Turk J Gastroenterol 2007; 18 (4): 225-229

Association between type 2 diabetes mellitus and *Helicobacter pylori* infection

Tip 2 diabetes mellitus ve *Helikobakter pilori* ilişkisi

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Background/aims: *It is well known that patients with diabetes mellitus are more prone to infection. In patients with diabetes mellitus, chronic infections are frequent and severe, due to the impairment of their immune status. The aim of this study was to determine the association between Helicobacter pylori infection and type 2 diabetes mellitus in the United Arab Emirates population. This is a case and control study comparison of type 2 diabetes mellitus and non-diabetic groups. The study was conducted at the primary health care clinics in United Arab Emirates during the period from June 2002 to August 2003. The study included 210 type 2 diabetes mellitus patients and 210 non-diabetic subjects.* ***Methods:*** *Helicobacter pylori was assessed by histopathological examination by measuring antibody profiles (IgG and IgA) among type 2 diabetes mellitus patients and the non-diabetic group.* ***Results:*** *The mean age of type 2 diabetes mellitus patients infected with Helicobacter pylori was 48.1 ± 7.9 years compared to 46.7 ± 5.4 years in the non-diabetic infected subjects. A positive antibody titer for Helicobacter pylori infection (IgA ≥300) was found in 76.7% of the diabetic subjects compared to 64.8% of the non-diabetic subjects (p<0.009). There was higher prevalence of Helicobacter pylori infection in diabetic obese patients than the non-diabetic subjects (23.6% vs 11.8%, p<0.001). Muscular (47.2%), gastrointestinal (29.8%), chronic bronchitis (22.4%), nausea (19.9%), anemia (18%), abdominal pain (12.4%), diarrhea (10.6%) and vomiting (7.5%) were more common in diabetic patients infected with Helicobacter pylori.* ***Conclusions:*** *The present study suggests that there is a significant association between Helicobacter pylori infection and type 2 diabetes mellitus. Helicobacter pylori infection was significantly higher in diabetic obese patients than non-diabetic subjects.*

Key words: Epidemiology, prevalence, immunoglobulin, IgG, IgA, antibodies, serology, type 2 diabetes mellitus, United Arab Emirates

Amaç: *Diabetes mellitus'lu hastaların enfeksiyona yatkınlığı bilinen bir hususturdiabetes mellituslu hastalarda, immün sistemin yetersizliğinden dolayı kronik enfeksiyon daha sık ve şiddetlidir. Bu çalışmanın amacı, Birleşik Arap Emirlikleri halkında, Helikobakter pilori enfeksiyonu ve tip 2 diabetes mellitus arasında olası ilişkinin araştırılmasıdır. Bu çalışma tip 2 diabetes mellitus ve non-diabetik grupların karşılaştırıldığı bir vaka-kontrol çalışmasıdır. Çalışma Birleşik Arap Emirlikleri'nde birinci basamak ünitelerinde Haziran 2002- Ağustos 2003 arasında yapıldı. Çalışmaya 210 tip 2 diabetes mellitus ve 210 non-diabetik hasta dahil edildi.* ***Metodlar:*** *Helikobakter pilori hastalarda histopatolojik örneklerde IgG ve IgA antikorları bakılarak araştırıldı.* ***Bulgular:*** *Helikobakter pilori ile enfekte tip 2 diabetes mellitus'luların ortalama yaşı 48.1 ± 7.9, non-diabetik kontrol grubunun ise 46. 7 ± 5.4 idi. Helikobakter pilori enfeksiyonu için pozitif antikor titresi (IgA≥300) diabetik hastaların %76.7'sinde, kontrol grubunun ise %64.8'inde görüldü (p<0.009). Diabetik obez hastalarda non-diabetik kontrollere göre daha yüksek Helikobakter pilori prevalansı mevcuttu (23.8% vs. 11.8%, p<0.001). Müsküler (%47.2), gastrointestinal (%29.8), kronik bronşit (%22.4), bulantı (%19.9), anemi (%18), karın ağrısı (%12.4) ve kusma (%7.5) Helikobakter pilori ile enfekte diabetik hastalarda daha sıktı.* ***Sonuç:*** *Bu çalışma Helikobakter pilori enfeksiyonu ile tip 2 diabetes mellitus arasında anlamlı bir ilişki olduğunu düşündürmektedir. Helikobakter pilori enfeksiyonu, diabetik obez hastalarda non-diabetik kişilere göre anlamlı olarak daha fazla saptanmıştır.*

Anahtar kelimeler: Epidemiyoloji, prevalans, immunoglobulin, IgG, IgA, antikorlar, seroloji, tip 2 diabetes mellitus, Birleşik Arap Emirlikleri

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Manuscript received: 13.02.2007 **Accepted:** 09.08.2007

INTRODUCTION

Helicobacter pylori (*H.pylori*) infection affects approximately 50% of the world population (1). It is now broadly accepted that infection with *H.pylori* is one of the most common chronic infections worldwide (2). *H.pylori* is a common infection in diabetics who do not have metabolically controlled hyperglycemia and these are individuals who are colonized by *H.pylori* infection in the gastric antrum (3, 4). However, data on the prevalence of *H.pylori* in type 2 diabetes mellitus (T2DM) patients are scarce and contradictory (3-7). Both the natural history of gastrointestinal symptoms and factors influencing symptom turnover in diabetes mellitus are unknown (3, 4-7). Hence, it is important to investigate the significance of T2DM as a risk factor for *H.pylori* infection.

The aim of this study was to determine the association between *H.pylori* infection and T2DM in a geographically defined Emirati population.

MATERIALS AND METHODS

Study Design

This is a case and control study comparison of T2DM and non-diabetic groups, who were evenly matched for age and sex. The study was conducted during the period from June 2002 to August 2003. The inclusion criterion was a minimum of three years of diabetes. Patients with previous history of anti-*H.pylori* treatment or those on regular non-steroidal anti-inflammatory drugs (which may interfere with dyspeptic symptoms) were excluded from the study. A questionnaire was used to collect information on their sociodemographic status, and their health status was assessed by recording their height, weight and blood pressure during physical examination and blood glucose, cholesterol (total), high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides and uric acid through analysis.

To determine the sample size based on the association of *H.pylori* with type 2 diabetes, we assumed an average frequency difference of 13% in diabetics versus non-diabetics, as given in the published reports (3-7). Under these parameters, we estimated that approximately 210 T2DM and 210 control subjects would provide 80% power to reject the null hypothesis at $p<0.05$.

Selection of Type 2 Diabetic Mellitus Subjects

Persons were classified as diabetic (cases) according to the American Diabetic Association (ADA) (8) criteria if both their venous blood glucose values were ≥7.0 mmol/L or if they were currently taking diabetic medication. We studied Emirati diabetic subjects diagnosed for type T2DM in accordance with the established diagnostic criteria. A total number of 210 diabetic Emirati patients aged 35-65 years were selected randomly from Primary Health Care Centers.

Selection of Non-Diabetic Subjects

Non-diabetic (control) subjects aged 35-65 years were identified from the community if both their venous blood glucose values were <6.1 mmol/L and if they had never taken any diabetic medication. Control subjects were proven as nondiabetic by a 75-g oral glucose tolerance test (OGTT) that was performed according to the World Health Organization (WHO) criteria (8). This group consisted of a sample of 210 Emirati subjects who visited the Primary Health Care Centers for any reason other than diabetes mellitus and were selected randomly from the daily appointment list.

A public health nurse measured the blood pressures of the study participants from the right arm with the subject in a sitting position. Three measurements were taken at 5-minute intervals after the subjects had rested for 20 minutes. A standard mercury sphygmomanometer with a random zero device was used for all measurements. The pressures at the first and fifth Korotkoff sounds were recorded as systolic and diastolic blood pressures, respectively. The average of the three readings was used in data analysis. Hypertension was diagnosed according to WHO criteria (12).

Height and weight were measured using standardized methods. The body mass index (BMI) was calculated as the weight in kilograms (with 1 kg subtracted to allow for clothing) divided by height in meters squared. Subjects were classified into three categories as: acceptable weight, BMI <25; overweight, BMI 25-30; and obesity, BMI >30 kg/m^2.

Biochemistry Data

Venous blood samples for determination of uric acid, triglycerides, total cholesterol and HDL-cholesterol were collected after an overnight fast, anticoagulated with EDTA and centrifuged to prepa-

re plasma. Serum samples for insulin were obtained by centrifuging clotted blood and were stored at -20°C until assay. A standard (75 g) OGTT was performed according to the WHO recommendations (8) and blood was sampled for glucose and insulin at 0, 30, 60, and 120 minutes. Severe insulin resistance was defined as fasting serum insulin level above 300 pmol/L, or peak (post-OGTT) insulin levels above 2100 pmol/L. Fasting insulin levels below 180 pmol/L or peak insulin levels below 900 pmol/L were considered to be normal. The level of LDL-cholesterol was calculated using the Friedewald et al. (9) formula. Uric acid levels were determined by using a commercial kit (Dimension clinical chemistry system, Dade International Inc., USA).

H. pylori Serology

Serum specimens were obtained from all cases and controls for *H.pylori* serology test. The sera were stored at -80°C until processed using a commercially available kit (Orion Diagnostica, Espoo, Finland). The test was performed according to the manufacturer's instructions. IgG antibodies against a low molecular weight fraction of *H.pylori* antigens were measured in duplicate with a validated in-house indirect enzyme-linked immunosorbent assay (ELISA) (11,12). A subject was considered to be positive for *H.pylori* if IgG and IgA anti-*H.pylori* antibody titers were >300 and >250, respectively. People with seropositive levels of IgG antibodies to *H.pylori* were assumed to be infected with *H.pylori*.

Student-t test was used to ascertain the significance of differences between mean values of two continuous variables and confirmed by non-parametric Mann-Whitney test. Chi-square was performed to test for differences in proportions of categorical variables between two or more groups. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated by using Mantel-Haenszel test. The level $p<0.05$ was considered to be the cut-off value for significance.

RESULTS

Table 1 shows the prevalence of *H.pylori* infection in the studied diabetic and non-diabetic subjects. According to IgA, positive antibody titer for *H.pylori* infection (IgA >250) was found at a significantly higher rate in diabetic subjects (63.3%) compared to non-diabetic subjects (48.1%) ($p<0.001$). Similarly, according to IgG antibody titer (IgG >300), *H.pylori* infection was determined in diabetic patients at a rate of 76.7% compared to an infection rate of 64.8% in non-diabetic subjects ($p=0.009$).

Table 2 shows the baseline physical and metabolic characteristics of diabetic and non-diabetic subjects with *H.pylori* infection. Obesity was more prevalent in *H.pylori* sero-positive diabetic patients than *H.pylori*-positive non-diabetic subjects. Furthermore, blood pressure, cholesterol, triglyceride and uric acid mean values were significantly associated with the presence of diabetes among subjects with *H.pylori* infection.

Table 3 shows the reported symptoms, signs and diseases among the diabetic patients and non- diabetic subjects with *H.pylori* infection. As can be seen, diabetic patients showed higher prevalence

Table 1. Prevalence of *Helicobacter pylori* infection in the diabetic and non-diabetic subjects

Characteristics	T2DM patients (N=210)	Non-diabetic subjects (N=210)	P-value
IgA > 250 titer			
H. pylori +	133 (63.3%)	101 (48.1%)	0.0023
H. pylori -	77 (36.7%)	109 (51.9%)	
***H. pylori* + by Gender**			
Male	62 (46.6%)	47 (46.5%)	NS
Female	71 (53.4%)	54 (53.5%)	
IgG > 300 titer			
H. pylori +	161 (76.7%)	136 (64.8%)	0.01
H. pylori -	49 (23.3%)	74 (35.2%)	
***H. pylori* + by Gender**			
Male	76 (47.2%)	68 (50.0%)	NS
Female	85 (52.8%)	68 (50.0%)	

NS = Not-significant

Table 2. Baseline physical and metabolic characteristics of diabetic and non-diabetic subjects with *Helicobacter pylori* infection

Variables	IgA > 250		IgG > 300	
	Diabetic n=133/210 Mean±SD	Non-diabetic n=101/210 Mean±SD	Diabetic n=161/210 Mean±SD	Non-diabetic n=131/210 Mean±SD
Age (in years)	48.1±7.9	46.7±5.4	47.2±6.8	45.7±6.6
Body mass index (kg/m^2)	29.8±4.7**	25.4±3.9	29.2±4.6	25.2±3.7
BMI >30 (%)	24.8%	12.7%	23.6%	11.8%
Blood Pressure				
Systolic	128.3±16.0**	124.6±12.1	128.1±15.6	124.7±12.5
Diastolic	83.3±9.9	81.7±9.6	83.5±9.7	81.6±8.1
Fasting Serum				
Glucose (mmol/L)	6.9±1.4**	5.3±0.5	6.8±1.6**	5.3±0.5
Total cholesterol (mmol/L)	4.8±1.1*	4.5±1.3	4.8±1.2	4.5±1.2
HDL cholesterol (mmol/L)	1.4±0.2	1.4±0.3	1.3±0.2	1.5±0.3
LDL cholesterol (mmol/L)	3.0±0.2	3.3±0.2	3.0±0.2	3.3±0.2
Triglyceride (mmol/L)	1.2±0.5*	1.1±0.6	1.3±0.6	1.1±0.7
Uric acid (mmol/L)	0.31±0.07	0.28±0.06	0.30±0.07**	0.28±0.06

*p<0.05, **p<0.01

Table 3. Reported symptoms and diseases among the type 2 diabetes mellitus patients and non-diabetic control subjects with *Helicobacter pylori* infection

DISEASE / SYMPTOMS	T2DM with *H. pylori* n=161 Yes (%)	Non-DM with *H. pylori* n=136 Yes (%)	Odds ratio [OR]	Confidence Interval 95% [CI]	p-value
Hypertension	31 (19.3)	17 (12.5)	1.67	0.84-3.33	0.115 (NS)
Anemia	29 (18.0)	12 (8.8)	2.27	1.06-4.95	0.022
Muscular symptoms	76 (47.2)	39 (28.7)	2.22	1.33-3.72	0.001
Lumbar pain	14 (8.7)	7 (5.1)	1.76	0.64-4.97	0.235 (NS)
Diarrhea	17 (10.6)	5 (2.6)	3.09	1.03-9.88	0.024
Abdominal pain, constipation	20 (12.4)	12 (8.8)	1.47	0.65-3.34	0.319 (NS)
Gastrointestinal	48 (29.8)	20 (14.7)	2.46	1.33-4.60	0.002
Nausea	32 (19.9)	9 (6.6)	3.50	1.55-8.25	0.001
Vomiting	12 (7.5)	2 (1.5)	5.40	1.12-35.50	0.0208
Chronic bronchitis	36 (22.4)	18 (13.2)	1.89	1.04-3.68	0.043

NS = Not-significant

rate of symptoms than control subjects. Muscular (47.2%), gastrointestinal (29.8%), chronic bronchitis (22.4%), nausea (19.9%), anemia (18%), abdominal pain (12.4%), diarrhea (10.6%) and vomiting (7.5%) were more common in diabetic patients infected with *H.pylori*.

DISCUSSION

H.pylori prevalence was significantly higher in T2DM patients than in non-diabetic subjects (63.3% vs 48.1% for IgA>250 titer and 76.7% vs 64.8% for IgG>300 titer). The prevalence of *H.pylori* infection in our community was slightly higher than rates described in other reports (3-7). The rate of *H.pylori* infection in Hong Kong Chinese (13) subjects with T2DM was lower than the rate in Qatar, around 50%, which is similar to that in non-diabetic subjects. Anastiosis et al. (14) reported that the prevalence of *H.pylori* infection in T2DM patients ranged from 30 to 78%, which is in accordance with our prevalence. The variability in the prevalence rates may be related to the epidemiological distribution of *H.pylori*. It has been speculated that alterations in glucose metabolism may promote *H.pylori* colonization (15).

Evidence has recently been published (3-7,15) suggesting that the prevalence of *H.pylori* infection might be increased in T2DM obese patients as opposed to the normal population. This is consistent with our study finding of a higher prevalence of *H.pylori* infection in T2DM obese patients (25%).

However, some authors (14,16) did not detect and confirm an association between *H.pylori* infection and diabetes. For example, a Greek study (14) did not support an association between *H.pylori* infection and diabetes mellitus. That study reported no difference between T2DM patients and non-diabetics with regard to the prevalence of both *H.pylori*

infection and *H.pylori*-related gastroduodenal disorders. Currently, there is no satisfactory explanation for the differences in results.

The current study confirmed that *H.pylori* prevalence was significantly higher in T2DM patients than in non-diabetic subjects, and this is consistent with the previous reported studies (3-6,13,18). These findings are generally explained by the impairment of cellular and humoral immunity in diabetics (4,13,18), by the reduction of both gastrointestinal motility and acid secretion and by the effect of a higher secretion of proinflammatory cytokines attributable to the *H.pylori* gastric infection itself. An Italian study (15) showed that although the prevalence of *H.pylori* infection was found to be significantly higher in T2DM patients than in controls, the prevalence rate of endoscopic lesions was comparable in the two groups, but the association between endoscopic lesions and *H.pylori* infection was significantly higher in diabetics. *H.pylori* is an important cause of chronic active gastritis and plays an important role in the etiology of peptic ulcer disease in humans (19-22). Furthermore, gastrointestinal symptoms in diabetes mellitus may be linked to diabetic complications, particularly peripheral neuropathy, and to poor glycemic control (3,4-7). The current study findings support the high prevalence of *H.pylori* among diabetic subjects.

CONCLUSIONS

Overall, the present study findings suggest an assoication between *H.pylori* infection and T2DM. Prevalence of *H.pylori* infection was significantly higher in T2DM obese subjects than non-diabetic subjects.

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