

Evaluation of Gastro-Duodenal Mucosa of Non-IBS / Non-Endoscopic EGD Disorders in Metabolic Syndrome

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ABSTRACT

Background: Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder, while metabolic syndrome (MetS) may contribute to gastrointestinal disturbances and microscopic mucosal inflammation (microscopic gastroduodenitis).

Aim: to assess the histopathologic and histochemical changes of gastroduodenal mucosa in the expected nonorganic disorders as diagnosed by endoscopy and in non-IBS (IBS-like+IBS-free) GIT disorder of patients with MetS.

Patients and Methods: A total of 839 patients attended the GIT endoscopy unit over a three-year period were categorized into two groups: those with gastroduodenal diseases (n=510) and those with no endoscopic abnormalities (n=329). Patients with no endoscopic abnormality were divided into four groups: I, IBS without MetS (n=39); II, IBS with MetS (n=53); III, non-IBS with MetS (n=158); and IV, non-IBS without MetS (n=79). Gastroduodenal biopsies were obtained and examined histopathologically using hematoxylin and eosin staining.

Results: Gastric lymphocytic cellular infiltration (LCI) differed significantly among groups ($p < 0.001$), with higher grades predominantly observed in Group II. Gastric eosinophilic cellular infiltration (ECI) also differed significantly ($p < 0.001$), with higher infiltration in Groups II and III. Duodenal LCI differed significantly ($p = 0.034$) in Group II compared with Groups I and IV. Duodenal ECI showed a highly significant difference ($p < 0.001$), with greater infiltration in Groups II and III compared with Groups I and IV.

Conclusion: Metabolic Syndrome is associated with increased gastroduodenal mucosal lymphocytic and eosinophilic infiltration, particularly among patients with IBS, suggesting a microscopic inflammatory process underlying the apparently functional gastrointestinal symptoms.

Keywords: Metabolic syndrome; irritable bowel syndrome; gastroduodenal mucosa; microscopic cellular gastritis; mucosal immune cell infiltration.

INTRODUCTION

Irritable bowel syndrome (IBS) is chronic gastrointestinal disorder characterized by recurrent abdominal pain associated with altered bowel habits and is considered one of the most prevalent disorders of gut–brain interaction worldwide [1]. IBS is further subtyped into four patterns: Diarrhea-predominant (IBS-D), Constipation-predominant (IBS-C), Mixed irritable bowel syndrome (IBS-M), Unclassified (IBS-U), Due to the lack of biological markers and organic lesions gastroenterologists rely on clinical findings for the diagnosis of IBS, based on the Rome IV criteria [2].

Metabolic syndrome (MetS) is a disorder defined by a cluster of metabolic abnormalities encompassing hypertension, central obesity, insulin resistance and atherogenic dyslipidemia, MetS is a major public health concern as a significant risk factor for cardiovascular atherosclerotic diseases and type 2 diabetes [3]. Several studies have demonstrated a higher prevalence of metabolic syndrome among patients with IBS compared with the general population. Obesity, insulin resistance, impaired glucose tolerance, dyslipidemia, and hypertension are more frequently encountered in IBS patients, particularly in those with diarrhea-predominant IBS (IBS-D). Similarly, patients with metabolic syndrome often report gastrointestinal symptoms such as abdominal discomfort, bloating, constipation, diarrhea, and visceral hypersensitivity [4]. Diabetes can affect every part of the GI tract, from the esophagus to the rectum, and causes various symptoms, including reflux, heartburn, nausea, vomiting, abdominal pain, diarrhea and constipation. Diabetes-induced GI complications are collectively referred to as diabetic gastro-enteropathy [5]. Gastrointestinal manifestations in chronic diseases like Diabetes Mellitus (DM) are typically associated with other microvascular complications [6].

Microscopic gastritis is a histologically confirmed inflammation of the gastric mucosa detected on biopsy examination, regardless the findings of endoscopy are whether normal or abnormal [7]. The diagnosis is mainly based on the microscopic detection of inflammatory infiltration of the lamina propria, gastric glands, or epithelium. In contrast to purely endoscopic gastritis, microscopic gastritis requires tissue confirmation as

endoscopic appearance often correlates poorly with histopathological inflammation^[8]. The hallmark histological finding in microscopic gastritis includes infiltration of inflammatory cells into the lamina propria and gastric epithelium. The infiltrating inflammatory cells may include neutrophils, lymphocytes, plasma cells, eosinophils, macrophages, or a mixture of cells depending on the type of gastritis and its stage^[9].

Aim of work

To assess the histopathologic and histochemical changes of Gastro-Duodenal mucosa in the expected non-organic diseases as diagnosed by endoscopic screening and non-IBS (IBS-like and IBS-free) GIT disorders in patients with Metabolic syndrome.

Patients and Methods

This cross-sectional study was conducted at the Hepatology and Gastroenterology and Infectious diseases Department, Faculty of Medicine, Al- Azhar University, Cairo, Egypt, Department of Hepatology, Gastroenterology and Department of pathology at Theodor Bilharz research institute. (from 1/4/2023 till 31/1/2026).

I. Patient Recruitment and Selection Criteria : A total of 839 adults presenting gastroduodenal manifestations underwent initial assessment. After detailed clinical evaluation and endoscopic examination, 329 patients with no apparent macroscopic abnormalities on upper gastrointestinal endoscopy were included in the final study population.

II. Inclusion Criteria: Symptomatic adult patients aged 18 years, undergoing either primary (naïve) or repeated screening Gastroscopy , with no detectable gross structural mucosal lesions.

IV. Exclusion Criteria: Patients aged < 18 years. Individuals with a documented history or ongoing follow-up for established structural gastrointestinal diseases (e.g., Inflammatory Bowel Disease, malignancy), gastrointestinal infections (including HIV, HBV, HCV, COVID-19, Salmonellosis, Shigellosis, or pathogenic E. coli), or systemic malignancies (except hepatocellular carcinoma 6 months' post-cure or extrahepatic malignancies 2 years disease-free) were excluded. Pregnant females and patients with severe, chronic debilitating disorders were also excluded.

V. Symptom-Based Patient Stratification

Enrolled subjects (n = 329) were segregated based on their symptoms against the Rome IV criteria into two primary cohorts: **IBS** (n = 92) and **non-IBS** (n = 237). The IBS Cohort fulfilled the definition of Rome IV criteria. Non-IBS Cohort Included patients with "IBS-like" symptoms (partially fulfilling Rome IV criteria, characterized by recurrent abdominal pain with alternating bowel habits for less than the required threshold) and "IBS-free" subjects presenting with vague gastro-colonic manifestations (e.g., postprandial dyspepsia, isolated abdominal distension, persistent flatulence, borborygmi, etc.). All enrolled population were screened for the presence of Metabolic Syndrome (Metabolic syndrome was defined according to the harmonized IDF/AHA/NHLBI criteria). The cohort was further stratified into the following four groups: - Group I (IBS / no-MetS (n = 39)): Fulfilling Rome IV criteria without metabolic syndrome. Group II (IBS / MetS (n = 53)): Fulfilling Rome IV criteria with concurrent metabolic syndrome. Group III (Non-IBS / MetS (n = 158)): Presenting with non-IBS symptoms with concurrent metabolic syndrome. Group IV (Non-IBS / no-MetS (n = 79)): Presenting with non-IBS symptoms without metabolic syndrome.

VI. Clinical and Biochemical Profiling

All participants underwent detailed medical history taking and systemic clinical examinations. Routine laboratory investigations included complete blood count (CBC), liver function tests (LFTs), and renal function tests (RFTs). To evaluate Metabolic Syndrome (MetS), targeted anthropometric and biochemical assessments were performed, including waist circumference (cm), systolic and diastolic blood pressure, fasting blood glucose (FBG), HbA1c, and a comprehensive lipid profile (total cholesterol, triglycerides, LDL, VLDL, and HDL).

VII. Gastroscopy and Tissue Sampling Protocol

Following an appropriate pre-procedure fasting period, gastroscopies were performed under conscious sedation utilizing midazolam, with continuous vital signs monitoring. High-definition visualization was achieved using Olympus EVIS EXERA III (GIF-HQ190) and Fujifilm 600 series video gastroscopes, ensuring excellent visualization of the mucosa. Complete examination was verified in all cases to exclude macro structural pathology. Multiple mucosal biopsy specimens were systematically obtained from predetermined sites, including Stomach and duodenum using standard biopsy forceps. Specimens were immediately fixed in 10% neutral-buffered formalin.

VIII. Histopathological and Histochemical Evaluation

Formalin-fixed, paraffin-embedded tissue blocks were sectioned at 4–5 μ m thickness. Sections were stained with Hematoxylin and Eosin (H&E) for baseline histopathological screening, and Masson's Trichrome stain was utilized for the histochemical evaluation of mucosal collagenous deposition. All slides were evaluated by an experienced pathologist blinded to the clinical groups. A semi-quantitative scoring system was applied to assess cellular and architectural parameters based on reference normal values:

Lymphocyte Cellular Infiltrate (LCI): Quantified as 11–30/HPF or >30HPF.

Eosinophil Cellular Infiltrate (ECI): Quantified as 11–30/HPF or >30HPF.

Goblet Cell Density (MGCD): Graded by percentage reduction (10 to 20% of average).

Architectural Parameters: Evaluated for gland number/size atrophy (90% or less of the average), crypt depth shortening (90% or less of the average), dysplastic or metaplastic changes, and mucosal collagenous material (MCM) thickness (10% > average).

IX. Statistical Analysis and Sample Size Calculation

Statistical analysis was conducted using SPSS version 25.0. Normality of quantitative data was verified via the Shapiro-Wilk test, and homogeneity of variance was assessed using Levene's test. Quantitative variables are expressed as Mean, Standard Deviation (SD) and analyzed using the independent Student's T-test or ANOVA where appropriate. Categorical variables are presented as frequencies and percentages (%) and analyzed using the Chi-Square test or Fisher's Exact test. Pairwise comparisons were executed using post-hoc tests with adjustment for multiple comparisons. Statistical significance was established at a threshold of $P < 0.05$.

X. Sample Size Justification:

The sample size was calculated based on pilot data, using a control-group standard deviation of 0.9 and a regression error standard deviation of 1.94. Assuming a true regression slope of 1.4, the calculation was performed to achieve 90% statistical power ($\beta = 0.10$) to reject the null hypothesis of a zero-regression slope, with a two-sided Type I error rate of 5% ($\alpha = 0.05$).

XI. Ethical Aspects

- 1- Approving study: - this study was approved by Committee of HGID Department and Committee of Faculty of Medicine at Al-Azhar University (approval certificate Trop.Med._1Med.Research_Inf.GIT.Liv.Dis._109).
- 2- Patient Consent: - All patients that were included in the current study signed approved consent from Al-Azhar University ethical committee.

Results

Baseline Characteristics and Comorbidities Across the Studied Groups

The distribution of comorbid conditions across the four studied groups revealed highly significant variation.

As detailed in Table 1, The distribution of diabetes across the four studied groups demonstrated a highly significant variation. the prevalence of diabetes was significantly higher in the metabolic syndrome groups, particularly in Group III (Non-IBS/MetS), where diabetes was present in 51.9% of patients, followed by Group II (IBS/MetS) at 39.6%. also, no diabetic cases were observed in Group I (IBS/no-MetS), while only 1.3% of patients in Group IV (Non-IBS/no-MetS) had diabetes. These differences were statistically significant across the relevant pairwise comparisons (all $p < 0.001$) (all $P < 0.001$, except II vs III, $P = 0.015$), whereas no significant difference was observed between Groups I and IV ($P > 0.900$).

Similarly, disturbed lipid profiles demonstrated a highly significant difference across the four groups ($p < 0.001$), with substantially higher frequencies observed in Groups II and III compared with the non-metabolic syndrome groups, Groups I and IV. Post-hoc pairwise comparisons confirmed significant differences between the metabolic and non-metabolic groups (all significant pairwise $p < 0.001$).

In contrast, the distribution of oral lesions did not differ significantly among the four studied groups. The overall comparisons were statistically non-significant ($p > 0.05$), and none of the pairwise comparisons demonstrated a statistically significant difference.

Table 1: Baseline Characteristics and Comorbidities Across the Studied Groups

Study populations	Diabetes Mellitus		Oral Ulcers (OU)			Disturbed Lipid Profile			
	No DM	Currentl y Diabeti c	No OU	Past History Of OU	Recurr ent OU	Norm al	Presen t	Pend ing	Under TTT

A. group I: IBS/no.MetS. (n=39)	39 (100.0%)	0 (0%)	29 (74.4%)	2 (5.1%)	8 (20.5%)	34 (87.2%)	4 (10.3%)	0 (0.0%)	1 (2.6%)
B. group II: IBS/MetS. (n= 53)	32 (60.4%)	21 (39.6%)	46 (86.8%)	1 (1.9%)	6 (11.3%)	11 (20.8%)	35 (66.0%)	0 (0.0%)	7 (13.2%)
C. Group III: no.IBS/MetS (n = 158)	76 (48.1%)	82 (51.9%)	123 (77.8%)	6 (3.8%)	29 (18.4%)	23 (14.6%)	90 (57.0%)	2 (1.3%)	43 (27.2%)
D. group IV: no.IBS/no.MetS (n = 79)	78 (98.7%)	1 (1.3%)	65 (82.3%)	4 (5.1%)	10 (12.7%)	76 (96.2%)	3 (3.8%)	0 (0.0%)	0 (0.0%)
P values:									
A vs B	<0.001		0.47			<0.001			
A vs C	<0.001		0.8			<0.001			
A vs D	>0.900		0.6			>0.13			
B vs C	0.015		0.7			0.15			
B vs D	<0.001		0.9			<0.001			
C vs D	<0.001		0.7			<0.001			
Overall	<0.001		>0.9			<0.001			

Abbreviations: DM, diabetes Mellitus; TTT, treatment; IBS; irritable bowel syndrome; MetS., Metabolic syndrome.

2. Clinical History and Symptom Presentation

The distribution of neurological and gastrointestinal symptoms across the four studied groups showed no statistically significant differences for most variables. As detailed in Table 2, the prevalence of headache did not differ significantly among the four groups (overall $p = 0.294$). The highest prevalence was observed in Group I (33.3%), followed by Group III (31.0%), Group IV (22.2%), and Group II (20.7%). All pairwise comparisons were non-significant ($p > 0.05$).

Similarly, fatigue was reported in 35.9%, 24.6%, 28.5%, and 26.6% of patients in Groups I, II, III, and IV, respectively, with no statistically significant difference among the studied groups ($p = 0.9$).

The distribution of colonic symptoms was also comparable across the four groups (overall $p = 0.4$), with no significant differences identified in any of the pairwise comparisons.

Aspirin and colchicine intake did not demonstrate a statistically significant difference across the four groups overall ($p = 0.054$). The majority of patients in all groups reported no intake, with proportions ranging from 78.5% to 96.2%. However, significant differences were observed between Groups II and IV ($p = 0.027$) and between Groups III and IV ($p = 0.006^*$).

In contrast, the use of anti-diabetic medications differed significantly among the four groups (overall $p < 0.001$). Insulin and oral hypoglycemic use was more frequent in Groups II and III, consistent with the higher prevalence of diabetes in these groups. Significant pairwise differences were observed between Groups I and III ($p = 0.002$), Groups II and IV ($p < 0.001$), and Groups III and IV ($p < 0.001$).

Table 2. Clinical History and Medication Profiles Among the studied Groups

Study populations	Headache	Fatigue	Colonic symptoms	Gastro-colonic	Aspirin / colchicine	Anti-diabetics
A. group I: IBS/no.MetS. (n=39)	13 (33.3%)	14 (35.9%)	7 (17.9%)	3 (7.7%)	2 (5.1%)	3 (7.7%)
B. group II: IBS/MetS. (n= 53)	11 (20.7%)	13 (24.6%)	6 (11.3%)	7 (13.2%)	8 (15.1%)	19 (35.8%)
C. Group III: no.IBS/MetS (n = 158)	49 (31.01%)	45 (28.5%)	31 (19.6%)	41 (25.9%)	34 (21.5%)	71 (44.9%)
D. group IV: no.IBS/no.MetS (n = 79)	18 (22.17%)	21 (26.6%)	9 (11.4%)	5 (6.3%)	3 (3.8%)	5 (6.3%)
P values:						
A vs B	0.17	0.9	0.4		0.3	<0.001

A vs C	0.7	0.7	0.3	0.3	0.002
A vs D	0.2	0.7	0.6	0.3	0.8
B vs C	0.1	0.6	0.15	0.8	0.9
B vs D	0.7	0.9	0.6	0.02	<0.001
C vs D	0.1	0.9	0.6	0.006	<0.001
Overall	0.2	0.9	0.4	0.054	<0.001

3. Gastrointestinal Presentation

The four studied groups exhibited distinct patterns in the distribution of gastrointestinal symptoms, as presented in Table 3. dyspepsia differed significantly among the groups (overall $p = 0.020$). Fatty-meal dyspepsia was more prevalent in Groups II and III, whereas dyspepsia triggered by all types of food was most frequently reported in Group I.

In contrast, the distribution of colonic symptoms was comparable across the four groups (overall $p = 0.4$). The majority of patients reported no colonic symptoms, with proportions ranging from 80.4% to 88.7%. All pairwise comparisons were non-significant ($p = 0.15$ – 0.8).

Similarly, GERD manifestations did not show a statistically significant overall difference among the study groups (overall $p = 0.064$). However, significant pairwise differences were observed between Groups II and IV ($p = 0.042$) and between Groups III and IV ($p = 0.016$).

Table 3. Comparison of GIT specific clinical manifestations in all study groups

Study populations	C.P. + diarrhea	C.P. + Const.	C.P.+ ABH	Chr. Diarrhea	Chr. Constipation	Dyspepsia	GERD symptoms
A. group I: IBS/no.MetS. (n=39)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	3 (7.7%)	31 (79.5%)	10 (25.6%)
B. group II: IBS/MetS. (n= 53)	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	41 (77.4%)	20 (37.7%)
C. Group III: no.IBS/MetS (n = 158)	0 (0.0%)	2 (1.3%)	13 (8.2%)	3 (1.9%)	4 (2.5%)	124 (78.5%)	62 (39.2%)
D. group IV: no.IBS/no.MetS (n = 79)	1 (1.3%)	1 (1.3%)	2 (2.5%)	0 (0.0%)	2 (2.5%)	68 (86.1)	17 (21.5%)
P values:							
A vs B	0.4					0.18	0.22
A vs C	0.3					0.09	0.4
A vs D	0.6					0.6	0.6
B vs C	0.15					0.059	0.5
B vs D	0.8					0.014	0.42
C vs D	0.6					0.2	0.016
Overall	0.4					0.02	0.064

Abbreviations: C.P.: colonic pain; ABH: alternating bowel habits

4. Metabolic and Biochemical Markers

HbA1c levels differed significantly among the four groups (overall $p < 0.001$), with the highest mean levels in Group III ($7.0 \pm 1.6\%$), followed by Group II ($6.9 \pm 1.8\%$), Group IV ($5.4 \pm 0.5\%$), and Group I ($5.3 \pm 0.5\%$). Significant pairwise differences were observed between Groups I and III, II and IV, and III and IV (all $p < 0.001$), while Groups I and IV ($p = 0.4$) and II and III ($p = 0.6$) were not significantly different.

Fasting blood glucose also differed significantly among the four groups (overall $p < 0.001$). Significant differences were observed between Groups I and III, II and IV, and III and IV (all $p < 0.001$), whereas Groups I and IV ($p = 0.12$) and II and III ($p > 0.9$) showed no significant differences. Overall, Groups II and III had higher fasting blood glucose levels than Groups I and IV.

Dyslipidemia markers (Total cholesterol, triglycerides, LDL, HDL, and VLDL) levels all differed significantly among the four groups (all overall $p < 0.001$). Total cholesterol, triglycerides, LDL, and VLDL were generally highest in

Group III, followed by Group II, whereas HDL showed the opposite pattern, with the highest level in Group I and the lowest in Group II. For total cholesterol, significant differences were observed between Groups I–II, I–III, II–IV, and III–IV.

Post-hoc analysis revealed significant pairwise differences for triglycerides between Groups I–II, I–III, and III–IV. LDL, HDL, and VLDL showed significant differences between Groups I–III, II–IV, and III–IV. The remaining pairwise comparisons were not statistically significant.

Table 4. Comparison of Laboratory Findings Among the studied groups

Study populations	HBA1c mean±SD	FBG mean±SD	Cholesterol mean±SD	Triglycerides mean±SD	LDL mean±SD	VLDL mean±SD	HDL mean±SD
A. group I: IBS/no.MetS. (n=39)	5.3 ± 0.5	88.1 ± 10.4	184.1 ± 51.8	109.9 ± 45.1	109.2 ± 52.9	23.4 ± 9.6	52.0 ± 11.8
B. group II: IBS/MetS. (n= 53)	6.9 ± 1.8	139.6 ± 56.1	220.9 ± 72.3	142.4 ± 58.6	146.8 ± 65.7	28.5 ± 11.7	44.2 ± 11.1
C. Group III: no.IBS/MetS (n = 158)	7.0 ± 1.6	140.0 ± 57.1	229.5 ± 63.5	147.7 ± 55.3	152.3 ± 56.2	30.2 ± 11.6	45.2 ± 11.0
D. group IV: no.IBS/no.MetS (n = 79)	5.4 ± 0.5	91.6 ± 13.3	186.8 ± 59.1	121.3 ± 51.8	111.9 ± 54.7	24.9 ± 10.6	50.4 ± 10.8
P values:							
A vs B	<0.001	<0.001	<0.015	<0.001	<0.001	<0.001	<0.001
A vs C	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.001
A vs D	0.4	0.12	0.4	0.2	0.7	0.4	0.4
B vs C	0.6	0.9	0.9	0.6	0.5	0.4	0.5
B vs D	<0.001	<0.001	<0.018	0.16	0.003	0.034	<0.001
C vs D	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Overall	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

5. Histopathological and Architectural Features of gastric Mucosa

As shown in table 5, **Lymphocytic cellular infiltrate** differed significantly among the four groups (overall $p < 0.001$). Group II (IBS + MetS) showed the highest proportion of elevated infiltration grades, This was significantly higher than in Group I (IBS + No MetS; $p < 0.001$), Group III (Non-IBS + MetS; $p = 0.028$), and Group IV (Non-IBS + No MetS; $p < 0.001$). A significant difference was also observed between Groups III and IV ($p = 0.004$), with higher infiltration grades in Group III, suggesting an association with the presence of MetS.

Eosinophilic cellular infiltrate also differed significantly among the four groups (overall $p < 0.001$). Group II demonstrated significantly greater eosinophilic infiltration than Groups I ($p < 0.001$), III ($p = 0.027$), and IV ($p < 0.001$). Group III also showed significantly greater eosinophilic infiltration than Groups I ($p = 0.044$) and IV ($p = 0.003$).

Gastric mucosal goblet cell density showed no statistically significant difference among the four groups (overall $p = 0.20$). Goblet cell density was within the normal range in the majority of cases, accounting for 94.9% of Group I, 96.2% of Group II, 95.6% of Group III, and 100% of Group IV. All pairwise comparisons were non-significant ($p > 0.05$), indicating a comparable distribution of goblet cell density across the four groups.

Table 5. Gastric histopathological cellular changes between study groups

Study populations	Lymphocyte cellular infiltrate		Eosinophil cellular infiltrate		Goblet cell density
	11-30/HPF	>30/HPF	11-30/HPF	>30/HPF	10-20% <average
A. group I: IBS/no.MetS. (n=39)	4 (10.3%)	2 (5.1%)	3 (7.7%)	2 (5.2%)	2 (5.1%)
B. group II: IBS/MetS. (n= 53)	14 (26.4%)	14 (26.4%)	17 (32.1%)	9 (17.0%)	2 (3.8%)
C. Group III: no.IBS/MetS (n = 158)	39 (24.7%)	18 (11.4%)	39 (24.7%)	11 (7.0%)	7 (4.4%)

D. group IV: no.IBS/no.MetS (n = 79)	7 (8.9%)	5 (6.3%)	6 (7.6%)	5 (6.3%)	0 (0.0%)
P values:					
A vs B	<0.001		<0.001		>0.9
A vs C	0.01		0.044		>0.9
A vs D	0.7		>0.9		0.11
B vs C	0.028		0.027		>0.9
B vs D	<0.001		<0.001		0.2
C vs D	0.003		0.003		>0.1
Overall	<0.001		<0.001		0.2

6. Gastric mucosal architectural study

The findings presented in Table 6 demonstrated no statistically significant overall difference in gastric gland number and size per LPF among the four groups (overall $p = 0.12$). The majority of cases were within the average range, accounting for 97.4%, 90.6%, 98.1%, and 98.7% in Groups I–IV, respectively. Post-hoc analysis revealed a significant difference only between Groups II and IV ($p = 0.026$), while all other pairwise comparisons were non-significant.

Gastric crypt depth shortening also showed no statistically significant difference among the four groups (overall $p = 0.8$). Crypt depth was within the average range in 100% of Groups I, II, and IV and in 98.7% of Group III. All pairwise comparisons were non-significant ($p > 0.05$), indicating a comparable distribution across the four groups.

Gastric mucosal collagenous material showed no statistically significant overall difference among the four groups (overall $p = 0.8$). The proportion within the average range was 100% in Groups I, II, and IV and 98.7% in Group III. All pairwise comparisons were non-significant ($p > 0.05$), indicating a comparable distribution of collagenous material across the groups.

Table 6. Gastric mucosal architectural study.

Study populations	Glands atrophy (<90%of average)	Crypt depth shortening (<90%of average)	Collagenous material (>10%of average)
A. group I: IBS/no.MetS. (n=39)	1 (2.6%)	0 (0.0%)	0 (0.0%)
B. group II: IBS/MetS. (n= 53)	5 (9.4%)	0 (0.0%)	0 (0.0%)
C. Group III: no.IBS/MetS (n = 158)	3 (1.9%)	2 (1.3%)	2 (1.3%)
D. group IV: no.IBS/no.MetS (n = 79)	1 (1.3%)	0 (0.0%)	0 (0.0%)
P values:			
A vs B	0.9	-	-
A vs C	>0.9	>0.9	>0.9
A vs D	>0.9	>0.9	-
B vs C	0.026	0.6	>0.9
B vs D	0.066	-	-
C vs D	>0.9	-	0.6
Overall	0.12	0.8	>0.8

7. Duodenal histopathological cellular changes .

Duodenal lymphocyte cellular infiltrate differed significantly (overall $p = 0.034$). The highest proportion of 11–30 lymphocytes/HPF was observed in Group II (37.7%), followed by Group III (29.1%), Group IV (20.3%), and Group I (15.4%). Similarly, >30 lymphocytes/HPF was most frequent in Group II (20.8%), followed by Group III (14.0%), Group IV (10.1%), and Group I (7.7%). Significant pairwise differences were observed between Groups I and II ($p = 0.004$) and Groups II and IV ($p = 0.005$), while all other comparisons were comparable.

Duodenal eosinophilic infiltration also differed significantly among the four groups (overall $p < 0.001$). Eosinophilic infiltration in the 11–30 cells/HPF category was most frequent in Group II (39.6%), followed by Groups III (25.3%), I (17.9%), and IV (7.6%). Infiltration of >30 cells/HPF was observed in 15.1%, 14.6%, 5.2%, and 11.4% of Groups II, III, I, and IV, respectively. Significant pairwise differences were observed between Groups I and II ($p = 0.008$), Groups III and IV ($p < 0.001$), and Groups I and IV ($p = 0.004$), whereas the remaining comparisons were not statistically significant.

Duodenal goblet cell density did not differ significantly among the four groups (overall $p = 0.8$). A 10–20% reduction below the average was observed in only 2.6%, 1.9%, 1.3%, and 2.5% of Groups I–IV, respectively. All pairwise comparisons were non-significant ($p > 0.05$), indicating comparable goblet cell density across the four groups.

Table 7. Duodenal histopathological cellular changes between study groups

Study populations	Lymphocyte cellular infiltrate		Eosinophil cellular infiltrate		Goblet cell density
	11-30/HPF	>30/HPF	11-30/HPF	>30/HPF	10-20% <average
A. group I: IBS/no.MetS. (n=39)	6 (15.4%)	3 (7.7%)	7 (17.9%)	2 (5.2%)	1 (2.6%)
B. group II: IBS/MetS. (n= 53)	20 (37.7%)	11 (20.8%)	21 (39.6%)	8 (15.1%)	1 (1.9%)
C. Group III: no.IBS/MetS (n = 158)	46 (29.1%)	22 (14.0%)	40 (25.3%)	23 (14.6%)	2 (1.3%)
D. group IV: no.IBS/no.MetS (n = 79)	16 (20.3%)	8 (10.1%)	6 (7.6%)	9 (11.4%)	2 (2.5%)
P values:					
A vs B	0.004		0.008		>0.9
A vs C	0.2		0.094		0.5
A vs D	0.9		0.2		>0.9
B vs C	0.2		0.2		>0.9
B vs D	0.005		<0.001		>0.9
C vs D	0.3		0.004		0.6
Overall	0.034		<0.001		0.8

8. Duodenal mucosal architectural study

The assessment of duodenal mucosal architectural features as shown in (table 8) revealed an overall preserved mucosal architecture across the four studied groups, with no significant differences in gland atrophy, crypt depth shortening, or bacterial infiltration.

Regarding gland atrophy, no statistically significant difference was observed among the four groups (overall $p > 0.9$). Gland atrophy was absent in Groups I, II, and IV (0%) and observed in only 0.6% of Group III. All pairwise comparisons were non-significant ($p > 0.05$), indicating no evidence of intergroup differences.

Similarly, crypt depth shortening showed no statistically significant difference among the four groups (overall $p = 0.8$). It was absent in Groups I, II, and IV (0%) and observed in only 1.3% of Group III. All pairwise comparisons were non-significant ($p > 0.05$), further supporting the comparable preservation of crypt architecture across the groups.

In keeping with these findings, duodenal mucosal bacterial infiltration was also comparable across the four groups (overall $p = 0.9$). Bacteria were absent in nearly all cases, accounting for 100% of Groups I and II, 96.8% of Group III, and 97.5% of Group IV. the remaining pairwise comparisons were non-significant.

Metaplastic changes were observed most frequently in Group II (5/53, 9.4%), compared with 0% in Group I, 1.2% in Group III, and 1.3% in Group IV. Although the overall difference did not reach statistical significance ($p = 0.061$), a significant pairwise difference was observed between Groups II and III ($p = 0.018$).

Table 8. Duodenal mucosal architectural study between study groups

Study populations	Glands atrophy	Crypt depth shortening	Bacterial infiltrate	Metaplastic changes
A. group I: IBS/no.MetS. (n=39)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B. group II: IBS/MetS. (n= 53)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (9.4%)
C. Group III: no.IBS/MetS (n = 158)	1 (0.6%)	2 (1.3%)	5 (3.1%)	2 (1.2%)
D. group IV: no.IBS/no.MetS (n = 79)	0 (0.0%)	0 (0.0%)	2 (2.6%)	1 (1.3%)
P values:				
A vs B	-	-	-	0.2
A vs C	>0.9	>0.9	0.7	>0.9
A vs D	>0.9	-	>0.9	>0.9
B vs C	>0.9	>0.9	0.7	0.018-
B vs D	-	-	>0.9	0.068
C vs D	-	0.6	>0.9	>0.9
Overall	>0.9	0.8	0.9	0.061

Discussion

The present study highlights a potential histopathological link between metabolic syndrome (MetS) and mucosal inflammation in IBS. Although IBS is traditionally considered a functional disorder without overt structural abnormalities, emerging evidence suggests that subtle immune and inflammatory changes may occur in a subset of patients. In the present study, the coexistence of MetS was associated with increased mucosal and intraepithelial lymphocytic and eosinophilic infiltration, suggesting that metabolic dysfunction may contribute to low-grade intestinal inflammation in IBS.

he greater burden of diabetes in the metabolic syndrome groups in the current study is in line with the well-established metabolic association between metabolic syndrome and type 2 diabetes mellitus. Previous systematic reviews and meta-analyses, including Zhang et al. (2025), have demonstrated a strong association between metabolic syndrome and diabetes, with metabolic syndrome being highly prevalent among patients with established type 2 diabetes. This close relationship is biologically well established, as both conditions share common underlying mechanisms, including insulin resistance and metabolic dysfunction. Therefore, the significantly higher prevalence of diabetes observed in Groups II and III in the present study is consistent with the established metabolic characteristics of MetS^[10].

A significantly higher prevalence of lipid profile abnormalities was observed in Groups II and III, both comprising patients with metabolic syndrome. was an expected finding and is well supported by the established relationship between dyslipidemia and MetS. Dyslipidemia constitutes one of the major metabolic abnormalities associated with MetS, with atherogenic dyslipidemia, particularly elevated triglyceride levels and reduced HDL-C being a characteristic feature of the syndrome. In agreement with the present findings, AlAnouti et al. (2020) reported a consistent association between metabolic syndrome and an atherogenic lipid profile. The significantly higher prevalence of disturbed lipid profiles observed in the MetS groups in the present study therefore appears to reflect the underlying metabolic characteristics of the syndrome rather than an independent effect of IBS^[11].

The distribution of oral ulcers did not differ significantly among the four groups. This finding should be interpreted cautiously, as it does not necessarily exclude an association between diabetes, metabolic syndrome, and oral mucosal lesions. Mauri-Obradors et al. (2017) reported several oral manifestations among patients with diabetes, although the evidence regarding oral mucosal lesions remains inconsistent. Thus, the present findings indicate no significant intergroup difference rather than evidence against a potential effect of diabetes or metabolic syndrome on oral health^[12].

Headache showed no statistically significant difference among the four studied groups. This finding indicates that headache distribution was comparable within the present study population. The absence of a significant intergroup difference is consistent with the heterogeneous and inconclusive evidence regarding the relationship between headache and metabolic syndrome. Andreeva et al. (2017) conducted a systematic review of observational studies investigating the bidirectional association between metabolic syndrome and migraine and

highlighted substantial gaps in the available evidence, including methodological limitations and insufficient data to establish a consistent association ^[13].

In the present study, fatigue showed no statistically significant difference among the four studied groups. Although fatigue is commonly reported among patients with type 2 diabetes, its occurrence is considered multifactorial and may be influenced by several clinical, psychological, inflammatory, and behavioral factors. Bi et al. (2021) highlighted the multifactorial nature of fatigue in patients with type 2 diabetes, suggesting that its presence cannot be attributed solely to metabolic abnormalities. Therefore, the lack of a significant difference in fatigue among the present study groups may reflect the multifactorial nature of this symptom and suggests that metabolic syndrome alone may not be a major determinant of fatigue distribution in this population ^[14].

Aspirin and colchicine use did not differ significantly among the four studied groups, although their use was numerically greater in the metabolic syndrome groups. This pattern may primarily reflect differences in underlying comorbidities and clinical indications for treatment rather than a direct association with metabolic syndrome or IBS. Khan et al. (2020) reported that aspirin use for primary cardiovascular prevention in patients with diabetes remains controversial, as their meta-analysis demonstrated no significant reduction in major adverse cardiovascular outcomes but a significantly increased risk of bleeding ^[15].

Similarly, Demidowich et al. (2019) demonstrated that colchicine treatment in adults with obesity and metabolic syndrome significantly reduced several markers of systemic inflammation, including C-reactive protein, erythrocyte sedimentation rate, white blood cell count, and absolute neutrophil count, although its effect on insulin sensitivity was not statistically significant ^[16].

Additionally, The use of anti-diabetic medications differed significantly among the four groups, with substantially higher use in Groups II and III, which also had a higher prevalence of diabetes. This finding is expected given the close relationship between metabolic syndrome, insulin resistance, and type 2 diabetes. Ford ES et al. (2008), in a systematic review and meta-analysis, reported a substantial burden of metabolic syndrome among patients with diabetes and highlighted the close interplay between glycemic control and metabolic abnormalities. Therefore, the higher use of anti-diabetic medications in the metabolic syndrome groups likely reflects their greater diabetes burden rather than an independent effect of IBS ^[17].

The predominance of heartburn and discomfort in the IBS groups is consistent with previous reports showing increased upper gastrointestinal symptoms among patients with IBS, likely due to visceral hypersensitivity and gut-brain axis dysfunction. Gastrointestinal symptom distribution was comparable across the four groups, in contrast to previous evidence by Mahadeva (2023) who suggests that obesity and metabolic dysfunction may contribute to functional gastrointestinal symptoms through low-grade systemic inflammation, alterations in gut microbiota composition, increased intestinal permeability, and dysregulation of the gut brain axis. However, these mechanisms did not translate into significant differences in symptom patterns in the current cohort. The lack of significant differences in the present study may reflect sample size limitations ^[18].

As expected, participants with metabolic syndrome Group II (IBS+MetS) and Group III (Non-IBS+MetS) exhibited significantly higher levels of triglycerides, total cholesterol, LDL-C, VLDL-C, and HbA1c. These findings are consistent with Ruiz-Saavedra et al. (2026), who highlighted the established metabolic profile of MetS, characterized by insulin resistance, hyperglycemia, and atherogenic dyslipidemia ^[19].

Lymphocytic and eosinophilic infiltrates showed significant variations across the study subgroups, suggesting a potential role of low-grade mucosal inflammation in IBS.

The higher lymphocytic infiltrate observed in Group II (IBS+MetS) and Group III (Non-IBS+MetS) compared with their corresponding counterparts may support previous evidence indicating increased immune cell activation in IBS patients.

The significantly higher gastric lymphocytic infiltration observed in the Group II (IBS+MetS) and Group III (Non-IBS+MetS) is consistent with previous evidence demonstrating mucosal immune activation in IBS (Ohman & Simrén, 2010) and chronic low-grade inflammation associated with metabolic syndrome (Esser et al., 2014). The coexistence of both conditions may enhance gastric inflammatory responses, which could explain the higher grades of lymphocytic infiltration observed in the current study ^[20,21].

Similarly, the increased eosinophilic infiltrate observed in Group II (IBS+MetS) is consistent with reports highlighting the contribution of eosinophils to mucosal immune responses and visceral hypersensitivity in IBS. IBS has been associated with increased mucosal eosinophils, while metabolic syndrome promotes chronic low-grade inflammation. Together, these mechanisms may account for the greater eosinophilic infiltration seen in our patients. These findings are consistent with Esser et al. (2014), who highlighted the pro-inflammatory nature of metabolic syndrome, supporting the higher eosinophilic infiltration observed in the current study ^[21].

Crypt depth, goblet cell density, metaplastic changes, and glandular characteristics were comparable across the study groups. These findings suggest that such histopathological features are unlikely to be major contributors

to the observed clinical differences. This is consistent with the findings of Ohman and Simrén (2010) who reported that IBS is primarily associated with immune and neuroimmune dysregulation rather than overt structural mucosal abnormalities^[20].

The absence of significant differences in gland number, crypt depth, goblet cell density, collagenous material, and bacterial infiltrate suggests preservation of the overall duodenal mucosal architecture across the studied groups, indicating that overt duodenal histopathological abnormalities were not a prominent feature in the study population.

Regarding collagenous changes, two cases were reported, which is consistent with Genta RM et al. (2021) findings about well-established rare prevalence in metabolic syndrome^[22].

The largely comparable histopathological findings across groups are consistent with Black et al. (2020), who reported that overt structural mucosal abnormalities are not consistently observed in functional gastrointestinal disorders despite evidence of subtle immune activation.^[23]

Conclusion

This study highlights a distinctive histopathological spectrum in patients presenting with IBS symptoms, revealing an association between metabolic syndrome and microscopic gastro-duodenal mucosal abnormalities, particularly inflammatory cellular infiltration. The presence of metabolic syndrome introducing an organic inflammatory component into a traditionally functional gastrointestinal disorder. Importantly, a normal endoscopic appearance does not exclude underlying microscopic pathology. Therefore, histopathological assessment of gastric and duodenal biopsies may improve diagnostic accuracy, particularly in patients with persistent or atypical symptoms and clinical warning signs such as abdominal pain, anemia, or unexplained weight loss.

Recommendations

Accordingly, the current research recommends the following: - 1. Gastric and duodenal biopsies should be considered in selected patients despite normal endoscopic findings, as microscopic abnormalities may be present in the absence of visible mucosal lesions 2. Microscopic gastro-duodenitis should be considered in patients presenting with IBS symptoms, particularly those with abdominal pain, anemia, or unexplained weight loss 3. Special attention should be given to patients with chronic metabolic or immune-mediated disorders, including diabetes mellitus, owing to their higher susceptibility to microscopic inflammatory changes 4. Histopathological assessment may help differentiate microscopic gastro-duodenitis from functional gastrointestinal disorders in patients with atypical or persistent symptoms 5. Re-evaluation of the ROME IV criteria in association with microscopic GIT-itis is recommended to reduce the possibility of misdiagnosing an organic disorder as a functional bowel disorder 6. Larger multicenter studies with increased sample sizes are needed to strengthen the evidence and validate the observed association between microscopic gastro-duodenitis, IBS, and metabolic syndrome.

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References

1. Drossman DA, Tack J. Rome Foundation clinical diagnostic criteria for disorders of gut-brain interaction (DGBI). *Gastroenterology*. 2022;162(3):675-679. doi:10.1053/j.gastro.2021.11.019.
2. Wellens J, Sabino J, Vanuytsel T, Tack J, Vermeire S. Recent advances in clinical practice: mastering the challenge—managing IBS symptoms in IBD. *Gut*. 2025;74(2):312-321. doi:10.1136/gutjnl-2024-333565.
3. Abboud M, Haidar S, Mahboub N, Mamo T, Papandreou D, Rizk R. Association between the metabolic syndrome and the irritable bowel syndrome: a cross-sectional study among a sample of Lebanese adults. *Br J Nutr*. 2025;133(8):1080-1089. doi:10.1017/S0007114525000650.
4. Dean YE, Loayza Pintado JJ, Rouzan SS, Nale LL, Abbas A, Aboushaira A, et al. The relationship between irritable bowel syndrome and metabolic syndrome: a systematic review and meta-analysis of 49,662 individuals. *Endocrinol Diabetes Metab*. 2025;8(2). doi:10.1002/edm2.70041.
5. Wegeberg AM, Brock C. Diabetes and the gastrointestinal tract. *Medicine (United Kingdom)*. 2024;52(5):304-310. doi:10.1016/j.mpmed.2024.02.013.
6. Camilleri M. Diagnosis and treatment of irritable bowel syndrome: a review. *JAMA*. 2021;325(9):865-877. doi:10.1001/jama.2020.22532.
7. Kistler AC, Henry C, Yan L, Jiang W, Kozuch P. Microscopic gastritis: a case series highlighting the diagnostic and therapeutic challenges. *Am J Gastroenterol*. 2014;109. doi:10.14309/00000434-201410002-00863.
8. Azer SA, Awosika AO, Akhondi H. Gastritis. [Updated 2024 Jun 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. PMID:31334970.
9. Rugge M, Savarino E, Sbaraglia M, Bricca L, Malfertheiner P. Gastritis: the clinico-pathological spectrum. *Dig Liver Dis*. 2021;53(10):1237-1246. doi:10.1016/j.dld.2021.03.007.
10. Zhang M, Lou B, Huang W. Navigating metabolic complexity and in-depth analysis of metabolic syndrome among diabetes mellitus patients: a systematic review and meta-analysis. *Iran J Public Health*. 2025;54(1):48-61. doi:10.18502/ijph.v54i1.17574.
11. AlAnouti F, Abboud M, Papandreou D, Mahboub N, Haidar S, Rizk R. Effects of vitamin D supplementation on lipid profile in adults with the metabolic syndrome: a systematic review and meta-analysis of randomized controlled trials. *Nutrients*. 2020;12(11):3352. doi:10.3390/nu12113352.
12. Mauri-Obradors E, Estrugo-Devesa A, Jané-Salas E, Viñas M, López-López J. Oral manifestations of diabetes mellitus: a systematic review. *Med Oral Patol Oral Cir Bucal*. 2017;22(5). doi:10.4317/medoral.21655.
13. Andreeva VA, Galan P, Julia C, Fezeu L, Hercberg S, Kesse-Guyot E. A systematic literature review of observational studies of the bidirectional association between metabolic syndrome and migraine. *Diabetes Metab*. 2019;45(1):11-18. doi:10.1016/j.diabet.2017.12.004.
14. Bi Y, Zhang L, Li X, Kan Y, Li S, Zou Y, Liu L, Yuan Y, Gong W, Zhang Y. Contributing factors of fatigue in patients with type 2 diabetes: a systematic review. *Psychoneuroendocrinology*. 2021;130:105280. doi:10.1016/j.psyneuen.2021.105280.
15. Khan SU, Ul Abideen Asad Z, Khan MU, Talluri S, Ali F, Shahzeb Khan M, et al. Aspirin for primary prevention of cardiovascular outcomes in diabetes mellitus: an updated systematic review and meta-analysis. *Eur J Prev Cardiol*. 2020;27(19):2034-2041. doi:10.1177/2047487319825510.
16. Demidowich AP, Levine JA, Onyekaba GI, Khan SM, Chen KY, Brady SM, et al. Effects of colchicine in adults with metabolic syndrome: a pilot randomized controlled trial. *Diabetes Obes Metab*. 2019;21(7):1642-1651. doi:10.1111/dom.13702.
17. Ford ES, Li C, Sattar N. Metabolic syndrome and incident diabetes: current state of the evidence. *Diabetes Care*. 2008;31(9):1898-1904. doi:10.2337/dc08-0423.
18. Mahadeva S. Obesity and functional gastrointestinal disorders: what is the link? *J Gastroenterol Hepatol*. 2023;38(3):344-345. doi:10.1111/jgh.16158.
19. Ruiz-Saavedra A, Vidal-Ostos De Lara F, Martínez JA. Cardiometabolic syndromes and associated cardiovascular risks: a narrative review. *J Vasc Res*. 2026;63(3):179-200. doi:10.1159/000549775.
20. Ohman L, Simrén M. Pathogenesis of IBS: role of inflammation, immunity and neuroimmune interactions. *Nat Rev Gastroenterol Hepatol*. 2010;7(3):163-173. doi:10.1038/nrgastro.2010.4.
21. Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. *Diabetes Res Clin Pract*. 2014;105(2):141-150. doi:10.1016/j.diabres.2014.04.006.
22. Genta RM, Turner KO, Morgan CJ, Sonnenberg A. Collagenous gastritis: epidemiology and clinical associations. *Dig Liver Dis*. 2021;53(9):1136-1140. doi:10.1016/j.dld.2021.03.010. PMID:33824091.
23. Black CJ, Drossman DA, Talley NJ, Ruddy J, Ford AC. Functional gastrointestinal disorders: advances in understanding and management. *Lancet*. 2020;396(10263):1664-1674. doi:10.1016/S0140-6736(20)32115-2.