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Research Article

Expression of Ghrelin Receptor (GHS-R1a) mRNA in Gastric Biopsies of Patients with H. Pylori-Associated Gastritis

Abdul Waheed Iqbal[1], Abdullah[2], Muhammad Saeed[3], Qurat ul Ain Javaid[4], Muhammad Imran Bajwa[5], Aisha Qaiser[6]

Affiliations:

[1] Consultant Gastroenterologist and Hepatologist, Services Hospital Lahore.
[2] Consultant Gastroenterologist, DHQ Hospital Daggar.
[3] Associate Professor, Biochemistry Department, Bolan Medical College Quetta.
[4] Associate Professor, Pathology, Rashid Latif Medical College, Lahore.
[5] Associate Professor, Department of Biochemistry, Margalla College of Dentistry (MIHS).
[6] Assistant Professor, Histopathology, Rahbar Medical and Dental College, Lahore.

Corresponding author: ABDUL WAHEED IQBAL

ABSTRACT: Ghrelin, a gastric peptide regulating appetite and mucosal integrity, is modulated by inflammation, and the functional ghrelin receptor GHS-R1a may be altered in Helicobacter pylori–associated gastritis. This experimental study examined GHS-R1a mRNA expression in gastric biopsies obtained from 90 dyspeptic adults undergoing diagnostic endoscopy, comprising 45 patients with confirmed H. pylori–associated gastritis and 45 H. pylori-negative controls matched for age and sex. Quantitative real-time PCR was used to evaluate GHS-R1a expression relative to β-actin. Findings show a significant downregulation of receptor expression in H. pylori-positive samples (0.42 ± 0.21) compared with controls (1.00 ± 0.38; $p < 0.001$). Expression correlated inversely with histologic inflammation scores ($r = –0.61$, $p < 0.001$) and bacterial density ($r = –0.53$, $p = 0.002$). Patients exhibiting moderate-to-severe chronic inflammation demonstrated the lowest receptor expression, suggesting functional suppression of ghrelin-mediated pathways. These results provide novel evidence that GHS-R1a transcription is attenuated in active H. pylori–associated gastritis, underscoring a potential mechanism linking infection-related mucosal inflammation with dyspepsia, altered appetite signaling, and gastric homeostasis. This receptor-level alteration may contribute to persistent symptoms and impaired mucosal repair in infected individuals. Future studies should explore therapeutic modulation of ghrelin signaling to enhance mucosal recovery following H. pylori eradication.

Keywords: ghrelin receptor, GHS-R1a, Helicobacter pylori

INTRODUCTION: Helicobacter pylori remains one of the most pervasive human bacterial pathogens, colonizing nearly half of the global population and causing a spectrum of gastric disorders ranging from chronic gastritis to peptic ulcer disease and gastric neoplasia. Despite substantial progress in molecular and translational gastroenterology, the intricate host–pathogen interactions underpinning disease expression are still incompletely understood. A growing body of research emphasizes that H. pylori-induced mucosal inflammation not only disrupts epithelial architecture but also perturbs numerous endocrine and neuroimmune pathways within the stomach. Among these, the ghrelin axis has emerged as a key integrator of mucosal integrity, energy homeostasis, and gastrointestinal function. Ghrelin, produced predominantly by the gastric oxyntic mucosa, exerts its biological effects by binding to the growth hormone secretagogue receptor GHS-R1a, a G-protein-coupled receptor that mediates appetite stimulation, gastric motility, cytoprotection, and regenerative responses. Alterations in ghrelin and its receptor may therefore represent a pivotal link between chronic inflammation and clinical manifestations of dyspepsia.[1-4]

GHS-R1a is widely expressed in gastric mucosal cells, vagal afferent neurons, and various extra-gastric tissues. Its activation induces downstream signaling through the Gαq/11 pathway, promoting intracellular calcium mobilization and modulating inflammatory responses. Multiple studies have documented decreased circulating ghrelin concentrations in patients with H. pylori infection, especially among those with significant corpus-predominant gastritis. However, comparatively little attention has been directed toward receptor expression itself, which plays an equally essential role in determining ghrelin sensitivity. Recent reports published from 2022 onward have highlighted that chronic gastric inflammation may impair receptor transcription via cytokine-driven signaling, oxidative stress, and alterations in epithelial differentiation. Yet conclusive data from human gastric biopsy samples remain scarce.[5-8]

The interaction between H. pylori virulence determinants and ghrelin signaling adds further complexity. Strains expressing the cytotoxin-associated gene A (CagA) protein are known to trigger robust inflammatory cascades, epithelial proliferation, and cytoskeletal rearrangements. These strains have also been implicated in modifying endocrine cell profiles in the stomach. Some experimental models suggest that CagA-mediated activation of NF-κB and STAT3 pathways may suppress GHS-R1a gene transcription, thereby reducing functional receptor availability. Similarly,

VacA-positive strains can induce mitochondrial injury and structural distortion of the oxyntic mucosa, potentially disrupting the niche of ghrelin-producing X/A-like cells. Although such mechanistic insights are compelling, their direct correlation with in vivo receptor expression in human gastric mucosa has not been investigated comprehensively.[9-12]

The clinical relevance of ghrelin receptor dysregulation extends beyond appetite and body-weight dynamics. Ghrelin has been shown to enhance gastric mucosal blood flow, promote epithelial restitution, and attenuate oxidative injury. Reduced receptor expression could therefore contribute to impaired mucosal healing, persistent dyspepsia, and heightened susceptibility to ulceration. Moreover, ghrelin signaling influences gastric accommodation and sensory transduction, both of which are frequently altered in functional dyspepsia. Emerging clinical data from 2023 and 2024 propose that receptor-level modulation may be associated with symptom severity and therapeutic responsiveness in gastritis patients. This indicates a potential role for GHS-R1a expression as a biomarker for disease activity or treatment outcome.

Despite these advances, there remains a major gap in translating molecular findings into clinically meaningful interpretations. The majority of published work has focused on circulating ghrelin levels, which, while informative, do not fully reflect tissue-level dynamics or receptor functionality. Furthermore, inter-individual variability in hormonal secretion can confound associations between serum measurements and mucosal pathology. Assessing GHS-R1a mRNA in biopsy specimens provides a more direct and reliable means of evaluating local regulatory mechanisms. Such data can help clarify whether reduced systemic ghrelin concentrations in infected individuals are accompanied by receptor downregulation, or whether compensatory receptor upregulation occurs in response to diminishing ligand availability.

The inflammatory microenvironment characteristic of H. pylori gastritis further underscores the need to investigate receptor expression. Gastric infiltration by neutrophils, mononuclear cells, and lymphoid aggregates alters epithelial turnover and disrupts endocrine cell differentiation. Proinflammatory cytokines, including IL-1β, TNF-α, and IL-6, are potent suppressors of various gastrointestinal receptors and signaling cascades. Understanding how these inflammatory mediators affect GHS-R1a transcription is crucial to unraveling the pathophysiology of chronic

gastritis. Studies published after 2022 increasingly suggest that complex crosstalk between cytokines and hormonal pathways may play a pivotal role in symptom generation and disease progression.

In view of this, evaluating GHS-R1a expression in H. pylori–associated gastritis provides a timely and necessary contribution to the evolving landscape of digestive endocrinology. It aligns with contemporary efforts to identify molecular biomarkers that elucidate disease mechanisms and inform personalized therapy. Given the high prevalence of H. pylori in South Asian populations and the substantial burden of dyspepsia in clinical practice, understanding these receptor-level changes has particular relevance. The present investigation was therefore designed to quantify GHS-R1a mRNA expression in gastric biopsies from patients with and without H. pylori gastritis, and to correlate expression levels with histologic severity and bacterial load. The aim was not only to expand the existing knowledge on ghrelin pathway alterations but also to provide a biological rationale for future interventional strategies targeting the ghrelin axis.

METHODOLOGY: This observational experimental study was conducted at At Services hospital lahore gastroenterology center over 12 months. Adult patients referred for upper gastrointestinal endoscopy due to dyspeptic symptoms were considered eligible. Sample size was calculated using Epi Info version 7, with expected effect size based on a 40% reduction in GHS-R1a expression in H. pylori-positive individuals reported in recent molecular studies, a confidence level of 95%, a power of 80%, and a ratio of 1:1 for case and control allocation. The resultant minimum sample size was 84 subjects; therefore, 90 participants were recruited, comprising 45 H. pylori-positive and 45 H. pylori-negative individuals matched for age and sex.

Inclusion criteria consisted of adults aged 18–70 years undergoing diagnostic endoscopy with adequate gastric biopsy specimens and consent for molecular analysis. Exclusion criteria included prior eradication therapy, proton pump inhibitor use within two weeks, known endocrine disorders, gastric malignancy, current steroid or immunosuppressive therapy, pregnancy, and refusal to provide verbal informed consent. Consent was obtained before endoscopy and documented in patient records, with ethical approval secured from the institutional review committee.

During endoscopy, two biopsies from the antrum and two from the corpus were collected for histopathological examination and H. pylori detection using modified Giemsa staining. An

additional biopsy specimen was stored in RNAlater at –80°C for molecular analysis. Histological grading of inflammation (mononuclear and neutrophilic activity) and bacterial density was performed independently by two blinded pathologists according to updated Sydney System criteria.

Total RNA from biopsy samples was extracted using a silica-column method, followed by spectrophotometric quantification and reverse transcription. Quantitative real-time PCR was performed using SYBR Green chemistry with primers specific for GHS-R1a and β-actin as the reference gene. Relative expression was calculated using the 2^-ΔΔCt method, with controls serving as the calibrator group. All procedures were performed under standardized laboratory conditions, and replicate reactions ensured result consistency.

Clinical and demographic data, histologic scores, and molecular findings were entered into a secure database. Statistical analysis employed parametric tests, with continuous variables expressed as mean ± standard deviation. Comparisons between groups used independent samples t-tests or ANOVA, while correlations applied Pearson's coefficient. Statistical significance was defined as $p < 0.05$.

RESULTS

Table 1. Demographic and Clinical Characteristics

Variable	H. pylori Positive (n=45)	H. pylori Negative (n=45)	p-value
Age (years)	41.8 ± 12.4	40.6 ± 11.9	0.63
Male sex, n (%)	24 (53.3)	23 (51.1)	0.82
BMI (kg/m²)	23.4 ± 3.1	23.7 ± 3.0	0.68

Explanation: Groups were comparable in baseline characteristics, minimizing confounding from demographic factors.

Table 2. Histological Findings and GHS-R1a Expression

Parameter	H. pylori Positive	H. pylori Negative	p-value
Chronic inflammation score	2.46 ± 0.63	1.12 ± 0.41	<0.001

| Neutrophil activity score | 1.78 ± 0.52 | 0.44 ± 0.21 | <0.001 |
| GHS-R1a mRNA expression (2^-ΔΔCt) | 0.42 ± 0.21 | 1.00 ± 0.38 | <0.001 |

Explanation: Significant downregulation of ghrelin receptor expression was associated with higher inflammatory scores.

Table 3. Correlations With Receptor Expression

Variable	Correlation coefficient (r)	p-value
Chronic inflammation	–0.61	<0.001
Neutrophil activity	–0.48	0.004
H. pylori density	–0.53	0.002

Explanation: Increasing inflammatory severity and bacterial burden correlated strongly with decreased GHS-R1a expression.

DISCUSSION: The findings of this study demonstrate a marked suppression of GHS-R1a mRNA expression in gastric biopsies from patients with H. pylori-associated gastritis. This downregulation aligns with contemporary evidence from molecular studies published between 2022 and 2024 suggesting that chronic mucosal inflammation may influence hormonally active pathways. The significant difference in receptor expression between infected and uninfected individuals underscores the biological relevance of the ghrelin axis in the pathophysiology of gastritis.[13-14]

The inverse correlation between GHS-R1a transcription and inflammatory severity highlights the role of cytokine-mediated epigenetic and transcriptional repression. Studies from recent years describe that IL-1β and TNF-α, abundantly expressed in H. pylori gastritis, exert suppressive effects on gastric endocrine gene expression. The present findings extend these observations to the ghrelin receptor, suggesting that inflammatory disruption affects not only ligand availability but also receptor sensitivity.[15-17]

The association between bacterial density and receptor downregulation supports the hypothesis that virulence-driven inflammatory intensity is a key determinant of endocrine alteration. High-

density colonization, especially by CagA- and VacA-expressing strains, has been shown to provoke oxidative stress, epithelial injury, and endocrine cell dysfunction. The current findings provide evidence that these virulence-linked mechanisms likely impair receptor transcription as well.[18-20]

Reduced ghrelin receptor expression may have important clinical implications. Ghrelin signaling enhances mucosal regeneration, modulates gastric motility, and contributes to appetite regulation. Therefore, decreased receptor availability could partly explain persistent dyspeptic symptoms, delayed recovery, and altered gastric physiology observed in chronic H. pylori infection. This aligns with recent clinical data linking hormonal axis disturbances with symptom severity in gastritis.

These findings also raise the possibility that eradication therapy may restore receptor expression. Recent studies from 2023–2024 have shown partial recovery of circulating ghrelin levels following successful eradication. However, tissue-level receptor restoration has not been studied extensively. The marked suppression noted here suggests that longitudinal evaluation before and after eradication would yield valuable insights.

Furthermore, receptor downregulation may contribute to the broader metabolic effects occasionally noted in chronically infected individuals, including weight fluctuations and appetite disturbances. Understanding the receptor component of ghrelin signaling is essential for interpreting these metabolic changes.

Overall, the results strengthen the evolving concept that H. pylori infection disrupts gastric homeostasis not only through structural inflammation but also by altering endocrine signaling mechanisms. The ghrelin–GHS-R1a axis, therefore, represents a promising target for future therapeutic or prognostic applications.

CONCLUSION: GHS-R1a mRNA expression is significantly suppressed in H. pylori-associated gastritis and correlates strongly with inflammatory severity and bacterial density. This receptor-level alteration highlights a previously underexplored mechanism contributing to dyspeptic

symptoms and impaired gastric homeostasis. Future studies should evaluate post-eradication restoration of receptor expression and its potential clinical implications.

REFERENCES

1. Ohtsu A, Takei Y. Evolutionary and functional diversity of the ghrelin system. Cell Mol Life Sci. 2022;79(2):78.
2. Zhao X, Xu Y, Sun X. Inflammatory regulation of gastric endocrine pathways in H. pylori gastritis. Front Immunol. 2023;14:1182334.
3. Sugiyama T, Asaka M. Helicobacter pylori pathogenesis and gastric mucosal integrity. Int J Mol Sci. 2022;23(17):9746.
4. Baniulyte G, et al. Cytokine-mediated modulation of gastric epithelial receptors. Gastroenterology. 2023;164:1020–1034.
5. Pályi B, et al. Ghrelin system alterations in gastric disorders. Int J Endocrinol. 2022;2022:8873251.
6. den Hoed CM, Kuipers EJ. Epidemiology of H. pylori infection. Helicobacter. 2022;27:e12872.
7. Shahi H, et al. Molecular mechanisms of H. pylori virulence. Microorganisms. 2023;11(1):145.
8. Jang HJ, et al. Regulation of ghrelin receptor signaling in inflammation. Mol Cell Endocrinol. 2023;565:111915.
9. Watanabe T, et al. Gastric mucosal repair and endocrine signaling. Dig Dis Sci. 2022;67:2114–2125.
10. Okeke F, et al. Ghrelin signaling in functional dyspepsia. Neurogastroenterol Motil. 2023;35:e14532.
11. Lee JH, et al. Role of gastric hormones in chronic gastritis. Sci Rep. 2024;14:10923.
12. Kim KW, et al. Patterns of gastric endocrine cell loss in H. pylori infection. J Pathol. 2022;256:123–133.
13. Alvarez-Arce A, et al. Host–pathogen interplay in the gastric microenvironment. Infect Immun. 2023;91:e00345-23.

14. Rossi M, et al. Ghrelin's cytoprotective effects in gastric mucosa. Int J Mol Sci. 2023;24(5):5123.
15. Chen Y, et al. Oxidative stress pathways in H. pylori gastritis. Free Radic Biol Med. 2024;205:21–32.
16. Salinas-García D, et al. Endoscopic findings and hormone regulation in gastritis. BMC Gastroenterol. 2023;23:322.
17. Yang L, et al. Ghrelin receptor downregulation under inflammatory stress. J Cell Physiol. 2022;237:530–540.
18. Choi MS, et al. Virulence factors and endocrine responses in H. pylori. Pathogens. 2023;12(4):567.
19. Lima JP, et al. Modulation of gastric motility through ghrelin pathways. J Neurogastroenterol Motil. 2024;30:127–139.
20. Kablak-Ziembicka A, Przewlocki T. Clinical significance of receptor assessment in inflammatory conditions. J Clin Med. 2021;10(20):4628.