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EFFECT OF HELICOBACTER PYLORI RELATED GASTRITIS ON THE RISK OF METABOLIC SYNDROME

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ABSTRACT

Evidence indicates that HP infection is also associated with metabolic syndrome. Specifically, a cross-sectional study of a large population of Japanese adults evaluated the concentration of HP-specific immunoglobulin G (IgG) and found that HP-infected subjects had a significantly higher risk of Metabolic syndrome (Gunji et al., 2008). Also, Chen et al, found similar relationship between H. pylori and metabolic syndrome. The underlying mechanisms of the metabolic syndrome-HP relationship remain unknown, although chronic inflammation is presumed to play a key role. Specifically, HP infection induces chronic gastritis and local chronic inflammation, stimulating the production of response inflammatory proteins and cytokines such as C-reactive protein, tumor necrosis factor alpha (TNF-a), interleukins (IL-1, IL-6, IL-8, IL-10), and eicosanoids (D'Elios and Czinn, 2014). As overexpression of these proteins contributes to the pathogenesis of Metabolic syndrome, therefor the risk of Metabolic syndrome is expected to be affected by the inflammatory burden associated with HP infection

Introduction

Helicobacter pylori (HP) is a spiral-shaped bacterium that resides in the human gastric mucosal layer or adheres to the epithelial lining of the stomach. HP infection usually occurs in child hood and persists for a long time. HP infection is involved in gastric diseases such as chronic gastritis, gastric ulcer, and gastric adenocarcinoma (Malfertheiner et al., 2012).

Although most HP infections are limited to the stomach, associations with certain extra-gastric manifestations has been noted, including iron-deficiency anemia, vitamin deficiency, obesity, impaired glucose tolerance, insulin resistance, and cardiovascular diseases .

Metabolic syndrome (MetS) is an insulin-resistant state induced by a combination of risk factors that precedes-type 2 diabetes and may lead to increased cardiovascular morbidity .

Evidence indicates that HP infection is also associated with metabolic syndrome. Specifically, a cross-sectional study of a large population of Japanese adults evaluated the concentration of HP-specific immunoglobulin G (IgG) and found that HP-infected subjects had a significantly higher risk of Metabolic syndrome . Also, Chen et al, found similar relationship between H. pylori and metabolic syndrome .

On the other hand, Naja et al., 2012, concluded that no obvious relationship could be found between the two conditions . These discrepancies may be related to the variation in HP-infection and gastritis status in the study populations.

The underlying mechanisms of the metabolic syndrome-HP relationship remain unknown, although chronic inflammation is presumed to play a key role. Specifically, HP infection induces chronic gastritis and local chronic inflammation, stimulating the production of response inflammatory proteins and cytokines such as C-reactive protein, tumor necrosis factor alpha (TNF-a), interleukins (IL-1, IL-6, IL-8, IL-10), and eicosanoids ''. As overexpression of these proteins contributes to the pathogenesis of Metabolic syndrome, therefor the risk of Metabolic syndrome is expected to be affected by the inflammatory burden associated with HP infection .

From a different perspective, HP infection may also be associated with malnutrition, as growth retardation is suspected in HP-infected children, and weight gain has also been observed after HP eradication .

Francois et al., 2011, reported HP eradication altered circulating meal-associated leptin and ghrelin levels and body mass index (BMI). The decrease in gastric secretory function may partially account for this HP-related malnutrition, as the levels of gastric hormones such pepsinogen (PG) I, gastrin, and ghrelin are known to decrease with the progression of atrophic gastritis . The decrease in ghrelin secretion induces loss of appetite, which influences food intake and body weight. This phenomenon likely affects the relationship between Metabolic syndrome and HP infection, suggesting an inverse effect of HP infection on over-nutrition and related Metabolic syndrome pathogenesis .

Furthermore, some reports suggested that atrophic gastritis, but not HP infection status, is associated with body mass index (BMI) .
Aim of the work

The aim of this study is to investigate the correlations of Helicobacter pylori infection and atrophic gastritis status on the risk of metabolic syndrome.

SUBJECTS AND METHODS

The current study is a Prospective cross sectional study conducted on:-

Group I: 34 patients of metabolic syndrome. Age ranges between 22 to 64years old; 21 male and 13 females, recruited from endoscopy unit at Minia university hospital from April 2017 to April 2018.

Diagnosis of metabolic syndrome is based on the revised National Cholesterol Education Program's Adult Treatment Panel III guidelines upon fulfilling three or more of the following criteria: abdominal obesity (waist circumference ≥ 94cm and ≥ 80cm for Egyptian men and women, respectively); triglyceride levels ≥ 150mg/dL; HDL cholesterol levels ≤ 40mg/dL and 50mg/dL for men and women, respectively; systolic/diastolic blood pressure ≥ 130/85mmHg or receiving medical treatment; and fasting plasma glucose levels ≥ 100mg/dL.

Group II: included 26 healthy subjects (14 male and 12 females) as a control group matched for age and sex.

Exclusion criteria:

Patients having any one of the following criteria were excluded from study:

1- Patients receiving medical treatment for hyperlipidemia or diabetes mellitus.
2- Patients with history of antibiotic treatment against HP.
3- Patients with advanced liver or renal dysfunction and neoplasms.

Clinical Study

Whole patient group was classified according to H.Pylori IgG status into two main groups:

*Group A: H.Pylori seronegative where HP-specific IgG levels (< 10 U/mL)

*Group B: H.Pylori seropositive where HP-specific IgG levels (≥10 U/mL), which is then sub classified into 3 subgroups:

*Group B1: Low positive where HP-specific IgG levels (10-30 U/mL).

*Group B2: Moderate positive where HP-specific IgG levels (30-50 U/mL).

*Group B3: High positive where HP-specific IgG levels (≥ 50 U/mL).

All subjects were subjected to the following:
1- Thorough History Taking.
Subject answered a standard questionnaire that included:

Personal history with special attention to name, age, sex, weight, height, residence, marital status, occupation and special habits of medical importance as cigarette smoking and daily alcoholic intake in the past 6 months.

2-Thorough clinical examination and Anthropometric measures:
Height, weight, and waist circumference &calculation of body mass index [BMI = weight (kg) / height (m2)] & Sitting blood pressure measurement after a 5-minute rest.

-Systolic and diastolic blood pressure were measured after 5 min of rest. Hypertension was defined as a previous medical diagnosis or tablets for treatment, or blood pressure > 140/90 mmHg according to European society of hypertension and the European society of cardiology (ESH/ESC) guidelines .

-Calculation of body mass index as proposed by the National institute of health; BMI= weight in kg. / (Height) meter2.

Body mass index (BMI) was defined as weight in kilograms divided by the square of the height in meters. Obesity was defined as a body mass index (BMI) of ≥30 kg/m2.

Interpretation of body mass index.

Underweight	18.5 or less
Normal weight	18.5 to 24.99
Overweight	25 to 29.99
Obesity (class 1)	30 to 34.99
Obesity (class 2)	35 to 39.99
Morbid obesity	40 or greater

(National Institute of Health, 2000)

Ethical aspects:

The study protocol was approved by the Institutional Ethics Committee All patients and control gave informed consent before participating in this study. The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice.

Investigations

1-Laboratory Investigations:
Sampling
5 ml of blood was withdrawn by sterile venipuncture after fasting overnight, left to be clotted then centrifuged and the separated serum was used for the immediate assessment of urea, creatinine, lipid profile and Fasting blood glucose level.

Another sample of same volume of venous blood was withdrawn. 2ml of its used for assessment of HbA1c and the rest for assessment of H.pylori IgG.

The following levels will be measured:
a) Fasting blood glucose level
Assayed using fully automated clinical chemistry auto-analyzer system Konelab 60i (Thermo Electron Incorporation, Finland).

b) Hemoglobin A1C (Glycated hemoglobin):
(Glycated hemoglobin) was assayed using boronate affinity by NycoCard READER II.

c) Serum urea & creatinine are measured by fully automated clinical chemistry auto-analyzer system Konelab 60i (Thermo-Electron Incorporation, Finland).

d) Lipid profile: Serum total cholesterol, high-density lipo-protein cholesterol(HDL-C), low-density lipoprotein and triglycerides concentrations assessed using fully automated clinical chemistry auto-analyzer system Konelab 60i (Thermo Electron Incorporation, Finland).

e) Measurement of HP-specific IgG concentration:
By using a commercially available Enzyme-linked Immune-sorbent assay kit.

FFASSESMENT OF H.PYLORI IGG.

By using a commercially available Enzyme-linked immune-sorbent assay kit.

PRINCIPLE OF THE TEST

Purified H. pylori antigen is coated on the surface of microwells. Diluted patients serum is added to the wells, and the H. pylori IgG-specific antibody, if present, binds to the antigen. All unbound materials are washed away. Enzyme conjugate is added, which binds to the antibody-antigen complex. Excess enzyme conjugate is washed off and a solution of TMB Reagent is added. The enzyme conjugate catalytic reaction is stopped at a specific time. The intensity of the color generated is proportional to the amount of IgG-specific antibody in the sample. The results are read by a microwell reader compared in a parallel manner with calibrator and controls.

ASSAY PROCEDURE:

1. Secure the desired number of coated wells in the holder.
2. Prepare 1:40 dilution for test samples, all six H. pylori standards, negative control, and positive control by adding 5 ml of the sample to 200 ml of sample diluent. Mix well.
3. Dispense 100 ml of diluted sera, six standards, and controls into the appropriate wells. For the reagent blank, dispense 100ml sample diluent in 1A well position. Tap the holder to remove air bubbles from the liquid and mix well for 10 seconds.

4. Incubate at room temperature for 30 minutes.
5. At the end of the incubation period, remove liquid from all wells. Rinse and flick the microtiter wells 4 times with diluted wash buffer (1x) and then one time with distilled water.
6. Dispense 100 ml of enzyme conjugate to each well. Mix gently for 10 seconds.
7. Incubate at room temperature for 30 minutes.
8. Remove enzyme conjugate from all wells. Rinse and flick the microtiter wells 4 times with diluted wash buffer (1x) and then one time with distilled water.
9. Add 100 ml of TMB Reagent to each well. Mix gently for 10 seconds.
10. Incubate at room temperature for 20 minutes.
11. Add 100 ml of Stop Solution to each well including the 2 blanks.
12. Mix gently for 30 seconds.

INTERPRETATION OF THE TEST:

H.Pylori seronegative where HP-specific IgG levels (< 10 U/mL)
Low positive where HP-specific IgG levels (10-30 U/mL).
Moderate positive where HP-specific IgG levels (30-50 U/mL).
High positive where HP-specific IgG levels (≥ 50 U/mL).

ASSESSMENT OF GLYCATED HEMOGLOBIN (HbA1c)

Quantitative determination of glycated hemoglobin in whole blood by using Boronate affinity assay (Weykamp et al, 2008).

The test principle

Nyco Card HbA1C is a boronate affinity assay. The kit contains test devices with a porous membrane filter test tubes prefilled with reagent and a washing solution. The reagent contains agents that lyse erythrocytes and precipitate hemoglobin specifically, as well as a blue boronic acid conjugate that binds cis-diols of glycated hemoglobin. When blood is added to the reagent, the erythrocytes immediately lyse. All hemoglobin precipitates. The boronic acid conjugate binds to the cis-diols configuration of glycated hemoglobin. An aliquot of the reaction mixture is added to the test device and all the precipitated hemoglobin, conjugate –bound and unbound, remains on top of the filter .any excess of coloured conjugate is removed with the washing solution. The precipitate is evaluated by measuring the blue (glycated hemoglobin) and the red (total hemoglobin) color intensity with the NycoCard READERII, the ratio between them being proportional to the percentage of HbA1cin the sample.

TEST PROCEDURE

1) Prepare sample:

Add 5 µL whole blood to the test tube with R1/Reagent. Mix well. Leave the tube for minimum 2 minutes, maximum 3 minutes.

2) Apply sample:

Remix to obtain a homogenous suspension. Apply 25 µL of the mixture to a TD/Test device. Hold the pipette approx.0.5cm above the test well and empty the pipette quickly in the middle of the test well. Allow the mixture to soak completely into the membrane. Wait for minimum 10 seconds.

3) Apply R2/Washing solution :

Apply 25 µL R2/Washing solution to the TD/Test Device. Allow the reagent to soak completely into the membrane. Wait for minimum 10 seconds.

4) Read the test result:

Read the test result within 5 minutes using NycoCard READERII

2-Gastric mucosal biopsy:

EGD was done after overnight fasting for 8hours.endoscopy done under mild sedation using I.V midazolam. Examination of esophagus, stomach and duodenum till second part using "Pentax video scope EG-2940"after being disinfected using standard technique.

Examination of stomach showing hyperemic antral mucosa ± superficial erosions and multiple biopsies were taken using biopsy forceps.

Biopsies were preserved in (10% formal saline) till prepared for Histopathological examination through dehydration to prepare paraffin block. Serial tissue sections from each paraffin block were cut at five µm and have been subjected to the following; Routine haematoxylin and eosin staining for reviewing the diagnosis of atrophic gastritis.

Atrophic gastritis defined as chronic gastritis with atrophy of glands and intestinal metaplasia involving antrum, body and fundus mucosa (Rembiasz et al., 2005).

Again another classification was done to whole group of patients according to Gastric Biopsy findings into 2 groups; Atrophic gastritis group and non-atrophic gastritis group.

Statistical analysis:

- Data were analyzed using Statistical Package for the Social Sciences (SPSS), Version 22. Graphics were done by Excel Microsoft office 2010.
- Quantitative data were presented by mean and standard deviation, while qualitative data were presented by frequency distribution.
- Chi-square test was used for comparing qualitative data between two groups.
- Independent sample t- test was used for comparing parametric quantitative data of two groups.
- Mann-Whitney test was used for comparing non-parametric quantitative data between two groups.
- Pearson's correlation was used two relate between two variables.
- The correlation coefficient, denoted symbolically r, defines the strength and direction of the linear relationship between two variables: Grades of r: 0.00 to 0.24 (weak or no correlation), 0.25 to 0.49 (fair correlation), 0.50 to 0.74 (moderate correlation), > 0.75 (strong correlation).
- Binary logistic regression analysis was used to study the effect of some independent variables (H. Pylori infection and gastric biopsy) on single dependent factor (metabolic syndrome).

The probability of less than 0.05 was used as a cut off point for all significant tests.

RESULTS

Demographic data of the patients:

The present study was conducted in Minia University hospital at endoscopic unit from April 2017 to April 2018. On 34 patients of metabolic syndrome. Age ranges between 22 to 64years old; (21 male and 13 females) Also, this study included 26 patients (14 male and 12 females) healthy subjects as a control group.

After applying the exclusion criteria, a total of 60 participants (35 men) were enrolled in the study. Of these, 39 were HP seropositive, and 34 were diagnosed with MetS.

Table (8): Examination of the studied group

Examination	The studied group (n =60)
H. Pylori IgG Seronegative Low positive Moderate positive High positive	21 (35%) 14 (23.3%) 12 (20%) 13 (21.7%)
Biopsy Atrophic gastritis Non atrophic gastritis	22 (36.7%) 38 (63.3%)

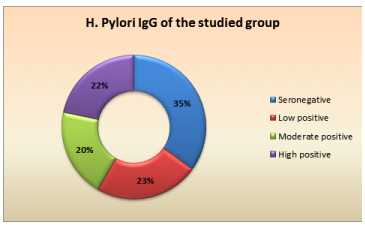

Fig (2): H. Pylori IgG Status in studied group

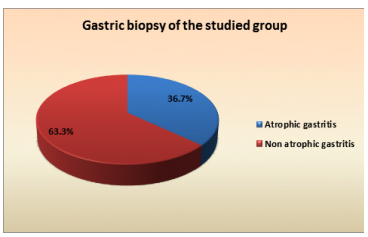

Fig (3): gastric biopsy Findings in studied group

Table (9): Socio-demographic characteristics according to metabolic syndrome

Socio-demographic characteristics	Metabolic syndrome (n =34)	Control (n =26)	P value
Age (years) Range Mean ± SD	22-62 44 ± 11.9	29-64 47.9 ± 8.9	0.282
Sex Male Female	21 (61.8%) 13 (28.2%)	14 (53.8%) 12 (46.2%)	0.538
BMI Range Mean ± SD	23.5-29.7 26.7 ± 1.6	23.7-28.9 26.5 ± 1.3	0.817
Waist circumference Range Mean ± SD	81-101 92 ± 6.6	73-99 84 ± 7.5	0.001*
HTN Yes No	26 (75.5%) 8 (23.5%)	10 (38.5%) 16 (61.5%)	0.003*
Smoking Yes No	10 (29.4%) 24 (70.6%)	6 (23.1%) 20 (76.9%)	0.582
Systolic BP Range Mean ± SD	110 - 160 140.6± 12.5	110-150 128.3 ± 10.6	0.001*
Diastolic BP Range Mean ± SD	70-105 90.6 ± 8.7	70-95 82.9 ± 6.9	0.001*

*There is significant difference (P-value <0.05).

The patients of metabolic syndrome and those of non-metabolic syndrome differed in terms of Waist circumference (92 ± 6.6 vs84 ± 7.5., respectively; p < 0.001).

Blood pressure was significantly higher in the metabolic syndrome group (systolic blood pressure, 140.6± 12.5 versus128.3 ± 10.6 mmHg, p = 0.001; diastolic blood pressure, 90.6 ± 8.7versus 82.9 ± 6.9 mmHg, p = 0.001).

Table (10): Laboratory data of the studied group according to metabolic syndrome

Laboratory data	Metabolic syndrome (n =34)	Control (n =26)	P value
FBS Range Mean ± SD	97-118 106.8 ± 3.9	87-112 94.4 ± 8.2	0.001*
HbA1c Range Mean ± SD	4.7-6.4 5.4 ± 0.39	4.2-6.3 4.8 ± 0.46	0.001*
BMI Range Mean Creatinine Range Mean ± SD± SD	0.5-1.2 0.82 ± 0.19	0.6-1.2 0.87 ± 0.19	0.305
Urea Range Mean ± SD	23-44 32.5 ± 5.7	22-42 28.9 ± 5.9	0.024*
T. cholesterol Range Mean ± SD	184-232 205.9 ± 10.7	169-217 189.9 ± 14.8	0.001*
HDL Range Mean ± SD	31-49 39.6 ± 5.2	32-55 45.6 ± 6.3	0.001*
LDL Range Mean ± SD	131-159 139.4 ± 7.3	120-144 133.7 ± 4.5	0.005*
Triglyceride Range Mean ±	151-182 158.1 ± 7.5	138-159 149.3 ± 6.2	0.001*
H. Pylori IgG Seronegative Low positive Moderate positive High positive	9 (26.5%) 7 (20.6%) 8 (23.5%) 10 (29.4%)	12 (46.2%) 7 (26.9%) 4 (15.4%) 3 (11.5%)	0.208
Biopsy Atrophic gastritis Non atrophic gastritis	18 (52.9%) 16 (47.1%)	4 (15.4%) 22 (84.6%)	0.003*

*There is significant difference (P-value <0.05).

In comparison between the patients of metabolic syndrome and those of non-metabolic syndrome there was significant statistical difference as regards:

FBS & glycated hemoglobin were significantly higher in the metabolic syndrome group with p value of 0.001 for both.

Also T.C, LDL-C and T.G were significantly higher in the metabolic syndrome group with p value of 0.001, 0.005 and 0.001 respectively.

Atrophic gastritis was significantly higher in the metabolic syndrome group with p value of 0.003.
HDL-C was significantly lower in the metabolic syndrome group with p value of 0.001.

There were no statistical differences between the two groups in terms of Creatinine and H. Pylori IgG status.

Table (11): Socio-demographic characteristics of the studied group According to H.pylori IgG status

Socio-demographic characteristics	Total (n =60)	Seronegative (n =21)	Seropositive (n =39)	P value
Age (years) Range Mean ± SD	22-64 45.7 ± 10.8	25-64 44.5 ± 10.6	22-63 46.3 ± 11	0.438
Sex Male Female	35 (58.3%) 25 (41.7%)	14 (66.7%) 7 (33.3%)	21(53.8%) 18 (46.2%)	0.337
BMI Range Mean ± SD	23.5-29.7 26.6 ± 1.5	23.8-28 26 ± 1.26	23.5-29.7 26.9 ± 1.5	0.025*

Waist circumference Range Mean ± SD	73-101 88.6 ± 8	73-99 88 ± 8.5	73-101 88.9 ± 7.8	0.592
Systolic BP Range Mean ± SD	110 - 160 135.3 ± 13.1	110-150 128.9 ± 11.9	110 - 160 138.7 ± 12.6	0.005*
Diastolic BP Range Mean ± SD	70-105 87.3 ± 8.8	70-95 81.9 ± 8.6	75-105 90.2 ± 7.6	0.001*
Smoking Yes No	16 (26.7%) 44 (73.3%)	7 (33.3%) 14 (66.7%)	9(23.1%) 30 (76.9%)	0.392

*There is significant difference (P-value <0.05).

The HP-seropositive and seronegative groups differed in terms of BMI (26.9 ± 1.5and 26 ± 1.26, respectively; p < 0.025) but not sex.

Blood pressure was significantly higher in the HP-seropositive group (systolic blood pressure, 138.7 ± 12.6versus 128.9 ± 11.9mmHg, p = 0.005; diastolic blood pressure, 90.2 ± 7.6versus 81.9 ± 8.6 mmHg, p = 0.001).

There were no differences between the HP-seropositive and seronegative groups in terms of smoking and alcohol drinking.

Table (12): Laboratory data of the studied group H.pylori IgG status

Laboratory data	Total (n =60)	Seronegative (n =21)	Seropositive (n =39)	P value
FBS Range Mean ± SD	87-118 101.4 ± 8.7	87-110 98.3 ± 8.2	87-118 103 ± 8.6	0.034*
HbA1c Range Mean ± SD	4.2-6.4 5.2 ± 0.5	4.2-5.4 4.9 ± 0.33	4.2-6.4 5.3 ± 0.52	0.001*
Creatinine Range Mean ± SD	0.5-1.2 0.84 ± 0.19	0.6-1.2 0.89 ± 0.19	0.5-1.2 0.82 ± 0.18	0.160
Urea Range Mean ± SD	22-44 30.9 ± 6.1	22-42 31.2 ± 5.9	22-44 30.8 ± 6.2	0.686
T. cholesterol Range Mean ± SD	169-232 199 ± 14.8	172-222 196 ± 14.8	169-232 200.6 ± 14.8	0.229
HDL Range Mean ± SD	31-55 42.2 ± 6.4	33-55 43.2 ± 6.9	31-54 41.7 ± 6.2	0.424
LDL Range Mean ± SD	120-159 136.9 ± 6.8	120-138 132.7 ± 3.9	131-159 139.3 ± 7	0.001*
Triglyceride Range Mean ± SD	138-182 154.3 ± 8.2	138-156 149.8 ± 5.5	139-182 156.7 ± 8.4	0.001*

*There is significant difference (P-value <0.05).

In comparison between seropositive H.pylori patients & seronegative subjects there was significant statistical difference as regards:

FBS & glycated hemoglobin were significantly higher in the HP-seropositive group with p value 0.034 and 0.001 respectively.

Serum LDL-C concentration was significantly higher in the HP-seropositive group (139.3 ± 7 vs. 132.7 ± 3.9 mg/dL; p = 0.001), Also serum TG was (156.7 ± 8.4 vs. 149.8 ± 5.5 with (p < 0.0001).

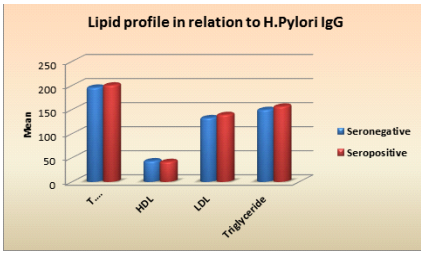

Fig (4): Lipid profile in relation to H.pylori IgG status

Table (13): Socio-demographic characteristics according to gastric biopsy Findings:

Socio-demographic characteristics	Atrophic gastritis (n =22)	Non atrophic gastritis (n =38)	P value
Age (years) Range Mean ± SD	28-62 46.3 ± 9.4	22-64 45.4 ± 11.7	0.830
Sex Male Female	13 (59.1%) 9 (40.9%)	22 (57.9%) 16 (42.1%)	0.928
BMI Range Mean ± SD	24.6-29.7 27.1 ± 1.5	23.5-29.4 26.3 ± 1.5	0.096
Waist circumference Range Mean ± SD	76-101 90.4 ± 8.1	73-99 87.6 ± 7.8	0.208
HTN Yes No	19 (86.4%) 3 (13.6%)	17 (44.7%) 21 (55.3%)	0.002*
Smoking Yes No	5 (22.7%) 17 (77.3%)	11 (28.9%) 27 (71.1%)	0.600
Systolic BP Range Mean ± SD	120 - 160 144.2 ± 110.4	110-155 130 ± 11.7	0.001*
Diastolic BP Range Mean ± SD	80-105 93.1 ± 6.24	70-100 83.9 ± 8.4	0.001*

*There is significant difference (P-value <0.05).

Table (14): Laboratory data of the studied group according to gastric biopsy findings

Laboratory data	Atrophic gastritis (n =22)	Non atrophic gastritis (n =38)	P value
FBS Range Mean ± SD	87-118 103.6 ± 8.2	87-113 100.1 ± 8.8	0.183
HbA1c Range Mean ± SD	4.2-6.4 5.3 ± 0.5	4.2-6.3 5.1 ± 0.48	0.061
Creatinine Range Mean ± SD	0.5-1.2 0.84 ± 0.18	0.5-1.2 0.85 ± 0.19	0.864
Urea Range Mean ± SD	22-44 31.2 ± 6.5	22-43 30.8 ± 5.8	0.902
T. cholesterol Range Mean ± SD	169-232 203 ± 16.5	169-222 196.6 ± 13.5	0.044*

HDL Range Mean ± SD	31-53 40.7 ± 6	32-55 43 ± 6.6	0.181
LDL Range Mean ± SD	131-158 141.2 ± 6.6	120-159 134.5 ± 5.7	0.001*
Triglyceride Range Mean ± SD	139-182 157.6 ± 9.2	138-178 152.4 ± 7	0.028*

*There is significant difference (P-value <0.05).

According to another grouping which depends on Histopathological finding of atrophic gastritis, there was significant statistical difference as regards SBP, DBP, total cholesterol, LDL-c & triglyceride between two groups.

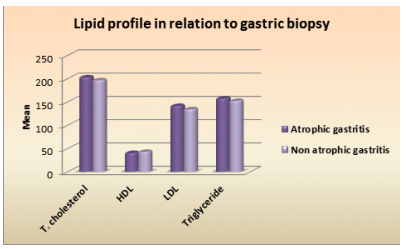

Fig (5): Lipid profile in relation to gastric biopsy findings

Table (15): Relation between H.Pylori infection and gastric biopsy

	Atrophic gastritis (n =22)	Non atrophic gastritis (n =38)	P value
H. Pylori IgG Seronegative Low positive Moderate positive High positive	0 (0%) 4 (18.2%) 7 (31.8%) 11 (50%)	21 (55.3%) 10 (26.3%) 5 (13.2%) 2 (5.3%)	0.001*

*There is significant difference (P-value <0.05).
Serum H.pylori IgG level was significantly higher in cases of atrophic gastritis with p value 0.001.

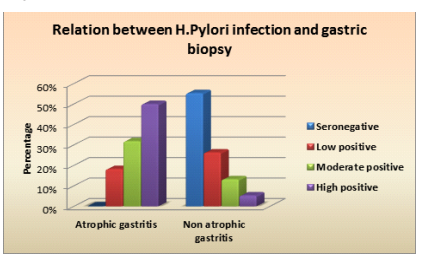

Fig (6): Relation between H.Pylori infection and gastric biopsy

Table (16): Correlation between different items and H. Pylori IgG

Variable	H. Pylori IgG	
	r	P value
Age	0.071	0.591
BMI	0.482	0.001*
Waist circumference	0.120	0.362
SBP	0.474	0.001*
DBP	0.518	0.001*
FBS	0.253	0.051
HbA1c	0.468	0.001*
Creatinine	-0.176	0.178
Urea	-0.016	0.903
T. cholesterol	0.235	0.071
HDL	-0.145	0.268
LDL	0.709	0.001*
Triglyceride	0.535	0.001*

*There is significant difference (P-value <0.05).

H. pylori IgG level has moderate positive correlation with DBP, LDL level and triglyceride level r is 0.518, 0.709 &0.535 respectively and fair positive correlation with BMI, SBP and HbA1c r is 0.482, 0.474 & 0.468 respectively.

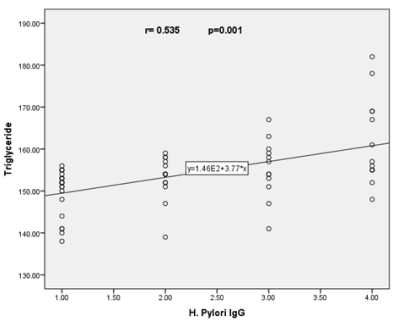

Fig (7): Correlation between TG and H. Pylori IgG. There is moderate positive correlation and this correlation is significant.

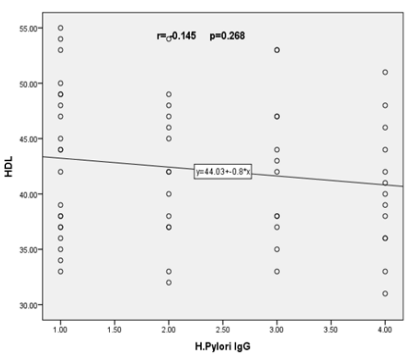

Fig (8): Correlation between HDL and H. Pylori IgG. There is weak negative correlation and this correlation is not significant

Table (17): Correlation between different items and gastric biopsy findings ()

Variable	Atrophic gastritis	
	r	P value
Age	0.043	0.747
BMI	0.242	0.062
Waist circumference	0.164	0.210
SBP	0.523	0.001*
DBP	0.501	0.001*
FBS	0.198	0.129
HbA1c	0.203	0.121
Creatinine	-0.023	0.859
Urea	0.031	0.815
T. cholesterol	0.212	0.103
HDL	-0.170	0.194
LDL	0.475	0.001*
Triglyceride	0.306	0.018*

*There is significant difference (P-value <0.05).

Atrophic gastritis has moderate positive correlation with SBP and DBP r is 0.523 and 0.501 respectively and fair positive correlation with LDL level and triglyceride level r is 0.475 & 0.306 respectively.

Table (18): Regression analysis to detect the effect of H.Pylori infection on metabolic syndrome.

	Atrophic gastritis		Non atrophic gastritis	
	Crude OR (95%CI)	P-value	Crude OR (95%CI)	P-value
H. Pylori IgG Seronegative Low positive Moderate positive High positive	Ref 1.75 (0.35 – 8.7) 3 (0.28– 31.6) 0.750 (0.04 – 13.7)	- - 0.661 0.771	- Ref 2 (0.09 – 44) 1.5 (0.09– 23)	- 0.494 0.361 0.846
H. Pylori IgG Seronegative Seropositive	-	-	Ref 1.8 (0.46 – 6.9)	- 0.395

The effect of HP-infection and AG on the risk of MetS was assessed by multiple logistic regression analyses, No significant association was detected between positive HP infection status and the risk of MetS after adjusting for age and sex.

Table (19): H.Pylori infection and gastric biopsy findings in relation to metabolic syndrome

	Metabolic syndrome (n =34)	Non metabolic syndrome (n =26)	P value
H. Pylori IgG Seronegative Low positive Moderate positive High positive	9 (26.5%) 7 (20.6%) 8 (23.5%) 10 (29.4%)	12 (46.2%) 7 (26.9%) 4 (15.4%) 3 (11.5%)	0.208
Biopsy Atrophic gastritis Non atrophic gastritis	18 (52.9%) 16 (47.1%)	4 (15.4%) 22 (84.6%)	0.003*

*There is significant difference (P-value <0.05).

The effect of HP-infection and AG on the risk of MetS was assessed by multiple logistic regression analyses. No significant association was detected between positive HP infection status and the risk of MetS after adjusting for age and sex. On the other hand, AG was significant risk of MetS.

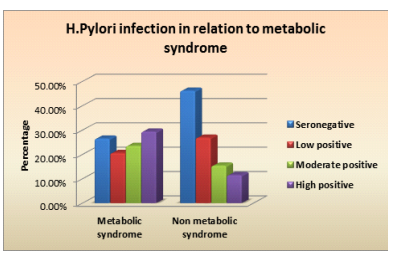

Fig (9): H.Pylori infection in relation to metabolic syndrome.

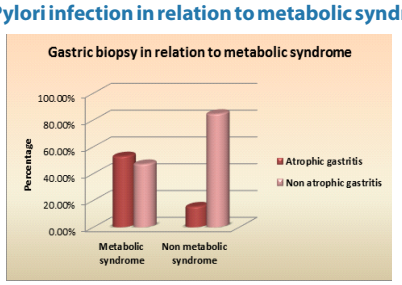

Fig (10): gastric biopsy findings in relation to metabolic syndrome

Table (20): Regression analysis to detect the effect of H.Pylori infection and gastric biopsy findings on metabolic syndrome.

Item	Crude OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
H. Pylori IgG Seronegative Low positive Moderate positive High positive	Ref 1.3 (0.34– 5.2) 2.6 (0.61– 11.7) 4.44 (0.94– 21)	- 0.678 0.194 0.060	Ref 0.839 (0.19– 3.6) 1.07 (0.19– 6.1) 1.1 (0.14– 8.3)	- 0.814 0.933 0.926
Gastric biopsy Non atrophic gastritis Atrophic gastritis	Ref 6.2 (1.7 – 21.8)	0.005*	Ref 5.7 (1.1 – 29.3)	0.034*

*There is significant difference (P-value <0.05).

When MetS risk of HP-infection status and AG status was calculated together, AG was significant risk but HP-infection lower the MetS risk. The group with low HP infection (i.e., with lowest serum concentration of HP IgG) showed the lowest OR adjusted for age, sex, smoking, drinking.

Taking this group as a reference, patients with low, moderate, and high HP infection status had ORs (with 95% confidence intervals [CI]) of 0.839 (0.19– 3.6), 1.07 (0.19– 6.1), and 1.1 (0.14– 8.30).

The participants were stratified according to the combination of HP infection and AG. AG was not noted among HP-seronegative participants.

Discussion

Both Hp infection and MetS are highly prevalent worldwide, and their prevalence is increasing with age, although local variations exist; the prevalence of MetS follows the ongoing epidemics of obesity and T2DM(Eusebi et al., 2014).

The major underlying mechanism responsible for the MetS, and Helicobacter pylori (Hp) has been proposed to be a contributing factor. There is growing evidence for a potential association between Hp infection and IR
syndrome or MetS and its related morbidity(Polyzos et al., 2011).

Furthermore, some reports suggested that atrophic gastritis, but not HP infection status, is associated with body mass index (BMI) (Torisu et al., 2008).

This study is a Prospective cross-sectional aiming to evaluate the correlation of Helicobacter pylori-infection and atrophic gastritis status on the risk of Metabolic syndrome.

After applying the exclusion criteria, a total of 60 participants (35 men) were enrolled in the study. Of these, 39 were HP seropositive, and 34 were diagnosed with MetS.

In present study we observed differences of MetS risk according to AG and HP IgG concentrations

In comparison between seropositive H.pylori patients & seronegative subjects there was significant statistical difference as regards BMI, The relationship between obesity and H. pylori infection is controversial. Obesity can alter innate and adaptive immunity, with relation between grade of obesity and immunity deterioration. Morbidly obese subjects have lower maturation of monocytes into macrophages and reduced polymorphonuclear bactericidal capacity. Severely obese patients have a significant decrease in NK cells activity in comparison to normal individuals matched for age and gender (Arslan et al., 2009).

In agreement with Rosenstock study on a Danish adult population with 2913 participants, people with upper quartile of BMI (> 26.8 kg/m2) were more likely to be seropositive to anti-H. Pylori IgG than persons with a lower BMI (Rosenstock et al., 2000).

Also in Swedish study which stated that the combined positive serology for H. pylori and Chlamydia pneumoniae were associated with higher BMI, therefore obesity might be a marker for greater susceptibility to infections. (Ekesbo et al., 2000).

In contrast to Cho and his colleagues who stated that the risk of H. pylori infection does not increase in overweight young persons and H. pylori positivity or CagA antibody status are not associated with the BMI or fasting serum leptin levels (Cho et al., 2005).

(Konturek et al., 2006) demonstrated that the eradication of H. pylori significantly increases the incidence of obesity in patients with peptic ulcer disease, since it increases the level of BMI, and/or enhances the appetite of asymptomatic patients, due to an elevation of plasma ghrelin and a reduction of leptin levels.

Regarding that H.pylori modify serum lipid profile, in our study we found that the Serum LDL-C concentration was significantly higher in the HP-seropositive group, Also serum TG was. The association of its infection with lipid profile changes was observed in 1996 in Finnish subjects, where serum cholesterol (C) and triglyceride levels were significantly higher in H. pylori infected male persons, after adjustment for age, BMI and smoking status (Niemelä et al., 1996).

In agreement with Satoh et al in 2010 & Kim et al in 2011 who suggested that the H. pylori infection is associated either with elevated total cholesterol or low density lipoprotein (LDL)-C and lower high density lipoprotein (HDL)-C and Apo A and B. Serum triglycerides were found also elevated in the study. The elevated LDL-C along with decreased HDL-C creates an atherogenic lipid profile which promotes atherosclerosis in different sites (carotid, cerebral, coronary and peripheral vessels).

In 2014, Buzás documented that the H. pylori induces a long-standing atherogenic lipid profile which could promote atherosclerosis, with its manifold clinical manifestations (coronary heart disease, stroke, peripheral vascular occlusive disease).

H. pylori infection may play a role as a trigger factor in the pathophysiology of IHD by inducing an inflammatory cascade concentrated on gastric mucosa depending on mucosal levels of IL1-alpha, IL-6, IL-8 and TNF-α. As stated by Di et al in 2007.

In current study we found that the FBS & glycated hemoglobin were significantly higher in the HP-seropositive group. the association of H.Pylori with glucose metabolism abnormalities is varied and differs between populations, the most consistent findings confirming the relationship of H. pylori and diabetes came from therapeutic trials, where both in type 1 and type 2 DM the rates of eradication of infection were significantly lower in diabetics than in nondiabetic patients (Demir et al., 2009).

In 2011 by Polyzos et al, reported that the link between H. pylori and IR is not already clarified, but many pathogenic mechanisms have been suggested.

At first In 2006 by (Aslan et al., 2006) who reported that the H. pylori infection causes inflammation, accumulation of ROS, and oxidative DNA damage. Enhanced ROS levels due to neutrophil infiltration and increased oxidative DNA damage have been reported in gastric mucosa of H. pylori-infected patients, also reduction of vitamin B12 and folate concentrations, due to the chronic atrophic gastritis, and the consequent increase of homocysteine(Evrengul et al., 2007) and H. pylori infection has been associated with lower ghrelin and increased leptin levels, which are associated with impaired energy homeostasis, lipid metabolism, elevated fasting insulin levels and insulin sensitivity (Roper et al., 2008).

In (2013), Abenavoli et al, suggested that the pro inflammatory and vasoactive substances, such as cytokines [tumor necrosis factor (TNF)-α, interferon- , interleukin (IL)-1, IL-6, IL-8, IL-10, IL-12], eicosanoids (leukotriene, prostaglandins), and acute phase proteins (fibrinogen, C-reactive protein) are released in infection and involved in the pathogenesis of IR.

In contrast to Devrajani & his colleagues who stated that the H. pylori infection could lower fasting blood glucose level in diabetics than in non-infected controls because both basal and meal-stimulated glucose is decreased (Devrajani et al., 2010).

HgbA1c is the most valuable indicator of long-term glycemic control. The relationship between H. pylori infection and HgbA1c levels is also controversial. In children with type 1 DM, H. pylori infection was associated either with similar (Khalil et al., 2007) Or increased (Bégué et al., 2002) HbA1c values as compared to non-infected controls. In a study on 7417 participants in the National Health and Nutrition Examination Survey, H. pylori and especially CagA+ status was associated with increased HbA1c levels and BMI after exclusion of confounders (Chen and Blaser, 2012).

In another study on asymptomatic Japanese subjects, H. pylori seropositivity was significantly higher in insulin resistant cases as compared to those without resistance after adjustment for gender, age, alcohol consumption, dietary habits, thus suggested that the infection independently promotes insulin resistance in asymptomatic population (Gunji et al., 2009).

Conversely, successful eradication of H. pylori infection with triple and quadruple regimen in type 2 DM did not led to significant decrease of plasma glucose and HbA1c levels as compared to pre-treatment levels and values found in non-diabetic controls (Vafaeimanesh et al., 2013).

As regard the relation between the serum H.pylori IgG level & atrophic gastritis ,we found the serum level was significantly higher in cases of atrophic gastritis thus explained by in most cases of HP infection occurs during childhood, but persists a long time and induces chronic gastritis. In the process of inflammation, HP-specific IgG is produced by activated immunocytes, and the concentration of HP-specific IgG reflects the progression of gastritis. In contrast to Kishikawa et al also demonstrated that the HP-specific IgG titer was associated with the degree of gastritis progression in a positive and negative manner in individuals diagnosed with non-atrophic and AG, respectively (Kishikawa et al., 2011).

In current study there is no significant association detected between positive HP infection status and the risk of MetS .There may be several explanations for our finding that. First, HP infection is known to affect micronutrient metabolism (Lahner et al., 2012), and several cross-sectional studies have indicated that HP infection causes growth retardation in children(Richter et al., 2001).

Observing 295 children over 3.7 years, after adjusting for other covariates, Mera et al. noted that children who were always HP negative or who achieved successful HP clearance grew significantly faster than those who remained HP-positive(Mera et al., 2012). Moreover, in adults, HP eradication has been shown to be followed by weight gain (Francois et al., 2011). In contrast to Gulcan et al who reported that HP-related gastric symptoms, not HP infection itself, induce malnutrition(Gulcan et al., 2010).

In 2009 , Jung et al, suggested that the genetic polymorphisms in host alleles associated with pro-inflammatory and anti-inflammatory cytokines such as IL-1β, TNF-α, IL-6, and IL-10 affect the phenotype of HP-related diseases.

Polymorphism in these cytokines associated genes affect gastric inflammation and HP colonization. As these cytokines also play important roles in the pathogenesis of MetS, such polymorphisms may affect the prevalence of MetS (D'Elios and Czinn, 2014).

Feuerer et al, suggested that there is relationship between

regulatory T cells (Treg cells) & MetS prevalence and HP infection. Specifically, reduced percentages of CD4 (+) Foxp3 (+) Treg cells were found in the abdominal fat of mice with genetic or diet induced obesity(Feuerer et al., 2009).

Łuczyński et al reported that the percentages of Treg cells in the peripheral blood were significantly lower in children with MetS than those in healthy children. On the other hand, Treg cells were shown to attenuate HP infection and gastric inflammation (Harris et al., 2008).

Our multiple logistic regression analysis revealed that AG was a significant risk factor for MetS.

HP IgG concentration was reported to reflect serum IL-6 levels(Nakagawa et al., 2013), IL-6 is one of the important cytokines that mediate humoral immunity and plays a role in the pathogenesis of gastritis and MetS. In 2015 Nam et al, noted that the gastric chronic inflammation induces MetS.

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