Original Article

Effect of *Helicobacter pylori* eradication on glycaemia control in patients with type 2 diabetes mellitus and comparison of two therapeutic regimens

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ABSTRACT

Background and study aims: The eradication rate of *Helicobacter pylori* (*H. pylori*) has been reported as being lower in patients with type 2 diabetes mellitus (DM) than in those without DM. The aim of the study was to assess the efficacy of the two *H. pylori* eradication regimens in patients without and with type 2 DM and to study the effect of *H. pylori* treatment on glycaemia control.
Patients and Methods: A total of 93 consecutive type 2 DM (non-insulin users) and 98 non-diabetic age- and sex-matched patients were enrolled. Patients were randomly assigned to one of the two treatment protocols all given twice daily: (a) a 14-day quadruple therapy comprising of omeprazole 20 mg, metronidazole 500 mg, amoxicillin 1 g and bismuth subcitrate 240 mg (OMAB) and (b) a 14-day triple regimen comprising of omeprazole 20 mg plus clarithromycin 500 mg and amoxicillin 1 g (OCA). Cure was defined as a negative ^{13}C-urea breath test at least 6 weeks after treatment.
Results: The *H. pylori* eradication rate with the OCA regimen was 63% in patients with type 2 DM (non-insulin users) and 87.7% in the control group ($p = 0.017$). The *H. pylori* eradication rate with the OMAB regimen was 38.2% in patients with type 2 DM and 55.1% in the control group ($p < 0.001$). Mean decrease of fasting plasma glucose and HbA1c level shows no statistically significant difference after *H. pylori* eradication.
Conclusion: This study suggests that the eradication rate of *H. pylori* with OCA or OMAB treatment is lower in patients with type 2 diabetes than in non-diabetics and *H. pylori* treatment in patients with type 2 DM has no role in the control of the glycaemia. The triple therapy (OCA) is superior to the quadruple protocol (OMAB) in *H. pylori* eradication of both DM and non-DM cases.

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Introduction

Diabetes mellitus (DM) is one of the most prevalent endocrine diseases and the importance of glycaemia control has been emphasised by studies showing that diabetic patients with higher levels of glycosylated haemoglobin (HbA1c) have more complications such as retinopathy, nephropathy and neuropathy [1]. Infections can lead to hyperglycaemia in patients with DM because the increased production of cytokines can stimulate the secretion of insulin counter-regulatory hormones [2]. Infection with *Helicobacter pylori* (*H. pylori*) induces gastric inflammation and has been associated with an increased production of cytokines such as tumour necrosis factor, interferon-γ and interleukins. The patients with concomitant *H. pylori* infection require higher doses of insulin and yet had higher levels of HbA1c than their uninfected counterparts [3].

Type 2 DM can present with many gastrointestinal symptoms and *H. pylori* can play a role in these diseases [4]. Xia et al. showed that the seroprevalence of *H. pylori* infection was not statistically different in patients with DM and non-diabetic controls [5]. This prevalence should be corrected for age and gender and there are no differences if an adjustment has been done [6]. Further, the eradication of *H. pylori* shows great differences between different ethnic groups and in patients with some chronic conditions [4].

Selection of the best drug regimens for effective eradication of *H. pylori* infection, especially in patients at risk of peptic-ulcer relapses, is already challenging. Nowadays, quadruple therapy has been produced as an effective drug regimen and even an alternative first-line treatment for eradicating *H. pylori* infection, especially in areas of high prevalence of antibiotic resistance [7]. Some recent studies have suggested that the effectiveness, compliance and side effects of quadruple regimen containing a gastric-acid inhibitor, a bismuth compound and amoxicillin might be comparable with proton-pump-inhibitor (PPI)-based triple therapy when administered as first-line treatment for *H. pylori* infection [8–11]. However, some

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J. Vafaeimanesh et al./Arab Journal of Gastroenterology 14 (2013) 55–58

Table 1
Baseline characteristics of study subjects in different groups.

Character	Groups				Total ($n = 191$)	p value
	DM + OMAB ($n = 47$)	DM + OCA ($n = 46$)	Control + OMAB ($n = 49$)	Control + OCA ($n = 49$)		
Age (years)	55.5 ± 10.6	55.1 ± 10.3	56.1 ± 9.7	55.6 ± 8.9	55.6 ± 9.8	0.23
Gender (M/F)	25/22	25/21	26/23	27/22	103/88	0.89
BMI (kg m^{-2})	27.9 ± 3.7	27.9 ± 3.5	27.4 ± 3.3	27.1 ± 3.9	27.5 ± 3.6	0.23
HbA1c (%)	9.5 ± 1.6	9.4 ± 1.7	–	–	–	0.57
Fasting Plasma Glucose (mg dl^{-1})	135.6 ± 37.5	135.6 ± 38.6	–	–	–	0.66

OMAB = omeprazole, metronidazole, amoxicillin and bismuth subcitrate.
OCA = omeprazole, clarithromycin and amoxicillin.
HbA1c = glycosylated haemoglobin.
DM = diabetes mellitus.

others could show slight differences in effectiveness, usually in favour of quadruple therapy [12,13].

Therefore, the advantages of quadruple therapy at present do not seem clear enough to change the current policies for *H. pylori* treatment. Further, the effect of prolonging the duration of quadruple therapy on treatment efficacy is already questioned. The primary aim of the study was to assess and compare the efficacy of the two *H. pylori* eradication regimens in patients without and with type 2 DM in the Iranian population. The secondary aim was to study the effect of *H. pylori* treatment on glycaemia control in diabetic patients.

Patients and methods

A prospective double-blinded, randomised clinical trial was conducted on 100 consecutive type 2 DM (non-insulin users) patients and 100 non-diabetic age- and sex-matched control patients with upper gastrointestinal symptoms between March 2009 and April 2011. All patients signed an informed consent form. This research was approved by the Ethics Committee of Research Center for Gastroenterology and Liver Disease at Shahid Beheshti University of Medical Sciences.

Patients had not been previously treated for *H. pylori* infection. Subjects were excluded if they had been taking non-steroidal anti-inflammatory drugs (NSAIDs), PPIs, bismuth preparations or antibiotics during the previous 8 weeks. Pregnant women and patients with a history of smoking, alcohol consumption, abdominal surgery, drug allergy, renal failure and hepatic impairment were not enrolled. Dyspepsia was defined as epigastric pain or discomfort lasting for at least 3 months. Patients with type 2 DM with previously diagnosed gastroparesis were excluded from the study. All patients were diagnosed to be *H. pylori* positive by histopathological examination. Gastroscopy was done using a video scope

(Olympus GIF-XQ260, Japan). Two specimens were obtained from the antrum. Type 2 DM patients were allowed to continue insulin and oral antidiabetic drugs during the study.

Patients were randomly assigned to one of the two treatment protocols all given twice daily: (a) a 14-day quadruple therapy comprising omeprazole 20 mg, metronidazole 500 mg, amoxicillin 1 g and bismuth subcitrate 240 mg (OMAB) and (b) a 14-day triple regimen comprising omeprazole 20 mg plus clarithromycin 500 mg and amoxicillin 1 g (OCA).

Patients were asked to return at the end of the treatment to assess compliance with therapy that was defined as consumption of >90% of the prescribed drugs. Medications were discontinued if any intolerable adverse events such as fever, urticarial rash or generalised body pain occurred. Cure was defined as a negative ^{13}C-urea breath test at least 6 weeks after treatment. HbA1c and fasting plasma glucose level were measured in all diabetic patients at the beginning of the study, 3 and 6 months later.

Statistically significant differences between groups were assessed using Student's *t*-test, chi-squared test as well as Fisher's exact test and one-way analysis of variance (ANOVA) test. A *p* value of 0.05 or less was considered statistically significant. All the data were analysed using Statistical Package for the Social Sciences (SPSS) 16 for Windows (SPSS Inc., Chicago, IL, USA) and the values were expressed as mean ± standard deviation (SD) for continuous variables and percentages for categorical variables.

Results

Among 100 patients in each group, 93 type 2 DM (non-insulin users) and 98 non-diabetic age- and sex-matched patients could continue the treatment protocols and underwent ^{13}C-urea breath testing. A total of 191 patients (53.9% male, between 45 and

Table 2
Upper GI endoscopic findings of study subjects in different groups.

Character	Group				Total ($n = 191$)	p value
	DM + OMAB ($n = 47$)	DM + OCA ($n = 46$)	Control + OMAB ($n = 49$)	Control + OCA ($n = 49$)		
Gastritis						
Normal	22 (46.8%)	21 (45.6%)	24 (48.9%)	23 (46.9%)	90 (47.1%)	0.57
Non-erosive	20 (42.5%)	19 (41.3%)	20 (40.8%)	21 (42.8%)	80 (41.9%)	0.90
Erosive	3 (6.4%)	4 (8.7%)	3 (6.1%)	2 (4.1%)	12 (6.3%)	0.57
Gastric Ulcer	2 (4.2%)	2 (4.3%)	2 (4.1%)	3 (6.1%)	9 (4.7%)	0.23
Duodenitis						
Normal	30 (63.8%)	29 (63.1%)	32 (65.3%)	31 (63.2%)	122 (63.9%)	0.90
Non-erosive	10 (21.3%)	9 (19.5%)	9 (18.3%)	11 (22.4%)	39 (20.4%)	0.57
Erosive	2 (4.2%)	3 (6.5%)	2 (4.1%)	2 (4.1%)	9 (4.7%)	0.57
Duodenal Ulcer	5 (10.6%)	5 (10.8%)	6 (12.2%)	5 (10.2%)	21 (10.9%)	0.23

OMAB = omeprazole, metronidazole, amoxicillin and bismuth subcitrate.
OCA = omeprazole, clarithromycin and amoxicillin.
DM = diabetes mellitus.

Table 3
H. pylori eradication findings of study subjects in different groups.

H. pylori eradication regimens	Groups		Total (n = 191)	p value
	DM (n = 93)	Control (n = 98)		
OMAB	18 of 47 (38.2%)	27 of 49 (55.1%)	45 of 96 (46.8%)	<0.001
OCA	29 of 46 (63.0%)	43 0f 49 (87.7%)	72 of 95 (75.7%)	0.017

OMAB = omeprazole, metronidazole, amoxicillin and bismuth subcitrate.
OCA = omeprazole, clarithromycin and amoxicillin.
DM = diabetes mellitus.

Table 4
Effect of H. pylori eradication on the control of glycaemia in patients with type 2 DM.

aCharacter	DM Subgroups (n = 93)		p value
	With H. pylori eradication (n = 47)	Without H. pylori eradication (n = 46)	
HbA1c decreases (%)			
After 3 months	0.23 ± 0.91	0.25 ± 0.85	0.54
After 6 months	0.19 ± 0.85	0.20 ± 0.91	0.77
Fasting plasma glucose decrease (mg dl^{-1})			
After 3 months	10.9 ± 12.1	9.5 ± 14.3	0.58
After 6 months	8.9 ± 16.8	9.4 ± 15.6	0.54

HbA1c = glycosylated haemoglobin.
DM = diabetes mellitus.

81 years, mean age ± SD: 55.6 ± 9.8 years) in four groups of subjects were studied. There were no statistical differences in the study groups in age, gender and body mass index (BMI) distributions (Table 1). Further, no significant differences were observed in HbA1c and fasting plasma glucose between the two diabetic groups at the beginning of the study.

Upper gastrointestinal endoscopy was performed for all of the study subjects (Table 2) and there was no significant difference in terms of the rate of gastritis and duodenitis among the four study groups. As shown in Table 3, H. pylori infection in both groups (DM and non-DM) was successfully eradicated in 72 of 95 patients (75.7%) with the OCA regimen and in 45 of 96 patients (46.8%) with the OMAB regimen, respectively (p = 0.003). The H. pylori eradication rate with the OCA regimen was 63% in patients with DM and 87.7% in the control group (p = 0.017). The H. pylori eradication rate with the OMAB regimen was 38.2% in patients with DM and 55.1% in the control group (p < 0.001).

In patients with type 2 DM, the mean decrease of HbA1c and fasting plasma glucose level in eradicated cases is similar to non-eradicated subjects 3 and 6 months after treatment (Table 4).

Discussion

Many researchers have explored the relationship between H. pylori and DM. There have been controversial results in these studies but in a large, well-designed study of Xia et al., there was no difference of the seroprevalence of H. pylori infection between patients with DM and non-DM controls [5]. Tseng [14] showed a higher incidence of H. pylori eradication in patients with type 2 DM and in insulin users among the diabetic patients. Further, Polyzos [15] studied a potential association between H. pylori infection, metabolic syndrome and insulin resistance, but further studies are needed to strengthen this association and to clarify whether there is a causative link between them.

According to several guidelines, first-line standard treatment for H. pylori eradication consists of triple therapy containing a PPI, amoxicillin and clarithromycin. In recent decades, the use of clarithromycin-based treatment and the widespread use of long-acting macrolides have resulted in considerable resistance of H. pylori strains to clarithromycin [16]. Standard triple therapy (omeprazole, clarithromycin and amoxicillin) has been shown to

be effective in the eradication of H. pylori in non-DM subjects [17,18]. In our control subjects, we found an eradication rate of 87.7%, which was compatible with the results in the literature.

According to the Maastricht III Consensus Report, [19] in patients with H. pylori infection, the PPI–clarithromycin–amoxicillin or metronidazole combination is the recommended first-choice treatment in populations with <15–20% clarithromycin resistance and, in populations with <40% metronidazole resistance, PPI–clarithromycin–metronidazole is preferable. H. pylori infection is usually eradicated by using multi-drug regimens. Recently, quadruple drug therapies using a PPI with bismuth triple therapy have been recommended to decrease the failure rates of H. pylori eradication caused by resistance to some antibiotics such as metronidazole and clarithromycin [20].

In the study by Demir et al. [21] of 89 type 2 diabetic patients, the eradication rate was 51% with standard triple therapy (PPI, clarithromycin and amoxicillin) and this could be increased by a quadruple regimen (pantoprazole, bismuth, tetracycline and metronidazole) to 85%. The eradication rate was significantly lower in the DM group than in the non-DM group. However, in our study, the H. pylori eradication rates were 63% in the OCA-DM group and 38.2% in the OMAB-DM group. Eradication rates in cases (DM and non-DM) that were administered OMAB treatment were significantly lower than in groups with OCA. It seems that low cure rates following quadruple in our study group can be due to antimicrobial drug resistance (particularly metronidazole) that is a main source of treatment failure following these regimens. Broad or inappropriate use of potent antibiotics results in low susceptibility of H. pylori to some common antibiotics such as metronidazole in our population that can lead to development of antibiotic resistance. (In Iran metronidazole resistance is higher than in Turkey.) In one study, it has been shown that tetracycline-containing quadruple therapy is highly effective in treating H. pylori-eradication failures of the amoxicillin-containing regimen [22]. However, in another study the results of 14-day tetracycline-containing sequential therapy for the first-line treatment of H. pylori in patients with type 2 DM were disappointing [23]. In a later 7-day trial, all patients received pantoprazole 40 mg and amoxicillin 1000 mg twice daily, followed by pantoprazole 40 mg, metronidazole 500 mg twice daily and tetracycline 500 mg four times per day for the remaining 7 days.

In diabetes, immunosuppression might predispose to the low eradication rate of *H. pylori* infection but other mechanisms may also explain this problem. Type 2 diabetics are more susceptible to many bacterial infections, which may lead to frequent use of antibiotics, and to the development of resistance [24]. In our study, the eradication rate of *H. pylori* with both OCA and OMAB treatment is lower in patients with type 2 diabetes than in non-diabetics.

Other factors that might influence the *H. pylori* eradication rate are diabetes duration, glycaemic level, obesity, being on oral hypoglycaemics or insulin and socioeconomic status. In Tseng's study, [14] a significantly higher incidence of *H. pylori* eradication in patients with type 2DM and in insulin users was seen. The odds ratios were attenuated with increasing diabetes duration, probably due to the occurrence of other co-morbidities. Additionally, lower socioeconomic status and the use of calcium channel blockers consistently show a higher rate of *H. pylori* eradication, but the uses of oral anti-diabetic agents do not. Although data seem to indicate an association between *H. pylori* infection and insulin resistance, further studies are needed to clarify whether there is a causative link between them. If a causal link is confirmed, this may have a major impact on the pathophysiology and management of insulin resistance syndrome, including type 2 DM and non-alcoholic fatty liver disease [15].

Toussy et al. [25] showed that the mean decrease of HbA1c level after 3 months in the case (treatment) group is more than in the control (without treatment) group; however, this difference is not statistically significant and very small. In our patients with type 2 DM, the mean decrease of HbA1c and fasting plasma glucose level in eradicated cases is similar to non-eradicated subjects 3 and 6 months after treatment. Thus, it suggests that *H. pylori* treatment in patients with type 2 DM has no role in control of the disease.

In conclusion, we found that the eradication rate of *H. pylori* with OCA or OMAB treatment is lower in patients with type 2 diabetes than in non-diabetics and *H. pylori* treatment in patients with type 2 DM has no role in control of the glycaemia. The superiority of 2-week triple therapy to 2-week quadruple protocol can be due to the low susceptibility of *H. pylori* to administered drugs such as metronidazole in the second regimen and also low resistance of used antibiotics such as clarithromycin in triple therapy in the Iranian population. Further studies with new antibiotic combinations are needed to find better methods of eradicating *H. pylori* in patients with type 2 DM.

Acknowledgements

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