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Original article

Prevalence of *Helicobacter pylori* infection among Egyptian patients with hypothyroidism and its relation to treatment resistance in Beni-Suef Governorate

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ABSTRACT

Background and rationale: Hypothyroidism is a common condition of thyroid hormone deficiency, which is readily diagnosed and managed but potentially fatal in severe cases if untreated. *Helicobacter pylori (H. pylori*) infection has been associated with an increased risk of thyroid diseases (TDs) and it may cause some sort of mal absorption to thyroxine replacement therapy causing a treatment refractory state. **Aim of work:** The aim of the work is to estimate the prevalence of *H. pylori* in hypothyroid patients and its relation to unresponsiveness to treatment. **Patients and method:** We analyzed 211 hypothyroid patient on treatment. We estimate stool antigen for *H. pylori* and correlate it with other parameters in hypothyroid patients. **Results:** Two hundred and eleven (211) patients were included in this study, of these, 101/211 (47.9%) were euthyroid on treatment and 110/211 (52.1%) had refractory hypothyroidism with high dose of LT4. The mean age of patients in our study was 55.67 ± 13.53 years, with 151 (71.6%) female patients. In the current study, we noticed that prevalence of *H. pylori* was higher in treatment refractory hypothyroidism than euthyroid patients. **Conclusions:** This study suggested that there is a significant association between *H. pylori* infection and treatment-refractory hypothyroidism. And eradication of *H. pylori* may help in overcoming the issue of resistant to thyroxine therapy.

Introduction

Levothyroxine (LT4) is the typical medication prescribed to treat hypothyroidism, one of the most prevalent diseases in the world affects about 5% of the general population. When the thyroid gland, which is found in the neck, does not produce enough thyroid hormone to meet the body's needs, hypothyroidism results. Heart disease, infertility, and delayed brain development in children can arise from this. Hypothyroidism can cause changes in body weight as well as fatigue, weakness, and depression, all of which can lower a person's quality of life. [1]. Refractory hypothyroidism, which can be characterized as a thyroid-stimulating hormone (TSH) level exceeding the upper limit of the reference range and receiving high daily LT4 dose of ≥1.9 μg/kg, is a common

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problem in clinical practice, even though its prevalence has not been fully determined [2]. Even in the absence of known medical conditions or medications that could impair LT4 absorption, such as gastrointestinal disorders, systemic medical conditions like cirrhosis, cardiomyopathy, nephrotic syndrome, concurrent use of other drugs (proton pump inhibitor, ferrous salts, calcium carbonate, laxatives, anticonvulsants), and dietary interferences, some patients actually still exhibit refractory hypothyroidism [3,4].

About 50% of people worldwide are infected with *Helicobacter pylori* (*H. pylori*), a Gram-negative flagellated bacterium that is primarily spread through feces and the mouth [4]. The primary target of the infection is the gastric environment, where the organism has colonized. While some Gram-negative bacteria cause an acute response in the host, the majority of infection carriers exhibit paucisymptomatic or asymptomatic state and exhibit complaints similar to dyspepsia. [5]

Additionally, the infection may play a role in the etiology of autoimmune thyroid diseases (ATD), such as Graves' disease (GD) and Hashimoto thyroiditis (HT), which are the main causes of hyperthyroidism and hypothyroidism, respectively. The mechanism is believed to be related to the molecular mimicry that occurs between thyroid constituents and *H. pylori* antigens. Additionally, patients with CagA-positive strains of the infection show a stronger association, which could be explained by the possibility of cross-reactivity between antibodies against the *H. pylori* CagA protein and thyroid gland follicular cells. The hypothesis that *H. pylori* infection plays a role in ATD is supported by the finding that eliminating the infection lowers thyroid autoantibody levels [6]. Numerous other autoimmune diseases, including metabolic syndrome, celiac disease, and diabetes, are also associated with *H. pylori* infection [7]. Likewise, a few studies have linked thyroid disorders and chronic *H. pylori* infection [8]. According to a study, 46.5% of women with autoimmune thyroiditis had *H. pylori* [8-11].

This study sought to ascertain whether *H. pylori* infection was associated with refractory hypothyroidism in patients who came to a tertiary care facility. Studying the disease determinants and interactions is crucial for evidence-based management of hypothyroidism, especially in light of the scant evidence regarding the role of *H. pylori* in this regard.

Subjects and methods

Study design and subjects

A case control study was conducted and included 211 Patients who visited the diabetes, endocrinology, gastroenterology, or outpatient clinics of Beni-Suef University Hospital in the Beni-Suef Governorate between July 2023 and November 2023, aged 24 to 85, were included in this case and control study. Two hundred and eleven (211) hypothyroid patients receiving levothyroxine replacement therapy 60 men and 151 women were included in the study. They were split into two primary groups: 101 patients in group I, who were treated for euthyroidism, and 110 patients in group II, who were treated for hypothyroidism. Before any person could participate in the study, their written informed consent was obtained.

Inclusion criteria

Patients, both male and female, who are over the age of 18 and who were compliant with treatment, and who were enrolled in outpatient clinics.

Exclusion criteria

Those undergoing treatment for *H. pylori* eradication, those with a history of gastric surgery, those with acid-peptic disease with a peptic ulcer on endoscopy, poor compliance, malabsorption syndromes, and gastrointestinal or liver malignancies.

Ethical considerations

Giving patients comprehensive information about the study. The Beni-Suef University ethical committee's approval, bearing approval number FMBSUREC/09072023/Mohamed, was obtained.

Confidentiality of data

Study records denoted by a code number was stored apart from all other records, including locator forms and informed consent forms, that contain names or other personal identifiers.

Methods

All patients enrolled in the study, was subjected to:

1. Carefully gathering medical history, including current drug use, smoking, physical activity, sex, age, education, behavior, and medical history.

2. A clinical assessment. Patients were measured for height, weight, and body mass index (BMI) while wearing loose clothing and no shoes.

3. The following laboratory tests were performed: serum creatinine, complete blood count (CBC), TSH, free T3, and free T4, alanine transaminase (ALT) and aspartate transaminase (AST).

4- *H. pylori* detection through stool antigen. Using SD Bioline *H. pylori* antigen testing kit (STANDARD DIAGNOSTIC, INC. Giheung-gu, Korea). This test kit contains the mouse monoclonal anti-*H. pylori* antibodies.

Statistical analysis

The SPSS (statistical program for social science, version 20) was used to analyze the data in the following ways: The terms mean, SD, and range are used to describe quantitative variables.

Qualitative variables expressed as percentages and numbers.

Results

The frequency of some demographic and clinical data in the studied groups were demonstrated in **tables (1), (2).**

I-Descriptive data

This **table (1)** shows that the mean age of participants is 55.67± 13.53. It also shows that females represented more than two thirds of participants. Regarding residence, 55.5% of participants was living in rural areas. Also, it shows that the mean BMI of study participants is 31.46± 5.16. Regarding blood picture of participants, the mean HGB concentration was 11.85± 1.55, the mean WBCS concentration 7.77± 2.98, the mean platelet concentration 258.85± 75.69. As regards liver functions, the mean ALT was 29.89± 14.68, and the mean AST was 30.64± 15.19. Regarding lipid profile, the mean total cholesterol was 193.17± 51.75, the mean triglycerides was 164.78± 62.87, the mean HDL cholesterol was 97.00± 39.21, and the mean LDL cholesterol was 48.96± 12.72.

Table 2 shows that nearly half of participants were diabetic and hypertensive. Around 43% of participants were positive for *H. pylori*. Regarding thyroid profile, the mean TSH was 8.05± 9.73, the mean free T3 was 2.05± 0.82, and the mean free T4 was 1.04± 0.44. The mean dose of thyroxine given to study participants was 131.52± 72.92. It also showed that nearly one quarter of participants is refractory to treatment.

II-Comparative data

Table 3 shows that there is a statistically significant association between thyroid function and *H. pylori* infection with 53.6% of hypothyroid patients was positive for *H. pylori*. There is a statistically significant difference between the euthyroid and hypothyroid groups regarding TSH, free T3, and free T4 levels. Regarding thyroxine dose, the hypothyroid group used more dose of thyroxine with statistically significant difference from the euthyroid group. Regarding response to treatment, there was statistically significant difference between study groups with one third of hypothyroid group being refractory to treatment.

This **table (4)** shows that there is a statistically significant association between *H. pylori* infection and response to treatment with nearly two thirds of refractory participants having *H. pylori* infection.

Table 1. Socio-demographic characteristics & Anthropometric measures of the participants

		Patients (n=211)
Age [Mean (SD)]		55.67 (13.53)
Sex	Males [n (%)]	60 (28.4%)
	Females [n (%)]	151 (71.6%)
Residence	Urban [n (%)]	94 (44.5%)
	Rural [n (%)]	117 (55.5%)
BMI (kg/m^2**)** [Mean (SD)]		31.46 (5.16)
Blood picture	**HGB** [Mean (SD)]	11.58 (1.55)
	WBCs [Mean (SD)]	7.77 (2.98)
	PLTs [Mean (SD)]	258.85 (75.69)
Liver functions	**ALT** [Mean (SD)]	29.89 (14.68)
	AST [Mean (SD)]	30.64 (15.19)
Lipid profile	**Total cholesterol** [Mean (SD)]	193.17 (51.75)
	TG [Mean (SD)]	164.78 (62.87)
	HDL [Mean (SD)]	97.00 (39.21)
	LDL [Mean (SD)]	48.96 (12.72)

SD= standered deviation, ALT= Alanine transaminase, AST=Aspartate transaminase, TG= triglyceride, HDL= High density lipoprotein, LDL= low density lipoprotein, HGB= Hemoglobin, WBC= whlte blood test, PLT= platelets

Table 2. Disease status of the participants.

		Patients (n=211)
DM	With [n (%)]	102 (48.3%)
	Without [n (%)]	109 (51.7%)
HTN	With [n (%)]	107 (50.7%)
	Without [n (%)]	104 (49.3%)
H. Pylori	Positive [n (%)]	91 (43.1%)
	Negative [n (%)]	120 (56.9%)
Thyroid function	Euthyroid [n (%)]	101(47.9%)
	Hypothyroidism [n (%)]	110 (52.1%)
Thyroid profile	TSH μUI/mL [Mean (SD)]	8.05 (9.73)
	Free T3 pg/mL [Mean (SD)]	2.05 (0.82)
	Free T4 ng/dL [Mean (SD)]	1.04 (0.44)
Thyroxine dose [Mean (SD)]		131.52 (72.92)
Response to treatment	Responsive [Mean (SD)]	159 (75.4%)
	Refractory [Mean (SD)]	52 (24.6%)

DM= diabetes, HTN= hypertension, TSH= thyroid stimulating hormone, Free T3= Free Triiodothyronine, Free T4= free tetraiodothyronine (Thyroxine).

Table 3. Comparison between euthyroid and hypothyroid participants regarding disease status.

		Euthyroid participants (n=101)	**Hypothyroid participants (n=110)**	***P*-value**
DM	With [n (%)]	50 (49.5%)	52 (47.3%)	0.746
	Without [n (%)]	51 (50.5%)	58 (52.7%)	
HTN	With [n (%)]	55 (54.5%)	52 (47.3%)	0.297
	Without [n (%)]	46 (45.5%)	58 (52.7%)	
H. pylori	Positive [n (%)]	32 (31.7%)	59 (53.6%)	0.001*
	Negative [n (%)]	69 (68.3%)	51 (46.4%)	
Thyroid profile	TSH μUI/mL [Mean (SD)]	2.12 (1.41)	13.50 (10.87)	< 0.001*
	Free T3 pg/mL [Mean (SD)]	2.43 (0.84)	1.70 (0.64)	< 0.001*
	Free T4 ng/dL [Mean (SD)]	1.31 (0.39)	0.79 (0.32)	< 0.001*
Thyroxine dose [Mean (SD)]		118.56 (63.99)	143.41 (78.67)	0.012*
Response to treatment	Responsive [Mean (SD)]	86 (85.1%)	73 (66.4%)	0.002*
	Refractory [Mean (SD)]	15 (14.9%)	37 (33.6%)	

Table 4. Relationship between response to treatment and *Helicobacter pylori* infection.

		Responsive to treatment (n= 159)	**Refractory to treatment (n= 52)**	***P*-value**
H. pylori	**Positive** (n= 91) [n (%)]	51 (32.1%)	40 (76.9%)	<0.001*
	Negative (n =120) [n (%)]	108 (67.9%)	12 (23.1%)	

Figure 1. Difference between euthyroid and hypothyroid participants regarding response to treatment.

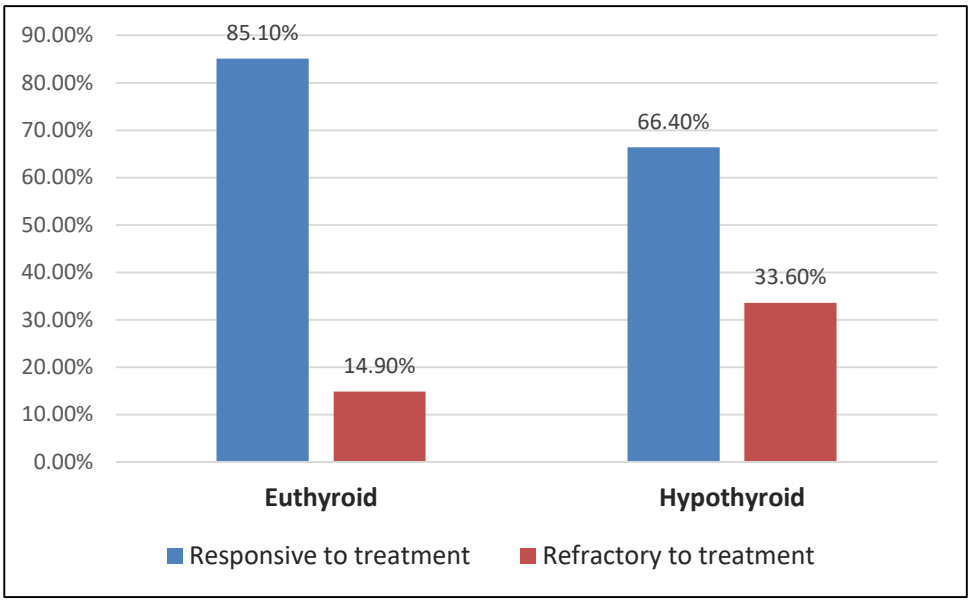
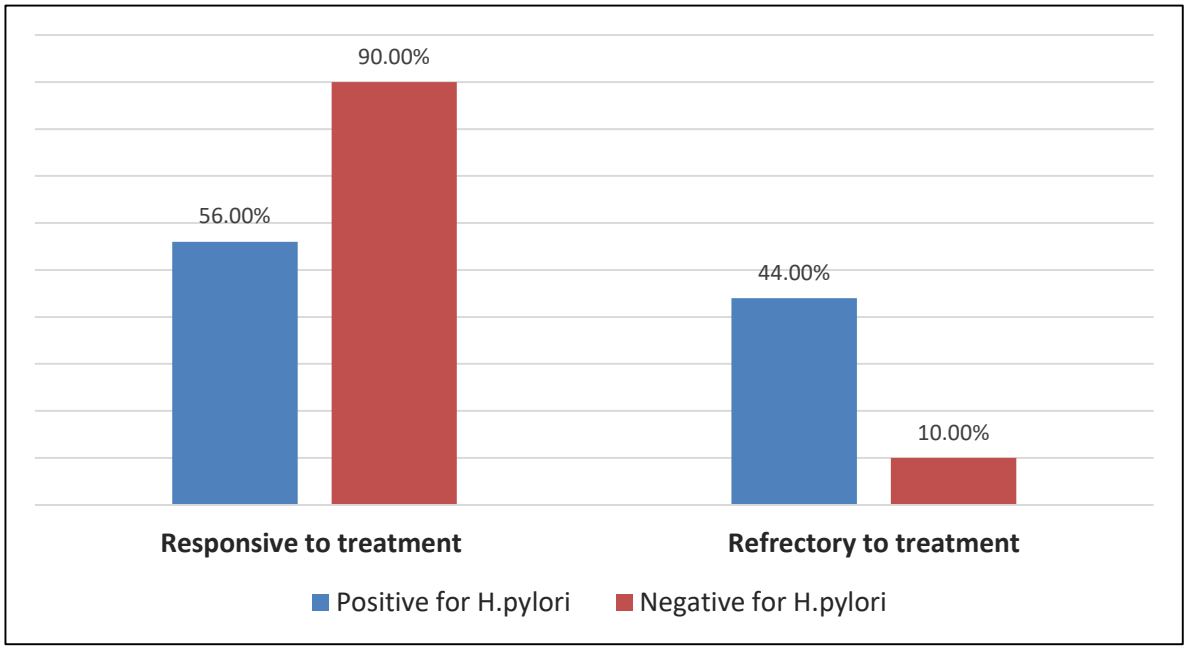


Figure 2. Relationship between *H. pylori* infection and response to treatment.



Discussion

This case-control study found an association between *H. pylori* infection with treatment-refractory hypothyroidism. The frequency of *H. pylori* infection was significantly different in both groups with *p* value <0.001.

One of the most prevalent endocrinology conditions outside of consultation is hypothyroidism, which results from decreased endogenous thyroxine synthesis. A wide range of clinical symptoms may be present. Thyroxine deficiency affects nearly every organ system in the body and is associated with increased morbidity and mortality [12]. Weight-based therapy is the suggested approach for thyroxine replacement to prevent health complications and improve quality of life [13]. Resistant hypothyroidism is a condition that arises when treatment with appropriate weight-based thyroxine (1.6 mcg/kg/day) is not sufficient to produce euthyroid status and the TSH level continuously exceeds the therapeutic level. This results in an increasing amount of thyroxine dose up titration, ongoing disease morbidity, and an impact on patient compliance and costs [14].

Therapeutic blood levels of thyroxine are contingent upon several factors, such as gastrointestinal malabsorption states, patient compliance, and thyroxine-drug interactions [15]. In this case, refractory hypothyroidism may be brought on by insufficient oral thyroxine absorption, which may be made worse by *H. pylori* infection [15]. However, the amount of data regarding resistant hypothyroidism does not conclusively support the role of *H. pylori*. This study was conducted to examine the association between *H. pylori* infection and treatment-resistant hypothyroidism in order to assist endocrinologists and general practitioners in managing this condition more effectively.

In this study, there were two groups: the patients, who were treated with daily thyroxine but had refractory chronic hypothyroidism, and the controls, who had a euthyroid biochemical profile. Overall, 43.1% of participants in the study had *H. pylori* infection, which is consistent with results from another study conducted by **Li et al.** [16]. A statistically significant correlation (p value <0.001) was observed in our study between *H. pylori* infection and refractory hypothyroidism. These results were consistent with the findings of **Bugadi et al**. who reported a significant correlation between these parameters [15]. Prior researches such as **Nazmy et al.** discovered that a significant proportion of individuals diagnosed with thyroid conditions also carried *H. pylori* infection, indicating that these bacteria are essential to the pathophysiology of thyroid-related disorders [17].

To further stratify the data, impact modifiers such as age, sex, and BMI were applied. Women were substantially more likely than men to be hypothyroid [16]. It corresponded with existing data, suggesting that women make up a sizable portion of hypothyroid patients.

Our try to mention in the current study emphasizes the importance of routine testing for refractory hypothyroidism because, in our patient population, there is a strong correlation between this illness and *H. pylori* infection. The fact that our study only had a small number of participants and was single-centered presented challenges. To further explore this connection, more multicentered studies using assessments with enhanced diagnostic validity are needed..

Conclusion

In conclusion, our study's findings demonstrated a robust correlation between *H pylori* infection and hypothyroidism, as well as a high frequency of both conditions that are resistant to treatment.

List of abbreviations

TSH: thyroid stimulating hormone, LT4: levothyroxine therapy, H. pylori: helicobacter pylori, SD: standard deviation, CBC: Complete blood count, Screat: serum creatinine, ALT: Alanine transaminase, AST: aspartate transaminase, BMI: body mass index, Free T3= Free Triiodothyronine, Free T4= free tetraiodothyronine (Thyroxine).

Conflicts of interests

None declared.

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