Iranian Journal of Microbiology
*Volume 18 Number 3 (June 2026) 306-311*
DOI: http://doi.org/10.18502/ijm.v18i3.21653

ORIGINAL ARTICLE

# *Helicobacter pylori* infection and the hypothalamic–pituitary axis: association with cortisol and thyroid-stimulating hormone levels in adults

**Nedaa Husein[1*], Muna M. Abbas[1], Dania Basha[2], Dima Tareq Owais[3], Nameer Amer Hanineh-Halasa[4]**

*[1]Department of Allied Medical Sciences, Zarqa University College, Al-Balqa Applied University, Zarqa, Jordan*
*[2]Department of Allied Medical Sciences, Al-Ahliyya Amman University, Amman, Jordan*
*[3]Department of Genetics, Precision Medical Laboratory Group, Amman, Jordan*
*[4]Department of Internal Medicine, Royal Medical Services (RMS), Amman, Jordan*

**Received:** February 2026**, Accepted:** May 2026

## ABSTRACT

**Background and Objectives:** *Helicobacter pylori* is a common chronic bacterial infection primarily associated with gastrointestinal disease. Increasing evidence suggests that *H. pylori* may also exert systemic effects beyond the stomach, including possible modulation of neuroendocrine pathways. This study aimed to investigate the association between *H. pylori* infection and alterations in serum cortisol and thyroid-stimulating hormone (TSH) levels as indicators of hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-thyroid (HPT) axis activity.

**Materials and Methods:** In this case-control study, 850 adults were enrolled, including 425 *H. pylori*-positive cases and 425 *H. pylori*-negative controls. Active *H. pylori* infection was determined using a monoclonal stool antigen test (HpSA). Fasting venous blood samples were collected between 08:00 and 10:00 AM under standardized conditions. Serum cortisol and TSH levels were measured using validated immunoassays. Group comparisons, correlation analysis, sex-stratified subgroup analysis, and receiver operating characteristic (ROC) curve analysis were performed.

**Results:** *H. pylori*-positive participants had significantly higher serum cortisol levels and lower TSH levels compared with controls (both $p < 0.001$). A significant inverse correlation between cortisol and TSH was observed only in infected participants ($r = -0.41$, $p < 0.001$). These hormonal alterations were evident in both sexes. ROC analysis showed moderate discriminatory performance for cortisol (AUC = 0.71) and fair-to-moderate performance for TSH (AUC = 0.67).

**Conclusion:** *H. pylori* infection was significantly associated with elevated cortisol levels, reduced TSH levels, and an inverse relationship between both hormones in adults. These findings suggest that chronic *H. pylori* infection may influence both HPA and HPT axis regulation and support further investigation into its systemic neuroendocrine effects.

**Keywords:** *Helicobacter pylori*; Cortisol; Thyroid-stimulating hormone; Hypothalamic–pituitary axis; Neuroendocrine regulation

## INTRODUCTION

*Helicobacter pylori* is one of the most prevalent chronic bacterial infections worldwide, colonizing the gastric mucosa of nearly half of the global population. It is well established as a major cause of chronic gastritis, peptic ulcer disease, and an important risk factor for gastric adenocarcinoma and muco-

*Corresponding author: Nedaa Husein, MSc, Department of Allied Medical Sciences, Zarqa University College, Al-Balqa Applied University, Zarqa, Jordan. Tel: +96-2795660200 Fax: +96-253989594 Email: nedaamicrobiology@bau.edu.jo

sa-associated lymphoid tissue lymphoma (1, 2).

Beyond its gastrointestinal manifestations, growing evidence suggests that *H. pylori* infection may exert extra-gastric systemic effects through persistent low-grade inflammation, immune activation, and metabolic disturbances. Chronic infection has been linked to cardiovascular, hematological, dermatological, and endocrine abnormalities in susceptible individuals (3, 4).

One proposed mechanism involves sustained production of pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). These mediators can influence hypothalamic signaling, stimulate the hypothalamic-pituitary-adrenal (HPA) axis, alter adrenocorticotropic hormone secretion, and subsequently increase cortisol production. Prolonged activation of this pathway may contribute to endocrine dysregulation and altered stress responses (5, 6).

Similarly, the hypothalamic-pituitary-thyroid (HPT) axis may be affected by chronic inflammatory states. Cytokine-mediated suppression of thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH), together with altered peripheral thyroid hormone metabolism, has been reported in several infectious and inflammatory conditions (7, 8).

Previous epidemiological studies have explored associations between *H. pylori* infection and thyroid-related parameters, particularly serum TSH and thyroxine levels. However, most available studies relied on serological data, secondary datasets, or focused on thyroid markers. Data evaluating simultaneous changes in both adrenal and thyroid axis biomarkers in individuals with active *H. pylori* infection remain limited (9, 10).

To address this gap, the present study investigated the relationship between active *H. pylori* infection confirmed by stool antigen testing, and serum cortisol and TSH concentrations in a large adult cohort. By assessing both HPA and HPT axis markers, in addition to sex-stratified and ROC analyses, this study aimed to provide further insight into the systemic neuroendocrine consequences of chronic *H. pylori* infection.

## MATERIALS AND METHODS

**Study design and population.** A case-control study was conducted between October 2025 and January 2026 at Precision Medical Laboratory (PMLab), Amman, Jordan. Adults aged ≥18 years were consecutively recruited and categorized into two groups according to active *H. pylori* infection status: *H. pylori*-positive cases and *H. pylori*-negative controls. Participants were referred for routine laboratory investigations or gastrointestinal evaluation.

**Sample size determination.** The minimum required sample size was calculated using a standard case-control formula assuming a moderate effect size (Cohen's d = 0.30), 80% statistical power, 95% confidence level, and a two-sided alpha of 0.05. To enhance precision, allow subgroup analyses, and account for incomplete data, the final sample size was increased to 850 participants (425 per group).

**Inclusion and exclusion criteria.** Eligible participants were adults aged ≥18 years with confirmed active *H. pylori* infection or negative infection status. Individuals with known thyroid disease, adrenal disorders, pregnancy, malignancy, chronic inflammatory disease, acute infection, or those receiving corticosteroids, thyroid medications, proton pump inhibitors, or antibiotics within the previous four weeks were excluded to minimize confounding.

**Diagnosis of *Helicobacter pylori* infection.** Active infection was determined using a monoclonal stool antigen test (HpSA), performed according to the manufacturer's instructions. The HpSA method was selected because it detects active infection rather than previous exposure and is widely accepted as a non-invasive diagnostic tool with good sensitivity and specificity. Due to logistical and cost considerations, confirmatory urea breath testing was not routinely performed.

**Blood sample collection.** Fasting venous blood samples (5 mL) were collected between 08:00 and 10:00 AM after an overnight fast to reduce circadian variation, particularly for cortisol assessment. Participants were seated and rested for approximately 15–20 minutes before venipuncture to minimize acute stress-related hormonal fluctuations. Samples were centrifuged at 3000 rpm for 10 minutes, and serum aliquots were stored at -20°C until analysis.

**Measurement of serum cortisol and TSH.** Serum cortisol and TSH levels were measured using commercially available immunoassay kits based on che-

miluminescent or enzyme-linked immunosorbent assay (ELISA) principles, following the manufacturer's protocols. Quality control sera were included in each analytical run to ensure assay accuracy and reproducibility. Hormone concentrations were expressed in µg/dL for cortisol and µIU/mL for TSH (3).

**Statistical analysis.** Data were analyzed using GraphPad Prism version 10.6.1 and SPSS version 31. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequency and percentage. Normality was assessed using the Shapiro-Wilk test. Group comparisons were performed using the independent-samples t-test or Mann-Whitney U test, as appropriate. Correlations were evaluated using Pearson or Spearman coefficients. Receiver operating characteristic (ROC) curve analysis was conducted to assess the discriminatory performance of cortisol and TSH. Multivariable linear regression analysis was additionally performed to evaluate whether *H. pylori* infection independently predicted cortisol and TSH levels after adjustment for age, sex, BMI, and smoking status. A p-value <0.05 was considered statistically significant.

**Ethical considerations.** The study protocol was approved by the Institutional Review Board of PMLab (IRB-PML-2025-047). Written informed consent was obtained from all participants. All procedures were conducted in accordance with the Declaration of Helsinki.

## RESULTS

**Baseline characteristics of the study population.** As Table 1 shows, the study included 850 adults equally distributed between the *H. pylori*-positive group (n = 425) and *H. pylori*-negative controls (n = 425). As shown in Table 1, no significant differences were observed between groups regarding age (41.8 ± 11.6 vs. 40.9 ± 12.1 years, p = 0.38), sex distribution (p = 0.66), body mass index (26.4 ± 4.3 vs. 25.9 ± 4.1 kg/m², p = 0.12), or smoking status (32.5% vs. 30.8%, p = 0.59). These findings indicate acceptable comparability between cases and controls.

**Serum cortisol and TSH levels according to *H. pylori* status.** As presented in Figs. 1 and 2, serum cortisol levels were significantly higher in *H. pylori*-positive participants compared with controls (18.9 ± 5.6 vs. 14.7 ± 4.8 µg/dL, p < 0.001). In contrast, serum TSH levels were significantly lower in infected participants than in non-infected controls (1.82 ± 0.74 vs. 2.36 ± 0.81 µIU/mL, p < 0.001).

**Correlation between cortisol and TSH.** Among *H. pylori*-positive participants, a significant inverse correlation was observed between serum cortisol and TSH levels (r = -0.41, p < 0.001), indicating that higher cortisol concentrations were associated with lower TSH values. No statistically significant correlation was found in the *H. pylori*-negative group (r = -0.09, p = 0.18), as Fig. 3 shows.

**Sex-stratified subgroup analysis.** As presented in Table 2, significant hormonal differences were observed in both sexes (Table 2). In males, cortisol levels were higher in infected participants than controls (17.6 ± 5.1 vs. 14.9 ± 4.6 µg/dL, p < 0.001), while in females the difference was more pronounced (20.1 ± 5.9 vs. 14.5 ± 4.9 µg/dL, p < 0.001). The absolute cortisol increase associated with infection was greater in females (Δ5.6 µg/dL) than in males (Δ2.7 µg/dL), suggesting a stronger endocrine stress response in women.

TSH levels were significantly lower in infected par-

**Table 1.** Demographic and baseline characteristics of the study participants.

| Variable | *H. pylori*–positive (n = 425) | *H. pylori*–negative (n = 425) | p-value |
|---|---|---|---|
| Age (years), mean ± SD | 41.8 ± 11.6 | 40.9 ± 12.1 | 0.38 |
| Sex (Male/Female), n (%) | 214 (50.4%) / 211 (49.6%) | 208 (48.9%) / 217 (51.1%) | 0.66 |
| BMI (kg/m²), mean ± SD | 26.4 ± 4.3 | 25.9 ± 4.1 | 0.12 |
| Smoking status (Yes), n (%) | 138 (32.5%) | 131 (30.8%) | 0.59 |

For continuous variables, the data is displayed as mean ± standard deviation (SD); for categorical variables, the data is displayed as a number (%). An independent-sample t-test for continuous variables and a chi-square test for categorical variables were used to determine p-values.

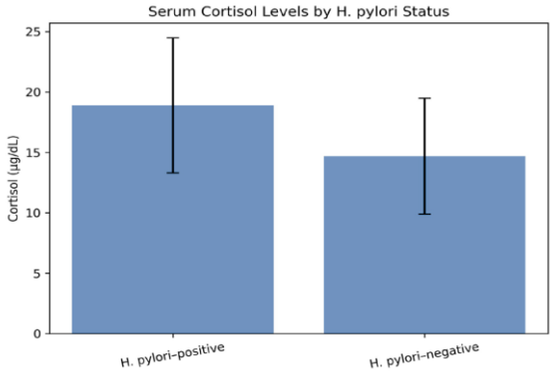


**Fig. 1.** Serum cortisol levels according to *Helicobacter pylori* infection status.

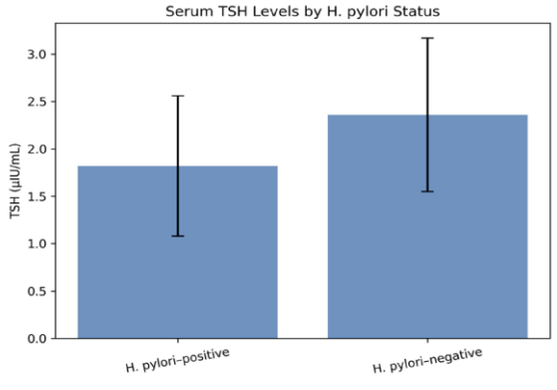


**Fig. 2.** Serum TSH levels according to *Helicobacter pylori* infection status.

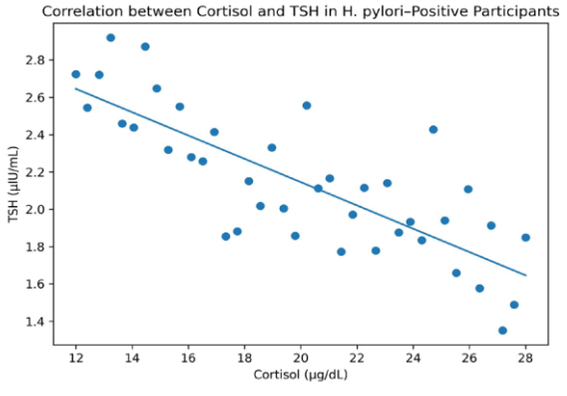


**Fig. 3.** Correlation between serum cortisol and TSH levels in *H. pylori*–positive participants.

ticipants of both sexes. In males, TSH decreased from 2.31 ± 0.79 to 1.94 ± 0.76 µIU/mL ($p < 0.001$), whereas in females it decreased from 2.41 ± 0.82 to 1.69 ± 0.71 µIU/mL ($p < 0.001$).

**ROC curve analysis.** Receiver operating characteristic (ROC) analysis was performed to evaluate the ability of serum cortisol and TSH levels to differentiate *H. pylori*-positive participants from *H. pylori*-negative controls. Serum cortisol demonstrated moderate discriminatory performance with an area under the curve (AUC) of 0.71, whereas serum TSH showed fair discriminatory performance with an AUC of 0.67. These findings suggest that both biomarkers have modest ability to distinguish infection status and may reflect systemic endocrine involvement associated with *H. pylori* infection rather than serving as standalone diagnostic markers, as Figs. 4 and 5 shows.

## DISCUSSION

The present study demonstrated a significant association between active *Helicobacter pylori* infection and altered neuroendocrine biomarkers in adults, characterized by elevated serum cortisol levels and reduced TSH concentrations. In addition, a significant inverse correlation between cortisol and TSH was observed exclusively in *H. pylori*-positive participants, suggesting coordinated dysregulation of both the HPA and HPT axes. These findings support the concept that chronic *H. pylori* infection may exert systemic effects beyond the gastrointestinal tract and influence endocrine homeostasis (7, 8).

The observed increase in serum cortisol levels among infected individuals is biologically plausible. Persistent *H. pylori* colonization has been associated with chronic low-grade inflammation and sustained immune activation, with increased production of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. These inflammatory mediators may stimulate hypothalamic corticotropin-releasing hormone pathways, increase ACTH secretion, and subsequently enhance cortisol release (7, 8). Although cortisol elevation may initially represent an adaptive anti-inflammatory response, prolonged activation of the HPA axis may contribute to broader endocrine dysregulation. Previous studies have also reported altered cortisol dynamics in individuals with *H. pylori* infection, although differences in disease chronicity, bacterial virulence factors, host immune responses, and assay methodology may explain inconsistent findings across studies (9).

Simultaneously, significantly lower TSH levels were identified in *H. pylori*-positive participants compared

**Table 2.** Sex-stratified analysis of serum cortisol and TSH levels according to *Helicobacter pylori* infection status.

| Parameter | Male with positive *H. pylori* status | Male with negative *H. pylori* status | Female with positive *H. pylori* status | Female with negative *H. pylori* status | p-value* |
|---|---|---|---|---|---|
| Cortisol (µg/dL), mean ± SD | 17.6 ± 5.1 | 14.9 ± 4.6 | 20.1 ± 5.9 | 14.5 ± 4.9 | < 0.001 |
| TSH (µIU/mL), mean ± SD | 1.94 ± 0.76 | 2.31 ± 0.79 | 1.69 ± 0.71 | 2.41 ± 0.82 | < 0.001 |

* p-values represent comparisons between *H. pylori*–positive and *H. pylori*–negative participants within each sex.

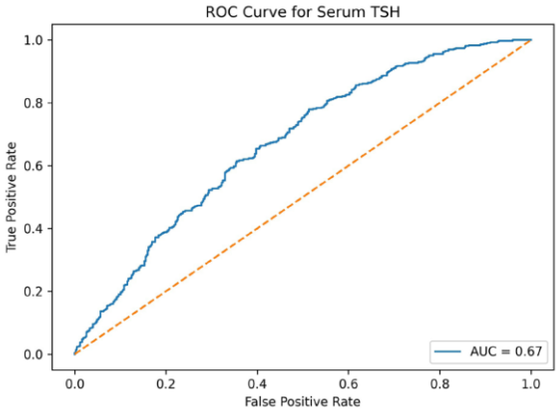


**Fig. 4.** ROC curve for serum cortisol in discriminating *H. pylori.*

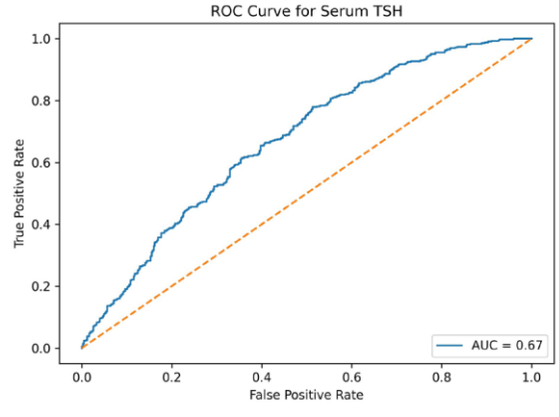


**Fig. 5.** ROC curve for serum TSH in identifying *H. pylori* infection.

with controls. This finding is consistent with emerging epidemiological evidence linking *H. pylori* infection with altered thyroid-related biochemical parameters. Population-based analyses have reported associations between *H. pylori* seropositivity and lower circulating TSH levels, sometimes accompanied by higher thyroxine concentrations (10). Chronic inflammatory states may suppress TRH secretion and blunt pituitary TSH release through cytokine-mediated mechanisms. In addition, inflammatory stress may alter peripheral thyroid hormone metabolism, producing patterns similar to non-thyroidal illness syndrome (11).

Another important finding was the significant inverse relationship between cortisol and TSH observed only in infected participants. This pattern further supports functional interaction between the HPA and HPT axes during chronic infection. Increased glucocorticoid activity has been shown to suppress TRH and TSH secretion, whereas inflammatory mediators may simultaneously stimulate cortisol production (11). The absence of this correlation in non-infected controls suggests that the hormonal interaction may be infection-related rather than a general physiological finding.

Sex-stratified analysis revealed that hormonal alterations were present in both males and females; however, the magnitude of cortisol elevation associated with infection was greater in females than in males. This may indicate sex-related differences in immune responsiveness, stress-axis sensitivity, or hormonal modulation. Previous evidence suggests that females often exhibit stronger inflammatory and endocrine responses under chronic stress conditions (12). Further studies are warranted to clarify the biological basis and clinical relevance of these sex-specific differences.

Receiver operating characteristic analysis showed modest discriminatory performance for cortisol and TSH. These biomarkers are not proposed as diagnostic tools for *H. pylori* infection; rather, their performance may reflect systemic endocrine responses associated with chronic infection. This observation may be relevant in the broader context of extra-gastric manifestations, where host-response biomarkers can provide insight into systemic disease burden rather than microbial detection alone (13).

Increasing evidence also supports a relationship

between *H. pylori* infection and thyroid disorders, particularly autoimmune thyroid disease. Several studies and meta-analyses have reported a higher prevalence of Hashimoto thyroiditis and Graves' disease among infected individuals, with reductions in thyroid autoantibody titers following bacterial eradication in some cases (14, 15). Proposed mechanisms include molecular mimicry between bacterial antigens and thyroid tissue, together with persistent immune activation.

The strengths of this study include the relatively large adult cohort, confirmation of active infection using stool antigen testing, standardized hormonal measurements, and subgroup analyses. Nevertheless, several limitations should be acknowledged. The cross-sectional case-control design does not permit causal inference. Free thyroid hormones (FT3 and FT4), ACTH, and inflammatory cytokines were not directly measured, which would have provided a more comprehensive characterization of HPA and HPT axis activity. In addition, bacterial virulence factors such as CagA status were not assessed.

In conclusion, active *H. pylori* infection was associated with elevated cortisol levels, reduced TSH concentrations, and an inverse hormonal relationship in adults. These findings suggest that chronic *H. pylori* infection may influence systemic neuroendocrine regulation and warrant further prospective mechanistic studies to clarify its role in extra-gastric disease manifestations.

## REFERENCES


1. Yang H, He L, Zhao X, Zeng Z, She X, Yang N, et al. The relationship between circadian syndrome and its components with *Helicobacter pylori* infection risk: a cross-sectional study. *BMC Infect Dis* 2025; 25: 982.
2. Gong J, Chen F, Jiang B, Zhou B, Ma X, Wang M, et al. Associations between blood systemic inflammatory markers and anxiety in *Helicobacter pylori*-infected patients. *Front Psychiatry* 2025; 16: 1671858.
3. Papadimitriou A, Priftis KN. Regulation of the hypothalamic-pituitary-adrenal axis. *Neuroimmunomodulation* 2009; 16: 265-271.
4. De Luca R, Davis PJ, Lin HY, Gionfra F, Percario ZA, Affabris E, et al. Thyroid hormones interaction with immune response, inflammation and non-thyroidal illness syndrome. *Front Cell Dev Biol* 2021; 8: 614030.
5. Lu T, Lu S, Lin J, Shao X, Chen D, Shen J. Association between *Helicobacter pylori* infection and thyroid hormone levels: analysis of the NHANES dataset. *Front Endocrinol (Lausanne)* 2025; 16: 1482073.
6. Figura N, Di Cairano G, Moretti E, Iacoponi F, Santucci A, Bernardini G, et al. *Helicobacter pylori* infection and autoimmune thyroid diseases: the role of virulent strains. *Antibiotics (Basel)* 2019; 9: 12.
7. Wolff ASB, Kucuka I, Oftedal BE. Autoimmune primary adrenal insufficiency: current diagnostic approaches and future perspectives. *Front Endocrinol (Lausanne)* 2023; 14: 1285901.
8. Silverman MN, Sternberg EM. Glucocorticoid regulation of inflammation and its functional correlates: from HPA axis to glucocorticoid receptor dysfunction. *Ann N Y Acad Sci* 2012; 1261: 55-63.
9. Koşan B, Yüksel O, Ustün I, Köklü S, Topal F, Yilmaz M, et al. Role of endogenous cortisol on *Helicobacter pylori* colonization. *Clin Biochem* 2008; 41: 917-919.
10. Wang J, Liu D, Xie Y. Association between *Helicobacter pylori* infection and serum thyroid stimulating hormone in the National Health and Nutrition Examination Survey 1999-2000. *Front Endocrinol (Lausanne)* 2022; 13: 1018267.
11. Fliers E, Bianco AC, Langouche L, Boelen A. Thyroid function in critically ill patients. *Lancet Diabetes Endocrinol* 2015; 3: 816-825.
12. Klein SL, Flanagan KL. Sex differences in immune responses. *Nat Rev Immunol* 2016; 16: 626-638.
13. Franceschi F, Tortora A, Gasbarrini G, Gasbarrini A. *Helicobacter pylori* and extragastric diseases. *Helicobacter* 2014; 19(Suppl 1): 52-58.
14. Hou Y, Sun W, Zhang C, Wang T, Guo X, Wu L, et al. Meta-analysis of the correlation between *Helicobacter pylori* infection and autoimmune thyroid diseases. *Oncotarget* 2017; 8: 115691-115700.
15. Dore MP, Fanciulli G, Manca A, Pes GM. Association of *Helicobacter pylori* Infection with autoimmune thyroid disease in the female sex. *J Clin Med* 2023; 12: 5150.