QOL in IBS-D. Additionally, our investigation unveiled an inverse relationship between omentin-1 levels and the concentrations of circulating pro-inflammatory cytokines in individuals with IBS-D. Remarkably, this study represents the initial endeavor to elucidate the link between omentin-1 and the clinical symptoms of IBS.

The significance of omentin-1 as a potential biomarker for IBS lies in its association with the clinical severity of gastrointestinal symptoms in patients with IBS. Our study revealed a notable link between lower serum omentin-1 concentrations and heightened GI symptom severity, particularly concerning abdominal pain, distention, flatulence, and rumbling in patients with IBS. To date, the diagnosis of IBS primarily is based on clinical symptoms and the exclusion of other organic diseases. However, these diagnostic criteria lack objectivity, potentially resulting in misdiagnosis or delayed diagnosis. Utilizing non-invasive and objective biomarkers like omentin-1 to manage IBS patients offers numerous advantages. Unlike invasive procedures such as colonoscopies or biopsies, these biomarkers do not cause additional discomfort or pain. They can be easily integrated into a patient's daily routine. Furthermore, non-invasive biomarkers yield objective measurement outcomes, removing the ambiguity associated with subjective evaluations. By assessing biomarkers like omentin-1, it becomes feasible to accurately track disease progression, monitor changes over time, and assess the effectiveness of treatments in individuals with IBS. Additionally, non-invasive biomarkers enable continuous and frequent monitoring, facilitating the timely detection of any shifts in the condition and guiding treatment decisions swiftly to cater to the specific needs of each patient. Moreover, investigating the clinical implications of omentin-1 as a biomarker extends beyond IBS. Research in other diseases has highlighted its relevance, with studies in rheumatoid arthritis showing decreased omentin-1 levels in synovial fluid[23] and its potential as a biomarker for reflecting degenerative processes in osteoarthritis.[24] Serum omentin-1 levels have even been suggested as predictors of long-term survival in critically ill patients in intensive care units.[25] In our study, we have demonstrated that serum omentin-1 levels hold the potential to indicate the severity of IBS, shedding light on its promising role as a valuable biomarker in the context of this condition.

Previous research has demonstrated that many IBS patients exhibit increased pain sensitivity to gut stimulation, referred to as visceral hypersensitivity.[26] The pathophysiology of IBS is linked to chronic low-grade inflammation, characterized by the infiltration of activated lymphocytes and mast cells, increased production of pro-inflammatory cytokines, and mucosal inflammation.[5,6] Inflammation is well-known to contribute to visceral hypersensitivity and abnormalities in gut motility, both of which are characteristic features of IBS.[26] Previous studies have shown that elevated serum levels of pro-inflammatory cytokines are directly associated with the severity of GI symptoms in IBS.[22,27,28] Our recent work demonstrated that inhibiting systemic or mucosal inflammation alleviated visceral hypersensitivity.[19] Omentin-1 is known to modulate inflammatory responses and exhibit anti-inflammatory properties. Our study revealed an inverse association between serum omentin-1 levels and concentrations of IL-1β, IL-8, IL-6, and TNF-α. Hence, the negative correlations observed between omentin-1 and the severity of GI symptoms in IBS may be explained by its anti-inflammatory functions. Additionally, the lower serum levels of omentin-1 in IBS patients might be attributed to its role in immunoregulation. However, further studies are warranted to elucidate the underlying mechanisms responsible for the down-regulation of omentin-1 in IBS.

The relationship between psychological disorders and the generation and progression of symptoms in IBS patients has been extensively documented. Many IBS patients have reported correlations between anxiety and depression and changes in stool patterns, as well as abdominal pain or discomfort.[26] Adipokines have been implicated in the pathophysiology of psychological disorders;[29] however, the understanding of the relationship between omentin-1 and psychological disorders remains limited. Recent evidence suggests that omentin-1 plays a role in protecting against anxiety and depressive-like behaviors.[30] Mice lacking omentin-1 displayed heightened central nervous system (CNS) inflammation, characterized by elevated levels of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6).[30] In our current study, we observed significant inverse associations between serum omentin-1 levels and psychological symptoms, even after adjusting for confounding factors. Furthermore, omentin-1 shows promise as a therapeutic agent for preventing or treating depression by enhancing barrier function and maintaining an endogenous anti-inflammatory balance to reduce proinflammatory cytokines.[30] This concept suggests that omentin-1 supplementation may be beneficial for treating IBS patients with psychological symptoms.

To the best of our knowledge, this study is the first to assess serum omentin-1 concentrations in patients with IBS and explore the potential correlation between omentin-1 and the severity of somatic and psychological symptoms in IBS patients. However, this study has some limitations. Firstly, our study had a relatively small sample size, which restricted the applicability of our conclusions. Subsequent research involving larger cohorts is necessary to confirm our conclusions and guarantee the strength of the identified correlations. Secondly, the lack of evaluation of mucosal inflammation and the absence of data on the association of omentin-1 with other IBS subtypes, such as constipation-predominant IBS, are additional limitations. Thirdly, the current study focused on the association between omentin-1 and IBS. Exploring the underlying mechanisms connecting omentin-1, systemic inflammation, and symptom severity in IBS would be advantageous for future research. Fourthly, although studies in mice have shown that omentin-1 supplementation improves intestinal inflammation severity in mice with colitis by regulating oxidative stress and intestinal barrier function,[31] and therapeutic effects of omentin-1 supplementation were also observed in osteoporosis,[32] and atherosclerosis.[33] We also found demonstrated that omentin-1 could protect against TNBS-induced IBS. However, clinical evidence is required to validate its efficacy and the effect of omentin-1 on IBS remains unknown, which needs future studies to investigated the potential value of omentin-1, as an anti-inflammatory adipokine for IBS treatment.

In conclusion, our study established a significant link between lower serum omentin-1 levels and increased severity of GI somatic and psychological symptoms. These results imply that omentin-1 might play a protective role in the pathogenesis of IBS, and supplementation of omentin-1 might be a potential component of a new therapeutic approach for IBS patients in the future, especially those with diarrhea-predominant IBS. Further studies are needed to provide additional evidence elucidating the role of omentin-1 in IBS and to support the beneficial effects of omentin-1 supplementation in clinical settings.

Data Sharing Statement

The data underlying the research results are available in the article.

Ethics Statement

All procedures involving animals were approved and performed in accordance with the Animal Care and Use Committee at Sichuan Provincial People's Hospital. Human studies were conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board for Clinical Research of Sichuan Provincial People's Hospital (202198).

Disclosure

The authors declared no competing interests for this work.

References

1. Black CJ, Ford AC. Global burden of irritable bowel syndrome: trends, predictions and risk factors. *Nat Rev Gastroenterol Hepatol*. 2020;17:473–486. doi:10.1038/s41575-020-0286-8
2. Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. *Clin Epidemiol*. 2014;6:71–80. doi:10.2147/CLEP.S40245

3. Rome F. Guidelines–Rome III diagnostic criteria for functional gastrointestinal disorders. *J Gastrointestin Liver Dis*. 2006;15:307–312.
4. Garg P. Inflammation in irritable bowel syndrome (IBS): role of Psyllium Fiber supplementation in decreasing inflammation and physiological management of IBS. *Turk J Gastroenterol*. 2021;32:108–110. doi:10.5152/tjg.2020.20229
5. Ng QX, Soh AYS, Loke W, et al. The role of inflammation in irritable bowel syndrome (IBS). *J Inflamm Res*. 2018;11:345–349. doi:10.2147/JIR.S174982
6. Liebregts T, Adam B, Bredack C, et al. Immune activation in patients with irritable bowel syndrome. *Gastroenterology*. 2007;132:913–920. doi:10.1053/j.gastro.2007.01.046
7. El-Salhy M, Gundersen D, Hatlebakk JG, et al. Low-grade inflammation in the rectum of patients with sporadic irritable bowel syndrome. *Mol Med Rep*. 2013;7:1081–1085. doi:10.3892/mmr.2013.1320
8. Ren Y, Zhao H, Yin C, et al. Adipokines, hepatokines and myokines: focus on their role and molecular mechanisms in adipose tissue inflammation. *Front Endocrinol*. 2022;13:873699. doi:10.3389/fendo.2022.873699
9. Recinella L, Orlando G, Ferrante C, et al. Adipokines: new potential therapeutic target for obesity and metabolic, rheumatic, and cardiovascular diseases. *Front Physiol*. 2020;11:578966. doi:10.3389/fphys.2020.578966
10. Batra A, Zeitz M, Siegmund B. Adipokine signaling in inflammatory bowel disease. *Inflamm Bowel Dis*. 2009;15:1897–1905. doi:10.1002/ibd.20937
11. Weidinger C, Ziegler JF, Letizia M, et al. Adipokines and their role in intestinal inflammation. *Front Immunol*. 2018;9:1974. doi:10.3389/fimmu.2018.01974
12. Baram MA, Abbasnezhad A, Ghanadi K, et al. Serum levels of chemerin, apelin, and adiponectin in relation to clinical symptoms, quality of life, and psychological factors in irritable bowel syndrome. *J Clin Gastroenterol*. 2020;54:e40–e9. doi:10.1097/MCG.0000000000001227
13. Yamawaki H, Kuramoto J, Kameshima S, et al. Omentin, a novel adipocytokine inhibits TNF-induced vascular inflammation in human endothelial cells. *Biochem Biophys Res Commun*. 2011;408:339–343. doi:10.1016/j.bbrc.2011.04.039
14. Kazama K, Usui T, Okada M, et al. Omentin plays an anti-inflammatory role through inhibition of TNF-alpha-induced superoxide production in vascular smooth muscle cells. *Eur J Pharmacol*. 2012;686:116–123. doi:10.1016/j.ejphar.2012.04.033
15. Watanabe T, Watanabe-Kominato K, Takahashi Y, et al. Adipose tissue-derived omentin-1 function and regulation. *Compr Physiol*. 2017;7:765–781.
16. Huang X, Li A, Long P, et al. The neutrophil-to-albumin ratio (NAR): a novel index in relation to clinical symptoms, quality of life, and psychological status in diarrhea-predominant irritable bowel syndrome (IBS-D). *J Inflamm Res*. 2024;17:3685–3695. doi:10.2147/JIR.S458363
17. Chen EY, Mahurkar-Joshi S, Liu C, et al. The association between a Mediterranean diet and symptoms of irritable bowel syndrome. *Clin Gastroenterol Hepatol*. 2024;22:164–72e6. doi:10.1016/j.cgh.2023.07.012
18. He C, Shi Y, Wu R, et al. miR-301a promotes intestinal mucosal inflammation through induction of IL-17A and TNF-alpha in IBD. *Gut*. 2016;65:1938–1950. doi:10.1136/gutjnl-2015-309389
19. Xu X, Dong Q, Zhong Q, et al. The flavonoid kurarinone regulates macrophage functions via aryl hydrocarbon receptor and alleviates intestinal inflammation in irritable bowel syndrome. *J Inflamm Res*. 2021;14:4347–4359. doi:10.2147/JIR.S329091
20. Kang SH, Choi SW, Lee SJ, et al. The effects of lifestyle modification on symptoms and quality of life in patients with irritable bowel syndrome: a prospective observational study. *Gut Liver*. 2011;5:472–477. doi:10.5009/gnl.2011.5.4.472
21. Monnikes H. Quality of life in patients with irritable bowel syndrome. *J Clin Gastroenterol*. 2011;45 Suppl:S98–101. doi:10.1097/MCG.0b013e31821fbf44
22. Burns G, Carroll G, Mathe A, et al. Evidence for local and systemic immune activation in functional dyspepsia and the irritable bowel syndrome: a systematic review. *Am J Gastroenterol*. 2019;114:429–436. doi:10.1038/s41395-018-0377-0
23. Senolt L, Polanska M, Filkova M, et al. Vaspin and omentin: new adipokines differentially regulated at the site of inflammation in rheumatoid arthritis. *Ann Rheum Dis*. 2010;69:1410–1411. doi:10.1136/ard.2009.119735
24. Xu L, Zhu GB, Wang L, et al. Synovial fluid omentin-1 levels are inversely correlated with radiographic severity of knee osteoarthritis. *J Investig Med*. 2012;60:583–586. doi:10.2310/JIM.0b013e31824443cb
25. Luedde M, Benz F, Niedeggen J, et al. Elevated omentin serum levels predict long-term survival in critically ill patients. *Dis Markers*. 2016;2016:3149243. doi:10.1155/2016/3149243
26. Spiller R, Aziz Q, Creed F, et al. Guidelines on the irritable bowel syndrome: mechanisms and practical management. *Gut*. 2007;56:1770–1798. doi:10.1136/gut.2007.119446
27. Collins SM, Piche T, Rampal P. The putative role of inflammation in the irritable bowel syndrome. *Gut*. 2001;49:743–745. doi:10.1136/gut.49.6.743
28. Choghakhori R, Abbasnezhad A, Hasanvand A, et al. Inflammatory cytokines and oxidative stress biomarkers in irritable bowel syndrome: association with digestive symptoms and quality of life. *Cytokine*. 2017;93:34–43. doi:10.1016/j.cyto.2017.05.005
29. Wedrychowicz A, Zajac A, Pilecki M, et al. Peptides from adipose tissue in mental disorders. *World J Psychiatry*. 2014;4:103–111. doi:10.5498/wjp.v4.i4.103
30. Ji L, Zhang L, Liang Z, et al. Role of omentin-1 in susceptibility to anxiety and depression like behaviors. *mol Cell Endocrinol*. 2023;574:111990. doi:10.1016/j.mce.2023.111990
31. Tao M, Yan W, Chen C, et al. Omentin-1 ameliorates experimental inflammatory bowel disease via Nrf2 activation and redox regulation. *Life Sci*. 2023;328:121847. doi:10.1016/j.lfs.2023.121847
32. Rao SS, Hu Y, Xie PL, et al. Omentin-1 prevents inflammation-induced osteoporosis by downregulating the pro-inflammatory cytokines. *Bone Res*. 2018;6:9. doi:10.1038/s41413-018-0012-0
33. Lin X, Sun Y, Yang S, et al. Omentin-1 modulates macrophage function via integrin receptors alphavbeta3 and alphavbeta5 and reverses plaque vulnerability in animal models of atherosclerosis. *Front Cardiovasc Med*. 2021;8:757926. doi:10.3389/fcvm.2021.757926