Association of virulent Helicobacter Pylori strain with Coronary artery disease and coronary risk factors

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Abstract: Background: *Helicobacter Pylori (H. pylori)* infection is the commonest infection in the world that has many extra gastrointestinal manifestations and probably Coronary artery disease (CAD) is one of them. The aim of this study is to investigate the relation between *Helicobacter pylori* infection with Coronary risk factors and CAD. **Patients and methods:** This prospective study enrolled 150 patients who referred to Specialized Medical Hospital, Mansoura University for coronary angiography. All patients were tested for *H. pylori* Stool Antigen Test and Serum Anti-CagA strain H. Pylori. According to result of coronary angiography, patients were divided into CAD + group and CAD – group. Both groups were compared as regard prevelance of *H. pylori* infection and CagA positive strain. **Results:** The study included 150 patients, 96 men and 54 women, 60%(90/150) CAD + group and 40% (60/150) CAD – group. There was no significant difference between CAD+ group and group CAD-group as regarding overall *H. pylori* infection when identified by stool antigen test, *P* value = 0.063. While, infection by CagA positive strain found to be statistically significant higher in CAD+ group compared to CAD- group, with *P* value = 0.012. There was a statistically significant positive association between *H. pylori* infection (identified by stool antigen test) and dyslipidemia, with *P* value < 0.05. **Conclusions:** Overall *H. pylori* infection is not independent risk factors for Coro/nary artery disease, but its pathogenic CagA strain is independent risk factors for Coronary artery disease**.**
[Elsayed A. Khalil, Ahmed Abdel Ghafar, Shreef A. Saker and Fathallh Elssadi . **Association of virulent Helicobacter Pylori strain with Coronary artery disease and coronary risk factors.** *J Am Sci* 2017;13(10):32-38]. ISSN 1545-1003 (print); ISSN 2375-7264 (online). http://www.jofamericanscience.org. 4. doi:10.7537/marsjas131017.04.

Keywords: virulent helicobacter pylori strain, coronary artery disease, coronary risk factor

1. Introduction

Helicobacter Pylori (H. pylori) infection is the most common infection round the world, particularly in developing countries that causes peptic ulcer and gastric cancer (1). It reported to be associated with many extra gastrointestinal manifestations like, Idiopathic Thrombocytopenic Purpura, unexplained iron deficiency anemia, neurological disorders such as stroke, Parkinsonism and Alzheimer's disease and some skin disorders (2).

Atherosclerosis is a multifactorial process that have traditional risk factors like hypertension, diabetes mellitus, smoking and obesity (3), but substantial proportions of patients with Coronary artery disease (CAD) do not have these traditional risks (4). Hence, the other factors which may affect this chronic process were evaluated, and chronic inflammation was one of those Coronary risk factors at that time (5).

Chronic inflammation is considered as a risk factor for vascular injury and CAD. Inflammation and atherosclerosis cause thrombosis, whereas the stimulus that generates the inflammatory response remained unclear, the associations of some kinds of infections as a cause of inflammation were introduced as one of the probable risk factor (4).

Over the last years, many studies were performed to investigate the relationship between *H. pylori* and atherosclerotic heart diseases where some authors found that CagA positive strains have a role in CAD (6). On the contrary, some studies did not show any association (7). It is proposed that undetectable chronic infection may stand behind these changes in inflammatory markers. This study was designed to investigate the relation between *H. pylori* infection with Coronary risk factors and Coronary artery disease.

2. Patients and methods

2.1. Patients. This is a prospective study that enrolled 150 patients refered to Specialized Medical Hospital, Mansoura University, from January 2014 to January 2015 for Coronary angiography where all patients underwent physical examination. In patient evaluation, age, gender, body mass index (BMI), history of hypertenion (systolic ≥ 140 or diastolic ≥ 90) or history of antihypertensive drugs, Diabetes mellitus (DM) (FBS ≥ 126) or history of DM on diet control or medical management, Dyslipidemia, according to national lipid association (NLP) expert panel recommendation 2015 based on adult treatment panel III (ATP-III) Dyslipidemia is an increase in the serum levels of one or more of the following (total

Cholesterol ≥ 250 mg/dl, LDL-C ≥ 100 mg/dl, and serum triglyceride ≥ 150 mg/dl) or decrease in the serum levels of HDL-C ≤ 40 mg/dl), history of anti-lipid lowering agents intake or family history of Dyslipidemia, history of cardiac diseases, stroke, Smoking (exsmoker less than 10 years is considerate to be a smoker) and laboratory markers (Complete blood count, Fasting blood sugar, total serum cholesterol, triglycerides, low denysity lipoproteins (LDL), high denysity lipoproteins (HDL), creatinine, CRP, ESR) were recorded.

Patients with hepatic failure, renal disease (creatinine ≥ 2 mg/dL), anaemia, malignancies, previous *H. pylori* infection treatment or upper gastrointestinal surgery were excluded.

2.2 H. pylori Stool Antigen Test (HPSAT). H. pylori stool antigen test were measured by using a One Step test device (ABON) for the qualitative detection of *H. pylori* Antigen in the feces. The One Step *H. pylori* antigen test device ABON (Biopharm Hangzhou) is a chromatographic immunoassay for the qualitative detection of *H. pylori* antigen in human feces, and providing results in 10 minutes. The sensitivity and specificity of the One Step *H. pylori* Antigen Test Device (feces) is > 99.9% relative to Endoscopic based methods. The relative accuracy is (97.5% - 100%) and confidence interval is 95%.

2.3. Serum Anti-CagA strain H. Pylori. Blood samples were collected from all patients, and serum was separated as soon as possible after centrifugation of the blood and stored at -20 C until used. This ELISA kit is based on the principle of double antibody sandwich technique to detect Human (Anti-HP-CagA-IgG), provided by Sun Red Technology Company, UK.

2.4. Coronary Angiography. Coronary angiography was performed in a Catheterization lab, within a Medical Specialized Hospital at Mansoura University, using Siemens Angiocore Machine (Germany). Coronary angiography was carried out via femoral artery, using Judkins method by experienced interventional Cardiologists. More than one Cardiologist reviewed the angiography films results, and the patient considered to have Coronary artery disease (CAD positive) if there is Coronary atherosclerosis (atheroma), either significant stenosis (> 50%) or insignificant stenosis (< 50%). The patient considered normal or have no coronary artery disease (CAD negative) if the Coronary angiography is normal.

2.5. Statistical analysis. Data were collected, processed and analyzed by using IBM-SPSS software version 21, four windows. Categorical data were expressed as count & percent and were compared by Chi-square test or Fisher's exact test. Logistic regression with calculation of Odds' ratio was performed to predict a nominal variable (e.g., normal versus abnormal coronaries on angiogram).

Quantitative data (e.g., age) were initially tested for normality using Shapiro-Wilk test. Data were considered normally distributed if $p>0.05$ and non-normally distributed if $p < 0.05$. If data were normally distributed, they were expressed as Mean ± SD and compared using the parametric Independent-Samples t-test for two groups. If data were not normally distributed, they were expressed as Median & Interquartile Range (IQR) and compared using the non parametric Mann-Whitney U test for two groups. Adjustment of other confounding variables was done in multivariable models. *P* value < 0.05 was considered statistically significant.

2.6. Ehics. The Approval by Mansoura medical ethics Committee (MMEC) of faculty of medicine was obtained, and written consents from patients participated in the study or from their family were also obtained.

3. Results

In our study 150 patients were divided in two groups, coronary artery positive (CAD +) group and coronary artery negative (CAD –) group according to results of Coronary Angiography. The CAD+ group subdivided into two subgroups (significant and insignificant atherosclerosis subgroups) is presented in table 1. The differences in demographic data and risk factors are shown in table 1. There was no significant difference between CAD + group and CAD - group as regard age and gender (*P* value as 0.543 and 0.279). However, DM, hypertension, dyslipidemia, smoking, and BMI were found to be significantly higher in CAD + group compared to CAD - group (*P* value as 0.0001, 0.002, 0.001, 0.007, and 0.031 respectively).

The differences in laboratory data of both groups are shown in table 2. There was no significant difference between CAD + group and CAD - group as regard serum levels of AST, ALT and Creatinine. However, Hemoglobin, fasting blood sugar, total Cholesterol, Triglyceride, LDL-C and CRP levels were found to be significantly higher in CAD + group compared to CAD - group (*P* value = 0.016, 0.021, 0.037, 0.016, 0.002 and 0.040 respectively). And Serum HDL-C level found to be significantly lower in CAD + group compared to CAD - group with *P* value = 0.030.

CAD+ group showed non significant expression of *H.pylori* infection when identified by stool antigen test, *P* value = 0.063. While, its CagA positive strain found to be statistically significant higher in CAD+ group compared to CAD- group, with *P* value = 0.012 (Table 4).

On the other hand, significant and insignificant atherosclerosis and subgroup do not show any difference as regard *H. pylori* infection or its CagA positive strains infection, *P* value = 1 (Table 5).

The simple logistic regression analysis showed that there was no significant association between *H. pylori* infection or its strains and DM, hypertension and obesity, with insignificant *P* value > 0.05. However, there was a statistically significant positive association between *H. pylori* infection and CagA positive strains and dyslipidemia, with *P* value < 0.05 (Tables 6 and 7).

On multivariate regression analysis, there was a significant positive association between *H. pylori* strain identified by anti-CagA test and Coronary artery disease even after adjustment of all confounding variables (risk factors), with *P* value < 0.05.

Table (1) Demographic data of the studied groups (CAD + and CAD -)

Feature	(CAD +) (n=90) Coronary artery diseasepositive group	Coronary rtery disease negative group (CAD -) (n=60)	(Chi-Square test)	
			X2	*P*
Sex **Male** **Female**	63 (70%) 27 (30%)	33 (55%) 27 (45%)	1.170	0.279
Smoking **Positive** **Negative**	51 (56.7%) 39 (43.3%)	9 (15%) 51 (85%)	8.680	0.007
DM **Positive** **Negative**	60 (66%) 30 (33.3%)	9 (15%) 51 (85%)	12.890	0.0001
Hypertension **Positive** **Negative**	57(63.3%) 33 (36.7%)	9 (15%) 51 (85%)	11.370	0.002
Dyslipidemia **Positive** **Negative**	63(70%) 27 (30%)	12 (20%) 48(80%)	12.000	0.001
Obesity **BMI≥30** **BMI<30**	54 (60%) 36 (40%)	18 (30%) 42 (70%)	0.855	0.038
Feature	**Coronary artery disease positive group (CAD +) (n=90)**	**Coronary artery disease negative group (CAD -) (n=60)**	**Mann -Whitney U-test (*P*)**	
Age (year)	57 (49.75 – 60.00)	54 (50 – 59)	0.543	
Weight (Kg)	99 (80 – 105.25)	85.5 (77.25 – 98.75)	0.053	
Height (Meter)	1.8 (1.78 – 1.88)	1.78 (1.75 – 1.84)	0.217	
BMI	32.40 (24.65 – 34.80)	25.35 (23.60 – 32.39)	0.031	

Table (2) Laboratory data of the studied groups (CAD + and CAD -)

Feature	Coronary artery disease positive group (CAD +) (n=90)	Coronary artery disease negative Group (CAD -) (n=60)	*P*
Hemoglobin (g/dl)	12.9 (12.42 – 13.73)	12.3 (11.8 – 12.97)	0.016
FBS (mg/dl)	113 (90 – 125.25)	96 (87.25 – 101)	0.021
Total cholesterol (mg/dl)	279.5 (174.25 – 298)	147 (126.25 – 261)	0.037
Triglycerides (mg/dl)	199.5 (130.5 – 253)	117 (106.25 – 186.75)	0.016
LDL-C (mg/dl)	103 (93 – 134.75)	89.5 (86 – 100)	0.002
HDL-C (mg/dl)	30.4 (35.40 – 25.50)	60.25 (55.30 – 65.20)	0.030
CRP (mg/dl)	8.3 (6 – 10.4)	6.3 (5.38 – 6.9)	0.040
AST (IU)	27 (21.75 – 29.25)	23 (20 – 29.75)	0.427
ALT (IU)	28 (24.75 – 29.25)	24 (20 – 30)	0.170
Creatinine (mg/dl)	1 (8.0 – 1.1)	0.95 (0.9 – 1.1)	0.694

Table (3) Laboratory data of the Coronary artery disease positive subgroups

	Coronary artery disease positive group (CAD+)		
Feature	**Significant atherosclerosis subgroup (n=45)**	**In significant atherosclerosis subgroup (n=45)**	***P***
Hemoglobin (g/dl)	12.7 (12 – 13.7)	13 (12.8 – 13.8)	0.162
FBS (mg/dl)	111 (88 – 127)	115 (90 – 119)	0.744
Total cholesterol (mg/dl)	280 (160 – 298)	277 (122 – 297)	0.595
HDL-C (mg/dl)	58 (51 – 66)	61 (51 – 64)	0.902
LDL-C (mg/dl)	105 (98 – 153)	101 (90 – 124)	0.187
Triglycerides (mg/dl)	200 (137 – 248)	199 (115 – 268)	0.870
Creatinine (mg/dl)	1 (0.9 – 1)	1 (0.7 – 1.1)	0.901
AST (IU)	26 (21 – 29)	29 (22 – 30)	0.367
ALT (IU)	28 (22 – 31)	28 (25 – 29)	0.838
CRP (mg/dl)	6.8 (5.1 – 7.5)	7.4 (5 – 8.9)	0.567

Table (4) *H. pylori* tests in the studied groups

Tests	**Coronary artery disease positive group (CAD+) (n=90)**	**Coronary artery disease negative group (CAD-) (n=60)**	X^2	*P*
Stool antigen test **Positive** **Negative**	60 (66.7%) 30 (33.3%)	24 (40%) 36 (60%)	3.46	0.063
Anti-Cag A **Positive** **Negative**	42 (46.7%) 48 (53.3%)	6 (10%) 54 (90%)	7.40	0.012

Table (5) *H. pylori* tests in CAD+ subgroups

Tests	**Significant atherosclerosis subgroup (n=45)**	**Insignificant atherosclerosis subgroup (n=45)**	**(Chi-Square test)**	
			X^2	*P*
Stool antigen test **Positive** **Negative**	30 (66.7%) 15 (33.3%)	30 (66.7%) 15 (33.3%)	0	1
Anti-Cag A **Positive** **Negative**	21 (46.7%) 24 (53.3%)	21 (46.7%) 24 (53.3%)	0	1

Table (6) Association between *H. pylori* infection (identified by SAT) and Coronary risk factors, by simple logistic regression analysis

outcome	**OR**	**95% CI of Or**	***P* value**
DM	1.040	0.339 – 3.190	0.945
Hypertension	0.900	0.292 – 2.717	0.854
Dyslipidemia	5.630	1.640 – 9.230	0.006
Obesity	0.867	0.283 – 2.651	0.802

Table (7) Association between *H. pylori* strain (identified by antiCagA) and Coronary risk factors, by simple logistic regression analysis

outcome	**OR**	**95% CI of Or**	***P* value**
DM	1.267	0.385 – 4.168	0.697
Hypertension	0.985	0.297 – 3.263	0.981
Dyslipidemia	4.846	1.287 – 8.255	0.020
Obesity	2.380	0.702 – 8.073	0.164

Table (8) Association between *H. pylori* (identified by anti-CagA) and Coronary artery disease by multivariate regression analysis

Model	OR	95% CI of Or	*P* value
Crude model	3.00	0.92 – 6.90	0.066
Model I	2.96	0.88 – 9.90	0.078
Model II	4.85	0.98 – 12.65	0.055
Model III	4.77	0.99 – 12.90	0.051
Model IV	1.46	0.33 – 6.29	0.611
Full Model	2.16	0.28 – 6.61	0.457

4. Discussion

It is broadly accepted that *H. pylori* infection is one of the most common chronic infections worldwide that frequently remain asymptomatic and may deliver their antigens that stimulate both local and systemic inflammatory response so, recently a possible association between *H. pylori* and extra gastric disorders has been suggested (8).

There is now growing body of evidence to strongly suggest that Coronary atherosclerosis may be primarily an infectious disease and chronic infection by *H. pylori* may be associated with the risk of Coronary artery disease (9).

An intense immune response against CagA positive *H. pylori* strains might be critical to precipitate Coronary disease mediated by antigen mimicry between CagA antigen and a protein contained in coronary atherosclerotic plaques. Whereas CagA negative strains provoke a significantly lower inflammatory response (10).

The present study designed to study the relation of *H. pylori* infection and its pathogenic CagA strain with Coronary atherosclerosis and Coronary risk factors. In the current study, smoking, DM, hypertension, dyslipidemia and obesity are significantly increased in CAD + group compared to CAD – group with statistically significant *P* value (0.007, 0.0001, 0.001, 0.001 and 0.031 respectively) (Table 1).

These findings are in agreement with a large body of earlier studies which suggested that, the traditional risk factors, including hypertension, smoking, diabetes mellitus, and dyslipidemia, could be implicated in the pathogenesis of Coronary atherosclerosis (11).

Our study showed a statistically significant high serum levels of fasting blood sugar (*P*=0.021), Triglycerides (*P*=0.016), total Cholesterol (*P*=0.037), LDL-C (*P*=0.002), Hemoglobin (*P*=0.016), CRP (*P*=0.040), and significantly low serum level of HDL-C (*P*=0.030) in CAD + group compared to CAD - group, with no statistically significant difference in the serum creatinine, ALT, and AST between both groups (*P*=0.694, 0.170 and 0.427 respectively) (Table 3). This result confirms the results seen in table 1, and agrees with worldwide studies of rational role of traditional risk factors in Coronary atherosclerosis (11).

As regard the statistically significant higher Hemoglobin level in CAD + group compared to CAD - group, this difference could be explained on the basis of secondary high Hemoglobin levels in smokers, as smoking is statistically significant high in CAD + group compared to CAD – group with significant *P* value = 0.007 (Table1). Our result was in agreement with Lakshmi et al. who found increased hemoglobin levels in smokers with Coronary artery disease (12).

Higher CRP level in CAD + group compared to CAD - group (*P* value = 0.040, table 3), could be explained as the atherosclerosis is the main underlying pathology of CAD, and the recent observations suggest that the atherosclerotic process is inflammatory disease and characterized by a low grade inflammation altering the endothelium of the Coronary arteries and associated with an increase in the levels of inflammatory markers such as acute phase proteins particularly CRP (13).

Our study revealed no statistically significant difference between CAD + group and CAD - group as regard overall *H. pylori* infection (identified by SAT), with *P* value = 0.063 (Table 4). In agreement with our study, Davoudi et al. studied 153 patients scheduled for Coronary angiography. *H. pylori* infection was seen in (58%) of the atherosclerotic group, and in (57.1%) of normal control group with no significant differences (14). In contrary to our study, Tewari et al. concluded that there was a statistically significant association between seropositivity of *H. pylori* and Coronary artery disease. However, Tewari et al., depend on ECG and medical records of patients on diagnosis of CAD, which is actually less accurate than Coronary angiography (15).

Our study showed significant increase in CagA strain infection among CAD + group as 46.7% (42/90) when compared to CAD - groupas 10% (6/60), with *P* value= 0.012 (Table 4). These results are similar to Bingsheng et al. study, who conducted that, there is significant increase in CagA infection in patients with Coronary atherosclerosis (16).

Our results can be explained on the base of; the CagA is a potent antigen which plays a main role in the inflammation and cytokines production (IL-6, IL-18 and TNF-alpha) as well as nuclear factor kappa-B (NF-κB) activation. Inflammation recently considered as one of the main risk factor for atherosclerosis, which leads to increase production of proinflammatory cytokines such as IL-6, IL-18 and TNF-alpha, and activation of the NF-κB pathway (17). This suggests that the inflammatory response to CagA positive *H. pylori* may mediate atherogenesis in patients with Coronary artery disease (18).

Our study showed a significant positive association between *H. pylori* infection and its pathogenic strain with dyslipidemia (Tables 6,7) by using simple logistic regression analysis (OR=5.630, 95% CI=1.640 – 9.230 and *P* value as 0.006) (OR = 4.846, 95% CI =1.287 – 8.255, with *P* value = 0.020).

Our results can be explained as chronic *H. pylori* infections cause inflammation by increasing expression of inflammatory cytokines such as TNF-α, IL-1 and IL-6 which activate adipose tissue lipoprotein lipase, and stimulation of hepatic fatty acid synthesis and influencing lipolysis. This resulted in mobilization of TG from tissue to blood circulation and thus elevated triglyceride in circulation is observed. In addition after *H. pylori* treatment, decreasing LDL-C, TG, TC levels and increasing HDLC levels were found, indicating that *H. pylori* eradication is important for prevention of dysipidemia (19).

The possible explanation of our result is depending on the fact that, the organisms expressing CagA gene are more potent than organisms not expressing CagA gene in the stimulation of proinflammatory cytokine release, with subsequent influences on the lipid metabolism, resulting in high lipid parameter levels and subsequent decrease in HDL-C level (20). Also, CagA positive strains enhance atherosclerosis in CAD patients by modifying oxidized LDL levels (21).

According to our result which explore the role of *H. pylori* infection and its CagA Strains in dyslipidemia, a new therapeutic strategy for treatment of dyslipidemia can be achieved through eradication of CagA Strain of *H. pylori* infection.

Finally we can consider that, *H. pylori* infection per say cannot causes Coronary atherosclerosis, but its pathogenic CagA strain genotype is mainly responsible for pathogenesis of Coronary atherosclerosis, either directly or indirectly through molecular mimicry or dyslipidemia. And in case of farther proving this association it well open a novel ways of treating, as well as, preventing Coronary artery disease by eradication of pathogenic CagA strain type of *H. pylori* infection.

5. Conclusion

We concluded that, Overall *H. pylori* infection is not independent risk factors for Coronary artery disease, but its pathogenic CagA strain is independent risk factors for Coronary artery disease. However the pathogenic CagA strain infections have no role in the severity of coronary artery disease.

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10/7/2017