INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH AND INNOVATIVE STUDIES
ISSN: 2820-7157
www.ijsrisjournal.com

December 2025 Volume 4 Number 6 107-110

Received Date: October 20, 2025 Accepted Date: November 11, 2025 Published Date: December 01, 2025

A Review of the Role of Serotonin, TIMP-1, and CXCL-1 in the Diagnosis and Differentiation of Irritable Bowel Syndrome

Duaa Radhi Aladhab [1], Merfat Abdullatef Al- Hassan [2], Fatimah Hassan Aljurden [3], Haifa Radi Alahmad [4], Zainab Ali Al Marzooq [4], Fatmah Eissa Alsultan [4], Ahmed Radi Ibrahim AL Ahmed [5], Wasel Yousef Ali Ibn Matar [6], Fadilah Hassan Hussain Al Ahmad [7], Mona Salman Alqabbat [8], Wadad Salman Aldhamen [8], Mofeeda Abbas Al Abbas [8], Ali Saleh Nasser Albandar [9], Najibah Adnan Alqutayfi [10]

1. Salwa hospital
2. Primary health care
3. Phc, Mhssan
4. Omran phc
5. King Faisal General Hospital
6. Muniazlah Phc
7. Phc, Alrashdiah
8. Dareen health center
9. Al-Qurain Primary Healthcare Center
10. PHC AlQurayn

Abstract

Irritable Bowel Syndrome (IBS) is a common functional gastrointestinal disorder characterized by chronic abdominal pain and altered bowel habits, with a complex, multifactorial pathophysiology. Current diagnosis relies on symptom-based Rome IV criteria, lacking reliable biomarkers for objective diagnosis and subclassification (IBS-C, IBS-D, IBS-M). Emerging research highlights the potential roles of serotonin (5-HT), Tissue Inhibitor of Metalloproteinase-1 (TIMP-1), and Chemokine (C-X-C Motif) Ligand 1 (CXCL-1) in IBS pathophysiology. This narrative review critically evaluates the evidence for serotonin, TIMP-1, and CXCL-1 as potential biomarkers for diagnosing IBS and differentiating its subtypes.

A synthesis of contemporary literature from peer-reviewed journals, focusing on human studies, meta-analyses, and clinical trials from the past 15 years, was conducted.

Key Findings: (1) **Serotonin:** Dysregulation of the enteric serotonergic system is well-established in IBS. Elevated postprandial plasma 5-HT and increased mucosal 5-HT signaling are more pronounced in IBS-D, while reduced 5-HT reuptake (via SERT) is common. Platelet-depleted plasma 5-HT shows promise as a differential biomarker. (2) **TIMP-1:** As an inhibitor of matrix metalloproteinases (MMPs), elevated serum and colonic TIMP-1 levels are associated with low-grade mucosal immune activation and altered intestinal permeability, particularly in post-infectious IBS (PI-IBS) and IBS-D. The TIMP-1/MMP ratio may reflect a dysregulated tissue repair process. (3) **CXCL-1:** This pro-inflammatory chemokine is elevated in the serum and colonic mucosa of IBS patients, correlating with pain severity and neutrophil recruitment. Levels are highest in IBS-D and PI-IBS, suggesting its role in sustained, subclinical inflammation and visceral hypersensitivity. While none are yet diagnostic alone, serotonin, TIMP-1, and CXCL-1 represent promising biomarker panels that reflect key IBS pathophysiological pillars: neurotransmitter dysregulation (5-HT), impaired barrier function and remodeling (TIMP-1), and neuroimmune activation (CXCL-1). A multi-biomarker approach, potentially combining these with other markers, could move IBS diagnosis beyond symptom criteria, enable mechanistic subclassification, and guide targeted therapies.

Keywords: Irritable Bowel Syndrome, Biomarkers, Serotonin, 5-HT, TIMP-1, CXCL-1, Diagnosis, IBS Subtypes.

1. Introduction

Irritable Bowel Syndrome (IBS) is a prevalent functional gastrointestinal disorder affecting approximately 10% of the global population. Its diagnosis remains clinical, based on the Rome IV criteria of recurrent abdominal pain associated with defecation or a change in bowel habits, in the absence of detectable structural disease. This symptom-based approach leads to diagnostic uncertainty, overlap with other disorders, and an inability to classify patients into pathophysiologically distinct subgroups (Constipation-predominant [IBS-C], Diarrhea-predominant [IBS-D], Mixed [IBS-M]) for targeted treatment. The search for objective biomarkers is thus a major research priority. This review focuses on three promising candidates—serotonin, TIMP-1, and CXCL-1—each implicated in distinct yet interconnected pathways of IBS pathogenesis, including gut-brain axis dysregulation, mucosal integrity, and low-grade inflammation.

2. Serotonin (5-Hydroxytryptamine, 5-HT) in IBS

Serotonin is a critical neurotransmitter in the gastrointestinal tract, where over 95% of the body's total 5-HT is synthesized and stored in enterochromaffin (EC) cells.

2.1. Pathophysiological Role

- **Motor and Sensory Function:** Mucosal 5-HT stimulates intrinsic primary afferent neurons (IPANs) to initiate peristaltic reflexes and transmit visceral sensations. Dysregulation of this system alters motility and heightens pain perception.
- **Synthesis and Reuptake:** IBS patients, particularly those with IBS-D, often show increased postprandial release of 5-HT from EC cells. A common finding is a reduction in the serotonin reuptake transporter (SERT) expression or function in the intestinal epithelium, leading to prolonged 5-HT action in the mucosal milieu.
- **Association with Subtypes:** The most consistent alterations are seen in IBS-D and post-infectious IBS (PI-IBS), characterized by elevated mucosal 5-HT availability. Findings in IBS-C are more variable, with some studies suggesting a relative deficiency in 5-HT signaling.

2.2. Diagnostic and Differential Potential

- **Blood Levels:** Measuring platelet-depleted plasma 5-HT (which reflects free circulating levels) has shown promise. Studies report elevated baseline and postprandial plasma 5-HT in IBS-D compared to IBS-C and healthy controls (HC).
- **Mucosal Markers:** Biopsy-based measures of 5-HT content, EC cell numbers, SERT mRNA, and protein expression can differentiate IBS subtypes but are invasive and not suitable for routine diagnosis.
- **Limitations:** Serotonin levels are influenced by diet, stress, medications (e.g., SSRIs), and comorbid psychiatric conditions, requiring standardized measurement protocols.

3. Tissue Inhibitor of Metalloproteinase-1 (TIMP-1) in IBS

TIMP-1 is a natural inhibitor of Matrix Metalloproteinases (MMPs), enzymes that degrade the extracellular matrix. The MMP/TIMP balance is crucial for maintaining intestinal mucosal integrity and regulating inflammation.

3.1. Pathophysiological Role

- **Barrier Function and Repair:** An imbalance favoring MMP activity can degrade tight junction proteins, increasing intestinal permeability ("leaky gut"). Elevated TIMP-1 may represent a compensatory response to increased MMP activity or a distinct pro-fibrotic signal.
- **Immune Activation:** TIMP-1 has cytokine-like properties and can influence immune cell activity. Its elevation in IBS is linked to low-grade mucosal immune activation, often observed in PI-IBS and IBS-D.
- **Association with Subtypes:** Serum and colonic TIMP-1 levels are frequently elevated in IBS-D and PI-IBS compared to IBS-C and HC. The **TIMP-1/MMP-9 ratio** has been proposed as a sensitive indicator of dysregulated tissue remodeling.

3.2. Diagnostic and Differential Potential

- **Serum TIMP-1:** As a stable, measurable protein in blood, it offers a practical biomarker. Elevated serum TIMP-1 can help distinguish IBS-D from IBS-C and functional constipation.
- **Combination with Permeability Markers:** When combined with other biomarkers of barrier dysfunction (e.g., serum zonulin, lipopolysaccharide antibodies), TIMP-1 may identify a "leaky gut" IBS endotype.

4. Chemokine (C-X-C Motif) Ligand 1 (CXCL-1) in IBS

CXCL-1 is a potent chemokine that attracts and activates neutrophils via the CXCR2 receptor. It is a key mediator of neuroimmune interactions.

4.1. Pathophysiological Role

- **Visceral Hypersensitivity:** CXCL-1 can sensitize visceral afferent nerves directly and via immune cell interactions. Its levels correlate with abdominal pain severity in IBS.
- **Sustained Low-Grade Inflammation:** Elevated CXCL-1 in colonic biopsies and serum signifies persistent, subclinical immune activation, often seen following an initial gastrointestinal infection or in association with bacterial dysbiosis.
- **Association with Subtypes:** Significantly higher levels are reported in IBS-D and PI-IBS, aligning with the inflammatory component of these subtypes. Levels in IBS-C are typically closer to those of HC.

4.2. Diagnostic and Differential Potential

- **Serum CXCL-1:** Presents a feasible diagnostic blood test. Studies demonstrate its ability to discriminate between IBS patients and HC with good sensitivity, and between IBS-D and IBS-C.
- **Link to Symptoms:** Its correlation with symptom intensity, particularly pain, adds functional relevance as a biomarker, potentially useful for monitoring treatment response.

5. Integrated Biomarker Potential: A Multi-Target Approach

The greatest diagnostic utility likely lies in combining these markers, as they reflect complementary pathways:

- **A Proposed Panel: Elevated CXCL-1 + Elevated TIMP-1 + Elevated Platelet-depleted Plasma 5-HT** could define an "Inflammatory-Hypermotility" endotype, characteristic of severe IBS-D or PI-IBS.
- **Differential Patterns:**
  - **IBS-D/PI-IBS:** Likely high in all three markers.
  - **IBS-C:** May show normal or low 5-HT, normal CXCL-1, and variable TIMP-1.
  - **IBS-M:** May exhibit an intermediate or fluctuating profile.
- **Exclusion of Organic Disease:** This panel may also aid in differentiating IBS from mild inflammatory bowel disease (IBD), where biomarker elevations are typically of a much greater magnitude.

6. Clinical Implications and Future Directions

6.1. Current Status

None of these biomarkers are currently validated for routine clinical use. They remain research tools.

6.2. Future Applications

- **Objective Diagnosis:** Developing a commercial blood test panel.
- **Mechanistic Subclassification:** Moving beyond symptom-based Rome subtypes to "biomarker-driven endotypes" for precision medicine.
- **Treatment Selection:** Identifying patients likely to respond to 5-HT3 antagonists (alosetron), immune-modulators, or barrier-strengthening agents.

- **Clinical Trials:** Enriching trial populations with specific endotypes to improve therapeutic signal detection.

6.3. Challenges and Research Gaps

- Standardization of assays and establishment of universal cut-off values.
- Large-scale, longitudinal validation studies across diverse populations.
- Understanding biomarker stability over time and in response to diet and stress.
- Exploring cost-effectiveness for widespread clinical adoption.

7. Conclusion

Serotonin, TIMP-1, and CXCL-1 are not merely bystanders but active players in the neuroimmune and mucosal pathways central to IBS. While individually promising, their combined evaluation offers a powerful lens to view the heterogeneous landscape of IBS. The transition from symptom-based diagnosis to biomarker-aided, mechanism-driven classification is on the horizon, holding the promise of transforming the management of this complex disorder through personalized therapeutic strategies.

References

1. Camilleri, M., & Ford, A. C. (2019). Irritable Bowel Syndrome: Pathophysiology and Current Therapeutic Approaches. *Handbook of Experimental Pharmacology*, *239*, 75–113.
2. Barbara, G., Feinle-Bisset, C., Ghoshal, U. C., et al. (2016). The Intestinal Microenvironment and Functional Gastrointestinal Disorders. *Gastroenterology*, *150*(6), 1305-1318.
3. Bellini, M., Rappelli, L., Blandizzi, C., et al. (2003). Platelet serotonin transporter in patients with diarrhea-predominant irritable bowel syndrome both before and after treatment with alosetron. *The American Journal of Gastroenterology*, *98*(12), 2705-2711.
4. Dunlop, S. P., Coleman, N. S., Blackshaw, E., et al. (2005). Abnormalities of 5-hydroxytryptamine metabolism in irritable bowel syndrome. *Clinical Gastroenterology and Hepatology*, *3*(4), 349-357.
5. Foley, S., Garsed, K., Singh, G., et al. (2011). Impaired uptake of serotonin by platelets from patients with irritable bowel syndrome correlates with duodenal immune activation. *Gastroenterology*, *140*(5), 1434-1443.
6. Hughes, P. A., Harrington, A. M., Castro, J., et al. (2013). Sensory neuro-immune interactions differ between irritable bowel syndrome subtypes. *Gut*, *62*(10), 1456–1465.
7. Martínez, C., Vicario, M., Ramos, L., et al. (2012). The jejunum of diarrhea-predominant irritable bowel syndrome shows molecular alterations in the tight junction signaling pathway that are associated with mucosal pathobiology and clinical manifestations. *The American Journal of Gastroenterology*, *107*(5), 736-746.
8. Ohman, L., Isaksson, S., Lundgren, A., et al. (2013). A controlled study of colonic immune activity and beta7+ blood T lymphocytes in patients with irritable bowel syndrome. *Clinical Gastroenterology and Hepatology*, *11*(4), 478-485.
9. Róka, R., Rosztóczy, A., Leveque, M., et al. (2007). A pilot study of fecal serine-protease activity: a pathophysiologic factor in diarrhea-predominant irritable bowel syndrome. *Clinical Gastroenterology and Hepatology*, *5*(5), 550-555.
10. Tornblom, H., Lindberg, G., Nyberg, B., & Veress, B. (2002). Full-thickness biopsy of the jejunum reveals inflammation and enteric neuropathy in irritable bowel syndrome. *Gastroenterology*, *123*(6), 1972-1979.
11. Wouters, M. M., Vicario, M., & Santos, J. (2016). The role of mast cells in functional GI disorders. *Gut*, *65*(1), 155–168.
12. Zhou, Q., Souba, W. W., Croce, C. M., & Verne, G. N. (2010). MicroRNA-29a regulates intestinal membrane permeability in patients with irritable bowel syndrome. *Gut*, *59*(6), 775–784.