Helicobacter pylori infection in type 2 diabetic patients and its relation to smoking

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Abstract: Background: -Helicobacter pylori (H. pylori) is a major human bacterial pathogen, the chronic infection of which causes a number of upper gastrointestinal effects. Chronic exposure to cigarette smoke in Helicobacter pylori infected patients enhances the risk of gastric mucosal atrophy and intestinal metaplasia. **Objectives:** evaluate the prevalence of H. pylori infection in type 2 diabetes patients and its relation smoking. **Subjects and methods: -** The study was carried out on 100 individuals divided into; 50 patients diagnosed as T2DM and 50 healthy volunteers formed the control group. All were subjected to history taking, clinical examination, H. pylori immunoglobulin G level, fasting blood glucose and lipid profile, Urea Breath Test (UBT) for the positive H. pylori IgG. **Results:** The difference of H. pylori prevalence between diabetics (54%) and control (28%) was significant **(p=0.008)** and maximum positivity was in groups with higher HbA1C level **(p=0.037).** In both groups, subjects with H pylori seropositivity had significantly high serum cholesterol, serum triglycerides, serum low-density lipoprotein (LDL) and low serum high-density lipoprotein (HDL) levels compared to negative H. pylori. In diabetic group there was statistically significant difference in the incidence of H. pylori positivity between smokers & non-smokers ***(p=0.016).*** H. pylori infection was more prevalent in males in diabetic group. **Conclusion**: higher frequency of H. pylori infection in diabetic patients(smokers more than nonsmokers), may indicate a potential association between H. pylori infection and T2DM. If the relationship between the two is established, preventive measures should be implemented for this treatable disorder especially in high risk communities.
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Key Words: H. Pylori infection, diabetes mellitus& smoking.

1. Introduction

Helicobacter pylori (H. pylori) is a major human bacterial pathogen, the chronic infection of which causes a number of upper gastrointestinal effects such as chronic gastritis, peptic ulcer disease, gastric malignancy, and gastric mucosa associated lymphoid tissue lymphoma **[1].**

Clinical studies have shown that smoking exerts many different effects in the gastrointestinal tract. Poisoned components of cigarette smoke reached the stomach either through the circulation or through the gastrointestinal tract, usually within swallowed saliva **[2, 3].** Chronic exposure to cigarette smoke in Helicobacter pylori infected patients enhances the risk of gastric mucosal atrophy and intestinal metaplasia **[4].** As has been previously reported by ***Rajashekhar et al.*** **[5],** both H. pylori infection and smoking are risk factors for acid peptic disorders.

The prevalence of diabetes mellitus has increased dramatically throughout the world **[6].** Diabetes mellitus is a multifactorial disorder resulting from genetic, environmental, lifestyle and social factors. Environmental factors account for a high proportion in the complex pathogenesis of diabetes mellitus**.** Chronic infection constitutes one of the major environmental etiologic factors.**[7]**

Helicobacter pylori infection may have an impact on cardiovascular conditions, insulin resistance, and metabolic syndrome potentially mediated by elevations in inflammatory markers such as C-reactive protein (CRP) and Interlukin-6 (IL-6) **[8].** Elevated levels of inflammatory cytokines may lead to phosphorylation of serine residues on the insulin receptor substrate, which prevents its interaction with insulin receptors, inhibiting insulin action **[9].** Mammalian stomach produces leptin and ghrelin, two hormones involved in energy homeostasis and whose interactions affect obesity, insulin sensitivity, and glucose homeostasis. Increasing evidence indicates that H. pylori is involved in the regulation of these hormones **[10].** There is paucity of data on the relationship between smoking and H. pylori infection in diabetic patients.

This current prospective study aimed to evaluate the prevalence of H. pylori infection in type 2 diabetes patients and its relation to smoking.

2. Subjects and methods

The current study was conducted an outpatient clinic in Riyadh city (Saudi Arabia) from January 2016 till November 2016.

After taking informed consent of each subject to participate in the study, they were classified into two groups as follows:

Diabetic group: -This group included 50 adult patients (aged ≥18 years) who were diagnosed to have diabetes as per Americans Diabetic Association (ADA; 2015) **[11]:**

Fasting glucose equal to or greater than 126 mg/dL (7.0 mmol/L) or Glucose concentration 2 h after the administration of 75 g oral glucose load equal to or greater than 200 mg/dL (11.1 mmol/L), Random glucose equal to or greater than 200 mg/dL or Hemoglobin A1-C equal to or greater than 6.5%.

Control group: - This group included 50 apparently healthy adults (aged ≥18 years) who had fasting plasma glucose <110 mg/dl to exclude diabetes or impaired glucose intolerance.

Exclusion criteria for studied groups:

1. Patients with type 1 diabetes.
2. History of intake of antibiotics, proton pump inhibitors, H2 receptor blockers, or antacids in last 4 weeks.
3. Patients with past and present evidence of active gastrointestinal bleeding, jaundice, or post gastric surgery.

Methods: -

1. Full history taking with stress and record of smoking history.
2. Thorough clinical examination.

The laboratory investigations included:

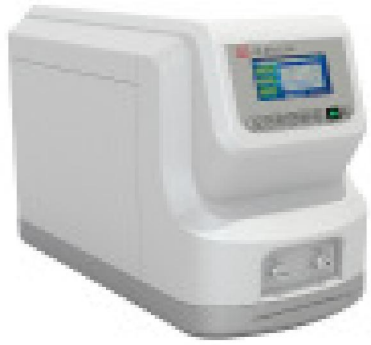
Sampling:-

Venous blood were withdrawn under aseptic precautions after fasting for 10 -12 hours and distributed as follows:

a) 2 milliliters whole blood was put in EDETA vacutainer (violet cap) and mixed up & down gently which was used to measure HBA1C for diabetic group.

b) Third generation immune-enzymometric assay employing Streptavidin-Biotin-based system was used to perform ELISA for diagnosis of H. pylori. The commercially available Anti-H. Pylori-IgG, M icroplate ELISA kit (Monobind Inc., USA) was used in this study.

H. pylori rapid test (C13) Urea breath test kits



Machine: IR-FORCE 200 CHINA

Individuals who had positive H. pylori IgG immunoassay in both groups were further tested for the presence of active and/or chronic H. pylori infection by urea breath test.

- **Test name**: urea breath test (C13).
- **Machine**: IR-FORCE 200 CHINA.
- **Principle**: the test depends on the ability of H. pylori to convert urea into carbon dioxide that has been labeled with isotopes and the ingested by the patient. The difference in carbon dioxide levels between the base line breath sample (before ingestion of urea) and the post administration breath sample is detected by IR-FORCE 200 CHINA spectrophotometer.
- **Sensitivity**: 96.9%.

Statistics:-

Data were collected and statistically analyzed, for descriptive statistical analysis means, SD minimum maximum values were calculated. To determine the correlations between variables, parametric Pearson correlations were used. The testing of the difference between mean values has been done by the Students T- test of difference or Pearson chi square test, for statistical analysis a program SPSS 16 for Windows surrounding has been used and P value for significance was set at 0.05.

3. Results

This study was carried out on 100 subjects who were divided into 2 groups diabetic group ***(40% were males and 60% female)*** and control (non diabetic) group ***(36% male and 64% female)***. Mean age of diabetic patients was ***(48 ± 11) year, while for*** the control group it was ***(34 ± 14) year.***

Out of the 50 diabetic patients there were ***15 (30%) smokers*** **[**10 cigarette smokers, 5 shisha smokers, mean duration of smoking was 28.4 ± 9.7 with mean smoking index 42.3 ± 22.6 pack years**]** and in the control group there were ***12 (24%) smoker*** **[**9 cigarette smokers and 3 shisha smokers with mean duration of smoking 13.1 ± 5.8, mean smoking index 20.4 ±12.5 pack years**]**.

As regard status of H pylori infection by IgG screening immunoassay it was ***positive in 29 (58%) and negative in 21 (42%)*** of patients in diabetic group, while in control group it was ***positive in 21 (42%) and negative in 29 (58%).***

In the present study, out of the 50 patients of type 2 diabetes, active and/or chronic H. pylori infection **[Positive UBT],** was found in ***27 (54%)*** while it was present in only ***14 (28%)*** of 50 controls, which was found to be highly significant ***(X^2 = 6.17, P= 0.008).***

Table (1) descriptive criteria of the study groups:-

			N	%
Gender	**Diabetic**	Male	20	40
		Female	30	60
	Control	Male	18	36
		Female	32	64
Age group	**Diabetic**	Less than 40	13	26
		41-50	25	50
		More than 50	12	24
	Control	Less than 40	39	78
		41-50	7	14
		More than 50	4	8
Smoking status	**Diabetic**	smoker	15	30
		Non-smoker	35	70
	Control	smoker	12	24
		Non-smoker	38	76
H Pylori Screening by IgG immunoassay	**Diabetic**	Positive	29	58
		Negative	21	42
	Control	Positive	21	42
		Negative	29	58
UBT.	**Diabetic**	Positive	27	54
		Negative	23	46
	Control	Positive	14	28
		Negative	36	72

Using Pearson Chi-Square test, out of 27 diabetic patients with H. pylori positive infection, the maximum number of H. pylori positive cases were in the age group 41-50 years ***(12 patients)***, also for the 23 H pylori negative diabetics, maximum number was in the same age group ***(13 patients)*** with no statistically significant difference between positive and negative cases. For the control population, maximum positivity was in age group < 40 years: ***10 persons*** out of the 14 H. pylori positive; and ***29 persons*** out of the 36 H. pylori negative, with no statistically significant difference between H. pylori positive and negative group.

As regard gender distribution, in diabetic patients H. pylori positive cases were more prevalent in ***males (16)*** than in ***females (11),*** in contrast to H. pylori negative diabetics where female cases were more prevalent than males: ***19 and 4 respectively*** and results were statistically significant ***(P =0.003).*** In control group there was equal gender distribution with ***7 males*** and ***7 females*** in H. pylori positive population, while the H. pylori negatives were ***11 males*** and ***25 females*** with insignificant differences ***(P =0.2)*** as shown in **Table (2).**

In diabetic group there was high prevalence of H. pylori infection among smokers ***12/15***than non-smokers ***15/35***which was highly statistically significant with ***p =0.016.*** While in control group there was no significant difference in H. pylori infection between smokers ***5/12***and nonsmokers***9/38,*** with ***p =0.198,*** **Table (2).**

H. pylori positivity was ***maximum*** in groups that had higher HbA1C level as demonstrated in **Table (3).**

Table (2) H. pylori in relation to age sex and smoking:-

		Diabetic group				Control group			
		H. pylori positive	H. pylori negative	Pearson Chi-Square	P value	H. pylori positive	H. pylori negative	Pearson Chi-Square	P value
Age	**< 40**	8	5	0.75	0.69	10	29	0.89	0.64
	41-50	12	13			3	4		
	>50	7	5			1	3		
Sex	**Male**	16	4	9.07	0.003	7	11	1.65	0.2
	Female	11	19			7	25		
Smoking	**Smokers**	12	3	5.83	0.016	5	7	1.46	0.198
	Non smokers	15	20			9	29		
Total		27	23			14	36		

Mean HbA1C among diabetics with H. pylori infection was slightly higher than H. pylori-diabetics **(9.23 ± 1.4% and 9.06 ± 1.9%, respectively, t- test = 0.37, P = 0.71)**, which is statistically insignificant **[Figure 1].**

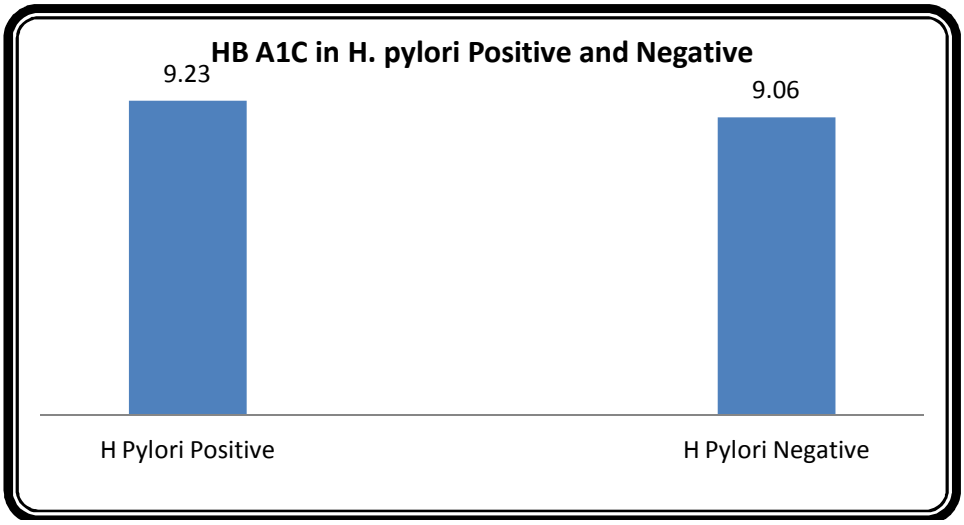


Figure (1) HBA1C in H pylori positive and negative diabetics

Table (3) H pylori infection in relation to HBA1C

	H. pylori infection		Total	***Pearson Chi-Square***	***P value***
	Positive	**Negative**			
Less than or 7	3	2	5	6.61	0.037*
7.1 - 8	1	7	8		
More than 8	23	14	37		
Total	**27**	**23**	**50**		

In diabetic group, 1 patients with H. pylori seropositivity had significantly high serum cholesterol, serum triglycerides, serum low-density lipoprotein (LDL) and low serum high-density lipoprotein (HDL) levels than those with negative H. pylori, while fasting blood sugar (FBS) is insignificantly higher in H. pylori negative patients. While in control group there is no statistical significant variations between H. pylori positive and negative individuals as depicted in in **Table (4).**

Table (4) Lipid profile in H pylori positive and negative subjects

Laboratory data	Normal values	Diabetic group			Control group		
		H. pylori positive	H. pylori negative	P value	H. pylori positive	H. pylori negative	P value
FBS (mg/dl)	<126	176.9±36.6	210.4±66.7	0.03	94.3±5.6	92.2±8.8	0.42
S. Cholestrol (mg/dl)	<200	213.8±35.3	175.4±37.9	0.00	176.4±47.5	179.2±28.4	0.8
S. Triglycerides (mg/dl)	<150	162.0±49.8	134.2±31.3	0.02	109.1±49.9	99±55.3	0.56
HDL (mg/dl)	> 35	32.6±10.0	38.2±9.5	0.05	36.4±12.7	42.6±14.1	0.16
LDL (mg/dl)	< 100	157.4±24.4	117.5±35.5	0.00	118.3.5±31.5	113.5±27.5	0.6

4. Discussion

Preceding studies have made conflicting reports about the association between H. pylori infection and type 2 diabetes. The present study found a higher prevalence of H. pylori infection in diabetics as compared to non-diabetics; which is in coincident with ***Bajaj et al.,*****[12]** ***and Zafar et al.,*****[13]** who study the prevalence of H. pylori infection in Indian diabetics and depend on UBT and histolgical examination of antral endoscopic biopsy for diagnosis of H. pylori infection**, *Han et al.,* [14]** who study prevalence of H. pylori infection in diabetic Chinese using UBT only for diagnosis**, *Rafat et al.,* [15]** who used H. pylori stool antigen in their study and ***Pareek and Kannan* [16]** who depend on IgG immunoassay for diagnosis of H. pylori infection. All report that H. pylori infection has been positively related to the prevalence of type 2 diabetes. While ***Mukhtar et al* [17]** found no such association.

We also found H. pylori infection positively associated with levels of fasting blood sugar in control group and HbA1c in diabetic group which is in accord with many studies **[12,13,14,15,17],** while fasting blood sugar was inversely related to H. pylori infection in diabetics which is in contrast with most studies **[12,13,14,15,17].** This may be due to fasting blood glucose level can reflect the influence of changes in the amount of exercise and diet content before examination, the fluctuations of which might confound evaluation of the association between chronic H. pylori infection and glucose level**[7].** However, HbA1c level, a more stable and reliable biomarker for average glycaemia in long-term blood glucose level, appears to be more valid to assess the effect of chronic H pylori infection on glucose regulation **[18].**

These results could be explained by considering the evidence that some strains of H. pylori are considered more virulent; inparticular, Cag-A-positive strains. They are presumed to have a higher pathogenic effect on gastric mucosa and are related to duodenal ulcerand gastric cancer. More specifically, Cag-A positive strains are associated with the increased production of cytokines such as tumor necrosis factor, interleukin-1, -6, and -8 that might alter the control of glycemia in DM patients. The inflammation hypothesis, however, was not substantiated in present study, since we did not measure IL-6 and CRP levels in H. pylori seropositive individuals or in those who had type 2 diabetes.

The present study provides evidences that H. pylori seropositivity was associated with atherogenic lipid profile among control and diabetic groups. H. Pylori infection was associated with significant increase in cholesterol, triglyceride and LDL level and also had significant effect on high-density lipoprotein (HDL) level. This is in agreement with findings of **[12,14, 15, 17].** Association of H. Pylori infection with atherogenic lipid profile may be due to lipopolysaccharides present in these gram-negative bacteria which stimulate the production of many cytokines including TNF- α, which inhibit lipoprotein lipase activity leading to mobilization of lipids from the tissues and elevated serum triglycerides and lower HDL cholesterol levels **[19].** Cardiovascular complications of diabetes mellitus are caused by dyslipidemia, in particular the increased LDL. H. pylori infection was reported to be more prevalent in CAD positive patients; this may be due to the disturbance in lipid metabolism associated with H. pylori infection **[20].**

Although women participation in this study was predominant, H. pylori infection was more prevalent in males; this was significant in diabetic group compared to the control group. This result is in accord with many studies that observed significant male predominance **[12, 13, 16],** while some found no such male predominance **[14, 15]**. We can explain male predominance in our study that may be due to another factor related to male sex such as smoking which is a common habit among Arabic adult males and is also associated with high H. pylori seropositivity.

In the present study, we explored the probable interaction between smoking status and H. pylori positivity in the diabetic and control individuals, there was no significant difference in H. pylori infection

between smokers and non smokers in control (non-diabetic) group and these agree with the study of ***Khalifa et al.*** **[21]** and ***Sharma et al.*** **[22]** who found that there was no statistical significant difference between smokers and non-smokers in Non Ulcer Dyspepsia(NUD)(non-diabetic) patients. But findings were contrary to the findings of ***Rajashekhar et al.,*****[5]** who had found an association of smoking with H. pylori positivity in (NUD) (non-diabetic)patients, While in diabetic group there was statistical significant difference in the incidence of H. pylori positivity between smokers & non-smokers, which can be explained by the synergistic effect of smoking and diabetes on the gastrointestinal tract, and the longer duration, higher smoking index in the diabetic group, however there are paucity of studies which explored the possible relation of smoking and H. pylori infection in diabetic patients.

Conclusion

Although this study prove that the prevalence of H. pylori infection was significantly higher in type 2 diabetes as compared to controls, diabetics with poor glycemic control had significantly increased prevalence of H. pylori infection as denoted by increased HbA1C level in H. pylori-positive diabetic group. Serum cholesterol, Serum triglyceride and LDL levels were significantly higher in H. pylori-positive as compared to H. pylori-negative diabetics; larger prospective studies investigating the impact of H. pylori infection on type 2 diabetes and its correlation with more specific biomarkers like CRP, TNF- α, interleukin-1, -6, and -8 are warranted. If the relationship between the two is established; preventive measures may be implemented for this treatable disorder especially in high risk communities. Also our study shows strong relation between smoking & H. pylori infection in diabetic patients which was not investigated thoroughly in previous studies, so we need more such studies to declare the effect of smoking on such group of patients which will add to the community health care awareness.

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