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Helicobacter pylori Infection as a Risk Factor for Coronary Artery Disease

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Authors' contributions

This work was carried out in collaboration between the two authors. Author ESK planned and designed the study, wrote the protocol, collected the samples, performed the practical laboratory activities, participated in the interpretation of the results and analysis, drafted and critically revised the manuscript. Author BAAA participated in planning and designing the study, sample collection, participated in the interpretation of the results. Both authors read and approved the final manuscript.

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ABSTRACT

Background: *Helicobacter pylori* (*H. pylori*) infection is the most common infection in the world and coronary artery disease (CAD) is probably associated with it.
Aim: The aim of this prospective study was to evaluate the association between *H. pylori* infection and other risk factors with suspected CAD patients and to investigate the influence of *H. pylori* infection on cardiovascular risk factors (lipid profile and. Highly sensitive C-reactive protein (hs CRP) levels).
Methods: Prospective cross sectional study was conducted to involve one hundred twenty patients with dyspeptic symptoms who involved 60 patients suffering from CAD and 60 controls who attended the gastrointestinal endoscopy clinic of the departments of internal medicine in AL-Quwayiyah General Hospital, Riadh, KSA. The study was carried out for six months from June to - November 2015. *H. pylori* were detected by rapid urease test, *H. pylori* IgG ELISA test and

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histopathology. Total cholesterol (TC), high density lipoprotein cholesterol (HDL- c) and triglycerides (TG) were measured by enzymatic methods using an automated chemistry analyzer. Low density lipoprotein cholesterol (LDL- c) was calculated using the Friedewald equation. hs CRP levels were estimated.

Results: *H. pylori* was confirmed in 80 (66.7%) of total 120 patients and controls by histology (gold method for diagnosis) and 80 (66.7%) by rapid urease test while 75 (62.5%) was detected by serology. There was no significant difference in age, sex or coronary artery risk factors between the two groups, but the prevalence of infectivity for *H. pylori* was higher in patients compared to controls (47{78.3%} versus 33 {55%} P<0.05). The patients with *H. pylori* infection had significant high triglyceride, low HDL-c and hs CRP levels than those with negative *H. pylori* (180.2±64.1, 29.1±7.3 and 14.8±7.8 versus 137.6±48.4, 45.6±8.9 and 9.2±7.1).

Conclusion: *H. pylori* infection increases the risk of CAD, and should be considered as a risk factor for CAD, also there was significant association between *H. pylori* infection and increased triglyceride hsCRP levels and decreased HDL-c. Further, prospective large trial is needed to confirm our finding.

Keywords: Helicobacter pylori; coronary artery disease; lipid profile and C-reactive protein.

1. INTRODUCTION

The most common risk factors for atherosclerosis process which cause CAD include diabetes, dyslipidemia, hypertension, and smoking [1]. The inflammation processes and atherogenesis have many similarities, and the role of an active inflammatory process in atherosclerosis pathogenesis of the coronary circulation is growing. Significantly, monocytes and macrophages are recognized as components of atheromatous plaques for several years.

The risk of cardiovascular events is associated with increased levels of the acute phase proteins, fibrinogen, hs CRP and proinflammatory cytokines [2]. For this reason, chronic inflammation is considered as a risk factor for CAD, and vascular injury, inflammation, and thrombosis are considered to cause atherosclerosis whereas the stimulus that generates the inflammatory response has remained unclear [3,4].

H. pylori is a bacterium that commonly colonizes the human stomach and causes chronic and active gastritis, peptic ulcer disease and is associated with increased risk of developing gastric cancer. Over the past decade, several studies have demonstrated that *H. pylori* infection is associated with the development of coronary atherosclerosis, and suggested a causal relationship although this issue is still controversial [5,6]. However, the mechanisms how *H. pylori* infection results in the coronary atherosclerosis, and the relationship between *H. pylori* infection and clinical and laboratory risk factors including blood pressure, smoking, blood glucose and lipids have not been fully understood.

Some studies suggest that *H. pylori* infection leads to elevated levels of serum TC, LDL-c, TG and CRP and decreased levels of, HDL-c. This is refuted by other studies. The effect of *H. pylori* infection on serum lipid profile and hs CRP levels remains a matter of debate. Many of these studies were carried out on western populations, in subjects with pre-existing coronary artery disease [7,8].

The aim of this prospective study was to evaluate *H. pylori* infection as risk factor and to investigate the influence of *H. pylori* infection on cardiovascular risk factors (lipid profile and hs CRP levels) among CAD patients.

2. SUBJECTS AND METHODS

2.1 Study Subjects

Patients with dyspeptic symptoms attended the gastrointestinal endoscopy clinic of the departments of internal medicine in AL-Quwayiyah General Hospital, Riadh, KSA. This Prospective cross sectional study was carried out for six months from June to - November 2015.

To determine CAD was directed by a history of coronary artery bypass graft surgery, a history of myocardial infarction, a history of percutaneous transluminal coronary stent and the presence of symptoms suggestive of CAD; such as exertional chest pain or dyspnea. The presence or absence of CAD was considered by collecting data from electrocardiogram (ECG), echocardiography, ECG stress test or coronary angiography. Exclusion criteria were: prior *H. pylori* eradication therapy, consumption of acid-suppressive drugs or antibiotics in the preceding 1 month, history of

vagotomy or operations on the upper gastrointestinal tract, known history of gastrointestinal pathology and patients on drug therapy known to alter lipid indices (e.g. β-blockers, oral contraceptive pills), and Patients receiving anti-hyperlipidemic therapy. Finally, a total of 120 subjects, 60 CAD patients and 60 CAD negative, controls were to be selected matched in age and sex with patients.

2.2 Data Collection

Information regarding underlying diseases, hypertension, diabetes mellitus, medication history and smoking was recorded using a standardised questionnaire.

2.3 Detection of Total Cholesterol, HDL-c, Triglycerides and hsCRP

Five ml of venous blood was obtained from each participant after an overnight fast (≥12 hours).

Total cholesterol, HDL- c and triglycerides were measured by enzymatic methods using an automated chemistry analyzer (Dimension RL Max) [9]. LDL -c was calculated using the Friedewald equation [10]. Total cholesterol by HDL -c ratio was calculated from the above values. hsCRP was measured using a turbidimetric assay (Quantex CRP ultra sensitive kits, BIOKIT, S.A., Barcelona, Spain) on auto-analyzer Hitachi 911, (ROCHE diagnostics, Indianapolis, Indiana, USA). The hsCRP kits measured ranges from 0.10 to 20.0 mg/L.

2.4 Detection of *H. pylori*

Gastroscopy using fiberoptic endoscope (EG 530 WR, Fujinon) with 2 antral biopsies from each patient, 5 cm from the pylorus. Sterile biopsy forceps were used and the flexible endoscopies and biopsy forceps were sterilized by cidex for at least 20 minutes, then washed with sterile saline. One specimen was used for doing RUT and the other preserved in formaline 10% and sent to histopathology laboratory in the regional laboratory and blood bank, Riadh, KSA. During endoscopic examination, patients were evaluated for the presence of antral gastritis, duodenal ulcer, doudenitis, gastroesophageal reflux diseas (GERD) and atrophic gastritis.

2.4.1 Rapid urease test

CLO-TEST tests were performed at the time of endoscopy and biopsy, according to the manufacturer's instructions (Delta West, Bentley, Australia).

2.4.2 *H. pylori* IgG ELISA test

The kit obtained from United diagnostics industry, Dammam, KSA. Automated Evolis machine (Biorad, USA) used For IgG detection.Reading the optical densities (O.D.) at 450nm or at 450/620 nm within 30 min. Take a new reading at 405 nm if the O.D. are higher than 2.000.

2.4.3 Interpretation of the results

Report the OD of the calibrators on a graph after subtracting the OD of the blank. The corresponding titer of the test sample can be obtained by extrapolation.

The degree of immunity can be interpreted as follows:

- IMMUNE (positive): when the anti-*H. Pylori* IgG concentration in the sample is > 15 AU/ml (for adult patients)
- NON IMMUNE (negative): when the anti-*H. pylori* IgG concentration is < 5 AU/ml
- DOUBTFUL: if the result is between the two values. In this case it is advisable to repeat the test in duplicate.

2.5 Statistics

Results are presented as mean ±SD (standard deviation). Statistical analysis was carried out using SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc., Chicago, IL, USA) and chi-square and Student t-tests were used to compare data. A value of $P<0.05$ was considered statistically significant.

3. RESULTS

In this study 120 patients were allocated in two groups according to positive (60 patients) and negative CAD, control group (60 patients).

The endoscopic findings were reported as antral gastritis, auodenal ulcer, doudenitis, GERD and atrophic gastritis (Table 1).

H. pylori was confirmed in 80 (66.7%) of total 120 patients and controls by histology (gold method for diagnosis) and 80 (66.7%) by rapid urease test while 75 (62.5%) was detected by serology (Table 2).

Table 1. Abnormal endoscopic findings in relations to *H. pylori* infections

lesion	Positive *H. pylori*		Negative *H. pylori*		Total		P value
	No	%	N	%	N	%	
NormaL	4	5%	6	15%	10	8.3%	NS
Antral gastritis	48	60%	17	42.5%	65	54.2%	P <0.05*
Duodenal ulcer	14	17.5%	4	10%	18	15%	P <0.05*
Doudenitis	3	3.75%	3	7.5%	6	5%	NS
GERD	5	6.25%	7	17.5%	12	10%	NS
Atrophic gastritis	6	7.5%	3	7.5%	9	7.5%	NS
Total	80	100%	40	100%	120	100%	

**There is significant statistical difference as P < 0.05; NS= non significant*

Table 2. Diagnosis of *H. pylori* infection

Test	Positive		Negative	
	No=120	%	No	%
Histology	80	66.7%	40	33.3%
Serology	75	62.5%	45	37.5%
Urease	80	66.7%	40	33.3%

The mean age was 37.8±15 (range 16-80) and 32.6±17 (range 19-75) among patients and controls respectively, and 40 of 60 patients (66.7%) and 41 of 60 (68.2%) controls were males.

In Table 3, demographic data on the patients and controls are listed. There was no significant difference in age, sex, smoking, DM or hypertension between the two groups, but the prevalence of seropositivity for *H. pylori* was higher in patients compared to controls (47{78.3%} versus 33 {55%} P<0.05).

The patients with *H. pylori* infection had significant high triglyceride, low HDL and high CRP levels than those with negative *H. pylori* (180.2±64.1, 29.1±7.3 and 14.8±7.8 versus 137.6±48.4, 45.6±8.9 and 9.2±7.1) (Table 4).

4. DISCUSSION

H. pylori infection is associated with various upper gastrointestinal pathologies such gastritis, peptic ulcers and gastric cancer. Endoscopy is the ideal procedure for identifying organic diseases of the foregut [11-14].

In this study, UGI endoscopy study revealed abnormal findings in 91.67% of the patients, similar finding found by Nkrumah et al. [15] in Saudi Arabia that noted 94% while Agbakwuru et al. [16] in Nigeria recorded 66%.

In the current study, the most common endoscopic findings were gastritis and duodenal ulcer occurring in 54.16% and 15% respectively. Walker et al. [17] also observed duodenal ulcer as the commonest findings in their studies 20.1%. The prevalence of duodenal ulceration encountered was also comparable to those seen in Kenya (21%) and pooled African data (26%) [18,19]. We found gastritis in 54.16% of patients while it was 53% obtained by Agbakwuru et al. [16] in Nigeria and 43% by Nkrumah et al. [15] in Saudi Arabia.

The histological identification of *H. pylori* in 66.7% of patients in this study is comparable with the rates in earlier reports of 53% and 61.6% from Riyadh [20] but lower compared with other regions such as Jeddah (85%) [21] and Dammam (87%) [22]. The wide variation in the prevalence of infection in different areas of KSA may be attributable to the differences in the methods of identification in part, and the demographic characteristics of patient-populations in different surveys [23].

H. pylori infection has been clearly linked to peptic ulcer disease and some gastrointestinal manifestations [24]. Chronic inflammation is a risk factor for atherosclerosis [25]. Inflammation arising from chronic infections including *H. pylori* have been studied, however the role of *H. pylori* in CAD is conflicting [24].

This study showed a higher prevalence of *H. pylori* infection positivity in patients with CAD compared to controls (78.3% versus 55%, P<0.05) this is in an agreement with Frank et al. [24] who compared patients with CAD and healthy controls and found *H. pylori* infection was significantly higher in patients of CAD (59%) Vs the healthy controls (39%). Similar reports from India made by Tewari R, et al. [26] and Tamer GS et al. [27] who that *H. pylori* infection was much higher in patients with CAD when compared with asymptomatic controls.

Table 3. Demoghraphic data of patients and control groups

Data	Patients N=60	Control (n=60)	P value
Age	37.8±15 (16-80)	32.6±17 (19-75)	NS
BMI (kg/m2)	29.5±4	26.6±7	NS
Male	40 (66.7%)	41 (68.2%)	NS
Female	20 (33.3%)	19 (31.7%)	NS
Smoking	40 (66.7%)	40 (66.7%)	NS
DM	12 (20%)	9 (15%)	NS
Hypertension	40 (60%)	33 (55%)	NS
H. pylori positivity %	47 (78.3%)	33 (55%)	P <0.05*

Table 4. *H. pylori* infection among CAD patients in relation to some laboratory data

Laboratory data	Positive *H. pylori* N =47	Negative *H. pylori* N =13	P value
Cholesterol(mg/dl)	199.6±57.5	214.6±59.5	NS
Triglyceride(mg/dl)	180.2±64.1	137.6±48.4	p<0.05*
HDL(mg/dl)	29.1±7.3	45.6±8.9	P= 0.01*
LDL(mg/dl)	138.1±42.2	144.1±61.2	NS
hsCRP (mg/dl)	14.8±7.8	9.2±7.1	P= 0.01*

The present study provides evidences that *H. pylori* infection was associated with atherogenic modified lipid profile among patients with CAD. *H. pylori* infection was associated with significant increase in triglyceride level and total cholesterol, Significant decrease in HDL-c level and non significant effect on level LDL-c.

This results supported by Kucukazman et al. [28] who found TC and LDL-c concentrations to be higher in positive *H. pylori* patients than in negative *H. pylori* patients. Also Sung et al. [29] reported higher TC, LDL-c, and TG levels but lower HDL-c levels in positive *H. pylori* patients. Similarly, Gen et al. [30] found TC, LDL-c, and TG levels to be higher but HDL levels to be lower in patients who were detected as positive *H. pylori* than in those who were detected as negative *H. pylori*.

Studies have been demonstrated that *H. pylori* are associated with low HDL-c level and that HDL-c level increases with eradication therapy. Hoffeister et al. [31] and Takashima et al. [32] demonstrated that *H. pylori* causes low HDL-c level, and Elizalde et al. [33] Ando et al. [34], Kanbay et al. [35] and Gen et al. [36] determined an increase in HDL-c levels of patients after successful *H. pylori* eradication therapy.

Longo-Mbenza et al. [37] determined that positive *H. pylori* patients have higher TG and TC but lower HDL concentrations than negative *H. pylori* patients and reported a decrease in TG and TC concentrations in positive *H. pylori* patients after eradication therapy compared with the concentrations before therapy.

hsCRP is a marker of inflammation and infection of the gastric mucosa with *H. pylori*, which causes an inflammatory reaction, the higher concentration of hsCRP in the *H. pylori*-infected group may be due to induction of subclinical micro-inflammatory reactions by *H. pylori* [38,39]. CRP is produced by liver and may also be a causal agent promoting atherosclerotic process [40-42].

H. pylori infection may lead to increase in risk of coronary artery disease, It is well documented that a rise in inflammatory cytokine-interleukin 6 which was found elevated in *H. pylori* infected individuals is primarily responsible for a rise in hsCRP production [43].

In the present study there is a statistically significant increase in hsCRP levels in *H. pylori* infected individuals (P= 0.01). Raised hsCRP levels have been shown to be associated with higher risk of cardiovascular events. This supported by Ridker et al. [43] who disclosed that subjects with raised levels of hsCRP but low levels of LDL-c are at a greater risk of future cardiovascular events than subjects with low levels of hsCRP but raised levels of LDL- c. This shows that *H. pylori* infection may lead to a significant increase in the risk for future

cardiovascular disease, independent of any effect on serum lipid levels.

5. CONCLUSION

H. pylori infection increases the risk of CAD, and should be considered as a risk factor for CAD, also there was significant association between *H. pylori* infection and increased triglyceride hsCRP levels and decreased HDL-c. Further, prospective large trial is needed to confirm our finding.

CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this paper.

ETHICAL APPROVAL

Ethical clearance was obtained from the AL-Quwayiyah General hospital's ethics committee.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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