The effect of *Helicobacter pylori* eradication on insulin resistance and HbA1c level in people with normal glucose levels: a prospective study

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Background and Aim. *Helicobacter pylori* (*H. pylori)* infection is reported to be associated with various extragastrointestinal conditions such as insulin resistance, diabetes mellitus and metabolic syndrome. These conditions are attributed to systemic inflammation, leptin or ghrelin changes due to *H. pylori* infection. Therefore, increasing trends in the management of *H. pylori* infection are ordered to maintain glycemic control. In this study, we evaluated the effect of *H. pylori* eradication on insulin resistance in patients with normal blood glucose concentrations.
Method. A total of 370 patients with successful eradication were included in the study. Patients with H. pylori were given triple eradication treatment. All patients with *H. pylori* infection were tested for fasting glucose, fasting insulin, glicated hemoglobin (HbA1c) at baseline and 6 months after eradication treatment. Also, insulin resistance was calculated using the homeostatic model assessment of insulin resistance (HOMA-IR). Body mass index was also determined as a metabolic syndrome criteria effecting insulin resistance.
Results. There were significant differences in fasting glucose, fasting insulin, HbA1c, and HOMA-IR values between before treatment and after treatment(P <0.04, <0.01, <0.01, <0.01). The favorable effect of eradication was more significant in patients with BMI≥25 mg/m^2(P<0.05).
Conclusion. Eradication treatment has beneficial effects on insulin resistance in patients with normal glucose concentrations.

Key words: Helicobacter pylori, insulin resistance, body mass index

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INTRODUCTION

H. pylori is a nonivasive, microaerophile, and spiral-shaped microorganism that causes severe gastric pathologies such as chronic active gastritis, peptic ulser, gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma[1,2]. *H. Pylori* is responsible for both gastric local inflammation and a systemic inflammation leading to extra-gastrointestinal tract conditions such as cardiovascular diseases, idiophatic thrombocytophenic purpurae (ITP), unexplained iron deficiency anemia, diabetes mellitus and insulin resistance[3-8]. The Maastricht IV consensus report declares that *H. pylori* eradication does not cause or worsen obesity and related illnesses[9]. Recent studies showed the relationship between *H. pylori* and insulin resistance or diabetes[10]. Accordingly, a favorable effect of *H. pylori* eradication on insulin resistance was also documented in some studies[11]. However, this relationship is not well defined yet due to some pitfalls in those studies[12]. If well-defined association between *H. pylori* and insulin resistance is established, we obviously change our approach to insulin resistance, type 2 diabetes and also metabolic syndrome regarding *H. pylori*. On the other hand, *H. pylori* and HbA1c level association in people with normal blood glucose concentrations is another major issue of concern. In this regard, we aimed to investigate the effect of *H. pylori* eradication therapy on insulin resistance in patients with normal blood glucose concentrations.

PATIENTS AND METHODS

This study is a prospective, controlled, single-blind study carried out in our gastroenterology department. Consecutive patients with dyspepsia were recruited between July 2012 and August 2012. In total 463 patients with *H. pylori* received triple eradication therapy. All 370 patients (female: 202, male: 168) whose *H. pylori* was eradicated were included in the study. The mean age of the patients was 39.4±14.2 years. Ninety three patients (20%) whose *H. pylori* eradication was unsuccessfull were excluded from the study and have been followed up in our outpatient clinic to be treated with other eradication regiments.

Informed consent was obtained from all patients. After approval, esophagogastroduodenoscopy was performed. Two specimens from the incisura angularis, antrum and corpus were obtained for histological analysis during endoscopy. The rapid urease test (RUT), (Endochoice Inc. US. CLO-rapid urease test) for qualitative assessment of urease activity, was performed on all those biopsy specimens for detecting *H.pylori* infection. Fresh antral and corporal biopsies were placed on slides and the results

were considered negative if there was no color change from yellow in one hour, while samples with color change toward pink were considered positive. The RUT can detect the presence of *H pylori*, within one hour with a satisfactory accuracy (>90%) (ref.[13]).

Patients with *H. pylori* infection were eradicated with triple treatment (amoxicillin 1000 mg, clarithromycin 500 mg, lansoprazole 30 mg, twice daily) for 14 days. Lansoprazole treatment (30 mg twice daily) was continued by all patients for 4 weeks more to complete the eradication therapy. Urea breath test (UBT) was performed for all patients after 6 weeks of treatment. The UBT using essentially [13C] urea remains the best test to diagnose *H. pylori* infection, has a high accuracy and is easy to perform. UBT's sensitivity is 88-95% and specificity is 95%-100% (ref.[14]).

All patients with *H. pylori* infection were tested for fasting glucose, fasting insulin, glycated hemoglobin (HbA1c) at baseline and 6 months after eradication treatment. Blood samples were obtained following an overnight (12 h) fast. HbA1c is routinely measured according to DCCT (Diabetes Control and Complications Trial) in our laboratory. This was why we also switched HbA1c values to IFCC (International Federation of Clinical Chemistry) via formulation of IFCCHBA1c (mmol/mol)= [DCCTHBA1c(%)-2.15]:0.915 in that study (Table 2).

Also, insulin resistance was calculated using the homeostatic model assessment of insulin resistance (HOMA-IR= fasting glycamia (mg/dL) X fasting insulinaemia (μU/mL)/405) which was first described by Matthews at al. in 1985 (ref.[15]). Body mass index (BMI) was calculated as body mass (kg)/height (m^2) for all patients at baseline and three months after eradication. No diet modification for weight loss was advised.

Table 1. Demographic and laboratory characteristics of patients.

	Female n=202	Male n=168	*P*
Age (year)	39.3±1.4	38.6±13.7	>0.66
Height (meter)	1.59±0.4	1.71±0.5	<0.001
Body mass (kilogram)	65.3±1.0	72.8±8.7	<0.001
BMI (kilogram/m^2)	25.8±4.1	24.9±3.2	<0.027
Hb (gr/dL)	13.2±1.1	13.8±1.2	<0.007
ALT (IU/L)	21.4±2.8	19.9±5.9	>0.569
Cr (mg/dL)	0,86±0,13	0,88±0,15	>0,419

BMI: Body mass index, Hb: Hemoglobin, ALT: Alanin aminotransferase, Cr: Creatinin

Exclusion criteria

Patients with hematologic abnormality, liver and kidney disease, diabetes mellitus and metabolic syndrome were excluded. Patients with a history of previous *H. pylori* eradication treatment, using NSAIDs, antibiotics, proton pump inhibitors within a month were also excluded from the study. Fasting glucose higher than 105 mg/dL, BMI>30 kg/m2, age younger than 16 years, pregnancy, lactation, alcohol consumption, and smoking were other exclusion criterias.

The patients who had H. pylori treatment failure (n=93, 20% of patients) were also excluded from the study.

This study was approved by the local ethics committee.

Statistical analysis

Numerical values were defined as means±standard deviation. Shapiro-Wilk test was used to determine the distribution of parameters. Paired-Samples t-Test was used for comparing the pre-treatment and post-treatment values of patients. P<0.05 was considered statistically significant. Statistical analysis were performed by SPSS v. 16, SPSS Inc. (Chicago, Illinois, USA).

RESULTS

The demographic and laboratory findings are shown in Table 1. There was no significant differences for age, alanine aminotransferase (ALT) and creatinine (Cre) between males and females (*P*>0.05). Hemoglobin level was lower and BMI was significantly higher in females compared to males (Table 1). There were significant differences in fasting glucose, fasting insulin, HbA1c, and HOMA-IR values between before treatment and after treatment (*P*<0.05). No significant differences was found in baseline BMI compared to after treatment (Table 2).

Table 2. Potential laboratory markers of HP activity at baseline (before HP eradication) and after 6 weeks of eradication therapy.

	Before eradication (n=370)	After eradication (n=370)	*P*
Fasting glucose (mg/dL)	93.36±7.41	92.18±7.26	<0.04
Fasting insulin (μU/mL)	11.24±6.38	10.92±5.13	<0.01
HOMA-IR	2.61±1.55	2.58±1.61	<0.01
HbA1C (%)	5.50±0.35	5.48±0.33	<0.01
HbA1C (mmol/mol)	36.6±3.8	36.4±3.6	<0.01
BMI (kilogram/m^2)	25.44±3.80	25.51±3.1	>0.189

HOMA-IR: homeostatic model assessment-insulin resistance, HbA1C: Hemoglobin A1C (glycated hemoglobin), BMI: Body mass index

Table 3. The effect of BMI on HOMA-IR and HbA1c levels before and after *H. pylori* eradication.

		Before eradication (n=370)	After eradication (n=370)	*P*
BMI<25(kg/m²) (n=169)	HOMA-IR	2.3±1.68	2.21±2.08	*P*>0.529
	HbA1C	5.43±0.34	5.41±0.32	*P*<0.015
BMI≥25(kg/m²) (n=201)	HOMA-IR	2.72±1.38	2.63±1.06	*P*<0.01
	HbA1C	5.56±0.35	5.54±0.34	*P*<0.04

BMI: Body mass index

When we chose a BMI value of 25, the favorable effect of eradication was statistically significant (Table 3).

DISCUSSION

This study has several important outcomes. The first major result is favorable HbA1c changes obtained after *H. pylori* eradication. That result is especially important because the study group was selected from the persons with normal blood glucose concentrations. Based on these results we could suggest eradication of *H. pylori* to prevent diabetes and associated diseases. Herein, BMI of 25 is important when selecting the population for association of blood glucose concentrations and *H. pylori.* A BMI cut-off value is an important tool to answer the question "who will benefit *H. pylori* eradication".

Indeed, the favorable effect of *H. pylori* eradication on insulin resistance was previously documented in some studies[16,17] . However, this relationship was not clear due to methodological pitfalls in those studies. Those pitfalls were selection of inappropriate or insufficient methods used for detecting of *H. pylori* infection and the population differences among different studies[18-20]. The relationship between inflammation and insulin resistance in type 2 diabetes has already been shown[21]. Similarly, a higher prevalance of *H. pylori* in patients with diabetes was shown in Turkey[22].

H. pylori causes systemic host inflammatory responses including cytokine production such as TNF-α, CRP, IL-1β, lipid-peroxides, hyperhomocysteinemia (HHcy) and intercellular-and vascular-cell adhesion molecules (ICAM-1 and VCAM-1, respectivelly) (ref.[22-26]). *H. pylori* infected gastric mucosa produces higher level of IL-17 which stimulates the synthesis of IL-8, an important neutrophil chemoattractant. IL-17 is also suggested to play an important role in the inflammatory response to the *H. pylori* infection. Those inflammatory cascades especially TNF-α and CRP are proposed be strongly associated with insulin resistance[27-29]. The systemic inflammation due to *H. pylori* might also lead to impairment in insulin secretion[30] . Pancreatitis, insulin producing pancreatic beta-cells injury, caused by systemic inflammation of *H. pylori* was also proposed to explain this association[31,32].

Leptin related mechanism is another proposed mechanism in this regard. In a study, leptin levels were found to be higher in patients with *H. pylori* infection. Authors suggested that high levels of leptin decrease the effect of insulin by phosphorylation of Ser-318 of IRS-1 (ref.[33]). Another study showed that low plasma ghrelin levels are associated with elevated fasting insulin levels and insulin resistance[34]. Plasma ghrelin concentrations were significantly lower in *H. pylori* positive than *H. pylori* negative controls[35].

Although there are several mechanisms proposed in *H. pylori* and insulin resistance association, there is not enough data to clarify the effects of *H. pylori* eradication on insulin resistance. Some studies showed the favorable effect of *H. pylori* eradication therapy on insulin resistance and metabolic syndrome components[11,17]. However, other studies do not support this benefit[12] .

CONCLUSION

The most important, different and new data in this study is the documentation of benefit of *H. pylori* eradication in people with normal blood glucose concentrations. The results showed favorable changes in all indices of blood glucose metabolism such as, HbA1c, HOMA, insulin levels after *H. pylori* eradication. Then the question might arise: who will benefit? Will we give it to all the people with *H. pylori*. In this regard, BMI higher than 25 mg/m² could be helpful. Eradication in patients with BMI>25 mg/m² had effects both on insulin resistance and HbA1c. On the other hand, eradication yielded only HbA1c decrease in patients with BMI less than 25 mg/m². We propose *H. pylori* as a predisposing factor in diabetes development . However, further studies are necessary to establish this pathogenesis.

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Author contributions: ZD, LF: study design; ZD: literature search; ZD, BE, MS: data collection and analysis; ZD, LF: data interpretation; LF: manuscript revision.

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