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Could *Helicobacter pylori* Infection Impair Glucose Tolerance in Obese Non-diabetic Subjects?

Ehsan Mohammad Rizk[1], Mervat Mashaly[1], Sahar Zakaria[2], Ahmed Abdel-Razik[2] and Neven Farouk Abbas[3*]

[1]Department of Clinical Pathology, Faculty of Medicine, Mansoura University, Egypt.
[2]Department of Tropical Medicine, Faculty of Medicine, Mansoura University, Egypt.
[3]Department of Internal Medicine, Faculty of Medicine, Mansoura University, Egypt.

Authors' contributions

This work was carried out in collaboration between all authors. Author EMR designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author MM managed the literature searches, analyses of the samples and author NFA collected blood samples after putting selection criteria. All authors read and approved the final manuscript.

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ABSTRACT

Helicobacter pylori (HP) is a common gastrointestinal infectious agent with half of the world's population being infected. In addition to its well-demonstrated role in gastroduodenal diseases, it may have a potential role in several extra-intestinal pathologies including metabolic, hematological, cardiovascular, neurological, autoimmune and skin diseases. There is a controversy about the prevalence of HP in obese patients and its association with metabolic alterations in those patients. This study aimed to detect the relation of HP infection to insulin resistance, glycated hemoglobin and lipid profile in obese subjects.

Subjects and Methods: This study was performed on 125 obese non diabetic subjects with BMI ≥30 kg/m^2 and age ranged from 22 to 52 years. They were 90 females and 35 males. They were divided according to seropositivity of *Helicobacter pylori* IgG antibody into HP positive & HP negative groups. HP positive group comprised 83 subjects (60 females and 23 males) and were

**Corresponding author: Email: nevenfarouk45@hotmail.com;*

further subdivided into CagA+ve (13 subjects) and CagA-ve (70 subjects). HP negative group included 42 subjects (30 females and 12 males). Blood glucose, lipid profile, HbA1C, insulin, *H. pylori* IgG and Cag A IgG antibodies were assayed. Both HOMA-IR and HOMA-B were calculated from fasting blood glucose and fasting insulin levels.

Results: A statistical significant increase in HOMA-IR, cholesterol, triglycerides, HDL-C and HbA1c was observed in HP positive group compared to HP negative group. There was a significant positive correlation between seropositivity to HP and both of HOMA-IR & elevated HbA1c. Among HP +ve subjects, both HOMA-IR and HbA1c were significantly elevated in anti-Cag A IgG positive than anti-Cag A IgG negative obese subjects. Multivariate logistic regression analysis showed that HP positive subjects were 7.189 & 19.2 times more susceptible to insulin resistance and increased HbA1c respectively than HP negative subjects. Also anti-Cag A IgG +ve persons were more susceptible to insulin resistance by 8.8 times more than negative subjects.

Conclusions: *H. pylori* infection is associated with dyslipidemia, IR and elevated HbA1c in obese subjects. Whether these metabolic alterations are due to HP infection or just an association needs further studies to determine the effect of HP eradications on these metabolic alterations.

Keywords: Insulin resistance; HbA1c; dyslipidemia; metabolic alterations; obese subjects.

1. INTRODUCTION

Helicobacter pylori (HP) is a frequent gastrointestinal infectious agent having worldwide distribution with half of the world's population infected [1].

It is a Gram-negative, microaerophilic, spiral bacterium found mainly in the gastric mucosa, inducing a strong inflammatory response with release of various bacterial and host dependent cytotoxic substances [2]. It is divided into 2 types; type I strains carry cytotoxin associated gene A (CagA) and vacuolating cytotoxin A (VacA), while type II strains do not express any antigens [3]. It is linked to different forms of gastritis, peptic ulcer disease, low-grade gastric lymphoma [4] and gastric adenocarcinoma [5], dieulafoy lesion [6]. Also, it may have a potential role in several extra-intestinal pathologies including metabolic, haematological, cardiovascular, neurological, autoimmune and skin diseases [7].

HP may promote insulin resistance by inducing chronic inflammation and affecting insulin-regulating gastrointestinal hormones, leptin and ghrelin, that are involved in energy homeostasis and whose interactions affect obesity, insulin sensitivity and glucose homeostasis [8-9].

The prevalence of both overweight and obesity is increasing worldwide. Obesity is associated with many complications as dyslipidemia, hypertension, diabetes mellitus and ischemic heart diseases. There is a controversy about the prevalence of *H. pylori* infection in morbidly obese patients ranging from 8.7% in candidates for bariatric surgery in a German cohort to 85.5% in a Saudi cohort with intermediate values in other series [10-11].

Little is known about the relation between HP and metabolic alterations in obese subjects including IR, elevated HbA1c and dyslipidemia, so the aim of this study was to explore the relation of HP to these alterations in obese non diabetic subjects.

2. METHODS

This is a cross-sectional study that was performed on 125 obese non diabetic subjects based on history and normal oral glucose tolerance curve, with BMI ≥30 kg/m^2 and age ranged from 22 to 52 years recruited from obesity and tropical clinics in Mansoura University and Specialized Medical hospitals. They were 90 females and 35 males. We excluded any participant who had abnormal oral glucose tolerance curve, medical disorders or drugs that may affect lipid profile or beta cell functions. All participants signed consent and the study was approved by Local Ethical Committee of Mansoura Faculty of Medicine. Based on the seropositivity of *H. pylori* IgG & Cag A IgG antibodies, subjects were divided into two groups:

1- **Anti- *H. pylori* IgG positive group:** Included 83 subjects (60 females and 23 males) with age ranged from 25 – 52 years.
2- **Anti- *H. pylori* IgG negative group:** Included 42 subjects (30 females and 12 males) with age ranged from 22 – 47 years**.** They further subdivided into:

a. Anti- Cag A IgG +ve: Included 13 subjects with age ranged from 25 – 52 years.
b. Anti- Cag A IgG: Included 70 subjects with age ranged from 22 – 52 years.

2.1 Sampling

Six ml fasting venous blood sample was withdrawn; one ml was put into EDTA tube for HbA1c assay and the remaining was put into plain tube, allowed to clot for 15 minutes and centrifuged at 7000 rpm for 5 minutes and the serum was separated into two aliquots, one used for determination of fasting serum glucose level and lipid profile and the other aliquot was stored at -20ºC for insulin, *H. pylori* and CagA IgG antibody assays.

2.2 Methods of Assays

a) Serum glucose, cholesterol, triglyceride, HDL-C and HbA1C concentrations were measured on a Cobas Integra 400 chemistry analyzer (Roche Diagnostics, Basel, Switzerland) Increased HbA1C is considered when it is more than 6% according to the ACE and AACE 2015 guidelines.
b) LDL-C calculated using Friedewald equation [12]:
LDL-C = TC – (HDL + TG/5), provided that TG level is not above 400 mg/dl.
c) Serum insulin was assayed by an enzyme-linked immunosorbent assay (ELISA) using insulin quantitative BIOS kit (Chemux BioScience, Inc, USA) [13].
d) *H. pylori*-specific immunoglobulin G antibody were measured by ELISA using the DRG kit (DRG International Inc, USA).
e) *H. pylori* Cag A immunoglobulin G antibody against CagA protein was assayed by ELISA using CagA IgG ELISA Kit (Omegadiagnostic pl, USA).
f) Calculations:

1. Homeostatic model assessment insulin resistance (HOMA-IR)
= fasting serum insulin (μU/ml) × fasting plasma glucose (mg/dl) / 405. It is interpreted as normal if ≤1.6 and as insulin resistant if ≥2.5 [14].
2. Homeostatic model assessment Beta cell % (HOMA-β%)
=360 x fasting insulin/ Fasting glucose (mg/dl) – 63 [15].
3. BMI was calculated from the weight (kg) and square of the height (m) as follows: BMI (kg/m^2) = body weight / $height^2$.

2.3 Statistical Analysis

Statistical analyses were performed in the SPSS statistical package programme (version 16, SPSS, Chicago, IL). Normality was measured with Kolmogorov Smirmov test. The results were expressed as percentages for categorical variables and as median (range) in non-normal distributed variables. The two-tailed Mann–Whitney U test was used to compare the median values of parameters between 2 groups. Spearman correlation coefficient test (r) was used to test a positive or negative relationship between two variables. Results were considered significant if p values ≤ 0.05.

3. RESULTS

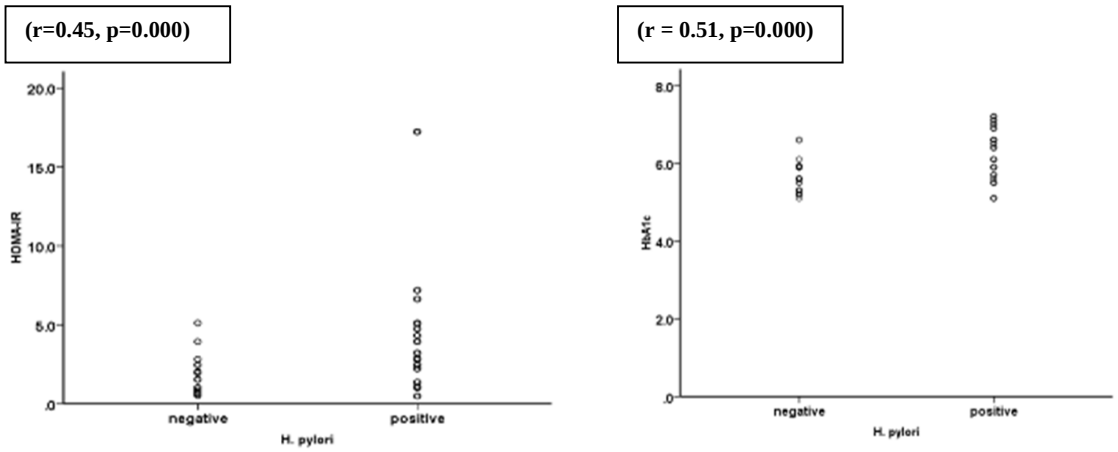
As shown in Table 1, there was a statistical significant increase in HOMA-IR, HbA1C, HOMA-B, total cholesterol, triglyceride and HDL-C levels in HP positive subjects in comparison with HP negative subjects. There were no significant differences in FBS and LDL-C between these two groups.

There were positive significant correlations between HP and both of HOMA-IR & increased HbA1C (r=0.45, p=0.000), (r = 0.51, p=0.000) respectively Fig. 1.

H. pylori +ve persons were 7.189 times more susceptible to insulin resistance than *H. pylori* -ve persons. Cag A +ve person were more susceptible to insulin resistance by 8.8 times more than negative subject. Also, HP +ve subjects were 19.2 times more susceptible to impaired HbA1C than negative subjects Table 2.

4. DISCUSSION

Helicobacter pylori is a worldwide infection affecting more than half of the world population with higher prevalence in developing countries than that in developed countries [16]. There is a controversy about the prevalence of *H. pylori* infection in obese patients; higher *H. pylori* prevalence were reported in obese patients when compared to lean patients [17,18-19] while, lower prevalence rates of *H. pylori* among obese patients were also reported [20,21-22]. In our study; 66.4% & 18.5% of obese subjects showed seropositivity for H.P IgG and Cag A IgG) which is lower than those observed by Gad and Hassan [23] who reported 88.73% for HP and 46.13% for Cag A and this may be due to difference in gender in two studies (mainly females in our study).



Correlation between *H. pylori* and HOMA-IR **Correlation between *H. pylori* and HbA1C**

Fig. 1. Spearman's correlation between *H. pylori* and both of HOMA-IR and HbA1C

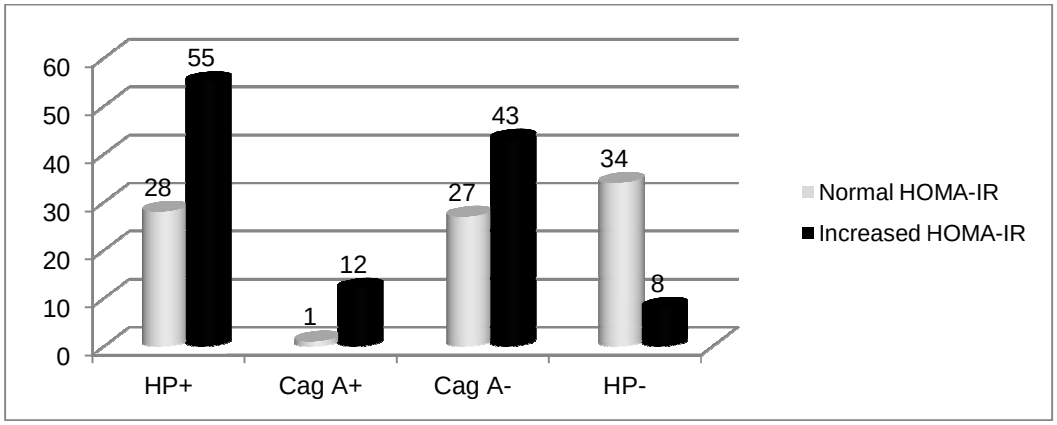


Fig. 2. HOMA-IR in studied groups

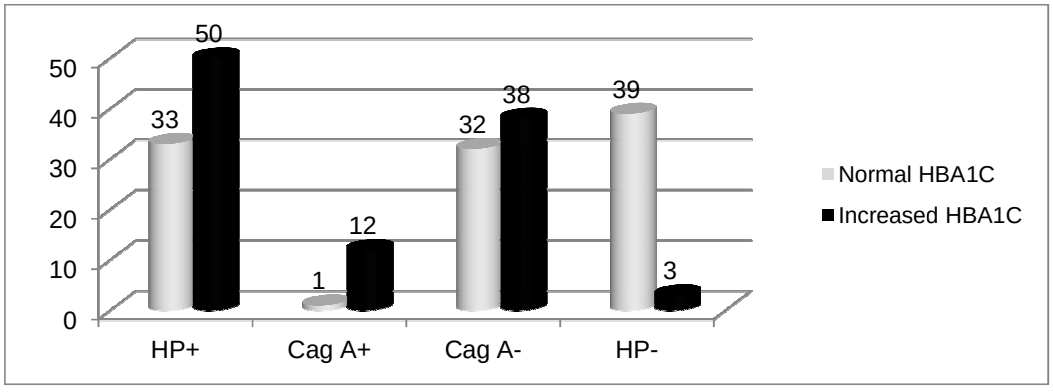


Fig. 3. HbA1c in studied groups

Table 1. Demographic and metabolic parameters in studied groups

	***H. pylori* –ve (n=42) Median (range)**	***H. pylori* +ve (n=83) Median (range)**			**p-value**	
		Cag A +ve (n=13)	**Cag A –ve (n=70)**	**Total H. pylori +ve (n=83)**	**p_1**	**p_2**
Age (years)	31 (22 – 47)	32 (25 – 52)	27 (22 – 52)	31.5 (25 – 52)	0.192	0.816
BMI (kg/ m2)	34.6 (30.8 – 48.7)	44.9(32 – 48.8)	39.1 (32 – 53)	39.5 (32.0 – 53.2)	0.000	0.048
FBS (mg/dl)	100 (83 – 115)	97 (89-122)	98.5 (83-122)	97 (83 – 122)	0.84	0.177
Fasting Insulin (uIU/ml)	6.0 (2.0 – 18.0)	22 (4.0 – 72)	12.5 (2- 72)	13.0 (2. 0 - 72)	0.000	0.001
HbA1c (%)	5.6 (5.1 – 6.6)	6.6 (5.1 – 7.1)	6.1 (5.1 – 7.2)	6.4 (5.1 – 7.2)	0.000	0.026
HOMA-IR	1.53 (0.5 – 5.1)	6.6 (0.99 –1 7.2)	2.8 (0.47 – 17.2)	3.2 (0.47 – 17.2)	0.000	0.001
HOMA- Beta	54.0 (17.5 – 135)	134.2(38.9-762.3)	125.5(22.5-762.3)	126.4 (22.5 – 762.3)	0.000	0.001
Triglyceride (mg/dl)	90 (51 – 366)	95 (60 -366)	85 (60- 217)	95 (60 – 366)	0.034	0.200
Cholesterol (mg/dl)	181 (149 – 230)	197 (149 – 243)	197 (149 – 243)	197 (149 – 243)	0.005	0.935
HDL-C (mg/dl)	54 (32 – 85)	54 (32-85)	57 (32-85)	50.5 (44 – 83)	0.017	0.283
LDL-C (mg/dl)	109 (68 – 154)	102 (73-167)	107 (68-167)	107 (68 – 167)	0.272	0.647

P1: H. pylori +ve versus H. pylori –ve; P2: Cag A +ve versus Cag A –ve

Table 2. Multivariate logistic regression analysis

Insulin resistance		B	P value	Odds ratio (95.0% C.I)
	Cholesterol	0.028	0.002	1.028 (1.010 -1.047)
	Triglyceride	0.010	0.034	1.010 (1.001 -1.019)
	H. pylori	1.973	0.000	7.189 (2.677- 19.308)
	cagA	2.178	0.047	8.828 (1.024-76.072)
Impaired HbA1C	LDLC	-0.028	0.001	0.972 (0.955 - .989)
	H. pylori	2.958	0.000	19.267 (5.027 - 73.847)
	Insulin	0.050	0.019	1.052 (1.008 - 1.097)

For insulin resistance: Model chi square = 45.58, constant = -7.806.
For Impaired HbA1C: Model chi square = 52.32, constant = 0.024

As regard lipid profiles, there was a significant increase in total cholesterol, triglyceride and HDL-C levels in HP positive subjects in comparison with HP negative subjects while no significant differences in LDL-C between two groups. There is a controversy about the association of H.P infection with dyslipidemia, some studies reported an association between HP seropositivity and atherogenic lipid pattern [24-25] while others has not been found such association [26,27].

We found a significant increase in HbA1c among HP positive group in comparison to HP negative group and those HP positive subjects were 19.2 times more susceptible to impaired HbA1C than negative subjects. This is in agreement with a large, cross-sectional study performed by Chen and Blaser [28] in which they examined the association between seroprevalence of *H. pylori* infection and the mean levels of HbA1c in 2 large national surveys; the National Health and Nutrition Examination Survey (NHANES) III and NHANES 1999–2000. They reported a positive association between *H. pylori* status and HbA1c levels among adult participants free of diabetes particularly among those with higher BMI and above 18 years of age. Also, we demonstrated that HbA1c is significantly elevated in Cag A positive than Cag A negative obese non diabetic subjects. This is consistent with Chen and Blaser [28] who reported a progressive increase in HbA1C when compared *H. pylori* –ve & *H. pylori* +ve/CagA -ve to *H. pylori* +ve/CagA +ve especiaaly after excluding those with diabetes.

H. pylori infection is associated with increased HbA1c through decreasing the ghrelin producing cells in the gastric mucosa thus lowering the levels of circulating ghrelin [29] and increasing gastric leptin levels [30,31]. Both hormones are involved in the regulation of appetite and energy expenditure. Ghrelin decreases energy expenditure and promotes weight gain [32], while leptin reduces food intake and increases energy expenditure [33].

In this study we found a significant increase in HOMA-IR among HP positive group. *H. pylori* +ve persons were 7.189 times more susceptible to insulin resistance than *H. pylori* -ve persons.

Many authors also reported an association between IR and HP and contributed such association to different mechanisms. Aslan et al [34] reported that *H. pylori* infection is associated with increased oxidative stress that may be the main cause for the development of IR, B cell dysfunction, impaired glucose tolerance and type 2 diabetes mellitus. However, Aydemir et al. [35] reported that decreased somatostatin, that regulates pancreatic insulin secretion and has an inhibitory effect on insulin release and increased gastrin hormone levels, may have a role in the development of IR in HP infected patients. On the other hand, Basso et al. [36] reported that chronic inflammation and production of a large amount of pro-inflammatory and vasoactive substances as IL-8, 10, 12 and C-reactive protein were found to be involved in the pathogenesis of IR. Also Hsieh et al. [37] reported that chronic atrophic gastritis with concomitant decrease in vitamin B12 and folate concentrations and increases in the homocysteine level may play a role in the pathogenesis of IR.

In contrary, no association between *H. pylori* infection and IR was reported by Gao et al [38] and Ozdem et al. [39]. The source of this discrepancy of results may be due to difference in age and methods of HP detection between the studies.

We also found that subjects infected with the virulent strain of *H. pylori* (anti Cag A IgG +ve) have a significant increase in HOMA-IR than subjects infected with Cag A –ve H pylori. These cag A +ve person found to be more susceptible

to insulin resistance by 8.8 times more than negative subject. This is in agreement with Rahman et al. [40] who demonstrated that HOMA-IR values is significantly more increased in Cag A +ve H pylori infected cases than Cag A –ve H pylori subjects. This can be explained by the known ability of Cag A +ve *H. pylori* to stimulate cytokine production, especially TNF-α and CRP [41]. These proinflammatory cytokines have been suggested to be strongly associated with HOMA-IR [42].

A significant increase in HOMA-B was observed in HP positive group in comparison to HP negative groups. This increase may be a compensatory mechanism against insulin resistance in those patients.

5. CONCLUSION

In conclusions, there is a significant increase of HOMA-IR, HbA1C and both cholesterol and triglycerides in HP positive group compared to HP negative group. Whether HP is an independent factor for these metabolic changes in obese subjects or just an association needs further studies to explore the benefit of HP eradications on these metabolic parameters.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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