Correlation Between Nutritional Status and Plasma Ghrelin and Leptin Levels in Patients With Inflammatory Bowel Disease

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Abstract- Leptin and ghrelin are key metabolic hormones involved in energy balance and inflammation. Their dysregulation has been implicated in chronic inflammatory conditions such as inflammatory bowel disease (IBD). However, their association with disease activity and nutritional status remains unclear. This study aimed to evaluate the association between serum ghrelin and leptin concentrations and disease activity, nutritional status, and inflammatory markers in patients with IBD. A case-control study was conducted involving fifty-five IBD patients (31 with ulcerative colitis [UC] and 24 with Crohn's disease [CD]) and fifty-five healthy controls, recruited from Mansoura Specialized Medical Hospital between January 2022 and January 2023. Disease activity was assessed using the Mayo score for UC, the Crohn's Disease Activity Index (CDAI) for CD, and fecal calprotectin levels. Plasma ghrelin and leptin concentrations were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits, according to the manufacturer's instructions. Blood samples were obtained after overnight fasting, immediately centrifuged, and plasma aliquots were stored at −80°C until analysis. All samples were analyzed in duplicate, and concentrations were expressed as pg/mL for ghrelin and ng/mL for leptin. A total of 110 participants were evaluated (34 active IBD, 21 inactive IBD, and 55 controls). Demographic characteristics showed no significant differences among the groups. Both hormones differed significantly across the disease activity categories (P<0.001). Leptin levels were highest in controls and lowest in active IBD, whereas ghrelin levels were highest in controls and lowest in inactive IBD. Ghrelin showed significant negative correlations with BMI, total nutritional score, and ALP, and a positive correlation with folic acid. Leptin correlated positively with BMI, ESR, and fecal calprotectin, and negatively with the nutritional score. Receiver operating characteristic (ROC) analysis demonstrated very poor predictive capacity for food decline, weight loss, and overall nutritional status for both leptin (AUC range: 0.106–0.308) and ghrelin (AUC range: 0.337-0.394). In conclusion, leptin and ghrelin levels in IBD patients appear to be more closely associated with disease activity and inflammatory burden than with nutritional status alone. Their combined assessment may offer descriptive insights into metabolic adaptation during active disease; however, these findings are associative and do not imply causality. Further longitudinal studies are required to clarify their potential clinical utility.

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Keywords: Inflammatory bowel disease; Leptin; Ghrelin; Inflammation; Nutritional status

Introduction

Inflammatory bowel disease (IBD) is significantly more prevalent in Western societies. Although the incidence of IBD is increasing worldwide and has the potential to become a global health issue, this rising trend represents a substantial public health and clinical burden (1).

Inflammatory bowel disease comprises two main subtypes: Crohn's disease (CD) and ulcerative colitis (UC) (2). Both subtypes are characterized by chronic inflammation of the gastrointestinal tract. Ulcerative

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colitis is confined to the colon, whereas Crohn's disease may involve any part of the gastrointestinal tract, and both UC and CD may present with extraintestinal manifestations (3). Ulcerative colitis specifically affects the epithelial lining of the colon and rectum (4). Rectal bleeding, ulcer formation on the mucosal surface, and disruption of the mucosal barrier are the primary pathological features of UC (5). Because disease activity fluctuates between active and inactive phases, understanding its relationship with nutritional and metabolic markers is clinically important.

The hormone ghrelin was originally discovered in gastric cells, where it functions as a nutrient-sensing and appetite-regulating hormone. It acts through a receptor that is highly expressed on immune cells (6). Although ghrelin is thought to play a role in reducing inflammation, evidence regarding its anti-inflammatory effects remains inconsistent, and its role in immune regulation is not fully understood (7). Therefore, its potential interaction with disease activity requires direct investigation.

Leptin is a 16-kDa hormone that is primarily produced and secreted by adipocytes (8). In most cases, serum leptin levels correlate with adipose tissue mass, although leptin synthesis has also been identified in several other organs (9,10). Leptin plays a crucial role in the regulation of whole-body energy balance; elevated serum leptin suppresses food intake, whereas reduced leptin levels stimulate appetite (11,12). Because leptin is influenced by both adiposity and inflammation, evaluating its relationship with IBD activity is particularly relevant (13).

Chronic and relapsing inflammatory conditions such as UC and CD have been associated with high rates of nutritional deficiencies (14). These findings highlight the importance of assessing nutritional markers in patients with IBD.

The Crohn's Disease Activity Index (CDAI) and the Mayo score are commonly used indices to assess disease activity in CD and UC, respectively, with total scores ranging from 0 to 12 and individual components scored from 0 to 3 (15–17). This study aimed to determine plasma leptin and ghrelin levels in patients with IBD (both active and inactive) compared with healthy controls, and to evaluate the associations between these hormone levels and the nutritional status of patients with inflammatory bowel disease.

Materials and Methods

Study design and setting

This research was a case-control study involving fifty-five patients with IBD (ulcerative colitis and Crohn's disease) and fifty-five healthy subjects serving as controls. The study design was chosen to allow simultaneous assessment of hormone concentrations and nutritional status across different disease activity groups. The study was conducted over one year, from January 2022 to January 2023, at the Inflammatory Bowel Disease Clinic of Mansoura Specialized Medical Hospital. All procedures, including clinical assessment, sample collection, and laboratory analyses, were performed within this time frame. This study was conducted and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (18).

Participants

Eligibility criteria

Patients with IBD, either Crohn's disease or ulcerative colitis (active or inactive), aged between eighteen and sixty years were included in the study. The exclusion criteria were age younger than eighteen years or older than sixty years, treatment with hormone-altering medications, *Helicobacter pylori* gastritis, diabetes mellitus, hepatic disease, renal disease, morbid obesity, and malignant conditions. These exclusion criteria were applied equally to both patients and controls.

Sources and methods of selection of participants

Patients with IBD were consecutively recruited from those attending the Inflammatory Bowel Disease Clinic.

Group A (IBD group; n = 55): This group included patients with ulcerative colitis (n = 31) and Crohn's disease (n = 24).

Group B (Control group; n = 55): This group comprised healthy individuals, including both fasting (n = 22) and non-fasting (n = 33) participants, with no evidence of IBD.

Variables

The primary outcomes were plasma concentrations of ghrelin and leptin. Predictor variables included IBD subtype (ulcerative colitis vs. Crohn's disease) and disease activity status (active vs. inactive). Potential confounders included BMI, total nutritional score, ESR, CRP, hemoglobin level, platelet count, serum albumin, liver function tests, renal function tests, vitamin D, vitamin B12, serum iron, and fecal calprotectin. Diagnostic criteria included the Mayo score for ulcerative colitis and the Crohn's Disease Activity Index (CDAI) for Crohn's disease.

Data sources and measurement

Clinical assessment

All participants were subjected to complete history taking and thorough physical examinations.

Blood sample collection

A ten‐milliliter venous blood sample was obtained from each participant by brachial vein puncture into citrate‐containing tubes. The samples were centrifuged for ten minutes to separate plasma, which was subsequently stored at a temperature below −20°C. Each participant provided a ten‐milliliter venous blood sample collected in tubes containing sodium citrate, citrate, dextrose, and citric acid. All samples were processed according to standard venipuncture procedures (19).

Disease assessment

All participants underwent a detailed clinical evaluation that included symptom duration, stool frequency, rectal bleeding, abdominal pain, systemic manifestations, and treatment history. Ultrasonographic assessment was performed after a fasting period of 6–8 hours to minimize intraluminal gas and optimize bowel visualization. The examination focused on bowel wall thickness, mural stratification, vascularity, and evidence of perienteric inflammation or fat proliferation. Increased bowel wall thickness was interpreted as a marker of active disease. Abdominal fat distribution was also assessed because of its potential influence on metabolic and hormonal parameters.

For patients with ulcerative colitis, disease severity was quantified using the Mayo Score, a validated composite index incorporating stool frequency, rectal bleeding, physician global assessment, and endoscopic appearance (20). The total score ranges from 0 to 12 and is categorized as remission (0–2), mild disease (3–5), moderate disease (6–10), or severe disease (11–12). Endoscopic scoring was based on mucosal findings such as erythema, friability, erosions, ulceration, and spontaneous bleeding.

Crohn's disease activity was evaluated using the Crohn's Disease Activity Index (CDAI), which integrates eight clinical and laboratory parameters, including stool frequency, abdominal pain severity, general well‐being, presence of extraintestinal manifestations, abdominal mass, hematocrit, body weight, and use of antidiarrheal medications (21). CDAI scores below 150 indicated remission, whereas scores between 230 and 450 denoted moderate to severe disease activity. This index provides a quantitative assessment of disease burden and was used to correlate inflammatory activity with biochemical, nutritional, and hormonal variables.

Nutritional assessment

Nutritional status was evaluated using the Mini Nutritional Assessment (MNA), body mass index (BMI), and specific nutritional history variables (22–24). Body weight was measured to the nearest 0.1 kg using a calibrated digital scale, and height was measured with a stadiometer. BMI was calculated as weight (kg) divided by height squared (m^2), in accordance with established procedures (25). BMI categories followed standard definitions: <18.5 underweight, 18.5–24.9 normal, 25–29.9 overweight, and ≥30 obesity.

The full MNA was administered to obtain the total nutritional score based on recent food intake, 3-month weight change, mobility, psychological stress, chronic disease, and BMI, according to Guigoz and colleagues (26). Classification thresholds included 24–30 (normal nutritional status), 17–23.5 (at risk of malnutrition), and <17 (malnourished). Individual MNA components were used to derive specific variables included in the analysis.

Food decline during the previous 3 months was assessed using the MNA dietary intake item, which categorizes individuals as having no decline, moderate decline, or severe decline in food consumption. Weight loss in the previous 3 months was evaluated according to standard MNA scoring criteria and categorized as >3 kg weight loss, 1–3 kg weight loss, unknown, or no loss (22–24).

Anthropometric measurements included mid-arm circumference (MAC) and triceps skinfold thickness, obtained using a Holtain caliper with 0.1 mm precision. Mid-arm muscle circumference (MAMC) was calculated using the validated formula:

MAMC=MAC−(3.1414×triceps skinfold thickness), to estimate lean body mass (27).

Laboratory analysis

Venous blood samples were collected into citrate‐containing tubes using standard aseptic venipuncture, centrifuged for 10 minutes to separate plasma, and stored at temperatures below −20°C until biochemical and hormonal analyses were performed. Hematological investigations included hemoglobin concentration, white blood cell (WBC) count, platelet count, and erythrocyte sedimentation rate (ESR). Biochemical analyses included measurements of serum iron, vitamin D, vitamin B12, folic acid, albumin, creatinine, urea, bilirubin, and liver enzymes (SGOT, SGPT, and ALP), as well as the international normalized

ratio (INR) and C‑reactive protein (CRP). Fecal calprotectin was quantified as a marker of intestinal inflammatory activity using standard immunoassay techniques.

Hormonal Assays

Plasma ghrelin and leptin concentrations were quantified using enzyme-linked immunosorbent assays (ELISAs). Ghrelin levels were determined via a competitive inhibition ELISA (DLR-GHRL-Hu; DL Sci & Tech, China), in which endogenous ghrelin competes with biotin-labeled ghrelin for binding to immobilized antibodies, resulting in an inverse signal–concentration relationship. Leptin levels were measured using a sandwich ELISA (DLR-LEP-Hu; DL Sci & Tech, China) employing monoclonal capture and detection antibodies, which generates a directly proportional relationship between absorbance and analyte concentration. Both assays utilized seven-point standard curves ranging from 0.156 to 10 ng/mL. Sensitivity thresholds were <0.047 ng/mL for ghrelin and <0.059 ng/mL for leptin, with intra-assay and inter-assay coefficients of variation (CV) maintained below 10% and 12%, respectively. All sample processing followed validated manufacturer protocols from Phoenix Pharmaceuticals and R&D Systems.

Assay procedures, reagent preparation, and sensitivity

Reagent preparation involved generating a stock solution with a concentration of 10 ng/mL and constructing seven-point standard curves at 10, 5, 2.5, 1.25, 0.625, 0.312, and 0.156 ng/mL. A blank solution was maintained at 0 ng/mL.

For the ghrelin assay, 50 µL of each sample, blank, or standard was added to the wells, followed by the addition of Detection Solution A, incubation at 37°C, washing cycles, addition of Detection Solution B, further incubation, addition of TMB substrate, and measurement of absorbance at 450 nm.

For the leptin assay, 100 µL of each standard, blank, or sample was added to the wells, followed by incubation with the detection solutions, wash cycles, TMB substrate incubation, reaction termination, and absorbance measurement at 450 nm.

Assay range and quality control

The detection range for both ghrelin and leptin assays was 0.156–10 ng/mL. The sensitivity of the ghrelin assay was below 0.047 ng/mL, while the sensitivity of the leptin assay was under 0.059 ng/mL. Intra‑assay coefficients of variation were below 10%, and inter‑assay coefficients of variation were below 12%. All assays were performed in duplicate. No reagents, standards, or samples were used until they had equilibrated to room temperature.

Bias

The detection range for both ghrelin and leptin assays was 0.156–10 ng/mL. Ghrelin assay sensitivity was below 0.047 ng/mL, and leptin assay sensitivity was under 0.059 ng/mL. Intra‑assay and inter‑assay coefficients of variation were maintained below 10% and 12%, respectively. All assays were performed in duplicate, and reagents, standards, and samples were allowed to equilibrate to room temperature before use.

Sample size calculation

The sample size estimate was calculated based on the mean plasma ghrelin levels in active and inactive cases of inflammatory bowel syndrome, as reported in prior research (28). Using G*Power to compute the difference between two means with a two‑tailed t‑test, assuming an effect size of 0.54, an alpha error of 0.05, and a power of 80%, the required sample size was 55 participants per group.

Quantitative variables

Values for BMI, hormone concentrations, inflammatory markers, and biochemical parameters were treated as continuous variables.

Statistical analysis

Comparisons among active, inactive, and control groups were performed using analysis of variance (ANOVA; F‑test). The Monte Carlo test and Fisher's exact test were applied to categorical variables when appropriate. Spearman correlation coefficients were calculated to assess associations between hormone concentrations and nutritional, inflammatory, and biochemical variables. Receiver operating characteristic (ROC) curve analyses were conducted to evaluate the predictive utility of leptin and ghrelin for food decline, weight loss, and overall nutritional status. No confounder‑adjusted models were applied, and no missing data occurred.

Results

A total of 110 individuals were analyzed, including 34 active cases, 21 non-active cases, and 55 controls. All eligible participants were included, with no exclusions, losses, or missing data; therefore, a flow diagram was

deemed unnecessary.

Demographic variables (age, sex, residence, and smoking status) showed no missing values and no statistically significant differences among groups: age ($P = 0.178$), sex ($P = 0.253$), residence ($P = 0.929$), and smoking status ($P = 0.183$) (Table 1).

Serum leptin and ghrelin levels differed significantly across the three groups ($P < 0.001$ for both). Leptin levels were highest in controls, intermediate in non-active cases, and lowest in active cases; conversely, ghrelin levels were highest in controls, followed by active cases, and lowest in non-active cases (Table 2).

Across six subgroups, leptin and ghrelin levels also demonstrated significant differences ($P < 0.001$). Leptin was lowest in active UC and CD, higher in non-active disease, and peaked in controls, whereas ghrelin exhibited the opposite trend, reaching the highest concentrations in fasting controls (Table 3).

Among active cases, folic acid showed a significant positive correlation with ghrelin ($P = 0.043$). Leptin correlated positively with ESR ($P = 0.017$), BMI ($P = 0.036$), and fecal calprotectin ($P = 0.001$) (Table 4).

Predictive analyses revealed poor performance for both hormones. Leptin displayed very weak predictive ability for food decline (AUC = 0.106, $P < 0.001$), while ghrelin also performed poorly (AUC = 0.394, $P = 0.070$) (Table 5). Similarly, both leptin (AUC = 0.242, $P < 0.001$) and ghrelin (AUC = 0.337, $P = 0.003$) showed minimal predictive value for weight loss (Table 6). Prediction of overall nutritional status was likewise weak for leptin (AUC = 0.308, P = 0.001) and ghrelin (AUC = 0.347, $P = 0.006$) (Table 7).

Table 1. Demographic characteristics of the examined groups

Characteristic	Active Group (Number=34)	Non-Active Group (Number=21)	Control Group (Number=55)	Test of Significance
Age (years) Mean±SD	32.0 ± 10.83	**30.5 ± 11.51**	27.4 ± 7.88	F=1.753, P=0.178
		Sex, n (%)		
Male	16 (47.06)	**8 (38.10)**	32 (58.18)	MC=2.745, *P*=0.253
Female	18 (52.94)	**13 (61.90)**	23 (41.82)	
		Residence, n (%)		
Rural	16 (47.06)	**10 (47.62)**	28 (50.91)	MC=0.147, *P*=0.929
Urban	18 (52.94)	11 (52.38)	27 (49.09)	
Smoking, n (%)	5 (14.71)	0 (0.00)	5 (9.09)	MC=3.397, *P*=0.183

Information is expressed as Mean ± Standard Deviation (SD) or Number (Percentage). MC: Monte Carlo test; F: One-Way ANOVA test; †: Fisher's Exact Test can be more suitable here because of a cell count of 0. A statistically insignificant variances have been observed between the groups for any demographic characteristic

Table 2. Comparison of serum ghrelin and leptin concentrations among active, non-active, in addition control groups

Hormone	Active Group (Number=34)	Non-Active Group (Number=21)	Control Group (Number=55)	Test of Significance
Leptin (pg/mL)	312.01 ± 50.89	596.82 ± 29.16	643.88 ± 185.26	F=46.76, *P*<0.001*
Ghrelin (pg/mL)	437.53 ± 41.96	240.07 ± 61.17	1160.35 ± 832.28	F=28.67, *P*<0.001*

* Statistically significant variance (P below 0.001). There were greatly significant variances in both ghrelin and leptin concentrations between the 3 groups

Table 3. Serum leptin & ghrelin concentrations across all examined subgroups

Group	N (%)	Leptin (picograms per milliliter), Mean ± SD	Ghrelin (picograms per milliliter), Mean ± SD
Active UC	19 (17.3%)	253.7 ± 39.61	442.5 ± 119.95
Active CD	15 (13.6%)	303.9 ± 29.09	383.0 ± 106.10
Non-Active UC	12 (10.9%)	513.3 ± 69.11	247.7 ± 82.59
Non-Active CD	9 (8.2%)	546.8 ± 97.93	197.4 ± 35.89
Fasting Control	22 (20.0%)	394.5 ± 91.19	1713.0 ± 628.87
Non-Fasting Control	33 (30.0%)	655.2 ± 154.76	500.2 ± 126.79
Test of Significance		F=67.199, *P*<0.001*	F=69.732, *P*<0.001*

UC: Ulcerative Colitis; CD: Crohn's Disease; There were greatly significant variances in both ghrelin and leptin concentrations across all 6 examined subgroups

Table 4. Association of Leptin and Ghrelin with Nutritional and Laboratory Variables in Active Disease Cases (Number equal thirty-four)

Parameter	Ghrelin (r, *P*)	Leptin (r, *P*)
Nutritional Status		
Total nutritional score	-0.494, 0.003*	-0.393, 0.022*
BMI	-0.484, 0.003*	0.361, 0.036*
Food Decline (Last 3 Months)	-0.137, 0.439	-0.138, 0.436
Weight Loss (Last 3 Months)	-0.063, 0.725	-0.063, 0.725
Hematological Parameters		
Hemoglobin	0.140, 0.431	0.036, 0.840
WBC Count	-0.293, 0.092	-0.073, 0.681
Platelet Count	-0.016, 0.930	-0.165, 0.350
ESR	-0.054, 0.761	0.407, 0.017*
CRP	0.218, 0.215	-0.040, 0.823
Biochemical Parameters		
Serum Iron	0.158, 0.371	0.110, 0.534
Vitamin D	0.058, 0.746	-0.038, 0.832
Vitamin B12	0.149, 0.400	0.134, 0.450
Folic A`	0.349, 0.043*	0.083, 0.640
Serum Albumin	0.162, 0.361	-0.275, 0.116
Serum Creatinine	0.254, 0.146	0.317, 0.067
Urea	0.193, 0.274	0.054, 0.762
Bilirubin	-0.034, 0.849	0.180, 0.308
Liver Function Tests		
SGPT	0.209, 0.235	0.187, 0.289
SGOT	0.032, 0.857	0.165, 0.350
ALP	-0.365, 0.034*	-0.093, 0.602
INR	0.091, 0.609	-0.063, 0.722
Others		
Fecal Calprotectin	-0.091, 0.608	0.524, 0.001*

ESR: Erythrocyte Sedimentation Rate; BMI: Body Mass Index. r: Spearman correlation coefficient. Only parameters with not more than one significant association are illustrated for brevity. Insignificant associations with other variables (e.g., WBC, Hemoglobin, Vit D, etc.) have been observed and are omitted

Table 5. Predictive Power of Ghrelin and Leptin for Food Decline in the Previous Three Months

Hormone	Cut-off (pg/mL)	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV	*P*
Leptin	305.0	0.106 (0.045–0.167)	62.2%	5.0%	44.7%	8.0%	<0.001*
Ghrelin	255.3	0.394 (0.286–0.502)	75.7%	26.0%	56.1%	46.4%	0.070

CI: Confidence Interval; AUC: Area Under the ROC Curve; PPV: Positive Predictive Value; NPV: Negative Predictive Value. nevertheless, the very low AUC illustrates poor predictive capability. Leptin illustrated very low predictive capability for food decline. Ghrelin failed to demonstrate significant predictive power. Neither hormone is a beneficial biomarker for expecting recent food decline

Table 6. Predictive Power of Leptin and Ghrelin for Weight Loss in the Last Three Months

Hormone	Cut-off (picograms per milliliter)	AUC (95 percent CI)	Sensitivity	Specificity	PPV	NPV	*P*
Leptin	310.4	0.242 (0.153–0.331)	56.9%	10.0%	41.3%	16.7%	<0.001*
Ghrelin	275.3	0.337 (0.232–0.441)	72.4%	20.0%	50.0%	38.5%	0.003*

CI: Confidence Interval; AUC: Area Under the ROC Curve; PPV: Positive Predictive Value; NPV: Negative Predictive Value. nevertheless, the very low AUC illustrates poor predictive capability. Leptin illustrated very low predictive capability for food decline. Ghrelin failed to demonstrate significant predictive power. Neither hormone is a beneficial biomarker for expecting recent food decline

Table 7. Predictive Power of Ghrelin and Leptin for Overall Nutritional State

Hormone	Cut-off (picograms per milliliter)	AUC (95 percent CI)	Sensitivity	Specificity	PPV	NPV	*P*
Leptin	414.5	0.308 (0.207–0.408)	53.1%	15.0%	98.3%	0.0%	0.001*
Ghrelin	415.0	0.347 (0.244–0.449)	57.1%	26.2%	98.4%	0.0%	0.006*

CI: Confidence Interval; AUC: Area Under the ROC Curve; PPV: Positive Predictive Value; NPV: Negative Predictive Value. nevertheless, the very low AUC illustrates poor predictive capability. Leptin illustrated very low predictive capability for food decline. Ghrelin failed to demonstrate significant predictive power. Neither hormone is a beneficial biomarker for expecting recent food decline

Discussion

The present study showed that baseline demographic characteristics—including residence, gender, age, and smoking history—did not differ significantly among the Crohn's disease, ulcerative colitis, and control groups. Consistent with this observation, a previous study (29) reported that ghrelin expression in ulcerative colitis is mainly associated with disease activity rather than demographic factors. Another study (28) similarly confirmed that circulating ghrelin and leptin concentrations are influenced by nutritional status and disease activity but remain largely independent of demographic variables.

Across groups categorized by disease activity, there was a clear and statistically significant variation in both leptin and ghrelin levels. Control subjects exhibited the highest mean leptin concentrations, followed by patients with non‑active IBD, whereas the lowest levels were observed in active IBD groups. Ghrelin concentrations were highest in controls, followed by active cases, and lowest in non‑active groups, with statistically significant differences between categories. These findings align with previous work (30), which reported markedly reduced serum leptin concentrations in patients with active ulcerative colitis and Crohn's disease and significantly higher levels among those in remission and healthy controls. Similarly, a study (31) demonstrated decreased leptin and increased ghrelin concentrations during active disease phases, reflecting the opposing regulatory patterns observed in the current study.

Correlation analyses revealed that ghrelin showed a significant negative association with total nutritional score, BMI, and ALP, and a significant positive association with folic acid. In contrast, leptin demonstrated a significant negative correlation with total nutritional score and positive correlations with ESR, BMI, and fecal calprotectin. These findings are consistent with previous research, which reported that lower serum leptin levels were associated with increased disease activity in IBD based on endoscopic evaluation (31). They are also in agreement with studies indicating that ghrelin concentrations in patients with ulcerative colitis and Crohn's disease are negatively correlated with BMI and positively correlated with disease activity (32,33).

However, despite these meaningful associations, ROC curve analysis revealed that leptin had a low predictive capacity for food intake decline over the preceding three months, while ghrelin likewise failed to demonstrate significant predictive ability. These results are consistent with previous evidence (34) indicating that, although leptin is related to fat mass and BMI, it has limited capacity to predict recent reductions in food intake among malnourished IBD patients. In contrast, other studies have reported that lower leptin concentrations are associated with malnutrition risk and reduced food intake, showing acceptable sensitivity in ROC analyses (35), and that ghrelin may serve as a potential biomarker for early nutritional decline in chronic gastrointestinal disorders (36). Furthermore, another study (37) suggested that although leptin and ghrelin correlate with adiposity and certain nutritional indices, their diagnostic performance in predicting current weight loss or overall nutritional status remains modest.

This study has several limitations that warrant acknowledgment. First, the cross-sectional design precludes any inference of causality or definitive temporal relationships between nutritional status, inflammatory activity, and plasma ghrelin and leptin levels. The observed associations therefore represent a snapshot at a single time point and may not capture dynamic changes throughout the disease course.

Second, the analysis was primarily univariable, and multivariable regression models were not employed to adjust for potential confounding factors, such as age, sex, body mass index, disease duration, medication use, and inflammatory burden. Consequently, residual confounding cannot be excluded, and the independent contribution of ghrelin or leptin to nutritional or

inflammatory parameters cannot be definitively established.

Third, the relatively modest sample size may have limited statistical power, particularly for subgroup analyses and exploratory ROC-based evaluations. Finally, hormone measurements were obtained at a single time point, which may not fully capture longitudinal fluctuations related to disease activity or nutritional interventions.

Despite these limitations, the study provides valuable associative data on the relationship between nutritional status and appetite-regulating hormones in patients with inflammatory bowel disease and highlights important directions for future longitudinal and multivariable research.

This study identified an inverse association between serum ghrelin and leptin concentrations in patients with inflammatory bowel disease, with both hormones being associated with disease activity and inflammatory markers. Compared with non‐active disease, active IBD was characterized by lower leptin and higher ghrelin concentrations. Leptin correlated with BMI, ESR, and fecal calprotectin, whereas ghrelin showed inverse correlations with BMI and total nutritional score and a positive correlation with folic acid. Although both hormones were associated with disease activity, they demonstrated limited accuracy as predictors of short‐term nutritional decline in this dataset. Given the case–control design, these findings should be interpreted as associative rather than causal, and larger longitudinal studies are required to clarify temporal relationships and potential clinical utility in IBD.

Ethical approval and consent to participate

Participants and their relatives provided verbal informed consent to participate in the study. Adequate measures were implemented to ensure participant confidentiality and data privacy. Ethical approval was obtained from the Research Ethics Committee of the Faculty of Medicine, Mansoura University, under IRB number **MD.21.12.571.R1**, dated **14 December 2021**.

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