Original Article

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Autoimmune Hypothyroidism Associated with *Helicobacter Pylori* Infection

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Abstract:

Objective: The study aimed to investigate the correlation between *Helicobacter pylori* (*H. pylori)* and thyroid autoimmunity.

Material and Methods: To demonstrate the possible correlation between *H. pylori* infection and autoimmune hypothyroidism, 200 individuals were enrolled in this research (100 patients with active *H. pylori* infection and 100 healthy controls). All of them were tested for serum levels of thyroid hormones, thyroid stimulating hormone (TSH), and autoantibodies, as well as *Helicobacter pylori*-Immunoglobulin G (*H. pylori*-IgG) and cytotoxin-associated gene A-Immunoglobulin G (cagA-IgG) antibodies.

Results: The study found that *H. pylori* infection was associated with higher levels of TSH, thyroperoxidase and thyroglobulin (TPO and TG) (p-value<0.000, 0.001 and 0.006, respectively) and a significant decrease in the levels of free-thyroid hormone (FT3 and FT4) (p-values=0.008 and 0.007 respectively) in patients compared with the control group. Moreover, using Pearson's correlation tests, significant proportional correlations were found between *H. pylori* IgG and TSH (r=0.302, p-value=0.001), and a significant negative correlation was found between anti-*H. pylori*-IgG and with FT3 and FT4 (r=-0.261, p-value=0.003 and r=-0.260, p-value=0.003, respectively). Moreover, Spearman's correlation results showed that *H. pylori* IgG was positively linked to TPO (r=0.531, p-value<0.001) and TG (r=0.320, p-value=0.001).

Conclusion: The current investigation found that *H. pylori* infection was linked to higher concentrations of thyroid autoantibody and TSH and lower levels of thyroid hormones, suggesting that the bacterium may play a role in the development of subclinical autoimmune hypothyroidism.

Keywords: anti-cagA. TPO, correlation, *H. pylori*-Abs. Hypothyroidism, TG

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Introduction

Helicobacter pylori (*H. pylori*) is a spiral, motile, negative-stained gram-stain pathogen with a variety of unusual properties. It is microaerophilic, and can convert urea to ammonia and carbon dioxide by producing urease, the enzyme which increases the gastric positive potential of the hydrogen ions (pH) in its local environment. However, it is not an acidophile and will not expand below pH 6[1]. People who are exposed to *H. pylori* infections may experience chronic and deteriorating gastritis; additionally, 1–10% of those who are infected may experience clinical complications like intestinal metaplasia, peptic ulcers, gastric-mucosa atrophy, gastric carcinoma or mucosa-associated lymphoid tissue lymphoma[2].

More than 50% of the planet's people have been found to have this bacterium or its antibodies. Most carriers of this bacterium don't exhibit any symptoms. Depending on the age, the existence of *H. pylori* in the mucus layer of the stomach varies from 20% of people in their 30s to 40–60% of persons aged about 60 years[3]. Adult infection prevalence in poor nations may reach 80% or more. Recently, it has been reported that the frequency of *H. pylori* was highest in Africa and Asian nations, and lower in Oceania and North America[4]. Besides gastric manifestations, patients may also suffer from extra-gastric symptoms, including neurologic diseases (stroke and Alzheimer's disease), dermatologic diseases (rosacea process and psoriasis), allergic disease (asthma and chronic urticaria), a respiratory disease (Coronavirus disease 2019), a hematologic disease (iron deficiency anemia), a cardiovascular disease (coronary atherosclerotic disease) an ophthalmic diseases (non-heterogeneous glaucoma), as well as endocrine and metabolic diseases (autoimmune thyroiditis and diabetes)[5-7]. However, the impact of *H. pylori* infection on thyroid function remains unconfirmed. Earlier studies have found that patients suffering from autoimmune Hashimoto's thyroiditis and Graves' disease were highly infected by *H. pylori*[8,9]. On the other hand, Işık et al. found no correlation between the infection and thyroid dysfunction or autoimmunity[10].

The majority of research that demonstrated a connection between *H. pylori* infection and thyroid autoimmunity looked at the presence of anti-*H. pylori* antibodies Immunoglobulin G, Immunoglobulin A and anti cytotoxin-associated gene A (IgG, IgA, and anti-CagA) in people who had abnormal thyroid function tests. In this research, the levels of these antimicrobial antibodies were compared to the concentrations of anti-thyroid antibodies, and distinct results were obtained. In the same context, this study aimed to assess the serum levels of free-thyroid hormones (FT3 and FT4), thyroid stimulating hormone (TSH) and thyroid antibodies thyroperoxidase and thyroglobulin (TPO and TG) in patients with an active infection of *H. pylori* and to examine if there was a link between these variables.

Material and Methods

Study participants

One hundred patients with current *H. pylori* infection (diagnosed by a positive stool antigen test, (manufactured by Linear Chemicals, Barcelona, Spain) of both sexes and aged between 6 and 73 years old (mean: 29.3±5.30) were included in this investigation. All of them were registered at the Internal Medicine Clinic of Al-Salam Teaching Hospital, Mosul City, Iraq between September 1, 2022, and March 1, 2023. Also, 100 apparently healthy subjects of comparable age and sex were enrolled in the study as a comparable control group. People with past or current autoimmune thyroid diseases (AITD), family histories of AITD, who were taking any medications known to interfere with the thyroid function test, and those suffering from one or more chronic diseases were excluded from the investigation. All patients and the control group accepted and signed a patient consent form supplied by the author.

Sample collection

Three milliliters of venous blood were drawn from each participant using an aseptic technique under the supervision of a clinician specializing in gastrointestinal diseases and saved in anti-coagulant-free tubes. The serum was then extracted from the blood samples using a centrifuge set to 6,000 round per minute. Following this, the obtained serum was placed in Eppendorf tubes and used on the same day for the serological procedures of the study.

Measurement of *H. pylori* IgG and anti-cagA antibodies

The blood concentration of anti-*H. pylori* and anti-CagA antibodies were measured using ELISA kits (Accubind Inc. USA and Sunlong Biotech, China), The ELISA equipment (ThermoScientific Comp. USA) and the blood was collected and assayed following the manufacturer's instructions.

Measuring the concentrations of hormones and autoantibodies in the blood

Soon after blood collection the levels of FT3, FT4, TSH, anti-TPO, and anti-TG were quantitatively estimated using the electrochemiluminescence immunoassay method and kits (Cobas in Penzberg, Germany).

Statistical analysis

Data were given and analyzed as mean, standard error, and percentage. The Statistics Package for Social Science software package (Ver. 24, IBM Com. USA) was used to analyze the results of the research. The independent t-test was used to assess the significance of the comparisons. Pearson's and Spearman's correlation tests were also used to clarify the association between thyroid antibodies, hormones and TSH. A *P* value equal to or less than 0.05, the results were considered as significant.

Results

The demographic data of the study participants (patients and healthy controls) are presented in Table 1. More than 30% of the *H. pylori* patients were aged between 21-40 years old. In terms of sex, females there were no more infected females than males in our study. Also, 10% of the patients were smokers.

Table 1 The demographic data of the study participants (patients and controls)

Demographic factor	HP-patients (N=100)		Control (N=100)	
	N	%	N	%
Age (years)				
≥20	17	17	19	19
21-40	33	33	30	30
41-50	21	21	25	25
51-60	19	19	15	15
≤61	7	7	11	11
Sex				
Male	45	45	43	43
Female	55	55	57	57
Smoker				
Yes	10	10	13	13
No	90	90	87	87

HP-patients=*Helicobacter pylori* patients

Table 2 Concentrations of anti-*H. pylori* IgG and anti-cagA IgG in patients and control

Parameters	HP-patients Mean±SE	Control group Mean±SE	Cut-off point	p-value
H. *pylori* IgG IU/L	87.23±7.68	12.06±1.22	>20 IU/L	0.010**
CagA IgG ng/ml	89.85±9.42	39.59±3.84	40 ng/ml	<0.000**

HP-Patients=*Helicobacter pylori* patients, IgG=Immunoglobulin G, CagA=cytotoxin-associated gene A, SE=standard error
**Results were significant at 0.01 level.

Table 3 FT3, FT4, and TSH concentrations in *H. pylori* patients and control group

Hormone	HP-patients Mean±SE	Control group Mean±SE	Reference value	p-value
FT3 (nmol/L)	3.67±0.10	4.80±0.19	3.5–7.8	0.008**
FT4 (pmol/L)	14.13±0.98	15.04±0.52	9.0–25.0	0.007**
TSH (µIU/ml)	8.77±0.32	2.50±0.15	0.4–4.5	<0.000**

HP-patients=*Helicobacter pylori* patients, FT=free-thyroid hormones, TSH=thyroid stimulating hormone, SE=standard error
**Results were significant at 0.01 level

Table 4 Levels of TPO and TG in *H. pylori* patients and control group

Antibody	Patients Mean±SE	Control Mean±SE	Reference value	p-value
TPO IU/L	276.39±4.28	4.11±0.57	<9	<0.001**
TG IU/L	27.85±0.93	11.56±0.63	<6	0.006**

TPO=thyroperoxidase, TG=thyroglobulin, SE=standard error
**Results were significant at 0.01 level

Table 5 Levels of thyroid hormones and TSH in *H. pylori* patients as shown in the results of the *H. pylori* IgG test

Thyroid Hormone	HP IgG + Mean±SE	HP IgG - Mean±SE	p-value
FT3 (pmol/L)	5.42±0.15	3.34±0.11	0.008**
FT4 (pmol/L)	15.33±0.32	5.06±0.28	<0.001**
TSH (µIU/ml)	8.20±0.85	2.48±0.23	<0.001**

HP-patients igG=*Helicobacter pylori* patients Immunoglobulin G, FT=free-thyroid hormones, TSH= thyroid stimulating hormone, SE=standard error
**Results were significant at 0.01 level

Table 6 Concentrations of thyroid antibodies in *H. pylori* patients as shown in the results of the *H. pylori* IgG test

Thyroid antibody	HP + Mean±SE	HP - Mean±SE	p-value
Anti-TPO (IU/L)	319.44±25.07	5.85±1.01	<0.001**
Anti-TG (IU/L)	7.12±0.93	1.91±0.46	<0.001**

HP-patients=*Helicobacter pylori* patients, SE=standard error
**Results were significant at 0.01 level

Table 7 Spearman's correlation test between thyroid autoantibodies and *H. pylori* IgG

Positive thyroid antibody tests	Positive *H. pylori* IgG test	
	R	p-value
Anti-TPO	0.531	<0.001**
Anti-TG	0.320	0.001**

H. pylori IgG=*Helicobacter pylori* patients Immunoglobulin G, Anti-TPO=Anti-thyroperoxidase, Anti-TG=Anti-thyroglobulin, SE=standard error
**Results were significant at 0.01 level.

The results presented in Table 2 show that the serum levels of *H. pylori* IgG and anti-CagA antibodies were noticeably greater in the patients compared to the control group (p-values=0.01 and 0.000).

Table 3 shows that patients with *H. pylori* had significantly lower levels of free thyroid hormones (p-values=0.008 and 0.007, respectively). While, TSH hormone levels were significantly higher in *H. pylori*-positive patients than in the control group (p-value=0.000). The current findings suggest that subclinical hypothyroidism may develop as a result of *H. pylori* infection.

Notably, the thyroid autoantibodies anti-TPO and anti-TG exhibited considerably higher serum concentrations (p-value<0.000 and p-value=0.006 respectively) in individuals with *H. pylori* infection (Table 4).

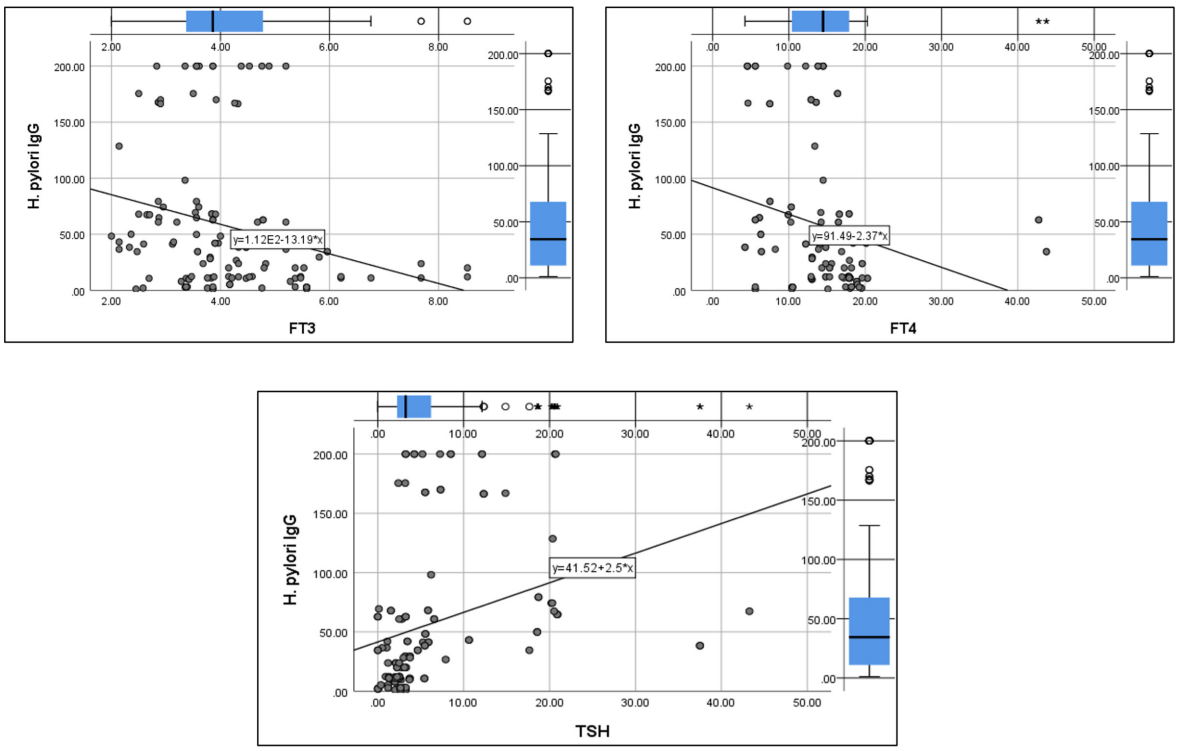
This study found that the levels of FT3 and FT4 were significantly decreased (p-value=0.008 and p-value<0.001 respectively), while the level of TSH was increased significantly (p-value<0.001) in patients with positive results for *H. pylori* IgG tests compared to those with negative results (Table 5). Moreover, using Pearson's correlation test, the results illustrated in Figure 1 show that *H. pylori* IgG was negatively linked to each of FT3 (r=-0.261, p-value=0.003) and FT4 (r=-0.260, p-value=0.003) and positively linked to TSH (r=0.302, p-value=0.001).

In the same context, the results of Table 6 show that the concentrations of antithyroid antibodies (anti-TPO and anti-TG) were significantly increased (p-value<0.001 for both) in the patients with positive tests of *H. pylori* IgG compared to those with negative results. Furthermore, Spearman's correlation (Table 7) showed that *H. pylori* IgG was positively linked to TPO (r=0.531, p-value<0.001) and TG (r=0.320, p-value=0.001).

It can be assumed from the above data, Tables 2-7 and Figure 1, that *H. pylori* infection is associated with increased levels of thyroid antibodies (TPO and TG) and TSH and decreased levels of thyroid hormones suggesting a role of the bacterium in the emergence of thyroid autoimmunity and may, in the future, contribute to the progression of autoimmune thyroid disease.

Discussion

The study found that the *H. pylori* infection rate was higher among people aged between 24-40 years old. Also, females showed a higher infection rate than males (Table 1). Studies on this subject have produced contradicting findings, as several studies found that the incidence of *H. pylori* infection increased with the age[11-13]. While other studies found that the female sex was linked to a higher incidence of infection and related to the age categories[14,15]. The current results could support a minor



FT3=free-thyroid hormone 3, FT4=free-thyroid hormone 4, TSH=thyroid stimulating hormone

Figure 1: Pearson's correlation test between *H. pylori* IgG with each of FT3 (r=-0.261, p-value=0.003), FT4 (r=-0.260, p-value=0.003), TSH (r=0.302, p-value=0.001)

role for age dominance concerning the percentage of infections by *H. pylori,* which may be related to increased exposure to the source of infection as people age, even if more investigations are required to explain the processes of age-related incidence of infection.

We found that higher levels of TSH, anti-TPO, anti-TG, and anti-cagA and lower levels of free thyroid hormones (Tables 3-6) were substantially correlated with anti-*H. pylori* IgG antibodies, providing evidence that infection with this pathogen may lead to the emergence of autoimmune hypothyroidism. According to earlier studies, microbes may be a substantial contributor to the etiology of autoimmune diseases[16], thyroid autoimmunity is among them[17]. Research during the past ten years has revealed several bacterial taxa that can cause Graves' disease and Hashimoto's thyroiditis[18]. An important pathogen that is expected to be involved in the emergence of AITD is *H. pylori*, however, endocrinologists disagree about the strength of this link and the potential interference of other factors[19]. Additionally, following our study, it was reported that the infection rate of *H. pylori* was higher in people who had thyroid autoimmunity and was associated with higher TSH concentrations and lower levels of thyroid hormones[20,9].

Bassi et al. (2014) discovered a significant rise in *H. pylori* prevalence in Graves' disease patients[21], while Hou et al. (2017) discovered no link between *H. pylori* infection and the development of AITD[22]. A positive link was discovered between *H. pylori* and the incidence of Graves' disease[23]. Other studies reported a strong relationship between Hashimoto's thyroiditis and the CagA-expressing strain of *H. pylori*[24,25].

Autoantibodies produced as a result of *H. pylori* infection can damage gastric epithelial cells, resulting in gastritis and the emergence of antibody-mediated cross-reactions that impair thyroid tissue. Therefore, it is likely that *H. pylori* infections are connected to thyroid abnormalities, suggesting that the bacterial infection was implicated in the pathophysiology and development of AITD[26].

A cross-reaction between thyroid and bacterial antigens was first proposed by Ko et al. (1997)[27] as a pathological mechanism involved in the development of AITD induced by *H. pylori*. Indeed, it has been reported that thyroid peroxidase and CagA *H. pylori* strains share similar amino acid sequences[27]. Additionally, the similarity of one peptide composed of 11 residues found in thyroid peroxidase and stomach parietal cell antigen demonstrates that the two antigens share an epitope[28]. In addition, eliminating the *H. pylori* infection has been shown to reduce the level of thyroid-specific autoantibodies[29]. Additionally, *H. pylori* may cause or worsen AITD in patients who have HLA. -DRB1[30]. It's interesting to note that patients with AITD exhibit heightened chemokine responses to *H. pylori*[31].

Study limitation

The current investigation discovered a significant association between an active *H. pylori* infection and the potential development of autoimmune hypothyroidism, as evidenced by elevated thyroid hormones and antibodies (anti-TPO, anti-TG) in those patients. The reliance on IgG antibodies to assess the association, which is continuous and may suggest a prior infection, is a drawback of the current study. Also, the anti-cagA antibodies suggest that the patients may proceed to some malignancy. Anti-*H. pylori* IgM type has to be used in future research to test these relationships.

Conclusion

The current study's findings show that anti-H. pylori antibodies are more prevalent in aged patients. Notably, patients with a current infection of *H. pylori* expressed decreased levels of free thyroid hormones and greater concentrations of TSH and thyroid autoantibodies suggesting an association between *H. pylori* infection and thyroid autoimmunity which could be involved in the development of subclinical autoimmune hypothyroidism and the progression to Hashimoto's thyroiditis.

Ethical approval

Permission for the present study was obtained from the scientific research ethics committee under the number 23 on Aug. 10. 2022. Blood samples were obtained under the supervision of a public health technician. Each study participant read and signed the patient consent form.

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