Original Article

DOI: 10.7860/JCDR/2021/46841.14635

Role of *Helicobacter pylori* Infection on Diabetic and Lipid Profile in Pre-diabetic Patients

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ABSTRACT

Introduction: *Helicobacter pylori* (*H.pylori*) infection is related to gastritis, peptic ulcers, gastric cancers and Mucosa Associated Lymphoid Tissue lymphomas (MALT). It is also associated with several extra-gastrointestinal pathologies owing to its association with increased production of proinflammatory cytokines, bacterial virulence factors and environmental factors. It may have an effect on onset of diabetes mellitus and alter lipid profile.

Aim: To find the effect of *H.pylori* infection on diabetic and lipid profile in pre-diabetic patients.

Materials and Methods: A single centre, cross-sectional study was conducted over a period from January 2019 to June 2020, on pre-diabetic patients (HbA1c 5.7-6.4%.). A total of 118 patients were recruited in the study and divided into two groups based on the *H.pylori* positive (group A) and negative (group B) results. HbA1c, Low Density Lipoprotein (LDL) and High Density Lipoprotein (HDL) were investigated at baseline, six months and 12 months and the results of the two groups were compared using student's t-test. Supply Support Planning and Execution (SSPE) Software version 20.0 were used for analysis of the collected data. A p-value<0.05 to be considered significant.

Results: Of the 118 patients, 96 (mean age 48.3 years) completed the study. There 59 (61.5%) were males and 37 (38.5%) were females. A total of 54 (56%) of the study population tested positive for the *H.pylori* colonisation. The study showed that patients infected with *H.pylori* (group A) had comparative rapid increase in the HbA1c levels (p-value=0.048) when compared with the non-infective group (group B). The group A also had statistically significant increase in the LDL cholesterol levels (p-value=0.032) and decrease in HDL cholesterol levels (p-value=0.02) than group B.

Conclusion: Infection with *H.pylori* is associated with increase in the level of HbA1c in pre-diabetics. It is also associated with increase in the LDL cholesterol levels and decrease in the HDL cholesterol levels. Eradication of the pathogen may help in preventing or delaying the progression of pre-diabetes and dyslipidemia. However, larger studies without any confounding factors are needed to establish the association between *H.pylori* infection and its effect on diabetic and lipid profile.

Keywords: Dyslipidemia, Gastric colonisation, Glycosylated haemoglobin, High density lipoprotein, Low density lipoprotein

INTRODUCTION

H.pylori is a gram negative, spiral shaped acid resistant micro-aerophilic bacillus that colonises the gastric mucosa of the humans [1]. Two-thirds of the infected adults acquire *H.pylori* before the age of 10 years and it is rarely eradicated by nature [2]. The colonisation induces a tissue response comprising the infiltration of the mucosa by both mononuclear and polymorphonuclear cells as well as downregulation of the immune system. This tissue response in the remote organs is mediated by a group of genes called the Cytocin Associated Gene (CAG) pathogenicity island (Pal) that encodes a secretion system that induces a proinflammatory cytokine response [1] causing the release of Interleukin (IL)-1, IL-6, IL-18, Tumor Necrosis Factor (TNF) and C-reactive Protein (CRP) that can affect remote tissues and organic systems [3].

Diabetes Mellitus (DM) is an emerging health problem with global prevalence of 8.5% among adults aged over 18 years [4]. Type II Diabetes Mellitus is a heterogeneous group of disorders characterised by development of insulin resistance, defective insulin secretion and excessive glucose production. Pre-diabetic state is a phase of impaired glucose tolerance 2 hours Postprandial Glucose (PG) in 75 g oral glucose tolerance test 140 mg/dL-199 mg/dL and/or impaired fasting glucose 100 mg/dL-125 mg/dL and/or HbA1c 5.7-6.4% [5]. Pre-diabetes is pathophysiologically similar to Type II Diabetes with basic defect being insulin resistance and early beta cell failure. The amplitude of large pulses and the rapid oscillations of insulin secretion are lost in pre-diabetes. In pre-diabetes, the glycaemic excursions are usually lower than normal and there is a delay and prolongation in the second phase of insulin secretion [6]. Recent studies have shown that colonisation with *H.pylori* is associated with increased development of diabetes mellitus [7-11]. A step towards identifying treatable causes of diabetes mellitus will aid the medical health system in developing new strategies in preventing the progression of pre-diabetes to overt diabetes mellitus.

Dyslipidemia is a complex disease and a major risk factor for adverse cardiovascular events [12]. High levels of Low Density Lipoproteins (LDL) and low levels of High Density Lipoprotein (HDL) are associated with increased incidence of stoke and myocardial infarction [13]. dyslipidemia also plays a major role in macrovascular complications of Diabetes [14]. There is increasing evidence for the role of *H.pylori* infection in the initiation, development or persistence of atherosclerosis and coronary heart disease [15,16]. Therefore, exploring the role of treatable causes of dyslipidemia like *H.pylori* may help in preventing the progression of dyslipidemia and its adverse effects.

The present study aimed to assess the possible role of *H.pylori* infection on diabetic profile and lipid profile in pre-diabetic patients.

MATERIALS AND METHODS

This single centre, cross-sectional study was conducted at Shadan Institute of Medical Sciences, Hyderabad, India from January 2019 to June 2020. Subjects were selected from the patients attending the Medical Outpatient Department (OPD) of the hospital, during the study period. Institutional Ethics Committee approved the study

protocol (IEC/SIMS/19/05). Written informed consent was taken from the patients before participation in the study.

All the patients included in the study were advised to be under regular follow-up and inform any changes in the life style, intake of any medications and development of any co-morbid conditions. A total of 118 patients were included in the study, out of which 12 developed co-morbid conditions (Diabetes Mellitus, hypertension and hyperlipidemia) during the study period and were commenced on medications, therefore excluded from the study. Four patients missed the follow-up and six patients had lifestyle modifications like diet control, yoga therapy and physical exercises, therefore were also excluded from the study. Finally, a total of 96 patients completed the study.

Inclusion criteria: Pre-diabetic patients, age 30-60 years of either gender with fasting glucose 100 mg/dL-125 mg/dL and/or HbA1c 5.7-6.4% [5] (as per American Diabetes Association (ADA) 2020 guidelines [17]) and those with high borderline lipid levels (as per National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines [18]) were included in the study.

Exclusion criteria: Known diabetics, hyperlipidemics, hypertensives, patients with history of intake of antibiotics, on proton pump inhibitors, on H2 receptor blockers or antacids (in the last four weeks), past or present evidence of gastrointestinal bleeding, jaundice or postgastric surgery, pregnant or lactating women.

All patients recruited in the study were investigated for pre-diabetes, lipid profile and *H.pylori* infection. Diabetic profile was evaluated by Glycosylated Haemoglobin (HbA1c) at the start of the study, after six months and at the end of 12 months study period with High Resolution chromatography [17]. Lipid profile included evaluation of LDL by Friedewald formula [19] and HDL by direct measurement by precipitation method [20]. *H.pylori* infection was detected by the presence of IgG antibodies using *H.pylori* IgG Enzyme-Linked Immunosorbent Assay (ELISA) test kit [21].

Amongst the 96 patients, 54 were positive for *H.pylori* infection and included in Group A. The remaining 42 patients were included in Group B.

STATISTICAL ANALYSIS

The data obtained was spread in Microsoft excel sheets and analysed using Supply Support Planning and Execution (SSPE) Software version 20.0. Results were expressed as Mean±SD. Data was analysed with appropriate statistical methods. Students t-test was used to compare the different parameters studied between the groups. The p-value less than 0.05 was considered as statistically significant.

RESULTS

A total of 96 subjects completed the study, out of which 59 (61.5%) were males and 37 (38.5%) were females, with a mean age of 48.3 years. Group A included 54 (56%) subjects who were positive for *H.pylori* infection and Group B included 42 (44%) subjects. The mean age of Group A (47.6 years) was lesser than that of Group B (49.0 years) [Table/Fig-1].

Age (Years)	Group A mean±SD	Group B mean±SD	Total mean±SD	p-value
Male	47.09±8.83	50.19±8.24	48.61±8.62	0.15
Female	48.54±8.46	46.66±7.42	47.78±8.00	0.20
Mean	47.68±8.53	49.04±8.08	48.31±8.37	0.42

[Table/Fig-1]: Age-wise distribution.

The Group A *H.pylori* positive patients included 32 males (59.3%) and 22 females (40.7%) and Group B *H.pylori* negative patients included 27 males (64.3%) and 15 females (35.7%) [Table/Fig-2].

There was no significant difference in the mean HbA1c, mean LDL and mean HDL between Group A and Group B at the start of the study (p-value >0.05) [Table/Fig-3].

Gender	Group A n (%)	Group B n (%)	Total n (%)
Male	32 (33.33)	27 (28.12)	59 (61.5)
Female	22 (22.91)	15 (15.62)	37 (38.5)
Total	54 (56)	42 (44)	96 (100)

[Table/Fig-2]: Gender-wise distribution.

Parameters	Group A	Group B	p-value
HbA1c			
Baseline (%)	6.08±0.19	6.07±0.2	0.83
6 months (%)	6.13±0.19	6.11±0.211	0.052
12 months (%)	6.2±0.39	6.15±0.34	0.47
LDL			
Baseline (mg/dL)	143.4±8.2	142.1±7.5	0.58
6 months (mg/dL)	144±7.41	143.63±6.48	0.58
12 months (mg/dL)	145.7±9	143.8±8	0.49
HDL			
Baseline (mg/dL)	44±5.9	42.6±4.7	0.27
6 months (mg/dL)	42.92±4.70	42.04±3.72	0.29
12 months (mg/dL)	43±5.84	42±4.7	0.34

[Table/Fig-3]: Mean HbA1c, LDL and HDL levels of Group A and Group B at the start of the study (0 Months), after 6 months and after 12 months.
(Students unpaired t-test was used to calculate p-value. p-value <0.05 to be considered significant; HbA1c: Glycated haemoglobin; LDL: Low density lipoprotein; HDL: High density lipoprotein)

However, when the result of HbA1c of Group A was compared at the start and end of the study, there was a significant difference with a p-value of 0.048 indicating that *H.pylori* infection may have a role on diabetic profile in pre-diabetic patients and may lead to rapid progression of pre-diabetes to diabetes. The difference of HbA1c levels in Group B was not statistically significant. The LDL and HDL levels of Group A before and at the end of the study also showed statistically significant difference [Table/Fig-4].

Parameters over 12 months	Group A		Group B	
	Mean Difference±SD	p-value	Mean Difference±SD	p-value
HbA1c (%)	0.1167±0.419	0.048	0.07±0.27	0.065
LDL (mg/dL)	2.33±7.71	0.032	1.71±6.2	0.07
HDL (mg/dL)	-1.07±3.48	0.02	-0.47±1.98	0.109

[Table/Fig-4]: Comparison of the p-value for HbA1c, LDL and HDL levels between Group A and Group B, over the 12 months study period.
(Students t-test was used to calculate the p-value; Level of significance at 0.05)

DISCUSSION

H.pylori is one of the most common type of bacteria colonising the human stomach. Most individuals however remain asymptomatic throughout life despite chronic gastritis [22]. Recent studies have shown that *H.pylori* infection is associated with increased incidence of Diabetes Mellitus [7-11,23], whereas some studies does not support any correlation between *H.pylori* infection and Diabetes Mellitus [24-27]. There is limited data to prove whether the infection leads to diabetes mellitus or diabetic patients are more prone to the infection due to immuno-compromised state [28].

Diabetes associated impairment of cellular and humoral immunity may enhance an individual's sensitivity to *H.pylori* infection [28]. DM is also associated with decreased gastrointestinal motility and acid secretion promoting pathogen colonisation and infection [23]. The present study was therefore conducted on pre-diabetic patients to avoid any confounding factors associated with diabetes and to assess for an association between *H.pylori* infection and progression of pre-diabetes.

The present study showed a significant effect of *H.pylori* on HbA1c suggesting the role of the organism in the early onset of DM. This is similar to the study conducted by Polyzos SA et al., [29]. A study conducted by Gunji T et al., in Japan on 1107 asymptomatic

subjects showed that *H.pylori* independently contributes to insulin resistance [30], which supports the present study result. However, a study by Park SH et al., showed that there is no effect of *H.pylori* eradication on insulin resistance [31].

Inflammation of the β-cells characterised by increased infiltration by macrophages, and release of cytokines like Interleukin-1β, IL-6, C-reactive Protein (CRP) and Tumor Necrosis Factor (TNF) causes impairment in the secretion of insulin resulting in the development of DM. A study by Oshima T et al., explained that *H.pylori* induces a release of several pro-inflammatory cytokines like IL-6, CRP and TNF-α, which leads to insulin resistance, supporting the role of *H.pylori* in causation of DM [32]. The organism colonises gastric mucosa and submucosa leading to infiltration of acute and chronic inflammatory cells comprising of neutrophils and monocytes, and release of several pro-inflammatory cytokines, which are implicated in the development of DM. However, few studies do not support the role of pro-inflammatory cytokines in the development of insulin resistance [23,33]. A study by Ridker PM et al., found no significant association between *H.pylori* seropositivity and cytokines release among socioeconomically similar US men [34].

Defect in β-cell function is implicated in the pathogenesis of DM. *H.pylori* titre can independently predict abnormal pancreatic β-cell function [35]. The pancreatic β-cells, which are responsible for the production of insulin are susceptible to inflammatory damage and oxidative stress. *H.pylori*-induced infection can therefore damage pancreatic β-cells and cause deficiency in insulin secretion leading to development of DM.

H.pylori causes gastritis, which affects the secretion of several hormones like ghrelin, leptin, gastrin and somatostatin. These hormones are involved in glucose homeostasis and insulin sensitivity. *H.pylori* also decreases the release of ghrelin, which causes insulin resistance [36]. It also increases the release of leptin which is directly correlated with insulin resistance [37]. Patients with *H.pylori* infection have elevated basal levels of gastrin which is known for its role in food related insulin release [35]. Somatostatin, which inhibits insulin release and regulates the secretion of pancreatic insulin, is decreased in *H.pylori* positive patients [38]. A study by Brown JE and Dunmore SJ, has a contradictory finding which suggests that leptin is involved in preventing the apoptosis of pancreatic β-cells, thus offering a protective role in preventing the onset of DM [39].

H.pylori is associated with several extra gastrointestinal manifestation and may contribute to the development of several cardiovascular risk factors [40]. A study by Mukhtar M et al., showed that *H.pylori* infection is associated with dyslipidemia and increased levels of oxidised LDL in Type 2 DM [41]. The present study showed that colonisation with *H.pylori* has an effect of lipid profile in pre-diabetic patients. It increases the levels of LDL and decreases the levels of HDL. The present study is supported by a study conducted by Kim HL et al., and also by a study by Pohjanen VM et al., [42,43]. The study result is also supported by a study by Chimienti G et al., and Takashima T et al., which showed an association between *H.pylori* and dyslipidemia [44,45]. However, the present study result is not supported by the study conducted by Ando TM et al., which showed no difference in the lipid profiles even after eradication of *H.pylori* infection [46]. This difference in the result may be due to affect of the degree of gastritis and the severity of gastric mucosal atrophy on the lipid metabolisms, since those are related to the production of pro-inflammatory cytokines and ghrelin from the gastric mucosa [47,48].

Chronic infection with *H.pylori* induces the release of pro-inflammatory cytokines like IL-6, interferon α and TNF-α. These pro-inflammatory cytokines acts on the adipose tissues, where they activate a series of reactions resulting in activation of lipoprotein lipase. These lipases act on adipose tissue and influence lipolysis [44]. They also have a stimulatory effect on the hepatic fatty acid synthesis. A study by Kim TJ showed that subjects with *H.pylori* infection had higher total cholesterol and LDL cholesterol, as well as lower HDL cholesterol, regardless of the other potential confounding factors such as age, sex, socioeconomic status, Body Mass Index (BMI), smoking status, alcohol consumption, and amount of exercise [49].

Most of the studies were performed on diabetic patients, who are more prone to infections and inflammatory changes, thus confounding the result. Moreover, *H.pylori* infection and dyslipidemia also affected socio-economic status, age, physical activity and exercise. So, larger studies, which take into consideration all the confounding factors, should be done. If the role of *H.pylori* is established, it can help in providing a better understanding of the pathologies associated with it and help in implementing preventive measures that decrease the world's burden of diabetes and dyslipidemia.

Limitation(s)

The study included only those patients who visited the OPD and were ready to take part in the study, so it might not represent the entire population. The follow-up period was too small to make specified conclusions as diabetes and dyslipidemia is a long-time process. Moreover, the degree of gastritis and degree of mucosal atrophy were not investigated, which might be related to the degree of the progression of Diabetes and lipid profile.

CONCLUSION(S)

Infection with *H.pylori* is associated with statistically significant increase in the level of HbA1c in pre-diabetic patients. It is also associated with increase in the LDL cholesterol levels and decrease in the HDL cholesterol levels when compared to the control population. It can be concluded from the present study that *H.pylori* may play a significant role in the development and progression of Diabetes Mellitus. It may also have a role in development of dyslipidemia by increasing the LDL cholesterol levels. However, larger Randomised Controlled Trials are needed to confirm the relationship and association between *H.pylori* and diabetic profile and lipid profile. There are number of confounding factors like age, environmental factors, infection, stress and life style which definitely has a role in the development of diabetes and dyslipidemia.

Acknowledgement

Authors are grateful to Dr Vasntha Prasad, Superintendent, Shadan Institue of Medical Sciences for permitting us to carry out the study.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Sep 22, 2020
- Manual Googling: Dec 24, 2020
- iThenticate Software: Jan 25, 2021 (20%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Sep 20, 2020**
Date of Peer Review: **Nov 05, 2020**
Date of Acceptance: **Jan 04, 2021**
Date of Publishing: **Mar 01, 2021**