

Molecular Crosstalk of the Motilin–Somatostatin– Vascular Endothelial Growth Factor Axis in Duodenal Dysfunction Underlying IBS-C and Functional Dyspepsia

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ABSTRACT

Background

The duodenal mucosa plays a pivotal role in gastrointestinal physiology through its endocrine cells (ECs), which secrete key regulatory factors including motilin (MLN), somatostatin (SS), and vascular endothelial growth factor (VEGF). Alterations in the expression of these mediators have been implicated in the pathogenesis of irritable bowel syndrome with constipation (IBS-C) and its overlap with functional dyspepsia (FD).

Objective

To determine the role of duodenal mucosal endocrine cells (ECs) secreting MLN, SS, and VEGF in the development of IBS-C and its overlap with FD.

Methods

The study included 35 patients with IBS-C and FD, 35 patients with IBS-C without FD, and 30 healthy controls. Participants underwent clinical, laboratory, instrumental, and immunomorphological investigations. To exclude organic intestinal pathology, all subjects underwent EGDS, colonoscopy and a fecal calprotectin content analysis. *H. pylori* verification was based on histiobacilloscopy data with the study of imprints' smears of the antral part of the stomach mucous membrane, stained according to Romanovsky-Giemsa. Statistical analysis was performed in SPSS 22.0 (SPSS Inc., USA) for Windows (Microsoft Corporation, USA), and $p < 0.05$ was considered statistically significant.

Results

The results demonstrated a significant reduction in MLN-secreting ECs, accompanied by increased SS- and VEGF-positive ECs in IBS-C with FD patients compared to other groups. The fecal calprotectin test showed that in IBS-C patients and in the patients with FD there is activation of the minimal statistically insignificant inflammatory process in the mucosal intestine (in IBS-C with FD – 52.7; in IBS-C – 43.8 and in healthy controls – 39.9 $\mu\text{g/g}$). The EC expression area in duodenum retrobulbar part (DRBP) secreting VEGF, MLN and SS in IBS-C with FD patients was characterised by a significant decrease in the area of expression of EC secreting MLN and high expression of EC producing SS and VEGF.

Conclusion

The findings highlight the contribution of duodenal EC dysfunction to impaired motility, visceral hypersensitivity, and low-grade inflammation, supporting the concept of the duodenum as a critical neuroendocrine hub within the gut–brain axis. This study underscores the relevance of MLN, SS, and VEGF as potential biomarkers and therapeutic targets in IBS-C and FD comorbidity.

Keywords

motilin; somatostatin; vascular endothelial growth factor; irritable bowel syndrome with constipation; functional dyspepsia.

INTRODUCTION

The duodenum (DU) is an important component of the digestive tract, functionally closely connected with the stomach and the rest of the intestine. The most important link between the stomach and intestine is duodenum retrobulbar part (DRBP)¹. This is confirmed by the data of a number of authors who described the important endocrine cells (ECs) role in the DU submucosa in the irritable bowel syndrome (IBS) development, which quite fully explains the clinical gastrointestinal tract (GIT) expression². The role of the DU in the gut-brain axis continues to be studied, but the role of DRBP in the development of functional dyspepsia (FD) remains unclear. The anatomical and connective

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tissues of the duodenum determine the specifics of signals, immune interactions, and hormone metabolism, which ultimately underpin key pathways of microbiota interaction³. The microbiota plays a crucial role in brain function, contributing to neurological symptoms. Current evidence suggests that the duodenal contents, including its microbiota, pathogens, neurohormones and allergies, act as triggering factors in IBS with FD^{2,4}. EC dysfunction appears to explain motility changes, visceral hypersensitivity, and abnormal intestinal secretion in IBS with FD patients⁵. The literature provides strong evidence that the underlying cause of both epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS) in FD is impaired gastroduodenal neurophysiology^{3,4}. At the same time, EC and stem cells and their precursors demonstrate a high degree of variability in the small intestine proximal and distal parts in IBS patients⁶. Particular attention should be paid to the data on the density variability of stem cells and EC in IBS patients' DU in contrast to the group of healthy individuals⁷.

Among EC, cellular structures secreting motilin (MLN), somatostatin (SS), and vascular endothelial growth factor (VEGF) are of great importance (**Figure 1**). Thus, MLN is a GIT hormone that is produced during fasting to stimulate GIT motility using the migrating motor complex (MMC). Studies have shown that MLN is important for initiating MMC phase III contraction⁸. SS is a key regulatory hormone in the gastrointestinal tract, synthesised and secreted by Delta-cells (DC) located in the stomach, small and large intestines, as well as in pancreas DC⁹. SS suppresses other hormones and enzymes' secretion, thereby slowing down the digestive processes¹⁰.

VEGF is defined as a potent proangiogenic factor secreted by parenchymal, endothelial and activated immune cells^{11,12}. This hormone belongs to the family of platelet-derived growth factors. VEGF regulates various biochemical processes associated with cell growth, proliferation and survival, and maintains their structural integrity¹¹. VEGF plays an important role in angiogenesis, inflammatory response, and energy metabolism.

Aim of the study. To determine the role of duodenal mucosal endocrine cells secreting MLN, SS, and VEGF in the development of IBS-C and its combination with FD.

MATERIAL AND METHODS

The study included 70 participants (18 - 45 years): 35 IBS-C with FD patients (21 women and 14 men), 35 patients without FD (20 women and 15 men). The patients included in the study met the Rome IV criteria for IBS and FD. The control group included healthy individuals who were selected after passing a medical examination (n=30). The groups were comparable in age and gender. Exclusion criteria: acute gastrointestinal diseases, gastric ulcer and duodenal ulcer, inflammatory bowel disease, diverticulitis, colonic stenosis, history of colon resection, viral hepatitis B and C, tuberculosis, liver cirrhosis, history of cancer, patient refusal to participate in the study.

Both patients and healthy controls were examined according to a single programme, including clinical and laboratory, instrumental and immunomorphological studies. To exclude organic intestinal pathology, all subjects underwent colonoscopy and a fecal calprotectin content analysis (normal reference values in adults are 5-50 mcg/g).

The abdominal pain syndrome manifestation was determined on the Visual Analogue Scale (VAS)¹³; the dynamics of the anxiety and/or depression manifestation – using the HADS (Hospital Anxiety and Depression Scale)¹⁴.

EGDS was performed before the start of therapy with subsequent DRBP mucous membrane targeted biopsy. *H. pylori* verification was based on histiobacilloscopy data with the study of imprints' smears of the antral part of the stomach mucous membrane, stained according to Romanovsky-Giemsa.

Tissue samples were fixed in 10% neutral buffered formalin (pH 7.2), then dehydrated in alcohols and embedded in paraffin according to the standard histological scheme. For histological examination, 4-6 µm thick sections were prepared, which were stained with hematoxylin and eosin.

For immunohistochemical staining of the DRBP mucosa serial 4-6 µm thick sections were prepared and placed on slides coated with poly-L-lysine. Studies were performed on deparaffinised and dehydrated sections using the avidin-biotin immunoperoxidase method. To verify the expression of endocrine cells (ECs) secreting MLN, somatostatin (SS) and vascular endothelial growth factor (VEGF), the primary antibodies listed in Table 1 were applied. Reference values for SS content were

considered to be 0.06–5.00 ng/ml; the regulatory factors MLN and VEGF, they were assessed based on their secretion levels. To assess the immunohistochemical staining results, a morphometric study was performed using a computer-aided microscopic image analysis system consisting of an Olympus IX73 microscope, an Olympus DP80 digital camera, and CellSens software. In each case, at least 5 fields of view were analysed at a magnification of x40 with measurement of the studied marker relative expression area using ImageJ software. Histological and morphometric analyses were performed blinded to clinical status.

Statistical analysis. In accordance with the study objective, normality of distribution was assessed using the Shapiro-Wilk test. When normal distribution was confirmed, statistical significance of differences between mean values was assessed using Student's t test for independent samples. If the distribution of at least one group was non-normal, groups were compared using the non-parametric Mann-Whitney U test. The sample size was determined using the following formula - n , where n is the number of cases in the sample, Δ^2 is the margin of sampling error, z_{α} is the error of the 1st kind at $\alpha = 0.05$, p is the prevalence of the trait in the sample, q is the frequency of the reverse event. Nominal variables were compared using contingency tables with Pearson's chi-square test. If any cell of a fourfold table contained fewer than 10 observations, Fisher's exact test was used to evaluate statistical significance. Statistical analysis was performed in SPSS 22.0 (SPSS Inc., USA) for Windows (Microsoft Corporation, USA), and $p < 0.05$ was considered statistically significant.

Results of the study. The distribution analysis of the IBS-C patients and those with FD did not reveal significant differences by gender, but in the overall morbidity structure a certain predominance of females was noted. In the IBS-C patients' clinical picture the leading symptoms were pain along the colon, decreasing or disappearing after defecation, accompanied by flatulence, a feeling of incomplete bowel evacuation. In IBS-C with FD patients having classical IBS-C symptoms signs of heaviness and fullness after eating and pain in the epigastric region dominated. It should be emphasised that in IBS-C patients the PDS subtype of FD predominated (Table 2). Bloating in the upper abdomen was 2 times more common in IBS-C with FD patients than in individuals with IBS-C alone ($p < 0.05$). In contrast to the above, bloating in the lower abdomen

did not have statistically significant differences in frequency of occurrence in both groups of patients

The findings suggest a statistically significant BMI increase in IBS-C patients compared to the healthy group. It is more pronounced in IBS-C with FD patients ($p < 0.05$; Figure 2). The HADS data analysis testifies to a statistically significant dominance of IBS-C with FD data (Table 3). It cannot be excluded that the higher prevalence of anxiety and depression is largely due to the presence and severity of a painful abdominal syndrome affecting both the upper and lower floor of the digestive tract in IBS-C with FD patients (Table 4).

Chronic gastritis associated with *H. pylori* was identified in 18 (51.4%) IBS-C with FD patients and in 16 (45.7%) patients with IBS-C without FD, and its frequency had no statistically significant differences between both patients' groups. Fecal calprotectin test shows that in IBS-C patients and in the patients with FD there is activation of the minimal statistically insignificant inflammatory process in the mucosal intestine (in IBS-C with FD – 52.7; in IBS-C – 43.8 and in healthy patients – 39.9 $\mu\text{g/g}$).

In DRBP, the morphological picture was presented by mucous membrane with preserved histoarchitectonics and signs of weakly expressed chronic inflammation. The obtained data indicate that the EC expression area in DRBP secreting VEGF, MLN and SS in IBS-C with FD patients was characterised by a significant decrease in the area of expression of EC secreting MLN and high expression of EC producing SS and VEGF ($p < 0.05$). Less significant expression area figures were determined in individuals with IBS-C compared to IBS-C with FD patients (Figure 3, 4 and 5 «A, B, C»).

DISCUSSION

The findings highlight the important role of the DU in the IBS and its combination with FD genesis. There is a close functional connection between the DRBP with the stomach and intestine, which may act as one of the major pathogenetic factors in the occurrence of not only IBS-C but also the formation of such combined pathology as IBS-C with FD. Abdominal pain syndrome is more pronounced in IBS-C with FD patients than in the patients without FD. According to our data severe abdominal pain was found virtually 3 times more frequently in IBS with FD patients. Similar findings have been reported by previous studies who state that more pronounced extraintestinal symptoms

and psychological disturbances are associated with pain in IBS-C¹⁴. A significant difference of VEGF level was found between IBS-C- with FD and IBS-C patients. The duodenal mucosa contains specialized endocrine cells that secrete motilin, somatostatin, and VEGF, which are increasingly recognized as pivotal mediators in the pathogenesis of IBS-C and its overlap with FD.

Reduced expression of MLN-producing ECs may impair migrating motor complex activity, contributing to abnormal motility and constipation, while increased SS secretion exerts inhibitory effects on gastric emptying and intestinal peristalsis, exacerbating dyspeptic symptoms¹⁵⁻²⁰. Simultaneously, VEGF overexpression has been linked to enhanced angiogenesis and low-grade inflammation in the duodenum, processes that perpetuate visceral hypersensitivity and abdominal pain, as our results showed²¹⁻²³. A meta-analysis of several studies demonstrated a link between inflammatory markers, fecal calprotectin, and high levels in patients with IBS²⁴. The results suggest that calprotectin is not a disease-specific marker for a particular disease. Its elevation can be observed with stress, functional bowel disorders, inflammation, and other factors. At the preclinical level, as in our study, during low-level inflammation of the intestinal mucosa, neutrophils migrate to the affected tissues and release calprotectin into the intestinal lumen. Thus, calprotectin concentration directly correlates with the number of neutrophils in the mucosa and the level of inflammation. This confirms our opinion that DRBP functions as a critical neuroendocrine hub within the gut-brain axis, where EC dysfunction alters gastrointestinal homeostasis and promotes comorbid anxiety and depression²⁵⁻²⁶. These findings indicate that EC-derived mediators not only regulate gastrointestinal physiology but also represent potential biomarkers and therapeutic targets for IBS-C with FD.

CONCLUSION

The present findings indicate that DU, namely its DRBP, plays an important role not only in the genesis of IBS-C but also in its combination with FD. In IBS-C with FD, there is pronounced pain syndrome and abdominal bloating, both in the upper and lower digestive tract. The findings suggest that the DRBP constitutes an important component of the neuroendocrine gut-brain axis. These findings improve our understanding of the roles of several clinical and biochemical parameters such as excess body mass as potential risk factors

in the IBS manifestation. In the current situation, functional gastrointestinal disorders may involve low-grade inflammatory processes. This is a breakthrough in understanding that a functional disease does not necessarily require a complete absence of minor manifestations typical of organic pathology. This can further increase therapeutic possibilities aimed at eliminating the underlying cause.

Conflict of interest

The authors declare that they have no potential conflict of interest.

Ethical approval: The study was approved by the ethics committee of Sechenov University (Protocol No. 25-22, December 8, 2022). Patients signed informed consent to participate.

Authors' contribution

Concept and design of the study — M.A. Osadchuk, E.D. Mironova;

Collection and processing of material—Y.S. Krylova, E.D. Mironova;

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Writing the text — M.A. Osadchuk, I.N. Vasileva, Y.S. Krylova, M.M. Osadchuk, E.D. Mironova, L.M.L. Luján, A.P. Iloki, J.C. Galvez, S.B. Iloki-Assanga;

Editing — M.A. Osadchuk, E.D. Mironova, I.N. Vasileva, S.B. Iloki-Assanga, M. Trushin.

Study design: cross-sectional observational study

Data collection: 11.2024-01.2026

List of abbreviations

BMI -- body mass index

DC -- Delta Cell

DRBP -- duodenum retrobulbar part

DU -- duodenum

EC -- endocrine cells

EGDS -- esophagogastrroduodenoscopy

EPS -- epigastric pain syndrome

GIT -- gastrointestinal tract

FD -- functional dyspepsia

HADS -- Hospital Anxiety and Depression Scale

H. pylori -- *Helicobacter pylori*

IBS -- irritable bowel syndrome

IBS -C -- irritable bowel syndrome with constipation

MLN -- motilin

MLN-R -- receptor

MMC -- gastric migrating motor complex

PDS -- postprandial distress syndrome

SS -- somatostatin

VAS -- visual Analogue scale

VEGF -- vascular endothelial growth factor

Table 1. Antibodies used for EC verification

Antigen	Antibodies Used	Control
MLN	(ab217287, 1:200, Abcam, UK)	Stomach
SS	ab108456, 1:500, Abcam, UK	Duodenum
VEGF	555036, 1:50, BD Biosciences, USA	Angiosarcoma

Table 2. IBS clinical picture

Symptoms	IBS-C and FD (n=35)	Frequency in %	IBS-C (n=35)	Frequency in %
Pain along the large bowel associated with defecation; stool frequency and shape change	35	100	35	100
Epigastric pain	21*	60	-	-
Bloating in the lower abdomen	17	48,6	15	43
Bloating in the upper abdomen	12	34,3	6	17,1
Feeling of fullness in the epigastric region after eating	14*	40	6	17,1
Constipation ($\geq 25\%$ of defecations) types 1 or 2 and $< 25\%$ types 6 or 7 on Bristol Stool Scale	35	100	35	100
Nausea	9	25,7	6	17,1
Belching air	6	17,1	4	11,8

Note: * $p < 0,05$ between IBS-C with FD and IBS-C groups

Table 3. HADS in IBS-C with FD patients and IBS-C FD free ones

IBS type	Normal	Subclinically manifested anxiety or depression	Clinically manifested anxiety or depression
IBS-C with FD (n=35)	7 (20%)*	24 (68,6)	4 (11,4%)
IBS-C (n=35)	16 (45,7%)	18 (51,4%)	1 (3%)

Note: * $p < 0.05$ between IBS-C with FD and IBS-C groups

Table 4. VAS in IBS-C with FD patients and in IBS-C FD free ones

IBS type	Dull pain (up to 2cm)	Moderate pain (2 to 4 cm)	Strong pain (4 to 6 cm)	Severe pain (6 to 8 cm)	Unbearable pain (8 to 10 cm)
IBS-C with FD (n=35)	6 *	21	8 *	-	-
IBS-C (n=35)	16	17	2	-	-

Note: * $p < 0.05$ between IBS-C with FD and IBS-C groups

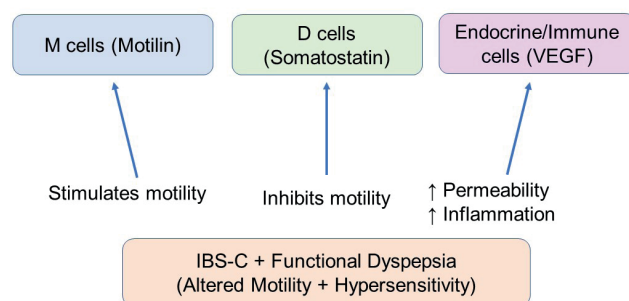


Figure 1. Illustrates the role of motilin, somatostatin, and VEGF secreted by duodenal mucosa cells in the development of IBS-C and its combination with functional dyspepsia.

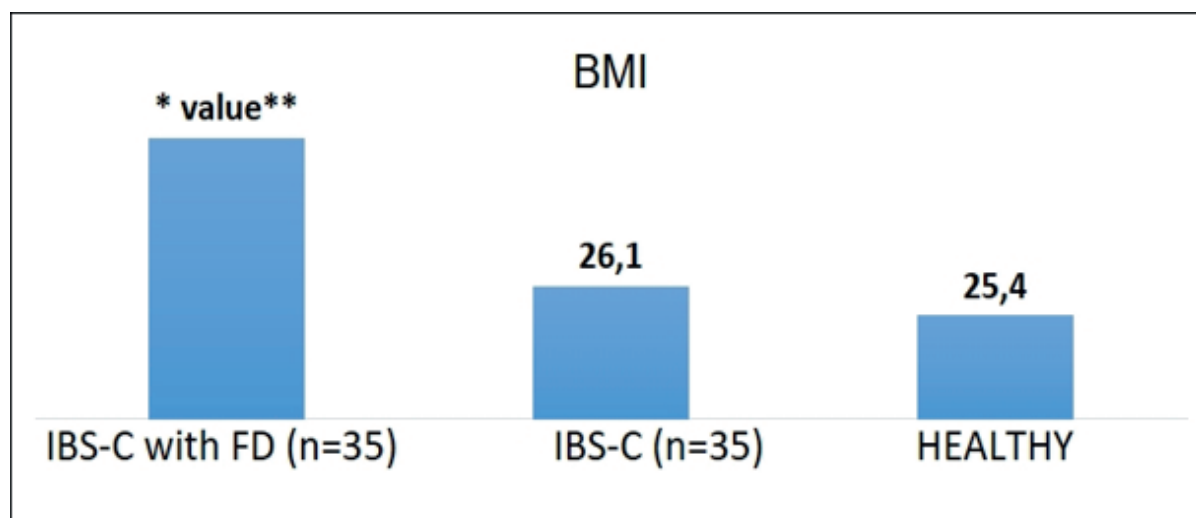


Figure 2. BMI of IBS-C with FD patients and IBS-C FD free ones

Note: * $p < 0.05$ between IBS with FD and IBS-C FD free groups

** $p < 0.05$ between IBS-C with FD and healthy groups

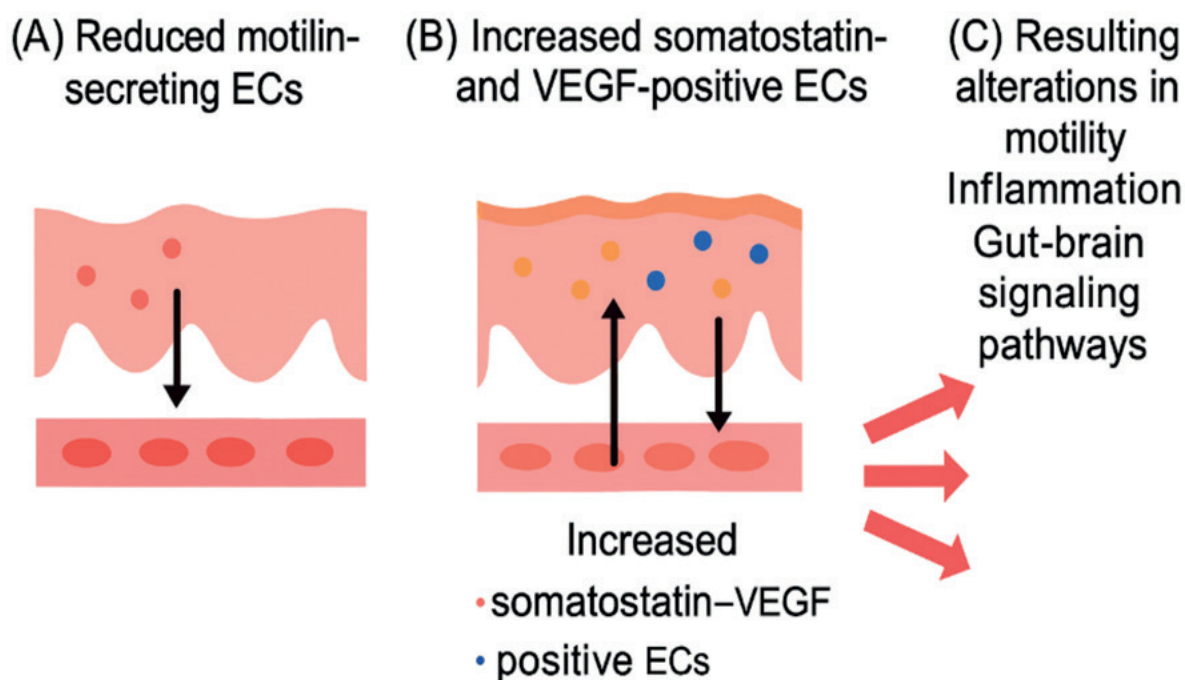


Figure 3. Schematic representation of duodenal mucosa endocrine cells in IBS-C and FD. (A) Reduced motilin-secreting ECs; (B) Increased somatostatin- and VEGF-positive ECs; (C) Resulting alterations in motility, inflammation, and gut-brain signaling pathways.

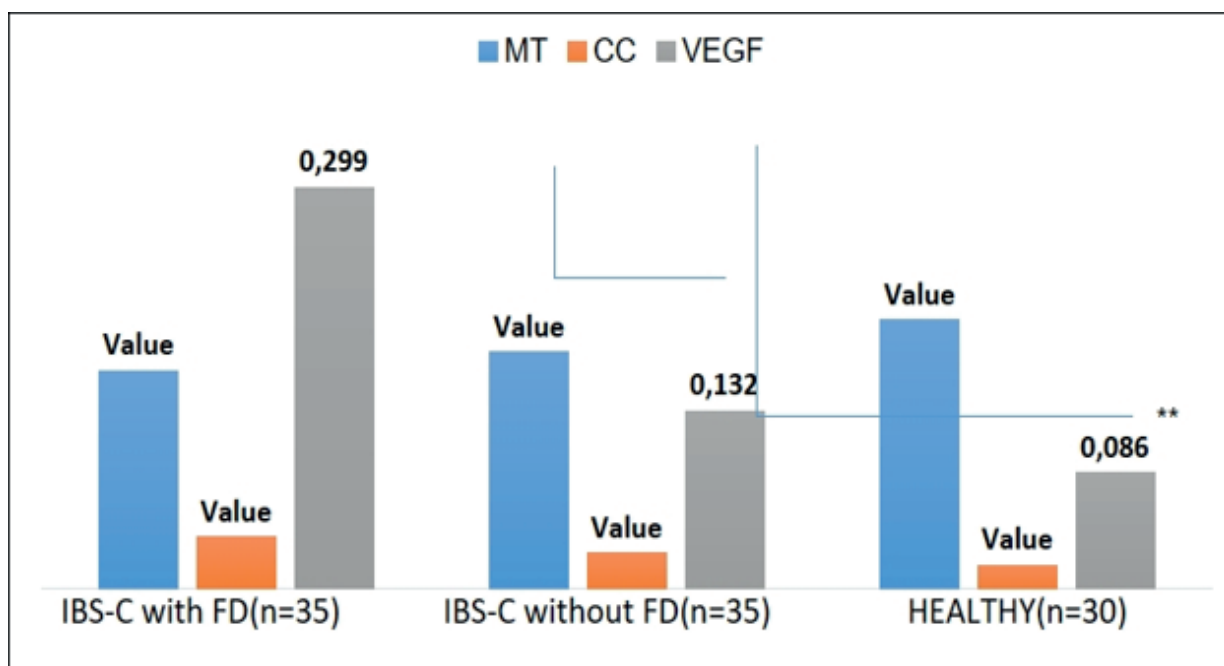


Figure 4. Expression area of EC producing MLN, SS and VEGF in DRBP of IBS-C patients and those with FD.

Note: * $p < 0.05$ between IBS-C with FD and IBS-C FD free groups

** $p < 0.05$ between IBS-C with FD and healthy groups

^ $p < 0.05$ between IBS-C FD-free and healthy groups

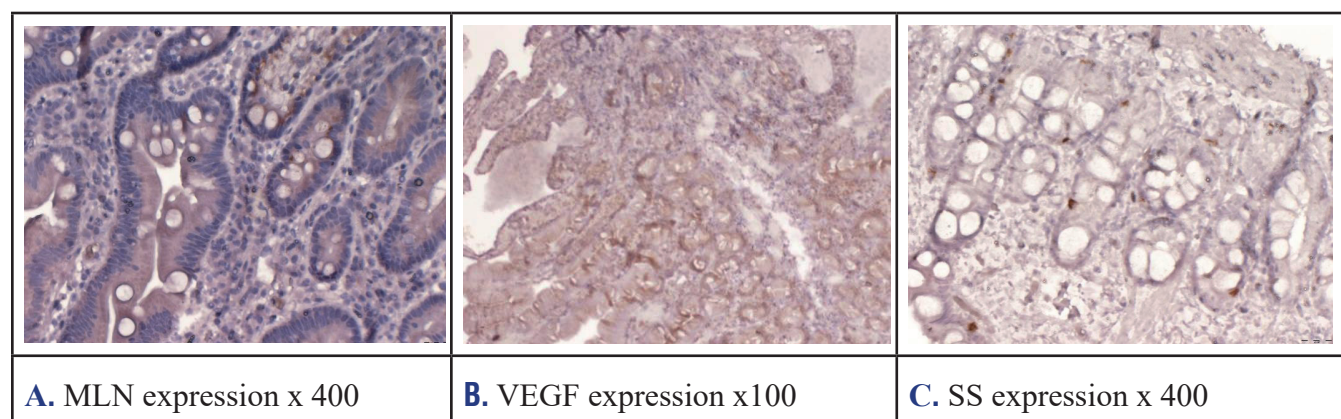


Figure 5. Immunomorphological picture of EC producing MLN, SS and VEGF in DRBP of IBS patients and those with FD

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