A Study of Relationship of Helicobacter Pylori Infection with Glycemic Control and Insulin Resistance in Adults with Type 2 Diabetes Mellitus

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Abstract: Background & Objectives: There are contradictory reports about whether any association exists between Helicobacter pylori (HP) infection and type 2 diabetes mellitus (Type 2 DM). Ouraim was to study the possible inter-relationship between HP infection, glycosylated hemoglobin (HbA1c) levels and Homoeostatic Model Assessment for Insulin Resistance (HOMA – IR) in type 2 diabetic dyspeptic patients referred for upper gastrointestinal endoscopy. Methods: The study was done on 100 dyspeptic patients – 50 with type 2 DM and 50 non-diabetic controls. Their antral and corpus biopsy samples were subjected to Rapid urease test for detection of HP. The diabetics were divided into those with and without HP infection into HP+ and HP- groups. Detailed history was taken and the following investigations were done – body mass index, waist circumference, fasting and post prandial blood sugar levels, HbA1c, fasting insulin levels and HOMA-IR for all patients. Results: HP infection was associated with type 2 DM in a statistically significant manner (P = 0.001). The mean age of HP+ diabetics was 54.89 ± 11 years and that of HP- was 56.56 ± 11.2 years. Mean body mass index of HP+ diabetics was 30.58 ± 3.2 kg/m^2 and that of HP- was 28.6 ± 2.5 kg/m^2. HP infection was associated in a statistically significant manner with high BMI and waist circumference in diabetics (P = 0.02 and P = 0.0049). Mean HbA1c in HP+ was 8.23±1.34% and in HP- was 8.62±1.6% (P=0.31). Average fasting insulin levels in HP+ was 8.7 ± 4.1µIU/ml and in HP- was 7.4 ± 3.7 µIU/ml (P=0.24) . Mean HOMA-IR was 4.3 ± 2.3 in HP+ and 3.7 ± 2.3 in HP- diabetics (P=0.34).Conclusion: Helicobacter pylori although significantly associated with type 2 DM as compared to non-diabetics, there was no correlation found with poor glycemic control or insulin resistance in them. Obese diabetics with high waist circumference had statistically significant higher prevalence of HP infection as compared to non-obese diabetics.[B Vaishnav Natl J Integr Res Med, 2018; 9(1):92-97]

Key Words: Helicobacter pylori; Diabetes Mellitus, Type 2; Hemoglobin A, Glycosylated; Insulin Resistance

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Introduction: Helicobacter Pylori (HP), a helical gram negative microaerophilic bacterium is found in the stomach and is thought to play a role in several gastrointestinal disorders like, gastric and duodenal ulcers, chronic gastritis of the antrum, gastric carcinomas etc[1, 2].In addition to this, it is also thought to play a direct or indirect role in the pathogenesis ofmetabolic syndrome, non-alcoholic fatty liver disease, iron deficiency anemia, type 2 diabetes and ischemic heart disease[3, 4, 5]. This is attributed to a chronic, low grade persistent inflammation due to HP.

The association between diabetes mellitus and HP infection remains controversial although many studies have been done which concluded that a definite relationship exists between the two. It is hypothesized that HP infection promotes atherosclerosis by altering lipid metabolism and this leads to the Metabolic syndrome, insulin resistance and finally to type 2 Diabetes[6,7]. Vice-versa is also true i.e. alteration of glucose metabolism in diabetics has been suggested as an etiologic factor in causing Helicobacter pylori colonization[8].

The aim of the current study is to evaluate the possible role of HP infection in type 2 Diabetes Mellitus and its complications and to find out whether any relationship exists between the HP infection and level of glycemic control and HP infection and insulin resistance.

Methods: The study was done in a tertiary care hospital of Pune, Maharashtra over a period of two years. A total of 100 patients who were referred for upper gastrointestinal endoscopy (UGIE) for complaints of dyspepsia were enrolled in the study. All procedures performed on the participants in this study were in accordance with the ethical standards of the institutional ethics committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Due approval from the institutional ethics committee was obtained. Informed consent was obtained from all individual participants included in the study. Patients with age < 18 years, those with history of treatment taken for HP infection or on proton pump inhibitors and with severe anemia were excluded. The subjects were then divided into those with Type 2 DM as cases and those without

Type 2 DM as controls which were age and sex matched. UGIE was done for all the patients. A detailed history about type 2 DM (its duration, treatment and complications) and physical examination was done and all the participants were subjected to the following laboratory investigations – Body Mass index (BMI), Fasting and Post-prandial blood sugar levels (FBS, PPBS in mg/dl), Glycosylated hemoglobin levels (HbA1c), Fasting plasma insulin levels in µIU/ml), Homoeostatic Model Assessment for Insulin Resistance (HOMA – IR) values were calculated. The Rapid Urease test was done on the antral and corpus biopsy samples collected during UGIE using a commercially available test kit for HP detection. Body Mass Index (BMI) was calculated using the following formula - Weight in Kilograms / (Height in meters)^2. A BMI between 18.5 - 24.9 kg/m^2 was considered to be normal. Patients with BMI of more than or equal to 25 kg/m^2 were considered to be overweight. Venous blood sample was collected after an overnight fasting of 12 hours and sent for FBS and plasma insulin levels. PPBS was done on venous blood collected at two hours post lunch. HOMA-IR was calculated using the following formula:

(Fasting blood sugar levels (mg/dL) X Fasting plasma insulin levels (µIU/ml))/405

Interpretation of HOMA-IR values was as follows –

- HOMA-IR < 1 – Insulin sensitivity present
- HOMA-IR > 1.9 – Early insulin resistance
- HOMA-IR > 2.9 – Mild insulin resistance
- HOMA-IR between 3 and 5 – Moderate insulin resistance
- HOMA-IR > 5 – Severe insulin resistance

Statistical tests like Student's t-test and Chi-square tests were applied to study whether there was any statistically significant correlation between HP infection amongst diabetics and non-diabetics; also between HP infection and the level of glycemic control (FBS, PPBS, HbA1c) and HP infection and HOMA-IR. All tests were two-tailed and a P-value of less than 0.05 was considered to be statistically significant. All results were expressed as Mean ± standard deviation (Mean ± SD).

Results: A total of 100 patients having dyspepsia, 56 males and 44 females were enrolled in the study. Of them, 50 patients were diabetics (60% males and 40% females) with an average age of 55.54 ± 11.7 years and having type 2 DM since 8.7 ± 6.1 years. The average HbA1c of the diabetic subjects was 8.4 ± 1.3%. Table 1 shows the clinical profile and comparison between the two broad study categories i.e. with Type 2 DM and without Type 2 DM.

Among type 2 DM subjects, H. Pylori was positive (HP+) in 28 (56%) patients and was negative (HP-) in 22 (44%) patients. Among non-diabetic controls, HP+ was found in 12 (24%) patients and HP- was found in 38 (76%) patients. Applying chi square test, P = 0.001 thus indicating that H.pylori was associated with type 2 DM in a statistically significant manner as compared to normal subjects with dyspepsia.

Table 1: Demographic and Clinical data of patients with and without type 2 DM

Parameter assessed	Cases (with Type 2 DM) n = 50	Controls (without Type 2 DM) n = 50	Statistical Test applied (Significance)
Age (years)	55.54 ± 11.7	49.46 ± 17	
Gender	Male – 30 (60%) Female – 20 (40%)	Male – 26 (52%) Female – 24 (48%)	
BMI (kg/m^2)	29.7 ± 3.2	23.3 ± 2.5	
Duration of type 2 Diabetes (years)	8.7 ± 6.1	Not Applicable	
Risk factors and co-morbidities Positive family history Hypertension Obesity Smoking Tobacco Alcohol	 12 (24%) 23 (46%) 18 (36%) 13 (26%) 21 (42%) 12 (24%)	 Not Applicable 2 (4%) 16 (32%) 3 (6%) 17 (34%) 5 (10%)	
Average Blood sugar level (mg/dl) Fasting Post-prandial	 200.7 ± 39.7 250.8 ± 60.1	 93.9 ± 6.4 108.3 ± 7.0	

Average HbA1c (%)	8.4 ± 1.3	4.9 ± 0.3	
Average HOMA-IR level	4.1 ± 2.3	2.2 ± 0.9	
H. Pylori positive by RUT	28 (56%)	12 (24%)	Chi-square test (p = 0.001, significant statistically)
H. Pylori negative by RUT	22 (44%)	38 (76%)	

Table 2 shows the salient clinical and laboratory parameters of the diabetic subjects based on their HP+ or HP- status. There was no statistically significant difference between demographic and clinical parameters like age, family history of DM and complications of type 2 DM among the two groups.

Table 2: Comparison of clinical characteristics of type 2 DM patients with reference to HP infection status

Parameter	DM with H.Pylori +ve (n = 28)	DM with H.Pylori -ve (n = 22)	Statistical Test and Outcome
Age (years)	54.89 ± 11	56.56 ± 11.2	Student's t-test (p=0.65, NS)
BMI (Kg/m^2)[a]	30.58 ± 3.2	28.6 ± 2.5	Student's t-test (p=0.02, S)
Waist circumference (cms)	104.5 ± 16.62	91.32 ± 14.45	Student's t-test (p=0.004965, S)
Positive family history for Type 2 DM	18	17	Chi-square test (p=0.32, NS)
Macrovascular complications of DM (CVA[b], CAD[c], PVD[d])	12	10	Chi-square test (p=0.85, NS)
Microvascular complications of DM (Neuropathy, Nephropathy, Retinopathy)	16	14	Chi-square test (p=0.64, NS)
Treatment OHA[e] Multiple OHA OHA + Insulin Only insulin	 2 (7.1%) 21 (75%) 1 (3.6%) 4 (14.3%)	 2 (9.1%) 18 (81.8%) 0 (0%) 2 (9.1%)	

a - BMI – Body mass index; b - CVA – Cerebrovascular accident; c - CAD – Coronary artery disease; d - PVD – peripheral vascular disease; e - OHA – oral hypoglycemic agent.

HP+ diabetics had a statistically significant higher BMI and waist circumference as compared to the HP- diabetics (P=0.02 and P=0.0049 respectively). Thus, our study showed that diabetic patients with higher than normal BMI and waist circumference were more prone to dyspepsia and H.pylori infection. There was no statistically significant difference between the prevalence of micro and macrovascular complications and the type of treatment taken in type 2 DM among the HP+ and HP- groups.

There was no statistically significant difference between the fasting and post prandial blood sugar levels, glycosylated Hb levels, fasting insulin levels and HOMA-IR values amongst the HP+ and HP- subgroups of diabetics (Table 3).

Table 3: Level of glycemic control and degree of insulin resistance with respect to HP infection amongst diabetic patients

Parameter	DM with H.Pylori +ve (n = 28)	DM with H.Pylori -ve (n = 22)	Statistical Test
HbA1c (%)	8.23 ± 1.34	8.62 ± 1.6	Student's t-test (p=0.31, NS)
FBS[a] (mg/dl)	200.8 ± 36.6	200.5 ± 44.1	Student's t-test (p=0.98, NS)
PPBS[b] (mg/dl)	244.4 ± 57.9	259.0 ± 63.1	Student's t-test (p=0.4, NS)
Fasting Insulin levels (µIU/ml)	8.7 ± 4.1	7.4 ± 3.7	Student's t-test (p=0.24, NS)
HOMA-IR[c]	4.3 ± 2.3	3.7 ± 2.3	Student's t-test (p=0.34, NS)

a - FBS – fasting blood sugar; b - PPBS – postprandial blood sugar; c - HOMA-IR – Homoeostasis Model assessment – insulin resistance

Discussion: Helicobacter pylori is probably the most common chronic bacterial infection affecting about 50% of the world's population[9,10,11]. A recentmeta-analysis of 41 studies involving 14,080 patients found increased prevalence of HP infection in type 2 DM

subjects[12].However, studies elucidating the relationship between the level of glycemic control and insulin resistance with HP infection are few and far between. Our study showed that there was a statistically significant higher prevalence of H.pylori in type 2 DM dyspeptic patients as compared to the non-diabetic controls. Similar results were obtained in several other studies[13, 14, 15, 16, 17]. However, in a study by Anastasios et al. and Demir et al., there was no association between HP infection and diabetes[18, 19].

This conflicting results to determine a possible association between HP infection and type 2 diabetes may be due to presence of several confounding factors like differences in duration of diabetes, presence or absence of conventional risk factors for diabetes, type of treatment being taken, dyspepsia duration and clinical spectrum, patient compliance for strict glycemic control, type of method used for detection of HP infection in the selected study groups. We used the Rapid Urease test method for detection of HP in the antral and corpus biopsy specimen from the stomach. This test is a cheap, rapid and simple alternative to the culture and histological tests for detection of HP infection which are time consuming and expensive. Like any other diagnostic test, the interpretation of RUT depends in part on the pretest probability of an infection[20].False negative RUT for HP is more frequent than the false positive RUT. A positive histology and culture for HP are the gold standard for the diagnosis of HP infection. However, RUT is a good screening test which when used judiciously is helpful to rule out HP infection.

The temporal association between Type 2 DM and HP infection has not been elucidated. Several theories have been put forward but none of them have been proven. Anastasios et al. hypothesized that in presence of HP colonization in the stomach, there is delayed gastric emptying which may cause prolonged hyperglycemia and poor glycemic control in type 1 DM[18]. Studies by Ikeda et al., Butler et al. and Bener et al. concluded that hyperglycemia in type 2 DM blunts the cellular and humoral immunity of the patients thus, predisposing them to HP infection[21, 22, 23]. H.Pylori produces a persistent low grade inflammation, induces mechanisms of molecular mimicry and interferes with the absorption of drugs and nutrients, thus, influencing the evolution of chronic diseases like diabetes[24]. Finally, whether HP infection predisposes to type 2 DM or vice versa is not yet fully known. The average HbA1c in diabetics was 8.4 ± 1.3% in this study. Thus patients had uncontrolled diabetes. Higher HbA1c values indicating a poor glycemic control is an independent risk factor for upper GI symptoms of dyspepsia[25]. Our study corroborated this finding. We further divided the diabetics into HP+ and HP- and checked their BMI, waist circumference, the level of glycemic control and evaluated them for the presence of insulin resistance.

The positive finding of our study was that HP+ diabetics had a statistically significant higher BMI values and waist circumference than the HP- diabetics. Studies by BenerA et al. and Perdichizzi et al. also showed higher prevalence of HP infection in obese diabetics[23, 26].This association could be explained by delayed gastric emptying and gastric mucosal changes due to non-enzymatic glycosylation processes in obese diabetics which facilitate the HP colonization. However, a Taiwanese study on morbidly obese non-diabetic patients showed an inverse relationship between HP infection and obesity[27].However, this study was not done on diabetics in particular. Thus further population based studies need to be carried out to prove this association between obesity, diabetes and HP infection.

We did not find any statistically significant association between the HP infection and glycemic control, insulin resistance in type 2 DM patients (FBS, PPBS, HbA1c, fasting plasma insulin levels, HOMA-IR values). In a meta-analysis of 13 different studies by Horikawa C et al., the conclusion was the same i.e. they too found insufficient evidence that HP infection was associated with poor glycemic control in diabetes[28].The eradication of HP infection did not improve the level of glycemic control in a Japanese study by Wada Y et al[29].These studies did not evaluate the relationship between insulin resistance and HP infection. A study by Gen R et al. showed statistically significant association of HP infection with higher HOMA-IR values and improvement in the HOMA-IR after eradication of HP infection[30].

Thus, although, the diabetic study population had highHbA1c values reflecting poor glycemic control, presence of HP infection did not correlate significantly with it. In a meta-analysis study by Dai YN et al., HP infection was associated with poor glycemic control in type 1 DM but not in type 2 DM and after eradication

therapy for HP, there was no improvement in the glycemic level in type 2 DM[31].

HP organism is phenotypically of two distinct subtypes. One which expressesthe cytotoxin associated gene A antigen (cagA Ag) and vacuolatingcytotoxin associated gene antigen (vacA Ag) (Type 1 bacteria), and the other in which cagA is absent and vacA activity is not manifested in spite of the vacA gene being present (Type 2 bacteria)[32]. The type 1 bacteria are more pathogenic than type 2 and induce a greater inflammatory response. Ibrahim et al demonstrated that infection with type 1 H.pylori bacteria (cagA Ag+) was strongly associated with poor glycemic control in T2DM patients[33]. This finding suggests that infection with type 1 HP may play a major role in worsening the glycemic control in type 2 DM by altering the host inflammatory responses. Small sample size, type of HP detection method used (RUT vs. the gold standard histology), not classifying the type of HP strain and not studying the effect of HP eradication therapy on glycemic control in diabetics were the limitations of our study.

To conclude, Helicobacter pylori infection although associated with type 2 DM in a statistically significant manner, neither altered the glycemic control nor was it associated with greater insulin resistance. Obese type 2 DM patients were more prone to harbor HP organism in their stomachs as compared to the non-obese diabetics. Further larger population based studies are required to study the impact of weight reduction on HP infection and HP eradication therapy on glycemic control and insulin resistance in type 2 diabetes.

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