Prevalence of undiagnosed thyroid dysfunction in correlation with *Helicobacter pylori* infection: cross-talk between Hashimoto's thyroiditis and *Helicobacter pylori*

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Background
Worldwide, the prevalence of thyroid dysfunction is increasing and it is one of the leading endocrine disorders. The objective of the present study was to assess the prevalence of undiagnosed thyroid dysfunction and its association with *Helicobacter pylori* (HP) infection and to clarify the association between HP and Hashimoto's thyroiditis.
Patients and methods
A cross-sectional study was conducted among 300 unrelated patients; 187 patients had normal thyroid function and 113 patients had thyroid dysfunction. The patients were stratified into one of the following five groups based on the reference of the normal thyroid function test; thyroid-stimulating hormone and free thyroxine were used as the screening tests to diagnose thyroid dysfunction. HP antigen in the stool and antibodies against cytotoxin-associated gene A (cag-A), anti-thyroid peroxidase (anti-TPO) antibodies, and anti-thyroglobulin (anti-TG) antibodies were measured.
Results
Our results show that the prevalence of thyroid dysfunction was found in 37.6% of the studied population. The most frequent dysfunction was subclinical hypothyroidism (44.4%), followed by overt hypothyroidism (20.6%). Interestingly, the prevalence was higher in association with HP infection diagnosed by HP antigen and cag-A antibodies. There was statistically significant positive correlation between HP antigen and anti-TPO as well as anti-TG. Regarding cag-A. There were statistically significant positive correlations between antibodies against cag-A and anti-TG as well as anti-TPO. Interestingly, stepwise linear regression analysis showed that serum thyroid-stimulating hormone levels were independently correlated with free thyroxine, HP.
Conclusion
The higher prevalence of thyroid dysfunction as observed in the current study was associated with Hashimoto's thyroiditis. Further future multicenter studies with a bigger sample size are needed to validate our findings.

Keywords:
anti-thyroid peroxidase, anti-thyroglobulin, cytotoxin-associated gene, Helicobacter pylori, Hashimoto's, thyroiditis, prevalence, thyroid dysfunction

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Introduction

Worldwide, the incidence of individuals with thyroid dysfunction is increasing and represents around 30% of the patients attending the endocrinology outpatient clinic[1]. Emerging evidence demonstrated that the prevalence of thyroid dysfunction varies according to age, sex, geographical factors, and iodine intake [2]. It is now widely accepted that hypothyroidism is more common in women than men and its prevalence increases with age [3]. Remarkably, among thyroid dysfunction diseases, subclinical hypothyroidism is the most common thyroid dysfunction [4].

Hashimoto's thyroiditis (HT) is an autoimmune thyroid disease [5]. Mounting evidence indicates that both genetic and environmental factors are involved in the pathogenesis of HT [6]. The suspected pathological causes of HT included environmental factors, bacteria, and viruses. There is now overwhelming evidence that different factors are suspected of being able to mimic the antigenic profile on the thyroid membrane, thus they have an important role in the pathogenesis of HT [7].

Helicobacter pylori (HP) is a Gram-negative, mobile bacterium, which typically colonizes and infect the gastric mucosa; the most virulent strains can be identified by the presence of the cytotoxin-associated gene A (cag-A) antigen [4]. There is compelling

evidence suggesting that antibodies against HP antigens cross react with the thyroid tissue [8]. The results of limited studies regarding the influence of HP as an environmental risk factor that may ameliorate the risk of HT are unclear. In light of the above, the objective of the present study was to assess the prevalence of undiagnosed thyroid dysfunction and its association with HP and to clarify the cross-talk between HP and HT.

Patients and methods

Patients

A cross-sectional study was conducted among 300 unrelated patients recruited from the diabetes and endocrinology outpatient clinic of Internal Medicine Department of Zagazig University Hospitals. Out of the studied 187 patients who had normal thyroid function and 113 patients who had thyroid dysfunction, the patients were stratified into one of the following five groups based on the reference of the normal thyroid function test. Notably, the American Thyroid Association recommends the combined use of thyroid-stimulating hormone (TSH) and free thyroxine (FT4) as the most efficient combination of blood tests for the diagnosis and follow-up of both ambulatory and hospitalized patients [9].

Diagnosis of HT was obtained based on clinical findings, positive serum antibodies to thyroid peroxidase (TPO Ab), and/or thyroglobulin (TG Ab). All participants underwent complete history taking and thorough clinical examination including BMI. Exclusion criteria included patients with a history of stroke, respiratory disease, heart failure, cancer, severe hepatic, renal diseases, acute illness, hormonal therapy, and active inflammatory diseases as well as antimicrobial drugs use for at least 3 months. We excluded patients with dyspeptic symptoms (epigastria pain, nausea, and heartburn), gastric diseases, or previous treatment for HP eradication. The ethics committee of Faculty of Medicine, Zagazig University approved our study protocol, and all the participants assigned a written informed consent.

Blood sampling

Blood samples were drawn from all patients after an overnight fast. Sera were separated after 1 h longstanding and stored at −80°C.

Biochemical measurements

We determined the fasting plasma glucose using the glucose oxidase method (Spinreact, Girona, Spain). Total cholesterol (TC), high-density lipoprotein cholesterol, and triglycerides (TG) were measured by routine enzymatic methods (Spinreact). Low-density lipoprotein cholesterol was calculated using the Friedewald formula [10].

Assay of thyroid function and autoantibody levels

The serum concentration of FT4, free triiodothyronine (FT3), serum thyrotropin (TSH) concentration, serum anti-TPO, and serum anti-TG were measured by Roche Cobas 8000-e602; Roche Diagnostics, Penzberg, Germany

Stool analysis for *Helicobacter pylori* antigen

Fresh stool samples were obtained and tested using rapid diagnostic test (HP Ag Rapid Test CE; CTK Biotech, San Diego, California, USA) for the detection of [11] HP antigen. Special IgE antibodies against cag-A will be done in the sera of all patients with HP-positive antigen by enzyme-linked immunosorbent assay method (Biokit S.A., Spain) [12].

Statistical analysis

Data were expressed using descriptive statistic (mean ±SD) and were analyzed. One-way analysis of variance test was done to compare the different parameters between more than two groups. The statistically significant differences in the frequencies of variants between the groups were tested using the χ^2 test. Multiple stepwise linear regression analysis was performed to detect the main predictors of TSH levels. *P* values were considered significant if less than 0.05. Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (version 20.0; SPSS Inc., Chicago, Illinois, USA).

Results

In an attempt to assess the prevalence of thyroid disorders this cross-sectional study was conducted among patients recruited from the outpatient clinic of Internal Medicine Department of Zagazig University Hospitals. Out of the 300 patients randomized, 113 (37.6%) had thyroid disorders. Among the various varieties of thyroid disorders, our study reported that the prevalence of clinical and subclinical hypothyroidism was 44.4 and 20.6%, respectively. Regarding hyperthyroidism, our results showed that the prevalence of clinical and subclinical hyperthyroidism was 19.2 and 15.8%, respectively.

Clinical and laboratory characteristics of the participants

Patients with thyroid dysfunction had statistically significant higher values of systolic blood pressure, TC, and TG compared with the euthyroid group

Table 1 Clinical, anthropometric, and biochemical characteristics of the studied groups

Parameters	Euthyroid group (*N*=187)	Thyroid dysfunction group (*N*=113)	*P* value
Age (years)	32.18±8.63	31.64±7.35	0.746
Sex (male/female)	32/155	16/97	0.179
Systolic blood pressure	122.34±7.25	137.52±7.07	<0.001*
Diastolic blood pressure	86.24±3.95	85.68±l4.182	0.466
Waist/hip ratio	1.091±0.244	1.167±0.30	0.149
BMI (kg/m^2)	28.58±5.425	29.38±5.87	0.445
Total cholesterol (mg/dl)	168.6±19.6	202.16±13.49	<0.001*
HDL cholesterol (mg/dl)	54.56±6.8	36.77±6.06	<0.001*
LDL cholesterol (mg/dl)	115.38±17.71	121.7±17.98	0.058
Triglycerides (mg/dl)	167.4±5.8	259.64±34.52	<0.001*
FPG (mg/dl)	86.34±9.261	89.18±9.187	0.098
FT3 (pg/ml)	0.70±0.181	1.019±0.208	<0.001*
FT4 (ng/dl)	1.05±0.347	2.43±1.2101	<0.001*
TSH (μIU/ml)	2.5±0.97	6.5±4.97	<0.001*
Anti-TPO (IU/ml)	58. 33±23.23	98.55 ±43.9	<0.001*
Anti-TG (IU/ml)	1.87±0.62	2.47±0.52	<0.001*

Anti-TG, anti-thyroglobulin; anti-TPO, anti-thyroid peroxidase; FPG, fasting plasma glucose; FT3 free triiodothyronine; FT4, free thyroxine; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TSH, thyroid-stimulating hormone. **P* value less than 0.05 when compared with the euthyroid group.

(Table 1). Regarding thyroid function tests, patients with thyroid dysfunction had higher anti-TPO, anti-TG, FT3, FT4, and TSH. On the other hand, patients with thyroid dysfunction had statistically significant lower values of high-density lipoprotein compared with the euthyroid group.

Association of thyroid disorders with clinical and biochemical characteristics

Thyroid dysfunction patients were classified according to the thyroid state. Our results detected statistically significant higher systolic and diastolic blood pressures as well as waist/hip ratio, BMI, TC, TG, and low-density lipoprotein in subclinical and clinical hypothyroidism compared with the euthyroid group. In addition, patients with hyperthyroidism had higher values of TG compared with the euthyroid group. As expected, our results demonstrated higher values of anti-TPO, anti-TG, FT3, FT4, and TSH in patients with subclinical and clinical hypothyroidism, while in the subclinical and clinical hyperthyroidism, there were higher levels of anti-TPO, anti-TG, FT3, and FT4 compared with the euthyroid group. TSH levels were statistically significantly lower in subclinical and clinical hyperthyroidism compared with the euthyroid group, *P* value less than 0.001 (Table 2).

Prevalence of anti-thyroid peroxidase (IU/ml) and anti-thyroglobulin (IU/ml) among the studied groups

Our results observed that the prevalence of +ve anti-TPO was more common in subclinical (84.5%) and clinical hypothyroidism (54.5%) compared with the euthyroid group (18.2%). Regarding anti-TG, the prevalence of +ve anti-TG was more common in subclinical (69%) and clinical hypothyroidism (83.9%) compared with the euthyroid group (13.4%). Nonetheless, regarding both anti-TPO and anti-TG the higher prevalence did not reach statistically significant difference, *P* value is less than 0.001 (Table 3).

Prevalence of *Helicobacter pylori* infection and cytotoxin-associated gene A-positivity among the studied groups

Our results perceived that there were statistically significant higher prevalence of +ve HP in subclinical (75.9%) and clinical hypothyroidism (54.8%) compared with the euthyroid group (36.4%). Regarding cag-A, the prevalence of +ve cag-A was more common in subclinical (75.9%) and clinical hypothyroidism (71%) compared with the euthyroid group (27.5%). Moreover, the prevalence of +ve HP was more common in subclinical (64.3%) and clinical hyperthyroidism (70%) compared with the euthyroid group (36.4%). Regarding cag-A, the prevalence of +ve cag-A was more common in subclinical (71.4%) and clinical hyperthyroidism (80%) compared with the euthyroid group (27.5%), *P* value less than 0.001 (Table 4).

Correlation between *Helicobacter pylori* infection and thyroiditis antibodies

Our results observed statistically significant positive correlation between HP antigen and anti-TPO (Fig. 1) as well as anti-TG (Fig. 2). Regarding cag-A, our results observed a statistically significant positive correlation between antibodies against cag-A and anti-TG (Fig. 3) as well as anti-TPO (Fig. 4).

Linear regression analyses to test the influence of the main independent variables against thyroid-stimulating hormone levels (dependent variable)

Stepwise linear regression analysis showed that serum TSH levels were independently correlated with FT4, HP antigen, and BMI, *P* value is less than 0.001 (Table 5).

Table 2 Anthropometric and biochemical characteristics of the studied groups

Parameters	SCHT (*N*=58)	CHT (*N*=31)	Subclinical hyperthyroidism (*N*=14)	Hyperthyroidism (*N*=10)	Euthyroid (*N*=187)
Age (years)	33.19±8.08	29.72±9.55	31.46±7.25	31.8±7.60	32.08±8.63
Sex (male/female)	8/50	4/27	3/11	2/8	32/155
Systolic blood pressure	146.2±5.7*	136.8±6.1*	138.1±2.1	133.8±5.3	122.34±7.25
Diastolic blood pressure	93.1±4.7*	92.1±5.6*	86.8±4.3	85.8±2.9	86.24±3.95
Waist/hip ratio	1.446±0.11*	1.49±0.18*	1.21±0.11	1.21±0.11	1.091±0.244
BMI (kg/m^2)	39.82±2.6*	42.57±1.72*	30.9±1.7	32.0±1.58	28.58±5.425
Total cholesterol (mg/dl)	199.9±11.7*	208.4±11.8*	178±18.01	193.5±25.2	168.6±19.6
Triglycerides (mg/dl)	266.9±24.4*	301.5 ±33.56*	232.6±8.8	209.6±9.9*	141.56±6.8
LDL cholesterol (mg/dl)	128.9±36.8*	148.5±4.9*	85.9±30.84	63.7±10.60	115.38±17.71
HDL cholesterol (mg/dl)	33.7±4.935*	33.78±2.15*	43±2.549	44.8±3.97*	54.56±6.8
FPG (mg/dl)	102.4±9.6*	121.1±9.0*	93.4±6.80	89±7.21	86.34±9.261
FT3 (/ml)	2.81±0.52*	2.12±0.35*	2.44±0.33*	1.01±0.416	0.70±0.181
FT4 (ng/dl)	3.01±0.52*	2.32±0.811*	2.64±0.733*	3.22±0.45	1.05±0.347
TSH (μIU/ml)	8.62±1.56*	18.48 ±10.82*	0.113±0.01*	0.107±0.01*	2.5±0.97
Anti-TPO (IU/ml)	77.32±3.58*	85.2±2.62*	83.1±2.522*	70.4±3.03*	58. 33±23.23
Anti-TG (IU/ml)	2.49 ±0.12*	2.75±0.46*	2.72±0.651*	2.63±0.58*	1.87±0.62

Anti-TG, anti-thyroglobulin; anti-TPO, anti-thyroid peroxidase; CHT, clinical hypothyroidism; FPG, fasting plasma glucose; FT3 free triiodothyronine; FT4, free thyroxine; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SCHT, subclinical hypothyroidism; TSH, thyroid-stimulating hormone. *P value less than 0.05 when compared with the euthyroid group.

Table 3 Prevalence of anti-thyroid peroxidase (IU/ml) and anti-thyroglobulin (IU/ml) among the studied groups

Parameters	SCHT (*N*=58) [*n* (%)]	CHT (*N*=31) [*n* (%)]	Subclinical hyperthyroidism (*N*=14) [*n* (%)]	Hyperthyroidism (*N*=10) [*n* (%)]	Euthyroid (*N*=187) [*n* (%)]	χ^2	*P*
Anti-TPO							
+ve	49 (84.5)	17 (54.8)	6 (42.9)	4 (40)	34 (18.2)	26.49	0.25
–ve	9 (15.5)	14 (45.2)	8 (57.1)	6 (60)	153 (81.8)		
Anti-TG							
+ve	40 (69)	26 (83.9)	0 (0)	0 (0)	25 (13.4)	121.1	0.19
–ve	18 (31)	5 (16.1)	14 (100)	10 (100)	162 (86.6)		

CHT, clinical hypothyroidism; SCHT, subclinical hypothyroidism; TG, thyroglobulin; TPO, thyroid peroxidase. *P value less than 0.05.

Discussion

HP infection has noteworthy public health consequences; hence, it is the most common human infection worldwide on the basis of the fact that ~50% of the world's populations are infected and that human beings are the main reservoir [13]. Emerging evidence demonstrated that the prevalence of thyroid dysfunction varies among populations of the same race in different geographical areas. Thereby, this study was carried out to investigate the prevalence of undiagnosed thyroid dysfunction. In addition, we aimed to investigate the association of thyroid dysfunction with HP infection and to explore the cross similarity between thyroiditis and HP infection regarding their pathogenesis.

Our study showed clear evidence that the prevalence of thyroid dysfunction was found in 37.6% of the studied population. Among thyroid dysfunction groups, the most common thyroid dysfunction is subclinical hypothyroidism (51.3%), followed by overt hypothyroidism (27.4%). However, the prevalence of hyperthyroidism was about 8.8% and 12.3% of the thyroid dysfunction group had subclinical hyperthyroidism. Previous studies also investigated the prevalence of thyroid disorders in a population-based study conducted on Indian populations. The most common thyroid disorders were subclinical hypothyroidism [14].

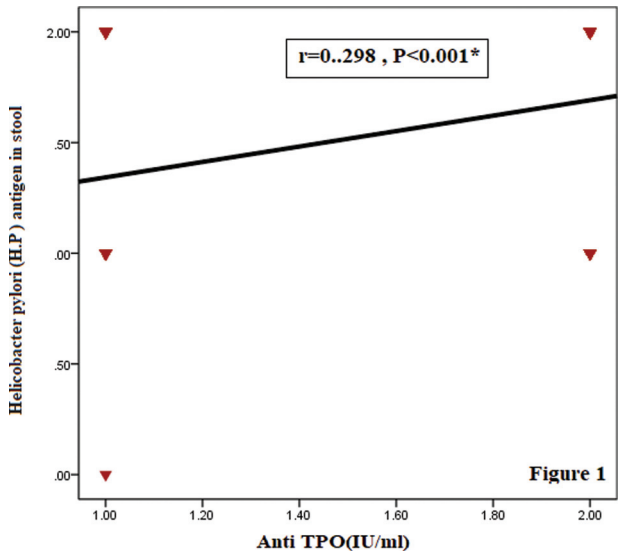
Regarding the prevalence of thyroid diseases in Arab countries, in a Saud Arabian study, the researchers showed clear evidence that the prevalence of thyroid disorders in Makkah region was very high, about 47.34% [15]. The study conducted by Nouh *et al.* [16] in Libya observed that the prevalence of hypothyroidism was 6.18%.

Table 4 Prevalence of *Helicobacter pylori* infection and cytotoxin-associated gene A-positivity among the studied groups

Parameters	SCHT (*N*=58) [*n* (%)]	CHT (*N*=31) [*n* (%)]	Subclinical hyperthyroidism (*N*=14) [*n* (%)]	Hyperthyroidism (*N*=10) [*n* (%)]	Euthyroid (*N*=187) [*n* (%)]	χ^2	*P*
HP							
+ve	44 (75.9)	17 (54.8)	9 (64.3)	7 (70)	68 (36.4)	17.05	0.004
–ve	14 (24.1)	14 (45.2)	5 (35.7)	3 (30)	119 (63.6)		
Cag-A							
+ve	44 (75.9)	22 (71)	10 (71.4)	8 (80)	52 (27.8)	41.6	0.025
–ve	14 (24.1)	9 (29)	4 (28.6)	2 (20)	135 (72.2)		

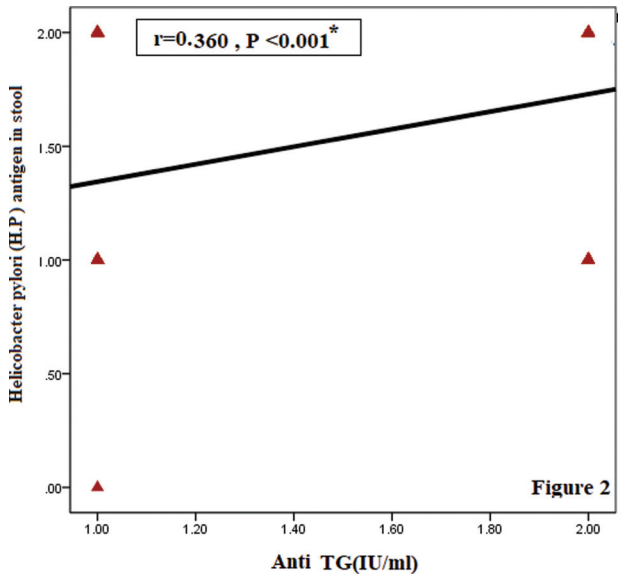
Cag-A, antibodies against cytotoxin-associated gene A; CHT, clinical hypothyroidism; HP, *Helicobacter pylori*; SCHT, subclinical hypothyroidism. **P* value less than 0.05.

Figure 1



Correlation between *Helicobacter pylori* antigen and anti-TPO (IU/ml). TPO, thyroid peroxidase.

Figure 2



Correlation between *Helicobacter pylori* antigen and anti-TG (IU/ml). TG, thyroglobulin.

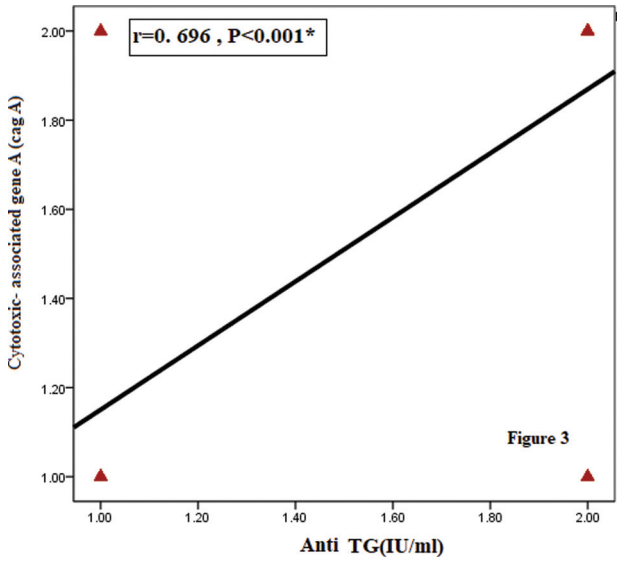
Even more interestingly findings from other researchers suggested that the prevalence of subclinical hypothyroidism was 2.3% [17]. Here, the evidence for these studies will be scrutinized and compared to provide a robust analysis of current knowledge. These results are in agreement with the results that were conducted in Delhi by Marwaha *et al.* [18]. They reported increasing the prevalence of subclinical hypothyroidism to reach about 19.3% of the study populations. A study by Yang *et al.* [19] found that the prevalence of hyperthyroidism varied between 1.2 and 2%, whereas subclinical hyperthyroidism oscillated between 1.1 and 3.9% depending on the iodine intake.

Regarding sex distribution, the present study demonstrated that thyroid dysfunctions were more common in women than men. Notably, our findings showed that female frequencies were more common in subclinical hypothyroidism and clinical hypothyroidism. On the other hand, men were more common in subclinical hyperthyroidism and clinical hyperthyroidism groups. These results were supported previously by Golden *et al.* [20] who reported that the percentage of hypothyroidism was higher for women than for men.

The main finding of the present study is that there were statistically significant higher prevalence of +ve HP and cag-A in subclinical and clinical hypothyroidism compared with the euthyroid group. Likewise, the prevalence of +ve HP was more common in subclinical and clinical hyperthyroidism compared with the euthyroid group.

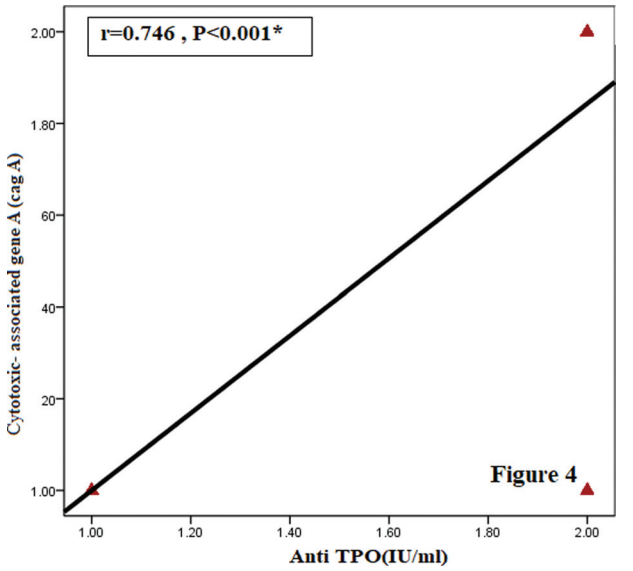
Concerning cag-A, the prevalence of +ve cag-A was more common in subclinical and clinical hyperthyroidism compared with the euthyroid group. Similar results were described in the Korani *et al.* [21] study; they investigated the relation between thyroiditis and HP infection and they found a statistically significant association between HP infection and HT.

Figure 3



Correlation between antibodies against cytotoxin-associated gene A (cag-A). TG, thyroglobulin.

Figure 4



Correlation between antibodies against cytotoxin-associated gene A (cag-A) and anti-TPO (IU/ml). TPO, thyroid peroxidase.

Table 5 Multiple stepwise linear regression analysis in the thyroid dysfunction group to test the influences of the main independent variables against thyroid-stimulating hormone levels (dependent variable)

Model	Unstandardized coefficients		Standardized coefficients	*t*	*P*	95% CI	
	B	SE	Beta			Lower bound	Upper bound
1							
Constant	8.278	0.276		30.044	<0.001*	7.736	8.821
FT4	–2.447	0.132	–0.731	–18.467	<0.001*	–2.708	–2.186
2							
Constant	0.403	1.275		0.316	0.752	–2.105	2.912
FT4	–2.413-	0.125	–0.720	–19.342	<0.001*	–2.658	–2.167
BMI	0.295	0.047	0.235	6.310	<0.001*	0.203	0.387
3							
Constant	–0.327	1.276		–0.256	0.798	–2.839	2.185
FT4	–2.393	0.123	–0.714	–19.448	<0.001*	–2.635	–2.151
BMI	0.276	0.046	0.220	5.940	<0.001*	0.184	0.367
HP	0.745	0.235	0.118	3.177	<0.001*	0.284	1.207

CI, confidence interval; FT4, free thyroxine; HP, *Helicobacter pylori*. **P* value less than 0.05.

Similarly, reports of Bertolat *et al.* [22] showed that individuals with high titer of anti-TPO were significantly infected by HP and treatment of HP causes significant reduction in anti-TPO Ab.

Similar results observed by de Luis *et al.* [23] found higher titer of anti-HP IgG Ab in Graves' and HT compared with the control group.

These similar results could be contributed to the fetal and structural similarities of these two organs; thyroid and stomach as HP infection could trigger the mechanism of autoimmune reaction such as increased thyroid antibodies [24]. On the contrary, a study by Tomasi *et al.* [25] found no association between HP infection and thyroiditis.

To better elucidate the association between HP infection and thyroiditis, our results observed a statistically significant positive correlation between HP antigen and anti-TPO as well as anti-TG. Regarding cag-A, there were statistically significant positive correlations between antibodies against cag-A and anti-TG as well as anti-TPO. Interestingly, stepwise linear regression analysis showed that serum TSH levels were independently correlated with FT4, HP. An interesting study from Bassi *et al.* [26]

demonstrated positive correlation between HP infection and GD, independent of the hormonal status.

Additionally, Bassi *et al.* [27] found increased HP prevalence only in hyperthyroid GD patients, but not in hypothyroid HT patients, although the strains involved in both GD and HT are, prevalently, carriers of cag-A antigens. There are intriguing reports suggesting that both GD and HT had higher prevalence of cag-A positive strains in HP-positive patients [28].

Conclusion

The prevalence of thyroid dysfunction was found in 37.6% of the studied population; the most frequent dysfunction was subclinical hypothyroidism (44.4%), followed by overt hypothyroidism (20.6%). Interestingly, the prevalence was higher in association with HP infection diagnosed by HP antigen and cag-A antibodies. Even more importantly, the higher prevalence of thyroid dysfunction was associated with HT.

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Conflicts of interest

There are no conflicts of interest

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